

The DNA sequence of the RK strain of human herpesvirus 7

by

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SUMMARY

Human herpesvirus 7 (HHV-7) was first isolated by Frenkel and colleagues in 1989 from CD4⁺ T-cells, during experiments concerning propagation of HHV-6. Uninfected cells underwent spontaneous cytopathic effect following conditions promoting T-cell activation. A new herpesvirus was isolated which was related to but distinct from human herpesvirus 6 (HHV-6). This virus was designated HHV-7 (RK).

HHV-7 is ubiquitous in the human population - probably more than 85% of people are infected. It is likely that HHV-7 is transmitted through saliva, with primary infection occurring before three years of age. The virus has no proven involvement in any disease. HHV-7 is a member of the Betaherpesvirinae and is more closely related to HHV-6 than to human cytomegalovirus (HCMV). The genome is approximately 145 kbp in length and has an overall structure like that of HHV-6, consisting of a long unique region (U) flanked by a direct repeat (DR).

Since 1984, the complete sequences of fourteen herpesvirus genomes have been published and at least four more have been completed. This has allowed comparative studies of individual genes and permitted extensive and detailed understanding of the relationships between the herpesviruses. In addition, recent reports based on molecular sequence analysis, have provided a detailed phylogeny and allowed an evolutionary timescale to be derived.

The aims of this project were to determine the complete DNA sequence of HHV-7 and to analyse the coding potential of the sequence. The work was initiated in collaboration with Professor N. Frenkel (Tel-Aviv University, Israel), who provided genomic DNA from the RK strain. During the course of this work the complete DNA sequences of HHV-6 strain U1102 and HHV-7 strain JI were published by other groups. Therefore, the HHV-7 strain RK sequence was compared with these two sequences in order to appraise evolutionary divergence and to re-evaluate the genetic contents of HHV-6 and HHV-7.

The HHV-7 RK genome was sequenced by direct shotgun cloning of random DNA fragments into an M13 vector. Approximately 7,000 fragments were sequenced and compiled into a

database with the aid of a computer. The genetic content of the sequence was interpreted using a suite of computer programs. This analysis was then extended to reassess the sequence of HHV-6. Special attention was paid to potential splicing.

The HHV-7 RK genome sequence obtained is 153,080 bp in length and comprises U (133,012 bp) flanked on each side by a copy of DR (10,034 bp). Four different reiterated sequences are present in the genome, two in U and two in DR. the latter comprise arrays of a human telomere-like element. Complexity and size resulted in one of these arrays being particularly challenging to resolve, and an unsatisfactory solution in this region is reflected in the likelihood that the sequence obtained is approximately 3 kbp longer than the actual genome. Analysis of the differences between HHV-7 RK and JI indicated that the lineages resulting in the two strains diverged from a common ancestor of the order of 10,000 years ago.

It was concluded on the basis of various analytical criteria that the HHV-7 genome contains 84 genes, only one of which has no direct counterpart in HHV-6. However, the latter is related to an adjacent gene which has an HHV-6 homologue. By the same criteria, HHV-6 contains 85 genes, two of which lack counterparts in HHV-7. One encodes a putative membrane glycoprotein and the other is a homologue of the adeno-associated virus type 2 *rep* gene. Furthermore, sequence comparisons between HHV-7 and HHV-6 also allowed the identification of putative splice sites in eleven genes. One of these genes is predicted to encode a previously unrecognised membrane glycoprotein.

This study lays the foundation for continuing experimental investigation of gene expression in HHV-7, particularly in regard to splicing.

CONTENTS

1.0. INTRODUCTION

1.0. FOREWORD	1
1.1. THE HERPESVIRIDAE	1
1.1.1. Overview.....	1
1.1.2. Clinical manifestations	3
1.1.2.1. General	3
1.1.2.2. Human herpesviruses	3
1.1.3. Life cycle.....	6
1.1.3.1. The lytic cycle.....	6
1.1.3.2. The latent cycle	7
1.1.4. Herpesvirus genes.....	7
1.1.5. Herpesvirus classification	8
1.1.5.1. Formal classification	8
1.1.5.2. Genetic classification.....	10
1.1.6. Genetic content.....	11
1.1.6.1. Genome sequences	11
1.1.6.2. Gene conservation	12
1.1.7. Genome evolution.....	13
1.1.7.1. Mechanisms	13
1.1.7.2. Phylogeny.....	15
1.1.7.3. Evolutionary timescale	16
1.2. HUMAN CYTOMEGALOVIRUS	18
1.2.1. Basic characteristics	18
1.2.2. Epidemiology	18
1.2.3. Cellular tropism	18
1.2.4. Growth properties	19
1.2.5. Disease and therapy	20
1.2.6. The HCMV genome	21
1.2.6.1. Size and structure	21
1.2.6.2. Origin of DNA replication	21
1.2.6.3. Genetic organisation	22
1.2.7. Gene complement	22
1.2.8. Captured genes	24
1.2.9. Gene families	24
1.3. HUMAN HERPESVIRUS 6	26
1.3.1. Basic characteristics	26
1.3.2. Epidemiology	26
1.3.3. Cellular tropism	27
1.3.4. Growth properties	28
1.3.5. Disease and therapy	28
1.3.6. Co-infection with other viruses.....	30

1.3.7. The HHV-6 genome	31
1.3.7.1. Size and structure	31
1.3.7.2. Relationships to other herpesviruses	32
1.3.7.3. Gene complement	32
1.3.7.4. Origin of lytic DNA replication	33
1.3.7.5. Gene families and captured genes	33
1.4. HUMAN HERPESVIRUS 7	35
1.4.1. Basic characteristics	35
1.4.2. Epidemiology	35
1.4.3. Cellular tropism	36
1.4.4. Growth properties	36
1.4.5. Disease	36
1.4.6. The HHV-7 genome	37
1.4.6.1. Size and structure	37
1.4.6.2. Genetic organisation	39
1.4.6.3. Gene complement	39
1.5. AIMS OF THE THESIS	40

2.0. MATERIALS AND METHODS

2.1. MATERIALS	41
2.1.1. Chemicals	41
2.1.2. Solutions and buffers	41
2.1.3. Enzymes	44
2.1.4. Radiochemicals	44
2.1.5. Bacterial growth media	44
2.1.6. Bacterial strains	45
2.1.7. DNA	45
2.1.8. Miscellaneous	45
2.2. METHODS	46
2.2.1. PREPARATION OF DNA	46
2.2.1.1. Production of viral DNA	46
2.2.1.2. Restriction enzyme digestion	46
2.2.1.3. Agarose gel electrophoresis	47
2.2.1.4. Precipitation of viral DNA	47
2.2.1.5. Sonication of viral DNA	47
2.2.1.6. Size selection of sonicated DNA fragments	47
2.2.1.7. DNA purification using GeneClean	48
2.2.2. PREPARATION OF TEMPLATES	48
2.2.2.1. T4 DNA polymerase end repair	48
2.2.2.2. Preparation of M13mp19 <i>Sma</i> I	49
2.2.2.3. Ligation	49
2.2.2.4. Transfection and electroporation	49
2.2.2.5. Preparation of DNA templates	50
2.2.3. DNA SEQUENCING	51
2.2.3.1. Preparation and deprotection of primers.	51
2.2.3.2. Polyacrylamide gel electrophoresis	51
2.2.3.3. Annealing primer	52

2.2.3.4. Sequencing reactions	52
2.2.3.5. Sequencing gel electrophoresis	53
2.2.4.0. GENOME ASSEMBLY AND ANALYSIS	55
2.2.4.1. Reading and assembly of sequences	55
2.2.4.2. Analysis of the completed sequence	55

3.0. RESULTS

3.1. RANDOM SHOTGUN SEQUENCING	56
3.2. PREPARATION OF VIRAL DNA	56
3.3. PREPARATION OF SEQUENCES	56
3.3.1. Identity and purity of the DNA	56
3.3.2. DNA purification	57
3.3.3. Fragmentation of the DNA	57
3.3.4. End repair and ligation	58
3.3.5. Transfection and electroporation	58
3.3.6. Growth of recombinant phage	59
3.3.7. Sequencing	59
3.4. ASSEMBLY OF THE DATABASE	59
3.4.1. Initial assessment of DNA templates	60
3.4.2. Automatic input of sequence data	60
3.5. ASSEMBLY OF REITERATED SEQUENCES	62
3.5.1. R2	62
3.5.2. R1	62
3.5.3. T1 and T2	63
3.6. EDITING THE DATABASE	64
3.6.1. Removal of single contigs	64
3.6.2. Editing the database	64
3.6.3. Errors in the sequence	65
3.7. THE HHV-7 RK GENOME SEQUENCE	65
3.8. GENOME SEQUENCE COMPARISONS	66
3.9. DIFFERENCES BETWEEN THE HHV-7 RK AND JI SEQUENCE	66
3.9.1. Reiterations	66
3.9.2. Rest of the genome	67
3.10. THE GENETIC CONTENT OF HHV-7 AND HHV-6	68
3.10.1. Examination of coding potential	68
3.10.2. The deduced layout of HHV-7 genes	69
3.10.3. The deduced layout of HHV-6 genes	70
3.10.4. Gene organisation	71
3.11. GENE SPLICING IN HHV-7 AND HHV-6	71
3.11.1. Detection of splice sites	72
3.11.2. Candidate spliced genes	72

4.0. DISCUSSION

4.1. THE DNA SEQUENCES OF HHV-7 RK AND JI	76
4.1.1. Strain divergence	76
4.1.2. Nucleotide differences	76

4.1.3. Genome ends77

4.1.4. Reiterations.....77

4.1.5. Resolution of the T1 reiteration.....78

4.2. FUNCTIONS OF THE TELOMERIC REITERATIONS 78

4.3. CODING POTENTIAL OF HHV-7 80

4.4. SPLICING 81

4.4.1. Splicing patterns in HHV-7 and HHV-681

4.4.2. Confirmation of splicing.....82

4.4.3. Origins of splicing82

4.5. PHENOTYPIC DIFFERENCES BETWEEN HHV-6 AND HHV-7 82

4.6. CONCLUSION 83

REFERENCES85

FIGURES AND TABLES

FIGURES

	After page
Fig. 1. Types of herpesvirus genome structure	9
Fig. 2. Herpesvirus evolution	15
Fig. 3. Genetic layout of the HCMV genome	21
Fig. 4. Genetic layout of the HHV-6 genome	31
Fig. 5. Comparison of the genetic content of HCMV, HHV-6 and HHV-7	31
Fig. 6. Genetic layout of the HHV-7 genome	37
Fig. 7. <i>HindIII</i> and <i>SalI</i> restriction profiles of HHV-7 RK genomic DNA	56
Fig. 8. Status of HHV-7 strain RK genomic DNA	57
Fig. 9. Purification of HHV-7 RK genomic DNA	57
Fig. 10. Status of randomly fragmented HHV-7 RK genomic DNA	58
Fig. 11. Recovery of 400-700 bp fragments from randomly fragmented HHV-7 RK genomic DNA	58
Fig. 12. Recovered 400-700 bp fragments of HHV-7 RK genomic DNA	58
Fig. 13. Database assembly	60
Fig. 14. Entry of a single sequence into the HHV-7 database	60
Fig. 15. The structure of the R2 reiteration in HHV-7 strains RK and JI	62
Fig. 16. The structure of the R1 reiteration in HHV-7 strains RK and JI	62
Fig. 17. The structure of the telomeric array (T2) from the right end of DR in HHV-7 strains RK and JI	63
Fig. 18. The structure of the telomeric array (T1) from the left end of DR in HHV-7 strains RK and JI	63
Fig. 19. Four unedited errors in the database	64
Fig. 20. Correction of four errors in the database	64
Fig. 21. The DR/U and U/DR junctions or right and left ends of the genome, respectively, as represented in the database	65
Fig. 22. Distribution of sequence differences between the HHV-7 RK and JI genomes	67
Fig. 23. Predicted layout of HHV-7 RK genes	69
Fig. 24. Predicted layout of HHV-6 U1102 genes	70
Fig. 25. Sequence-derived evidence for splicing U66	72
Fig. 26. Sequence-derived evidence for splicing U7	73
Fig. 27. Sequence-derived evidence for splicing U15	73
Fig. 28. Sequence-derived evidence for splicing DR1	73
Fig. 29. Sequence-derived evidence for splicing DR6	73
Fig. 30. Sequence-derived evidence for splicing U12	74
Fig. 31. Sequence-derived evidence for splicing U17	74

	After page
Fig. 32. Sequence-derived evidence for splicing U79	74
Fig. 33. Sequence-derived evidence for splicing U90	74
Fig. 34. Sequence-derived evidence for splicing U91	74
Fig. 35. Hydrophobicity profiles generated using Pepplot from the U91 proteins potentially expressed by splicing	74
Fig. 36. Sequence derived evidence for the splicing of U100, in the form of alignments of putative amino acid sequences in HHV-7 and HHV-6	75

TABLES

	After page
Table 1. HCMV genes and encoded proteins	21
Table 2. HHV-6 genes and encoded proteins	31
Table 3. HHV-7 genes and encoded proteins	37
Table 4. Stages in assembly of the HHV-7 database	60
Table 5. Custom oligonucleotide primers used to extend sequences in order to join contigs	61
Table 6. Telomeric repeat elements in HHV-7 RK, and the code used for their assembly	63
Table 7. Errors in the DNA sequence of HHV-7 strain RK	65
Table 8. Errors in the DNA sequence of HHV-7 strain JI	67
Table 9. Differences between HHV-7 strains RK and JI	67
Table 10. Differences between the genome sequences of HHV-7 strains RK and JI	67
Table 11. Features of the HHV-7 (RK) genes	69
Table 12. Predicted splice sites in the HHV-7 and HHV-6 genomes	71
Table 13. Proposed modifications to HHV-6A (U1102) genes	71

Abbreviations

°	degrees Celsius
μCi	microcurie
μg	microgram
μM	micromolar
A	adenine
AAV-2	adeno-associated virus 2
AIDS	acquired immune deficiency syndrome
APS	ammonium persulphate
ATP	adenosine triphosphate
BGM	bottom gel mix
bp	base pairs
BP	before present
BPB	bromophenol blue
C	Cytosine
CBMC	cord blood mononuclear cells
cDNA	complementary DNA
CFS	chronic fatigue syndrome
Ci	Curie
CIP	calf intestinal phosphatase
CNS	central nervous system
contig	Contiguous sequence
CPE	Cytopathic effect
dATP	2'-deoxyadenosine-5'-triphosphate
dCTP	2'-deoxycytidine-5'-triphosphate
ddATP	2'3'-dideoxyadenosine-triphosphate
ddCTP	2'3'-dideoxycytidine-triphosphate
ddGTP	2'3'-dideoxyguanosine-triphosphate
ddTTP	2'3'-dideoxythymidine-triphosphate
dGTP	2'-deoxyguanosine-5'-triphosphate
DNA	Deoxyribonucleic acid
DNase	Deoxyribonuclease
dNTPs	Deoxyribonucleoside triphosphates
DR	Direct repeat
DR	Direct repeat
DR _L	Direct repeat left
DR _R	Direct repeat right
DTT	Dithiothreitol
dTTP	2'-deoxythymidine-5'-triphosphate
dUTPase	Deoxyuridine triphosphate nucleotidohydrolase
E	Early
<i>E.coli</i>	<i>Escherichia coli</i>
EDTA	Ethylenediaminetetra-acetic acid
EtBr	Ethidium bromide

EtOH	Ethanol
G	Guanine
g	Gram
GCR	G-coupled receptor
gp	glycoprotein
h	hour
HPV	human papilloma virus
IE	immediate early
Ig	immunoglobulin
IPTG	isopropyl- β -D-thiogalactoside
IR _L	internal long repeat
IR _S	internal short repeat
kbp	kilobase pair
L	late
l	litre
M	molar
mg	milligram
MIE	major immediated early
min	minute
ml	millilitre
mM	millimolar
mRNA	messenger RNA
MS	multiple sclerosis
nm	nanometer
OBP	origin-binding protein
ORF	open reading frame
<i>ori</i>	origin of replication
<i>ori_L</i>	origin of replication in U _L
<i>ori_S</i>	origin of replication in U _S
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PEG	polyethylene glycol
R1	reiterated sequence 1
R2	reiterated sequence 2
R3	reiterated sequence 3
RNA	ribonucleic acid
RNase A	ribonuclease A
rpm	revolutions per minute
RR	ribonucleotide reductase
RT	room temperature
SDS	sodium dodecyl sulphate
T	thymidine
T1	telomeric reiteration 1
T2	telomeric reiteration 2
TEMED	N, N, N', N' -tetramethethylene diamine
TGM	top gel mix
Tris	Tris (hydroxymethyl) aminomethane
TR _L	long terminal repeat

TR _s	short terminal repeat
U	unique
U	unique sequence
U _L	long unique
U _s	short unique
UV	ultraviolet
v/v	volume/volume
w/v	weight/volume
w/w	weight/weight
<i>wt</i>	wild type
X-gal	5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside

Herpesviruses

Virus name	Common abbreviation	ICTV designation
Alcelaphine herpesvirus	AHV-1	AHV-1
Bovine herpesvirus 1	BHV-1	BHV-1
Channel catfish virus	CCV	IHV-1
Epstein-Barr virus	EBV	HHV-4
Equine herpesvirus 1	EHV-1	EHV-1
Equine herpesvirus 2	EHV-2	EHV-2
Equine herpesvirus 4	EHV-4	EHV-4
Herpes simplex virus type 1	HSV-1	HHV-1
Herpes simplex virus type 2	HSV-2	HHV-2
Herpesvirus ateles	HVA	AHV-2
Herpesvirus of turkey	HVT	MHV-1 ^b
Herpesvirus saimiri	HVS	SHV-2
Human cytomegalovirus	HCMV	HHV-5
Human herpesvirus 6	HHV-6	HHV-6
Human herpesvirus 7	HHV-7	HHV-7
Kaposi's sarcoma-associated herpesvirus	KSHV	(HHV-8)
Marek's disease virus	MDV	GHV-2
Murid herpesvirus 68	MHV-68	MHV-4
Murine cytomegalovirus	MCMV	MHV-1 ^a
Pseudorabies virus	PRV	SHV-1
Salmonid herpesvirus 1	SalHv-1	SalHv-1
Salmonid herpesvirus 2	SalHv-2	SalHv-2
Simian herpesvirus	B virus	CHV-1
Varicella-zoster virus	VZV	HHV-3

^a Murid herpesvirus 1. ^b Meleagrid herpesvirus 1.

One and three letter abbreviations for amino acid residues

Amino acid	Three letter code	One letter code
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

Chapter 1

Introduction

1.0. FOREWORD

This chapter is divided into four sections. Section 1.1. provides a thumbnail description of several aspects of the Herpesviridae, including clinical manifestations, life cycle, classification, genetic content and evolution. Sections 1.2., 1.3. and 1.4., refer to the members of the human Betaherpesvirinae: human cytomegalovirus (HCMV), human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7), respectively. These viruses are related and share many common features. Thus, the information in each section is similarly organised, and includes sub-sections concerning general characteristics, epidemiology, tropism, growth properties and diseases of the viruses, with emphasis placed on their genetic makeup. The chapter concludes with a short statement of the thesis aims.

1.1. THE HERPESVIRIDAE

1.1.1. Overview

The Herpesviridae are eukaryotic viruses, and number more than 100. They infect both warm and cold-blooded vertebrates, in a broad range from fish to man (Roizman and Sears, 1993; Fenner *et al.*, 1987) and at least one invertebrate, the oyster (Comps and Cochenne, 1993). The best studied infect humans, cattle, chickens, horses, mice and monkeys. Herpesviruses are well adapted to their hosts. Most display a high degree of host specificity, although a single host may become infected by several herpesviruses; for example, there are at least eight human herpesviruses. However, some, such as pseudorabies virus (PRV) and B virus, are less host specific and may infect a range of species.

Herpesvirus lytic infection typically follows a lifecycle of adsorption and penetration into the cell and migration of the viral DNA to the nucleus where gene expression occurs in a sequentially ordered cascade, with three main phases: immediate early (IE), early (E) and late (L). Transcription, viral DNA replication and capsid assembly take place in the nucleus. DNA is packaged into the capsids which then acquire tegument and envelope. Virions are released from the cell by exocytosis.

A common property of herpesviruses is the ability, following primary infection, to persist in an inapparent (or latent) form for the lifetime of the host, with only a small subset of viral genes

being expressed (Kieff and Liebowitz, 1990; Rock, 1993). Occasionally, latent virus may reactivate under the influence of as yet poorly defined stimuli.

Herpesvirus epidemiology is not linked to geographical or seasonal factors and age does not correlate with susceptibility to infection. It is possible, however, to predict the levels of seroconversion to herpesviruses in a population in relation to age. For example at three years of age 90% of people have antibodies to human herpesvirus 6 (HHV-6). Herpesvirus infection may be transmitted horizontally or vertically by direct contact of mucosal surfaces (through saliva, sexually or in breastmilk), but respiratory droplet infection is also common.

Membership of the Herpesviridae is based on virion morphology. The DNA genome which is in a liquid crystalline state (Booy *et al.*, 1991) is packaged within an icosahedral capsid, 100-110 nm in diameter and composed of 162 capsomeres: 12 pentavalent capsomers at the vertices, 60 hexavalent capsomers at the 20 faces and 90 hexavalent capsomers along the 30 edges (Wildy *et al.*, 1960). The capsid is enclosed within a proteinaceous layer (the tegument); (Roizman and Furlong, 1974), which in turn is surrounded by a host-derived lipid envelope, containing viral glycoproteins (Morgan *et al.*, 1959; Asher *et al.*, 1969; Spear and Roizman, 1972; Stannard *et al.*, 1987). Herpesvirions range in diameter between 160 nm and 230 nm, averaging 180 nm (Szilagyi and Berriman, 1994).

Herpesviruses have large, linear, double-stranded DNA genomes (Furlong *et al.*, 1972) which range in size from 125 kbp (e.g. varicella zoster virus; VZV) to 240 kbp (e.g. murine cytomegalovirus; MCMV) and exhibit an impressively wide range of base compositions from 32-75% G+C (Honess, 1984). A characteristic of herpesvirus genome structure is the presence of terminal or internal repeated sequences, in direct or inverse orientation. Herpesviruses contain between about 70 (e.g. herpes simplex virus type 1; HSV-1) and 200 genes (e.g. human cytomegalovirus; HCMV). The great majority of the genome codes for protein, and the genes are arranged in about equal numbers on each DNA strand.

1.1.2. Clinical manifestations

1.1.2.1. General

Primary infections by herpesviruses are often asymptomatic or slight, and recrudescence infection may occur once (e.g. VZV) or many times (e.g. HSV-1). Herpesvirus infection combined with conditions of immune suppression can prove fatal. For example, bone marrow transplant patients suffering from interstitial pneumonitis due to HCMV infection risk 25% mortality. In addition, infection with certain herpesviruses, such as Epstein-Barr virus (EBV) and Marek's disease virus (MDV), can result in carcinoma or lymphoma (Epstein *et al.*, 1964; Evans and Niederman, 1991; Fenner *et al.*, 1987), and the recently discovered Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8 or HHV-8) probably plays a significant causative role in Kaposi's sarcoma (Moore *et al.*, 1996). More unusually, a few herpesviruses are capable of infecting more than one species under natural or near-natural conditions. B virus causes an HSV-1-like disease in monkeys but brings about fatal ascending paralysis and encephalitis in humans (Fenner *et al.*, 1987). PRV primarily infects swine, but in cattle causes "mad-itch", resulting in death within a few hours; also dogs suffer a rabies-like illness which is also invariably fatal (Fenner *et al.*, 1987).

1.1.2.2. Human herpesviruses

Currently, most research effort is put into the human herpesviruses and herpesviruses of domestically important animals. Humans are host to at least eight herpesviruses, seven of which are etiologic agents of a number of diseases.

HSV-1 is ubiquitous in human populations and is typically acquired by the age of five years via respiratory droplets and through contact with mucosal surfaces or abraded skin. Primary infection is usually subclinical, and lifelong latent infection is established in neurons of the sensory ganglia (Baringer and Swoveland, 1973; Fraser *et al.*, 1981). Subsequent reactivation can be periodically triggered by a number of factors including stress, UV radiation and immune suppression (Hill *et al.*, 1978). During primary and recurrent infection the virus causes vesicular lesions of the skin and mucosa. Infection is generally limited to the oropharynx but may involve the eyes and the genitalia (Whitley, 1985; Cameron, 1993).

The clinical pathologies associated with HSV-1 and herpes simplex virus type 2 (HSV-2) are not strictly separated (Nahmias *et al.*, 1991). However, HSV-2 is transmitted sexually, although infection may occur at birth (Whitley, 1985; Cameron, 1993), and lesions are localised to the mucous membranes and skin of the genitals. HSV-2 reactivation usually occurs more frequently than that of HSV-1 (Timbury, 1991; Whitley, 1990).

VZV can spread by airborne infection or by direct contact (Johnson, 1982) and causes two distinct diseases (Hope-Simpson, 1965; Gelb, 1990). Primary infection causes the childhood disease varicella (chickenpox), a generally benign condition characterised by a fever and a vesicular rash. Complications are rare but symptoms may be more severe in adults, where pneumonia is common. The virus establishes latent infection in the dorsal root or cranial nerve ganglia. VZV reactivation causes the disease zoster (shingles), where painful vesicles appear in the area of skin enervated by the affected ganglia. The incidence and severity of zoster increases with age and in the immunocompromised (Schrimpf *et al.*, 1972; Kennedy, 1987; Timbury, 1991), and can leave the victim with the distressing condition of post-herpetic neuralgia.

EBV initiates infection via the oropharynx (Sixbey *et al.*, 1983, 1984) and establishes latent infection in B-lymphocytes. Primary EBV infection is commonly asymptomatic in children, but during adolescence and adulthood the virus may cause infectious mononucleosis (glandular fever). In addition, EBV is implicated in cancers, such as Burkitt's lymphoma, a highly malignant B-cell lymphoma which is common in African children and virtually confined to areas where malaria is endemic, and nasopharyngeal carcinoma which is common among southern Chinese populations (Neiderman *et al.*, 1976; Epstein and Achong, 1986). The selective geographic and racial distribution of these tumours suggests the influence of genetic and environmental factors, as well as EBV infection, in the progression towards disease (Miller, 1990; Timbury, 1991).

HCMV primary infection is often asymptomatic or self-limiting with the only evidence of infection being an increase in antibody titre (Alford and Britt, 1990). Transmission is thought to occur most commonly by salivary contact, but the virus may also be acquired sexually (Emery and Griffiths, 1990). The virus establishes latency in monocytes (Taylor-Wiedeman *et al.*, 1991). The most

serious aspect of HCMV infection occurs if the host is immunocompromised through immaturity or suppression. For example, HCMV can act as a major pathogen of the foetus and allograft or AIDS patients (Alford and Britt, 1990; Emery and Griffiths, 1990; Black and Pellet, 1993).

HHV-6 is typically acquired by the age of two years (Yoshikawa, 1993) and can persist in T-lymphocytes (Salahuddin *et al.*, 1986), possibly establishing latency there (Frenkel and Wyatt, 1992). The virus has been isolated from the saliva of normal adults (Pietroboni *et al.*, 1988a; Harnett *et al.*, 1990; Levy *et al.*, 1990) and this may act as a vehicle for transmission (Wyatt and Frenkel, 1992). HHV-6 isolates may be segregated into two groups, termed variants A and B (HHV-6A and HHV-6B), based on biological and immunological properties and genomic analysis (Wyatt *et al.*, 1990; Ablashi *et al.*, 1991; Schirmer *et al.*, 1991; Aubin *et al.*, 1993). HHV-6A is not associated with disease but HHV-6B is the etiologic agent of exanthem subitum (roseola infantum), a childhood febrile illness (Yamanishi *et al.*, 1988).

Human herpesvirus 7 (HHV-7) has been shown to replicate preferentially in activated CD4+ T-lymphocytes (Frenkel *et al.*, 1990) and has also been isolated from the saliva of up to 81% of healthy adults (Wyatt and Frenkel, 1992; Black *et al.*, 1993; Yoshikawa *et al.*, 1993; Hidaka *et al.*, 1993). HHV-7 primary infection is usually acquired by three years of age (Wyatt *et al.*, 1991; Clark *et al.*, 1993; Hidaka *et al.*, 1993), but a potential site for HHV-7 latent infection has not been identified, nor has transfer by saliva been proved to be the mode of virus transmission. HHV-7, like HHV-6, has been associated with a proportion of exanthem subitum cases (Tanaka *et al.*, 1994).

Kaposi's sarcoma (KS) is a neoplasm of uncertain histogenesis occurring in both HIV-1-infected and uninfected persons (Moore *et al.*, 1996). Kaposi's sarcoma-associated herpesvirus (KSHV), or HHV-8, was discovered in an AIDS-KS lesion by representational difference analysis and shown to be present in almost all AIDS-KS lesions (Chang *et al.*, 1994). These findings have been confirmed and extended to nearly all KS lesions examined from the various epidemiologic classes of KS (Boshoff *et al.*, 1995; Dupin *et al.*, 1995; Moore *et al.*, 1996; Schalling *et al.*, 1995; Chang *et al.*, 1995).

1.1.3. Life cycle

The life cycle of herpesviruses is divided between lytic and latent phases. This can best be illustrated by briefly considering the life cycle of the best-studied herpesvirus, HSV-1; its general aspects apply to the other herpesviruses. Certain properties of EBV are also considered. Specific details relating to HCMV, HHV-6 and HHV-7 are discussed later.

1.1.3.1. The lytic cycle

Initial association of HSV-1 with the host cell is mediated by viral envelope glycoproteins, which also have important roles in adsorption and penetration of the virus (Campadelli-Fiume, 1994). After the virus envelope fuses with the plasma membrane, the nucleocapsid is released into the cytoplasm and migrates to the nucleus where the DNA enters via nuclear pores. At least some of the tegument proteins also enter the nucleus, although the process by which this occurs is not clear. Transcription and replication of viral DNA and capsid assembly take place in the nucleus.

Gene expression occurs in a co-ordinated, regulated and sequentially ordered cascade with three main phases: immediate early (IE or α), early (E or β) and late (L or γ) (Honess and Roizman, 1975; Roizman and Sears, 1990). Overall, proteins encoded by 74 genes are expressed during the cycle. Some IE proteins are trans-acting regulators of virus genes, and initiate cascade expression. E genes encode several enzymes involved in DNA replication and nucleotide metabolism, as well as a subset of glycoproteins and some uncharacterised proteins. L genes encode many virion structural proteins (Honess and Roizman, 1975).

Replication starts in the nucleus, with circularisation of viral genomic DNA by direct ligation of the termini. Viral DNA synthesis is initiated from the viral origins of replication (ori_s and ori_L) to produce DNA in an endless conformation, probably as head-to-tail concatemers, by a rolling circle mechanism (Roizman, 1979; Jacob *et al.*, 1979). Replicated DNA is cleaved specifically into unit-length molecules and packaged into preformed capsids.

The processes by which the capsid acquires tegument and envelope are not fully understood. The envelope is derived from altered host membranes and contains viral glycoproteins, which

are processed into their mature forms in the Golgi apparatus. Virions are released from the cell by exocytosis (Rixon, 1993; Spear, 1985).

1.1.3.2. The latent cycle

Latent infections are produced by all of the human herpesviruses, but are established at sites that are specific to the virus. For example, HSV-1 and VZV become latent in sensory ganglia, whereas EBV latently infects circulating B lymphocytes (Kieff and Liebowitz, 1990; Bastian *et al.*, 1972).

In its latent form, HSV-1 DNA is present either as a circular molecule or as a concatemer (Rock and Fraser, 1983, 1985; Efsthathiou *et al.*, 1986) and is not thought to integrate into the host DNA (Mellerick and Fraser, 1987). EBV latent DNA is also maintained as covalently closed circular episomes (Lindhal *et al.*, 1976), and both HSV-1 and EBV latent genomes are apparently present in multiple copies in the latently infected cell. In addition, EBV infection can result in cell transformation and proliferation that may lead to carcinomas or lymphomas (Zur Hausen *et al.*, 1970).

The products of viral genes expressed during the latent state appear to function in maintenance of and reactivation from latency (Steiner *et al.*, 1989; Dambaugh *et al.*, 1986; Speck and Strominger, 1989), but differ between HSV-1 (latency-associated transcripts or LATs) (Spivack and Fraser, 1987; Deatly *et al.*, 1988) and EBV (Epstein-Barr virus nuclear antigen or EBNA proteins) (Lindahl *et al.*, 1974).

1.1.4. Herpesvirus genes

The functions of many herpesvirus genes have been assigned from experimental data and from comparisons with genes of known function from other organisms. Herpesvirus proteins may be grouped into five functional categories, as illustrated by McGeoch and Schaffer (1993).

Firstly, control proteins that influence viral transcription or that modulate the infected cell to facilitate viral replication (Everett, 1987). Secondly, essential components of the DNA replication machinery, including DNA polymerase and associated processivity factor, a protein which

recognises the origins of viral DNA replication in certain herpesviruses, a single-stranded DNA-binding protein and the three constituents of a helicase-primase complex (Challberg, 1991). Thirdly, enzymes engaged in nucleotide metabolism or DNA repair, including thymidine kinase, uracil-DNA glycosylase, dUTPase, ribonucleotide reductase (two subunits), a deoxyribonuclease and thymidylate synthase (in VZV and certain other herpesviruses) (Morrison, 1991). Fourthly, virus structural proteins, including components of the capsid, tegument and envelope (Rixon, 1993). Lastly, proteins involved in pathogenesis or latency, including those that which modulate the immune response of the host, such as G protein coupled receptors in certain herpesviruses (Chee *et al.*, 1990; Gompels *et al.*, 1995; Nicholas, 1996).

Experimental analyses of the phenotypes of HSV-1 mutants indicate that approximately half of its complement of genes is not absolutely essential for viral growth in cell culture on a gene-by-gene basis (Roizman and Sears, 1990; McGeoch and Schaffer, 1993). It is assumed that these genes confer a selective advantage *in vivo*.

1.1.5. Herpesvirus classification

1.1.5.1. Formal classification

A formal system of classification for the herpesviruses has been developed (Roizman *et al.*, 1981; Roizman *et al.*, 1992), in which the family Herpesviridae is divided between three subfamilies, the Alpha-, Beta- and Gammaherpesvirinae. Since little genetic information was available at that time, this division depended on biological criteria alone.

The Alphaherpesvirinae are classified on the basis of a moderately wide host range *in vitro*. They exhibit a relatively short reproductive cycle, efficiently destroy infected cells and spread rapidly in culture. Many members of this subfamily have been shown to establish latent infections in sensory ganglia. Members of the Alphaherpesvirinae include HSV-1, HSV-2, VZV, PRV and equine herpesvirus 1 (EHV-1).

The Betaherpesvirinae typically (though not exclusively) demonstrate a restricted host cell range *in vitro*, and infected cells often become enlarged, forming cytomegalia. The reproductive cycle is relatively long and infection progresses slowly in culture, with cell lysis occurring several days

after infection. Latency among the Betaherpesvirinae is as yet poorly understood but may occur in secretory glands, lymphoreticular cells and kidney cells. HCMV, MCMV, HHV-6 and HHV-7 are now amongst those viruses grouped in the Betaherpesvirinae.

In the Gammaherpesvirinae, host range *in vitro* is typically restricted to cells from animals to which the natural host belongs. The viruses of the Gammaherpesvirinae exhibit reproductive cycles of variable length. They are lymphotropic and infect either B- or T-lymphocytes; some also cause infections in epithelial and fibroblastoid cells. Infection of lymphocytes, even at the lytic stage, often occurs without the production of infectious progeny. Latency is frequently established in lymphoid tissue. Well-studied viruses from this subfamily include EBV, herpesvirus saimiri (HVS) and HHV-8.

Since this initial classification of the herpesviruses, significant effort has been channelled into determining the structures and DNA sequences of herpesvirus genomes, and attempts have been made to use the emerging data in classification. Genome size and nucleotide composition have proved unsuitable criteria in classification, as many members of each subfamily have genomes of similar size and G+C content may vary widely (Honest, 1984). Genome structure is a somewhat more suitable aid in herpesvirus classification. A characteristic of herpesvirus genome structure is the arrangement of reiterated sequences positioned within and at the ends of the genomes, either in direct or inverse orientation. On this basis the herpesviruses may be grouped into six categories (Fig. 1.0). Although there is no exclusive correlation between type of genome structure and the formal herpesvirus classification system, group 5 genomes are characteristic of many of the Alphaherpesvirinae and group 2 genomes of many of the Gammaherpesvirinae (Davison, 1993).

More recently, the classification system was refined (Roizman *et al.*, 1992), to take into account herpesvirus genome structures and more importantly, relationships between DNA or protein sequences and gene arrangements. The three subfamilies were each divided into genera: the Alphaherpesvirinae into the genera Simplexvirus (e.g. HSV-1 and HSV-2) and Varicellovirus (e.g. VZV); the Betaherpesvirinae into the genera Cytomegalovirus (e.g. HCMV), Roseolovirus (HHV-6) and Muromegalovirus (e.g. MCMV); and the Gammaherpesvirinae into the genera Lymphocryptovirus (e.g. EBV) and Rhadinovirus (e.g. HVS).

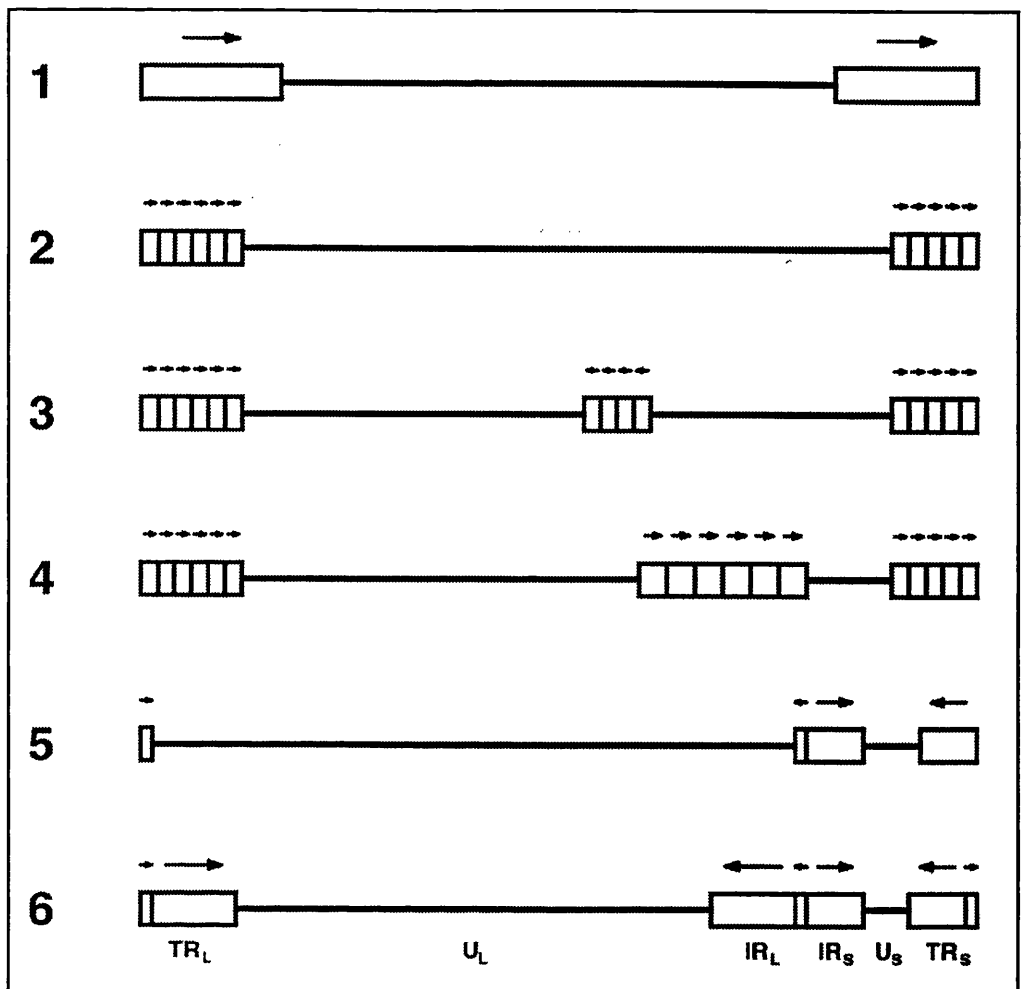


Fig. 1. Types of herpesvirus genome structure

From Davison and McGeoch (1995). Unique and repeated sequences are seen as lines and rectangles, respectively. Arrows indicate locations and orientations of repeated regions. The genomes are not to scale.

1 A long unique sequence flanked by large direct terminal repeats (CCV, EHV-2, HHV-6 and HHV-7) (Chousterman *et al.*, 1979; Davison, 1992; Browning and Studdert, 1989; Telford *et al.*, 1995; Martin *et al.*, 1991; Gompels *et al.*, 1995; Nicholas, 1996).

2 A long unique sequence flanked by multiple smaller tandem direct repeats at the genome termini (HVS and HHV-8) (Bornkamm *et al.*, 1976; Albrecht *et al.*, 1992; Russo *et al.*, 1996).

3 A long unique sequence flanked by multiple smaller tandem direct repeats at the genome termini, and in inverse orientation at an internal location (LHV-1) (Cebrian *et al.*, 1989).

4 Multiple smaller direct tandem repeats at the genome termini plus a different sequence repeated a variable number of times at an internal location (EBV) (Given and Kieff, 1979; Baer *et al.*, 1984).

5 A short unique sequence flanked by large inverted repeats, and a long unique sequence flanked by smaller inverted repeats (EHV-1 and VZV) (Whalley *et al.*, 1981; Telford *et al.*, 1991; Dumas *et al.*, 1981; Davison and Scott, 1986).

6 Short and long unique sequences each flanked by a pair of large inverted repeats; small direct repeat (the a sequence) at the genome termini, also present in inverse orientation at the IRL/IRS junction (HSV-1 and HCMV) (McGeoch *et al.*, 1988; Weststrate *et al.*, 1983; Chee *et al.*, 1990).

1.1.5.2. Genetic classification

Comparative genetic data used as the sole criteria also support a subdivision of mammalian herpesviruses into three subfamilies termed the α -, β -, γ -herpesviruses (reviewed by: Davison, 1993; Davison and McGeoch, 1995; McGeoch *et al.*, 1993, 1995). Perhaps surprisingly, this division for the most part agrees with the formal system. In the genetic scheme the genera Simplexvirus and Varicellovirus correspond to the α_1 - and α_2 -herpesviruses, the genera Lymphocryptovirus and Rhadinovirus correspond to the γ_1 - and γ_2 -herpesviruses (Honess, 1984), and the genera Cytomegalovirus/Muromegalovirus and Roseolovirus to the β_1 - and β_2 -herpesviruses.

Only a few viruses were wrongly classified using the formal system: HHV-6 is genetically a β -herpesvirus and not a member of the Gammaherpesvirinae as suggested by its lymphotropism (Lawrence *et al.*, 1990). Similarly, the lymphotropic MDV and HVT were originally classified as members of the Gammaherpesvirinae (Roizman *et al.*, 1981), their gene content most closely resembles that of the α -herpesviruses (Buckmaster *et al.*, 1988). EHV-2 was suggested as a member of the Betaherpesvirinae, on the basis of its growth properties (Plummer *et al.*, 1969; Roizman *et al.*, 1981), however its DNA sequence confirmed that it is a γ -herpesvirus (Telford *et al.*, 1995).

Genetic data, involving DNA sequences and their interpretations in terms of gene organisation and encoded protein sequences, are now the primary tool in classification. For example, HHV-8 is accepted as a γ_2 -herpesvirus solely on the strength of sequence data.

1.1.6. Genetic content

1.1.6.1. Genome sequences

Since 1984, the complete sequences of fourteen herpesvirus genomes have been published: those of EBV, VZV, HSV-1, HCMV, EHV-1, HVS, channel catfish virus (CCV), EHV-2, HHV-6, HHV-7, HHV-8, MCMV, murine herpesvirus 68 (MHV-68), bovine herpesvirus 1 (BHV-1), and alcelaphine herpesvirus (AHV-1) (Baer *et al.*, 1984; Davison and Scott, 1986; McGeoch *et al.*, 1988; Chee *et al.*, 1990; Albrecht *et al.*, 1992; Davison, 1992; Telford *et al.*, 1992; Telford *et al.*, 1995; Gompels *et al.*, 1995; Nicholas, 1996; Russo *et al.*, 1996, Rawlinson *et al.*, 1996; Virgin *et al.*, 1997; Schwyzer *et al.*, 1996; Ensser *et al.*, 1997). At least four more have been completed: those of HSV-2, equine herpesvirus 4 (EHV-4), a second strain of HHV-8, and, in this thesis, a second strain of HHV-7. Together, these sequences total well over two million base pairs.

Analysis of DNA sequences has provided comprehensive insight into genetic content. Herpesviruses contain between about 70 genes in smaller genomes (e.g. HSV-1 and VZV) to perhaps 200 genes in larger genomes (e.g. HCMV). The genes are densely packed and arranged in about equal numbers on each DNA strand. Most are expressed as single exons from their own promoters, although families of genes arranged tandemly on the same strand commonly share a single polyadenylation site (Wagner, 1985). Overlap between genes in different reading frames on the same strand or on opposing strands is rare and usually not extensive. Few genes are spliced in the α -herpesviruses, but splicing is more common in the β - and γ -herpesviruses (McGeoch and Davison, 1995; Davison and Clements, 1996).

The extensive availability of sequence information has also facilitated comparisons between herpesviruses. DNA sequence comparisons are of limited general use in the evaluation of detailed genetic relationships, because of the wide divergence of the family. Relationships are most easily detected at the level of primary amino acid sequence. Mapping and analysis of open reading frames (ORFs: DNA sequences clear of in-frame termination codons that are potentially translatable into proteins) have allowed comparative studies of individual genes and permitted extensive and detailed understanding of the relationships between the herpesviruses. In particular it was apparent at a relatively early stage that the function of a gene in a poorly

understood genome could be inferred from its similarity to a gene from a better characterised genome, such as that of HSV-1 (Davison and Wilkie, 1983; Davison, 1993).

1.1.6.2. Gene conservation

When the genetic contents of the sequenced herpesviruses were compared it became clear that members of the same subfamily share the great majority of genes in a very similar layout. For example, the rather distantly related α -herpesviruses, VZV and HSV-1, share 64 genes arranged colinearly in both genomes (McGeoch and Schaffer, 1993). This has also been demonstrated for the γ herpesviruses (HVS and EBV) and β -herpesviruses (HCMV and HHV-6; Albrecht *et al.*, 1992; Gompels *et al.*, 1995). Differences are much more marked however, when comparisons are made between members of different subfamilies (Davison, 1993), both in that divergence of individual genes is greater and in that the order of conserved genes is disrupted by large scale rearrangement of gene blocks (Davison and Taylor, 1987; Chee *et al.*, 1990; Albrecht *et al.*, 1992). When the genomes of EBV and VZV were compared, conserved genes were observed to be separated into four blocks which are arranged differently in each genome (Davison and Taylor, 1987). Similar comparisons involving HCMV (Chee *et al.*, 1990) showed conserved genes to be present in seven rearranged gene blocks.

About 40 ubiquitous (or "core") genes have been identified which have homologues in all three subfamilies (Davison and Taylor, 1987; Chee *et al.*, 1990; Albrecht *et al.*, 1992; Telford *et al.*, 1992, 1995; Gompels *et al.*, 1995; Nicholas, 1996). The estimate of core genes is approximate, as several genes exhibit lower or undetectable levels of amino acid homology and yet have apparent counterparts in each genome that are similar in size, location, orientation and (in some cases) distribution of hydrophobic residues (Davison, 1993). Relatively few genes are found in representatives of two subfamilies and not the third.

The core genes are located in the long unique region of herpesvirus genomes. They are not restricted to any of the five functional groupings mentioned above (in Section 1.1.4.), but are presumably responsible for aspects common to the lifestyle of all herpesviruses (Davison, 1992; McGeoch and Davison, 1995).

In addition to the core genes, each subfamily contains a subset of unique (or non-core) genes, which are presumably responsible for survival in particular ecological niches. Some genes are unique to genera. For example, EBV encodes latency genes that are not found in HVS (Baer *et al.*, 1984; Albrecht *et al.*, 1992), and HCMV contains several genes lacking counterparts in HHV-6 (Chee *et al.*, 1990; Gompels *et al.*, 1995). Many non-core genes have roles in latency, pathogenesis or immune evasion.

The gene complements of herpesviruses have also diverged by the acquisition of additional cellular genes and development of multigene families (McGeoch *et al.*, 1990). Core genes with cellular homologues (e.g. DNA polymerase), probably derived at very early times from the host cell, and non-core genes with cellular counterparts probably represent more recent acquisitions from the host genome which supply functions of value to a virus in a particular niche (McGeoch and Davison, 1995).

1.1.7. Genome evolution

1.1.7.1. Mechanisms

The herpesviruses are a very divergent family and appear to have used two broad types of molecular mechanisms to arrive at their present state; namely extensive nucleotide mutation and several types of recombination (Davison and McGeoch, 1995; McGeoch, 1989).

Nucleotide mutation involves changes to the base composition of herpesvirus genomes by local substitution/insertion/deletion changes, the end result being the modification of protein functions or the generation of genes *de novo*, (for example the US11 gene of HSV-1; Rixon and McGeoch, 1984). The very large variation in base composition within the Herpesviridae is striking, stretching from 32 to 75% G+C (canine herpesvirus 1 and B-virus, respectively; Honess, 1984), even between herpesviruses in the same genus. PRV and VZV, for example, have G+C compositions of 74% and 46%, respectively. Intragenomic heterogeneity in base composition is also marked, with repeat elements commonly displaying higher G+C compositions than unique sequences (McGeoch, 1989). For example, the HVS genome comprises a unique sequence of 35% G+C flanked by non-coding tandem direct repeats of 71% G+C (Borkmann *et al.*, 1976; Albrecht *et al.*, 1992). The force behind nucleotide compositional bias has not been identified,

although an error-prone DNA polymerase (in HSV-1) (Hall *et al.*, 1985; Honess, 1984) and differing sizes of nucleotide pools caused by the presence or absence of specific enzymes involved in nucleotide anabolism, such as thymidylate synthase (Honess, 1984; Honess *et al.*, 1989), have been suggested as playing a part.

Another interesting facet of nucleotide mutation is "CpG suppression" (shortage of the CG dinucleotide), which is linked to mutations caused by methylation of cytosine residues in CG doublets. CpG suppression is observed commonly throughout γ -herpesvirus genomes, only at certain locations in β -herpesviruses (notably the IE gene regions), and not at all among the α -herpesviruses (Honess *et al.*, 1989; Chee *et al.*, 1990; Gompels *et al.*, 1995; Nicholas, 1996). The site of methylation of herpesviruses is thought to be the latent genome (Honess *et al.*, 1989).

Recombination processes have played roles in genome evolution by gene duplication, gene capture and rearrangement of genes on a small or large scale (McGeoch, 1989). The presence of gene families (or sets of related genes) is ample evidence that gene duplication has occurred in the herpesviruses. Gene families grow by the process of gene duplication, divergence and eventual partitioning of function, and are most common amongst the β -herpesviruses. For example, HCMV contains nine different gene families (Chee *et al.*, 1990). Gene duplication on a smaller scale has also been reported in α -herpesvirus genomes (McGeoch, 1990).

All herpesviruses contain genes with clear cellular homologues which have presumably been obtained by capture of host genes. This has probably occurred by reverse transcription of cellular mRNAs rather than by integration of genomic DNA, since most captured genes are not spliced. Many captured genes encode enzymes involved in nucleotide anabolism and DNA repair, such as DNA polymerase, dUTPase, thymidine kinase, uracil-DNA glycosylase and thymidylate synthase (Harrison *et al.*, 1991; Mullaney *et al.*, 1989; Honess *et al.*, 1986; Thompson *et al.*, 1987). Others may function in modulation of immune or pathogenic processes: for example, the HSV-1 RL1 gene (McGeoch and Barnett, 1991) and possibly the HHV-6 adeno-associated virus type 2 rep gene (Thomson *et al.*, 1991; Gompels *et al.*, 1995). However, it is

notable that no unambiguous cellular homologue has been identified for any herpesvirus structural gene.

Large scale differences in gene layout between the herpesvirus subfamilies show that gene rearrangement occurred in ancient times (Chee *et al.*, 1990; Albrecht *et al.*, 1992; Davison and Wilkie, 1983; Davison and Taylor, 1987). Evidence of gene rearrangement during relatively recent herpesvirus evolution comes from studies of the *Us* regions of HSV-1 and VZV (Davison and McGeoch, 1986) and from EHV-1 (Telford *et al.*, 1992). Gene rearrangement appears to have depended largely on the expansion and contraction of the flanking inverted repeats.

1.1.7.2. Phylogeny

The conserved set of mammalian herpesvirus core genes has provided strong evidence that the three subfamilies evolved from a common evolutionary origin (Davison, 1992; McGeoch *et al.*, 1995). This points to a common ancestor for mammalian and (from incomplete sequence data) avian herpesviruses which would have contained the set of core genes, plus, perhaps, other genes that are absent from present-day herpesviruses (McGeoch, 1989). Fig. 2a. is an illustrative tree of the Herpesviridae, showing descent of two major groups from a putative ancestor (McGeoch *et al.*, 1995).

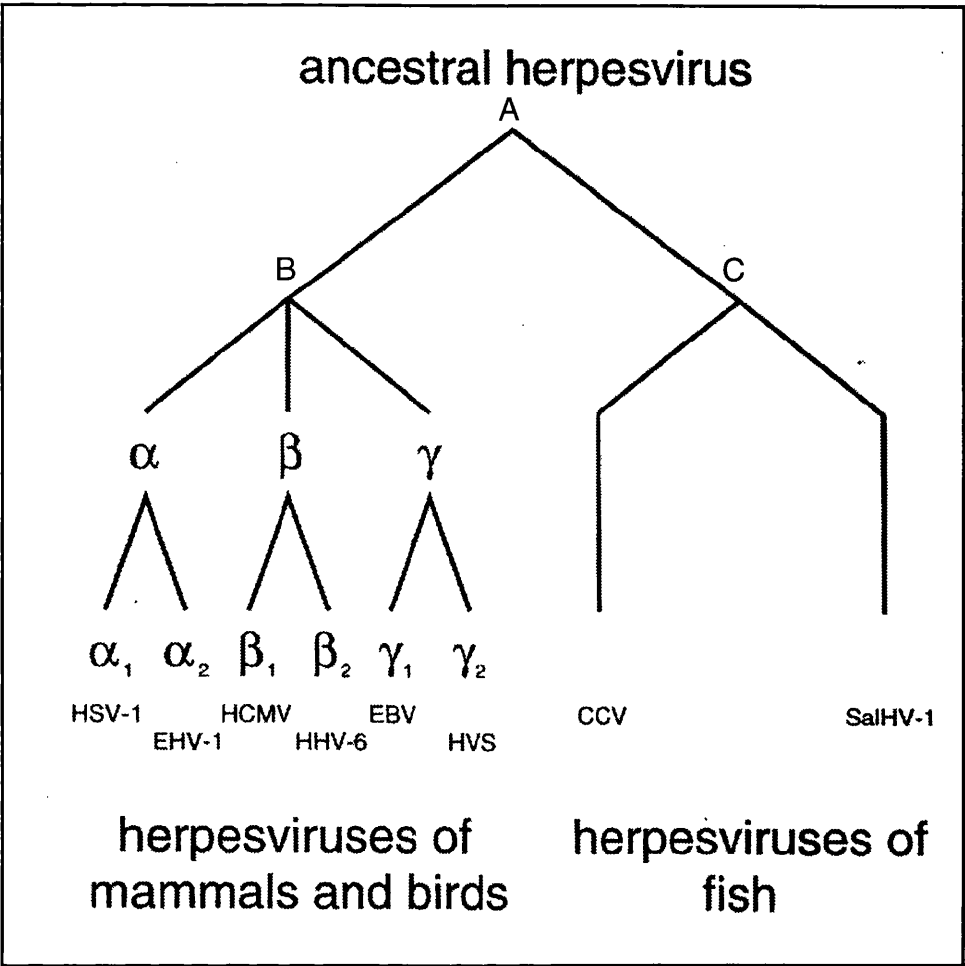
Considering the extremes of divergence displayed by the family, it seems likely that the herpesvirus constitute a very ancient lineage and that the evolutionary space they have explored is extensive (McGeoch, 1992). It is also evident that the herpesvirus evolutionary clock must run faster than that of their hosts (McGeoch, 1989). Many core genes may have been captured from host cells and subsequently adapted to the needs of the virus, as mentioned above, but no convincing examples of cellular homologues of major structural genes have yet been identified. This may mirror the disparity between cellular and viral structure, in contrast to the functions of DNA replication and nucleotide metabolism and repair which are likely to be similar for the virus and host cell. It may be that viral structural genes did evolve from cellular precursors, but that their sequences have been changed radically during evolution to fit novel roles (McGeoch, 1992).

Fig. 2. Herpesvirus evolution

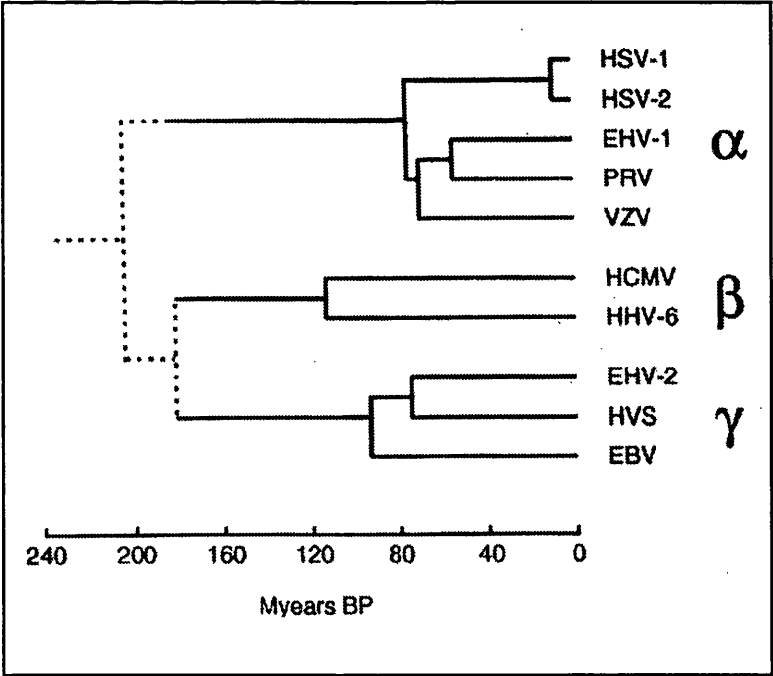
A) A scheme for the evolution of present day herpesviruses from ancestors B and C, which may in turn have originated from ancestor A. It is clear that the mammalian/avian herpesviruses are related and have descended from an ancestral herpesvirus (B) which itself was probably a recognisable herpesvirus with at least 40 genes. Fish herpesviruses have evolved from another progenitor (C) of similar complexity. Nevertheless, the mammalian/avian and fish herpesviruses share evolutionary origins, this places their ancestor (A) much farther in the past. From Davison and McGeoch (1995).

B) Phylogenetic tree distinguishing the α -, β - and γ -herpesvirus subfamilies. Horizontal portions of branches are proportional to assigned divergence values. Subfamily groupings are indicated by Greek letters. The timescale is shown at the foot. The oldest part of the tree is shown as a broken line to indicate the lower level of confidence in data for this region. From McGeoch *et al.* (1995).

A



B



The phylogeny of mammalian and avian herpesviruses has resulted in a rather self-contained view of herpesvirus evolution. Our understanding, however, has expanded recently owing to an analysis of the DNA sequence of a fish herpesvirus, CCV, (Davison, 1992). The CCV gene set, with the exception of a few captured genes, lacks any convincing genetic relationship to the mammalian and avian herpesviruses that would indicate a common origin.

Two possible conclusions may be drawn from these findings. CCV may have evolved completely separately from mammalian and avian herpesviruses. Although feasible, this interpretation seems unlikely. CCV particles have the complex virion morphology and capsid structure of herpesviruses (Davison and Davison, 1995; Booy *et al.*, 1991), a group 1 genome similar in size to that of some other herpesviruses (see Fig. 1), and certain aspects of gene arrangement like those of other herpesviruses. Alternatively, CCV and the mammalian and avian herpesviruses may share a common ancestor, but have diverged to an extent that a genetic relationship is no longer detectable. At present, this appears to be the more reasonable view.

Preliminary studies of other fish herpesviruses, salmonid herpesvirus 1 (SalHV-1) (A. J. Davison, unpublished data) and salmonid herpesvirus 2 (SalHV-2) (Bernard and Mercier, 1993) indicate a distant relationship to CCV rather than to mammalian/avian herpesviruses. Thus, it is likely that CCV is a member of a group of relatively little studied fish herpesviruses that is comparable in genetic complexity and evolutionary breadth to the mammalian/avian herpesviruses.

1.1.7.3. Evolutionary timescale

Recent reports, based on molecular sequence analysis (McGeoch and Cook, 1994; McGeoch *et al.*, 1995), have provided a detailed phylogeny and evolutionary timescale for the mammalian/avian herpesviruses.

A robust phylogenetic tree was assembled which clearly distinguished the three recognised herpesvirus subfamilies and the major sublineages (genera), this is illustrated in Fig. 2b. A root position for the tree was established and a timescale was constructed for the tree. The timescale was constructed from the mammalian fossil record, on the assumption that the herpesvirus speciation leading to contemporary herpesviruses within each of the sublineages to a large

extent represents cospeciation with hosts. It was then estimated that the three subfamilies arose approximately 180-220 million years before present, that the major sublineages diverged 80-60 million years before present (probably before the mammalian radiation) and that herpesvirus speciation within the sublineages took place in the last 80 million years.

1.2. HUMAN CYTOMEGALOVIRUS

1.2.1. Basic characteristics

HCMV strains were independently isolated by Smith (1956), Rowe *et al.* (1956) and Weller *et al.* (1957). HCMV is formally designated as human herpesvirus 5 (HHV-5) the prototypic β -herpesvirus. As a member of the Betaherpesvirinae it is most closely related to HHV-6 and HHV-7, which contain homologues to the US22 gene family, in addition to the herpesvirus core genes which are located in the HCMV genome between genes UL45 and UL114 (Lopez and Honess, 1990; Gompels *et al.*, 1995) (see Sections 1.2.6., 1.2.7. and 1.2.9.). HCMV-infected cells contain particles with characteristic herpesvirus morphology (Irmieri and Gibson, 1983 and 1985; Sarov and Abady, 1975; Smith and de Harven, 1974, 1978), in addition to "dense bodies" in almost equal numbers (Craighead *et al.*, 1972; Sarov and Abady, 1975; Irmieri and Gibson, 1983; Klages *et al.*, 1989; Landini *et al.*, 1987) and less abundant "non-infectious enveloped particles" (Sarov and Abady, 1975). HCMV replication *in vitro* is characterised by the appearance of foci containing large refractile cells (or cytomegaly) (Weller *et al.*, 1957).

1.2.2. Epidemiology

HCMV is ubiquitous in the human population, and the prevalence of antibodies in normal adults ranges from 40 to 100% (Krech, 1973). Transmission of HCMV occurs by person-to-person contact and infection can occur at any age. Congenital infection is relatively uncommon, but transmission during birth and from breast milk is very common in developing countries. Infants and young children excrete HCMV in their urine and respiratory tract and may be sources of infection for adults and other children (Stagno and Cloud, 1994). The most important mode of transmission post puberty is probably sexual (Handsfield *et al.*, 1985), especially among sexually active male homosexuals (Drew *et al.*, 1981; Collier *et al.*, 1987), and reinfection is common in sexually active populations (Drew *et al.*, 1984; Spector *et al.*, 1984). HCMV can also be transmitted via blood products and transplanted organs. (Van der Meer *et al.*, 1996)

1.2.3. Cellular tropism

HCMV exhibits tropism *in vitro* most commonly for primary human fibroblast cells. Interestingly, HCMV can be recovered from many different types of cell *in vivo*, including epithelial cells,

peripheral blood mononuclear cells, cells derived from the central nervous system and endothelial cells (Britt, 1996).

1.2.4. Growth properties

Although HCMV is a lytic virus, individuals rarely exhibit clinical evidence of infection. Several *in vitro* properties of the virus, including slow replication, restricted cell tropism, and limited cell-to-cell spread, may contribute to its limited pathogenicity in normal hosts. This important aspect of HCMV biology has been reviewed recently by Stenberg and Kerry (1995) and Mocarski (1996).

As in other herpesviruses, HCMV attachment and cell membrane fusion and penetration are mediated by viral envelope glycoproteins (Rasmussen, 1990; Keay and Baldwin, 1991). Following entry of the virion into the cell the genome is transported to the cell nucleus (Mocarski, 1996).

Expression of HCMV genes is highly regulated and has been divided into three phases: immediate early (IE), early (E) and late (L). Expression of IE genes does not require protein synthesis (DeMarchi, 1981; Stinski *et al.*, 1983, 1991), and the encoded proteins are thought to be involved in the initiation and modulation of virus replication (Stinski *et al.*, 1991). Following IE gene expression, the protein products of the E genes can be detected, many encoding replicative enzymes such as the DNA polymerase. Late gene expression then occurs with the production of virion structural proteins. The virus is notoriously slow growing *in vitro*, and older studies have documented a replicative cycle of nearly 48 hours.

Virus assembly begins with formation of the capsid (Gibson *et al.*, 1993), into which newly replicated concatameric DNA is packaged as unit-length molecules. Tegument components and the envelope are then added and the mature virion is released either by lysis of the infected cell or by a process similar to reverse endocytosis (Britt, 1996).

Like all herpesviruses, HCMV remains with its host for life after primary infection. However, a true latent infection with HCMV has not been demonstrated in the human host, and the site(s) of viral persistence or latency remain unclear, although sensitive polymerase chain reaction (PCR)

methods have identified a monocyte population in peripheral blood of healthy carriers as a site of viral DNA persistence (Taylor-Wiedeman *et al.*, 1991; Mocarski, 1996). Persistence in the presence of an ongoing host immune response remains a characteristic of HCMV, and therapeutic immunosuppression commonly leads to activation of viral replication. Whether the virus enters latency, or continues persistent low level replication, has not been resolved.

1.2.5. Disease and therapy

Primary infection with HCMV in normal adults is often asymptomatic but may be manifested by a self-limiting mononucleosis-like syndrome in less than 1:1000 cases (Horwitz *et al.*, 1986). In contrast, infections in immunocompromised hosts range from similar asymptomatic infection to fulminant life-threatening disease. HCMV is associated with different diseases depending on type and level of immunosuppression.

In AIDS patients, HCMV infection is commonly manifest as retinitis and gastrointestinal dysfunction (Jacobson and Mills, 1988; Jabs *et al.*, 1989; Dietrich and Rahmin, 1991; Gallant *et al.*, 1992; Spector *et al.*, 1993). In allograft transplantations the majority of morbidity for HCMV disease occurs when the recipient is seronegative but the donor is seropositive (Ho *et al.*, 1975; Smiley *et al.*, 1985; Meyers *et al.*, 1986; Appereley and Goldman, 1988; Winston *et al.*, 1990; Wingard *et al.*, 1988). The risk for and the manifestation of HCMV disease are associated with the organ of transplant. For example, pneumonia is a major problem in bone marrow or lung transplant recipients, whereas hepatitis is quite common after liver transplantation.

The risk of fetal infection with HCMV correlates with the lack of pre-existing seroimmunity in women infected with the virus during pregnancy. Infants with congenital infection exhibit many of the findings of both AIDS patients and allograft recipients infected with HCMV (Becroft, 1981; Boppana *et al.*, 1992). Post-natally, HCMV infections are self-limiting, but frequent central nervous system (CNS) sequelae result from damage secondary to fetal infection (Stagno *et al.*, 1983; Demmler, 1991; Boppana *et al.*, 1992; Fowler *et al.*, 1992; Williamson *et al.*, 1992).

The therapeutic agents for invasive HCMV infections include two inhibitors of the viral DNA polymerase, foscarnet and ganciclovir (Faulds and Heel, 1990; Chrisp and Clissold, 1991). However, both agents are toxic (Chrisp and Clissold, 1991) and viral resistance can develop

following treatment (Faulds and Heel, 1990). A third agent, HPMPC, or cidofovir, also exhibits potent antiviral activity against HCMV (De Clercq, 1993), but its use is limited by its toxicity (Lalezari *et al.*, 1995; Cherrington *et al.*, 1996).

1.2.6. The HCMV genome

The features of the HCMV genome discussed below have been derived largely from Weston and Barrell (1986), Chee *et al.* (1990) and Bankier *et al.* (1991). Table 1 lists the genes present in the HCMV genome, and Fig. 3 shows the genome structure and relative arrangement of the genes

1.2.6.1. Size and structure

The most widely used HCMV strain in the laboratory is a vaccine strain derived from multiple passage in cell culture, AD169. The genome of HCMV strain AD169 is 229,354 bp in length. The nucleotide composition is 57.2% G+C, but varies across the genome (Chee *et al.*, 1990). The AD169 genome structure is in group 1, similar to that of HSV-1 (Fig. 1). It comprises a long unique sequence (UL: 166,972 bp) flanked by inverted repeats (TRL: each 11,247 bp), and a short unique sequence (US: 35,418 bp) also flanked by inverted repeated sequences (IRS and TRS: both 2,514 bp). Each unique sequence bounded by repeated sequences is free to invert, and hence the genome is found in four equimolar isomers (Fig 3).

Interestingly, recent findings suggest that compared with the published DNA sequence, most isolates of HCMV strain AD169 contain an additional 929 bp after nucleotide 54,612 (Dargan *et al.*, 1997). This sequence is unrelated to the 15 kbp fragment of additional DNA present in clinical isolates and the Toledo strain of HCMV but not in AD169 (Cha *et al.*, 1996).

1.2.6.2. Origin of DNA replication

The HCMV origin of lytic DNA replication (*ori_L*) is adjacent to the gene encoding the single-stranded DNA binding protein (UL57). *Ori_L* is complex and maps to a 1.5 kbp region that is extremely rich in repeated sequences and binding sites for various transcription factors (Anders *et al.*, 1992; Anders and Punturieri, 1991; Hamzeh *et al.*, 1990; Masse *et al.*, 1992). This contrasts with the lytic or latent origins of replication in EBV or HSV-1 (Mocarski and Roizman,

TABLE 1. HCMV genes and encoded proteins

Frame	Strand	Start	K-ATG	Stop	Length	MW	Old Name	(ref)	Family	Comments
HCMVJ1L	C	3		929	309	33 176		1		Overlaps J11 & J1S
HCMVTRL1		934	970	1 902	311	34 822	HKLF1	1		= HCMVIRL1
HCMVTRL2		1 893		2 237	115	12 324				= HCMVIRL2
HCMVTRL3		3 141	3 192	3 533	114	13 252				= HCMVIRL3. Glycoprotein?
HCMVTRL4	C	3 785		4 435	217	24 929				= HCMVIRL4. ORF in major early transcript (GREENAWAY and WILKINSON 1987)
HCMVTRL5		4 185	4 266	4 607	114	12 835				= HCMVIRL5
HCMVTRL6	C	5 615	5 947	6 010	111	12 286				= HCMVIRL6
HCMVTRL7	C	6 598	6 843	6 921	82	9 718				= HCMVIRL7
HCMVTRL8		7 227	7 284	7 670	129	14 302				= HCMVIRL8
HCMVTRL9		7 501		7 929	143	15 909				= HCMVIRL9
HCMVTRL10		8 101	8 182	8 694	171	19 035				= HCMVIRL10; D at position 38 is N in IRL10. Glycoprotein
HCMVTRL11		8 648	8 726	9 427	234	26 661			RL11 family	= HCMVIRL11. Glycoprotein
HCMVTRL12		9 431	9 434	10 681	416	47 417			RL11 family	= HCMVIRL12. Glycoprotein
HCMVTRL13		10 778	10 796	11 236	147	15 888				= HCMVIRL13. Glycoprotein exon?
HCMVTRL14		11 140	11 143	11 700	186	21 827			RL11 family	First 35 amino acids identical in IRL14. Glycoprotein exon?
HCMVUL1		11 771	11 810	12 481	224	25 578			RL11 family	Glycoprotein
HCMVUL2	C	12 868	13 047	13 131	60	6 763				Glycoprotein exon?
HCMVUL3	C	13 010	13 324	13 330	105	12 307				
HCMVUL4		13 434	13 464	13 919	152	17 751			RL11 family	Glycoprotein exon?
HCMVUL5		13 986	14 013	14 510	166	18 861			RL11 family	Glycoprotein exon?
HCMVUL6		14 522	14 612	15 463	284	31 447			RL11 family	Glycoprotein exon?
HCMVUL7		15 523	15 526	16 191	222	24 354			RL11 family	Glycoprotein exon?
HCMVUL8		16 198	16 234	16 599	122	13 787			RL11 family	Glycoprotein exon?
HCMVUL9		16 606	16 612	17 295	228	26 889			RL11 family	Glycoprotein
HCMVUL10		17 222		18 199	326	37 366			RL11 family	Glycoprotein exon?
HCMVUL11		18 268	18 295	19 119	275	31 382			RL11 family	Glycoprotein
HCMVUL12	C	19 103	19 321	19 351	73	8 250				Glycoprotein exon?
HCMVUL13		19 143	19 320	20 738	473	54 614				Glycoprotein exon?
HCMVUL14		20 798	20 843	21 871	343	38 567				Glycoprotein
HCMVUL15	C	21 639		22 604	322	35 338				
HCMVUL16		22 342	22 414	23 103	230	26 148				Glycoprotein
HCMVUL17		23 151	23 214	23 525	104	12 672				
HCMVUL18		23 631	23 637	24 740	368	41 736	H3O1	2		Glycoprotein homologous to class 1 HLA (BECK and BARRELL 1988)
HCMVUL19		24 701	24 740	25 033	98	11 281				
HCMVUL20		25 233	25 299	26 318	340	38 703				Glycoprotein. Homologous to TCR-γ?
HCMVUL21	C	26 500	27 024	27 039	175	19 940				
HCMVUL22	C	27 263		27 646	128	14 132				Hydrophobic
HCMVUL23	C	27 866		28 891	342	39 341				
HCMVUL24	C	28 936	30 009	30 171	358	40 187			US22 family	
HCMVUL25		30 030	30 057	32 024	656	73 541			US22 family	
HCMVUL26	C	32 212	32 775	32 994	188	21 156			UL25 family	
HCMVUL27	C	32 834	34 657	34 723	608	69 222				
HCMVUL28	C	34 757		35 893	379	42 739			US22 family	
HCMVUL29	C	35 926	37 005	37 092	360	40 779			US22 family	
HCMVUL30	C	37 138	37 500	37 533	121	14 047				
HCMVUL31		37 682		39 763	694	76 061				
HCMVUL32	C	39 850	42 993	43 050	1048	112 689				Large structural phosphoprotein (pp150) (JAHN et al. 1987)
HCMVUL33		43 128	43 251	44 420	390	43 806			GCR family	Multiply hydrophobic. Homology to G-protein-coupled receptors
HCMVUL34		44 500		46 011	504	56 185				
HCMVUL35		46 042	46 093	48 012	640	72 531			UL25 family	
HCMVUL36EX2	C	48 246		49 751	408.7	47 518	HJLF4	3		
HCMVUL36EX1	C	49 354	49 776	49 863	67.3	7 483	HJLF3	3		US22 family
HCMVUL37EX3	C	49 913		50 842	310	35 476	HJLF2	3		IE glycoprotein exon 3
HCMVUL37EX2	C	50 893		51 015	14.3	1 561	HJLF1	3		IE glycoprotein exon 2
HCMVUL38	C	51 131	52 123	52 138	331	36 738	HZLF3	3		
HCMVUL37EX1	C	52 218	52 706	52 763	162.7	19 116	HZLF2	3		IE glycoprotein exon 1
HCMVUL39		53 024		53 395	124	13 533				
HCMVUL40	C	53 216	53 878	53 893	221	24 368				Glycoprotein
HCMVUL41	C	53 936		54 358	141	16 767				
HCMVUL42	C	54 384		54 854	157	17 066				Glycoprotein exon?
HCMVUL43	C	54 604	55 164	55 245	187	20 993			US22 family	
HCMVUL44	C	55 214	56 512	56 668	433	46 234				Encodes ICP36 protein family (LEACH and MOCARSKI 1989)
HCMVUL45	C	56 656		59 400	915	101 670				Homology to large subunit of ribonucleotide reductase (NIKAS et al. 1986)*

Frame	Strand	Start	K-ATG	Stop	Length	MW	Old Name	(ref)	Family	Comments
HCMVUL46	C	59 519	60 388	60 562	290	33 028				Capsid assembly? PERTUISET et al. (1989)*
HCMVUL47		60 282	60 390	63 335	982	109 962				
HCMVUL48		62 921	63 335	70 057	2241	253 227	HFRF0	4		Virion protein? (BATTERSON et al. 1983*; MCGEOCH et al. 1988a)*
HCMVUL49	C	70 403	72 112	72 334	570	63 852	HFLF5	4		
HCMVUL50	C	72 072	73 262	73 283	397	42 902	HFLF4	4		Glycoprotein?
HCMVUL51	C	73 287	73 757	73 910	157	16 968	HFLF3	4		
HCMVUL52		73 748	73 796	75 799	668	74 122	HFRF1	4		
HCMVUL53		75 789	75 795	76 922	376	42 314	HFRF2	4		
HCMVUL54	C	76 906	80 631	80 655	1242	137 104	HFLF2	4		DNA Polymerase (KOUZARIDES et al. 1987a)
HCMVUL55	C	80 775	83 492	83 654	906	102 005	HFLF1	4		gB (CRANAGE et al. 1986)
HCMVUL56	C	83 458	86 007	86 019	850	95 870	HFLF0	4		
HCMVUL57	C	86 577	90 281	90 326	1235	133 880				Major DNA-binding protein (ANDERS and GIBSON 1988)
HCMVUL58		90 864		91 235	124	14 418				
HCMVUL59	C	91 205	91 573	91 597	123	13 945				
HCMVUL60	C	92 336		92 815	160	18 241				
HCMVUL61	C	92 847		94 139	431	44 310				
HCMVUL62	C	94 114		94 764	217	23 686				
HCMVUL63		95 331		95 717	129	14 792				
HCMVUL64	C	95 904		96 203	100	11 245				
HCMVUL65		96 315		96 620	102	11 525				Segments in frame with 67-kDa phosphoprotein sequence of DAVIS and HUANG (1985)
HCMVUL66	C	96 475		96 816	114	13 921				
HCMVUL67	C	97 098	97 436	97 451	113	13 218				Glycoprotein exon?
HCMVUL68	C	97 750	98 079	98 100	110	12 728				
HCMVUL69	C	98 202	100 433	100 532	744	82 679				Transactivator? (MCGEOCH et al. 1988a)*
HCMVUL70	C	100 536		103 721	1062	120 928				DNA replication? (MCGEOCH et al. 1988b)*
HCMVUL71		103 239		104 471	411	45 728				
HCMVUL72	C	104 558	105 721	105 751	388	43 576				dUTPase? (PRESTON and FISHER 1984)*
HCMVUL73		105 629	105 737	106 150	138	14 868				Glycoprotein
HCMVUL74	C	106 128	107 525	107 585	466	54 236				Glycoprotein exon?
HCMVUL75	C	107 904	110 132	110 153	743	84 453				gH (CRANAGE et al. 1988)
HCMVUL76		110 324	110 327	111 301	325	36 070				
HCMVUL77		110 787	110 907	112 832	642	71 188				Virion protein? (ADDISON et al. 1984*; MCGEOCH et al. 1988a)*
HCMVUL78		112 864	112 924	114 216	431	47 358				
HCMVUL79	C	114 277	115 161	115 779	295	33 846				
HCMVUL80		115 084	115 198	117 321	708	73 853				Assembly protein read from internal start (ROBSON and GIBSON 1989)
HCMVUL81	C	117 311		117 658	116	12 796				
HCMVUL82	C	117 489	119 165	119 189	559	61 950			UL82 family	pp71 (RUGER et al. 1987)
HCMVUL83	C	119 355	121 037	121 094	561	62 900			UL82 family	pp65 (RUGER et al. 1987)
HCMVUL84	C	121 312	123 069	123 306	586	65 430				
HCMVUL85	C	123 104	124 021	124 090	306	34 596				
HCMVUL86	C	124 186	128 295	128 415	1370	153 875	HaLF1	5		Major capsid protein (CHEE et al. 1989b)
HCMVUL87		128 265	128 355	131 177	941	104 805				
HCMVUL88		131 144	131 177	132 463	429	47 691				
HCMVUL89EX2	C	132 466		133 629	378	42 776				Conserved herpesvirus spliced gene (COSTA et al. 1985)*
HCMVUL90	C	133 639	133 836	133 920	66	7 445				
HCMVUL91		133 784	133 835	134 167	111	12 028				
HCMVUL92		134 020	134 140	134 742	201	22 512				
HCMVUL93		134 693	134 711	136 492	594	68 464				
HCMVUL94		136 008	136 353	137 387	345	38 382				
HCMVUL89EX1	C	137 382	138 389	138 803	296	34 323				Conserved herpesvirus spliced gene (COSTA et al. 1985)*
HCMVUL95		138 352	138 388	139 980	531	57 214				
HCMVUL96		139 821	140 016	140 360	115	13 108				
HCMVUL97		140 373	140 484	142 604	707	78 234	HSRF3	6		Phosphotransferase? (CHEE et al. 1989a)
HCMVUL98		142 626	142 701	144 452	584	65 273				DNase (MCGEOCH et al. 1986)*
HCMVUL99		144 311	144 392	144 961	190	20 924				Phosphoprotein pp28 (MEYER et al. 1988)
HCMVUL100	C	145 229	146 344	146 413	372	42 862				Multiply hydrophobic
HCMVUL101		146 353		146 697	115	12 184				DNA replication? Position only (MCGEOCH et al. 1988b)*
HCMVUL102		146 747		149 140	798	85 615				DNA replication? Position only (MCGEOCH et al. 1988b)*
HCMVUL103	C	149 311	150 057	150 108	249	28 637				
HCMVUL104	C	150 008	152 098	152 167	697	78 508				Virion protein? (WELLER et al. 1983*; MCGEOCH et al. 1988a)*

Frame	Strand	Start	K-ATG	Stop	Length	MW	Old Name (ref)	Family	Comments
HCMVUL105		151 806	151 926	154 793	956	106 501			Helicase (MARTIGNETTI 1987; CRUTE et al. 1989)*
HCMVUL106	C	154 950	155 324	155 330	125	14 500			
HCMVUL107	C	155 420		155 869	150	17 374			
HCMVUL108		156 016		156 384	123	14 501			
HCMVUL109	C	157 517	157 810	157 816	98	11 709			
HCMVUL110	C	157 896		158 276	127	14 224			
HCMVUL111	C	159 479		159 799	107	11 565			
HCMVUL111A		159 615	159 678	159 911	78	8 582			ORF in transforming region (RAZZAQUE et al. 1988)
HCMVUL112		160 484	160 589	161 392	252.3	26 415			Common N-terminus of four phosphoproteins (WRIGHT et al. 1988)
HCMVUL113		161 301		162 797	499	51 105			Probably spliced to UL112; internal splicing? (WRIGHT et al. 1988)
HCMVUL114	C	162 973	163 722	163 758	250	28 354			Uracil-DNA glycosylase (WORRAD and CARADONNA 1988)*
HCMVUL115	C	163 697		164 614	306	34 110			
HCMVUL116	C	164 533		165 564	344	37 519			
HCMVUL117	C	165 474	166 745	166 757	424	45 464			Glycoprotein exon?
HCMVUL118	C	166 861		167 487	209	24 599			
HCMVUL119	C	167 558	167 983	168 037	142	14 729			Glycoprotein exon?
HCMVUL120	C	168 041	168 643	168 700	201	22 768			Glycoprotein exon?
HCMVUL121	C	168 697	169 236	169 269	180	20 138			Glycoprotein
HCMVUL122	C	169 367		170 878	494.7	51 084			Glycoprotein
HCMVUL123EX4	C	171 009		172 274	405.7	45 622			IE2A. Spliced to IE1 EX4. Also KATG at 170599 (STENBERG et al. 1985)
HCMVUL123EX3	C	172 301		172 654	61.7	6 865			IE1 gene exon 4 (STENBERG et al. 1984; AKRIGG et al. 1985)
HCMVUL123EX2		172 659	172 765	172 873	23.7	2 658			IE1 gene exon 3 (STENBERG et al. 1984; AKRIGG et al. 1985)
HCMVUL124		172 783	172 798	173 253	152	15 887			IE1 gene exon 2 (first coding exon) (STENBERG et al. 1984; AKRIGG et al. 1985)
HCMVUL125	C	173 114		173 419	102	11 000			Glycoprotein
HCMVUL126	C	173 508		173 909	134	15 910			
HCMVUL127		174 453	174 495	174 887	131	15 248			
HCMVUL128	C	174 868		175 284	139	16 036			
HCMVUL129	C	175 357		175 704	116	13 288			Glycoprotein exon?
HCMVUL130	C	175 665	176 306	176 438	214	24 653			Glycoprotein exon?
HCMVUL131	C	176 644	176 871	177 042	76	8 243			
HCMVUL132	C	176 934	177 743	177 845	270	29 973			
HCMVIRL14	C	177 776	178 324	178 327	183	20 750			Glycoprotein
HCMVIRL13	C	178 231	178 671	178 689	147	15 888			First 35 amino acids identical in TRL14
HCMVIRL12	C	178 786	180 033	180 036	416	47 417			= HCMVTRL13. Glycoprotein exon?
HCMVIRL11	C	180 040	180 741	180 819	234	26 661		RL11 family	= HCMVTRL12. Glycoprotein
HCMVIRL10	C	180 773	181 285	181 366	171	19 034		RL11 family	= HCMVTRL11. Glycoprotein
HCMVIRL9	C	181 538		181 966	143	15 909			= HCMVTRL10; N at position 38 is D in TRL10. Glycoprotein
HCMVIRL8	C	181 797	182 183	182 240	129	14 302			= HCMVTRL9
HCMVIRL7		182 546	182 624	182 869	82	9 718			= HCMVTRL8
HCMVIRL6		183 457	183 520	183 852	111	12 286			= HCMVTRL7
HCMVIRL5	C	184 860	185 201	185 282	114	12 835			= HCMVTRL6. Glycoprotein exon?
HCMVIRL4		185 032		185 682	217	24 929			= HCMVTRL5
HCMVIRL3	C	185 934	186 275	186 326	114	13 252			= HCMVTRL4. ORF in major early transcript (GREENAWAY and WILKINSON 1987)
HCMVIRL2	C	187 230		187 574	115	12 324			= HCMVTRL3. Glycoprotein?
HCMVIRL1	C	187 565	188 497	188 533	311	34 822	HKLF1	1	= HCMVTRL2
HCMVJ11		188 538		189 560	341	36 544			= HCMVTRL1
HCMVIRS1		189 702	189 765	192 302	846	91 050	HQRF1	1	Positions 1 to 309 overlap J1L; 118 to 341 overlap J1S V at position 190 is L in TRS1. Sequences diverge after position 549
HCMVUS1	C	192 332		192 967	212	23 481	HQLF3	1	US1 family
HCMVUS2	C	193 119	193 715	193 850	199	23 112	HQLF2	1	US2 family
HCMVUS3		194 133	194 690	194 924	186	21 575	HQLF1	1	US2 family
HCMVUS4		194 832		195 188	119	13 089			Glycoprotein
HCMVUS5		195 203	195 230	195 607	126	14 451			Spliced IE glycoprotein (WESTON 1988)
HCMVUS6	C	195 403	195 951	195 975	183	20 640	HXLF6	1	US6 family
HCMVUS7	C	196 377	197 051	197 069	225	26 271	HXLF5	1	US6 family

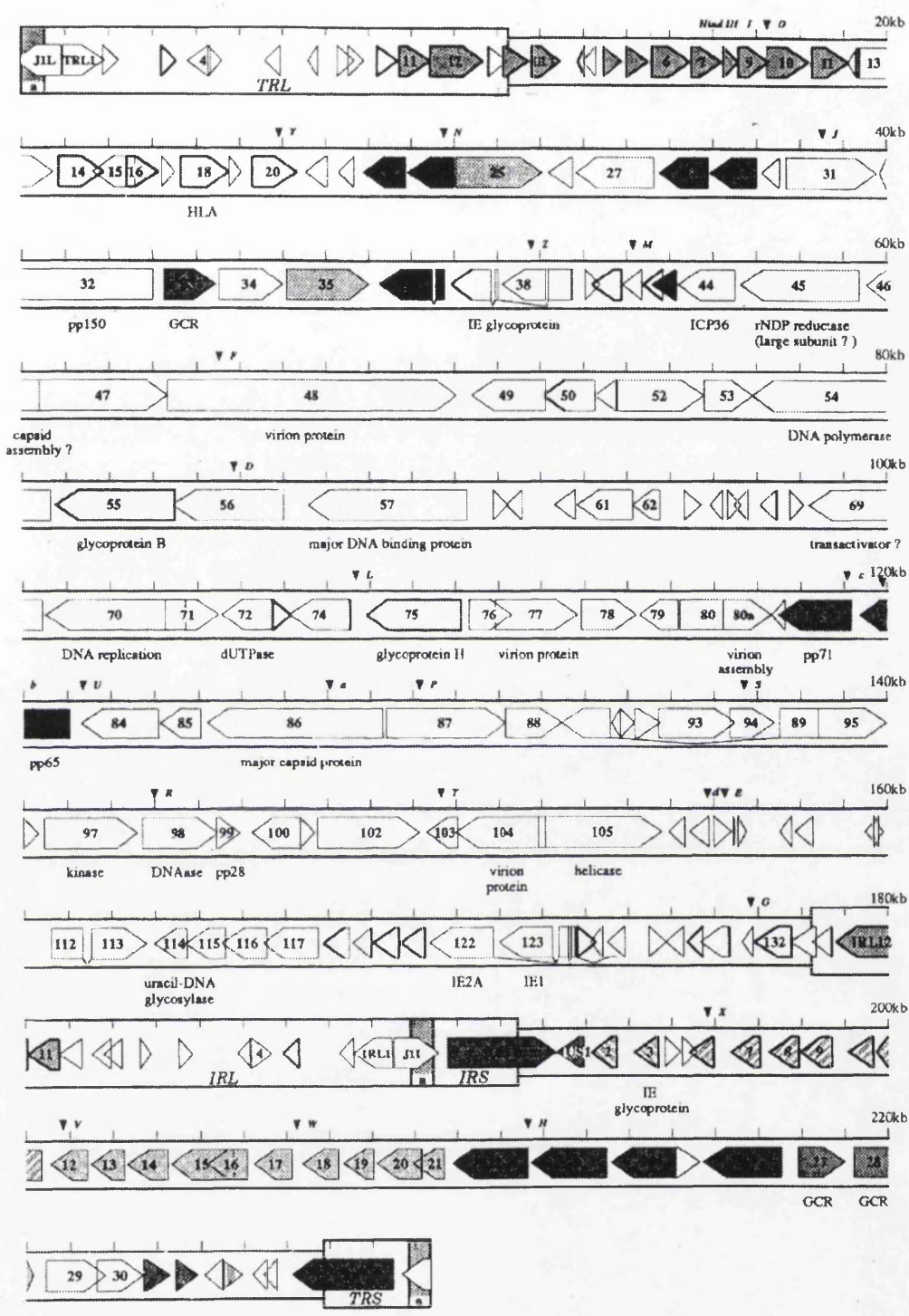
Frame	Strand	Start	K-ATG	Stop	Length	MW	Old Name	(ref)	Family	Comments
HCMVUS8	C	197 256	197 936	197 960	227	26 634	HXL F4	1	US6 family	Glycoprotein
HCMVUS9	C	197 954	198 694	198 772	247	28 054	HXL F3	1	US6 family	Glycoprotein
HCMVUS10	C	199 083	199 637	199 646	185	20 772	HXL F2	1	US6 family	Glycoprotein
HCMVUS11	C	199 716	200 360	200 366	215	25 265	HXL F1	1	US6 family	Glycoprotein
HCMVUS12	C	200 549	201 391	201 562	281	32 470	HVL F6	1	US12 family	Multiply hydrophobic
HCMVUS13	C	201 474	202 256	202 307	261	29 461	HVL F5	1	US12 family	Multiply hydrophobic
HCMVUS14	C	202 328	203 257	203 311	310	34 198	HVL F4	1	US12 family	Multiply hydrophobic
HCMVUS15	C	203 305		204 756	484	53 049	HVL F3	1	US12 family	Multiply hydrophobic
HCMVUS16	C	204 153	205 079	205 091	309	34 718	HVL F2	1	US12 family	Multiply hydrophobic
HCMVUS17	C	205 227	206 105	206 144	293	31 910	HVL F1	1	US12 family	Multiply hydrophobic
HCMVUS18	C	206 376	207 197	207 266	274	30 195	HWL F5	1	US12 family	Multiply hydrophobic
HCMVUS19	C	207 338	208 057	208 132	240	26 424	HWL F4	1	US12 family	Multiply hydrophobic
HCMVUS20	C	208 107		209 177	357	39 890	HWL F3	1	US12 family	Multiply hydrophobic
HCMVUS21	C	208 978	209 694	209 793	239	26 586	HWL F2	1	US12 family	Multiply hydrophobic
HCMVUS22	C	209 874		211 652	593	66 971	HWL F1	1	US22 family	Early nuclear protein (MOCARSKI et al. 1988)
HCMVUS23	C	211 717	213 492	213 510	592	68 886	HHL F7	1	US22 family	
HCMVUS24	C	213 591	215 090	215 105	500	57 928	HHL F6	1	US22 family	
HCMVUS25		215 097		215 633	179	19 655				
HCMVUS26	C	215 730	217 538	217 574	603	70 022	HHL F5	1	US22 family	
HCMVUS27		217 859	217 904	218 989	362	41 996	HHR F2	1	GCR family	Multiply hydrophobic. Homology to G-protein-coupled receptors
HCMVUS28		219 083	219 200	220 168	323	37 189	HHR F3	1	GCR family	Multiply hydrophobic. Homology to G-protein-coupled receptors
HCMVUS29		220 420	220 426	221 811	462	51 068	HHR F4	1		
HCMVUS30		221 537	221 618	222 664	349	39 115	HHR F5	1		
HCMVUS31		222 674		223 264	197	22 936	HHR F6	1	US1 family	
HCMVUS32		223 325	223 385	223 933	183	22 058	HHR F7	1	US1 family	
HCMVUS33	C	224 075		224 485	137	15 775	HHL F3	1		
HCMVUS34		224 408	224 480	224 968	163	17 767	HHR F8	1		Glycoprotein exon?
HCMVUS35	C	225 212		225 538	109	12 966	HHL F2	1		
HCMVUS36	C	225 429		225 758	110	12 352				
HCMVTR S1	C	226 115	228 478	228 541	788	83 983	HHL F1	1	US22 family	L at position 190 is V in IRS1. Sequences diverge after position 549. Overlaps J1L & J1I
HCMVJ1S	C	228 683		229 354	224	23 797				

A compilation of reading frames of HCMV strain AD169, from Chee *et al.* (1990).

The orientations, coordinates, and theoretical sizes are tabulated, together with the locations of predicted Kozak consensus ATG codons. For spliced genes exon coordinates represent open reading frame coordinates: donor and acceptor positions are not shown. Lengths are shown in amino acids. References given in the comments section are not referred to in this thesis.

Fig. 3. Genetic layout of the HCMV genome

The genome scale is in kbp, and the thinner and thicker portions of the genome denote the unique regions and repeats, respectively. Abbreviations: TRL/S, long/short terminal repeat; IRL/S, long/short internal repeat; J1, junction frame 1. Protein-coding regions are shown as arrowed boxes pointing in the direction translation, and contain the gene nomenclature. ORFs predicted to be expressed as spliced mRNAs are indicated on the diagram. Abbreviations: HLA, human leukocyte antigen homologue; pp, phosphoprotein; GCR, G-protein-coupled receptor homologue; IE, immediate early; ICP, infected cell protein. From Bankier *et al.* (1991).



1982; Spaete and Frenkel, 1985). An origin of DNA replication operating in the latent phase of HCMV infection has not been identified.

1.2.6.3. Genetic organisation

The HCMV genome contains approximately 200 densely packed genes (J1L, TRL1,-TRL14, UL1-UL132, IRL14-IRL1, J1I, US1-US36, TRS1, J1S) which are arranged about equally on both strands of the genome with little overlapping (Fig. 3). Transcription signals are commonly present within the preceding gene, and some genes share common polyadenylation sites. Splicing appears to be limited to four groups of exons: the IE genes (UL36/UL37 and UL122/UL123), which are spliced in a complex manner (Kouzarides *et al.*, 1988; Weston, 1988; Stenberg *et al.*, 1989), a highly conserved late core gene (UL89) of unknown function (Costa *et al.*, 1985) and UL112 which encodes four phosphoproteins by alternative splicing and may also be spliced to UL113.

1.2.7. Gene complement

A comprehensive list of genes and their functions is given in Table 1, and their positions are shown in Fig. 3. The HCMV IE genes map in two major loci, termed IE (UL36-38) and major IE (or MIE) (UL122-UL123), although four more IE genes (TRL4, TRS1-IRS1, US3 and possibly U69) are located elsewhere (Stasiak and Mocarski, 1992; Stenberg *et al.*, 1984, 1985, 1989). The most abundantly expressed transcripts are IE1 and IE2A (UL122 and UL123, respectively), which are expressed through splicing from a single transcription start site. In contrast to the bulk of the HCMV genome, the MIE region is CpG suppressed (Honess *et al.*, 1989).

HCMV DNA replication uses the set of six herpesvirus-common replication functions that have been best studied in HSV-1: DNA polymerase (UL54) (Hirai *et al.*, 1976; Hirai and Watanabe, 1976; Huang, 1975), single-stranded DNA-binding protein (UL57) (Anders and Gibson, 1988; Kemble *et al.*, 1987), a processivity factor (UL44) which associates with DNA polymerase and prevents its dislocation from the DNA template (Ertl and Powell, 1992), and the predicted three-component helicase-primase complex (UL70, UL101/102 and UL105). However, in addition, several other genes may play a role, including the regulatory genes (mentioned above) required to activate gene expression, as well as two genes that have uncertain roles in viral replication,

UL112/113 which encodes four phosphoproteins by alternative splicing (Wright *et al.*, 1988) and UL84 (He *et al.*, 1992).

HCMV proteins involved in nucleotide metabolism and DNA repair include, uracil-DNA glycosylase (UL114), a putative dUTPase (UL72), deoxyribonuclease and the large, but not the small, subunit of ribonucleotide reductase (UL45). HCMV does not encode a thymidine kinase but does encode another kinase which can modify nucleosides, UL97 (Littler *et al.*, 1992; Sullivan *et al.*, 1992, 1993).

The capsid proteins comprise the major capsid protein (UL86), the two components of the intercapsomeric triplex UL46 and UL85, a small protein associated with the exterior surface of the capsid (UL49) and the protease and the major and minor scaffolding proteins encoded by UL80 and UL80a. The tegument is made up of as many as 20 proteins, many of which are phosphorylated (Gibson, 1981, 1983), with the basic phosphoprotein (UL32) and the lower matrix protein (UL83) being most abundant (Gibson, 1983). Minor tegument proteins include the upper matrix protein (UL82), which functions as a transactivator of gene expression (Liu and Stinski, 1992), the product of UL99 which is highly immunogenic (Irmiere and Gibson, 1985; Martinez *et al.*, 1989; Meyer *et al.*, 1988; Pereira *et al.*, 1984) and UL56 which is likely to be involved in virion maturation (Bogner *et al.*, 1993). However, a full understanding of the functions of many tegument proteins has not yet emerged. At least 17 other genes potentially encode additional tegument proteins (Mocarski, 1996). At least 54 genes have characteristics of glycoproteins, as listed in Table 1. Three envelope glycoproteins are encoded by the core genes: gB (UL55), which is likely to have roles in virion penetration into cells, transmission from cell to cell and fusion of infected cells (Navarro *et al.*, 1993), and gH (UL75) which is thought to be involved in membrane fusion and complexes with the product of UL115 (gL) during transport to the cell surface (Kaye *et al.*, 1992; Spaete *et al.*, 1993).

US27, US28 and UL33 make up the G-coupled receptor (GCR) gene family. Each gene has seven potential hydrophobic domains and contains motifs which show homology to the opsin family of cell surface receptors. This diverse family of receptors mediate their responses via G-proteins and transduce different signals in a variety of systems, including vision, olfaction,

memory and learning, and regulation of the circulatory system, among others (Chee *et al.*, 1990). In addition, UL100 and the 10 genes that go to make up the US12 gene family also contain multiple potential hydrophobic domains, and may act in similar ways to the G-coupled protein receptors.

1.2.8. Captured genes

In addition to genes directly involved in replication, several genes have clear counterparts in the cellular genome and may play roles in the virus-host interaction. HCMV gene UL18 encodes a glycoprotein which has homology to cellular HLA class I proteins (Beck and Barrell, 1988; Chee *et al.*, 1990). The MCMV genome also has a MHC class I homologue (Rawlinson *et al.*, 1996), which is thought to contribute to immune evasion through interference with natural killer cell-mediated clearance. UL20, which is in close proximity to UL18, has low level similarity to regions of the human T-cell receptor γ chain (Beck and Barrell, 1991). The function of UL20 is unknown, but if it is a T-cell receptor homologue, the virus may be able to use the protein to interact with CD3 and infect T-cells (Borst *et al.*, 1987; Brenner *et al.*, 1987).

1.2.9. Gene families

HCMV is strikingly different from other herpesviruses in the evident expansion of the genome by gene duplication and divergence (Weston and Barrell, 1986; Chee *et al.*, 1990; Mocarski, 1993). Fifty-two of the predicted open reading frames listed in Table 1 can be grouped into nine families of related genes: three pairs (UL25 and UL35; UL82 and UL83; and US2 and US3) and six larger groups: US1 gene family, US6 gene family, RL11 gene family, US12 gene family, US22 gene family and GCR gene family. Unfortunately, little is known about the function of many members of these families, although three families (R11, US2 and US6) are predicted to encode glycoproteins, and possibly compose a gene superfamily. Some US22 genes are spliced and expressed as IE proteins in HCMV or MCMV, but it is not known whether this extends to all of the family (Kouzarides *et al.*, 1988; Messerle *et al.*, 1991). There is evidence for a role in transcriptional activation for UL36 (Colberg-Poley *et al.*, 1992) and IRS1/TRS1 (Stasiak and Mocarski, 1992) but similarly it is not known if all US22 gene products are involved in transactivation. The gene families are clustered in U_S and at one end of U_L , parts of the genome

that appear to be unique to the β -herpesviruses. Most are conserved in MCMV (Rawlinson *et al.*, 1996), and some in HHV-6 and HHV-7 (Gompels *et al.*, 1995; Nicholas, 1996).

1.3. HUMAN HERPESVIRUS 6

1.3.1. Basic characteristics

HHV-6 was first isolated in 1986 from the peripheral blood lymphocytes of patients with lymphoproliferative disorders, some of whom were also infected with HIV-1 (Salahuddin *et al.*, 1986). The virus was subsequently isolated from AIDS patients (Becker *et al.*, 1988; Downing *et al.*, 1987; Lopez *et al.*, 1988; Tedder *et al.*, 1987), children with exanthem subitum (ES), patients with a variety of other disorders (Agut *et al.*, 1988; Becker *et al.*, 1988) and healthy adults (Lopez *et al.*, 1988). HHV-6 has a typical herpesvirus morphology (Biberfeld *et al.*, 1987; Yoshida *et al.*, 1989; Kramarsky and Sander, 1992), with a very distinct tegument layer (Roffman *et al.*, 1990). Like HCMV, the most noticeable effect of HHV-6 infection *in vitro* is the enlargement (cytomegaly) of host cells and the occurrence of multinucleated cells (syncytia) 3 to 5 days after infection (Pellett and Black, 1996).

Two major subgroups or variants (A and B) of HHV-6 have been identified by restriction endonuclease analysis, sequencing, monoclonal antibody reactivity and cell culture properties (Ablashi *et al.*, 1993; Schrimmer *et al.*, 1991; Aubin *et al.*, 1991). The A strains, including GS and U1102, are less frequently observed and have no definite association with human disease, but are often isolated from immunocompromised patients, suggesting a possible link with AIDS. The prototype of B strains is Z29, which is the etiologic agent of ES (Yamanishi *et al.*, 1988).

1.3.2. Epidemiology

Serological surveys indicate that maternal antibodies to HHV-6 can be detected in more than 90% of infants' serum at birth, but that these decrease during the first six months to as low as 5%. Antibody levels to HHV-6 then increase between six months and five years, with 80% of children developing an antibody response by 13 months (Balachandra *et al.*, 1989; Briggs *et al.*, 1988; Brown *et al.*, 1988; Huang *et al.*, 1992; Yoshikawa *et al.*, 1989; Okuno *et al.*, 1989). In most geographical areas, about 90% of people over the age of two years are HHV-6 seropositive (Linde *et al.*, 1988; Linde *et al.*, 1990; Parker and Weber, 1993; Saxinger *et al.*, 1988; Yoshikawa *et al.*, 1989; Okuno *et al.*, 1989; Levy *et al.*, 1990).

Evidence of nearly identical restriction endonuclease profiles from cases during an ES outbreak in an orphanage nursery (Okuno *et al.*, 1991), and from siblings and mothers of children with ES (Mukai *et al.*, 1994), suggests that HHV-6 is transmitted horizontally to infants, although the mode of transmission remains uncertain. It has been widely reported that HHV-6 is present in the saliva and throat swabs of nearly all adults (Levy *et al.*, 1990; Pietroboni *et al.*, 1989; Pietroboni *et al.*, 1988; Brown *et al.*, 1988; Asano *et al.*, 1992), that HHV-6 antigens can be detected in saliva and bronchial gland epithelium (Fox *et al.*, 1990; Krueger *et al.*, 1990), and that DNA has been detected in saliva by polymerase chain reaction (PCR) (Cone *et al.*, 1993; Jarrett *et al.*, 1990; Kido *et al.*, 1990). Questions have been raised over the specificity of some of the analytical reagents used to detect HHV-6 in these tests, with respect to HHV-7 (Pellett and Black, 1996), but it seems reasonable to suggest that HHV-6 infection can be transmitted through saliva.

Possible vertical transmission of HHV-6 has also been suggested. HHV-6 is present in vaginal swabs, including specimens from pregnant women (Leach *et al.*, 1994; Okuno *et al.*, 1995), suggesting the possibility of perinatal and sexual infection. Also, Hall *et al.* (1994) reported that nearly 30% of new-borns had HHV-6 DNA in their mononuclear cells. In contrast, immunoglobulin (Ig) M with activity against HHV-6 is not found in peripheral blood from new-borns (Farr *et al.*, 1990) and rarely in specimens of cord blood cells (Dunne *et al.*, 1992). In addition, only one of 52 aborted fetuses of HIV-1 positive women was HHV-6 positive by PCR (Ando *et al.*, 1992). HHV-6 DNA sequences have not been found in breast milk (Dunne and Jevon, 1993; Takahashi *et al.*, 1988), suggesting that breast feeding is not a route of transmission.

1.3.3. Cellular tropism

HHV-6 replicates optimally in CD4⁺ T-cells (Lusso *et al.*, 1988; Takahashi *et al.*, 1989) and displays limited replication in CD8⁺ T-cells, natural killer cells, monocytes, epithelial cells, brain-derived cells (Levy *et al.*, 1990; He *et al.*, 1996) and EBV infected B lymphocytes (Ablashi *et al.*, 1991). CD4 is not believed to be the membrane receptor used by HHV-6, as infection is not inhibited by anti-CD4 antibodies (Lusso *et al.*, 1989). The cellular receptor of HHV-6 is not known. Interestingly, HHV-6 A strain induces CD4 in CD3⁺ CD4⁻ CD8⁺ lymphocytes, rendering them susceptible to HIV-1 infection (Lusso *et al.*, 1991).

1.3.4. Growth properties

The growth cycle of HHV-6 requires 4 to 5 days for the production of extranuclear enveloped virions (Black *et al.*, 1989; Kramarsky and Sander, 1992). However, a regulatory cascade for the virus has not been described, and little is known of the regulation of specific viral genes, largely as a result of the difficulty involved in growing high titre virus (Pellett and Black, 1996).

Of interest are unusual cytoplasmic invaginations (tegusomes) in the infected cell, in which capsids appear to acquire a tegument layer (Roffman *et al.*, 1990). Tegusomes have been observed in cells infected with HHV-7, but have not been noted in cells infected with other herpesviruses.

At any given time, 5% of the population may be seropositive for HHV-6 IgM (Suga *et al.*, 1992); HHV-6 DNA can be detected in the lymphocytes of up to 90% of healthy individuals (Cone *et al.*, 1993; Cuende *et al.*, 1994; Jarrett *et al.*, 1990), and HHV-6 antigens can be found in salivary glands (Fox *et al.*, 1990; Krueger *et al.*, 1990), lymph node tissue (Levine *et al.*, 1992) and neurons and glial cells in the brain (Challoner *et al.*, 1995). Such a high level of HHV-6 in the human population is unlikely to be due solely to reinfection. It is thought that following primary infection, HHV-6 develops a persistent infection that persists for the lifetime of the host. However, the site(s) of HHV-6 persistent infection is not known, although one report has been proposed that the virus may reside in monocyte/macrophage cells (Kondo *et al.*, 1991).

1.3.5. Disease and therapy

HHV-6 has been cited as possible cause of certain malignancies, such as Hodgkin's disease (Clark *et al.*, 1990; Torelli *et al.*, 1992; Di Luca *et al.*, 1994), non-Hodgkin's lymphoma (Jarrett *et al.*, 1988; Josephs *et al.*, 1988), angioimmunoblastic lymphadenopathy with dysproteinemia (Luppi *et al.*, 1993a), Langerhans cell-histiocytosis (Leahy *et al.*, 1993), Kaposi's sarcoma (Bovenzi *et al.*, 1993), cervical carcinoma (Chen *et al.*, 1994a) and oral carcinoma (Yadav, *et al.*, 1994). However, a direct involvement of HHV-6 in human malignancies has not been proven, and it is difficult to differentiate virus that is a passenger in tumour tissue from that which has a role in tumour etiology. Nonetheless, HHV-6 DNA has been reported to integrate into host cell chromosomes (Luppi *et al.*, 1993b), and has the ability to transform cultured murine fibroblasts

and human epidermal keratinocytes *in vitro* (Razzaque, 1990; Razzaque *et al.*, 1993; Thompson *et al.*, 1994). In addition, HHV-6 DNA can accelerate the tumourigenesis induced by human papillomavirus-immortalised (HPV) human cervical cells transplanted into nude mice (Chen *et al.*, 1994b).

The role of HHV-6B as the causative agent of ES, also known as roseola infantum and sixth disease, was proposed in 1988 (Yamanishi *et al.*, 1988). In most cases, ES is characterised by a high fever which typically lasts for three days and a rash (roseola) that appears as the fever subsides, lasting one to three more days. However, primary HHV-6 infection may lack the typical rash (Suga *et al.*, 1989; Pruksananonda *et al.*, 1992). The disease normally resolves without complications (Asano *et al.*, 1991 and 1994; Okada *et al.*, 1993), but high fever can in some cases lead to convulsions, respiratory tract and tympanic inflammation, intestinal symptoms, meningitis and meningoencephalitis (Pellett and Black, 1996; Suga *et al.*, 1989; Pruksananonda *et al.*, 1992). In a manner similar to HCMV infection, individuals who acquire primary HHV-6 infection in adulthood can develop a self-limiting febrile illness which resembles infectious mononucleosis (Steeper *et al.*, 1988) or hepatitis (Irving *et al.*, 1990; Sobue *et al.*, 1991).

HHV-6 has been associated with chronic fatigue syndrome (CFS), but serological studies reveal conflicting reports. CFS patients have been reported to have higher than average antibody titres for HHV-6 (Ablashi *et al.*, 1988; Balachandran *et al.*, 1991; Buchwald *et al.*, 1992; Dale *et al.*, 1989; Levine *et al.*, 1992; Read *et al.*, 1990; Reeves *et al.*, 1992) or antibody titres for HHV-6 that are similar to control patients (Gold *et al.*, 1990; Marshall *et al.*, 1991; Wakefield *et al.*, 1988). These results must be interpreted in light of the fact that higher than average antibody titres to other viruses (e.g. HCMV, EBV, measles virus) are also seen in CFS patients compared to controls (Holmes *et al.*, 1987).

Current evidence points to a possible role for HHV-6 in the pathology of multiple sclerosis (MS). HHV-6 has an association with acute nervous system disease (Asano *et al.*, 1992; Caserta *et al.*, 1994; Drobyski *et al.*, 1994; Hall *et al.*, 1994; Huang *et al.*, 1991; Kondo *et al.*, 1993; Suga *et al.*, 1993; Ward and Grey, 1994; Yamanishi *et al.*, 1988). The virus can grow in cells derived from the nervous system (Ablashi *et al.*, 1987), persists in the CNS of children (Caserta *et al.*, 1994), and is present in nearly all adult brains (Challoner *et al.*, 1995; Luppi *et al.*, 1994). In

addition, MS sufferers have higher than normal antibody titres to HHV-6, the virus has been detected in the cerebrospinal fluid of MS sufferers, and the distribution of HHV-6 antigen in their brains appears significantly different from normal (Sola *et al.*, 1993; Wilborn *et al.*, 1994; Challoner *et al.*, 1995).

As with HCMV, there is some evidence that HHV-6 may act as an opportunistic agent in immunosuppressed patients suffering from AIDS or undergoing organ or bone marrow transplants (Okuno *et al.*, 1990). The conditions that are associated with infection in the immunocompromised host include interstitial pneumonia in AIDS, bone marrow and organ transplant patients (Carrigan *et al.*, 1991; Knox and Carrigan, 1994; Cone *et al.*, 1993) and encephalitis in AIDS and bone marrow transplant patients (Drobyski *et al.*, 1993; Carrigan and Knox, 1994). The evidence linking HHV-6 with these conditions is based on the temporal association between the signs of disease, antibody levels to HHV-6 and detection of viral antigens and DNA.

No systematic trials have been performed to test the efficacy of drugs for the treatment of HHV-6 infection *in vivo*. However, several compounds have been tested for their ability to inhibit HHV-6 growth in cell culture. Of the compounds tested, gancyclovir and foscarnet inhibit HHV-6 infectivity more effectively than acyclovir, a pattern shared with HCMV (Agut *et al.*, 1991 and 1989; Burns and Sandyford, 1990; Russler *et al.*, 1989; Streicher *et al.*, 1988). In addition, the cytokines IFN- α and IL-2 exert inhibitory effects on HHV-6 infection in cell culture (Kikuta *et al.*, 1990; Roffman and Frenkel, 1990).

1.3.6. Co-infection with other viruses

HHV-6 has been reported to interact with several other viruses. HHV-6 superinfects B cells latently infected with EBV and may induce EBV lytic replication (Ablashi *et al.*, 1988; Flamand *et al.*, 1993). The observed increase in HHV-6 specific antibodies during HCMV primary infection suggests that HHV-6 may be activated by HCMV. Similarly, HHV-7 primary infection can activate (presumably latent) HHV-6, which can then outgrow the HHV-7 infection (Frenkel and Wyatt, 1992). HHV-6 has been shown to transactivate a HPV promoter and enhance expression of HPV RNA (Chen *et al.*, 1994a).

Perhaps most interesting is that HHV-6 has been proposed as a cofactor with HIV-1, capable of speeding the progression of AIDS. Several lines of evidence support this claim. The HIV-1 transactivator, *tat*, enhances HHV-6 replication (Sieczkowske *et al.*, 1995); HHV-6 (strains A and B) is a potent transactivator of HIV-1 (Lusso *et al.*, 1989; Ensoli *et al.*, 1989; Horvat *et al.*, 1989); and HHV-6 induces two cytokines, TNF- α and IL-1 β (Flamand *et al.*, 1991), which are known to enhance replication of HIV-1 *in vivo*. These findings are made more relevant because HHV-6 and HIV-1 share tropism for CD4⁺ T-cells (Lusso *et al.*, 1988).

In contrast, studies of the prevalence of antibodies to HHV-6 and HIV-1 are confusing and have variously shown no difference in HHV-6 prevalence between HIV positive groups and control groups (Brown *et al.*, 1988; Essers *et al.*, 1991; Fox *et al.*, 1988), higher (Ablashi *et al.*, 1988) or lower prevalence to HHV-6 in HIV-1 positive people, or no positive correlation between seroprevalence to HHV-6 and progression to AIDS (Spira *et al.*, 1990; Chen *et al.*, 1992).

1.3.7. The HHV-6 genome

The features of the HHV-6 genome discussed below have been derived largely from Lawrence *et al.* (1990), Lindquister and Pellett (1991), Martin *et al.* (1991), Nicholas and Martin (1994), Nicholas (1994) and Gompels *et al.* (1995). Table 2 gives a list of the genes present in the HHV-6 genome, Fig. 4 shows the genome structure and relative arrangement of the genes, and Fig. 5 compares the gene arrangements of the human β -herpesviruses.

1.3.7.1. Size and structure

The published sequence of HHV-6 strain U1102 (Gompels *et al.*, 1995) is 159,322 bp in length (Nicholas, 1996) and consists of a unique region (U) (143,147 bp), flanked by single copies of a directly repeated sequence (formally DR_L and DR_R; referred to here as DR) (8,087 bp), as shown in Fig. 4.0. The overall nucleotide composition is 43% G + C, but it is lower in U (41%) and higher in DR (58%) (Gompels *et al.*, 1995; Lindquister and Pellett, 1991). Genes located in the direct repeat are prefixed by the term DR and genes in the unique sequence by U.

There are three major reiterations designated R1, R2 and R3 positioned in or adjacent to the IE-A region near the right end of U (Gompels *et al.*, 1995). R1 is located within U86, which is

TABLE 2. HHV-6 genes and encoded proteins

name	strand	start	stop	name	old name	closest homologue	gene family	gene block	comment
LTI	C	338	3						
DR1	-	501	791				DR1/DR6		- CXC motif
DR2	-	791	2650			HCMVUS26*	HCMVUS22		
DR3	C	2979	2404						
DR4	-	2746	3045						
DR5	C	4171	3737						
DR6	-	4725	5033				DR1/DR6		- CXC motif
DR7	-	5629	6717			HCMVUS22*	HCMVUS22		- transformation, transactivator
DR8	-	7237	7566		SJRF1				- SR domain
LJ1	C	8432	7470		SJLF1				- across DRL junctional telomeric repeats
U1	-	8245	8613		SJRF2				- SR domain
U2	C	9816	8719		SHL1	HCMVUL23*	HCMVUS22		
U3	C	11276	10158		SHL2	HCMVUL24*	HCMVUS22		
U4	C	13092	11488		SHL3	HCMVUL27*	U4/U5		
U5	C	14548	13217		SSL1	HCMVUL27*	U4/U5		
U6	-	14619	14864						
U7	C	15936	14911		SSL2	HCMVUL28*	HCMVUS22		
U8	C	17091	16024		SFL1	HCMVUL29*	HCMVUS22		
U9	C	17552	17241		SFL2				
U10	-	17604	18911		SFR1.P1RF0	HCMVUL31*			
U11	C	21578	18969		P1LF1	HCMVUL32*			- pp100 major antigenic structural protein, basic phosphoprotein, BPP
U12EX	-	21680	21710		347:39747+				- U12 exon,spliced donor/acceptor 21710,21800+
U12	-	21856	22809		P1RF1	HCMVUL33*	GCR		- G-protein coupled receptor homology;EBV induced EBI1
U13	-	22898	23215		EFRF1				
U14	-	23316	25142		EFRF2	HCMVUL25*			- homology to HCMV'UL25/35' family
U15	C	25992	25663		EPLF3				
U16EX	C	27349	26262		312:36092+	HCMVUL36EX2*			- IE-B;U16exon,spliced acceptor/donor 27034,27187
U16	C	-27116	26262		285:32908	HCMVUL36*	HCMVUS22		- IE-B;transactivator,
U17	C	27349	26951		EPLF1	HCMVUL36EX1*	HCMVUS22		- IE-B;U16exon17,acceptor/donor 27034,27187
U18	C	29389	28511		EJLF6	HCMVUL37EX3*			- IE-B;homology to HCMV IE glycoprotein
U19	C	30818	29652		EJLF4	HCMVUL38*			- IE-B
U20	C	32337	31072		EJLF3		IG		- glycoprotein;Ig chain C domain
U21	C	33641	32343		EJLF2				- glycoprotein
U22	C	34347	33742		EJLF1				- glycoprotein
U23	C	35085	34378		EJLF1				- glycoprotein
U24	C	35655	35395		EoLF1				- glycoprotein exon? glyco site,TM
U25	C	36814	35867		EPLF3	HCMVUL43*	HCMVUS22		
U26	C	37809	36925		EPLF2				
U27	C	38978	37800		EPLF1	HCMVUL44***		I	- pp41.pol processivity,transactivator,HCMV ICP36
U28	C	41434	39023		P2LF2	HCMVUL45***		I	- large sub-unit ribonucleotide reductase,RR1
U29	C	42356	41460		P2LF1	HCMVUL46***		I	- capsid assembly and DNA maturation; minor capsid protein, mCP
U30	-	41884	45129		P2RF1	HCMVUL47***		I	- HCMV capsid assembly,myosin
U31	-	45150	51380		HHRF1	HCMVUL48***		I	- large tegument protein,high molecular weight protein, HMWP
U32	C	51721	51458						
U33	C	53135	51726		XJLF3	HCMVUL49***		I	- capsid protein
U34	C	53916	53089		XJLF2	HCMVUL50***		I	- possible virion protein,TM
U35	C	54253	53936		XJLF1	HCMVUL51*			
U36	-	54252	55703		XJRF1	HCMVUL52***		I	- probable virion protein
U37	-	55710	56501		XJRF2	HCMVUL53***		I	- nuclear phosphoprotein?
U38	C	59588	56553		XJLF0.Pol	HCMVUL54***		II	- DNA polymerase
U39	C	62080	59591		gpB	HCMVUL55***		II	- glycoprotein B
U40	C	64214	62037		tp	HCMVUL56***		II	- transport protein
U41	C	67620	64225		mdbp	HCMVUL57***		II	- major DNA binding protein
U42	C	70598	69057			HCMVUL69***		III	- conserved herpesvirus transactivator-
U43	C	73405	70826			HCMVUL70***		III	- helicase/primase complex; HSV primase
U44	-	73446	74084			HCMVUL71***		III	
U45	C	75218	74091		BHLP3	HCMVUL72***		III	- putative dUTPase
U46	-	75291	75542		BHRF1	HCMVUL73***		III	- membrane/secreted protein
U47	C	77867	75915		variable gp	HCMVUL74*			- membrane/secreted glycoprotein
U48	C	80118	78037		gH,BHLP1	HCMVUL75***		IV	- glycoprotein H
U49	-	80277	81032		BHRF2	HCMVUL76***		IV	- fusion protein
U50	-	80812	82476		BHRF3	HCMVUL77***		IV	- virion protein
U51	-	82574	83476		XKRF1	opioid ⁸ /HCMVUL78*	GCR		- G-protein coupled receptor homology; HVS GCR
U52	C	84274	83501		XKLF1	HCMVUL79*			
U53	-	84281	85864		OR.XKRF1	HCMVUL80***		IV	- protease; U53a in-frame assembly protein, AP
U54	C	87427	86054		1L	HCMVUL82/83*			- tegument pp65/72K, possible transactivator IE genes
U55	C	88803	87508		2L	HCMVUL84*			
U56	C	89873	88986		3L	HCMVUL85***		V	- probable capsid protein
U57	C	93912	89878		4L.mcp	HCMVUL86***		V	- major capsid protein,MCP

name	strand	start	stop	name	old name	closest homologue	gene family	gene block	comment
U58	-	93924	96239	772:88748	5R	HCMVUL87**			
U59	-	96239	97288	350:39884	6R	HCMVUL88*			
U60	C	98256	97291	322:36084	7L	HCMVUL89EX2***		VI	- late spliced gene(U60/66),possible DNA packaging protein
U61	C	98578	98234	115:13578					
U62	-	98427	98681	85:9579	8R	HCMVUL91*			
U63	-	98632	99279	216:24783	9R	HCMVUL92**			
U64	-	99260	100585	442:51392	10R	HCMVUL93***		VI	
U65	-	100545	101549	335:37878	11R	HCMVUL94***		VI	
U66	C	102486	101572	305:35930	12L	HCMVUL89EX1***		VI	- late spliced gene(U60/66),possible DNA packaging protein
U67	-	102458	103516	353:39533	13R	HCMVUL95***		VI	
U68	-	103519	103860	114:13075	14R	HCMVUL96**			
U69	-	103866	105551	562:63718	15R	HCMVUL97***		VI	- ganciclovir kinase; conserved phosphotransferase
U70	-	105562	107025	488:56646	16R	HCMVUL98***		VI	- alkaline exonuclease
U71	-	106965	107195	77:8469	17R				- position HCMV pp28k,HSV myristilated virion protein
U72	C	108312	107281	344:38993	18L	HCMVUL100***		VI	- integral membrane protein, gM
U73	-	108325	110664	780:89719	19R,HDRF0	HSVUL9+			- origin binding protein
U74	-	110636	112621	662:76318	HDRF1	HCMVUL102***		VI	- helicase/primase complex
U75	C	113408	112662	249:28762	HDLF2	HCMVUL103***		VI	
U76	C	115305	113320	662:77236	HDLF1	HCMVUL104***		VI	- possible virion protein
U77	-	115100	117571	824:93288	HDRF2	HCMVUL105***		VI	- helicase/primase complex; helicase
U78	C	119038	118712	109:12725	EDLF5				
U79	-	120164	121195	344:39273	EDRF1	HCMVUL112*			- HCMV in vitro replication;spliced
U80	-	-121170	121763	198:22256	EDRF2	HCMVUL113*			- HCMV in vitro replication; spliced
U81	C	122577	121813	255:29039	EDLF4	HCMVUL114***		VII	- uracil-DNA glycoylase
U82	C	123405	122656	250:28962	gL,BDLF3	HCMVUL115***		VII	- glycoprotein gL; gH accessory protein
U83	-	123528	123818	97:10411	EDRF3				- CC chemokine?
U84	C	124953	123928	342:39557	EDLF2	HCMVUL117*			- spliced in HCMV
U85	C	125853	124984	290:32901	EDLF1		IG		- OX-2 homology; glycoprotein
U86	C	-128136	125992	715:80040	BCLF1	HCMVUL122*			- IE-A;HCMVIE2 homology, SR domain repeats
U87	C	130043	127554	830:91391	BCLF0				- IE-A;glycoprotein?, highly charged,pro repeats
U88	-	131034	132272	413:44136					- IE-A;open all frames, cys repeats
U89	C	135610	133094	839:93712	pRF3/4;RF2				- IE-A;HCMV IE1 position, transactivator
U90	C	135948	135667	94:10651	pRF2;RF1				- IE-A; spliced U89
U91	-	-136485	136826	114:12897					- IE-A;spliced antisense IE1?
U92	C	-138492	138052	147:15878					- kpn repeats, part duplicate U93
U93	C	-139124	138534	197:21371					- kpn repeats, part duplicate U92
U94	C	142866	141397	490:55849	HCLF2	AAV2 Rep 68/78			- parvovirus replication, transactivation
U95	-	142941	146303	1121:124069	HCRF2	MCMVIE2*	HCMVUS22		- positional/sequence homologue MCMVIE2
U96	C	146940	146644	99:12128	HCLF1				
U97	C	148077	147811	89:10384					
U98	C	-149391	148744	296:24698					
U99	C	149766	149488	93:10559					- signal sequence
U100	C	150437	149871	189:21609	gp82/105				- spliced glycoprotein gp82/105
RJ1	C	151571	151143	143:16221					- across DRR junctional telomeric repeats
DR1	-	151734	152024	97:11677			DR1/DR6		- CXC motif
DR2	-	152024	153883	620:67151		HCMVUS26*	HCMVUS22		
DR3	C	154212	153637	192:19404					
DR4	-	153979	154278	100:10562					
DR5	C	155404	154970	145:15637					
DR6	-	155958	156266	103:12129			DR1/DR6		- CXC motif
DR7	-	156862	157950	363:40831		HCMVUS22*	HCMVUS22		- transformation, transactivator
DR8	-	158470	158799	110:12766					- SR domain

A compilation of reading frames of HHV-6 strain U1102, from Gompels *et al.* (1995). ^a Start is the first base ATG (or its complement), except as indicated by a dash, where first base in ORF or exon is listed. Stop is third base in stop codon. + indicates spliced gene encoded molecular weight.

^B ***conserved in α -, β - and γ -herpesviruses; **conserved in β - and γ -herpesviruses; *conserved in β -herpesviruses; ** conserved in β - and α -herpesviruses.

^C Properties for proteins are derived mostly from homologues described in HSV-1, VZV, EHV-1, or HCMV (Davison and Scott, 1986; McGeoch *et al.*, 1988; Chee *et al.*, 1990; Telford *et al.*, 1992).

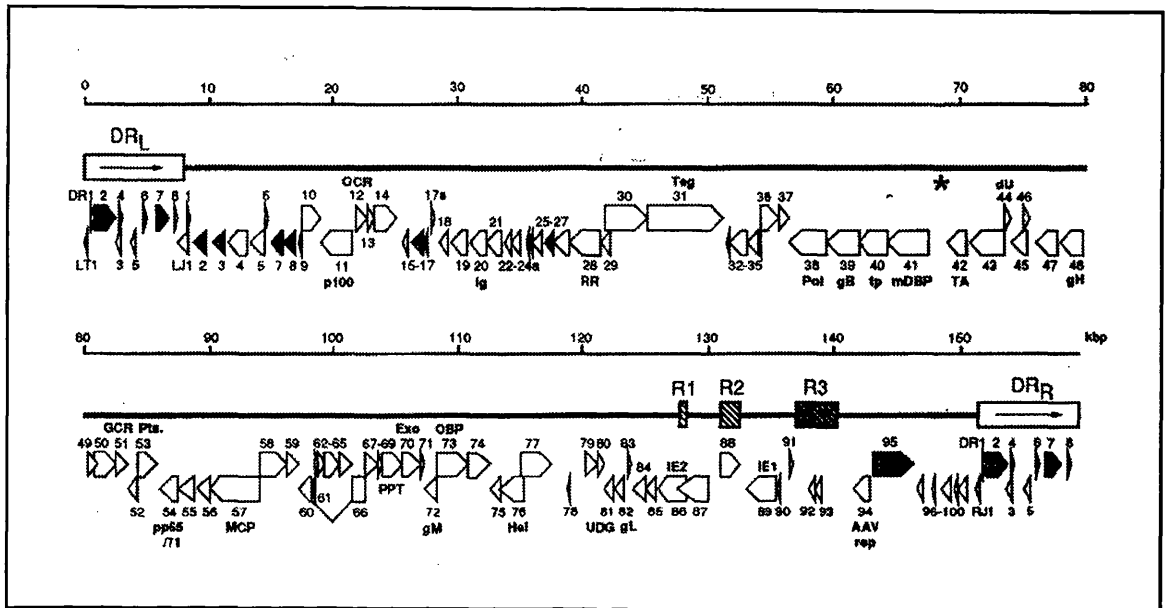


Fig. 4. Genetic layout of the HHV-6 genome.

Predicted HHV-6 gene organisation, from Gompels *et al.* (1995). Repeat regions are boxed, DRL, DRR, R1, R2, R3, and the long unique (UL) region is indicated by a solid line. Protein coding regions are indicated as open arrows and are numbered DR1-DR8 in the direct repeats and U1-U100 in UL. The ori-lyt is indicated by a star on UL. Abbreviations are, GCR (G-protein coupled receptor), RR1 (large subunit of ribonucleotide reductase), TEG (tegument protein), POL (DNA polymerase), tp (transport protein), mDBP (major single-stranded DNA binding protein), TA (conserved herpesvirus transactivator), Pts (protease/assembly protein), exo (alkaline exonuclease), OBP (origin binding protein), UDG (uracil DNA glycosylase), Hel (helicase), MCP (major capsid protein), AAV rep (Adeno-associated virus replication protein homologue), IG (immunoglobulin superfamily). The US22 gene family are shaded.

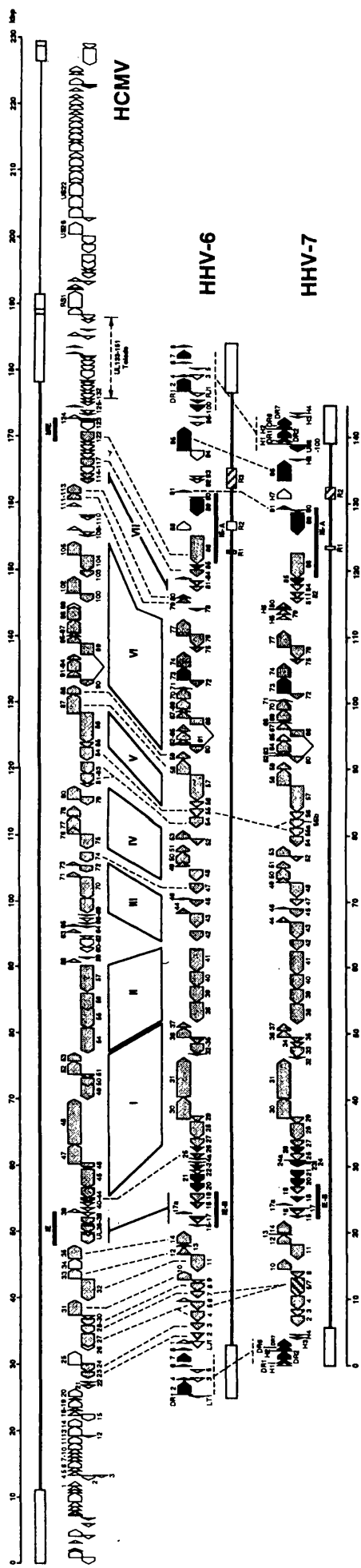


Fig. 5. Comparison of the genetic content of HCMV, HHV-6 and HHV-7.

Alignment of the genomes of HCMV (AD169), HHV-6 (U1102), and HHV-7 (J1), showing homologous (shaded) and nonconserved (open) genes in these β -herpesviruses; from Nicholas (1996). Solid areas indicate genes between HHV-6 and HHV-7 but not present in HCMV. The herpesvirus-conserved gene blocks (I to VII) are indicated. Major divergence loci between HCMV and HHV-6/HHV-7 correspond to terminal sequences, regions between HCMV UL38-UL43 and UL57-UL69, and sequences within and around the MIE locus (UL122/123). HHV-6/HHV-7 US22 genes U95, DR2, and DR7 have approximately positional counterparts in HCMV, but these corresponding genes are not necessarily the nearest homologs. The locus at which additional genes (UL133 and UL151) have recently been identified in HCMV strain Toledo (Cha et al., 1996) is included.

homologous to HCMV IE-2 (Birney *et al.*, 1993; Nicholas, 1994; Gompels *et al.*, 1995). The R2 region contains approximately 250 bp of simple TG dinucleotide repeats and creates a large ORF in all 6 reading frames (Gompels *et al.*, 1995), although it is doubtful that any are actually expressed as protein. R3 is an array of more than 25 copies of a 110 bp tandem reiteration.

Both ends of each copy of DR contain arrays of a simple repeat (GGGTTA)_n, similar to human telomeric sequences (Kishi *et al.*, 1988; Martin *et al.*, 1991a; Gompels *et al.*, 1995). The telomeric repeats form an imperfect array near the left end of DR, and approximately 60 perfect tandem copies of the sequence near the right end of DR (Gompels and Macaulay, 1995; Thomson *et al.*, 1994), although the number of copies in each region may vary (Martin *et al.*, 1991a; Gompels and Macaulay, 1995; Thomson *et al.*, 1994). The significance of the telomeric repeats has not been established. Cleavage/packaging sites, pac-1 and pac-2, are positioned between the telomeric repeats and the ends of DR (Gompels *et al.*, 1995; Thomson *et al.*, 1994).

1.3.7.2. Relationships to other herpesviruses

The core genes are compactly arranged across 86 kb in the centre of U. Overall, the HHV-6 genome is arranged colinearly with that of HCMV, but diverges near the genome ends (Efsthathiou *et al.*, 1992; Neipel *et al.*, 1991). As a result, genes contained at the left end and in U_s of the HCMV genome, including the HLA class 1 homologue (UL18) and most of the glycoprotein gene families (RL11, US6 and US12) are absent from the HHV-6 genome. In a reciprocal fashion those genes unique to HHV-6 are found largely outside the region of colinearity with HCMV (Gompels *et al.*, 1995).

1.3.7.3. Gene complement

The HHV-6 genome contains 121 closely packed ORFs (LT1, DR1-DR8, LJ1, U1-U100, RJ1, DR1-DR8), encoded on both DNA strands, with little overlapping (Gompels *et al.*, 1995). Splicing is thought to operate for several pairs of ORFs: U60 and U66 (Lawrence *et al.*, 1990), U17 and U16 (Nicholas and Martin, 1994), U90 and U91 (Schiewe *et al.*, 1994) and U96 to U100 (Pfeiffer *et al.*, 1995).

The HHV-6 genome contains two IE loci, IE-A (U86-U91) and IE-B (U16-U19), which are roughly analogous to HCMV MIE and IE-2 respectively, and which are also CpG suppressed (Kouzarides *et al.*, 1988; Nicholas and Martin, 1994). HHV-6 genes with homologues in HCMV are listed in Table 2.

Several HHV-6 genes lack detectable counterparts in HCMV. These are also listed in Table 2 and include: the telomeric repeat ORFs LT1, LJ1 and RJ1; the R2 ORF U88; glycoprotein ORFs U20, U21, U22, U23, U24 (although there are glycoprotein genes in the corresponding region of the HCMV genome they are unrelated); the spliced ORFs U96-U100 encoding gp105; U85, which is a homologue of OX-2 and a member of the Ig family; the origin binding protein encoded by U73; the AAV-2 rep gene homologue, U94; the IE proteins encoded by U89/U90 and the U91 protein; and ORFs DR1, DR3, DR4, DR5, DR8, U1, U6, U9, U13, U15, U26, U32, U61, U78, U83, U92 and U93. Many of the genes unique to HHV-6 are located towards the genome ends and include regions which may be expressed by splicing.

1.3.7.4. Origin of lytic DNA replication

HHV-6 contains an origin of DNA replication (*ori*) upstream of the major DNA-binding protein gene (U41) in a position corresponding to *ori_L* in HCMV (Hamzeh *et al.*, 1990; Anders *et al.*, 1992; Gompels *et al.*, 1992; Jones and Teo, 1992; Masse *et al.*, 1992; Dewhurst *et al.*, 1993). *ori_L* is complex and comprises an AT-rich sequence and two 137 bp imperfect direct repeats. It contains two origin-binding protein binding sites (OBP-1 and OBP-2), and is adjacent to a GC-rich motif. It is noteworthy that the origin binding protein of HHV-6 (U73) is a counterpart of the α -herpesvirus origin binding protein, and lacks a homologue in HCMV (Chee *et al.*, 1990). Thus, HHV-6 *ori_L* has features of both the β - and α -herpesviruses, in containing a complex set of repeat motifs and sequences which bind the origin binding protein.

1.3.7.5. Gene families and captured genes

The HHV-6 genome contains several gene families, DR1/6 (DR1 and DR6), U4/5, (U4 and U5) US22 (DR2, DR7, U2, U3, U7, U8, U17, U25, and U95) GCR (U12 and U51) and Ig (U20 and U85), some of which are related HCMV genes (Chee *et al.*, 1990) (see Table 2).

The DR1/DR6 proteins share a CxC motif (X = unspecified residue) and appear to be unique to HHV-6. U4/5 are tandemly duplicated positional homologues of HCMV UL27. Members of the US22 gene family are the most numerous related genes in the HHV-6 genome, having nine members (two repeated in DR). They are related to varying extents to the 12 members in HCMV (see Table 2) (Kouzarides *et al.*, 1988; Chee *et al.*, 1990); U95 is also related to the MCMV IE2 gene (Messerle *et al.*, 1991). There is evidence for a role in transcriptional activation for HHV-6 U16 (Geng *et al.*, 1992; Nicholas and Martin, 1994) and DR7 (Thompson *et al.*, 1994), DR7 also appears to have a role in cellular transformation *in vitro* (Thompson *et al.*, 1994).

The U12 and U51 proteins are cellular GCR homologues, and are distantly related to HCMV GCR gene family (Gompels *et al.*, 1995; Chee *et al.*, 1990). GCRs are similar to chemokine receptors, which interact with a family of proinflammatory cytokines that function in the migration and activation of leukocytes and thus mediate the inflammatory response (Oppenheim *et al.*, 1991; Gerard and Gerard, 1994). Interestingly, HHV-6 U83 may also act as a CC chemokine.

U20 and U85 encode glycoproteins with domains similar to those of the Ig superfamily (Gompels *et al.*, 1995), although the significance of the former is doubtful. These proteins may play a role in cell-to-cell contact via protein-protein interactions (Williams and Barclay, 1988).

Notably, HHV-6 encodes a homologue of the parvovirus, adeno-associated virus type 2 rep gene. The function of the gene product in HHV-6 is unknown, but in AAV this protein functions as a transcriptional regulatory protein and is an essential component of the DNA replication machinery (Thomson *et al.*, 1991). On the basis of close (24% identity) amino acid sequence similarities between the AAV-2 and HHV-6 rep genes, HHV-6 U94 probably represents a gene captured during coinfection of a single cell by AAV-2 and an HHV-6 progenitor (Thomson *et al.*, 1991).

1.4. HUMAN HERPESVIRUS 7

1.4.1. Basic characteristics

HHV-7 (strain RK) was first isolated in 1989 from the CD4⁺ T-cells of a 26 year old healthy individual (Frenkel *et al.*, 1990), during experiments concerning propagation of HHV-6. Uninfected cells underwent spontaneous cytopathic effect (CPE) following conditions promoting T-cell activation, and subsequent electron microscopic analyses revealed particles with the characteristic herpesvirus morphology including a clearly visible tegument layer. However, the virus was distinct from other herpesviruses, including HHV-6 A and B variants, as shown by restriction endonuclease blot hybridisation analyses, nucleotide sequencing, and interactions with monoclonal antibodies. The novel virus was designated HHV-7 (Frenkel *et al.*, 1990).

1.4.2. Epidemiology

HHV-7 is ubiquitous in the human population - probably more than 85% are infected (Ablashi *et al.*, 1995; Wyatt *et al.*, 1991; Berneman *et al.*, 1992b). The prevalence rates both for adults and for children appear lower in Japan than in the USA or Europe (Yoshikawa *et al.*, 1993; Wyatt *et al.*, 1991).

It is likely that HHV-7 is transmitted through saliva, many workers have isolated HHV-7 from saliva and noted that the salivary system is a source of persistent production of infectious HHV-7 (Wyatt and Frenkel, 1992; Sada *et al.*, 1996; Hidaka *et al.*, 1993; Black *et al.*, 1993). HHV-7 has also been consistently isolated from the peripheral blood mononuclear cells (PBMC) of young children (Ablashi *et al.*, 1995). In addition, HHV-7 has been found at the cervix (Okuno *et al.*, 1995), suggesting possible sexual transmission of the virus.

HHV-7 infection occurs early in childhood, perhaps later than HHV-6 infection at three years of age (Wyatt *et al.*, 1991; Yoshikawa *et al.*, 1993), but one study reported little difference in the prevalence of antibodies to both viruses in relation to age (Clark *et al.*, 1993). Although the great majority of human sera contain antibodies to both HHV-6 and HHV-7, as tested by immunofluorescent antibody (Berneman *et al.*, 1992b; Wyatt *et al.*, 1991), very few sera contain antibodies to HHV-6 or HHV-7 alone.

1.4.3. Cellular tropism

HHV-7 has a more limited host range than HHV-6, but grows well in CD4⁺ lymphocytes (PBMC) and adequately in the immature T-cell line SUP T1 (Frenkel *et al.*, 1990; Berneman *et al.*, 1992b). The CD4 molecule is a critical part of the cell receptor used by HHV-7 (Lusso *et al.*, 1994), although it has been proposed that HHV-7 infection selectively down-modulates surface expression of cellular CD4 (Lusso *et al.*, 1994; Furukawa *et al.*, 1994). This is in direct contrast to HHV-6, for which CD4 is not the cellular receptor, and which is thought to enhance CD4 presentation during infection (Lusso *et al.*, 1991; Furukawa *et al.*, 1994).

As HIV-1 is also associated with the CD4 receptor and infects CD4⁺ T-cells, it is interesting that preadsorption of CD4⁺ T-cells with HHV-7 results in inhibition of HIV-1 replication (Lusso *et al.*, 1994).

1.4.4. Growth properties

Little can be said about the HHV-7 lytic cycle except that it is likely to be similar to that of HHV-6. A regulatory gene cascade has not been described for HHV-7, and little is known of the regulation of specific viral genes, largely as a result of the difficulty involved in growing high titre virus. As with HHV-6, tegusomes are evident in HHV-7 infected cells.

The high prevalence of HHV-7 and its presence in the saliva of healthy individuals (Wyatt and Frenkel, 1992; Wyatt *et al.*, 1991; Berneman *et al.*, 1992b; Black *et al.*, 1993; Ablashi *et al.*, 1995; Frenkel and Roffman, 1996) are unlikely to be maintained by lytic reinfection alone, but probably involves latent virus. HHV-7 was first isolated from CD4⁺ T-cells, most likely following reactivation from latency, and PBMCs have been proposed as a site of HHV-7 latency (Frenkel *et al.*, 1990; Katsadanas *et al.*, 1996). HHV-7 infection has been reported to mediate reactivation of HHV-6 in cells infected with both viruses (Frenkel and Wyatt, 1992; Katsadanas *et al.*, 1996).

1.4.5. Disease

Unlike HHV-6, which is widely accepted as a causative agent of ES (Yamanishi *et al.*, 1988), HHV-7 has no proven involvement in any disease. Recent reports of several seroconversions to HHV-7 during convalescence from ES have suggested that HHV-7 may cause a proportion of

ES cases (Tanaka *et al.*, 1994; Hidaka *et al.*, 1994; Ueda *et al.*, 1994; Asano *et al.*, 1995; Portolani *et al.*, 1995). However, in all but one of these cases the patients had previously seroconverted to HHV-6. Also, it has been suggested that primary HHV-7 infection may appear to cause ES as a result of its ability to reactivate HHV-6 (Asano *et al.*, 1995; Frenkel *et al.*, 1992; Frenkel and Roffman, 1996; Katsafanos *et al.*, 1996).

HHV-7 was recovered from one patient with CFS (the JI strain; Berneman *et al.*, 1992), but serological studies have found no association between HHV-7 infection and the disease. One report (Kawa Ha *et al.*, 1993) described a case of chronic EBV-like infection where no viruses other than HHV-7 could be isolated, but again no pathogenic link was established. In addition, HHV-7 is known not to be the etiologic agent of Kawasaki disease (Burns, 1994).

1.4.6. The HHV-7 genome

The features of the HHV-7 genome discussed below have been derived largely from Secchiero *et al.*, (1995), Ruvolo *et al.*, (1996) and Nicholas (1996). Table 3 gives a list of the genes represented in the HHV-7 genome, Fig. 5 compares the gene arrangements of the human β herpesviruses and Fig. 6 shows the genome structure and relative arrangement of the genes.

1.4.6.1. Size and structure

The complete nucleotide sequence of HHV-7 strain JI was derived using plasmid and lambda clones by Nicholas (1996). The following description of the genome content is derived from this analysis except where stated otherwise.

Genome structure is identical to that of HHV-6, with a single long unique component (U) flanked by large terminal direct repeats (DR_L and DR_R), approximately 133 kbp and 6 kbp in length, respectively (Nicholas, 1996; Ruvolo *et al.*, 1996; Secchiero *et al.*, 1995). The genome of HHV-7 stain JI is thus approximately 14 kbp shorter than that of HHV-6 strain U1102. The nucleotide composition of HHV-7 is 43% G+C overall, and is lower (38%) in U and higher (54%) in DR (Secchiero *et al.*, 1995).

TABLE 3. HHV-7 genes and encoded proteins

ORF ^a	Sense ^b	Position ^b				Length (aa) ^c	Homology with HHV-6 (%Sim/%Id) ^d	Homolog(s) ^e								Comments
		Start	Stop	N-Term Met?	Poly(A)			HHV-6	HCMV	HVS	EBV	EHV-2	EHV-1	VZV	HSV-1	
H1	+	33	542	N	853*	169										
DR1	+	368	826	N	853*	152	57.1/44.0	DR1								US22 gene family, DR1/DR6 homology
DR2	+	898	2100	N	3917*	400	58.1/37.0	DR2								US22 gene family
H2	+	2267	2506	Y	3917*	79										
DR6	+	2562	3050	Y	3917*	161	71.6/58.8	DR6								US22 gene family, DR1/DR6 homology
DR7	+	3122	3910	Y	3917*	262	77.8/60.5	DR7								US22 gene family, transactivator
H3	-	4224	3976	Y	3040	82										
H4	-	4745	4449	Y	3040	98										
U2	-	7417	6338	Y	6248*	359	69.6/51.1	U2	UL23							US22 gene family
U3	-	8732	7578	Y	7514	384	65.4/49.3	U3	UL24							US22 gene family
U4	-	10382	8754	Y	7514	542	75.5/59.2	U4	UL27							
U5/7	-	13004	10407	Y	10411*	865	71.2/49.7	U5	UL27							US22 gene family (HHV-6 U7)
							80.2/60.7	U7	UL28							
U8	-	14262	13174	Y	11850	362	69.0/51.0	U8	UL29							US22 gene family
U10	+	14608	15963	Y	15885*	451	71.6/51.5	U10	UL31							
U11	-	18249	15982	Y	15971	755	55.6/30.7	U11	UL32							Structural phosphoprotein
U12	+	18396	19436	Y	19481	346	67.7/45.7	U12	UL33							GCR homolog, chemokine receptor
U13	+	19521	19817	Y	20424*	98	54.6/37.1	U13								
U14	+	19885	21831	Y	21925*	648	67.9/53.5	U14	UL35							HCMV UL25/35 gene family
U15	-	22244	22564	Y	22075	106	84.9/64.1	U15								
U16	-	23547(A)	22772	N	22754	264	74.8/56.5	U16	UL36x2							IE-B, transactivator (spliced to U17)
U17Ex	-	23836	23620(D)	Y		72	55.5/41.7	U17Ex	UL36x1							IE-B, transactivator (spliced to U16)
U17	-	23836	23570	Y	22754	88	54.5/39.8	U17								
U17a	+	24318	24587	Y	24707	89	46.6/29.3	U17a								
U18	-	25600	24713	Y	24578	295	71.4/43.9	U18	UL37x3							IE-B, homologous to HCMV IE glycoprotein
U19	-	26922	25945	Y	25504	325	59.9/40.1	U19	UL38							IE-B
U20	-	28211	27036	Y	27027	391	53.2/23.4	U20								Ig gene family?
U21	-	29494	28202	Y	28127	430	55.8/32.2	U21								Glycoprotein
U23	-	30418	29903	Y	29904*	171	55.6/29.4	U23								Glycoprotein, EHV-1 gJ homology
U24	-	30772	30524	Y	30455*	82	63.2/36.8	U24								Glycoprotein
U24a	-	31129	30776	Y	30671	117	57.1/33.9	U24a								
U25	-	31898	30936	Y	30671	320	70.7/48.9	U25	UL43							US22 gene family, transactivator
U26	-	32869	31988	Y	31959	293	60.4/30.4	U26								
U27	-	33951	32857	Y	31959	364	83.8/67.6	U27	UL44	(59)	(BMRF1)	(59)	(18)	(16)	(UL42)	DNA polymerase processivity factor
U28	-	36484	34064	Y	34059	806	70.2/47.1	U28	UL45	61	BORF2	61	21	19	UL39	Ribonucleotide reductase (large subunit)
U29	-	37347	36487	Y	36457	286	77.5/53.3	U29	UL46	62	BORF1	62	22	20	UL38	Minor capsid protein (mCP)
U30	+	37362	40178	Y	37548	938	66.0/45.9	U30	UL47	63	BOLF1	63	(23)	(21)	(UL37)	Capsid assembly, myosin
U31	+	40179	46358	Y	46994	2,059	65.3/46.2	U31	UL48	64	BPLF1	64	24	22	UL36	Large tegument protein
U32	-	46627	46355	Y	46385*	90	80.7/65.9	U32		(66)	(BFRF2)	(66)	(25)	(23)	(UL35)	
U33	-	48041	46608	Y	46385*	477	78.5/59.4	U33	UL49							Virion protein
U34	-	48768	47992	Y	47906	258	75.0/59.1	U34	UL50	67	BFRF1	67	(26)	(24)	(UL34)	Virion protein?
U35	-	49119	48805	Y	48775	104	78.6/58.3	U35	UL51				27	25	UL33	
U36	+	49118	50575	Y	51089*	485	77.3/58.2	U36	UL52	68	BFLF1	68	28	26	UL32	Probable virion protein
U37	+	50577	51356	Y	51613*	259	80.5/63.0	U37	UL53	69	BFLF2	69	29	27	UL31	

U38	-	54401	51363	Y	51533	1,012	81.6/66.7	U38	UL54	9	BALF5	9	30	28	UL30	DNA polymerase
U39	-	56869	54401	Y	53919*	822	72.1/56.4	U39	UL55	8	BALF4	8	33	31	UL27	Glycoprotein B (gB)
U40	-	58997	56832	Y	56686	721	75.4/56.0	U40	UL56	7	BALF3	7	32	30	UL28	Transport protein (tp)
U41	-	62395	59000	Y	58773*	1,131	84.1/63.3	U41	UL57	6	BALF2	6	31	29	UL29	Major DNA-binding protein
U42	-	64352	62772	Y	62714*	526	75.7/57.0	U42	UL69	57	BMLF1	57	5	4	UL54	Transactivator
U43	-	67086	64501	Y	64470	861	76.9/61.2	U43	UL70	56	BSLF1	56	7	6	UL52	Primase
U44	+	67143	67754	Y	67750	203	70.7/58.5	U44	UL71	55	BSRF1	55	(8)	(7)	(UL51)	
U45	-	68898	67759	Y	67763*	379	69.3/51.2	U45	UL72	54	BLLF2	54	9	8	UL50	dUTPase
U46	+	68930	69190	Y	69186*	86	72.8/53.1	U46	UL73	53	BLRF1	53	(10)	(9A)	(UL49a)	
U47	-	70579	69638	Y	69235*	313	46.6/25.4	U47	UL74							
U48	-	72889	70817	Y	70714	690	63.7/39.0	U48	UL75	22	BXLF2	22	39	37	UL22	Glycoprotein H
U49	+	73003	73722	Y	73765*	239	68.6/51.9	U49	UL76	20	BXRF1	20	37	35	UL24	Fusion protein
U50	+	73538	75202	Y	76287	554	73.4/54.9	U50	UL77	19	BVRF1	19	36	34	UL25	Virion protein
U51	+	75304	76188	Y	76287	294	64.6/36.1	U51	UL78	74						GCR, opioid ^R homolog
U52	-	76949	76185	Y	75932	254	79.9/55.5	U52	UL79	18	BVRF1.5a/b	18				
U53	+	76957	78495	Y	79010	512	67.1/52.4	U53	UL80	17	BVRF2	17	35	33	UL26	Protease/assembly protein
U54	-	79870	78503	Y	78443	455	66.3/41.4	U54	UL82/83							Tegument protein transactivator
U55A	-	81201	79918	Y	79891	427	56.8/32.6	U55	UL84							Replication function?
U55B	-	82577	81285	Y	79891	430	46.4/20.7	U55	UL84							Replication function?
U56	-	83511	82630	Y	82431	293	82.6/65.2	U56	UL85	26	BDLF1	26	43	41	UL18	Capsid protein
U57	-	87551	83514	Y	83098	1,345	82.6/68.4	U57	UL86	25	BcLF1	25	42	40	UL19	Major capsid protein (MCP)
U58	+	87563	89890	Y	90111*	775	75.7/61.3	U58	UL87	24	BcRF1	24				
U59	+	89838	90881	Y	90942*	347	58.9/38.7	U59	UL88							
U60	-	92005(A)	90878	N	90793	394	86.9/75.7	U60	UL89x2	29b	BDRF1	29b	44	42	UL15x2	Late spliced gene (U60/U66) DNA packaging
U62	+	92017	92244	Y	92564	75	81.7/50.7	U62	UL91	30	BDLF3.5	30				
U63	+	92216	92281	Y	93008	211	84.5/71.8	U63	UL92	31	BDLF4	31				
U64	+	92829	94148	Y	94363*	439	64.5/40.7	U64	UL93	32	BGLF1	32	45	43	UL17	
U65	+	94111	95103	Y	95318	330	77.1/60.1	U65	UL94	33	BGLF2	33	46	44	UL16	
U66	-	95985	95122(D)			309	76.2/62.3	U66	UL89x1	29a	BGRF1	29a	47	45	UL15x1	Late spliced (U60/U66) DNA packaging
U67	+	95984	97024	Y	97041	346	70.3/51.7	U67	UL95	34	BGLF3	34	(48)	(46)	(UL14)	
U68	+	97024	97868	Y	97971*	114	71.1/48.9	U68	UL96	35	BGLF3.5					
U69	+	97371	99011	Y	99096*	546	71.8/54.0	U69	UL97	36	BGLF4	36	49	47	UL13	Phosphotransferase
U70	+	99013	100455	Y	100554	480	72.5/52.0	U70	UL98	37	BGLF5	37	50	48	UL12	Alkaline exonuclease
U71	+	100392	100613	Y	100609*	73	64.4/53.4	U71								
U72	-	101676	100636	Y	100640*	346	81.1/59.0	U72	UL100	39	BBRF3	39	52	50	UL10	Integral membrane protein (gM)
U73	+	101693	104456	Y	104067	787	75.4/58.2	U73					51	UL9	Origin-binding protein (OBP)	
U74	+	104007	105986	Y	106055	659	64.4/40.6	U74	UL102	(41)	(BBLF3)		(54)	(52)	(UL8)	Helicase/primase complex
U75	-	106743	105973	Y	105977*	256	64.9/45.6	U75	UL103	42	BBRF2	42	55	53	UL7	
U76	-	108589	106667	Y	106633*	640	78.5/59.7	U76	UL104	43	BBRF1	43	56	54	UL6	Virion protein?
U77	+	108435	110897	Y	111009	820	85.7/74.9	U77	UL105	44	BBLF4	44	57	55	UL5	Helicase
H5	+	112811	113311	N	114614	166										
U79	+	113502	114203	Y	114614	233	70.6/44.7	U79	UL112							HCMV replication, spliced (UL112/UL113)
H6	+	114257	114505	N	114614	82	64.1/48.7	U79(C)								HHV-6 U79 homology (C terminus)
U80	+	114557	115189	N	115347*	210	57.0/40.4	U80	UL113							HCMV replication, spliced (UL112/113)
U81	-	115948	115184	Y	115161	254	79.1/58.5	U81	UL114	46	BKRF3		61	59	UL2	Uracil-DNA glycosylase
U82	-	116778	116038	Y	115986	246	62.1/40.0	U82	UL115	(47)	(BKRF2)		(62)	(60)	(UL1)	Glycoprotein L
U84	-	118043	117111	Y	116463*	310	65.7/46.5	U84	UL117							Spliced in HCMV
U85	-	118913	118071	Y	117885	280	60.8/37.7	U85								OX-2 homology, glycoprotein
U86	-	122708	119091	Y	119082	1205	57.0/41.4	U86	UL122							IE-A, HCMV IE2 homology
U89	-	128668	125420	Y	125424*	1,082	60.7/36.4	U89								IE-A, transactivator

U90	-	129051	128776	N		91	69.6/39.1	U90	IE-A, exon in HHV-6
U91	+	129122	129625	Y	130111	167	47.7/27.0	U91	
H7	+	130829	132112	Y	132157	427			DraI repeats
U95	+	133382	136204	Y	136293	940	52.8/29.7	U95	MCMV IE2 homolog, US22 gene
H8	-	136579	136307	Y	136257	90			
U98	-	138451	137945	N		168	52.2/31.2	U98	Homology to HHV-6 gp82/105
U99	-	138692	138375	N		105	61.3/37.6	U99	Homology to HHV-6 gp82/105
U100	-	138999	138751	Y		82	44.4/23.5	U100	Homology to HHV-6 gp82/105
H1'	+	139080	139589	N	139900*	169			
DR1'	+	139415	139873	N	139900*	152	57.1/44.0	DR1	US22 gene family, DR1/DR6 homology
DR2'	+	139945	141147	N	142964*	400	58.1/37.0	DR2	US22 gene family
H2'	+	141314	141553	Y	142964*	79			
DR6'	+	141609	142097	Y	142964*	161	71.6/58.8	DR6	US22 gene family, DR1/DR6 homology
DR7'	+	142169	142957	Y	142964*	262	77.8/60.5	DR7	US22 gene family, transactivator
H3'	-	143271	143023	Y	142087	82			
H4'	-	143792	143496	Y	142087	98			

A compilation of reading frames of HHV-7 strain JI, from Nicholas (1996). ^a HHV-7 ORFs are named after their HHV-6 homologs (Gompels, et al., 1995); ORFs unique to HHV-7 are prefixed with "H" and numbered 1 to 8.

^b The positions and orientations of the ORFs are indicated, together with the positions of the first downstream polyadenylation signals (AATAAA, ATTAAG*). Polyadenylation signals overlapping ORF C-terminal sequences are indicated (+). Determined (U16/U17Ex) and predicted (U60/U66) splice donor (D) and acceptor (A) sites are indicated.

^c The sizes of ORF translation products (starting at the N-terminal methionines where these occur) in amino acids (aa) are shown.

^d The values for percent similarity (% Sim) and identity (% Id) between HHV-7 and HHV-6 homologs are based on BESTFIT alignments (Devereux *et al.*, 1984), with gap and length weights set at 3.0 and 0.1, respectively.

^e Homologous genes were identified by database searches and pairwise alignments. Listings of homologous genes were based on these analyses and on data from comparisons of other herpesvirus proteins (Albrecht, *et al.*, 1992; Chee *et al.*, 1990; Gompels *et al.*, 1995; McGeoch, 1989). Genes that show only limited sequence similarities to HHV-7/HHV-6/HCMV genes but are colinear (and in some cases functionally analogous) are given in parentheses.

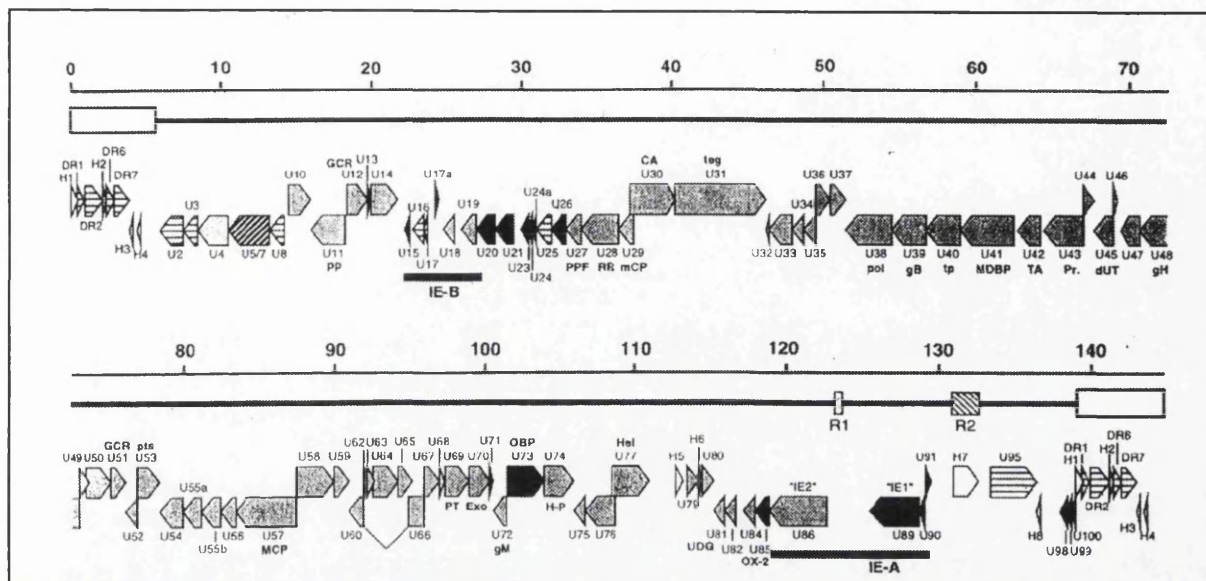


Fig. 6. Genetic layout of the HHV-7 genome.

Predicted HHV-7 gene organisation, from Nicholas (1996). Repeat regions are boxed and the long unique (UL) region is indicated by a solid line. Protein coding regions are indicated as open arrows. Several are homologous to HHV-6 genes (solid areas) and HHV-6/HCMV genes (shaded areas). Genes apparently unique to HHV-7 are unshaded. Lightly shaded ORFs (horizontal lines) correspond to members of the US22 gene family (DR1, DR2, DR6, DR7 and U95 are not conserved in HCMV).

HHV-7 ORFs with homologs in HHV-6 are named after their HHV-6 counterparts; HHV-7 unique ORFs are prefixed with "H" and successively numbered (from left to right on the genome). ORF U5/7 encodes a translation product with N-terminal homology to HHV-6 U7 (and HCMV U28) and C-terminal homology to HHV-6 U5 (and HCMV U27). Abbreviations are: pp, pp100 structural phosphoprotein; GCR, G-protein-coupled receptor; PPF, DNA polymerase processivity factor; RR, ribonucleotide reductase; mCP, minor capsid protein; CA, capsid assembly protein; teg, large tegument protein; pol, DNA polymerase; gB, glycoprotein B; tp, transport protein; MDBP, major DNA-binding protein; TA, herpesvirus conserved transactivator; Pr., primase; dUT, dUTPase; gH, glycoprotein H; pts, protease/assembly protein; MCP, major capsid protein; PT, phosphotransferase; Exo, alkaline exonuclease; gM, glycoprotein M; OBP, origin binding protein; H-P, helicase-primase complex component; Hel, helicase; UDG, uracil-DNA glycosylase; OX-2, OX-2 membrane antigen.

In common with HHV-6, HHV-7 has repetitive sequences upstream of the IE-A locus, designated R1 and R2. HHV-7 R1 is located between U86 and U89 in an analogous position similar to the R2 repeat in HHV-6. HHV-6 R2 is an array of TG repeats but HHV-7 R1 is complex, described as comprising two complete 84 bp repeats and two 67 bp partial repeats, with multiple copies of a simple repeat (TAAAT) scattered within and around the larger repeats. HHV-7 R2 is homologous to HHV-6 R3 (Gompels *et al.*, 1995; Martin *et al.*, 1991a, b) and is located upstream from the IE-A locus. It is described as comprising 16 well conserved 105 bp repetitive motifs, flanked by two copies of a partially conserved repeat. Size heterogeneity in this region of the HHV-7 genome has been reported, and may correspond to different numbers of 105 bp repeats in different viral isolates (Ruvolo *et al.*, 1996).

HHV-7 does not contain an equivalent of the HHV-6 R1 repeat present in U86 (Nicholas, 1994), although the HHV-7 U86 gene product does contain a region which is similarly rich in serine and basic residues at a corresponding location.

As in HHV-6, the HHV-7 genome contains arrays of human telomere-like tandem repeats ($[(GGGTTA)_n]$ and related sequences) close to both ends of DR (Secchiero *et al.*, 1995; Ruvolo *et al.*, 1996). The HHV-7 telomeric repeat region at the left end of DR is longer and more complex than that in HHV-6, and that at the right end is shorter and simpler. In addition, the HHV-7 telomeric repeat regions at the right end of DR varies in length between 1.2 and 1.7 kbp in plasmid clones (Nicholas, 1996).

The function of the telomeric repeats is not known, but their presence in the genomes of several lymphotropic herpesviruses, including α -herpesviruses (MDV) and γ -herpesviruses (EHV-2) (Kishi *et al.*, 1991, 1988; Telford *et al.*, 1995), has provoked a range of suggestions. Possible functions for the telomeric arrays are mentioned in the discussion.

The origin of lytic replication (ori_L) is positioned upstream of the major DNA-binding protein gene (U41), as in HHV-6, and is closely related to, but considerably shorter than, its HHV-6 counterpart (van Loon *et al.*, 1997). HHV-7 also encodes a homologue of the α -herpesvirus origin-binding protein (U73).

1.4.6.2. Genetic organisation

The HHV-7 genome contains 101 closely packed ORFs encoded on both DNA strands, with little overlapping (Fig. 6). Splicing is thought to occur in several genes, but splice sites have been predicted only for two pairs of ORFs (U60 and U66; U17 and U16).

1.4.6.3. Gene complement

HHV-7 gene functions have been inferred from previous experimental findings with other better characterised herpesviruses (notably HSV-1, HCMV and HHV-6) or from the functional characteristics of cellular homologues (see Table 3). The arrangement of the genes within the HHV-7 genome is shown in Fig. 6, and the gene arrangements of HCMV, HHV-6 and HHV-7 are compared in Fig. 5. HHV-6 and HHV-7 are very similar in gene layout, and predicted protein sequences are generally well conserved (as listed in Table 3).

Eight HHV-7 ORFs (H1-H8) lack detectable counterparts in HHV-6, and 22 HHV-6 ORFs lack HHV-7 counterparts (LT1, DR3, DR4, DR5, DR8, LJ1, U1, U6, U9, U12EX, U22, U61, U78, U83, U87, U88, U92, U93, U94, U96, U97, RJ1). Thus, HHV-7 lacks an equivalent of the AAV-2 *rep* gene. Gene fusion and duplication events also appear to have occurred in HHV-7. Two HHV-6 ORFs (U5 and U7) are fused in HHV-7 to give U5/7. Also, U55 is duplicated in HHV-7, giving U55A and U55B.

1.5. AIMS OF THE THESIS

The project was initiated in October 1993, as a collaboration with Professor N. Frenkel (Tel-Aviv University, Israel) who provided genomic DNA from HHV-7 strain RK. The aims were to determine the complete DNA sequence of HHV-7 by random shotgun cloning of genomic DNA and to interpret the coding potential of the sequence. During the course of this work the complete DNA sequences of HHV-6 strain U1102 and HHV-7 strain JI were published (Gompels *et al.*, 1995; Nicholas, 1996). Therefore, the HHV-7 strain RK sequence was compared with these two sequences in order to approve evolutionary divergence and to re-evaluate the genetic content of HHV-6 and HHV-7.



Chapter 2

Materials and Methods

2.1. MATERIALS

2.1.1. Chemicals

The chemicals used were of analytical grade and most of these were supplied by BDH Chemicals or Sigma Chemical Co. Exceptions were ammonium persulphate (APS) and N,N,N',N'-tetramethylethylenediamine (TEMED) (Bio-Rad Laboratories Ltd), dGTP, dATP, dTTP, dCTP, ATP (each at 100 mM), deaza-dGTP, ddGTP, ddATP, ddTTP, ddCTP (each at 5 mM) (Pharmacia) and N,N-dimethyl formamide (Cruachem Chemicals).

2.1.2. Solutions and buffers

TE:	10 mM Tris-HCl pH 8 1 mM EDTA
10 x TBE:	109 g/l Tris 55 g/l boric acid 9.3 g/l EDTA
50 x TAE buffer:	242 g/l Tris 57.1 g/l glacial acetic acid 11.6 g/l EDTA
DF dyes:	37.2 g/l EDTA 100 g/l Ficoll 400 5 x TBE 1% (w/v) bromophenol blue
Buffer A:	330 mM Tris-acetate (pH 7.9) 100 mM magnesium acetate 660 mM potassium acetate 5 mM dithiothreitol (DTT) (supplied by Boehringer Mannheim as buffer A)

5 x ligase buffer:	250 mM Tris-HCl (pH 7.5) 50 mM MgCl ₂ 5 mM DTT 25% (w/v) PEG 6000
X-gal:	40 mg/ml 5-bromo-4-chloro-3-indoyl β -D-galactopyranoside in dimethyl formamide
IPTG:	30 mg/ml isopropylthio- β -D-galactoside
PEG/NaCl:	20% (w/v) PEG 6000 2.5 M NaCl
Phenol/TE:	phenol equilibrated with TE
Sodium acetate/ethanol:	10 ml 3 M sodium acetate (pH 5.5) 240 ml ethanol
TM buffer:	100 mM Tris-HCl (pH 8.0) 100 mM MgCl ₂
Chase solution:	0.25 mM each of dGTP, dATP, dTTP and dCTP

dNTP/ddNTP solutions: volumes are in μl

	G	A	T	C
water	2000	1000	2000	2000
0.5 mM 7-deaza-dGTP	50	1000	1000	1000
0.5 mM dTTP	1000	1000	50	1000
0.5 mM dCTP	1000	1000	1000	50
5 mM ddGTP	15			
5 mM ddATP		2		
5 mM ddTTP			50	
5 mM ddCTP				7

40% Acrylamide solution: 40% (w/v) Acrylogel 5 premix; deionised

Top gel mixture: 460 g/l urea
0.5 x TBE
acrylamide solution to 6% (v/v)

Bottom gel mixture: 460 g/l urea
50 g/l sucrose
50 mg/l bromophenol blue
2.5 x TBE
acrylamide solution to 6% (v/v)

Formamide dyes: 1 g/l xylene cyanol FF
1 g/l bromophenol blue
10 mM EDTA
in deionised formamide

50 x TAE buffer/formamide solution: 960 μl deionised formamide
40 μl 50 x TAE

2.1.3. Enzymes

All restriction endonucleases and buffers were obtained from Bethesda Research Laboratories (BRL) or Boehringer Mannheim. Other enzymes included:

Calf intestinal phosphatase (1 unit/ μ l):	Boehringer Mannheim
T4 DNA polymerase (3 U/ μ l):	Boehringer Mannheim
T4 DNA ligase (4 U/ μ l):	Stratagene
Klenow fragment of <i>E. coli</i> DNA polymerase I (20-50 U/ μ l)	provided by Dr. E.A.R. Telford (Joyce and Grindley, 1983)

2.1.4. Radiochemicals

Deoxyadenosine (^{35}S) thiophosphate (dATP ^{35}S) (NEG0345; Du Pont)	Specific activity: 500 Ci/mmol (12.5 $\mu\text{Ci}/\mu\text{l}$)
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2.1.5. Bacterial growth media

2YT broth:	85 mM NaCl 1% (w/v) bactopectone 1% (w/v) yeast extract
L-Broth:	177 mM NaCl 1% (w/v) bactopectone
L-Broth Agar:	1.5% (w/v) agar in L-broth
Top agar:	0.6% (w/v) bacto-agar in water

2.1.6. Bacterial strains

Escherichia coli MAX Efficiency DH5 α F'IQ competent and lawn cells (phenotype: F' ϕ 80d/lacZ Δ M15 Δ (lacZYA-argF)U169 *deoR* *recA1* *endA1* *hsdR17* (*r_k⁻*, *m_k⁺*) *supE44* λ - *thi-1* *gyrA96* *relA1/F'* *proAB*⁺ *lacI^qZ Δ* M15 *zzf::Tn5*[Km¹]) were used (Gibco-BRL).

2.1.7. DNA

HHV-7 (strains RK) genomic DNA was provided by Prof. N. Frenkel (Tel-Aviv University). Bacteriophage M13mp19 RF I DNA (0.01 μ g/ μ l) and DNA markers (123 bp DNA ladder (1 μ g/ μ l) and 100 bp DNA ladder (1 μ g/ μ l)) were obtained from Gibco-BRL. Oligonucleotide primers were synthesised by Dr J McLauchlan, Mr J McGeehan and Mr R Reid using a Cruachem PS250 DNA synthesiser.

2.1.8. Miscellaneous

The following items were used in addition to standard laboratory materials and equipment:

Whatman 3 MM chromatography paper:	Whatman International Ltd
Kodak X-OMAT XS-1 film:	Kodak Ltd
BioMax MR autoradiographic film:	Kodak Ltd
Electroporator II and electroporation cuvettes 0.1 cm:	Invitrogen
EDP-Plus and EDP-Plus M-8 pipettes:	Rainin Instrument Co. Inc.
Geneclean II Kit:	BIO 101, Inc.
S/P Multi-Tube Vortexer:	Baxter
ECPS 3000/150 Electrophoresis constant power supply:	Pharmacia

2.2. METHODS

2.2.1. PREPARATION OF DNA

2.2.1.1. Production of viral DNA

The production of viral DNA was carried out in the laboratory of Professor N Frenkel. Four samples of HHV-7 RK genomic DNA, totalling several micrograms, were provided.

Human cord blood mononuclear cells (CBMCs) were treated with phytohemagglutinin for 2 days in RPMI 1640 medium containing 10% (v/v) fetal calf serum, 50 mg/ml gentamycin (Frenkel *et al.*, 1990; Berneman *et al.*, 1992a; Black and Pellett, 1993). The cells were then incubated for 2 h at 37° with concentrated aliquots of HHV-7 (RK). Following adsorption, the cells were diluted with medium to 10⁶ cells/ml (approximately 300 ml total), and incubated further at 37° (Frenkel and Rapaport, 1995). The typical cytopathic effect (CPE) of HHV-7 infection, characterised by ballooning of cells and the appearance of limited syncytia, became evident at about 14 days after infection. The cells were harvested by centrifugation, rinsed in phosphate-buffered saline and pelleted by once more. The cells were resuspended in 10 mM Tris-HCl pH 7.5, 10 mM NaCl, 1.5 mM MgCl₂, 0.6% (v/v) Nonidet P40, Dounce homogenised and separated into nuclear and cytoplasmic fractions by centrifugation. The fractions were treated with 0.5% (w/v) sodium deoxycholate and incubated with 50 mg/ml DNase I and 10 mg/ml RNase A, and capsids were prepared by density centrifugation on sucrose gradients as described by Gibson and Roizman (1972) and Vlazny *et al.* (1982). DNA was extracted from capsids by SDS-proteinase K lysis as described by Di Luca *et al.* (1990).

2.2.1.2. Restriction enzyme digestion

Digestion of DNA using restriction enzymes was carried out in accordance with the manufacturer's instructions. A typical digest would involve 1 U of enzyme per 0.5 µg DNA in a volume of 20 µl, incubated for 1 h at 37°.

2.2.1.3. Agarose gel electrophoresis

100 ml of 0.6-1.5% (w/v) agarose in 1 x TBE (or TAE) was dissolved by boiling and allowed to cool to 65°. The agarose was poured into a horizontal slab gel template (15 cm x 10 cm) that had been sealed with tape and contained a Teflon well-forming comb. When the agarose was set the tape was removed, and the gel was placed into an electrophoresis tank and filled with 1 x TBE buffer. DNA samples (along with appropriate size markers) were mixed with 0.2 volumes of DF dyes prior to loading. Following electrophoresis at 100 V for 1-2 h, the DNA was stained for 30 min with 0.5 µg/ml ethidium bromide (EtBr) in 100 ml 1 x TBE. The DNA was visualised by short wave UV transillumination (302 nm) for analytical gels or by long wave UV transillumination (365 nm) for preparative gels. The gels were photographed using a photo-imager system (Appligene).

2.2.1.4. Precipitation of viral DNA

50% PEG was mixed with HHV-7 genomic DNA containing 1 M NaCl to a final concentration of 8% and incubated overnight at 4°. The DNA was pelleted by centrifugation for 10 min at 12,000 rpm, washed twice with 95% ethanol, dried in a lyophilizer, and resuspended in 50 µl of water. 5 µl was electrophoresed on a 1.5% agarose gel (containing 1 x TBE) for 2 h at 50 V. The DNA was stained with EtBr and photographed.

2.2.1.5. Sonication of viral DNA

50 µl of HHV-7 genomic DNA prepared by PEG precipitation was placed in a 1.5 ml microfuge tube and sonicated in a Pulsatron sonicating waterbath for 60 sec. 5 µl was electrophoresed at 50 V for 2 h on a 1.5% agarose gel (containing 1 x TAE). The gel was stained with EtBr and photographed.

2.2.1.6. Size selection of sonicated DNA fragments

50 µl of sonicated DNA fragments was mixed with 10 µl of DF dyes and loaded on a 1.5% (w/v) agarose gel (containing 1 x TAE). A 100 bp ladder was included as a

DNA marker in a separate lane. The samples were electrophoresed at 50 V for 2 h. The agarose gel was divided in two halves, and the half containing the DNA ladder was stained with EtBr and photographed. Reassembly of the gel over a UV light source made it possible to excise blocks of agarose containing DNA fragments of a specific size without the need to contaminate the DNA with EtBr stain. Thus, 400-700 bp fragments of DNA were separated from the bulk of the randomly sonicated DNA.

2.2.1.7. DNA purification using GeneClean

Sonicated DNA was recovered from the agarose blocks using a commercial kit (GeneClean II). The blocks were mixed with three volumes (1 g/ml) of sodium iodide solution, and incubated at 55° until the agarose had dissolved. 6 µl of 'Glassmilk' silica matrix (which binds DNA in the presence of high concentrations of sodium iodide) was added to each sample and mixed by rotation for 30 min. The silica was pelleted by brief centrifugation and the supernatant was removed. The silica was resuspended by vortexing in 200µl of wash solution and pelleted. This was repeated three times and the silica allowed to air dry for 12 min. The pellet was resuspended in 25 µl of TE and the DNA was eluted by incubation at 55° for 5 min. The silica was pelleted by brief centrifugation and the DNA solution was transferred to a fresh microfuge tube and stored at -20°.

2.2.2. PREPARATION OF TEMPLATES

2.2.2.1. T4 DNA polymerase end repair

45 µl of sonicated DNA fragments was mixed with 5.0 µl of 10 x Buffer A, 5.0 µl of 2 mM dNTPs and 3 µl (3U) of T4 DNA polymerase, and incubated for 1 h at 37°. The end-repaired DNA was purified by phenol/chloroform extraction and ethanol precipitation. The purified DNA was dissolved in 20 µl of TE.

2.2.2.2. Preparation of M13mp19 *Sma*I

20 µg of M13 mp19 RF I DNA (1 µg/µl) was added to 191 µl of water and mixed with 10 µl (100 U) of *Sma*I, 4 µl (4 U) of calf intestinal phosphatase and 25 µl of 10 x Buffer A, and incubated for 5 h at 25°. The linearized, dephosphorylated M13 DNA was purified by phenol/chloroform extraction and ethanol precipitation and resuspended in water at 0.1 µg/µl.

2.2.2.3. Ligation

2 µl of sonicated, end-repaired HHV-7 DNA fragments was added to 9.5 µl of water and mixed with 2 µl (0.2 µg) of *Sma*I-cleaved, dephosphorylated M13 mp19 RF DNA, 4 µl of 5 x ligase buffer, 2 µl of 10 mM ATP and 0.5 µl (2 U) of T4 DNA ligase and incubated overnight at 16°. Two 20 µl control ligations were also employed, both lacking HHV-7 DNA fragments and one lacking ligase. The ligations were diluted to a final volume of 100 µl with water and the DNA was purified by careful phenol/chloroform extraction and ethanol precipitation. The ligated DNA was resuspended in 50 µl of water and stored at -20°.

2.2.2.4. Transfection and electroporation

300 ml of L-broth agar was melted in a microwave oven, cooled to approximately 50° and poured into ten 90 mm Petri dishes. The plates were allowed to set and were then dried open and inverted for 1 h at 37°.

100 µl of competent *E. coli* cells (DH5αF') was added to a precooled 15 ml Falcon 2006 tube, followed by 5 µl of ligated DNA. The cells were mixed gently with the DNA and incubated on ice for 30 min. The cells were transformed by heat shock at 43° for 2 min and placed on ice for 2 min. The transformed cells were then transferred to 15 ml of top agar containing 50 µl of IPTG, 100 µl of X-gal and 1 ml of a fresh overnight culture of *E. coli* DH5αF' (grown in 2YT broth). The top agar

was spread onto the L-broth agar plates (3 ml/plate) and allowed to set for 30 min. The plates were inverted and incubated overnight at 37° and stored at 4° for up to 20 days. A typical transfection would yield a mixture of blue plaques (phage without insert) and clear plaques (phage containing insert DNA).

Electroporation was employed as an alternative method of transfecting bacterial cells. *E. coli* (DH5 α F') cells were grown to mid-log phase in 400 ml of L-broth, chilled, centrifuged at 3,000 rpm in a Sorvall RC-5B superspeed centrifuge for 30 min, and then washed extensively with water to reduce the ionic strength of the cell suspension. The cells were resuspended in 10% glycerol at a concentration of 3×10^{10} cells/ml, frozen in dry ice, and stored at -70°.

Electroporation was carried out according to the manufacturer's instructions (Invitrogen). 2 μ l of ligated DNA was mixed with 50 μ l of electrocompetent cells, deposited into an 0.1 cm electroporation cuvette, which was electropulsed at 1500 V, with a capacitance of 50 μ F and a resistance of 150 Ω . 200 μ l of a fresh overnight culture of *E. coli* (DH5 α F') was added to facilitate transfer of the samples to tubes containing top agar, IPTG and X-gal, as described above. The top agar mixtures were spread onto the L-broth agar plates, which were then inverted, incubated overnight at 37° and stored at 4°.

2.2.2.5. Preparation of DNA templates

200 ml of 2YT broth was inoculated with 2 ml of a fresh overnight culture of *E. coli* (DH5 α F') grown in 2YT broth. 1.2 ml aliquots were dispensed into six 24 well plates. Clear recombinant M13 plaques were visualised on a light box and transferred to the wells using sterile cocktail sticks. The plates were incubated at 37° for 6 h in a humidified benchtop shaking incubator. 1 ml aliquots were transferred to 1.5 ml microfuge tubes and centrifuged for 5 min at 12,000 rpm to pellet the bacteria. The supernatants were tipped into fresh tubes, and 120 μ l of

20% PEG/2.5M NaCl was added. The samples were mixed vigorously and incubated overnight at 4°.

Phage was pelleted by centrifugation for 5 min at 12,000 rpm and the supernatants were aspirated using a water pump. Each pellet was resuspended in 100 µl of TE and mixed vigorously with 50 µl of phenol/TE for 1 min using a multitube vortexer. The samples were vortexed twice more with time intervals of 1 h and 10 min, respectively, between vortexing. Following centrifugation at 12,000 rpm for 2 min, the upper aqueous layer were transferred to fresh tubes. 250 µl of sodium acetate/ethanol was added to each tube, and the samples were mixed several times by inversion and incubated overnight at -20°.

Phage DNA was pelleted by centrifugation for 5 min at 12,000 rpm. The supernatants were aspirated using a water pump, and the pellets were washed with 500 µl of 95% ethanol. The ethanol was aspirated using a water pump and the pellets were air dried at 37° for 30 min, dissolved in 30 µl of TE, and transferred to 96 well microtitre plates. The plates were sealed and stored at -20°.

2.2.3. DNA SEQUENCING

2.2.3.1. Preparation and deprotection of primers.

Oligonucleotides were eluted from the column matrix in 1.5 ml of ammonia and deprotected by incubation at 55° for 5 h. The oligonucleotides were lyophilised overnight, resuspended in 200 µl of water and stored at -20°.

2.2.3.2. Polyacrylamide gel electrophoresis

The purity of freshly prepared oligonucleotides was checked by electrophoresis on a 16% polyacrylamide gel.

Two well washed glass plates separated by 1.5 mm spacers were sealed with 38 mm Scotch electrical tape and secured by two large foldback clips positioned over each spacer. 125 μ l of 25% (w/v) APS and 125 μ l of TEMED were added to 50 ml of acrylamide solution in 1 x TAE. The mixture was poured into the gel sandwich, and a 20 tooth Teflon well-forming comb was inserted. The gel was allowed to set for 10 min before the clips and tape were removed from the bottom of the gel. The gel sandwich was secured to the electrophoresis apparatus and 1 l of 1 x TAE buffer was added to the electrophoresis tanks.

5 μ l of each oligonucleotide solution was mixed with 5 μ l of TAE/formamide solution, denatured for 5 min at 100°, and cooled on ice for 5 min. The 20 tooth Teflon comb was removed from the gel and the samples were loaded onto the wells alongside a 10 μ l marker sample of formamide dyes. The samples were electrophoresed at 150 V for 3 h until the bromophenol blue dye had migrated half-way through the gel. The gel sandwich was removed from the electrophoresis apparatus and the plates were separated. The gel was covered with clingfilm and placed on a fluorescent screen, visualised by shading under UV irradiation and photographed.

2.2.3.3. Annealing primer

Annealing reactions were carried out in 96 well microtitre plates. DNA templates were thawed and vortexed briefly, and 4.5 μ l from each template was transferred to a fresh microtitre plate using an EDP-Plus M-8 pipette. 15 μ l of annealing mixture (225 μ l M13 specific primer (diluted 1:1000), 180 μ l TM buffer and 1095 μ l water) was dispensed onto the wall of each well using an EDP-Plus pipette. The microtitre plate was sealed, vortexed and briefly centrifuged in a Beckman GPR tabletop centrifuge. The plate was incubated at 37° for 30 min and stored at -20°.

2.2.3.4. Sequencing reactions

Template DNA was sequenced by the dideoxynucleotide chain termination method based on that of Sanger *et al.* (1977). Sequencing reactions were performed in 96 well microtitre plates, each plate providing material sufficient for eight sequencing gels. Annealed DNA templates were thawed and briefly vortexed. 2.5 µl of annealed template DNA was transferred into each of four wells (for G, A, T, or C reactions) in four fresh 96 well microtitre plates using an EDP-Plus M-8 pipette.

Four sequencing mixtures sufficient for 96 sequencing reactions were made up: 10 µl 0.1M dithiothreitol (DTT), 250 µl of the appropriate dNTP mixture (dGTP, dATP, dTTP or dCTP), 8 µl dATP³⁵S and 2 µl Klenow fragment (diluted 1:15). 2.5 µl aliquots from these mixtures were dispensed to the sides of appropriate wells using an EDP-Plus pipette. The microtitre plates were sealed, vortexed and briefly centrifuged in a Beckman GPR tabletop centrifuge, and incubated at 37° for 10 min. Using an EDP-Plus pipette, 2.5 µl of chase solution (containing Klenow fragment) was aliquoted to the side of every well. The microtitre plates were sealed, vortexed, centrifuged and incubated at 37° for 10 min. The sequenced templates were stored at -20°.

2.2.3.5. Sequencing gel electrophoresis

Buffer gradient gels were prepared in pairs or groups of four. For each gel, two clean siliconised glass plates were polished with 95% ethanol, and the sequencing gel sandwich assembled around a pair of vertically positioned (0.4 mm) spacers. The sandwich was sealed on the sides and bottom using 38 mm Scotch electrical tape and secured with two large foldback clips positioned over each spacer.

60 ml of top gel mixture (TGM) and 12 ml of bottom gel mixture (BGM) were cooled on ice. 25 µl or 95 µl respectively of 25% (w/v) ammonium persulphate (APS) was dispensed into the BGM and TGM solutions. The same volumes of TEMED were also dispensed and the two solutions were mixed.

12 ml of polymerising TGM were drawn into a 25 ml pipette, followed by 12 ml of polymerising BGM. The interface was disturbed with a few air bubbles and the mixture was pipetted slowly into the gel sandwich. Bubbles were dislodged by striking the glass plates vigorously. The remaining 35 ml of polymerising TGM was dispensed evenly into the sandwich and bubbles were removed. The gel sandwich was placed almost horizontally and two narrow 24 lane sharks-tooth combs were inserted adjacently, 0.5 cm into the gel (teeth uppermost). Three large foldback clips were positioned to secure the combs, and the gel was allowed to set for 30 min. The clips and the tape from the bottom of the gel sandwich were removed. The gel was clamped into a BRL model S2 sequencing kit and the reservoirs were filled with 0.5 x TBE. The combs were removed from the gel and the well was washed out three times with 0.5 x TBE using a 60 ml syringe fitted with a needle.

Several non-buffer gradient gels were also made. These were assembled identically to the buffer gradient gels mentioned above but lacked BGM and were comprised wholly of TGM.

The microtitre plate containing sequenced templates was thawed, and 2.5 μ l of formamide dyes were added to each well using an EDP-Plus pipette. The covered plate was vortexed briefly, placed in a boiling waterbath for 1 min to denature the samples and chilled on ice for 5 min. The combs were repositioned with their teeth touching the surface of the gel, and 2 μ l from each well were loaded onto the gel from left to right, in the order GATC.

Samples were electrophoresed on buffer gradient gels at 60W until the lower dye front (bromophenol blue) reached the bottom of the gel (approximately 2 h). The gel sandwich was removed from the sequencing apparatus, and the glass plates were separated using the point of a pair of scissors. The gel was soaked three times with 10% acetic acid for 5 min in a fume hood, transferred onto two sheets of

3 MM paper, and covered with clingfilm. The gel was dried on a gel drier for 1 hour at 80° under vacuum and exposed to X-ray film overnight.

2.2.4.0. GENOME ASSEMBLY AND ANALYSIS

2.2.4.1. Reading and assembly of sequences

DNA sequence data were read from the autoradiographs using a computer-linked gel reading device (Summagraphics digitizer) and were labelled according to template number on the microtitre plates. The database was compiled by a computer-driven process of overlapping individual sequences, using version 1.0 of Staden's sequence assembly package (SAP) (Staden, 1987). Software was operated in a DEC Alpha 2100 computer.

2.2.4.2. Analysis of the completed sequence

The completed DNA sequence of HHV-7 RK was manipulated and analysed using the Wisconsin package, Genetics Computer Group (GCG) Madison, Wisconsin (Devereux *et al.*, 1984), running on Open VMS AXP, version 7.1. Several of the programs used are listed below. Assemble was used to construct the genome sequence from the database consensus sequence. Composition was used to determine the nucleotide composition of the sequence. Gap was used to align the DNA and protein sequences. Candidate open reading frames were identified using Frames. Findpatterns was used to identify candidate polyadenylation sites. Codon usage was examined using Codonfrequency and Codonpreference. Hydrophobicity profiles were prepared using PepPlot, using the parameters described by Kyte and Doolittle (1982). DNA sequences were translated using Ptrans (Taylor, 1986).

Chapter 3

Results

3.1. RANDOM SHOTGUN SEQUENCING

Of the complete herpesvirus sequences obtained in this Institute, four (CCV, EHV-1, EHV-2 and EHV-4) were determined by direct random shotgun sequencing of genomic DNA (Davison, 1992; Telford *et al.*, 1992, 1995, unpublished data). The procedure has been described by Davison (1991) and involves sequencing by the dideoxynucleotide chain termination technology (Sanger *et al.*, 1977) large numbers of random genomic DNA fragments generated by sonication of genomic DNA and cloned directly into bacteriophage M13 vector. The DNA sequences are visualised by autoradiography following electrophoresis on high resolution denaturing gels, and "read" using a computer linked gel reading device (usually a digitiser). A database is compiled using Staden's sequence assembly program (SAP) (Staden, 1987) and every nucleotide in the completed sequence is manually checked on both strands and edited by reference to the autoradiographs. Lastly, the sequence is analysed using programs from Wisconsin Package Version 9.0, Genetics Computer Group (GCG), Madison, Wisconsin. For this project, given the limited availability of HHV-7 DNA, the whole procedure was tested using HSV-1 DNA until good quality sequence data was reliably produced.

3.2. PREPARATION OF VIRAL DNA

Viral DNA was produced in the laboratory of Professor Niza Frenkel at the Tel-Aviv university, Israel, and the procedure is described in Section 2.2.1.1. Four samples of HHV-7 RK genomic DNA (HHV-7 a to d), totalling several micrograms, were provided by Professor Frenkel.

3.3. PREPARATION OF SEQUENCES

3.3.1. Identity and purity of the DNA

The identity of one representative sample was checked by restriction endonuclease analysis with *Hind*III and *Sa*I, followed by agarose gel electrophoresis (Fig. 7). Although the restriction patterns were somewhat blurred, they appeared to match published profiles (Wyatt and Frenkel, 1992), thus confirming that this sample was HHV-7 RK DNA.

Aliquots of the four samples were assessed for contamination with smaller DNA fragments by electrophoresis. A few micrograms of full length genomic DNA was detected in each sample

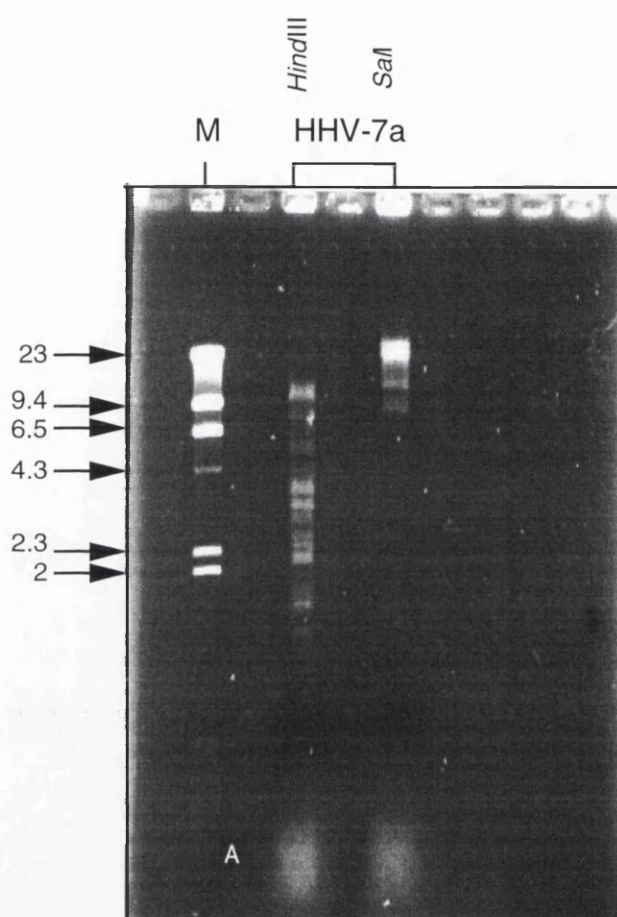


Fig. 7. *HindIII* and *Sal I* restriction profiles of HHV-7 RK genomic DNA .

The EtBr-stained 0.7% (w/v) agarose gel shows HHV-7a DNA digested with *HindIII* or *SalI*. M is a *HindIII* digest of bacteriophage lambda DNA as size marker (kbp). A is smaller size DNA contamination.

(Fig. 8). Each sample also contained a much larger amount of smaller DNA fragments. HHV-7b and d displayed a smear of larger size DNA contamination (smaller than genome size, up to several kbp), and HHV-7d additionally contained smaller size (100 bp or less) fragments. HHV-7a and c showed no evidence of larger size DNA contamination, but did contain substantial amounts of smaller size fragments. Prior to purification, at least 50% of each HHV-7 DNA sample was estimated to comprise the contaminating smaller DNA fragments. The provenance of these fragments was not determined, and they may represent residual genomic or cellular DNA degraded during treatment of capsids with DNase.

Based on the predicted size of the HHV-7 genome (145 kbp; Black and Pellett, 1993), completion of the DNA sequence was calculated to require 5,000-5,500 clones (200-230 sequencing gels). A contamination level of 10% (involving an additional 560 clones) might have been acceptable, but 50% contamination would have doubled the size of the task. Thus, starting with DNA that was as pure as possible was fundamental to the efficiency of the project.

3.3.2. DNA purification

One sample of genomic DNA (HHV-7a; cytoplasmic fraction), which was heavily contaminated with fragments smaller than 100 bp (Fig. 8), was purified by precipitation using 8% polyethylene glycol (Section 2.2.1.5.). This step effectively removed the contaminating DNA (Fig. 9). An attempt was made also to purify the remaining samples (HHV-7b, c and d), by centrifugation on a glycerol gradient, as described by Van Zijl *et al.* (1988), but only a very small quantity of full-length DNA was finally recovered (data not shown).

3.3.3. Fragmentation of the DNA

It was important to start with fragmented DNA of an appropriate size (400-700 bp). If the fragments were too large they would not ligate efficiently into the M13 vector, and this would have increased the amount of effort needed to generate the required number of clones. Equally, if the fragments were too short, more M13 recombinants would have contained multiple inserts, and this would have increased the number of non-contiguous sequences in the database.

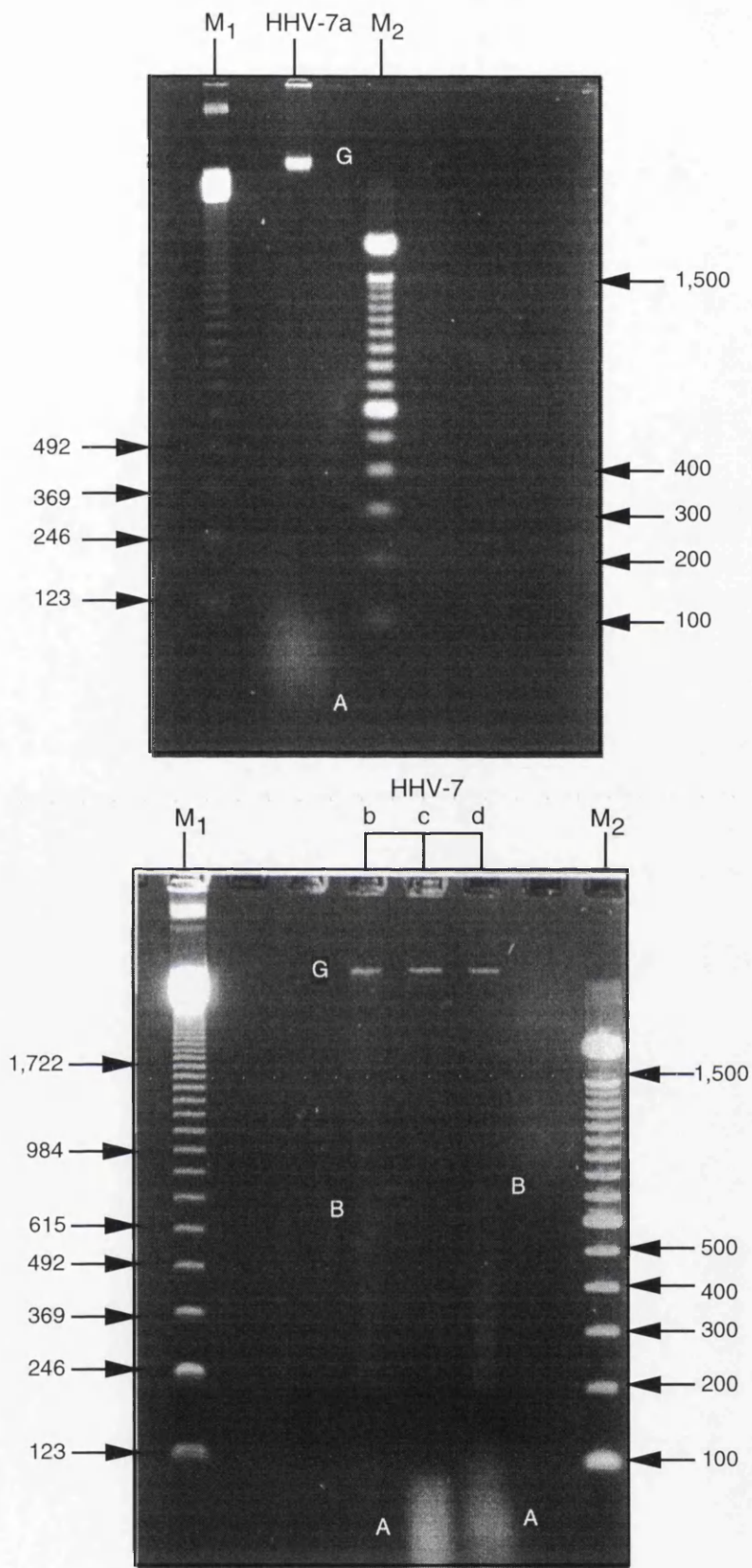


Fig. 8. Status of HHV-7 strain RK genomic DNA

The EtBr-stained 0.7% (w/v) agarose gels show untreated HHV-7 a to d. G is full length genomic DNA, A and B are smaller and larger size contaminants, respectively, M1 and M2 are 123 bp and 100 bp DNA ladders as markers.

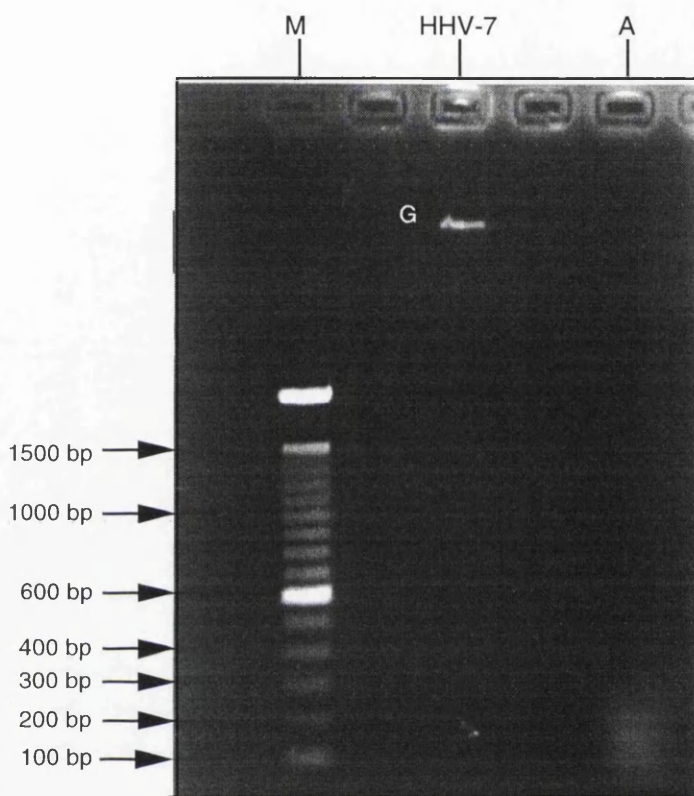


Fig. 9. Purification of HHV-7 RK genomic DNA.

The EtBr-stained 0.7% (w/v) agarose gel shows PEG-precipitated HHV-7 RK genomic DNA. G is full length genomic DNA precipitated by PEG, and A is small size contaminants. M is a 100 bp DNA ladder as markers.

50 μ l of purified genomic DNA from sample HHV-7a was fragmented by sonication. 5 μ l of sonicated DNA was visualised by electrophoresis to assess the extent of fragmentation, and a sufficient proportion of the DNA was found to be close to 600 bp in size (Fig. 10). The remaining 45 μ l of DNA was electrophoresed on an agarose gel, utilising a 100 bp DNA ladder as a marker. The agarose gel was divided into two halves and the half containing the marker was stained with EtBr. The gel was reassembled and the marker visualised by long wavelength UV irradiation. Sonicated HHV-7 fragments in the range of 400-700 bp were excised from the gel (Fig. 11), and purified using a GeneClean II kit. The purified DNA fragments were resuspended in 50 μ l of TE, and an aliquot of 5 μ l was visualised by electrophoresis to assess recovery (Fig. 12).

3.3.4. End repair and ligation

In order to clone the sonicated DNA fragments into the vector it was necessary to repair any ragged ends. The fragments were treated with T4 DNA polymerase in the presence of the four dNTPs to produce flush ends, and ligated into dephosphorylated *Sma*I-cleaved bacteriophage M13 mp19 RF I DNA.

3.3.5. Transfection and electroporation

DNA templates were generated by transfection of ligated DNA into *E. coli* DH5 α F', as described in Section 2.2.2.3.. A typical transfection yielded a mixture of blue (M13 phage lacking insert) and clear plaques (M13 phage containing HHV-7 insert DNA). Plaque numbers were invariably low, probably as a result of the small amount of HHV-7 DNA in the ligation. In an attempt to enhance the yield, electroporation was employed as an alternative. It was not, however, more efficient. In total, approximately 600 clones were made by electroporation.

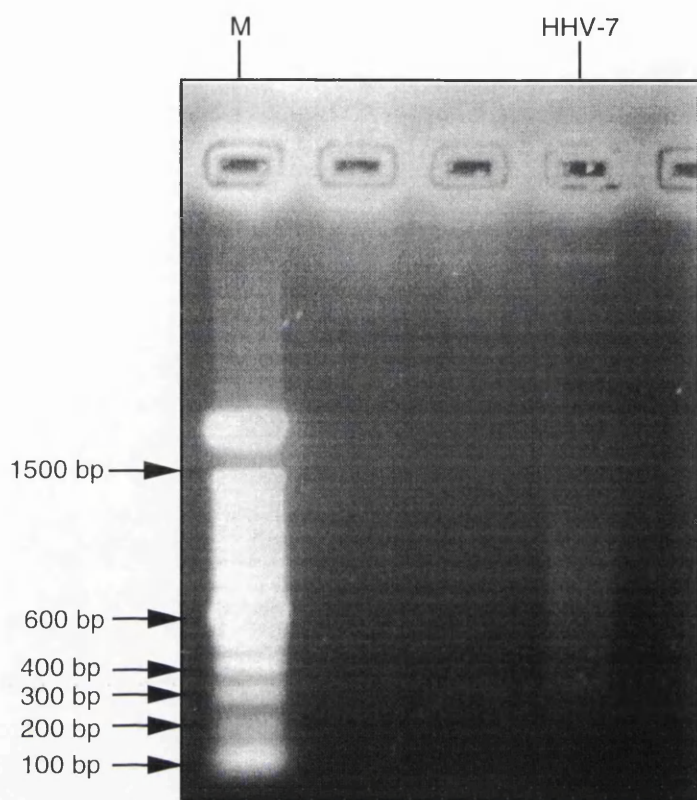


Fig. 10. Status of randomly fragmented HHV-7 RK genomic DNA.

The EtBr-stained 0.7% (w/v) agarose gel shows HHV-7 DNA randomly fragmented by sonication. M is a 100 bp DNA ladder as markers.

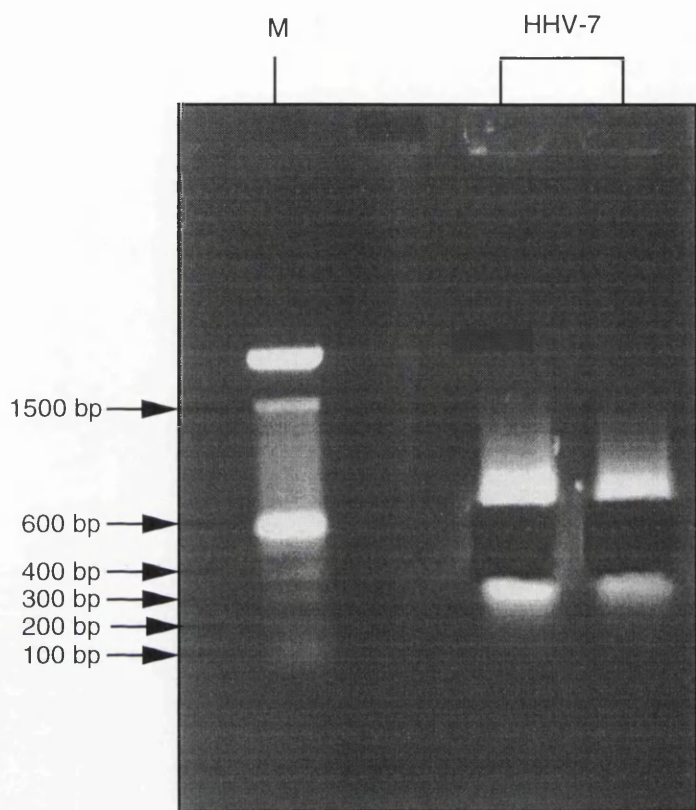


Fig. 11. Recovery of 400-700 bp fragments from randomly fragmented HHV-7 RK genomic DNA.

The EtBr-stained 0.7% (w/v) agarose gel shows randomly fragmented HHV-7 DNA following excision of the 400-700 bp fragments. M is a 100 bp DNA ladder as marker.

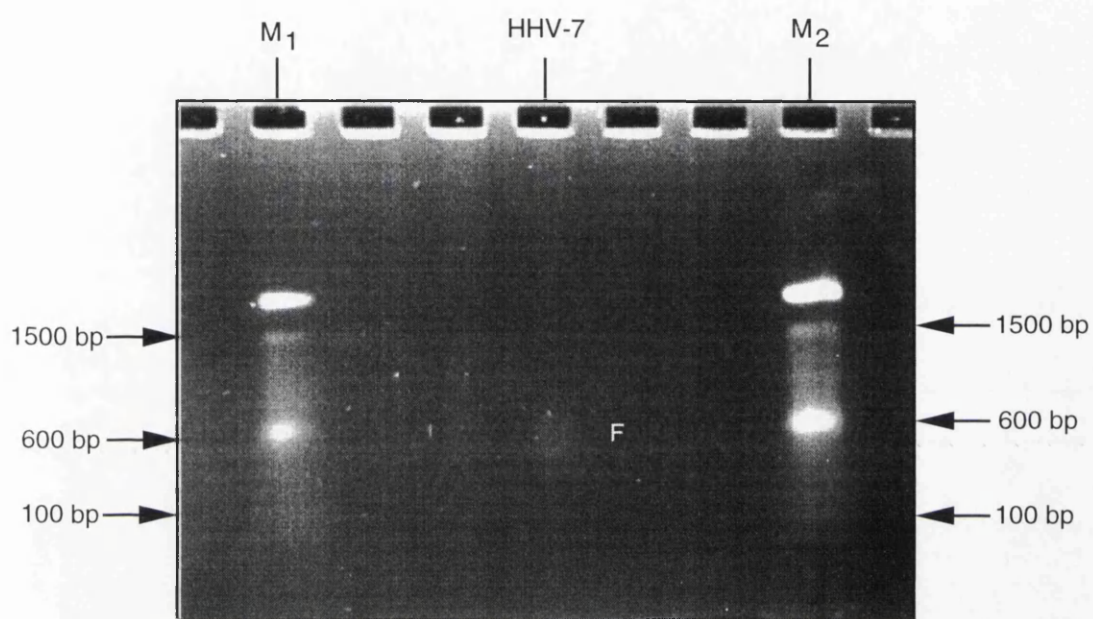


Fig. 12. Recovered 400-700 bp fragments of HHV-7 RK genomic DNA.

The EtBr-stained 0.7% (w/v) agarose gel shows 400-700 bp randomly generated fragments of HHV-7 RK DNA (F), M1 and M2 are 100 bp DNA ladders as markers.

3.3.6. Growth of recombinant phage

Growth and harvesting of clones was usually spread over three days, and clones were processed in sets of 144. On the first day, clear plaques were picked from agar plates, and recombinant phage was grown in small cultures of *E. coli* and precipitated overnight by PEG precipitation. On the second day, phage was pelleted and template DNA extracted using phenol, ethanol precipitated and resuspended.

Initially, 5,200 templates were generated, but this number proved to be insufficient owing to a significant number of poor quality templates. A further 1,800 templates were prepared and sequenced in order to bring the project to a successful conclusion. This brought the final number of templates to approximately 7,000.

3.3.7. Sequencing

Typically, templates were sequenced in batches of 96 or 192. Templates were loaded on gels in batches of 24, and the gels were run in groups of two, four or eight. In total, about 290 sequencing gels were involved in the project. Autoradiographs were read into a computer using a Summagraphics digitizer and an average of 207 nucleotides were obtained from each template, although sequences of over 300 bp were not obtained uncommonly. Rare templates with very short inserts (less than 30 bp) were ignored, along with poor quality sequences. The templates were stored in 96 well microtitre plates (74 in total). Each plate was divided into four sections (1-4) which corresponded to four sequencing gels, each accommodating 24 templates (1-24). Thus, in the database, reading 14_4.12 was for example the sequence generated from template 12 in the fourth quarter of plate 14. Thus, every sequence in the database was easily associated with the template and autoradiograph from which it was obtained.

3.4. ASSEMBLY OF THE DATABASE

The database was compiled with the aid of Staden's sequence assembly package (SAP; Staden, 1987), which facilitates computer-driven overlapping of individual complementary sequences. The general stages in the assembly of the sequence database are summarised below. Assembly of reiterated sequences presented unusual problems and is discussed in Section 4.2.7.

3.4.1. Initial assessment of DNA templates

In the initial stages of the project, a check was made on the quality and identity of the templates by entering approximately 200 sequences into SAP. A number of encouraging observations were made: the sequences were of an appropriate length; the number of overlaps between sequences was empirically similar to those found at the same stage in previous herpesvirus sequencing projects (Davison, 1991); several sequences contained a short reiteration (TAACCC) characteristic of the telomeric repeats of HHV-6 and HHV-7; and some sequences evidently originated from the HHV-7 major capsid protein gene (Mukai *et al.*, 1995). These observations provided reassurance that the majority of templates contained HHV-7 DNA.

3.4.2. Automatic input of sequence data

The progress of the assembly of the database is charted graphically on Fig. 13 and recorded in Table 4. Before being added to the database, sequences were checked for the presence of M13 vector sequence. Once entered into SAP, each batch of new sequences was automatically screened against those already in the database, with four potential outcomes. Each new sequence would: match and be joined to a stretch of contiguous sequences (contig) in the database; not match the database and be added as a single sequence contig; overlap a contig but fail to meet the entry criteria, and be rejected as a poor match; or match, and thus join, two contigs. Entry criteria included the minimum size of overlap between sequences (15 bp), the maximum percentage of non-matching nucleotides and number of padding characters needed to optimise the match. These criteria could be adjusted, but in the majority of the project were 15 bp, 12% and 8 characters, respectively. An example of entry of a single sequence resulting in the joining of two contigs is shown in Fig. 14. The new sequence overlapped two contigs and was added to the end of the contig with the closest match. The elongated contig was then compared with the second contig, in order to reassess the quality of the overlap, and the two contigs were joined.

A significant number of overlapping sequences were refused automatic entry into the database, even under the most relaxed criteria, owing to the accumulation of errors in the database. By necessity these sequences were entered manually (stage A in Table 4 and Fig. 13).

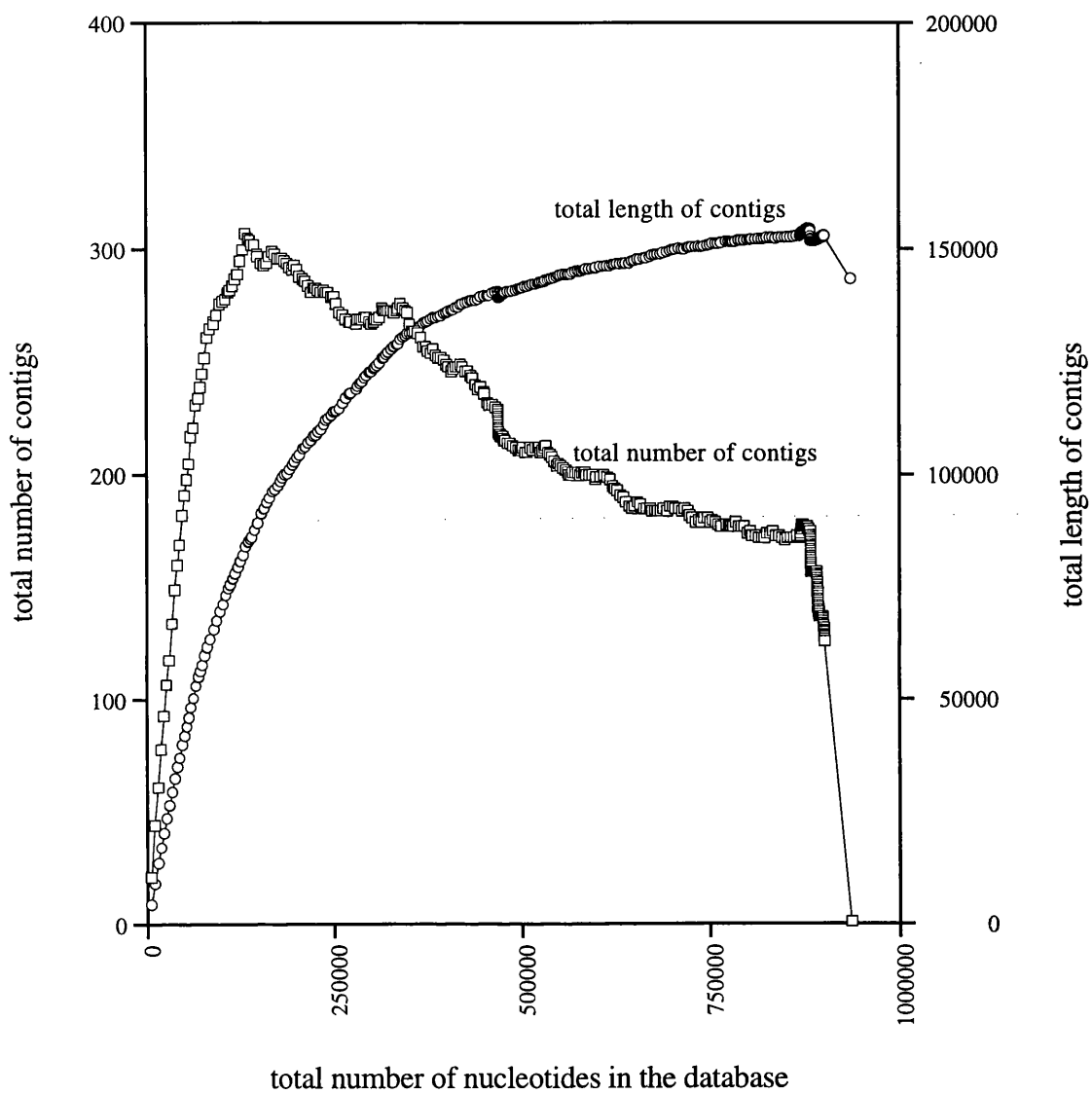


Fig. 13. Database assembly

Table 4. Stages in assembly of the HHV-7 database.

Stage	Number of Sequences	Number of Contigs	Total number of characters ¹	Total contig length
A) Automatic and manual input of sequences	4,285	170	882,813	153,712
B) Searching the database with contig ends	4,321	157	890,834	151,961
C) Entry of extended sequence data from manual reading, long gels and custom primers	4,401	126	901,286	152,952
D) Input of reiterated sequences	4,691	162 ²	-	-
E) Removal of contigs containing 1-2 sequences ³	4,522	1	936,051	143,424 ⁴

¹Total number of nucleotides and padding characters.

²The number of contigs increased because several sequences containing repeats were present in the database initially, and were duplicated when the completed repeat arrays were entered (Section 3.5).

³Duplicated contigs were also removed.

⁴The final total contig length (prior to editing), representing the unique sequence and one copy of the direct repeat.

```

Gel reading name=dp65_1.24 A
Gel reading length= 286
Searching for overlaps
Strand 1
Strand 2
No matches found
Total matches found 2 B
Trying to align with contig 4370
Padding in contig= 5 and in gel= 0 C
Percentage mismatch after alignment = 9.6
Best alignment found D
106555 106565 106575 106585 106595 106605
ATCTATAC,A AGGTTGCCT TAGATTT,GG ,AATGATCCT ,AAAATTTAA AGTTGAGTTC
***** * ***** * ***** * ***** *****
ATCTATACAA AGGTTGCCT TAGATTTTG AATGATCCT AAAAATTA AGTTGAGTTC
1 11 21 31 41 51
106615 106625 106635 106645 106655
TATATATGTT GGTATGTCA, GAGTTGTTGA TCCA--TATT ATAT
***** ***** ***** ***** * * *
TATATATGTT GGTATGTCAA GAGTTGTTGA TCCAATAAT TTA
61 71 81 91 101
Trying to align with contig 3902 E
Padding in contig= 0 and in gel= 0
Percentage mismatch after alignment = 0.7
Best alignment found
1 11 21 31 41 51
GATAATATTA TTGCTTCACA TATTGTAAG GCCTTAAAA ATAAAGATAC TATGCTTATT
***** ***** ***** ***** *****
F GATAATATTTG TTGCTTCACA TATTGTAAG GCCTTAAAA ATAAAGATAC TATGCTTATT
143 153 163 173 183 193
61 71 81 91 101 111
TTTTAAATGC CAGAGTTTGT GTTGATTGAC GTATTTTTTT AACTAAGTT GAAATTAAGT
***** ***** ***** ***** *****
TTTTAAATGC CAGAGTTTGT GTTGATTGAC GTATTTTTTT AACTAAGTT GAAATTAAGT
203 213 223 233 243 253
121 131 141
TTTTCATGTA TCGATGTGCT TTTT
***** *****
TTTTCATGTA TCGATGTGCT TTTT
263 273 283
Overlap between contigs 4370 and 3902 G
Length of overlap between the contigs= -43
Entering the new gel reading into contig 4370
This gel reading has been given the number 4401
Trying to align the two contigs
Padding in contig= 0 and in gel= 0 H
Percentage mismatch after alignment = 0.7
Best alignment found
106697 106707 106717 106727 106737 106747
J GATAATATTTG TTGCTTCACA TATTGTAAG GCCTTAAAA ATAAAGATAC TATGCTTATT
***** ***** ***** ***** *****
GATAATATTTA TTGCTTCACA TATTGTAAG GCCTTAAAA ATAAAGATAC TATGCTTATT
1 11 21 31 41 51
106757 106767 106777 106787 106797 106807
TTTTAAATGC CAGAGTTTGT GTTGATTGAC GTATTTTTTT AACTAAGTT GAAATTAAGT
***** ***** ***** ***** *****
TTTTAAATGC CAGAGTTTGT GTTGATTGAC GTATTTTTTT AACTAAGTT GAAATTAAGT
61 71 81 91 101 111
106817 106827 106837
TTTTCATGTA TCGATGTGCT TTTT
***** *****
TTTTCATGTA TCGATGTGCT TTTT
121 131 141 K
Completing the join between contigs 4370 and 3902

```

Fig. 14. Entry of a single sequence into the HHV-7 database

- A- new sequence (dp65_1.24)
- B- 1st contig (4370) matched by the new sequence
- C- details of the closeness of the match
- D- display of the match
- E- 2nd contig (3902) matched, and details of the closeness of the match
- F- display of the match
- G- new sequence joined to the end of 1st contig
- H- new sequence and 1st contig match 2nd contig
- J- display of the match
- K- contigs joined (by the new sequence)

Screening the contig ends - To reduce further the number of contigs in the database, sequences from the ends of each contig were compared against the whole database to ascertain whether any contigs could be joined (stage B in Table 4 and Fig. 13). Also, the autoradiographs from which the sequences at the contig ends had been obtained were carefully re-examined by eye with the aid of a light box, and many sequences were extended. These extended sequences were instrumental in promoting contig joining (stage C in Table 4 and Fig. 13).

Database assessment - By this stage, the database was in an advanced state. Although there were still a relatively large number of contigs, only eight contained more than two gel readings (multiple sequence contigs), and ranged in size from 300 bp to 46.5 kbp. The remainder (126 contigs) were all single sequence contigs except one, which contained two sequences. Although a few single sequence contigs overlapped poorly with the multiple sequence contigs, most did not match, even under the most relaxed conditions. In addition, the ends of three of the multiple sequence contigs and the middle of a fourth contained reiterated sequences. These were in various stages of organisation and were by no means complete.

Final joins - In order to assemble the multiple sequence contigs, several appropriate templates from the contig ends were resequenced and electrophoresed over an extended period on gels lacking a buffer gradient, in an attempt to produce elongated "reads" that might overlap other contigs. To extend these data, customised primers (Table 5) were also made to match sequences at the contig ends. The combined use of these approaches allowed the remaining multiple sequence contigs to be assembled into one large contig (Fig. 13 and stage D in Table 4).

Table 5. Custom oligonucleotide primers used to extend sequences in order to join contigs.

Primer	Sequence	Location*
P503.01	CCC AAT GAG TAC ATT	69970-84
P762.18	AAT GAC TGT GAC AAA	114893-907
P494.06	ACC GTA TTG GTA CAT	142939-53
P181.07a	GAT GAA AGA TTT CTA	115322-36
P181.07b	ACA TCG ATA CAT GAA	115184-98
P113.17a	GTC GGT GAA TGT AGA	25980-94
P113.17b	ATT ATA CTA GCA GAT	25752-66
P423.23a	GAT GTC TAT AGC ATC	46251-15
P423.23b	ATA GAT AGA GCT GAA	46440-54
P494.10	CAA TTT ACA CAT AGA	69769-83
P514.15	CAG TTA ATG TTG CCA	51777-91
P491.24a	TTG CCT TTA AAA GAA	25438-52
P491.24b	AGG AAG CAC TAC ACC	25563-77
P692.21	AAT AAC ATT GTT GAC	46829-43
P634.03	ATG GAT CAT AGA GTA	51015-29
P741.07	CAT ATC ACA GTG AGA	51355-69

*Location of the primer in the completed HHV-7 RK genome (bp), regardless of strand.

3.5. ASSEMBLY OF REITERATED SEQUENCES

Four regions containing sequences reiterated in head-to-tail orientation were observed within the database: R1, R2 and two sets of telomeric reiterations (T1 and T2). None of the regions assembled readily in the database and each had to be dealt with individually.

3.5.1. R2

R2 involved 71 sequences, each containing all or part of a 105 bp reiterated sequence. Although very similar, the reiterations were not identical and displayed nucleotide substitutions, deletions or insertions. Three approaches were attempted to determine the order of the reiterations. Firstly, a special database was created specifically for the R2 sequences. The SAP algorithm, however, lacked the sensitivity required to assemble automatically so many almost identical sequences. Secondly, each sequence was screened against the others to provide information about how they overlapped. These data were then transcribed onto a series of cards to produce a "jigsaw", each carrying one sequence name and the names of the sequences it could overlap. Eventually, most of the sequences were matched, by eye, to one of two groups. Unfortunately, the two halves of the "jigsaw" could not be joined and the arrangement of the reiteration remained incomplete. Eventually, assembly of the R2 sequences was completed by making sequence alignments by eye in a simple computer text file. Differences between the 105 bp reiterations made it possible to group overlapping sequences, and then to join groups together. During this process all of the sequences were checked against the autoradiographs and many sequences were extended. Also, templates were resequenced to lengthen some sequences. The sequences were assembled successfully and the arrangement of the 105 bp reiterations was determined. The completed sequence of RK reiteration R2 can be seen in Fig. 15, alongside its counterpart in JI.

3.5.2. R1

The R1 array has a structure like that of R2, but contains fewer reiterations and involved fewer sequences. Hence the sequence was readily determined in a manner similar to that used for R2. The completed sequence of RK reiteration R1 can be seen in Fig. 16, alongside its counterpart in JI.

RK

1 ATTTAAATCTTTGAAA. CAA. CAGGAATTGCGGTTGTCTTCTCAGCAAGTTCTACACATTCCCACTCGCTTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
2 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTACGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
3 ATTTAAATATGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTACGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
4 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGAGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
5 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
6 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
7 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGTCTTCTCAGCAGGTTTATGAGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
8 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC -
9 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGTCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC -
10 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
11 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGATTCTCACC CG. TTTAGGCAGGAAAGACCCCGACCCACATAAACCCTGAC +
12 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TT. AGGCAGGAAAGACCCGAACCACATAAACCCTGAC -
13 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCATCC G. TTTAGGCAGGAAAGACCCCGACCCACATAAACCCTGAC +
14 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGTAGGAAAGACCCGAGCCGCATATAAACCCTGAC -
15 ATTTAAATATGTGAAAATAAACAGGAAGTGGGTTATAGTTTCTAGATTTACATCTCG. CTAAGGCAGGAAAGACCTTTAACCGCAAAAGCCACTGAT *
16 TTTTAAACTTGTGAAAATAA. CAGGAA

J1

1 ATTTAAATCTTTGAAA. CAA. CAGGAATTGCGGTTGTCTTCTCAGCAAGTTCTACACATTCCCACTCGCTTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
2 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTACGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
3 ATTTAAATATGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTACGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
4 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGAGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
5 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC *
6 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGTCTTCTCAGCAGGTTTATGAGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
7 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
8 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
9 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGAGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
10 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
11 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGTCTTCTCAGCAGGTTTATGAGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC +
12 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCCAACCACATAAACCCTGAC -
13 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCGAACCACATAAACCCTGAC +
14 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCATCC G. TTTAGGCAGGAAAGACCCCGACCCACATAAACCCTGAC +
15 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGCCTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGCAGGAAAGACCCGAGCCGCATATAAACCCTGAC -
16 ATTTAAACCCGTGAAAACAA. CAGGAAGTGGGTTGACTTCTCAGCAGGTTTATGGGTTCTCACC CG. TTTAGGTAGGAAAGACCCGAGCCGCATATAAACCCTGAC *
17 ATTTAAATATGTGAAAATAAACAGGAAGTGGGTTATAGTTTCTAGATTTACATCTCG. CTAAGGCAGGAAAGACCTTTAACCGCAAAAGCCACTGAT *
18 TTTTAAACTTGTGAAAATAA. CAGGAA

Fig. 15. The structure of the R2 reiteration in HHV-7 strains RK and J1.

Nucleotides differing from the consensus 105 bp sequence are displayed as bold characters.

- * Counterparts found in both strains, in identical positions.
- + Counterparts found in both strains, in different positions.
- No counterpart found in the other strain.

RK

ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGTAAATATTTGCACATGCTAATGTGTTTCATGTGGGTAT
ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGCATATATTTGCACATACTAATGTGTTTCATGTGGGTAT
ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGCATATATTTGCACATACTAATGTGTTTCATGTGGGTAT
ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGTAAATATTTGCACATGCTAAT

Jl

ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGTAAATATTTGCACATGCTAATGTGTTTCATGTGGGTAT
ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGCATATATTTGCACATACTAATGTGTTTCATGTGGGTAT
ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGCATATATTTGCACATACTAGCATATATATGTAAT
ATGTACATATTACATAATATATGCTAGTAAATGATTACATGCACTAGTAAATATTTGCACATGCTA

Fig. 16. The structure of the R1 reiteration in HHV-7 strains RK and Jl.
Nucleotides differing those in the first repeat (84 bp) are displayed as bold characters.

3.5.3. T1 and T2

T1 and T2 comprise arrays of a simple hexameric element (TAACCC) which is similar to human telomeric sequences, plus a total of 34 types of related element, mostly hexanucleotides but some longer (Table 6). The telomeric arrays are quite different from R1 and R2. The reiterations are small and numerous and, to complicate matters further, are split between two loci near either end of DR. Neither T1 nor T2 was successfully assembled using SAP. As the telomeric elements varied in sequence, the approach used to resolve R1 and R2 was attempted. However, the large number (229) of separate sequences and reiterated elements therein made assembly by eye difficult. Thus, it was essential to simplify the data. This was done by representing each type of reiteration as a single character. The predominant element (TAACCC) was represented as a dash, and related elements were designated as letters or symbols (listed in Table 6). This made overlapping the sequences by eye much easier. As with R1 and R2, overlapping sequences were grouped, and then the groups were linked together.

Of the two telomeric reiterations, the region at the right end of DR (T2) is the smaller, containing 148 elements. A single solution which included all of the telomeric reiterations from this region was obtained quickly, and is displayed in Fig. 17. Unfortunately, assembly of the larger telomeric reiteration (T1) at the left end of DR, which apparently contains 663 elements, proved more difficult. Every sequence was checked manually and many were extended by eye or by resequencing before a solution was reached. The solution was the best that could be obtained from the available data, and is displayed in Fig. 18. It should be noted, however, that a few (less than ten) random sequences could not be incorporated. Differences between the telomeric reiterations of RK and JI are described later (Section 3.9.1.) .

Table 6. Telomeric repeat elements in HHV-7 RK, and the code used for their assembly.

Repeat ⁺	Letter code
TAACCC	-
TAAGTC	B
TAGCTC	C
TGACCC	D
CAGCCC	E
CAACCC	G
TAAGCC	H
TAAACC	J
GAACCC	K
TAGCCC	L
TAAGTTCACCC	P
TAGGGCTG	Q
TAGGTC	R
CGGCCC	S
TAAATC	T
TAGCTGC	V
TACCCT	A
AATCCC	I
AACCCC	M
AATCCG	W
AATCTC	X
GATCCC	Y
TAATCC	Z
AAACCC	U
TAACCG TAACCT TAACCA TAGGCC TCACCC TTAGCCC CAATCC TAACTC TAAGTT TCACTG TAACAC	<p style="text-align: center;">★ (rare repeats)</p>

⁺The repeat elements appear as they do in the genome sequence, and are complementary to the classic GGGTTA repeat.

RK

--* L* -L-C* C* D* -H-* CP--* DD-QS-L-ZZZL-QS-L--LQSJ---S---QS---QSKL--LQSK
L--LQS--LQSJ-LQS--QS--QS--QSK-----U-QS--QSK---QS--QS--* QS----QSKL
--DD-----

Jl

--* L* -L-C* C* D* -H-* CP--* DD-* S-L--ZZL-QS-L---QS--QSK----QS--QS--QSK-
--QS--QS--* QS----QSKL--DD-----

Fig. 17. The structure of the telomeric array (T2) from the right end of DR in HHV-7 strains RK and Jl.

The telomeric repeats are represented by a letter code, which is displayed alongside the repeats in Table 6.

RK

--C---C---B-D-B-D---C--C---L-----R---B--B-----D-C-----B--B-*B--
-----B-----B-----R---B--B-----D-C-----B---B-----B--B--
-----B-----B--B--B-----G--CH-G--CH-G--CB-G--CH-G--CH-G--CB-G--CPG--
CPG--CH-G--CH-G--CH-G--CB-G--CPG--CB-G--CB-G--CH-G--CH-G--CH-G--CH-G--CPG--
-CB-G--CB-G--CH-G--CB-G--CH-G--CB-G--CPG--CPG--CH-G--CPG--CH-G--CH-G--CH-G
--CH-G--CH-G-CPG--CH-G--CH-G--CJ-E---CB-G--CH-G--CH-G--CB-G--CB-G--CH-G--C
H-G--CH-G--CH-G--CH-G--CH-G--CB-G--CB-G--CB-G--CH-G--CH-G--CB-G--CPG--CH-G
--CB-G--CH-G--CH-G--CH-G--CH-G--CPG--CH-G--CPG--CPG--CH-G--CPG--CJ-E---CB-
G--CH-G--CB-G--CH-G--CH-E--CH-G--CPG--CB-U--CPGG-CB-U--CB-G-C*-E--C***C

JL

----CH-E--CH-G-C***C

Fig. 18. The structure of the telomeric array (T1) from the left end of DR in HHV-7 strains RK and JL.

The telomeric repeats are represented by a letter code, which is displayed alongside the repeats in Table 6.

3.6. EDITING THE DATABASE

3.6.1. Removal of single contigs

The sequence was completed without inclusion of the single sequence contigs. A very few short or poor quality single sequence contigs appeared to contain HHV-7 DNA inserts, as evidenced by partial matching of their sequences with the multiple sequence contig. However, the majority matched neither the multiple sequence contig nor each other, and were assumed to comprise cellular DNA. Thus, following entry of the completed reiterated sequences into the database (described above), the single sequence contigs were removed and the number of contigs was reduced to one (Fig. 13 and Table 4).

3.6.2. Editing the database

A paper copy of the single multiple sequence contig was printed, and every nucleotide in the sequence was checked (on both strands) by reference to the autoradiographs. There were many areas of uncertainty, and each was resolved by checking all the sequences in the region against the autoradiographs. Regions for which data were obtained on only one strand were examined particularly closely during editing. Finally, remaining ambiguities were resolved by analysis of specific templates from both strands using the universal or custom primers. Figs. 19 and 20 display the resolution of four typical errors in the database.

To correct the errors in the database, it was necessary to work from right to left along the contig, since following every correction the sequence to the right was renumbered by SAP. Manual correction of errors was time-consuming, and so corrections were entered using a batch file which could be left to run unattended. In all, the sequence was determined an average of 8.2 times per nucleotide, and 97% was determined on both strands. In addition, the proportion of random sequences obtained that did not match the final genomic sequence indicates that the DNA was 97% pure.

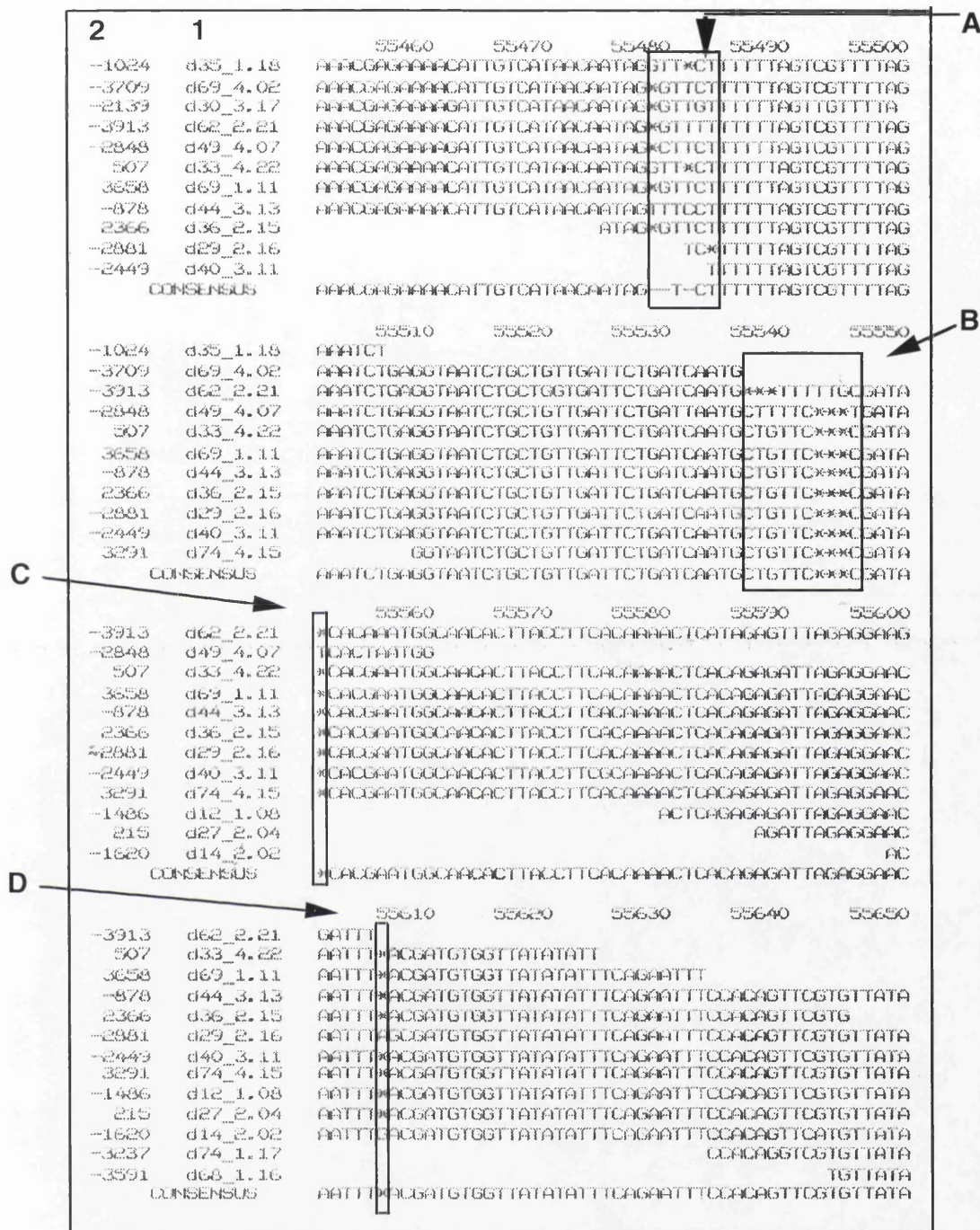


Fig. 19. Four unedited errors in the database.

The errors are all of a similar nature. A contains several sequences that are incorrect and B requires correction of two sequences, whereas C and D require single nucleotide deletions. 1 are the names of individual sequences and 2 are their SAP designations; sequences in the complementary strand are denoted with a dash. Asterisks are padding characters entered by the program.

		61240	61250	61260	A	61270	61280
-1024	d35_1.18	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
-3709	d69_4.02	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
-2139	d30_3.17	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
-3913	d62_2.21	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
-2848	d49_4.07	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
507	d33_4.22	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
3658	d69_1.11	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
-878	d44_3.13	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
2366	d36_2.15		ATAG	STTCT	TTTTTAGTCGTTT	TAGA	
-2881	d29_2.16			STTCT	TTTTTAGTCGTTT	TAGA	
-2449	d40_3.11			STTCT	TTTTTAGTCGTTT	TAGA	
	CONSENSUS	AAACGAGAAACATTGTCATACCAATAG	STTCT	TTTTTAGTCGTTT	TAGA		
		61290	61300	61310	B	61320	61330
-1024	d35_1.18	AATCT					
-3709	d69_4.02	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
-3913	d62_2.21	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
-2848	d49_4.07	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
507	d33_4.22	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
3658	d69_1.11	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
-878	d44_3.13	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
2366	d36_2.15	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
-2881	d29_2.16	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
-2449	d40_3.11	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
3291	d74_4.15	GGTAATCTGCTGTTGATTCTGATCAATG					
	CONSENSUS	AATCTGAGGTAATCTGCTGTTGATTCTGATCAATG					
		61340	61350	61360		61370	61380
-3913	d62_2.21	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
-2848	d49_4.07	AATGG					
507	d33_4.22	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
3658	d69_1.11	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
-878	d44_3.13	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
2366	d36_2.15	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
-2881	d29_2.16	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
-2449	d40_3.11	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
3291	d74_4.15	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
-1486	d12_1.08		ACTCACAGAGATTAGAGGAAACAATTT				
215	d27_2.04		AGATTAGAGGAAACAATTT				
-1620	d14_2.02		ACAATTT				
	CONSENSUS	AATGGCAACACTTACCTTCACAAAACTC	CACAGAGATTAGAGGAAACAATTT				
	D	61390	61400	61410	61420	61430	
507	d33_4.22	ACGATGTGGTTATATATTT					
3658	d69_1.11	ACGATGTGGTTATATATTT					
-878	d44_3.13	ACGATGTGGTTATATATTT					
2366	d36_2.15	ACGATGTGGTTATATATTT					
-2881	d29_2.16	ACGATGTGGTTATATATTT					
-2449	d40_3.11	ACGATGTGGTTATATATTT					
3291	d74_4.15	ACGATGTGGTTATATATTT					
-1486	d12_1.08	ACGATGTGGTTATATATTT					
215	d27_2.04	ACGATGTGGTTATATATTT					
-1620	d14_2.02	ACGATGTGGTTATATATTT					
-3237	d74_1.17						
-3591	d68_1.16						
	CONSENSUS	ACGATGTGGTTATATATTT					

Fig. 20. Correction of four errors in the database (see Fig. 19).

3.6.3. Errors in the sequence

At this stage, and not before, the completed sequence was compared to that of HHV-7 strain JI (Nicholas, 1996), using the Gap program. The RK sequence differed from that of JI at approximately 200 positions. These positions were then reassessed carefully, by reference to autoradiographs as well as by resequencing templates when appropriate. As a result, 35 errors were identified in the RK sequence and corrected. The nature of these errors and their locations in the RK genome are listed in Table 7. Errors were located in regions of the genome that had been sequenced on one strand only or were covered by a single sequence, although several were located within compressions (aberrant migration of partially base paired sequencing products).

3.7. THE HHV-7 RK GENOME SEQUENCE

The structure of the HHV-7 genome comprises a long unique sequence (U) flanked by a direct repeat (DR). However, the database contained U flanked by portions of one copy of DR, since no evidence of differences between the DR sequences emerged when compiling the database. Thus, in order to construct the genome sequence from the database consensus, it was important to define the DR sequence. This was accomplished by locating by eye the ends of the genome, which also correspond to the U-DR and DR-U junctions. It is rare for the ends of two random sequences to map at the same nucleotide, in contrast to sequences from the ends of the genome. Thus, the genome ends, which are shown in Fig. 21, are denoted by a sharp change in contig depth at two specific points in the database.

The right genome end of RK (Fig. 21a) is identical to that of JI, but the left end is one base pair shorter, containing six rather than seven C residues (Fig. 21b). Most clones from the left terminus had six C residues and none had seven. As fragments were end-repaired prior to ligation, no information was obtained on unpaired nucleotides at the genome termini.

The HHV-7 RK genome sequence was reconstructed from the database consensus sequence using the Assemble program. The sequence is 153,080 bp in length, and comprises U (133,012 bp) flanked on each side by a copy of DR (10,034 bp). Overall, the genome contains 36% G+C,

Table. 7. Errors in the DNA sequence of HHV-7 strain RK

Position (bp)		Difference ^a	Sequence change		ORF
HHV-7 RK	HHV-7 JI		RK	JI	
8219 / 151251	/ 143316	ID	A	-	non-coding
8242 / 151274	/ 143338	ID	-	T	non-coding
14051	9830	ID	-	C	U4
18376	14156	S	G	T	U8
18996	14776	ID	-	G	U10
25580	21361	ID	-	G	U14
25589	21372	ID	-	A	U14
44347	40131	ID	-	G	U30
45463	41247	ID	-	A	U31
45493	41278	ID	-	A	U31
45499	41285	S	G	A	U31
56906	52692	ID	-	A	U38
60250	56044	ID	A	-	U39
60886	56670	ID	-	C	U39
67891	63674	ID	G	-	U42
67893-4	63676-7	MS	GG	AA	U42
73894	69677	S	A	C	U47
74201	69984	ID	G	-	U47
78657	74440	ID	-	A	U50
84842	80618	ID	-	G	U55A
91135	86913	ID	-	G	U57
106813	102592	ID	-	T	U73
106819	102598	ID	-	T	U73
110369	106150	S	C	G	U75
112891	108672	ID	-	T	U77
114913	110698	ID	-	A	U77
114931-4	110717-8	ID	--	TG	U77
114936	110720	S	G	A	U77
123110	118897	ID	G	-	U85
125010	120784	ID	-	T	U86
129563	125349	S	T	G	non-coding

^a ID is insertion or deletion, S is substitution and MS is multiple substitution.

A

		DR		U		
		6159	6169	6179	6189	6199
-4516	td47_1.15	GCGCGCAGCACTCAGTGAAAAACA				
-4514	td44_4.02	*C*CGCAGCACTGAGTGAAAAACA				
-4518	td46_4.14	TCGCGCAGCACTGAGTGAAAAACA				
-4558	d34_1.10	GCGCGCAGCACTCAGTGAAAAACA				
-4503	td76_3.10	GCGCGCAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
-4510	td14_3.21	GCGCGCAGCACTCAGTGAAAAACA				
-4513	td46_2.05	TCTCACATCACTCAGTGAAAAACA				
-4557	d10_3.16	GCGCGCAGCACTCAGTGAAAAACA				
-4509	td4_4.20	GCGCGCAGCACTCAGTGAAAAACA				
-4515	td38_1.07	GCGCGCAGCACTCAGTGA				
-4504	td32_4.21	GCACGCAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
-4506	td73_3.24	GCGCGCAGCACTCAGTGAAAAACACCGTTTCGTATTTCAAATCCTAAATA				
-4512	td73_2.17	GCGCGCAGCACTCAGTGAAAAACA				
-4500	td61_3.24	GCGCGCAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
-4560	d65_2.22	GCGCGCAACACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
-4501	td66_3.23	GCGCGCAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
-4505	td29_2.11	GCGCGCAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
4508	td62_1.23	GCGCGCAG*ACTCAGTGAAACACAAGTTTGTGCACGAGAAAGACGCTGCC				
-4499	td15_2.21	GCGCGCAGCACTCAGTGAAAAACA*GTATGTGCACGAGAAAGACGCTGCC				
-4370	ED71_2.20	CAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
CONSENSUS		GCGCGCAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCC				
DR/U junction						

B

		U		DR		
		139160	139170	139180	139190	139200
4389	ED12_3.14	CTTTATGTGCAGGCTTATTC	CCCCCGTTTCGTATTTCAAATCCT			
4390	ed79_2.10	CTTTATGTGCAGGCTTATTC	CCCCCGTTTCGTATTTCAAATCCT			
4473	td65_2.04	CTTTATGTGCAGGCTTATTC	CCCCCGTTTCGTATTTCAAATC*TAAATA			
4474	td69_1.02	CTTTATGTGCAGGCTTATTC	CCCCCGTTTCGTATTTCAAATCCTAAATA			
4476	td44_3.11		CCCCCGTTTCCTATTTCAAATCCTAAATA			
4477	td52_3.09		CCCCCGTTTCGTATTTCAAATCCTAAATA			
-4475	etd10_3.12		CCCCCGTTTCGTATTTCAAATCCTAAATA			
-4478	td46_3.09	CTTTATGTGCAGGCTTATTC	CCCCCGTTTCGTATTTCAAATCCTAAATA			
4479	td43_1.08		CCCCGTTTCGTATTTCAAATCCTAAATA			
4564	d14_2.15		TTTCGTATTTCAAATCCTAAATA			
4480	td32_3.09		CGTATTTCAAATCCTAAATA			
4481	td36_2.01		CGTTTCGTATTTCAAATCCTAAATA			
4482	td44_2.18		CCCCCGTTTC*TATTTCAAATCCTAAATA			
4483	td33_2.16		GTTTCGTATTTCAAATCCTAAATA			
4484	td25_3.20		CCCGTTTCGTATTTCAAATCCTAAATA			
4485	td47_2.02		CCCCCGTTTCGTATTTCAAATCCTAAATA			
4486	td73_3.18		TATTTCAAATCCTAAATA			
4487	td19_1.17		TATTTCAAATCCTAAATA			
4563	d71_4.22		CGTTTCGTATTTCAAATCCTATTTT			
4488	td70_3.19		CCCCCGTTTCGTATTTCAAATCCTAAATA			
4565	d79_1.22		ATTTCAAATCCTAAATA			
-4489	td74_1.16		CCGTTTCGTATTTCAAATCCTAAATA			
4490	td31_3.21		CCCCCGTTTCGTATTTCAAATCCTAAATA			
CONSENSUS		CTTTATGTGCAGGCTTATTC	CCCCCGTTTCGTATTTCAAATCCTAAATA			
U/DR junction						

Fig. 21. The DR/U and U/DR junctions, or right and left ends of the genome (Figs. A and B), respectively, as represented in the database.

Sequences from the genome ends begin or terminate with DR, whereas those from within the genome span the DR/U junctions.

U and DR containing 34% and 52% G+C, respectively. The sequence has been deposited with the GenBank Data Library under accession number AF037218.

3.8. GENOME SEQUENCE COMPARISONS

Sequence comparisons were carried out using the HHV-7 RK sequence, the HHV-7 JI sequence (Nicholas, 1996; accession U43400, version 5, 22. May 1997) and the HHV-6 U1102 sequence (Gompels *et al.*, 1995; accession X83413, version 16, 17 February 1997). For certain comparisons, published sequences from other HHV-6 strains were utilised.

3.9. DIFFERENCES BETWEEN THE HHV-7 RK AND JI SEQUENCES

3.9.1. Reiterations

The sequences of HHV-7 RK and JI were compared using the Gap program and were found to differ at various locations throughout their lengths. The differences are greatest between the regions containing reiterated sequences R1, R2, T1 and T2. R1 and R2 are located toward the right end of U, whereas T1 and T2 are located near the beginning and end, respectively, of each DR (Fig. 22).

R1 in the RK sequence comprises three copies of a complex 84 bp element and one partial copy of 68 bp; the reiterations differ at two nucleotides only. The R1 arrays from RK and JI are very similar, as shown in Fig. 16. The first and second 84 bp elements in JI are identical to those in RK, but the third element is 3 bp shorter and contains several mismatches, also the partial copy is shorter (66 bp).

R2 consists of an array of 105 bp elements that differ at several positions. RK contains 15 copies of the element followed by a partial copy of 26 nucleotides, and JI has 17 elements plus the partial copy. The R2 arrays from RK and JI are compared in Fig. 15. Several reiterated elements are identical between the strains and some are positioned analogously, but other elements are unique. The arrangement of elements is similar in both strains at the extremities of the array, but differs in the central region. Interestingly, within each strain the elements closest to the edges of the array are the most imperfect.

T1 and T2 are similar in RK and JI in that they consist largely of the telomeric element TAACCC, but differ in the length of the arrays. T2 is the shorter reiteration, consisting of 148 elements and is displayed in Fig. 17, alongside the analogous reiteration in JI. T1 near the left end of DR consists of 633 elements (Fig. 18). It is likely, however, that the solution for T1 is not a correct representation of the actual sequence in this region. This aspect is taken up in the Discussion (Section 4.1.4.).

Bacterial clones containing T1 and T2 in the JI genome contain 20 and 106 copies of the repeated element, respectively (Secchiero *et al.*, 1995). Both are thus smaller than in RK, the former markedly so. Towards the edges of T2 the telomeric elements are arranged similarly between the strains, but the central portion of the RK array is absent in JI.

3.9.2. Rest of the genome

The two HHV-7 sequences also differ at many locations outside the reiterations. The validity of these differences was assessed carefully in the RK sequence, through reference to the database and the autoradiographs, in addition to resequencing several templates. Differences between the strains were thus identified as genuine differences, or errors in either the RK or JI sequences.

Errors in the RK sequence numbered 35 and are recorded in Table 7 (see Section 3.6.3.). Errors in the JI sequence were defined as deletions or insertions which caused frameshifts in coding regions identified by Nicholas (1996) that resulted in sub-optimal amino acid sequence conservation between HHV-7 and HHV-6. Only four errors were noted, two in ORF U38 (2 bp deletion at 57718 and a 1 bp deletion at 57733) and two in ORF U53 (1 bp deletion at 81361 and a 2 bp deletion, plus a 2 bp substitution at 81380), each causing a local shift from and then back into the correct reading frame (Table 8). It is possible that other differences may also result from errors in the JI sequence, but there was no evidence to support this. Therefore, all other disparities were classified as reflecting genuine strain variation. The types and distribution of the differences are listed in Table 9, and a summary is given in Table 10. Fig. 22 shows the layout of the differences between HHV-7 RK and JI, on the HHV-7 RK genome (the Fig. also includes the

Table. 8. Errors in the DNA sequence of HHV-7 strain JI

Position (bp)		Difference ^a	Sequence change		ORF
HHV-7 RK	HHV-7 JI		RK	JI	
57718	53497-8	ID	TG	--	U38
57733	53512	ID	C	-	U38
81361	77138	ID	A	-	U53
81380-3	77159-60	ID, S	CACG	---TC	U53

^a ID is insertion or deletion and S is substitution.

Table. 9. Differences between HHV-7 strains RK and JI

Genome location (bp)		Difference ^a	Nucleotide change		ORF ^b	Amino acid change	
RK	JI		RK	JI		JI	RK
4130/147175	184/139231	SS	G	A	non-coding		
4178/147223	232/139279	SS	A	T	non-coding		
4761/147806	815/139862	SS	A	G	non-coding		
5211/148256	1255/140302	NS	G	A	DR2	S	N
5572/148617	1626/140673	SS	C	G	DR2		
5836/148881	1890/140937	SS	G	C	DR2		
5986/149031	2040/141087	SS	G	C	DR2		
6058/149103	2112/141159	ID	C	-	non-coding		
6282/149327	2335/141382	SS	A	G	non-coding		
6335-6/149380-1	2388-9/141435-6	MS	TG	CA	non-coding		
6433/149478	2486/141533	SS	C	G	non-coding		
6626/149671	2679/141726	NS	A	G	DR6	N	D
7227/150272	3280/142327	SS	A	G	DR7		
7876/150921	3929/142976	ID	A	-	non-coding		
7926/150972	3978/143025	ID	A	-	non-coding		
7995/151041	4045/143092	ID	A	-	non-coding		
8618/151664	4668/143715	ID	A	-	non-coding		
8828/151873	4877/143924	SS	T	G	non-coding		
10144	5914	SS	T	C	non-coding		
10397	6177	SS	C	G	non-coding		
10429	6209	SS	C	T	non-coding		
10533	6313	SS	A	G	non-coding		
10604	6384	NS	A	G	U2	F	S
10662	6442	SS	A	G	U2		
10826	6606	NS	T	C	U2	N	S
11314	7094	NS	T	A	U2	E	D
11329	7109	SS	G	A	U2		
11663	7443	ID	A	-	non-coding		
11782-84	7561-63	MS	GGG	AAA	non-coding		
11786	7565	SS	G	A	non-coding		
11877	7656	SS	G	A	U3		
12042	7821	SS	C	T	U3		
13986	9765	SS	A	G	U4		
14532	10311	SS	A	G	U4		
15120	10899	SS	G	A	U5		
16038	11817	SS	A	T	U5		
16941	12720	NS	A	T	U7	C	S
18747	14526	SS	T	A	non-coding		
19157	14937	NS	A	G	U10	E	G
19614	15693	SS	T	C	U10		
20310	16089	NS	C	T	U11	D	N
20893	16672	SS	G	A	U11		
20896	16675	SS	A	G	U11		
20956	16735	SS	A	G	U11		
21513	17292	NS	A	G	U11	Y	H
25119	20898	SS	C	T	U14		
25532	21311	NS	G	A	U14	R	H
26264	22043	SS	T	A	non-coding		
26525	22304	SS	G	A	U15		
28914	24693	SS	G	T	non-coding		
29880	25659	ID	-	A	non-coding		
30669	26449	SS	G	A	U19		
36169	31949	ID	T	-	non-coding		
36863	32642	NS	C	G	U26	M	I
37076	32855	NS	C	G	U26	M	I
41483	37262	NS	C	T	U29	R	K
43070	38849	SS	T	A	U30		
43847	39626	SS	G	A	U30		
44420	40199	SS	T	C	U31		
45038	40817	SS	G	A	U31		
45093	40872	NS	T	A	U31	S	T
45559	41340	NS	C	A	U31	A	D
46100	41879	SS	G	A	U31		
48014	43793	NS	G	A	U31	M	I
48188	43967	SS	A	G	U31		
51648	47427	SS	C	A	U33		
54801-2	50580-1	MS	AT	GC	U37	I	A

55352	51131	SS	C	T	U37		
55388	51167	SS	C	T	U37		
57272	53051	NS	T	C	U38	K	E
57480	53259	SS	A	G	U38		
57531	53310	SS	T	G	U38		
57857	53633	SS	A	G	U38		
58092	53878	SS	G	A	U38		
58889	54675	SS	T	C	U39		
59788	55564	NS	C	T	U39	D	N
59876	55652	SS	G	A	U39		
60539	56315	SS	G	A	U39		
60683	56459	SS	C	T	U39		
61228	57004	NS	T	G	U40	N	T
61732	57508	NS	C	T	U40	G	E
62949	58725	SS	A	G	U40		
64136	59912	SS	A	T	U41		
64163	59939	SS	A	G	U41		
64535	60311	SS	A	G	U41		
66238	62014	NS	G	A	U41	P	S
66970	62746	SS	G	C	non-coding		
67524	63300	SS	A	G	U42		
69466	65242	SS	T	A	U43		
72576	68352	SS	A	G	U45		
72583	68359	SS	G	A	U45		
74828	70604	SS	A	C	non-coding		
76742	72518	NS	T	G	U48	L	F
77170	72946	ID	-	A	non-coding		
78065	73842	NS	G	A	U50	R	H
78889	74666	NS	T	G	U50	L	V
78939	74716	SS	G	A	U50		
79103	74878	NS	T	C	U50	V	A
79152	74929	SS	G	A	U50		
79305	75082	SS	T	A	U50		
79820	75597	SS	G	A	U51		
81079	76856	NS	G	A	U52	L	F
81436	77210	NS	T	C	U53	V	A
82224	77998	NS	A	G	U53	M	V
82744-7	78514	ID	TCTG	-	U54		
84702	80472	NS	A	G	U55A	F	L
84813	80583	NS	C	G	U55A	V	L
84929	80699	NS	C	T	U55A	R	K
85653	81423	SS	G	A	U55B		
87406	83176	SS	C	T	U56		
88182	83952	SS	G	A	U57		
89460	85230	SS	C	T	U57		
89493	85263	SS	T	G	U57		
90090	85860	SS	C	A	U57		
90435	86204	SS	C	T	U57		
90927	86697	SS	A	G	U57		
90996	86766	SS	A	G	U57		
92542	88312	SS	C	T	U58		
92980	88750	NS	A	C	U58	R	S
97463	93233	NS	A	G	U64	I	M
97984	93754	NS	A	C	U64	Y	I
98138	93908	SS	C	G	U64		
98853	94623	NS	T	G	U65	I	M
99922	95692	SS	A	G	U66		
101182	96952	SS	C	T	U67		
101207	96977	NS	T	C	U67	L	S
105406	101176	SS	T	C	U72		
106411	102181	SS	C	T	U73		
107348	103118	NS	C	T	U73	L	F
107938	103708	SS	G	T	U73		
109107	104877	SS	C	T	U74		
111155	106925	SS	G	A	U76		
111725	107495	SS	T	C	U76		
112108	107878	NS	T	C	U76	N	D
112448	108218	SS	A	G	U76		
113231	109001	SS	A	G	U77		
113244	109014	NS	G	A	U77	A	N
113252	109022	SS	G	A	U77		
115353	111122	ID	A	-	non-coding		
120833	116602	NS	A	T	U82	N	K
121143	116912-4	ID	-	TTC	non-coding		

121627	117399	NS	C	T	U84	E	K
121685	117457	NS	A	G	U84	I	T
123077	118849	NS	G	T	U85	S	Y
123239	119011	SS	T	G	non-coding		
123249	119021	SS	A	T	non-coding		
123309	119081-2	ID	--	TT	non-coding		
125104	120879	SS	C	T	U86		
125200	120975	SS	T	C	U86		
125389	121164	NS	G	T	U86	D	E
130991	126766	SS	T	C	U89		
131119	126892	NS	G	A	U89	P	S
131326	127099	NS	C	T	U89	A	T
134546	130318	ID	A	-	non-coding		
136728	132711-31	ID	-	TATTTA ATTATT ACTGTT TCA	non-coding		
137805	133809	NS	A	G	U95	D	G
140260	136264	SS	G	A	non-coding		
140569	136573	SS	T	C	non-coding		
140943	136947	SS	T	C	non-coding		
141306	137309	ID	A	-	non-coding		
141965	137968	NS	A	G	U100	C	R

^a ID is insertion or deletion, SS is synonymous substitution, NS is non-synonymous substitution and MS is multiple substitution.

^b Encoding potential is based on subsequent analysis in this thesis (Fig. 11).

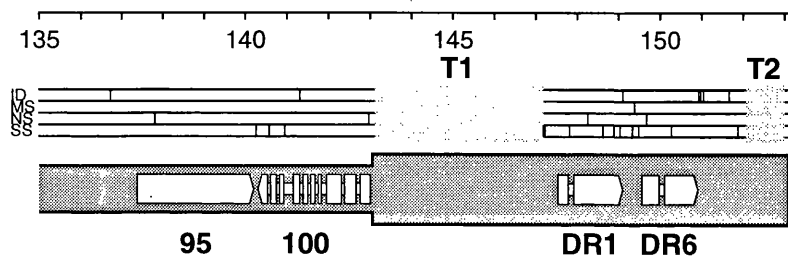
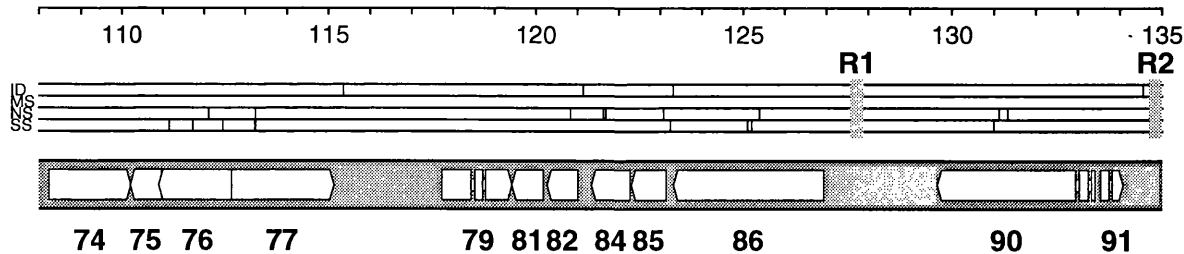
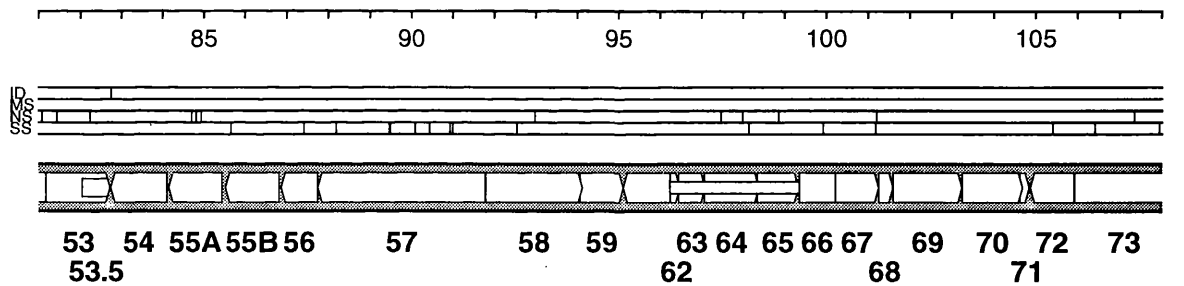
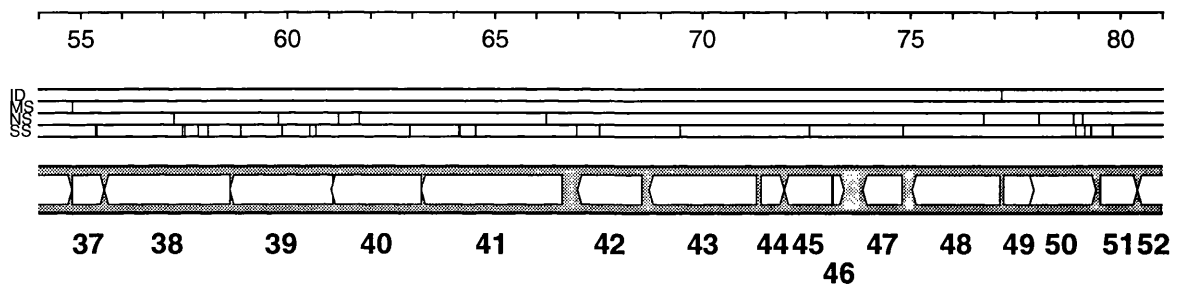
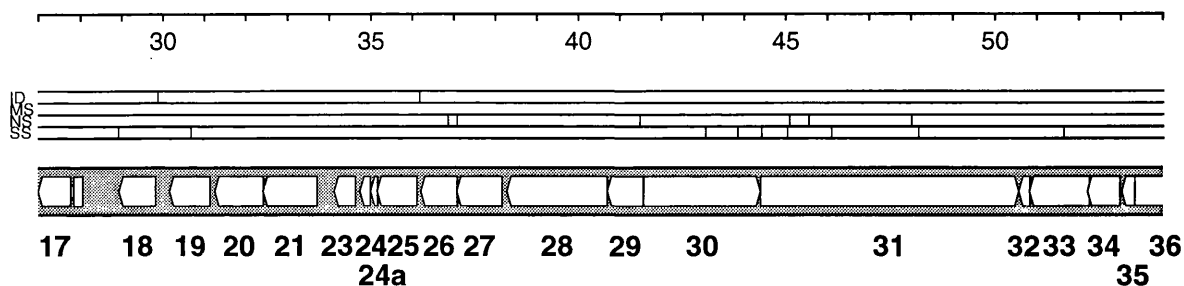
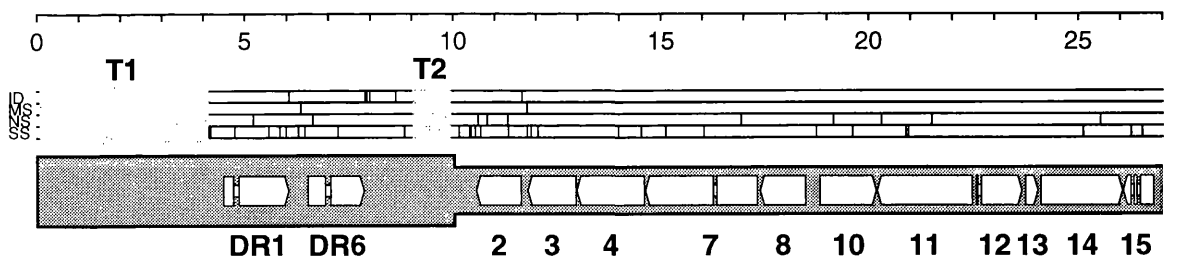
Table 10. Differences between the genome sequences of HHV-7 strains RK and JI (excuding tandem repeats)

type of difference	genome region		
	DR	U	total ^a
synonymous substitution	10	84	104
nonsynonymous substitution	2	46	50
multiple substitution	1	2	4
insertion/deletion	5	10	20
total	18	142	178

^aU plus two copies of DR

Fig. 22 Distribution of sequence differences between the HHV-7 RK and JI genomes.

The RK genome is shaded, the thinner and thicker portions denoting U and DR, respectively. The scale is in kbp. Protein-coding regions (DR1, DR6, U2-U100; deduced in Section 4.10.2) are shown as open arrows above the gene nomenclature; the U prefix has been omitted. ORFs predicted to be expressed as spliced mRNAs are connected by open horizontal bars. The differences between the strains are categorised into insertion/deletion (ID), multiple substitution (MS), non-synonymous substitution (NS) or synonymous substitution (SS), and their locations are marked. Differences within the reiterated sequences are not given, and the reiterated sequences (R1, R2, T1 and T2) are shown as shaded rectangles above the genome.



gene layout of HHV-7 which is discussed in Section 3.10.2.). As anticipated, the majority of differences do not affect coding capacity. Moreover, differences that do affect coding potential are scattered throughout the genome, and appear not to be clustered in particular genes. This indicates that no small subset of genes has been subject to unusual evolutionary pressures since divergence of the two strains.

3.10. THE GENETIC CONTENT OF HHV-7 AND HHV-6

3.10.1. Examination of coding potential

Although various criteria may be used to predict the genetic content of a nucleotide sequence, they are to some extent arbitrary. Thus, the results of such an analysis actually take the form of a spectrum of probabilities ranging from candidates with strong coding potential (usually ORFs with counterparts in other genomes), to others that are less certain (usually smaller ORFs lacking counterparts). This may lead to inclusion of false positives and false negatives into the overall picture. Also, specific factors may have a dominant effect on individual candidates regardless of other considerations; independent data on gene expression, for example.

The previous detailed predictions of the coding capacities of the HHV-7 JI and HHV-6 U1102 genomes were used as a starting point for the analysis of the genetic content of the RK sequence. An amino acid sequence counterpart in HHV-6 and a candidate polyadenylation signal close downstream or downstream from a subsequent ORF in the same orientation (i.e. expressed as part of a 3' coterminal family of genes), were the primary criteria for accepting potential HHV-7 genes. ORFs unique to each genome but substantial in size and possessing appropriate polyadenylation signals were then included. Similarities to proteins encoded by other herpesviruses and by other organisms, and potential splicing (Section 3.11.), were also taken into account. Some previously identified ORFs were excluded because they suffer from combinations of features indicating that they are less likely to encode proteins, such as small size, lack of suitable initiation codons, significant overlap with other genes, presence of reiterated sequences, absence of suitable polyadenylation signals and lack of sequence similarity to other proteins. The Codonpreference program was also used to assess whether codon usage patterns would aid identification of protein coding regions. However, codon usage

was found not to be significantly biased to help substantially. A more detailed account of the predicted coding capacities of RK sequence is given in the following subsection.

Throughout the analysis a conservative approach was taken and proposed coding was restricted to strong candidate genes only. However, this approach is biased towards the exclusion of ORFs that are unique to either HHV-6 or HHV-7 (false negatives), rather than the inclusion of ORFs that do not encode proteins (false positives). Nevertheless, each candidate gene was considered carefully in developing the following view of HHV-7 and HHV-6 gene content, both in terms of the exclusion of marginal ORFs and in identification of potentially spliced genes. Thus, this analysis is considered a more accurate representation of the genetic contents of HHV-7 and HHV-6 than were previously available.

3.10.2. The deduced layout of HHV-7 genes

The deduced layout of HHV-7 genes is shown in Fig. 23 and details are listed in Table 11. A loose copy of Fig. 23 is included at the back of this thesis. In addition, a listing of genetic features and an alignment of predicted amino acid sequences with the genome sequence is given in Appendix I. Also, evidence for splicing in several genes is discussed fully in Section 3.11.

The nomenclature for ORFs developed for HHV-6 and extended to HHV-7 JI was employed for RK, except that several ORFs potentially expressed by splicing are identified only by the 5'-proximal ORF. 19 different JI ORFs (Fig. 6, Table 3) have not been included by name in the analysis of RK (Fig. 23, Table 11). DR2, DR7, U5, U16, U17ex, U60, U80, U89, H6, H8, U98 and U99 now form exons in spliced genes (Section 3.11.2.). The remaining HHV-7 JI ORFs lacking counterparts in HHV-6 (H1, H2, H3, H4, H5 and H7), in addition to U17a, are considered unlikely to encode protein. H1 spans reiteration T1 and lacks an initiation codon. H2 is small (79 codons). H7 is also small (82 codons), and spans R2. H5 is 166 codons in length and lacks an initiation codon. Lastly, ORFs H3 and H4 are small (82 and 98 codons, respectively), lack candidate polyadenylation signals and importantly, are disrupted by insertions or deletions in RK. U17a is small (89 codons), and is not convincingly related to a corresponding HHV-6 ORF.

Fig. 23 Predicted layout of HHV-7 RK genes.

The genome is shaded, the thinner and thicker portions denoting the unique region and terminal direct repeats, respectively. The scale is in kbp. Protein-coding regions (DR1, DR6, U2-U100) are shown as open arrows above the gene nomenclature; the U prefix has been omitted. ORFs predicted to be expressed as spliced mRNAs are connected by open horizontal bars. Candidate polyadenylation signals (AATAAA, ATTAAA or AGTAAA) are indicated by vertical arrows in the appropriate strand. Reiterated sequences (R1, R2, T1 and T2) are shown as filled rectangles above the genome, and the minimal fragment shown to act as an origin of DNA replication (*ori*) is indicated (van Loon *et al.*, 1997).

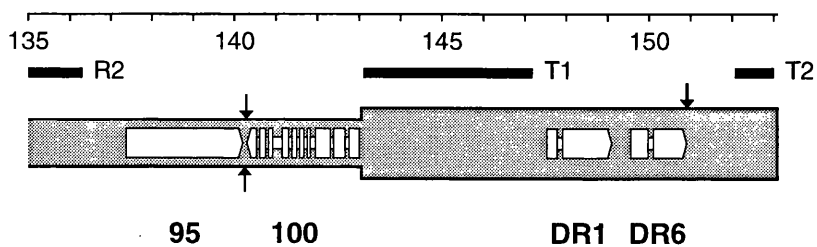
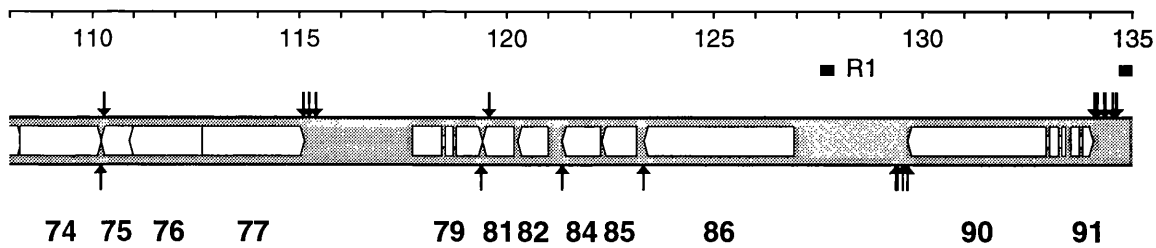
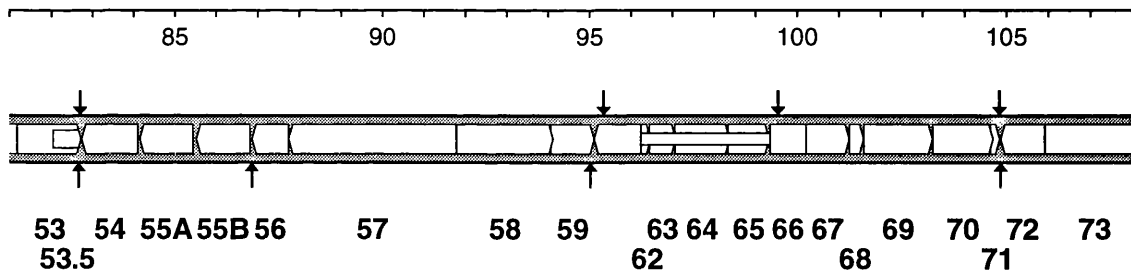
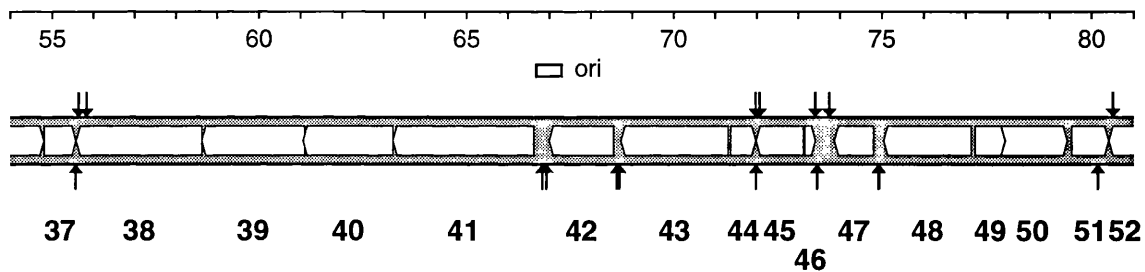
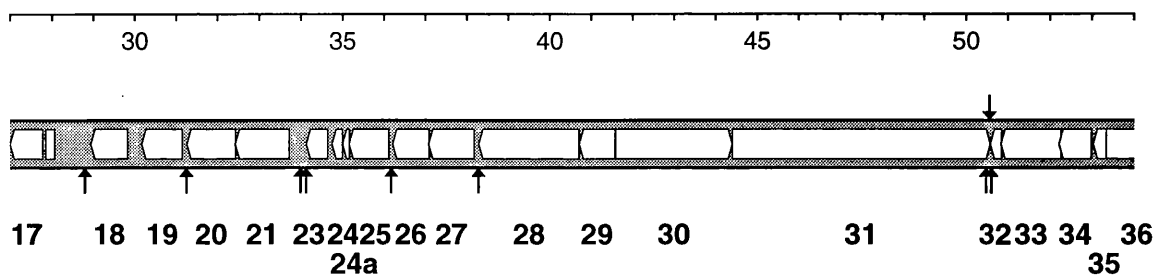
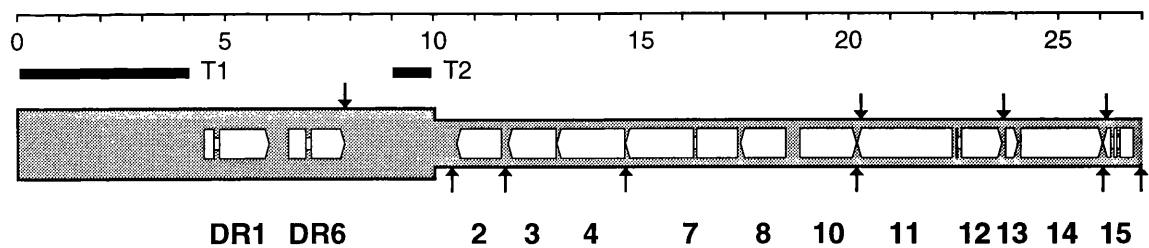


Table 11. Features of HHV-7 (RK) genes.

GENE ^a	STRAND	START ^b	STOP ^c	CODONS	ID ^d	PROPERTIES ^e	
DR1	ex1	+	4485	4728	475	33	HCMV US22 gene family; exon 1 starts at 4466
	ex2		4863	6046			
DR6	ex1	+	6509	6926	406	59	HCMV US22 gene family
	ex2		7055	7857			
U2		-	11637	10558	359	48	HCMV US22 gene family
U3		-	12953	11799	384	49	HCMV US22 gene family
U4		-	14603	12975	542	59	Related to U7 exon 2
U7	ex1	-	17324	16348	>871	54	HCMV US22 gene family (exon 1); related to U4 (exon 2); exon 1 starts at 17326
	ex2		16266	14628			
U8		-	18483	17395	362	51	HCMV US22 gene family
U10		+	18829	20184	451	50	
U11		-	22470	20203	755	31	Structural phosphoprotein
U12	ex1	+	22566	22598	333	47	G protein-coupled receptor
	ex2		22689	23657			
U13		+	23742	24038	98	33	
U14		+	24106	26052	648	50	HCMV UL25/UL35 gene family
U15	ex1	-	26785	26469	191	68	
	ex2		26393	26321			
	ex3		26249	26064			
U17	ex1	-	28057	27841	330	53	HCMV US22 gene family; IE-B ^f transactivator
	ex2		27768	26993			
U18		-	29821	28934	295	44	IE-B membrane glycoprotein
U19		-	31142	30165	325	34	IE-B protein
U20		-	32431	31256	391	22	Probable membrane glycoprotein
U21		-	33714	32422	430	31	Probable membrane glycoprotein
U23		-	34638	34123	171	-	Probable membrane glycoprotein
U24		-	34992	34744	82	28	Contains a hydrophobic domain
U24A		-	35166	34996	56	25	Contains a hydrophobic domain
U25		-	36118	35156	320	47	HCMV US22 gene family
U26		-	37090	36209	293	30	
U27		-	38172	37078	364	68	Processivity subunit of replicative DNA polymerase; [UL42]
U28		-	40705	38285	806	47	Ribonucleotide reductase large subunit [UL39]
U29		-	41568	40708	286	53	Capsid protein; component of intercapsomeric triplex [UL38]
U30		+	41583	44399	938	46	Tegument protein [UL37]
U31		+	44400	50579	2059	46	Very large tegument protein [UL36]
U32		-	50848	50576	90	66	Capsid protein; located on tips of hexons [UL35]
U33		-	52262	50829	477	59	Virion protein
U34		-	52989	52213	258	56	Membrane-associated phosphoprotein [UL34]
U35		-	53340	53026	104	58	Role in DNA packaging [UL33]
U36		+	53339	54796	485	58	Role in DNA packaging [UL32]
U37		+	54798	55577	259	62	[UL31]
U38		-	58625	55584	1013	67	Catalytic subunit of replicative DNA polymerase [UL30]
U39		-	61093	58625	822	56	Envelope glycoprotein gB [UL27]
U40		-	63221	61056	721	56	Role in DNA packaging [UL28]
U41		-	66619	63224	1131	68	Single-stranded DNA-binding protein [UL29]
U42		-	68546	66996	516	56	Post-translational regulator of gene expression [UL54]
U43		-	71310	68725	861	61	Component of DNA helicase-primase complex; primase [UL52]
U44		+	71367	71978	203	58	[UL51]
U45		-	73122	71983	379	50	[UL50] ^g
U46		+	73154	73414	86	52	Membrane protein [UL49A]
U47		-	74803	73862	313	23	
U48		-	77133	75041	690	39	Envelope glycoprotein gH; complexes with gL [UL22]
U49		+	77226	77945	239	52	[UL24]
U50		+	77761	79425	554	55	Role in DNA packaging [UL25]
U51		+	79527	80411	294	35	G protein-coupled receptor
U52		-	81172	80408	254	56	
U53		+	81180	82721	513	52	N-terminal protease domain acts in capsid maturation and is a capsid protein; C-terminal domain is the minor capsid scaffold protein [UL26]
U53.5		+	82029	82721	230	51	Major capsid scaffold protein [UL26.5]
U54		-	84100	82736	454	42	Virion transactivator
U55A		-	85431	84148	427	33	Related to U55B
U55B		-	86807	85515	430	21	Related to U55A
U56		-	87741	86860	293	65	Capsid protein; component of intercapsomeric triplex [UL18]
U57		-	91781	87744	1345	68	Major capsid protein; forms hexons and pentons [UL19]
U58		+	91793	94120	775	61	
U59		+	94068	95111	347	38	
U62		+	96247	96474	75	45	

U63		+	96446	97081	211	68	
U64		+	97059	98378	439	41	Role in DNA packaging; tegument protein [UL17]
U65		+	98341	99333	330	59	Tegument protein [UL16]
U66	ex1	-	100215	99352	663	72	Role in DNA packaging; putative terminase [UL15]
	ex2		96235	95108			
U67		+	100214	101254	346	52	[UL14]
U68		+	101254	101598	114	48	
U69		+	101601	103241	546	53	Serine-threonine protein kinase; tegument protein [UL13]
U70		+	103243	104685	480	52	Deoxyribonuclease; role in maturation/packaging of DNA [UL12]
U71		+	104622	104843	73	53	Myristylated tegument protein [UL11]
U72		-	105906	104866	346	59	Envelope glycoprotein gM; role in virion envelopment [UL10]
U73		+	105923	108286	787	58	Origin-binding protein; helicase [UL9]
U74		+	108237	110216	659	41	Component of DNA helicase-primase complex [UL8]
U75		-	110973	110203	256	45	[UL7]
U76		-	112819	110897	640	59	Minor capsid protein; role in DNA packaging [UL6]
U77		+	112665	115127	820	75	Component of DNA helicase-primase complex; helicase [UL5]
U79	ex1	+	117733	118429	506	42	Probable role in DNA replication
	ex2		118522	118712			
	ex3		118788	119420			
U81		-	120179	119415	254	58	Uracil-DNA glycosylase [UL2]
U82		-	121009	120269	246	38	Envelope glycoprotein gL; complexes with gH [UL1]
U84		-	122271	121339	310	42	
U85		-	123141	122299	280	37	Probable membrane glycoprotein; related to OX-2
U86		-	126934	123317	1205	29	IE-A ^b protein
U90	ex1	-	133408	133323	1199	28	IE-A transactivator; exon 1 starts at 133434
	ex2		133244	133033			
	ex3		132949	129648			
U91	ex1	+	133539	133740	153	27	Probable membrane glycoprotein
	ex2		133817	134076			
U95		+	137378	140201	940	25	HCMV US22 gene family
U100	ex1	-	142997	142753	603	28	Envelope glycoprotein gp105; exon 1 starts at 143000
	ex2		142658	142377			
	ex3		142303	141947			
	ex4		141826	141749			
	ex5		141672	141565			
	ex6		141494	141381			
	ex7		141298	141144			
	ex8		140914	140815			
	ex9		140742	140599			
	ex10		140532	140304			
DR1	ex1	+	147531	147774	475	33	HCMV US22 gene family; exon 1 starts at 147512
	ex2		147909	149092			
DR6	ex1	+	149555	149972	406	59	HCMV US22 gene family
	ex2		150101	150903			

^a Protein-coding exons (ex) are listed. Genes with counterparts in all mammalian herpesviruses are shaded.

^b First exons: from first nucleotide of first complete codon (U7) or initiation codon (other ORFs). Subsequent exons: from first nucleotide.

^c To last nucleotide of stop codon or exon.

^d Percentage identical amino acid residues to the HHV-6 counterpart as determined by Gap at default values; U23 proteins did not align at these settings.

^e Properties derived from the current analysis and summaries in Gompels *et al.* (1995), Nicholas (1996) and numerous other herpesvirus genome sequence papers. For genes with counterparts in all mammalian herpesviruses, the HSV-1 nomenclature is given in square parentheses; where identification is based on positional data, the HSV-1 gene is shown in italics.

^f Immediate early B locus.

^g Related to HSV-1 UL50 encoding deoxyuridine triphosphatase, but probably lacking enzymatic function.

^h Immediate early A locus.

HHV-7 RK is thus considered to contain 84 different genes, two of which (DR1 and DR6) are present twice in DR, giving a total of 86 genes in the genome (Table 11, Fig. 23). The weakest candidate, U24a, is small and poorly conserved, but encodes a protein containing a highly hydrophobic domain in both HHV-7 and HHV-6. Indeed, all of the proposed HHV-7 genes but one have clear HHV-6 homologues. The exception, U55B, is a sizeable member of a 3' coterminal family, and has been shown previously to be related to an adjacent member, U55A, which is analogous to HHV-6 U55. In addition, all of the proposed HHV-7 genes have candidate polyadenylation signals (AATAAA, ATTAATA or AGTAAA) near the 3' end of the ORF or ORF family, as shown in Fig. 23.

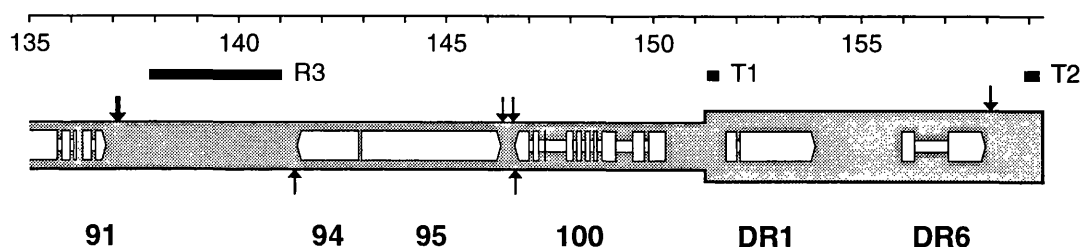
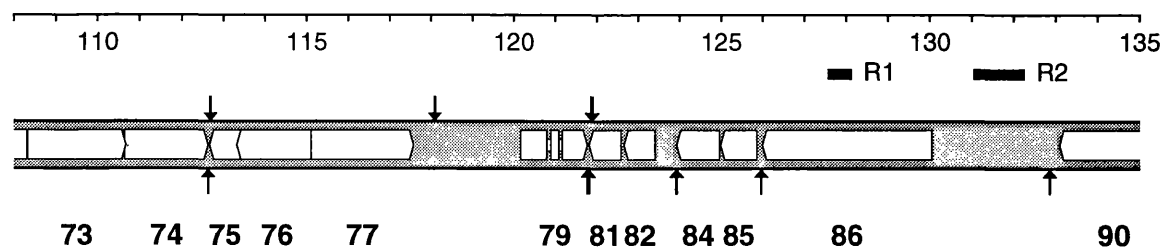
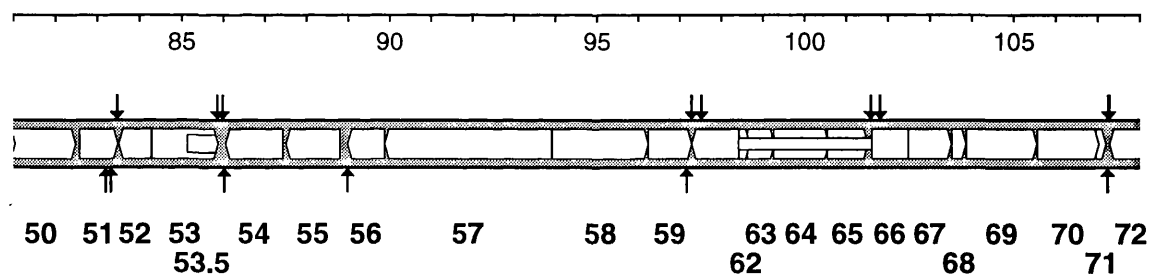
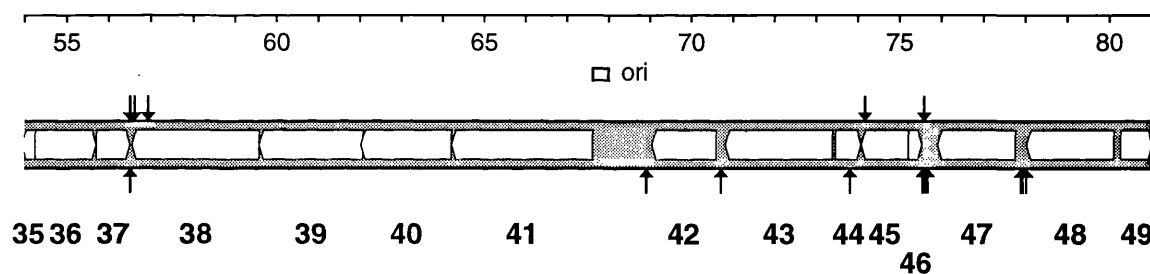
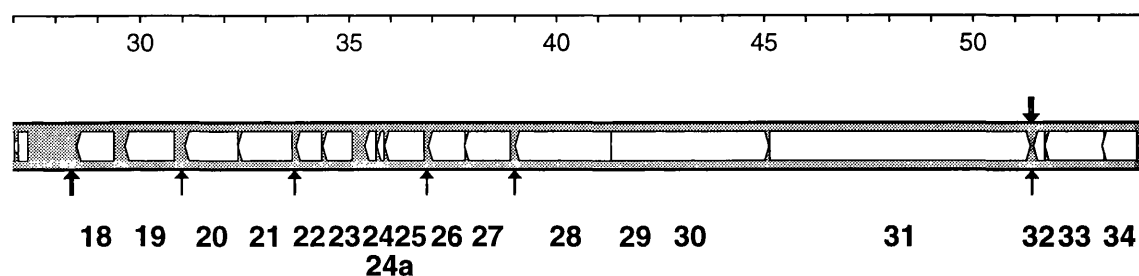
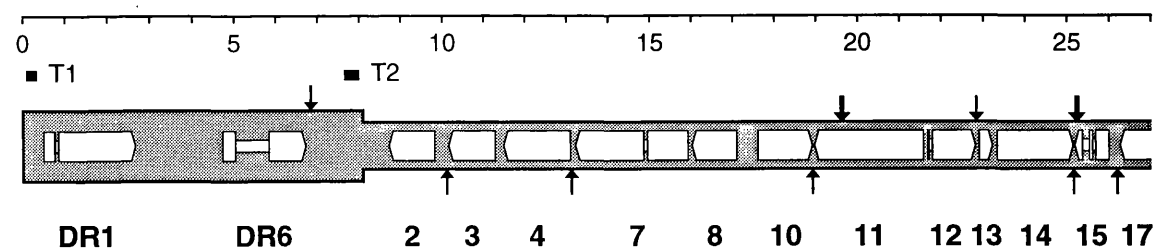
3.10.3. The deduced layout of HHV-6 genes

The criteria used above were applied to the HHV-6 U1102 sequence, and yielded the deduced gene layout, which is given in Fig. 24. The HHV-6 genome is predicted to contain 85 different genes, two of which (DR1 and DR6) are present twice in DR giving a total of 87 genes in the genome. All of the proposed genes have appropriate polyadenylation signals except U2, which has a CATAAA element instead. Of the 22 HHV-6 ORFs identified by Gompels *et al.* (1995) that lack HHV-7 counterparts, only two are strong candidates for encoding complete proteins: U22 a potential membrane glycoprotein and U94 a homologue of the adeno-associated virus type 2 *rep* gene. HHV-6 U87 now forms part of U86 owing to a sequence error by Nicholas (1994) that was corrected by Nicholas (1996). Most ORFs lacking counterparts in HHV-7 (LT1, DR3, DR4, DR5, DR8, LJ1, U1, U6, U9, U61, U78, U83, U88, U92, U93 and RJ1) are considered unlikely to encode proteins. U21ex, U96 and U97 are predicted to form exons in spliced genes, in addition to conserved ORFs DR2, DR7, U5, U16, U17, U60, U79, U89, U98 and U99.

Specific features responsible for excluding ORFs that lack HHV-7 counterparts from the genetic content of HHV-6 are as follows. U9, U61 and U83 (104, 115 and 97 codons, respectively) are small. DR5 (145 codons), DR8 and U78 (110 and 109 codons, respectively) are small and also lack candidate polyadenylation signals. U92 and U93 (147 and 197 codons, respectively), are larger but span R3 and lack suitable initiation codons. U88 is relatively large (413 codons), but spans R2. LT1 (112 codons) and RJ1 (143 codons) span reiteration T1; LT1 also lacks a

Fig. 24 Predicted layout of HHV-6 U1102 genes.

The genome is shaded, the thinner and thicker portions denoting the unique region and terminal direct repeats, respectively. The scale is in kbp. Protein-coding regions (DR1, DR6, U2-U100) are shown as open arrows above the gene nomenclature; the U prefix has been omitted. ORFs predicted to be expressed as spliced mRNAs are connected by open horizontal bars. Candidate polyadenylation signals (AATAAA, ATTAAA or AGTAAA) are indicated by vertical arrows in the appropriate strand. Reiterated sequences (R1, R2, R3, T1 and T2) are shown as filled rectangles above the genome, and the minimal fragment shown to act as an origin of DNA replication (ori) is indicated (Dewhurst *et al.*, 1993).



candidate polyadenylation signal. LJ1 (321 codons) spans T2 and lacks a candidate polyadenylation site. DR3 (192 codons), DR4 (100 codons) and U6 (103 codons) overlap other genes; also, DR3 overlaps the 3' end of DR1 and lacks a consensus polyadenylation signal.

3.10.4. Gene organisation

About half of the genes in HHV-7 and HHV-6 have counterparts in all sequenced mammalian herpesviruses; these are termed core genes and are highlighted in Table 11. Gompels *et al.* (1995) and Nicholas (1996) pointed out that most of the non-core genes are located towards the genome termini. However, many non-core genes have counterparts in HCMV (Chee *et al.*, 1990) or MCMV (Rawlinson *et al.*, 1996). Several belong to the US22 gene family.

Where possible, amino acid sequence similarity between HHV-7 and HHV-6 was also used as a guide to locating initiation codons and possible splice sites (Section 3.11.1). This resulted in modifications to the locations of some HHV-7 genes from those reported for JI; details are incorporated in Tables 11 and 12. Also, modifications to the HHV-6 U1102 interpretation from comparisons with RK resulted in 5' truncation of ORFs U14, U27, U30, U44, U47, U67 and U76. All but one is reduced in size by approximately 5-10%; U47 is truncated to almost 50% of its original size. These modifications for HHV-6 genes are listed in Table 13; a few were stated or implied in Nicholas (1996), or in HHV-6 sequence papers predating Gompels *et al.* (1995).

3.11. GENE SPLICING IN HHV-7 AND HHV-6

Drawing largely on data from other herpesviruses (especially HCMV) and, in some cases, on experimental data from HHV-6, Gompels *et al.* (1995) and Nicholas (1996) indicated that splicing may occur in certain HHV-7 and HHV-6 genes. However, the detailed situation is unclear. Splice sites were predicted for HHV-6 (Lawrence *et al.*, 1990) and U17, U18 and U20 (Nicholas and Martin, 1994), and splicing patterns were deduced from transcript mapping data for U90, U91 and U100 (Schiewe *et al.*, 1994; Pfeiffer *et al.*, 1995). Subsequently, Gompels *et al.* (1995) listed sites only for HHV-6 U12 and U17, with three of the four sites apparently incorrect, as described below. Nicholas (1996) indicated that splicing may occur in certain HHV-7 genes, but predicted splice sites only for U66 and U17. In reassessing this aspect of HHV-7 gene organisation, substantial support was found from sequence comparisons for splicing in

Table 12. Predicted splice sites in the HHV-7 and HHV-6 genomes

RK ORF		JI ORF	HHV-7 acceptor	HHV-7 donor	HHV-6 acceptor	HHV-6 donor
consensus			YYYYYYYYYYNY AGG	MAG GT TRAGT	YYYYYYYYYYNY AGG	MAG GT TRAGT
DR1	exon 1	DR1	TCTCTTCTATCAC AGA	CAT GT AAGC	CTATTCTTACTCT AGG	TAT GT GAGT
	exon 2	DR2	TTTGCTCTATCGC AGG	none	TTTGGTTTCCCT CAGG	none
DR6	exon 1	DR6	none	GCG GT GAGT	none	GCG GT GAGT
	exon 2	DR7	TCTACATCCCGGC AGC	none	CGCGTCCCATCAC AGC	none
U7	exon 1	U7	AAGTTAATTTTGC AGA	TAG GT ATGT	TTATGTTTCAAAC CAGA	CAG GT GGGT
	exon 2	U5	GATGTTCTTTT CAGA	none	TTTTTCTTACA CAGG	none
U12	exon 1	-	none	CTG GT ATGA	none	CTG GT AAGT
	exon 2	U12	AACTTTTTTT CACAGC	none	CAATATCTTTAAT AGC	none
U15	exon 1	U15	none	ACG GT GAGT	none	AAG GT GGGT
	exon 2	-	CTCTTTTATTT CAGG	GCG GT AAGA	GTTTTCTTTT CAGG	GCG GT GAGT
	exon 3	-	TTTTTTTTCTTT AGT	none	GTTTTTTTTTT TAGT	none
U17	exon 1	U17	none	TAT GT AAGT	none	TGT GT AAGT
	exon 2	U16	TTGTTGTTTT CATAGG	none	TCCTTTTAAACA AGG	none
U66	exon 1	U66	none	CAC GT AAGT	none	CAC GT AAGT
	exon 2	U60	TCATTTTCTTCT CAGA	none	TCATTCCCCTCT CAGA	none
U79	exon 1	U79	none	AAG GT TAGT	none	ATG GT TAAAT
	exon 2	H6	AACATGTTTTCTT AGA	CAG GT GGGT	TTGTTGCAATTT CAGA	CAG GT GGGT
	exon 3	U80	GTTTCTTTCTTT AGG	none	ATCTTTTATTTT AGG	none
U90	exon 1	-	GGTTTGTTATTGT AGG	TGAG GT AGGT	TTCATTGGCTAT CAGC	AGAG GT AAGT
	exon 2	U90	TAAATTTTATTAC AGA	CAG GT ATTT	TATTTATACTTAC CAGC	CTG GT AAGT
	exon 3	U89	TTCTTTAAATTCT AGC	none	TCTTTTACATCCT AGC	none
U91	exon 1	U91	none	CAG GT TTGT	none	CTG GT TAGT
	exon 2	-	TATTTTTTCTTGT AGA	none	ATGGTTTGTTTT AGA	none
U100	exon 1	U100	AAAATCTCTTCGC AGA	ACAG GT AAGT	CGAAATTTTCA CAAGA	ACG GT AAGG
	exon 2	U99	TTTAATTCTTCTA AGG	ATG GT AAGC	TTTAATTTATCGC CAGC	ATG GT GAGT
	exon 3	U98	GTACCCGCTTATT AGT	AGT GT AAGT	ATTTATTCAC CTCAGT	CGT GT AAGT
	exon 4	-	TATTTTTTTTTT AGA	AAT GT AAGA	TTCGTTTTTTGT CAGG	ACT GT AAGT
	exon 5	-	AATFGTGTTCGC AGT	CAG GT AAT	TTATGTTTCTAAC CAGA	ACG GT GAGT
	exon 6	-	GCTTCTTCATCCT AGA	TTG GT AATT	TCCGGTTATGCAC CAGC	ATG GT GAGC
	exon 7	-	TTTTTTTCATACC AGC	ACAG GT GGAA	TTTCTTAATTTGC CAGC	AGG GT GGGC
	exon 8	-	TTTTTTTAATTCT AGC	CAT GT GAGT	TTTCGACCTGCCT AGA ^a	AAT GT AAGT
	exon 9	-	ATTCTCGTTCGC AGC	CAG GT GAGC	TTGATATTTGTT CAGT	TAG GT ATTA
	exon 10	H8	CATTTTCTCTTT AGT	none	TGTTTTTTTTT AGT	none

^a Another acceptor site (GCTACCGCTTTTT**AGC**) is located further upstream. It could extend coding similarity between HHV-7 and HHV-6 exon 8, but is in an inappropriate reading frame.

Table 13. Proposed modifications to HHV-6A(U1102) genes.

GENE ^a	STRAND	START ^b	STOP ^c	CODONS	REASON FOR CHANGE	
DR1	ex1	+	501	759	689	Putative splicing; exon 1 starts at 500
	ex2		843	2653		
DR6	ex1	+	4725	5028	395	Putative splicing
	ex2		5837	6720		
U7	ex1	-	15921	14948	>872	Putative splicing; exon 1 starts at 15923
	ex2		14858	13214		
U12	ex1	+	21680	21712	351	Correction of splice sites
	ex2		21790	22812		
U14		+	23331	25145	604	5' truncation
U15	ex1	-	25992	25676	191	
	ex2		25602	25530		
	ex3		25364	25179		
U17	ex1	-	27349	27121	334	Definition of splice sites
	ex2		27034	26259		
U24A		-	35847	35674	57	Not previously identified
U27		-	38903	37797	368	
U30		+	42325	45132	935	5' truncation
U44		+	73470	74087	205	
U47		-	77768	75912	618	5' truncation
U53.5		+	85133	85867	244	
U66	ex1	-	102486	101614	666	Definition of splice sites
	ex2		98415	97288		
U67		+	102485	103519	344	5' truncation
U76		-	115257	113317	646	
U79	ex1	+	120164	120794	474	Definition of splice sites
	ex2		120891	121087		
	ex3		121170	121766		
U86		-	130044	125989	1351	Error correction
U90	ex1	-	136112	136054	941	
	ex2		135965	135772		
	ex3		135664	133092		
U91	ex1	+	136267	136477	153	Definition of splice sites
	ex2		136580	136830		
U100	ex1	-	150282	149873	656	Definition of splice sites; exon 1 starts at 150295
	ex2		149771	149490		
	ex3		149081	148746		
	ex4		148628	148551		
	ex5		148454	148347		
	ex6		148255	148142		
	ex7		148055	147895		
	ex8		147383	147374		
	ex9		147223	147095		
	ex10		146984	146642		
DR1	ex1	+	151735	151993	689	Putative splicing; exon 1 starts at 151734
	ex2		152077	153887		
DR6	ex1	+	155959	156262	395	Putative splicing
	ex2		157071	157954		

^a Protein-coding exons (ex) are listed. Coordinates include an extra G residue at 128132 (in U86) as indicated by Nicholas (1996).
^b First exons: from first nucleotide of first complete codon (U7) or initiation codon (other ORFs). Subsequent exons: from first nucleotide.
^c To last nucleotide of stop codon or exon.

nine genes in addition to U66 and U17 (U7, U15, DR1, DR6, U12, U79, U90, U91 and U100), and splicing patterns were predicted.

3.11.1. Detection of splice sites

Regions of the RK genome in which splicing had been demonstrated experimentally in HHV-6, regions in which splicing was suspected, and regions lacking obvious coding potential, were examined for possible splicing. Selected regions of the RK genome and analogous sequences in HHV-6 were initially assessed for amino acid sequence similarity outwith the borders of previously predicted genes. In order to do this, conceptual translations of the HHV-6 and HHV-7 sequences were created (in all six reading frames) using the Ptrans program. The amino acid sequences were then examined by eye for similarity. In regions where similarity extended upstream from the proposed initiation codon or did not extend to the stop codon, or where local similarity was detected outwith established ORFs, sequences were analysed for the presence of consensus splice donor and acceptor sites (Krainer and Maniatis, 1988).

Splicing was proposed when candidate sites were located similarly in the HHV-6 and HHV-7 genomes, so that two exons could in principle be joined in the same register and express the conserved, and not the non-conserved, polypeptide regions. Table 12 summarises splice sites proposed from the analysis for the two genomes, and lists the ORFs previously recognised in HHV-7 J1 that are proposed to form exons in spliced genes.

3.11.2. Candidate spliced genes

U66 - U66 is the only putatively spliced gene which has counterparts in all sequenced herpesviruses, and splice sites have been predicted previously for HHV-6 and HHV-7. Splice sites for this gene are located identically in all herpesviruses, and those in HSV-1 have been mapped experimentally (Dolan *et al.*, 1991). U66 is thus used as a benchmark for other HHV-7 spliced genes discussed below. Fig. 25 shows that significant amino acid sequence similarity between the exons in HHV-6 and HHV-7 does not extend beyond the proposed splice sites into the intron, that the splice sites are in the same register in HHV-7 and HHV-6, and that the exons are joined appropriately.

U66 internal splice

HHV-7

H E T I K S I A L E A S C Y N I H v s n k f f l p t y y a f t d w t
ACGAACAATAAAAGTACAGCACTGTTTGCTAGTTGTTACAACACTCAC*Gtaagta*acaaatttttcttacctacttactatgcgtttacagactggac
g k e y - - y y i k t q s I y r I k l r s f s s a S I R G Q S
aggaaaggagtattaa.....tagtattacataaaaactcagtcctttatcgcgtttaaaactccgt *tcat*tttcttctcagAGTATACGTGGTCAGAC

HHV-6

H Q N I K S I A L E A S C Y N I H v s t i n l t l f s e i k n -
ATCAAAATATAAGAGCACAGCACTTTTCGCCAGCTGCTACAATACACAC*Gtaagta*actatcaatttaactttattttcagaaataaaaaattaa.....
- k g r l s f h s s q n r I l s r I t p n s f p s a S I R G Q S
.....taaaaaggtcgtctttcgtttcacagttctcaaaatcgtcctttatcccgtttaacgccgaat *tcat*tccctctcagAGTATACGCGGACAGAC

Fig. 25.
Sequence-derived evidence for splicing in the coding regions gene U66 (HHV-7 and HHV-6). Amino acid sequences extending to the stop codon (hyphen) defining the 3' end of the upstream ORF and from the stop codon defining the 5' start of the downstream ORF are shown. The dots indicate a sizeable region of the intron that is not shown. For this Fig. and Figs. 26-34 relevant DNA sequences are shown with appropriate conceptual translation products aligned from left to right. The DNA sequences begin and end at arbitrary points within the exons, except where stated otherwise. Conserved amino acid residues are underlined. Proposed intron sequences (flanked by splice donor and acceptor sites as listed in Table 12) are shown in lower case in the DNA sequence. Amino acid residues excluded from the protein predicted to be expressed *via* splicing are also shown in lower case. Consensus splice donor and acceptor sites are shown in italics, and previously identified initiation codons which are now thought to map internally are doubly underlined.

U7 - U7 was not previously suspected of being spliced. In HHV-6, U5 and U7 were regarded as substantial ORFs in different reading frames. In HHV-7 JI, U5 and U7 are in the same frame and are thus represented by a single, apparently fused ORF (U5/7). However, the data in Fig. 26 suggest that ORFs U7 and U5 form two exons of a single gene in both genomes (U7 in Table 12). Thus in this model, the spliced U7 gene is flanked at its 5' end by U8 which, like exon 1, contains US22 motifs, and at its 3' end by U4, which is related to exon 2 (Fig. 23). There is also a somewhat weaker indication that U7 may be spliced at its 5' end, since amino acid sequence similarity between HHV-7 and HHV-6 extends upstream from the proposed initiation codon. However, an upstream coding exon but was not identified. U8 is a possibility, but this arrangement would result in a protein with the unusual structure of two contiguous US22 domains.

U15 - U15 was not previously suspected of being spliced. Fig. 27 strongly supports the presence of three exons. Amino acid sequence conservation between HHV-6 and HHV-7 is high, and splice donor and acceptor sites are located identically in the two genomes. The ORFs previously identified as U15 in HHV-6 and HHV-7 JI contain exon 1 only.

DR1 and DR6 - Despite the lack of direct experimental data, splicing events were previously proposed for DR1, DR6, U12, U17 and U79. Nicholas (1996) reported that DR1 is related to DR6 and DR2 to DR7, and that each ORF contains motifs characteristic of the US22 gene family. He also noted that HHV-7 DR1 and DR2 lack initiation codons, in contrast to their HHV-6 counterparts, speculating that these might be supplied by splicing, and commented that splicing of DR1 to DR2 and DR6 to DR7 would result in proteins containing the US22 motifs in their usual order. Fig. 28 supports the view that DR1 and DR2 form exons in a spliced gene (Table 12). Similarly DR6 and DR7 are likely to be spliced (Table 12 and Fig. 29). Although DR1 can supply its own initiation codon it also contains a splice acceptor site at its 5' end, and thus may be spliced to an unidentified upstream non-coding region. In contrast DR6 does not have a splice acceptor site at its 5' end and is unlikely to be spliced upstream.

U12 - In the analysis of the HHV-6 genome, U12 was referred to as a spliced gene but the predicted donor and acceptor sites appear to be incorrect. Splicing in HHV-7 JI U12 was not

U7 internal splice

HHU-7

E N L N R M L N G E S P I L R K K P R H M Y P R C D R y u k i k v
GAAATTTGAACAGAAATGTTAAATGGAGAGTCTCCGATTCTTCGGAGAACCACGGCATATGTATCCAAAGGTGTGA *TAGgtatgtaagatcaaagttc*
l l f g i l y t i l l m v p w m f f f r L L K N M P S L L E A U I
ttcttttcggtattctctacacaatactcttactgatgggtccatg *gatgttctttttcag*ATTATTGAAGAACATGCCAAGTATTCTGTTTGCAGTGCf
S S E I S N P L U Q S U I K E L H P I I I P N G D T E L K Y I U P
CTCATCTGAATCAGTAATCCTCTTGTTCAAGTGTTACAAAGTTTCTACATCCATCATCATTCCAACCGGAGACACGGAAGTACATTGTTCCG
U T E S R L I N G L Q A S A A G R E G L K G L R L C S D G U I W N
GTGACAGAATCCAGACTAATCAACGGCCTTCAAGCATCAGCTGCTGGACGCTTTGGATAAAGGGCTAAGATTATGTTCAGATGGTGTATTATTGGAATf
R L I D Y E Y E M F K Y P S I F T R A A D K F L L Q L R D L K E
GGTTGATAGACTATGAGTACGAATGTTCAAGTATCCATCACTTTACAGGGGCTGATAAATTTCTTTTGCAGTTGCGCGATTAAATTT

HHU-6

- a s a y u r a k g q u g g c v l c
E N L N R M L N G E L P U L R S K P R H M C U R K D R w u d v f c
GAGAATCTCAATAGGATGTTGAATGGGAGTTGCCGTTCTCCGTAGTAGCCTCGGCATATGTGCGTGCGAAAGGA *CAGgtgggtggatgtgtctgtc*
r f p e r i i i r g w r l p a n f f f s y n r L U K D R S K L L E
u v f q r g -
tcgttttccagagaggataattatttcgaggatggagactccccgctaacttttttttttcttacaacagGCTTGTGAAGACCGTAGCAAAATTTCTGTTI
A U R L D E E D S P T U K F I I K E L T P U F U G R L P A T N R F
GCGGTGCGTCTGGATGAAGAGGATTACCGACGGTTAATTTATCACAAAATTTCTCACGCCGTTATTCGTGCGTGCAGTACCAACAGGTTTC
U U P U S R A A R L T N G L Q G T A A A R E G L K G L H P S S D C L I
TTGTTCCCGTCTCCCGCGCCAGGTTGACGAACGGTCTGCAGGGGACCGCAGCAGTAGATTGGCATTAAAGGACTACATCCCTCTTCGGACTGCTTGGT
W N I L U D Y E Y E T Y K Y P S I Y I R A A D Q I A D M U K D L K E
GTGGACATACTGGTGGATTATGAGTATGAACCTACAGGTATCCTTCCACCTACATCAGAGCCGATCAGATTGCGGACATGGTGAAGACTTAAATTT

U7 upstream splice

HHU-7

- s q v n f a e L U P U C N D U C I E P T P D L P S F D E A U E L
taatcacaaagttaatttttgagAAATTGTTCTGTGTGCAATGATGTTTGCAATTGAACCGACTCCGGATTACCGTCTTTTGATTTTGCCGTTGAGTTGC
L L S S Y G E G M E L U R N G I K C C L A W P P N Y U L I F G E E Y
TGCTGTCTTCATATGGAGAGGGCATGGAGATAGTTCGCAATGGTATAAAGTGCTGTCTTGCTTGCCGCCAAACTATGTGCTTATTTTGGCGAATTTTf

HHU-6

- l i l e t e g g e r v l c e s i l l y s v f m f q t e L U P U C
tgactgatacttgaaacggaggggcggagagcgagtcctgtgtgaaagtattttactttattctgtgt *ttatgtttcaaacag*AGATCGTACCGGTCTGCA
N D E F A L S S C U P T L D E D U D U L S A A Y G D G L E L S S P I
ACGACGAGTTGCGCTTGTATCATGTGTGCTACTTTGGATTTTGATGTGGACGTTCTGTCTGCAGCTTACGGAGACGGGTTGGAATCAGTTCTCCGGE
L R C C I A W P P M Y A L T L G E E Y
CTTGCGATGTTGTATCGCCTGGCCTCCCATGTATGCATTAAACCCTGGGTGAGTTTTA

Fig. 26.
Sequence-derived evidence for splicing U7. Details of the layout are the same as in Fig. 25.

U15 internal splices

HHU-7

M E T W R R Q R L Q E F R E L C P L Q I L M T L S N I I S K U E T
ATGGAACCTGGAGAAGACACGACTACAGGAATTTTCGCGAGCTGTGTCCACTACAGATATTGATGACGTTATCTAATATTATATCTAAGTGGAGACAF
I Y I K Y L E Q M D E N I T Y R F I F S G L I L T T I U I K S U U I
TCTATATAAATATCTTTTTCAATGGATTTTAATACACATATAGATTTATTTTTCTGGATTAACTTAACCACAACTGTGACAAAGTCTGTAGTGAT
E A L E I I K R W Q E I K Q I E N L D U H K T E D C Y I U A Q E T
TGAAGCTTTGTTTATTATTAAGAGATGGCAAGAAATCAAGCAGATTTTCAATCTAGATGTCCACAAACTGAGGATTGTTATATCGTCGCTCAATTCACF
H L P U K R - - p r s f i f r K I
CACATACCTGTAAACGgtgagtgccacctctattatttctacacaaacgagtttcaaaattttattgtctaaccgccgtcttttattttcagGAAATCA
T A L L Y M M I T K H E K Q L E L N M I Y A v r k i i f k n n k c s
CAGCATTATTGTATATGATGACARCAAGCATGAAAGCAACTTTTCTTAACATGATTAT GCGgtgagaaatcatttttaaaataataaatgttc
- E L E E S H L R L G D D E H E N A I M E E
s v k d i i t f f f f s f -
ttctgtaaaagatcttttaacatttttttcttttagTTTCTAGAAGAAAGTCATCTGAGGCTTGAGACGATGAGCATGAAACGCGATAATGTTTTTTI
S Y I E R L Q L I R D U L I E I I Q K L K N U E I N Q I I A L U L S
CATACATAGAACGACTCCAACTGACCAGAGATGTTTAATTGAGATTATTCAAAGCTAAAAACGTGGAAATTAATCAACAATTGCCCTTGTGTTGTC
Y N E L A K -
ATACAATGAATTAGCTAATAA

HHU-6

M D U W K R Q R L Q E C R E L C P L P U L M S L S N M F S K I E I
ATGGATGTGTGGAGCGTCACGGCTTCAAGAAATGCCGTGAATTGTGTCTTTGCGTGTATTATGTCACTGTGCAATATGTTTTCAAAATCGAAATCC
U Y U K Y L E K M D E S I M Y R Y I L P A L I L S M I U I K S L U I
TATACGTTAAATATCTATTTAAATGGACTTTTCTACTATGTATAGATATATTTACCGGCTCTTACGTTGAGTATGACGGTTACAAATCCCTAGTTAT
E M L E I L K R W E D I D Q F E R L N I R K U N D C F I U A Q E N
TGAATGTTATTTATTTAAAGATGGGAGATATTGATCAATTTTTTAGATTGAACATCCGGAAAGTAAACGACTGTTTCATCGTAGCTCAGTTCAAC
H L P I K R w v i i - - c m p i n v f f f y r K L I
CATATTCCTATAAAGgtgggtactgatttaagtatacgtggaagcgagcgggctaagtgtatgccgattaatgtgttttcttttacagGAAGTTAAT
U L L Y M L I S R Q E K Q L E L N M I Y A v s i i l y s r f q d i
GTGTTGTTGATATGTTAACCTAGACAGAAAAACAGCTTTTCTCAATATGATATAT GCGgtgagtttgattttgtacagtagatttcaagatatat
I n c n -
taaatgttaattaggtgcttggtccattaggttgctagactatacttttctggtggttaatttagtgtttaagttaaagttatattggattggatggatac
- E L E K S H L R L G D D E E Q N A I R E E S Y U
aattgatggtttgtgttttttttttagTTTTAGAGAAGAGTCACCTTAGACTTGGTGATGATGAAGAACAGAAATGCTATTCGTTTTTTTCTTACGTT
D D L H L I R D I L L E M I H K L K N T E I N Q I M E L L L S Y N
GATGATTTACCTAACGCGGGATATTTTATGGAGATGATCCACAGCTCAGAATACGGAATCAATCAACAATGGAACTTTTATTATCGTACAATC
E L A R -
AATTGGCTAGATAA

Fig. 27.
Sequence-derived evidence for splicing U15. The whole putative U15 gene is shown, the DNA sequences extend from the proposed initiation codon (ATG) in exon 1 to the stop codon (TAA) in 3. Details of the layout are the same as in Fig. 25.

DR1 upstream and internal splices

HHU-7

- p t g s a a k s v l p r p c a r g n c r r r a a a s p p s r a d
tgacctactgggagcgccgccaatctgttttgcggcgccctgcgcgcgcgggaactgtcggcgccgctgctgctagcccgccctccagagctccct
s l r l p p h d c h s p f h l f y h r l c v t p p M T A A T T E H l
ccctccgtctgcctcctcacccttgccactcacccttccatctcttctatcacagACTCTGTGTTACCCACCTATGACTGCTGCAACCACAGAACATTT
A L R A A L N R Y H H L L L G R H K L S L U C N Y U T A H R Q Q L
TGCTCTCCGCGCGGCACTCAATCGTTACTGGTGGCTGCTTCTGGGACGACACAAGCTCAGTTTGGTATGCAACTACGTCACAGCTCATCGCCAACAGTTF
L P L P H P E Q E F L Q L D P A P Y S N L R N R U A H H L H R G H
CTGCCGCTGCCGTGGCCCGAACAGGAATTTCTCCAACCTTGACCCGGCCCCCTACTCCAATCTCCGCAACCGTGTCTGCTCACCATCTCCATCGCGGCTGGC
P A A H N T c k l p y i s f t n p r l t -
CAGCGGCACACAACA CATgt aagctaccgtacatctctttcacaaacccaaggctcacatagagacaagcacaaagctcgcgcaatgacattaaacctcc
- r l c s i a a E D P R P Y F P N A K U K L L
catcattgtcctttcctgtcgtttgccgataacgtcttctgctctatcgagGTTTCGACCCCCGCTCTTACTTCCCCAATGCTAAAGTCAAGCTGCTTC

HHU-6

p s h n r i t l f t t l t l i l a s a p n a a p l s h h h p l d l
cctagccataaacgcataaactctgttcacaacctaactaactcctcgcatccgcacctaacgctgcccctctttcacaccatcacccctgccgcttc
q l h l l p d s r p a c f y t c p p l y s y s r M P L T U R A G H l
aaactcaccctcttccatctcgccccgctgtttctacacttgcgcgccct ctattcttactctagGATGCCGCTAACGGTGCCTGCCGGGCACGC
P Y R L P L S N Y H H L L L G R H S L R H U H S Y L R L H K G L R
GCCATATCGTCTTCCGCTCTCAATTAATTGGTGGCTACTCTTGGGTCGACATTCCCTTCGTCATGTTTATTCTACCTGCGTCTGCACAGGGTCTACGC
I P L P H P E Q E C L H L H P K P Y K C L L R Y P C I T R Q P H L
ATTCTTTACCTTGCCCCGAGCAGGAATGCCTACATTACATCCTAAGCCTTACAAGTGTCTCCTGCGTTACCCCTGTATAACAGACACCCGCATCTTC
- v s y t f p l f h m i y c v l s t t p g t f
L Q G H P T K S S L c e c h i h f h f f t -
TTCAGGGCTGGCCTACGAAGTCTTCTC TATgtgagtgcatatacatttccactttttcacatgattttattgcgttttgcctactacacgggtacattt
w f p s a E D P K P Y H P S A D S K L L
tggtttccctcagGGTTCGACCCCTAACCCCTACCATCCTTCGGCCGACAGCAAGTTGCTAC

Fig. 28.
Sequence-derived evidence for splicing DR1. The 5' end of DR1 supplies its own initiation signal, and also contains a splicing site to an upstream non-coding region. Details of the layout are the san as in Fig. 25.

DR6 internal splice

HHU-7

W P P N W S L E L H H D P Y R D A R A Q I U W S H R W G W P A I H
TGGCCGCCTAACTGGAGCCTGGAACCTTACCACGATCCCTATCGAGACGCCAGAGCACAACCGTTTGGAGTCACCGCTGGGGATGGCCTGCACACACAC
U T A R T U R D C a e c k q c d t l l s q l s y p i n f l l m y - l f i n v l s
TGACAGCTCGCACGGTGCGGGACT GCGgtgagtgtaagcagtgtagacattgttatcgcaattgtcttacccgattaaactttttattaatgtattaagc
t l s s r v t u v f f v v i y i p a A L D T H M Y U C C G R G E K
actctttcttcacgtgtgactgttggtttttgttgta tctacatcccggcagCCCTCGACACGCAT ATGTACGTGTGCTGCGGACGCGGAGAAAGT

HHU-6

W P P C W C L E L H H D P Y R D A R S A I U W G H R W G W P A I H
TGGCCGCCGTGCTGGTGTCTAGAACTCCACCACGATCCGTACAGAGACGCCAGAAGTGCCACCGTGTGGGGCCACCGCTGGGGTTGGCCAGCGACGCACG
U R P R C U Q D C a e -
TGAGACCCAGATGCGTTCAAGACT GCGgtgagtaaacgtacgggagcgagccgaggggagggatgtcggtcagacagtgagtgagtaacaggttcgt.....
.....tttctgcgttatggcatcctcgcattagtcaccattcctgtcgcggtgtgcttttcgctttgaattgtacgcgacaggatacgaatccgttatact
p q g h s d h g c m r h l p f h g m p l r v q m f c a f f i r s e
ccacaagggcatagcgaccacggctgt atgcggcatctcccggtccacgggatgcctttgcgtgtgcagatgttctgtgctttttttataggtcagagc
t t d k n k a t p t i t f m v s c c f v w v k r l f y r v g r i h t
ccacagacaaaaataagggcaacgcccaccataacgtttatggtttctgtgttttgtttgggttaaacgcctcttctatcgtgtcgccggatccatcc
u q s l t y a r p i t A L D S C L Y U C C G Y G E K
tgttcaatcgttgacgtacgcgcgtcccatcacagCCCTAGACTCCTGTCTGTACGTATGTTGCGGATACGGAGAGAAAC

Fig. 29.
Sequence-derived evidence for splicing DR6. Details of the layout are the same as in Fig. 25.

mentioned. Evidence that U12 contains two exons (U12 is the second exon) is given in Fig. 30, and the locations of the acceptor and donor sites are recorded in Table 12.

U17 - U17 was predicted previously to be a spliced gene with two exons (U16 and U17) in HHV-6 and HHV-7 JI. The analysis of HHV-7 RK supports alignments made for splice sites in HHV-7 JI and for the acceptor, but not the donor in HHV-6. Evidence for splicing in U17 is shown in Fig. 31.

U79 - U79 comprises three exons in HHV-7 RK (Fig. 32). This spliced gene was previously represented as U79 (exon 1), H6 (exon 2), and U80 (exon 3) in HHV-7 JI and as U79 (exons 1 and 2) and U80 (exon 3) in HHV-6. However, splice donor and acceptor site locations were not established in these analyses.

U90 - Schiewe *et al.* (1994) reported from mRNA transcript mapping that U90 is spliced in HHV-6. Although splicing was mentioned for these ORFs in the HHV-7 JI and HHV-6 sequence analyses, no details were given. As can be seen from the analysis of HHV-7 RK in Fig. 33 and Table 12, U90 comprises three exons: exon 1 was previously unidentified; and exons 2 and 3 correspond to U90 and U89 in the HHV-6 and HHV-7 JI sequences, respectively.

U91 - Schiewe *et al.* (1994) also reported that the U91 gene contains two exons. Exon 1 was noted in the HHV-7 JI sequence and exon 2 in the HHV-6 sequence, each recorded as U91. In both cases the other exon was not recognised. Evidence of splicing in U91 is given in Fig. 34. The putative HHV-6 and HHV-7 proteins contain two pronounced hydrophobic regions (one near the N terminus and the other about two-thirds through the protein), as illustrated in Fig. 35. This indicates that the U91 protein is likely to be associated with membranes. In addition, both proteins contain a single consensus site for N-linked glycosylation in the region between the hydrophobic domains, and the HHV-7 protein has two additional sites near the C terminus. Thus, U91 may encode a previously unrecognised membrane glycoprotein.

U12 internal splice

HHU-7

M D I L L D F Q K I L v - - s n v m i c y s f a k n v t f a f l i
ATGGACACTCTAATTGATTTCCAAAAATCCTGgtatgataatctaattgtatgatttgetacagctttgetaaaaatgttacctttgcatttttaatcc

i l q n f f s q H D E E Y K Y N Y T Q I T P I U R K A Q R L E S U I
tcttgcaaaactttttttcacagCATGATGAAGAGTACAAGTACAATTATACGTGTATTACGCCACAGTACGGGAAGCCCAAGACTTGAAGCGTAAT

HHU-6

M D I U L E L S K L L v s i q t s i l p n i l m -
ATGGACACTGTCATTGAGCTGTCCAAACTTCTGgtaagtcttcagacatcattgttaccgaatatTTtaatgtagcgtaacatgaaaataacatt caatc

- R N E E F K G N A S Q T S T P I L K T A R I M E S A U
tctttaatagCGCAATGAAGAGTTCAAAGGCAATGCTTCTGTACCTCGACACCCACGCTAAGACAGCACGAATCATGGAGAGCGCAGT

Fig. 30.
Sequence-derived evidence for splicing U12; DNA sequences extend from the proposed initiation (ATG) in exon 1. Details of the layout are the same as in Fig. 25.

U17 internal splice

HHU-7

L S P L R D M P E R T I S E T E L Q D L C k I a k q s k h f q e y
ATTCGCCTTTGC GG GATATGCCTTTCAGAACTACTAGTGAACCGAGCTGCAAGACC *TATgtaagttgcaaaagcagtc*caaacatttccaatgtgtcc
m m f - - v f v v f i a C Y L L C C N E R L Q U I G F L S A K N D L
tgatgttctaataagttttgttgttttcatagGTTGCTATCTCCTATGTTGCAATGAAGGTTACAAGTCATCGGTTTTCTGAGTGCTAAAACGACGT
T T A A A K I I I L L G E E E R E Y A L D E E K E N
AACACAGCAGCTGCTAAACCATCATTCTTCTCGGAGAAGAGAGCGTTTCTATGCTTTGGACTTCGAAAAAGAAAATT

HHU-6

L S T L C K I P E P I K S A A E L Q E M C k y a c f v s v i w e y
ATTCGACACTGTGTAAATTCATTTCCACAAAGTCTGCCGCAGAGTTGCAAGAAA *TGTgtaagtatcagtgtttcgtgtcagttctgtgggtgtgtcc*
s r f c c e n k v i f p f k q a S L L L C C P E R L Q L L G Y U S
i l v f v v k i k l f f l l n k v r y y f a a r k d c n y l d m f l
ttctcgttttgttggtgaaaaataaagttattttccttttaacaagGTTTCGTTATTACTTTGCTGCCCGGAAGATTGCAACTACTTGGATATGTTTC
U W G E E T R D U C L T K I L V F A G E D E K E Y G L D E U N E T
s g e r r l v m c a -
GTCTG6GGGAGGAGACTCGTGATGTGTGCCTAACTAAACGTTGGTGTGTTGCGGGAGAAGACGAAAAATTTTACGGTCTCGATTTTGTGAATGAGACAC

Fig. 31.
Sequence-derived evidence for splicing U17. Details of the layout are the same as in Fig. 25.

U79 internal splice

HHU-7

E D D R R N E K Q D L E a - - c I
GAAGATGACCGTCGAAACGAAAAACAGACCTCG AAGgttagttgccttttttctaaatcactagtcctaaatatgacttggtgaattttttagtgtct
r f l h k h v f l D A S K E K R M K U H H E K R H A E E Q A N E E
aagggtttttacataaacaatgttttcttagATGCATCCAAAGAAAAAGGATGAAGTGCATCACGAAAAACGTCATGCGGAAGAACAAAGCAACGAAGAG
U A S S S Q L S S R I P E G A L S P T I S I D L Q E Y Q E F E D F
GTTGCTTCTTCGAGTCAGTTATCAAGTAGAATACCAGAGGGTGCGTTATCGCCCACTATTCTATTGATCTTCAGGAATATCAGAATTGAGGATTTTC
D K R I C G Q v a a v l g l - - Q I
ACAAGCGCATTTGTGGGCAGgtgggtggagttttgggtttatgatgcatttttattgcagttttttatgtggttaaagatgtttctttcttttagGGGAA
N Q D A U C K K U Q S D E S E C I N K P L E Q F R E K L
GAATCAAGACGCTGTATGCAGAAGATCCAAAGTGATGAAGTTTTTGTATAAATAAACCGTTAGAGCAGTTTAGAGAGAACTAA

HHU-6

E D K Q P D K K E E S D a k y k c i v v v n f y f s c v t v v d f
GAAGACACGCAACCGGACAAAAGGAGGAATCGG ATGgtaaatataaatgtatagttgttgtaaatttttatttttcgtgtgtcacgggtcgtggactttt
f l n s i c f v a i s E L P K E K R Q K Y H D M K R N L E E Q S H E
ttttaaatagtatctgtttgttgcaattttcagAACCTTCTAAGGAGAGAGACAGAGTACCATGACATGAACGTAAATTTGGAGAGAACAAAGTCACGF
D G I T L T S T T L U N G A U E G A L P P C I S I D N H E D Q Q H
GGATGGCATAACACTAACTTCTACGACACTCGTAATGGAGCGGTTGAGGGTGCGTTACCGCCCTGTATTCTATTGATAATCACGAAGATCAACACAT
D E L D K R A Y A Q v a a v s g s p k p r s s g s l l c v s k a d
GATGAATTAGACACGCGCTTATGCG CAGgtgggtggagtttcgggttcgccaaaacctaggctttcgggggtctttgttggtgcgtatctaagctgatc
- G T N R E G L S N E D N Y G N E R L N K S L E Q L R A K L
l f i l g d e p r r s i q -
tttttatttttagGGGACGAACCGAGAGGTCTATCCAATGAAGATAATTATGGGAATTTTCGGCTTAATAAGTCTTTAGAACAGCTTAGGGCCAACTTC

Fig. 32.
Sequence-derived evidence for splicing U79. Details of the layout are the same as in Fig. 25.

U90 upstream and internal splices

HHU-7

g v a k h t d k t M E R S G A T S P M L I U G Q P S E T M A S N D I
GTGTGGCTAACATACAGATAAACTATGGAAGAAGTGGAGCTACTTCACCTATGTTGATTGTTGGACAACCATCTGAACCATGGCATCGAATGACGF
R H I E - - f i c n k i y k f y u r Y H P
AAGCATAT *TGAgtaggt*aaacctaataatattttaatacaaaaaagacagatttaatttctctgtaataaaattta *taaattttattacag*ATATCACCCf
D T T U E E T I R D I L Q D S L K C N P S E D N T L F Q E L D S E
GATACCACCGTGGAAAGAGCCATCAGAGACATATTGCAAGACAGTTTAAATGCARCCCTTCCTTTGATAATACTCTCTTCCAGAATTGGATTCTTTTC
D F L D S I S S N D I A T A N A S Y S T N U E E G A S S D I K L A I
ATTCCTTGACTCAATATCATCTAATGATATTGCAACGGCAAAATGCTTCCTATTCCACAATGTTGAAGAAGGAGCTTCCTCGGATATTAACTGGCAGC
- T G S
g i f f s f s y i - - I I A Q S I S
AGgtatatttttttcattttcttacatataaaatatgatatatgtgtacagatttcataatttagactttt *tcttttaaattctag*CTCAGTCCATTAGTC
A C I Q G I L K S U N A A M
CCTGCATCCAAGGTATTCTTAAATCCGTGAATGCTGCCATG

HHU-6

a q - a v s q f a s - y t M E P A K P S G N N M G S N D E R M Q e .
CACAGTAGGCGGTGTCTCAATTTGCATCTTAATATACAATGGAGCCAGCAAAACCCTCTGGAACACACATGGGATCCAATGATGAACGTATGCAAGAgtc
- s . l l d l s y l r l f g n f s k y l k n i y t u s Y R P D I
agtatgattagtcattattagatctatcttatttaagattatttgggaatttttctaagtaacttaaaaaatatt *tatacttacag*CTACCGTCCCGATCC
M M E E S I K E I L E E S L M C D T S E D D L I I P G L E S E G L
AATGATGGAAGAATCTATCAAGAATATTGGAAGAGAGTCTCATGTGTGATACATCCTTCGATGACCTGATTATTCCAGGCCTTGAAGCTTTGGTCTT
I I P E S S N N I E S N N U E E G S D G E L K T L A g k y m n y i
ATTATACCAGAGTCTTCCACACACATAGAGTCCATATGTAGAGAAGGATCAGATGGAGAGTTGAARACTTTAGCTGgtlaagtacatgaattatattc
- h t q n i f f y I I A Q S A G
i c p k i e n k k k h s f k h v t y n i l r i s s f t s -
tatgtcccaagatagaaaaaagaaaaaacatagttttaaccatgtgacatataacatactcagaatatct *tcttttacatcctag*CTCAGTCCGCTGGC
N C I Q S I G A S U K A A M
AATTGCATCCAAAGTATTGGTGCATCAGTGAGGCTGCCATG

Fig. 33.
Sequence-derived evidence for splicing U90. Details of the layout are the same as in Fig. 25.

U91 internal splices

HHV-7

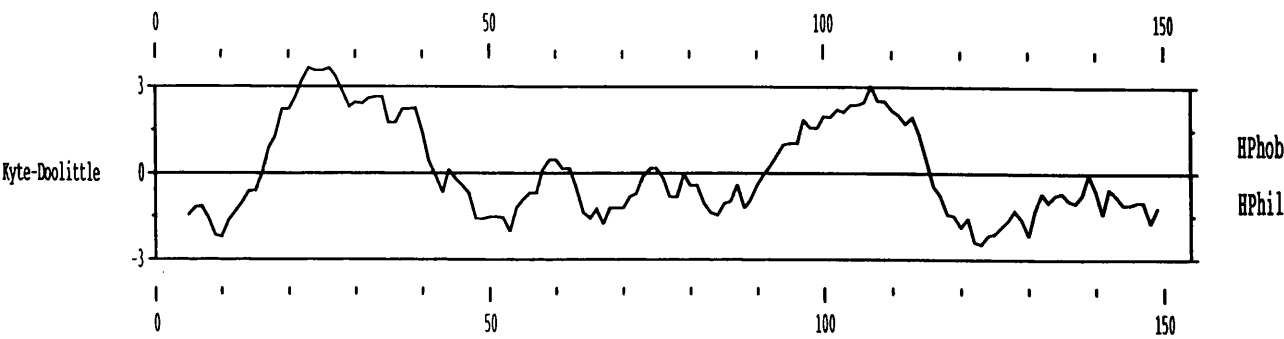
M Y T L E Y E K R U S R P K L T Y W L I L A I L F U E L I I I G S
ATGTATACTCTGGATATGAAAACGTGTATCAAGGCCAAACTTACTTATTGGATCATTTTGGCAATATTATTGTTTTTTAATAAATACTGGATCTC
U L I U I E T L S I Q R T T L N A Q N D K I S T U U P E L T S N S I
TATTAATTGTAATTGAAACTCTGTCAATTCAAGAAGCAGACTTTGAATGCTCAAAATGATAAACAGTACTGTTGTTCCAGAATTAACATCTAATTCTC
- i f f i v D Q T I U T N F
g l f s y k m s l f k k k v c n s v n m n i f s c r s n n c d k f
AGgtttgttcagctataaaatgtcattgtttaaaaaaaagtttgtaactctgttaatatgaatatTTTTTctttagATCAACAACACTGTGACAAATT
S A S S K P T L S S K Q P G H L Q A L I
f c k f -
TTCTGCAAGTTCTAACCCTCTTAGCAGTAACAACCCGGATGGATACAGGCACTA

HHV-6

M G K K S S T G T G K T N L K L L A C L L L I E L M A I I F L L I
ATGGGGAAAAATCATCTACTGGAAGTGGAAAACTAATCTAAGATAGTGGCATGTCTACTATTGATATTTCTAATGGCAACATATTTTGCTAATAC
L E I I S G Q R Y S N D D S E G U I A A L K H U S T P T T N C T E
TGGAATTATATCGGGCCAAAGATATTCCAATGATGATTCCGAGGTGTGACTGCGGCGCTGAAGCATGTAGCACACCTACTACCAACTGCACTGAAC
T T P g - - r i c l f y f n v l i i y l h t f l k n e k k n i t d
CACTACTCCTGgttagtgaaggatatgtctttttattttaatgtattgattatatatttgcatatccttaagaatgaaaaaaaaaatatcacggat
g l f l D S U I S Q A M E N K E S M K K N E G E P P U H L Q A L I
ggtttgttttagATTCCGTACGAGCCAGCCATGGAAAACAAGAATCAATGAAAAAATGAAGGGGACCTCCAGTTTGGATTCAAGGCTTAACTF

Fig. 34.
Sequence-derived evidence for splicing U91. Details of the layout are the same as in Fig. 25.

HHV-7 U91



HHV-6 U91

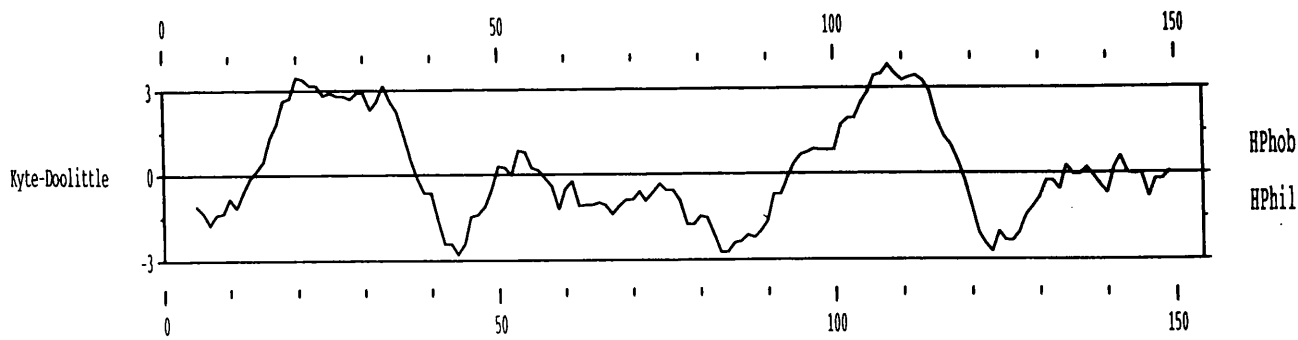


Fig. 35

Hydrophobicity profiles generated using Pepplot from the U91 proteins potentially expressed by splicing.

U100 - Of the spliced genes recognised in HHV-6 and HHV-7, U100 is the most complex. The region at the right end of U contains several short ORFs which are expressed in HHV-6 as a multiply spliced mRNA encoding the virion envelope glycoprotein gp105 (Pfeiffer *et al.*, 1995). The mRNA contains ten coding exons (here termed exons 1-10) and two upstream non-coding exons. The likelihood of splicing in this gene was pointed out in the HHV-7 JI sequence analysis, but no splicing pattern was deduced. In the HHV-6 sequence, U100 is represented by U100 (exon 1), U99 (exon 2), U98 (exon 3), U97 (exon 7) and U96 (exon 10), and in this part of the HHV-7 genome, three of the four ORFs were reported to be counterparts of those in HHV-6. A scheme for U100 splicing in HHV-7 RK is given in Table 12. An amino acid alignment of the putative U100 proteins from HHV-6 and HHV-7 is shown in Fig. 36.

The amino acid similarity for the most part is convincing, although less so in the regions encoded by exons 1 and 10. In addition, it was necessary to propose that the exon 8 and exon 10 acceptor sites are not located similarly in HHV-7 and HHV-6, although they are in the same register in each genome. Indeed, it is curious that use of an alternative acceptor site for HHV-6 exon 8 located upstream from the site mapped by Pfeiffer *et al.* (1995) could significantly extend the similarity with the HHV-7 exon 8 polypeptide; details (see Fig.36) The site is an incorrect reading frame, however, so this point remains unsolved. Of the 18 cysteine residues in the HHV-7 U100 protein, 14 are conserved in HHV-6. Three of the remainder are encoded by ORF 8. U100 in HHV-7 JI corresponds to exon 1, U99 to exon 2, U98 to exon 3 and H8 to exon 10. The status of upstream non-coding exons identified in HHV-6 by Pfeiffer *et al.* (1995) is unknown.

Other possible splice sites were noted during the analysis, including those consistent with splicing of U12 exon 1 to U13 and the 3' end of U19 to an unidentified downstream exon. However, the evidence in these instances was weak, and they have not been included in Table 12. Moreover, in a few regions where splicing might reasonably be suspected, such as that containing U24 and U24a, no supporting evidence was forthcoming.

```

< 1
HHV-7  MVQLHYIIFALLIKICTNTVPLEKARTAITLEDIIENLINENMHNASSTRYIGLSS.....
HHV-6  MATARLSAMKPPRSCALIFLCAFSMATAPTNATAHRRAGTVKSTPPPEDKHSTAKYDKDIYFNIYEGRNSTPRRTLSEIISKFSTSEMLSLKRVKAF
con    M-----TA-T-----

1 > 2
HHV-7  .....EERQSLLEYTRCTSFSCCEWPDQAQVILLETTLCIPLKENSGLVGRGLREKIMSKGLSEVLSVTTGLHYSLNNGFGSKQNSLLYVKRM
HHV-6  VPVDENPTTTLEDIADILNYAVCDDNSCGCTIETQARIMFGDIIICVPLSADNKGVRNFKDRIMPKGLSQILSSSLGLHLSLLYGAFGSNYNSLAYMRRL
con    -----E---L-Y--C---SC-C---A-----C-PL-----GVR-----IM-KGLS--LS---GLH-SLL-G-FGS--NSL-Y--R-

2 > 3
HHV-7  NTANILTSLVLPARHRWERREQYTQSSAQCELQIRADFKKMRYSGIAFRTQISLAIVRKDNKGYEWETCMQFSQWKEEDFNIPKVNMTSEKPLYDACC
HHV-6  KPLTAMTAIRFCPMTTKLELRQNYKVETLCELIVSIEILKIRNNGGQTMKTLTSFAIVRKDNQGQDWETCTRFAPVNIEDILRYK.....RVANDTCC
con    -----T-----P-----E-R--Y-----CEL-----K-R--G---T--S-AIVRKDN-G--WETC--F-----ED---K-----D-CC

3 > 4
HHV-7  PDKNSRENTTYAWRWSEHPWTET.TIEPWRDIDIIRQIPTDERCLTNT.TVFQSTYGGIWCSPKNDTTARNYVTTVILFPIALLEIERLFDITIGQKTQVQ
HHV-6  RHRDVQHGRRT..LESSNS.WTQTQYFEPWQDIVDVYPINDTHCPNDSYVVFETLQGFQWCSRINKNETKNYLSSVLGFRNALFETEELMETIAMRLAS
con    -----T-----S---WT-T---EPW-DI-----D--C-----VF---G--WCS--N----NY---V--F--AL-E-E-L--TI-----

4 > 5
HHV-7  .....TIDTLLLTFLKKDDRTTKKLISNKSLSN
HHV-6  .....VYTMQDQVQKPLSVTWMDFNLVISDYGRDVNNL
con    .....K---K-L-

5 > 6
HHV-7  DMFPHPRHQSFNSREFDPAIVSAMWQDFPSKISTDLQYDVLLTPSKDFGPCSIKIKTDSAKTEFDNGRLL..TIDTLLLTFLKKDDRTTKKLISNKSLSN
HHV-6  QILSMVGQGGTTIRIDIPAIVSALWHSLENLTNNIKYDIASPTHMRPALCTIFVQTGTSKQRFNRAGLLMVNNIFTVQGRYTTQNMFERKEYVYKHLG
con    -----Q---R--DPAIVSA-W---P---TT--YD-----C-I---T---K--F-N--LL-----K---K-L-

6 > 7
HHV-7  .....WEGIKAARINSNYGANEDPTPKLLEVEEFFDYIYEATCTTTEMRYPERKAQVQVFASSKDSKKFFKSSVKRQNRDI
HHV-6  TKSAMLARKNGPRYLQMEGPRYLQMETFISDLFRHECYQDNYYVLDDKQLQMEFYPTTHSNELLFPSEATLPSPWQEPFSSPWPEPTFPSRWYLLNNTNY
con    -----AR-N-----P--L--E-F-----C-----K-Q-----F--S-----

7 > 8
HHV-7  AQLCNTSELQPKLESCCDEY...LRFTDGDVIELTCDGNIYQAGGITCTPIYTSTTIIHEIKPTPNKPKTKTQPMPPWIDLNKAFS.....
HHV-6  QALCQplfstlpkitssccdsyvvlnsstsvsslistclDGEILFQNEGQKFCRPLTDNRTI....VYTMQDQVQKPLSVTWMDFNLVISDYGRDVNNL
con    --LC-----lpk--sccd-y-----t-----tc-DG-I--Q-G--C-P---TI-----W-D-N--S-----

8 > 9
HHV-7  .....WEGIKAARINSNYGANEDPTPKLLEVEEFFDYIYEATCTTTEMRYPERKAQVQVFASSKDSKKFFKSSVKRQNRDI
HHV-6  TKSAMLARKNGPRYLQMEGPRYLQMETFISDLFRHECYQDNYYVLDDKQLQMEFYPTTHSNELLFPSEATLPSPWQEPFSSPWPEPTFPSRWYLLNNTNY
con    -----AR-N-----P--L--E-F-----C-----K-Q-----F--S-----

9 > 10
HHV-7  .....WEGIKAARINSNYGANEDPTPKLLEVEEFFDYIYEATCTTTEMRYPERKAQVQVFASSKDSKKFFKSSVKRQNRDI
HHV-6  TKSAMLARKNGPRYLQMEGPRYLQMETFISDLFRHECYQDNYYVLDDKQLQMEFYPTTHSNELLFPSEATLPSPWQEPFSSPWPEPTFPSRWYLLNNTNY
con    -----AR-N-----P--L--E-F-----C-----K-Q-----F--S-----

```

Fig. 36. Sequence-derived evidence for the splicing of U100, in the form of alignments of putative amino acid sequences in HHV-7 and HHV-6. Exons are numbered 1-10 and their junctions are indicated by arrows. Dots indicate padding characters. Conserved amino acid residues are shown in upper case. Lower case residues in HHV-6 are potentially encoded by the HHV-6 DNA sequence upstream of exon 8, but lack a suitable splice acceptor site and are not encoded by anmRNA analysed by Pfeiffer *et al.* (1995); see text for details.

Chapter 4

Discussion

4.0. DISCUSSION

This chapter allows me the opportunity to comment on the implications of several aspects of the results. These include: the relationship between HHV-7 strains RK and JI; the putative functions of the telomeric elements; the coding potential and importance of splicing in the HHV-7 genome; and the phenotypic differences between HHV-7 and HHV-6.

4.1. THE DNA SEQUENCES OF HHV-7 RK AND JI

4.1.1. Strain divergence

McGeoch and Cook (1994) estimated an overall rate of sequence change of 1×10^{-7} synonymous substitutions per synonymous site per year in the gB gene, based on cospeciation of herpesviruses with their hosts over periods up to 60 Myears. Although this value was claimed as an order of magnitude estimate only, it was considered compatible with estimates derived by analysis of HSV-1 isolates from human populations established over a much shorter period (0.1 Myear). On this basis, the presence of 84 synonymous substitutions (Table 10) in the U regions of HHV-7 RK and JI (which, unlike DR, is not potentially subject to intragenomic homologous recombination) indicates that the lineages resulting in the two strains diverged from a common ancestor of the order of 10,000 years ago. In contrast, based on comparisons between the amino acid sequence of the HHV-7 gB gene and existing alignments derived from several other gB genes (McGeoch *et al.*, 1995), HHV-7 and HHV-6 are estimated to have diverged 50-60 million years ago (D.J. McGeoch, personal communication).

4.1.2. Nucleotide differences

This is the first occasion when complete sequences from two strains of one herpesvirus have each been compared in their entirety. As anticipated, the majority of nucleotide differences between HHV-7 RK and JI do not affect coding capacity (Table 9 and 10). Moreover, differences that do affect coding potential are scattered throughout the genome and appear not to be clustered in particular genes (Fig. 22). This indicates that no small subset of genes has been demonstrably subject to unusual evolutionary pressures since divergence of the two strains.

4.1.3. Genome ends

Sequences containing the genome termini were identified in the database since they share one end. Most of the clones from the left genome terminus of HHV-7 RK had six C residues and none had seven (Fig. 21), although the possibility of heterogeneity was suggested by the presence of less than six C residues in a few terminal clones. As fragments were end repaired (using T4 DNA polymerase) prior to ligation, no information was obtained on unpaired nucleotides at the termini. The genome termini of another HHV-7 strain (R-2), also sequenced from end-repaired DNA, are identical to those of RK (Secchiero *et al.*, 1995). Sequences from the termini of HHV-7 JI have not been determined directly. However, Secchiero *et al.* (1995) sequenced regions of HHV-7 JI concatameric DNA (consisting of head to tail copies of the genome) which span the DR-DR junction and thus correspond to a fused version of the termini, including any unpaired residues normally present at the termini. Sequences corresponding to the left genome terminus contain between four and six C nucleotides, and in some instances one or two additional residues at the DR-DR junction itself. This supports the length variability of the stretch of C nucleotides present at the left terminus of RK. Similarly, sequence variation in terminal base composition has previously been observed in HHV-6 (Thomson *et al.*, 1994). The right terminus of the published JI genome sequence is identical to that of RK (Fig. 22a), but the left terminus is one base pair longer, containing seven rather than six C nucleotides (Fig. 22b). The origin of this additional nucleotide is unclear.

4.1.4. Reiterations

Singer and Frenkel (1997) used Southern blot hybridisation of *Bam*HI-cleaved HHV-7 RK genomic DNA to determine the approximate length of the *Bam*HI fragments from the left and right ends of the genome. These fragments contain the telomeric arrays T1 and T2. They estimated the restriction fragment from the left end (containing T1) to be 4.5 kbp in length, and that of the right end (containing T2) to be 3.8 kbp. From the RK DNA sequence, the *Bam*HI fragment at the right end is 3811 bp in length, correlating very closely with the experimentally determined size. However the length of the fragment containing T1 in the DNA sequence is about 1.7 kbp longer than that determined experimentally. Thus, it is likely that the solution for T1 sequence is not a correct representation of the genome sequence. This may reflect either the intractability of this region or sequence heterogeneity occurring in the genome or in M13

recombinants. Variability in the genome itself is supported by the observation that the terminal *Bam*HI fragment identified by Singer and Frenkel (1997) is heterogeneous in size. Therefore, it must be emphasised that although the size of the RK genome as derived from the sequence is 153080 bp, the actual size of the major species is likely to be a little less than 150 kbp.

The corresponding sequences in JI genomic DNA are likely to be different, however, since they vary in size in different plasmid clones (Ruvolo *et al.*, 1996). In support of the view that HHV-7 does not have unique genome size, Frenkel and Roffman (1996) reported that the genomes of different HHV-7 strains range in size from 140 to 150 kbp, and suggested that the main cause of variation involves the telomeric reiterations.

4.1.5. Resolution of the T1 reiteration

If, as appears probable, the T1 array is heterogeneous in sequence even within a single HHV-7 strain, this would somewhat reduce the imperative to realise a single solution for T1. If further investigation of the array were required, longer sequences could be generated from M13 clones using an automatic sequencer. Such sequences would still be unable to span the T1 array, but might prove less difficult to overlap. However, even longer sequences from a heterogeneous target would not provide a single solution.

An alternative would be to sequence DNA from a viral clone. This would at least provide a representative array from one variant in a heterogeneous population. Cloned purification of HHV-7 is likely to be problematic, however, given the growth properties of the virus.

4.2. FUNCTIONS OF THE TELOMERIC REITERATIONS

The human telomere-like elements in HHV-7 (and HHV-6) comprise arrays of a tandem repeat (TAACCC)_n, and related sequences (Martin *et al.*, 1991a; Secchiero *et al.*, 1995). In addition to HHV-7 and HHV-6, human telomere-like repeats have been reported in the genomes of other lymphotropic herpesviruses, including alphaherpesviruses (MDV) and gammaherpesviruses (EHV-2) (Kishi *et al.*, 1991, 1988; Telford *et al.*, 1995).

Whether these elements are functionally related to those at human telomeres is a matter of speculation, and resemblance of the repeated elements to human telomeric repeats may be coincidental. Nevertheless, it seems unlikely that different herpesviruses would independently generate (or capture) tandem arrays of the same element unless functionally driven. Furthermore, such small reiterated elements are relatively uncommon in herpesvirus genomes. It is likely, then, that telomeric elements have been acquired and retained in order to perform a function of benefit to the viruses. Consequently, several authors have suggested possible functions in lytic phase replication or latency.

It is perhaps significant that in HHV-6, HHV-7 and MDV (but not EHV-2) the telomeric arrays are located near the genome ends and adjacent to the conserved *pac-1* and *pac-2* sites, which direct cleavage and packaging of replicated DNA to unit-length genomes. In view of this, several authors (Secchiero *et al.*, 1995; Frenkel and Roffman, 1996; Thomson *et al.*, 1994; Gompels and Macaulay, 1995; Gompels *et al.*, 1995; Martin *et al.*, 1991) have proposed that the telomeric reiterations could play a role in the cleavage of concatemers (Liu and Gilbert, 1994) or DNA packaging during lytic phase replication (Deiss *et al.*, 1986).

In addition, it has been suggested that the telomeric reiterations may play a role in maintenance of the latent state. Positioned at the herpesvirus genome termini, the telomeric elements may enable the linear genome to survive as a distinct mini-chromosome in the dividing host cell and also achieve segregation during cell division (Thomson *et al.*, 1994; Gompels *et al.*, 1995; Gompels and Macaulay, 1995). Alternatively, Torelli *et al.* (1995) proposed that herpesviruses containing telomeric elements may achieve latency *via* a different route. The arrays may enable viral DNA to integrate into the telomeres of host cell chromosomes. However, the ability to segregate during cell division, is likely to be advantageous to the viral genome only if it is normally latent in dividing cells. The site(s) of persistent infection for HHV-7 and HHV-6 are not known, although both display tropism for non-dividing T-cells. Additionally, evidence in support of HHV-7 or HHV-6 integration into the host genome is scarce, nor is there any expectation of integration from what is known of other herpesviruses.

Secchiero *et al.* (1995) speculated that the telomeric arrays in HHV-6 and HHV-7 might be involved in the regulation of viral gene expression. Additionally, Gompels and Macaulay (1995) observed that monomers of the telomeric element are distributed around HHV-6 ori, suggesting a possible role in lytic phase replication. In contrast, telomeric elements are not located near HHV-7 RK ori. However, this does not completely rule out a role for the telomeric elements in HHV-6 lytic replication since the structure of its origin is different from that of HHV-7.

4.3. CODING POTENTIAL OF HHV-7

As a result of this study, HHV-7 RK is considered to contain 84 different genes (Table 11) and HHV-6 is predicted to contain 85 different genes. Two genes (DR1 and DR6) are present twice in each genome. The deduced layouts of HHV-7 and HHV-6 genes are shown in Figs. 23 and 24, respectively. In addition, HHV-7 genetic features and an alignment of predicted amino acid sequences with the genome sequence are given in Appendix I.

As expected, the HHV-7 RK contains approximately 40 core genes, and in addition approximately 30 more genes have counterparts in HCMV. All but one of the remainder have direct counterparts in HHV-6. Even the one exception gene, U55B, is related to U55A, and is thus also homologous to HHV-6 U55. HHV-7 U55B and U55A are also homologous to HCMV UL84, which may encode an essential replication function (Iskenderian *et al.*, 1996). Whether this is an example of the HHV-7 genome generating diversity by gene duplication or, alternatively, expulsion of genetic material from HHV-6 and HCMV is unclear; the former seems more likely.

HHV-6 contains only two genes that are absent from HHV-7: U22 which is a putative membrane glycoprotein, and a homologue of the AAV-2 *rep* gene, U94 (Gompels *et al.*, 1995). The function of U94 is unknown.

Gene U91 was not previously recognised as encoding a putative membrane glycoprotein in HHV-7 and HHV-6. The amino acid sequences of the two proteins contain two pronounced hydrophobic regions (one near the N terminus and the other about two-thirds through the

protein), as well as a single consensus N-linked glycosylation site of the form NXS or NXT located between the two hydrophobic domains. In addition, U91 in HHV-7 has two further potential N-linked glycosylation sites near the C terminus. Each hydrophobic domain is likely to anchor in the host cell, and possibly the virion membrane. If the central region is situated outside the cell, each protein could be N-glycosylated. Alternatively, if the central region resides within the cell, only HHV-7 U91 is likely to be N-glycosylated.

4.4. SPLICING

4.4.1. Splicing patterns in HHV-7 and HHV-6

Drawing largely on the correspondence between the HHV-6 and HHV-7 gene arrangements, and in some cases on experimental data from HHV-6, it was possible to determine splicing patterns in 11 out of the total of 84 HHV-7 genes. Sites in 9 of these genes represent new predictions.

The comparative aspects of the analysis ensured that substantial confidence can be placed in the predicted splicing patterns. Some reservations should be stated, however. Heavy reliance on homology between HHV-7 and HHV-6 will have restricted recognition of spliced genes to those which are conserved in both viruses. Splicing in genes that are unique to one virus, and splicing involving non-coding exons are unlikely to have been identified from DNA sequences alone. Also, examples of complex splicing (such as that in U100) or alternative splicing are likely to have remained undetected. Thus, although splicing is likely to be common in HHV-7 and HHV-6, it is expected that the full extent of splicing has not yet been appreciated.

Some of the genes potentially spliced in HHV-7 and HHV-6 also have counterparts in HCMV and MCMV. Indeed, it was evidence for splicing in certain HCMV genes that led to initial suspicions of splicing in their HHV-7 and HHV-6 counterparts (e.g. U17). However, the evolutionary distances between HHV-7 or HHV-6 and HCMV or MCMV precluded the easy identification of corresponding splicing patterns in HCMV or MCMV.

4.4.2. Confirmation of splicing

Identifying spliced genes using sequence data only is a speculative occupation. It is notable that experimental data relating to splicing are limited for HHV-6 and completely absent for HHV-7. Consequently, further experimental investigation into splicing in both genomes would be useful. Transcript mapping by Northern blotting, S1 nuclease analysis, primer extension and cDNA cloning are the obvious routes.

4.4.3. Origins of splicing

HHV-7 U66 is the only core gene that is spliced in all of the sequenced herpesviruses. In contrast, examples of splicing have been documented among α -, β - and γ - non-core genes, particularly within the genomes of HCMV and EBV. Several HCMV non-core genes, including UL36/UL37, UL122/UL123 and UL112, are spliced, and some make use of alternative temporally regulated splicing (Mocarski, 1996). In the EBV genome all of the EBNA genes, plus LMP-2, which are latency associated and specific to EBV, express highly spliced transcripts. In contrast, the lytic cycle genes of EBV, many of which are core genes, are either unspliced or contain one or two short introns (Sample, 1994).

Thus, it is notable that non-core genes are more likely to exhibit splicing than core genes. Many of these genes probably originated from the host genome by gene capture, or were generated *de novo* in relatively recent evolutionary times (Davison and McGeoch, 1995; McGeoch, 1989). It is unlikely that splicing in recently acquired genes reflects splicing in the host genome, since gene capture seems to occur by reverse transcription processes. However, splicing (particularly alternative splicing) may be introduced to modify the expression of genes that are recently established in the viral genome. In addition, although gene duplication is a method of diversity well established in the herpesviruses (e.g. the US22 family), splicing may also be employed as an aid to divergence, particularly since it requires less DNA (Krainer and Maniatis, 1988).

4.5. PHENOTYPIC DIFFERENCES BETWEEN HHV-6 AND HHV-7

Although HHV-6 and HHV-7 have very similar genetic contents, their long evolutionary divergence (50-60 Myears) is reflected in disparate DNA and encoded protein sequences.

Indeed, the level of amino acid sequence similarity is significant but, for many genes, modest (Table 11). Therefore, the hope of identifying the genetic causes of phenotypic differences by sequence comparisons appears forlorn at present. These differences are, in any case, likely to be multifactorial.

Phenotypically HHV-7 and HHV-6 are very similar, but the two viruses do differ in several ways. Both replicate optimally in CD4⁺ T-cells, but whereas HHV-6 has a wider host range, that of HHV-7 is more limited (Ablashi *et al.*, 1991; Frenkel *et al.*, 1990). The cellular receptor used by HHV-6 is not known, but is believed not to be CD4. By contrast, CD4 appears to be a critical part of the cell receptor used by HHV-7. Moreover, HHV-7 infection selectively down-modulates surface expression of cellular CD4, but HHV-6 enhances CD4 presentation during infection (Lusso *et al.*, 1989, 1991, 1994). HHV-6 infection occurs early in childhood and 80% of children develop an antibody response by 13 months. HHV-7 infection also occurs in childhood, but later than HHV-6 infection, perhaps taking up to three years from birth to develop a similar level of infection (Briggs *et al.*, 1988; Brown *et al.*, 1988; Okuno *et al.*, 1989; Wyatt *et al.*, 1991). The B variant of HHV-6 is widely accepted to be a causative agent of ES (Yamanishi *et al.*, 1988), but the A variant and HHV-7 have no proven involvement in any disease.

The relationship between the two variants of HHV-6 (A and B) is much closer than that between HHV-6 and HHV-7. The variants share approximately 95%-99.5% DNA sequence identity and approximately 95%-100% amino acid sequence identity (Ablashi *et al.*, 1993). Yet HHV-6 A and B also differ phenotypically in several ways, including: differential tropism for different CD4⁺ T cell lines; and the etiologic link of the B variant to ES. Therefore, it is perhaps surprising that the phenotypes of HHV-6 and HHV-7 do not differ more significantly.

4.6. CONCLUSION

The determination of the complete sequence of HHV-7 RK has facilitated detailed genetic comparisons between two strains of the virus and allowed re-evaluation of the genetic content of HHV-7 and HHV-6. Thus, the study has achieved several goals: facilitated the study of microevolution over the whole genome length; reinforced our appreciation of the variability of reiterated sequences in the HHV-7 genome and its implications in genome size; improved our

understanding of the genetic content of HHV-7 and HHV-6; led to detailed predictions of splicing in HHV-7 and HHV-6; and categorised U91 as a spliced, putative membrane glycoprotein in HHV-7 and HHV-6. This analysis thus lays the foundation for further experimental studies of gene expression in HHV-7.

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Appendix 1

CCCCCGTTTCGATTTCAATCCTAATAACCCCCGGGGGTAAGGGGGAGCTAACCCTAACCCTAGCTCTAACCCTAACCCTAACCCTAGC	100
telomeric	
reiteratopm T1	
TCTAACCCTAACCCTAACCCTAAGCTAACCCGTACCCCTAACCCTAAGCTAACCCGTACCCCTAACCCTAACCCTAACCCTAGCTCTAACCCTAACCCTA	200
GCTCTAACCCTAACCCTAACCCTAACCCTAGCCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAGGTC	300
TAAACCCTAACCCTAACCCTAAGCTAACCCTAACCCTAAGCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAGCTCTAAC	400
CCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAAGCTAACCCTAACCCTAAGCTAACCCTAACCTCTAGCTAACCCTA	500
ACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAAGCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAAGTC	600
TAAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAGGCTAACCCTAACCCTAACCCTAAGCTAACCCTAACCCTAAGCTAAC	700
CCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAGCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTA	800
ACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAAGCTAACCCTAACCCTAACCCTAAGCTAACCCTAACCCTAACCCTAACCC	900
TAAACCCTAACCCTAAGCTAACCCTAACCCTAAGCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAAG	1000
TCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAACCCTAAGCTAACCCTAACCCTAAGCTAACCCTAACCCTAAGCTAACCCTA	1100
ACCCTAACCCTAACCCTAACCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCC	1200
CAACCCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAG	1300
CCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGTTTCACCCCAACCCTAACCCTAACCCTA	1400
GCTCTAGTTTCACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCC	1500
TAAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGTTTCACCCCAAC	1600
CCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTA	1700
ACCCCAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTC	1800
TAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGTTTCACCCCAACCCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAACCCTAACC	1900
CTAGCTCTAGCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAAC	2000
CCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGTTTCACCCC	2100
AACCCTAACCCTAACCCTAGCTCTAGTTTCACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGT	2200
TTACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAG	2300
CTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCC	2400
AGCTCTAGTTTCACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACC	2500
CTAACCCTAGCTCTAACCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCTCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAAC	2600
CCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCTCTAACCCCAACCCTAACCCTAACCCTAGCTCT	2700
AAGCTCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACC	2800
CTAGCTCTAGCTCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAACCCTAACCCTAGCTCTAGCCCTAACCCCAACCCTAAC	2900

CCCTAACCCCTAGCTCTAAGCCTAACCCCAACCTAACCTAACCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAGCTCTAAGTCTAACCC	3000
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
AACCCCTAACCCCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAGCTCTAAGC	3100
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CTAACCCAGCCCTAACCCCTAACCCCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGTTTACCCCAACCTAACCCCTAG	3200
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CTTAAAGCCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCAACCTAACCT	3300
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
AACCCCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCAAC	3400
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CTAACCCCTAACCCCTAGCTCTAAGTTTACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGTTTA	3500
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CCCCAACCCCTAACCCCTAACCTAGCTCTAAGTTTACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAACCTAGCTCT	3600
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
AAGTTTAACCCCAACCTAACCCCTAACCTAGCTCTAACCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGTCTAACCCCAACCTAACCC	3700
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CTAACCCCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCA	3800
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CCCTAACCCCTAACCCCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAACCTAGCTCTAAGCCTAACCCCAACCTAACCCCTAACCCCTAGCTCTAAGTTT	3900
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CACCCCAACCCCTAACCCCTAACCCCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAACCCCTAGCTCTAAGTTTACCCCAACCCCAACCCCTAACCCCTAGCT	4000
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CTAAGTCTAACCCCAACCTAACCCCTAACCCCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAGCTCTAAGTCTAACCCCAACCTAACCCCTAG	4100
>> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >> >>	
CTCTACTGTACCCCTAACCTAGCTCCAGGTCATCTGTTCTAGATCCTATCCATATCTGCCCTGACTCCTGGTTCCATACCGCTCCGAGCCCAACCTC	4200
>> >> >> >> >>	
CGTCCCGCCCTCCTCTGTTCTCCATGCCCTGCCCTTCTCAACCCCTCCTCTTCCACGCCACATTGCCCTGCACTCCGCGCTCTCTTGGCTGTGCGCCC	4300
TGCCTTTCCGTGACCTACTGGGAGCGCCGCCAATCTGTTTTGCCCGCCCTGCGCGCGGGAACTGTGCGCGCGCGCTGCTGCTAGCCCGCCTTCC	4400

DR1
exon 1

AGAGCTCCCTCCCTCCGTCTGCCCTCCTCACCCCTTGCACCTCACCCCTTCCATCTCTTCTATCACAGACTCTGTGTTACACCACCTATGACTGCTGCAACCA	4500
>start of DR1 exon 1	
T E H F A L R A A L N R Y W W L L L G R H K L S L U C N Y U T A H R	39
CAGAACATTTTGGCTCTCCGCGCGGCACTCAATCGTTACTGGTGGCTGCTTCTGGGACGACACAGCTCAGTTTGGTATGCACTACGTCACAGCTCATCG	4600
Q Q L L P L P W P E Q E F L Q L D P A P Y S N L R N R U A H H L H	72
CCACAGTTACTGCGCTGCCGTGGCCGACAGGAAATTTCTCCACTTGACCGGGCCCCCTACTCCAATCTCCGCACCGGTGTGCTCACCATCTCCAT	4700
R G W P A A H N T	81
CGCGGCTGGCCAGCGGCACACACACATGTAGCTACCGTACATCTCTTTCACAAACCCAGGCTCACATAGAGACAGCACAGCTCGCGCAATGACAT	4800
end of DR1 exon 1 >	

DR1
exon 2

TAAACCTCCCATCATTTGCTCTTCTGTCGCTTTGCCGATAACGCTTTTGTCTATCGCAGGTTTCGACCCCGCTCTACTTCCCAATGCTAAGTC	94
start of DR1 exon 2 >	4900
K L L P L G S I T L T R S F S S D E P H P I G D D U H H S H D R G	127
AAGTGTCTCCGCTCGGCTCCATCACCCCTTACCAGATCATTTCCAGTGACGAGCCTCATCTATTGGTGATGATGTGCATCACAGTCATGACCGGGGTG	5000
D Y H T U I C S W L T G T S P I L U L L Q G P D G S I Y C H D U Y R	167
ACTACCATCTGTTATCTGCACTGGCTCACAGGAACCTCCCCGATCTAGTGCTGCTTCAAGGACCGGACGGCAGCATCTATTGCCACGACGTGTACCG	5100
G R L Y L U A H S U S L F A R L G L R H C E P L Y A A P A W K H U	194
CGCGCGATTGTATCTCGTGGCCCACTCTGTATCGTTGTTGCCAGGCTAGGCCCTTGCCTACTGCAACCTTTATATGCGGCACCCAGATGGAAGCACGTT	5200
P L P S M W U A S P P A S A T L T Q T L A U S A T H G L D A L Y S	227
CCTCTGCCAGCATGTGGGTGGCGAGCCCGCCAGCGTCCGCCACCTCACGCAACACTCGCCGTGAGTGCCACGCAACGCTGTGACGCGTTTACTCGC	5300
L L K I H R G T P C S L I H P U N G Y U L D M I L T G A S F Q E A P	261
TGCTAAACCTCCACAGGGAATCCGTTGTCGTATCCACCCCGTAACGGCTACGCTCTGGACATGATACTGACGGGCGGCTCATTCCAGAGAGCAC	5400
C Q N T R T S U K T T P H U M D A U C G G R G S W L S I G Y L U K	294
CTGCCAAACACTCGCACGTCGGTTAAACACACGCCACATGTATGGACGAGTCTCGGCTGGCCGCGGGTCATGGCTGTCCATCGGCTACCTAGTAAG	5500
M P H I H L A U T R T C L U T A I D U R Q N F L W R U A D D A L L	327
ATGCCGACATTCACCTGGCGGTGACCCGACATGTCTGGTACCGCATAGATGTCCGACAAACCTTTCTTGGCGGTGGCGGACGACGCGCTGCTAT	5600
F L U T G S L L L L S R P T A D L T S W S C L Q Q E P U W R N C L D	361
TCCTGGTCACCGTAGTCTTTTACTACTGTGCGGGCGGACCGGACACTTGACGTCTTGGTCATGTTTACAGCAGAACCTGTGTGGAGGAACTGTCTAGA	5700

T R G E Q D E T E D Q E M K Q S T S K K Q N E N K K L N T S K K H 394
TACGCCGCGGAGACAGGATGAGACAGAGACCAAGAGATGAACCAAGCACAAGCAAAAGCAAAATGAGATAAAAACTCACACCTCAAAAAACAC 5800
T R U S S A I P T F P L S L R E T P P E A R S P A U L A A A T Q S 427
ACCCGCGTATCGTCGGCAATTCGACCTTTCCCTGAGTCTCCGAGAACGCCGCGAGAGCCAGGCCGCTCGCGCGCGCCACCCAGTCTC 5900
H K T R A I S T H N A T T T I R I P R L P S Y L L E A R L L S U T A 461
ACAAAACCTCGAGCGATCTCGACGATAATGCCACGACACAAATAAGATACCGCGCTTCCAGTTACCTGCTGGAAGCGCGTCTGTTGCTCGTGACAGC 6000
I L K D T K K K K T Q P Q A - 475
TATCCTGAAGACACAAAGAAAAAACCAGCCCTCAGGCGTAGCAGCTGCGACGCTCAGCGCGGTGTCTGAAGCTCGCCAGGTCTCGCGTAAAG 6100
AACAGATGTGAACCTCAGATGTACCAACCAATAATACGGGTTCCGCTATAAAAGTGCACCTCTATTCCCGTTCTTATCCCCGTTCTAECTCTTCCTTG 6200
TATCATACCTTGCATGTTAACCGGATCCCGTGATCTTACACACATACACACACACAACTTGGTGAGGTAACACAGAAATCTCACTAECTCATAAT 6300
CCCCACACGCTTACCACCACTAAAAATGGTTATGACCAAACTGGCAATAGTCTATCTTCTTTTCTTTCCATTACAGCCCAATGTGCAGTACTCGTG 6400
GGTCCACACACGAAGAGACTGTAGAGACCTTCTTTAAGTAGACCTTAGAGACACCAAAATACACCCACACCAAAAAAAGAGAAACACAA 6500

DR6
exon 1 M S A E M L R A U Q L Q P R A R G H S S S P T S P P L E G E P 31
CAAGGCCAATGAGTGCAGAATGCTCCGCGTGTTCAGCTCCAGCCAAGACGCCGGGACATTCTCATCTCCCACTTCCCTCCACTCGAAGGAGAGCC 6600
S P K R L Q S S N S H Q G R R G R P K P R A K T W S E A L S H R S 64
CAGTCCCAAGAGACTCCAATCGAGCAACAGTCACCAAGGGCGTAGAGGCAGACCTAAACCCAGAGCTAAACATGGAGCGAAGCTTTATCCACCGGTCC 6700
F L N I Y A W L S L S R G S P R K U Y G Y A F A H R G E L U A L P 97
TTCTCAACATTTACGCGTGGTGTCTTTGAGTCGAGGGTCTCCGCAAAAGTGATCGGATATGCTTTCAGGCACAGAGGAGAACTCGTAGCATTGCCAT 6800
W P P N W S L E L H H D P Y R D A R A Q T U W S H R W G W P A T H U 131
GGCCGCTAAGTGGAGCTGGAATTCACCAAGATCCCTATCGAGAGCCAGAGCACAAACCGTTGGAGTACCCGCTGGGGATGGCTGCACACACAGT 6900
T A R T U R D C 139
GACAGCTCGCACGGTGGGGACTGCGGTGAGTGTAAGCAGTGTGACACATTGTTATCGCAATTGTCTTACCCGATTAACTTTTTATTATGTATTAGCA 7000
end of DR6 exon 1 >

DR 6
exon 2 A L D T H M Y U C C G R G E K L 155
CTCTTTCTTACGCTGTACTGTTGTGTTTTTTGTTGTTATCTACATCCCGGACCCCTCGACACGCATATGTACGTGTGCTGCGGACGCGGAGAAAGTT 7100
start of DR6 exon 2 >
Q P U G Y U R N R A A P S D L N S L R U L L I A R D G A M Y U H H 188
GCAGCCCGTCGGATACGTACGCAACAGAGCCGCGCTTCAGACCTGAATCTGTACGCGTCTCTCATAGCCAGGAGCGAGCAATGTATGTGCATCAC 7200
M R T A R L C R L A S S U T E F A R R G L Q R E S E U Y E D D U S 221
ATGAGAACGGCGGACTGTGCCGCTAGCCAGCAGTGTGACCGAATTCGCGGACGAGGGCTGCAGCGAGAAATCCGAGGTTTATGAGATGATGTTTCCT 7300
L P D R R U G S A T A I H L F D U I T Q A A D U H D L L T U A G L C 255
TGCCAGACCGCTCAGTAGGTTGCGCAACGGCCATTACCTGTTGACGTAAATACCCAGGACCGATGTCCAGACCTACTACCGTGGCCGGACTGTG 7400
Q T H T G U S C Q L W Y T D H D P H T U A G A A R F T L T U A R Q 288
TCAGACTCACACCGGCGTACGCTGCCAATCTGGTATACAGACCAGATCCCCACACCGTCGCTGGGGGCGGACGCTTCACTGACGGTGCACGGCAG 7500
Q Y R L W P N A R R K L L Q H L H P D H P L G L W L L C A U L T Y 321
CAGTATCGATTGTGGCCAAACGCACGACCAAACTGCTGCAGACCTACATCCGGACCAACCACTTGGGCTGTGGCTGTTGTGTCGGCTGCTCACGTACG 7600
D A K E T N R A U P P U T P G A E T U W U I U T G R G A I L G F W P 355
ATGCAAAAGAGAGCAATCGCGCAGTGCCACCCGTACGCGAGGGGCGGAACCGGTGTTGGGTGATAGTTACTGGCAGGGGTGCCATTCTAGGATTCTGGCC 7700
E S A K M C R L A S S M K G L W K N G A R A L K G H W T Y A A P G 388
AGAGAGCGCCAAATGTGCAAGTTGGCCTCGCTATGAAGGACTCTGGAAGAACGGAGCGCGGGCTAAAGGTCACTGGACATACGCGACCCCGGC 7800
R H R A G E A W P L C A H Y Q S P R - ----- 406
CGGCATAGAGCGGAGAGGGCTGGCCTTTGTGTGCACTACCAATCTCTAGATAGAACAAATTAAGGATTAAAAAAGAGAAAAAGTACAA 7900
GAGTGTATCGGAAACAGCGTGTCAAAAAAACAATCCACATACTCTAGAACAACATGTACCCAAAATAGTCCGTGTCAAACTGGGAAAAA 8000
AAAAATCACCTTCTCTGTTGCCACTAGAGGGAGTACCGAAGGTGATGGCAGAGAGGCCACGCTGTAATGACTGTGACGTTTGGCGGTGAACCAATTGCT 8100
GTTCTTGCTGGCTCAGACACAATCACGTGATTAGATTCTTTTCTGTTTCTAAGGTGTGCCGGGAGGAGACATGCCCTTTCTGAGACATTATGAGA 8200
TTTGCTGCCAGAGAACCACTGACTTGGACTTACTTTCTGTTTCTAAGCTGCCCTTAGCGATGAATGCTCTTTAGCGTTAGCCATGAGGCTAGCGTG 8300
ATCTGTATAGTACATAAGTTTCTAAGAAATGTTTTTAAACAATATCATGTCCAAAAGTCCGAGTGACTAAATTTCTGTAAATGAAGGCAATTT 8400
AAACAGGATACAGACAGTTGTGGCAGTGGTCCGTTTCTGTTTCTGTTTCTTACGCGGCTGACGAGGTAAAGTGTCTCAGTCCATATTGTTGCTG 8500
TGCCACCGTAGTTAGCGGTGGCATACTAAAACTCCGATAGATGCAGAACAAATACACCGAAACCAACGCTGTGGAACCGACCACTTTATAAACAA 8600
ACGGCCTTATCACCTGGAAAAAACAATAAAATAGGCAATGATACCTGACTTTCCATTGGAACCTGCCGAACCTGACCACAAATCCCATGCTA 8700
AATCCCTGAACACTGCCAACGTCGCTACAGGTTTTTCCGGATCGAGCCGAGCAAGCTTAACTGAGGTACACACGACTTTAATTACGGCAACG 8800
CACAGCTGTAGCTGCAGGAAGATATCTCGTAGCAATGTAGTCTACATCAAGCGAGGTTGTAGAGCTTACCTACATGAATACACCTCTAAGC 8900
ATAACCTGTGCGGACAGTGAGACACGAGCCGTAATTCAAACTCAACCAACCGAGTCTAAGTCTACCTAATCGTACAGTAACCTACAACT 9000

CTAATCCTAGTCCGTAAACCGTAACCCCAATCCTAGCCCTTAGCCCTAACCCCTAGCCCTAACCCCTAGCTCTAACCTTAGCTCTAACTCTGACCCCTAGGCCCT 9100
telomeric < > > > > > > > > > > > > > >
reiteration T2

AACCCTAAGCCTAACCTAACCGTAGCTCTAAGTTTAAACCTAACCTAACCTAACCATGACCCCTGACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAG 9200
> > > > > > > > > > > > > > >

CCCTAACCCCTAATCCTAATCCTAATCCTAGCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAGCCCTAACCCCTAACCCCTAGCCCTAGGGCTGCGGCCCTAA 9300
> > > > > > > > > > > > > > >

ACCTAACCCCTAACCCCTAGAGCTGCGGCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAGCCCTAACCCCT 9400
> > > > > > > > > > > > > > >

AACCCTAGCCCTAGGGCTGCGGCCCTAACCCCTAGCCCTAACCCCTAGCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAGCCCTAGGGCTGCGGCCCT 9500
> > > > > > > > > > > > > > >

CTAACCTAACCCCTAGCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAG 9600
> > > > > > > > > > > > > > >

GGCTGCGGCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAGGGCTGCGGCCCT 9700
> > > > > > > > > > > > > > >

AACCCTAACCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAACCTTAGGGCTGCGGCCCTAACCC 9800
> > > > > > > > > > > > > > >

CTAACCCCTAACCCCTAACCCCTAGGGCTGCGGCCCTAACCCCTAACCCCTAACCCCTAACCCCTAGCCCTAGCCCTAACCCCTAACCCCTAACCCCTAACCCCT 9900
> > > > > > > > > > > > > > >

AACCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCTAACCCCT 10000
> > > > > > > > > > > > > > >

end of DR --->--- start of UL
TCTGCGAGCCGCGCGCAGCACTCAGTGAAAAACAAGTTTGTGCACGAGAAAGACGCTGCCAAACCGCAGCTGCAGCATGAAGGCTGAGTGCACAAATTTTG 10100

GCTTTAGTCCCATAAAGGCGGGCTTCCCGTAGAGTAGAAACTGCAGCGCGGCGCACAGAGCGAAGGCGAGGGCTTTCAGACTGTTTGCCAGGCGCAGT 10200

CTGCATCTTACCAATGATGATGCGAAGCAGAAAAATGTTCTTTCTTAGCATATGCGTGGTTAATCCTGTTGTGGTCATCACTAAGTTTTCAGGCTTTTG 10300

GCAAGGCATGAAAAATAACATTACTATTGGACTGTTTATACTTATCTTCAATGTTCTACTCACAGCAGCGAAGGGGACACTAGAAAACTCCCAACTAG 10400

AACTACGAGGCGGAACAGCAATGGAACCCAGACGTGTTTTTACTTTTATTTTCTGAATCATTTAATAGCATACAGTACGGCTCTCCGAATCGAAGC 10500

TAATCTGAGAGCAAGACAAAGAGCACTGTAAACTGAAGGCAAAAAACCCCCGCTTAAAAAAGAAATTTTCATATTCGCGAGCTCTTCCGAAGCCCCC 10600
U2 - F L I E Y N R L E E S A G 346

CGAAAAACACACAGATCGCTAAGGGTGTCTGGACTGAGCTCAGTATCCGGTAAGCCTCCAAAGCAGATGGACATAACTATATTCTCGTGGTAATTGAA 10700
R F C C L D S L T D P S L E T D R Y A E L A S P C L S Y E R P L Q U 312

CTACCGGAACGTGGATGCAAGTGACGGGTAACTGCATGGCCCAAGCGTTTCTATCAGGAAGCGATAGTTTTTAAGAGTCTCCTGGCGCCATGGCCAA 10800
U P U H I C T U P L Q M A W A N R D P F R Y N K F L R R A G M A L 279

AAAAACCTAAACTACAAGCCAGTTAAGCAGGGCTCCTCCGGAACATCCAGAGCGTAGACAGCAGCCCAAGCGATCCATAAGAACCCGTTGCTTTTGA 10900
F U R F S C A L N U U A G G R U D L A Y U A G L R D M L U R Q K R 246

AGAGACCACGACGAGGATCTTCCGACAACTTTCCGATACCCAGGCAACGACGCTAGGAATGAACCTCCACCGCTCTCCATGGTCTCCGGGA 11000
L L G R G L C R G U F K G I U U A U G R R P I F R W R E G H D E P U 212

CGGAAATTCGAAGCAGCAGCCTTTAGGCCACGGAAGAGGCACAGAGCCTTGTGGAAGCAACGCGAAATTCAAACATCTCCACCCCGCACATAGG 11100
S F E F L U G K P W P L P U L A K D F A U A F N L U D E U G C M P 179

GCCGAAGAAAAACCCCCGAACGATGGACTCGAAAAAGCGTACACAGGGTCAATCTGCGCAGACCAGCTTCCAGAGACCATAGGGGTGTCGCA 11200
G F F F G G S U I S E F F A Y U P D F R A L G R K W L G Y P T D A 146

ACTCTGTAATGGCGTTGTCCACGGAACGGTTAATGCATAAATTCACCCGATCTCCAATAGCATCAAGCAGATAATCAGAATAGAGCACCAGAC 11300
U R Y I A N D U S R N F A Y F E G R D G I L M L A S L D S Y L U L G 112

CGATGACCCAACTTCCACAAAGGACAGCAGACAAATTTCTGTTAATCTGAGACTTCTGTTTCCGAATGCCAAGCATCTCCGAAGAGGCAACCT 11400
I U W U E U F P C C U F N R T L K C U E D E S I G L M E S S A F R 79

CAACTCAGCGCCGGAAGGCCACACGAGAGGAAGTGCATGGTGAGCATATTGCAAAACAAATGAGCAACGCTCTCCGAAGATACGGTTTCCGACGCGAAG 11500
L E A G S P W U L P L R H H A Y Q L U F H A U D G F S U T E A A F 46

CTCTGCAAAACGTTGGTCCAGTAGACCTCCGGAACAGGTGATTCACTGTATTGATTCCAGATTAAACAAACCGTTGATGCAATTCGACTCAACAGCCG 11600
S Q L F T T W Y U E P U P S E U T N S E L N F L G N S A N S E U A T 12

TTTCCACACCGGAATCCAAAGCGGGAATCTGACATACCTAGCAACATGCAATGATCAGAGAAAAAAACAGTGAATGCACAGAGACAAATACAAT 11700
E U G S D L L P S D S M 1

CAAACTCATACTCTAAGGCACGACGCTGTTTATTATTAATACCATGTCAATTTCAAACCCACCGCAACACAGGCAATAAAGGGAGAGGTCACAACTT 11800
U3 ----- 385

AGCAACGAAAAATCTGGGTTCCAACTCAGGAACGCTGCCCGCTCATCTGCTCTTGACGCCAAGAGAGAGGTCGCACTGCCCTGCTGGCAGTTTT 11900
C R F I Q T G U D P F A A R E D A R A A L F L L D C D G Q R A T K 352

CAGATAAAAGCGCAGCAAAATGACACAAATGGTTTCTGGCACCATTGGGCTGAGCCGCGTAAAGGTGTGATGTTTATAGAGTTACGCACACCGGACA 12000
 L Y F R S S F H C L P K Q C W K P Q A A Y F T H H K Y F N R U G U 319
 AACCTAAAAACCTGAAACTCTCTGCGATGAAAGTCAAGTTCCTGCGGGATCGTTATCATTAAACCCATAAATTTTCCCGAGCAGTCAGCGTAAGGG 12100
 F R F U Q F S E A I F T L N G D P D N D N F G Y I K G S C D A Y L S 285
 AAATCTAGCTCCGCTGAAAAACATTTTCAGTCCGAGGCTCGCAAGAACACATATCAGCTAAACACTTTTTATCTCCGGCTCAGAAACAAATGA 12200
 I R A G D S F C K L G F S A F F C M D A L U S K I E P D S U F H F 252
 ACTGCTTTCTGTGATGAACAGGATATTCTCTCTGCGGCCATCGCAACTCAAAATTTTACCAGATGCCTGTCCGAATGCCAAATTTTCAGCG 12300
 S D K R H H F L I N E R A P W R L E F K E G L H R D R F A L I E A 219
 CATGTTGTAGCTTCAATCTCTGATCTGATACCTCAAAATGCGAGACCTTACACAAACGATGCGTACAGACATCTTTTGAGACCTTTCTCAAAA 12400
 C T T I A E I E P D S U E F Q L C K C L U Y A V L C R K L G K R L F 185
 AACTGTCAATAGTGTACCCACGCGCATAGTTGATCAGGAATAACGTTGTATGTGCATAACGCGGCCAATTTCCCAAGTAAGATAACCAATCATC 12500
 S D I T D G U R C L Q D P F L T T H A Y U R G U K G L L I U U D D 152
 AGTCTCATACTCAGTTCGTAACAGTCGTACAGTATGTTTATGTAAACAGAACAGTAACTTCTCAGGACACACACCAACGCGGCTACTTTTG 12600
 T E Y E L E Y U T T U T H K I Y G L U T L E E P C C U L A A Y K K 119
 AGCTTATCTTCTCATATCCCTCCACACCATAGTCAAACAGTTCAAACCCCTCTGAAAAACCAAGGCACCCCTCAATGCGGATTCAGAAACAAA 12700
 L K D E E Y G E U G Y T L U L E F G E P F U L P U R L H P N L F L F 85
 ACATTTTACTATTAATAATTTGTATAACACGTAGAAATCCACGAGTTTAGCTTAGCAGATTCAAGATTTTCTTTTCTTTTATCAGATA 12800
 M K L S N F N T Y U R L F D U L K A K A S E F I K E K R K K D S L 52
 AACGTTTTCTCAACGTTGGCAACCTTCAATCCTTTTTCCCGTCAACATGAGCAACATATTTCTGTATAACGAATTTTCTTTTTTAATCTTTGCC 12900
 F T K E U N A U K L D K K G D U H A U Y K R I F S N E K K L D K A 19
 ACACTCTCAAAACACGCTCTTCAAAATGAAGTCAGACCCCAATCTGCCATACTTAATCGTACCTAGCGTATTATATCTTTGTGCCCGGTTTCG 13000
 U U R L U R E E F N F D S G L D A M 1
 - Y D K H U P K A 535
 CAAAGGGCAGAAAGCCACCGCGAATGCGACGCGACTGGCGAATGGTAATCCGCGGTGCTGAGACTCTTTAAAGCCCTTTCTCACCGAACCTCT 13100
 F P C F A L R P I R A S Q R I T F G R H Q S E K F L R K R U S U A 502
 CCTTTGTGCGATCCTGTGTTCAAGATCTTAACCTCAAAGACCTCCACCCCTAACCGCATGCGGCACTACGTTTGAACAACCACTCCAAAGATGC 13200
 R Q R M R H E F I R U E F S G G G R U A H P U U N P F L G S W L H 469
 GTCCATATAAATGCAATCTTGACACCGAAAAACGCACTGGATTGTCATGTAGTGCAGCTTTAAGGATTCGTAATCCTTCCAATATATCGTGCC 13300
 T G Y L N C D Q C R F F R U P N D M Y H L K L P N T F G E L I D H R 435
 TTAACCTCCGAGCTAAGTGTAAGAAGACGACGAACAGTTAAGCTACCTTCTTTGACACAGTGTCTTAGGAGAGCTCTACTCTATGATTCTGTT 13400
 L E R A L H L L F C S C T L A U K K Q C L H E L L A R U R H N Q K 402
 ACTGTAGGAGCTACTAGAATAGAAGCCACTTCAAGAAAGCGGACAGTGGCGGGAATGGACATCATTGTGACTGCTAAGTGACTACCTAAACT 13500
 S Y S A U L I S A U E L F A S C H R P I S M U N H S S F H S G L U 369
 GCTAATCTCTACAAACGTTTTCAACTCCTTCAAAGGTAGTATCCTTATTTCTAAAGACTAAGACTGCGCGAAAAACGCGCTATTTTGCCAAT 13600
 A L K R C U N E U G E F P L I R I E L F U L S Q A F F R A I K D L D 335
 CACGAGAGATGCGTTCTTACTCTGCGCGCCAGGAAAGACATAAATGATATTACATAAATCTTTAAATGTTTCTTTCTAGATGACTATTCCTAA 13700
 R S I R E R U R R A L F L C L I I N C Y I K L I N R E L H S N G L 302
 AATTTATCATGTAGAATGGCAATGTTTTCGATTCCATTGCTTTTCAGTATTAACCTCCGCGCGAGATCTTTGTCAATCTCTCTCAACGCGTAAGCT 13800
 I E D H L I P L T K S E M A K L I L E A G L D K D I S E R U R L A 269
 TCATCATTAGTTAATGTAATGCTGGAGATCAAGTCTGTGGAAGTCTGTATATCGGACAAATGTAGGACGCGCCCTTCTCTCCGCTTCAAAA 13900
 E D N T L H D Q Q L I L D Q P S F D Q I D S L H L U G R E R A K L F 235
 AACGAGAAATAGCGCTTGCACATTCCTCCGCACTACAAAGATTAGATACAAAGTGATAATTCATCAGGAATGAAAAAAATTTTGTGCTCTAA 14000
 R S F L A K R C E G C S C L N S U U G F H Y N M U F S F F I K D D L 202
 GAAATTTTAAATAGGAGATTGGAAGGCGCTACGACTTCACCAAGCTATTTCTCGGATTGGAGTAACTCAACAACTCAACAAATATATTGAATCA 14100
 F N K L L L N S P A U U E G A I E K P N P L L E F L S L L I N S D 169
 CAGCGATTCTAAGCATAAAAATTTGAAGAACAAATGAATCAAGGCTCCATTAACGATTAAAGTGAGACGAAGAGTGTCGCGCTTTTCTCCAGCTA 14200
 C R N R L M F F Q L F L S D L L E M L R N F H S S L T D R K E G A U 135
 CAAATATTTCCGCTATTGTAATGAGCCAAAGCTGTAGCTTTAGTCAGAACTCGATAAACGGAGAGTGCACTCTTCAACCTTAGACTTTGAAGAA 14300
 F Y E A I T F H A L A T A K T L U R Y F P S T C E E F R L S Q L F 102
 CGCGAGAAACCGCTAAAGTCATTGTTGCCCTTGCTCCCTTTTAAATGAACGGAGTTTTTCTCCACTAAACAGCCCATAGTAGACTGTCATCGTAA 14400
 A L F G D L T M T A K D R R K F S U S N K E U L U A W L L S D D Y 69
 AATTTAAGCCTCGAGTTTGAACAAATCTTCTGAAGTGAGATGACCGCTATCCGCAATCATCTCTCTGTGAGCTCATTCAAGTTGAGCTTAACCTCG 14500
 F K L G R T Q F L D E S T L H G S D A I M E E T L E N L N U D L E C 35
 ATGAGTTAAATGCCGTCCATGACAGATAAGGATGATTGGTATAACATACGTAATGCGATTCTTAGCGGCCCTTACAAACATCATAATCGATTAAATC 14600
 S N F A T W S L Y P H N P I U Y T I R N R L P G K C U D Y D I L D 2

 CATTACGCAATCCTTGTCAAATGTTTATTCATTCCATCACTAGCATCGACTTCAACACAGGCTAACGTTTCTACATTGGCAAGTAACACAGTCA 14700
 M 1
 - E N G D S A D U G U C A L T E U N A F Y C L D 849

U4

TTCTGAATCTTGTCAAGACCCCCAGCTTATACCTACAGCTCTTACATCTTTTCTGGACTGGTCTGGAATTTCCATTCCCAAAATTTCCAAATATT 14800
N Q I K D L G G L K Y G U A R U D K E P S T Q F N G N G F N G F Y K 816

TGAGACCACTGAAAAAAGTGCCATTGCTCCATTAATGTTTTGTGTTACTTAATATTCAGCTTCGATGTTCCAGATCGATCTCTCCAGCACATCTAT 14900
L G S F F L A M A G N I N K T N S L Y E A E I N U I S R E L U D I 782

GAGCTCTTTTCTTAGCATTCTCATGAGAACCTGGTGTAGATTATTTGCAGCAACCAAGTCCGTGTGCTTCGCAGGCTGCCTTTGGATGTAAGA 15000
F S K E K A N U I F F G P A L N N A A U L D T H K A P Q R Q I Y L 749

TGATGCAATAAAGCTTTCCATGAGGTTGTTTCATCATAGTTTTTGTAAATACGGAATTTCAAGCTCATCTTTATCACTTCTAAGCAGTTGAAAATAA 15100
H H L Y F S E M F N T E D Y N K Y Y P I E F S M K I U E L C N F I F 682

AGTTTGGAGGTGTGCCAGGGTTTCTGCAATATCTTTAACCTGCTTCAACATATTGAATAAACGATATTGTTTCATACACCCCTTACTGCCAGTTTCAT 15200
N S S T G P N R U I D K U Q K L M N F Y U I N N M C G K S G L K M 649

TTCCATTTCCATGCTAGACTCCAGTTCTTTAATTCATCTAAGTACACATCATARTACATTTTCAGTTCAGTAACCAAAACACTGTTAAGAGTTTGAATT 15300
E C E M S S E L N K L E D L Y U D Y Y M K L E T F L U S N L T Q I 616

ATGAAAGCAAAACACAATGTTACTAAGATATTCAACAGATTCTTTTGTCTGACCCATATCCACAGTAACCGAGATAGGAACCTGGAAATGTTCAA 15400
I F L L F U I N S L I N L L N R K D Q G M D U T U S I P F R S H E I 582

TCTGCCCTCAATAAACTTAACACAAATCTTTGGCTACAACATAGAAAGATTAGATATTTCTCAGATAAATGTGGAATAATAGGTAATCGATCTT 15500
Q G E I F S L C L D K A U F M S L N S Y K E S L H P F I P L D I K 549

ACCAAGCTGGAAGAAATGTAATTTGACAGAGCCAGGATTCTTTTTCATGTGCTACATTTTTAACCTGAAAAAATGTATCGACATTCTTCGCAA 15600
G L A P F F H L K U S G P N K K M T G U N K F R F F N Y R C E E C 516

CCACAAATAGTAAAAAGTGCTCAAGTAAGTACAACTGAAACGATCAAAAAATCGCGTCTGAAGATGATTCTGTTTTGTTTGCATTTCTGCTTAA 15700
G C F L L F H E L L Y L Q F R D F F D A R F F S E T K N Q M E T K F 482

AAGATTCTGCTCAAAATGCACAGCTAAAGCCCCCTAAGTTCTGCTTAGATTCTTTACTCAATTCCTCAATTTTCCATCTAGTTAAAAAATAACATAGA 15800
S E S W F A C S F G G L K Q K S E K S L E K L K G D L K F F L M S 449

AAGGTACTCATATAGGTAGGCACACCATGATCCATTCAGGCTTAGCACCAATTAACATGATGCCAGAAATAGAACCTACAGCTGCAGTTTA 15900
L Y E C L Y A C W Y G I G P K A G L N F L S A G S Y F G U A A L K 416

GTAATGCACTGCCATTTGGGGTCAAAATCTTCCATAAATTTAAATCGCGCACTGCAAAAGAAATTTATCAGCCCTTGTGAAGTTGATGGACTTGA 16000
T I C Q W K P D F D E M F K L D R L Q L L F K D A R T F T S P Y K F 382

ACATTTCTGACTCATAGTCTATCAACCTATTCCAATAACACCATCTGAACATAATCTTAGCCCTTTTATTCARAGCGTCCAGCAGCTGATGCTTGAG 16100
M E Y E Y D I L R N W I U G D S C L R L G K I G F A G A A S A Q L 349

GCGTTGATTAGTCTGGATTCTGTACCCGGAACATGTACTTCAGTTCGCTGCTCCGTTTGGATGATGATTGGATGTAGAACTTTGTAACACTTTGA 16200
G N I L R S E T U P U I Y K L E T D G N P I I I P H L F K T U S Q 316

ACAAGAGGATTACTGATTTTCAGATGAGTGCCTGCAACAGAACTTGGCATGTTCTTCAATAATCTGAAAAGACATCCATGGAACCATCAGTARGA 16300
U L P N S I E S S H U A F L I S P M N K L L < start of U7 exon 2 294

U7
exon 1 < end of U7 exon 1

GTATTGTGTAGAGATACCGAAAGAGAGACTTTGATCTTTACATACCTTATCACACCTTGGATACATATGCCGTGGTTTCTCCGAGAAATCGGAGACTC 16400
R D C R P Y M H R P K K R L I P S E 276

TCCATTTAATCTGTTCAATTTTCCGCTCACTTTCACTCACATAAATCAAACTGTCATCATGCCAGTTTCCAGGCGATATCTTTCTTTGTATAAGAGT 16500
G N L M R N L N E A E S E S U Y I L S D D H W N L A Y R E K Y L L 243

TCTTCAACCTCGCCTGATAAATCTCTAATAGACCTTGCACCTTTGTTGATCTGTTATCACATAACATAAATGTGAATTTGGGACCTAGTAGGA 16600
E E F G R A I F E R I S R A U K N I K N D C Y U Y I H F N P G L L I 209

TGACAGCTCTACATTTGGCTCTACCTGACATCTCGCGCAGTTCCATGACACATACCTTTCTTCTAGTATTTTTTCGGAATACCAGAACCTGTGAT 16700
U A R C N P E U Q C R A C T G I U U Y K R R L I K E L I G S G T I 176

GTAATGGATCTATTGGAAGACAGAAAGCAAAATCAAAATTTGAAAGCATGATACGAATTTTGGCCACATTGGCGATTGACAAAATCTTTAAG 16800
Y H I D N S S C F S L D F N Q F A D I R I K Q G C Q R N U F N K L 143

GCTGGAATATTTTTTGTAGAGTACGAACTCCTCAGGCTGCATTTGGTTTCTCCGTACCACAGTCTGCTAGCTCATATCTAATCAATCCTTGCAA 16900
A P I N K Q L L U F E E G S C K T E G Y W L R D L E I D L E I R A F 109

AAGGTGGGAATTTCTCAGCCGATACGCAAAATGTGCAGGAGATTCCGCTATGATGTACAAATTCATCTGTGACCGTATCTAATGCAAGCATCTTATT 17000
P P F N R L G I S C F H A P S E A I I Y L E D T U T D L A L M K N 76

TGATGAGCAGTACATCAAAATGATCAAGTCCGGGTCCGGTTCTCGGTAATTTGGATGTGCATAACCAACAGCGCAAGAAATTCGTCTGCTCCTACC 17100
S S C Y M U F P D F D P D P E R Y N P H A Y G U A C L F E D A G U 43

AAATTACTCCAATCATAAGTGTGACACTACGCTACATTTGAATGATAAAATTCGCCAAATAAAGCACATAGTTTGGCGCCAGCAAGACAGCACT 17200
L N S W D Y T I U S R A C K F H Y F E G F I L U Y N P P W A L C C K 9

TTATACCATTCGCAACTATCTCCATGCTTCTCCATATGAGACAGCAGCACTCAACGGCAAAATCAAAAGACGGTAATCCGGAGTCGGTTCATGCA 17300
I G N R U I E M 1

AACATCATTGCACACAGGAACAATTTCTGCAAAATTAACCTGTGATTAGTACTTCGTCACCTTCAGAAAATTAATAACCATAAAGTACTGTTACTT 17400
< start of U7 exon 1

ACTTAGATACCGAGGAGTACTGTTGAACCGGTGCACTTCCAAGAGTTGATAATCTTCCAATCTGGCAGTGACTTTTCCAATTTTATCATACCAAAATCT 17500
 S L Y W S Y Q Q U P A S G L T S L R G F R A T U K G I K D Y G F D 329
 CCACAATATCTCGCGAAGCCGATCCTTGC AAAAGTCAGTAACCAATCAGCAATCCGCGTCAACACTTTATCAATCCAATCATAATAATAATTGCTCCTG 17600
 G C Y R A F G I R A F T L L C D A I R T L U K D I W D Y Y Y I A G T 295
 TTTCTCCAATGCATAGATTGGTCTCAACCATAGTCTTCGGCTGAATATTTAAAAAACCTAAACAACTACTTTTCAACAGTGCCCTCTGTTCTTC 17700
 E G I C L I P R L G Y D E A S I N L F G L U U U K E F L A E Q E E 262
 AATCTTTTTTGGTCTGAGGTGCCACAGTGATGTTTTCTGTCTTGCAAGGATTACGCTGTAAGATTGGAGTTTCCAACGAAGTTTAAACCAAGTG 17800
 F R K Q D S T G C H I N K R D Q L I L A T F I P T E L R L K L G T 229
 TTTATGAACGAAGTGTTCATCTCTGCTAACGTTTTACACCTTGC CAATTCATCTAATTCGGAGAGCATTGAATATAATTTCTCTCAAGCCTTTTA 17900
 N I S U F H E I E A L T K C R A L E D L E S L M S I Y N R A R L A K L 195
 GTGCCAAGCTGTTTTCTGTAAATCTTAGACAGTAATCAAAATTAAGTGGTTCCTGTAATATCTAAGTCTTTAAGAGTCTCCAATTTTCAAACTT 18000
 A L A T K R N F R L S S N L N L P E Q L L G L D K L T E L K E F K 162
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 P G D Y Y F R T Y U P E S C T I U N T G L I G F R U F K D F D E A 129
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 I Y Y L U D D E L D H C F I R S S K G U F I P U D K R G I Q I A G I 95
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 L C L N E K F G Q Y H D N L E A L Q Q E S Y G A U D U P Q A L R L 62
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 W L N K P W I L S L C E N R H R E T L L R I G P F D T F R C L N K 29
 AATCCCTTAACATCCATCATTTAGTTGTCCACACAGGCAAGTTTATATTGTTCTGCCATCGTCTCAAATTTTTCATTGAAGTGAATGTGGTAA 18500
 L E R L L G D N L Q G U C P L T K Y Q E A M T E F N K M 1
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 TTTTCGCCCTAAGTAAC TACCTTA AAAATGGCTATAGCAGAAAGCGGAGCGTTCGAATAAATGTCAATCTTGGAAATCCATCGCTTCCATACAAAA 24
 N P I I Y M R R H L S F Y U E L L K F I I H Q Y E Q C F L P P K G 57
 AATCCTATATCTACATCGTAGACATCTCTCTTTTATGTGGAGTTATTA AAAATTTATCATTCATCAATATGAGCAATGTTTTTACCACCGAAAGGA 19000
 T I L Y H N G L I E L N T L I I D L N Q Q I T S K Q Q I Y S W T S I 91
 CGATACTTTACCACATGGCTTAATCGAATAAATCTTAAATATCGATCTGAATCACAATTTACATCGAACAGCAGATCTATAGTTGGACGAGCAT 19100
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 W L S G S F S F P L S L S C A Y A L T G U S S T I Y M L P F I P Y 157
 TGGTATCTGGGAGTTT TAGCTTCCATGAGTTAAGTTGTGCATACGCCCTCAGTGGCGTATCTTCAACATCTATATGTTACCATTTATCCATATA 19300
 K F P M T Y U D F S T L R T Y E U T S E Y G S I Q I I K Q R N F L F 191
 AATCCCAATGACTTACGTAGACTTTTTCGACACTTCGAACATACGAGGTACAGTGAAATATGGATCAATCCAATTTATAAAACAGCGGAATTTTATT 19400
 L G I I R D L S W K S Q R D N K N F I L K A M F U G N W L G I Q I 224
 TTTGGGAATATACGGGATCTGTCATGGA AAAGTCAGAGGGATACAGAATTTTATCTGAAAGCAATGTTCTGCGAAACTGGTTAGGGATACAAT 19500
 P E A F A L R L F N N T R F S I Q D F E F S I N I Q N I N L T R D 257
 CCAGAGCTTTTGCAATGAGACTTTTATAACACACGGTTTTCTATTCAGGATTTGGAATTTCTCATTACATACAAAATATAAACCTTACTAGGGACA 19600
 N K I L G S L S T U S C D Q M P P N L S P E N L P N Y L U I Q F E L 291
 ATAAATTTTGGGTCTCTTTCACGGTTCTTGTGATCAGATGCCACCAACTTGTCTCCAGAGAACTCTCCAACATATCTAGTTATTTCAGTTCAAT 19700
 U S T L A N P D H L L F S C N P K L F F T G D I L N S A I N L Q H 324
 GGTTTCAACTCTCGCAATCTGATCATCTACTGTTTTCTTGCAATCCCAATTTGTTTTTCAAGGAGATATCTGAACAGCGCTATAAATTTACACAT 19800
 S P N H Y E L T U V A P H N L H F Y P S C F H I U T L P I Q F S S 357
 AGTCCTAATCATTATGAGCTTACAGGTACGCCACCATAAATTTACATTTCTATCCAGCTGTTTTTATATAGTAACATTACCAATTCAGTTTTCATCCA 19900
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 GAATGATAGACAGATGTTGGTGTCAAGCTATCTAATGAAGGCTACTTTGAAGTACAAATGTGCCCATGGGTACAGAAATCTCCTCTTCAATTTGTTAT 20000
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 Q E L K I N K D I T R I G N U N L P K E N F L H Y N S - 451
 CAAGAAATTA AAATTAAGAACATTACCCGAATAGGAACGTAACCTTCAAAAGAAAATTTCTTACATTATAATAGCTAATCTTTATTCAACTGTG 20200
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 - U U D E E S H T L H S U L K N U I D D D K Q U S N E L D I L D K 724
 TATCGCCATCTTCTGAGCCTTGCTAGCACCGAAAATGGTATTTTGCCTCTCTTGGCTGTTAAAGTGAACCTGAATCAAAATCTGGATTTTCAGCAT 20400
 D G D E Q A K S A G F I T N Q T E K G T L L S G S D F D Q I E A N 691

U10

U11

TGTTAAAAAATGGAGACCCGACAGGCTGCATCTTTTCAGTGAAGCTAAATTTTGAATAAAGGATCTCTCTTTCTGGAGTTCAAGTAATCTTCAGG 20500
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TTGTTGTCATTGAAGTCGCAATGTTAGAACATCTGTTTTTTTCGGGGGTCGAGTACGCTTTTAAAGCTTCGCTCTTCTAACTAATGTATCCGTAA 20600
N N D N F T A I N S U D T K K P P E L U D K L S R E E L S I T D T F 624
AATCCGTTAATAATTTCTTAACCTTTTACCTAGTCCTGATTCAAAAAGTTCTTTTGAAGAGATCGTTCCTTCTACTAAGATCCAGTAATGAAGAACT 20700
D T L L K K U K E G L G S E F L E K Q L L D N R R S L D L L S S S 591
CGGAGTCCACTTCACATCTTTGACTAATGATTTTTTTAGCTGAAGAGCACTCTCTTTTCTTTCATTGAAGCGTTTACGCTATTAGTACCTATCATA 20800
P T W K U D K U L Q N K K A S S A S E K E K M S A N U D N T G I M 558
TTTAAAGTCTTGGTGGAGAAATTTGCTTTATTTCCATTTTTTTGCTTAATGCTTTTTTGATCTTGTGGAGGCAATGACATTTTCATTATGCTCGTCATCAA 20900
N L T K T S S N A K N G N K Q K I S K Q D Q P P L S M E N H E D D F 524
AACTTTGTAGTTCTCGTGGACAAATTTCTTTTCTGCGTTTTTCTGAAGGAAGTTAAAAATGCTTTCATTATTTTGTGTTAATGTTTTGATTGCTTCTCG 21000
S Q L N E H U I E K R R K E S P L K F I D E N N Q K I T K I R E R 491
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L E L I K Q L D N T S N K S L Q D R S Q U G N Q R N U E N E P L F 458
AAGGTAGAGTGATAATCAATTTTATTTTGGGTAGCTGAAGTACGTTAACTTTTGGTGAGTAACTGCTATTACTTTGTTTGAAGTTGTGTAGATCTA 21200
F T S H Y D I K N K P L Q U U N U K P S S U I D I U K N S N H L D L 424
GTTTGCTCAAGGTATCTATAACTTGGTTAATACCGTCTGGTGCCACAGCAATTTTCATTGAATGGTTTACTTTGTCCTCTGGTCTGTCATAGTTTGATC 21300
K S L T D I U Q N I G D P A U A I E N F Q N U K D E P R H M T Q D 391
AGTTAAATCAAGTATTTCACTGCTAGTATTCTGTGCATTTTTTTAGAAATGTTTATAGACGTGGAAATTTCTTGGCTCGTCCAATATCATGGAATCCTTT 21400
T L D L I E T Q L I R H M K K S N N I S T S N R P E D L I M S D K 358
TTTACCAGGATAACAACCCATCTTCAGAGCCTACAATAAATCTTTGGATAGCGTGTGTGTACTCCGTTGTTCAAGTTTTATAAATGGTCTGGATTAA 21500
K U S S L L G D E S G U F L D K S L T N N S R Q E T K I F P E P N F 324
ATGATGAACCATACGAAGTTTTTTAGAACTACTCTCAATGATTGCTTAAGACGATTTTCGACAAATCTGTTAAACTTTGAATGTCTGAATCGGTTT 21600
S S G Y S T K K S S S E F Q N S L S S K S L D T L U K F T Q I P E 291
AGGAGTAATTTTACACGATCATCCCATGTACTCTTACGGGAGAGCATGTAAGTCAAGACTTTTGTATATACATCAAGTCTTCGGTTAAATTTTA 21700
P T F K U R D D W T S K U P L A H L E L S K T I U D F D E T L I K 258
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F F S T U R H S T L P L S L I Q Y S Y I S U F N K N N E I A K L I A 224
CATTTTTCTTTTCATTATGATTTAATGCGAGTTTCTCCATGTTATCCAGGATCCATGTAATGTAATTAATAAATTTCCCAAGATAAGCAATCGATT 21900
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I N T U Y Y G N E N W P D U I Q Y I T F S L M N N K A K Q L N E G 158
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I E A R E E T T L N U Y D A A H T U T G W R L F S G L K L L D K A U 124
CGTTTTTAAATTTCTGTTTCAAGCCCACTTTGTTAAAGATGTTAAACTAGATAATCAGTAATCATCTGTCTTTGCTCTAAGTAATCTTTTCAAGATTTT 22200
N K F E T E F G U K N F S T L S S Y D T I M Q R Q E L Y D K L I K 91
TTGCACCTTTAGTATTTCTTGCACAACTTCCTCATAGTCTGGTTTCTTTTACACAGGTTTGATGAAATAAATCCAAAGATCAAAATGTTGTAAGT 22300
Q U K L I E Q W U E E Y D P K K K C L T Q H F Y I W L I L N N Y L 58
GTTTTACATTGTTAATGGAATTTCCAGTTTAAACGATACATTGACTCAAAATCCATGGATTTTTCGCAATATCAACACTGGTAAGACGATATGTTTT 22400
T K U N N I S N G T K U I C Q S L I W P N E R I D U U P L S S I N E 24
CAAAAAATCGAGATAAAAAACACTTTGCTTCATCCGAATCCAGCAAGGGTAATGTGACATTTTCTGACTCGTTTTTCTGTTGAGCATTATTGAA 22500
F F R S L F C K A E D S I W A F P L H S M K M 1

U12
exon 1 M D T L I D F Q K I L 11
CACTTCTAAAAAATAGTTTAATAGTCTCTATTTTCTCTTTGATTAGATACATGCGCTGCCGACATGGCACTCTAATTGATTTCAAAAAATCCTGGT 22600
end of U12 exon 1 >

U12
exon 2 H D E E 15
ATGATAATCTAATGTTATGATTTGCTACAGCTTTGCTAAAAATGTTACCTTTGCAATTTTATCATCTTGCAAACTTTTTTTCACAGCATGATGAAGAG 22700
start of U12 exon 2 >
Y K Y N Y T C I T P T U R K A Q R L E S U I N G I M L T L I L P U 48
TACAGTACAATTATACGTGATTACGCCACAGTACGGAAGCCCAAGACTTGAAGCGTAATTACGGAATTATGCTACGCTGATCTTCTGTTA 22800
S T U U I C T L L I Y Y K W T K Q T I T S P Y L I T L F I S D S L H 82
GTACTGTTGCTATGCACTCTGCTAATCTACTACAATGGACAAACAGACATTAATCTCCATATCTTATCACACTCTTTATTAGTATCTTTACA 22900
S L T U L L L T L N R E A L T N L N Q A L C Q C U L F U Y S A S C 115
TTCATTGACTGTGTTACTTCTCACTTGAACCGAGAGCTCTCACAACCTTAATCAGGCTTTGTGTCATGTGTGCTTTTGTATACAGTGCCTCTGC 23000
T Y S L C M L A U I S T I R Y R T L Q R R T L N D K N N N H I K R 148
ACATACAGTCTGTGATGCTAGCAGTAATATCCCAATACGCTATCGAACCTGCAAGAGAGGACATTAACGACAAAAACAAATATCATATTAAAGGA 23100

N U G I L F L S S A M C A I P A U L Y U Q U E K K K G N Y G K C N I 182
 ACCTTGGAAATTTATTCTGTCTCTGCCATGTGTGCCATTCAGCAGTATTATATGTTCAAGTGGAAAAGAAAAAGGCAATTTGGAAATGTAATAT 23200

H I S T Q K A Y D L F I G I K I U V C F L W G I F P T U I F S Y F 215
 ACACATCTCAACGCAAAAGCATATGACTTGTATTATAGGAATTAARATTTGTCTATTGTTTTCTCTGGGGAAATTTTCCAACGTGCTATTTTCAGCTATTTT 23300

V U I F G K T L R A L T Q S K H N K T L S F I S L L I L S F L C I 248
 TATGTGATTTTGGTAAGACCTTGCCTGCTTGACCCAAGTAACATAACAAAACCTGTCATTCTATTAGCTTACTGATCTATCCTTTTTATGTATTC 23400

Q I P N L L U M S U E I F F L V I A N T S C L G T I Q R E I U Q I I 282
 AAATACCAATCTCCTAGTATGTCTGTGGAAATTTTTTTTTTGTATATAGCAATACTCTCTGCTTAGGCACCATACAAAGAGAAATTTGTGCAATAT 23500

S R L M P E I H C L S N P L U V A F T R T D F R L R F Y D F I K C 315
 ATCTAGATTAATGCCGAATACACTGCTTGTCTAATCCGCTAGTATATGCATTCAGTACAGACAGATTCCGATTACGATTTTACGATTTTCATTAATGT 23600

N L C N S S L K R K R N P L T I K N - 333
 AATTTGTGTAATTCATCTTTAAAGAGAAAGAAATCCTCTGACATAAAATTTGAACAGTGAAGCTTGCTTAAACCTTTGAAATTTTTTGTGATTTT 23700

U13 ----- M T L N O Q P S N C R L I T A N D P U L 20
 AAATAAAATTTAAATCAATTTATCCTAAGCTTTTCAGGCTATGACTTTGAATCAACAGCCATCTAATTCGAGACTAATTACAGTCAACGATCCAGTACT 23800

A S N F T M Q P T F K I A D K K U U L R D H N Y I A U K D F U L S 53
 TGCATCGAATTTTACAATGCAGCCTACTTTTAAATAGCCGATAAGAAAGTGTACTCAGAGATCATAATTACATTGCAGTCAAGAGATTTTGTCTATCA 23900

R S F M H C I R C Q E K I E K K T S D S I R A Y S I K P D F M F Y 86
 AGGTCTTTTCATGCATTGCATTCGATGTCAGGAAAAATGAAAGAGAGACATCCGATAGCATTAGAGCATATTCATTAGCCAGATTTTCATGTTTTATG 24000

D S D D E U R S S P F L - 98
 ACTCAGACGACGAAGTTCGTTCTGACCATTTTATACAAATATTTAAAGTAGCTGAATGTACGTTCTGAACAGTCTGAACGGATCCGCTGAACGCAG 24100

U14 M E Q Q K G F S I P F F U T D E N C N F U P E I L P R I H T K F 32
 ACACATGGAACAGCAAAAGGATTTTCGATTCCATTTTGTCTACTGACGAAACCTGCACTTTGCGCTGAATATTACCTCGTATACATACTAAT 24200

L K D U L I A D S Y N S U S W A N S F I P M P I Q T L E Q I M U L 65
 TCTTAAAGATGCTTAATTTGCCGATTCCTACAACTCTGTTAGTTGGGCAACAGTTTTATTCCTATGCTTCAAAAGCTTGAACAAATTTATGTTCTT 24300

I T K F K F S R S R D F L F P U I R L A U H I N R F H T G K K Q L 98
 ATAACAAAGTTCAAGTTTTCTCGCTCGCGTGATTTTTTATCCAGTAATTCGATTAGCTGTTTCATATCAATAGGTTCCACACAGGGAAGAACAGCTGA 24400

K T M I E I M K S L F N T E E A M R R F D E A L M I L F S N E Q T N 132
 AAACCATGATAGAATTTATGAAGAGCTTGTTAACACCGAAGAGGCTATCGACGATTCGATGAAGCATTGATGATTCTATTTCTAATGAGCAAAACCA 24500

T Y M T N I A L S M H E N G L P D S K F M N A L K M I Y R A G N S 165
 TACTTACATGACAAACATAGCTTTATCGATGCATGAGATGGTCTTCCAGATTCAAATTTATGAATGCTCTAAATGATTTACAGAGCTGGAATTTCT 24600

F D N Q P D N D I E S Y N E K L K I Y N Y L I K I P K Y T L K A G 198
 TTTGATAATCAACGAGCAATGATATGAAGAGCTACACGAGAAATTAAGATCTACAACTACCTAATTAATTAACCTAAGTACACACTAAAGCTGGAG 24700

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 TTGATTTATATGAATATGAAGATCTTTTCGATTGGAATCCAAGACAACTACTTTATTAATTCACATCTCGTAATGATTTTTCATTGAAGCTAT 24800

Y N D U L F L U S A W N M I I N Y K K E Q R A L F S W I T F E I N 265
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S L M E N U U L A A F Q L P D L K E M T L D L S A L I A N M N L L 298
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K P N D D Y S P H F K L I I N K F F E I G I F U T K S Y I C I L P S 332
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F U K S Q L I S F E N U L S S N R H A E D U T F I L T S S K E S D 365
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D E Y D E D K P P R Q U D P D R V D N I L M E S D F F N U K P E N 398
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A F S E I A L M P I S H D K I I D U N N S N I Q U L E T E L A H T N 432
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S T P A R N S N S I R T T P U L N I S R P G S T T P S G N S A R Y 498
 TCTACACCCGCGGGAATTTCAATTTCTATTCGTACAACTCCAGTTCTAATATATCCAGACCAGGAGCACTACACCTCTGGGAATCTGCAAGATATG 25600

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P T F R U S R S A T P I E R S S R S A S I I S G E S U P G F F N D 565
 CCCACGTTCCGTGTTTCTAGGAGTGCACTCCATAGAAGAGGTTCCAGATCTGCTAGTATATTTCTGGAGAAATCTGTTCTCGGTTTTTAAATGAC 25800

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D E D S M N A P Q S P Q S I V S I S S Y U S T D D Q L L H S P T N S 632
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 exon 3

 ATTGTTTGATTATTTCCACGTTTTTTAGCTTTTGAATAATCTCAATTAACACATCTCTGGTCAGTTGGAGTCGTTCTATGTATGAAAAAACATTATCG 26200
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< start U15 exon 3
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 N E H E D D G L R L H S E E L F 131

< end U15 exon 2 < start U15
 TAAAAATGATTTTCTTACCGCATAATCATGTTTAAAGAAAGTTGCTTTTCATGCTTTGTTGTCATCATATACATAATGCTGTGATTTTCTGAAAA 26400
 A Y I M N L F L Q K E H K T T M M Y L L A T I K 107
 U15 exon 2

exon 2 < end of U15 exon 1
 TAAAGAGCGGGGTTAGACATAAATTTTGAARACTCGTTTGTGTAAGATAATAGAGGTGGACTACCGTTTTACAGGTATGTGTGTAATTGAGCGAC 26500
 R K U P I H T F Q A U 96
 U15 exon 1

GATATAACATCCTCAGTTTTGTGGACATCTAGATTGAARATCTGCTTGATTCTTGCCATCTCTTAATAATAAACAAAGCTTCAATCACTACAGACTTT 26600
 I Y C D E T K H U D L N F I Q K I E Q W R K I I F L A E I U U S K 63

GTCACAGTTGTGTTAATGTTAATCCAGAAAAATAATCTATATGTTGATTAAATCCATTTGAAAAAGATATTTTATATAGATTGTCTCCACTTTAG 26700
 T U T T T L T L G S F I F R Y T T N F D M Q F L Y K I Y I T E U K S 29

ATATAATATTAGATAAGCTCATCAATATCTGTAGTGGACACAGCTCGCGAAATTCCTGTAGTCGTTGTCTTCCAGGTTTCCATTTCTCACAAGAGAA 26800
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 ----- - I E 329
 U17 exon 2

CGTCTTCATCAGATGTATCCACTTCTCTGAARACTCTCACTTAATATATAGCTAATCCGGCAGCGGTGGGAGGTCGGATAAATTTTCATGAGTAATTTG 27100
 D E D S T D U E R F D E S L Y I A L G A A H P C T P Y I E H T I T 296

TAATTCCTTGGAAAAAATTTGTATGTGCGATATGTTCTAATCTATCCCTGTCTTAATAACATTCAAATTTTCTGCAATTTTGACACAGGGACCGATC 27200
 L N R P F F K Y T R Y T R U I G Q R L L C E F N E A I K U C P G I 263

CCGGTTCCAAATGCGTCAATACCATAAATAAACCTTTTAAATCCATTAATAAATAACTTTTAGGAACATTAAAGTTTTTACCGACGCTGCCAATGA 27300
 G T G I A D I G Y I F G K L D M M L F L S K P F M L N K G U S G I I 229

TATGTCATAGTATGGCATATGTGCATAACGTCAGCTAGAAAATTCATCTGTGCGATTAGGGAATTTCTCTTTTCTGGTTAGAACAAACTAGTTT 27400
 H G Y Y P M N D Y U D A L F N W E T R N P F E E K R T L F L U L K 196

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 U D N K A S L F G I U Q L R E N C C L L Y C C 73

< end of U17 exon 1
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 L D Q L E T E S T T R F P M D R L P S I 53
 U17 exon 1

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U18

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Y S A S L D E L E K Y K Y W D L W S S K W T K R L F R K Y I T E N 208
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U19

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U20

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U21

U23

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U24	TGTTTTAAGCACGCAAAAAAGTGCTGGAATCGGTGTAATAATTCAGGGCTTCGTACCCCATATCGAAGATTGAAGATGTGTAGAATAAGAATCAGACA	34800
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	TAGATAACCGATATTATGAGACATGCCAGTATTATAAAGTCCCTCTTCGGCGCACATTTTGTATTCAGAACTAGAAGTTGAATTTATTGTTCTTGGT	34900
	L I U S I I L C A L I I F T G R R A R U N K I E S S T S N I T R P	32
U24a	GATAGATTTTCTGATGCAAAAAACGGATGATCGTGGACATTTGCAACATTACATCATTATAAGAAGGTGGCGGTGTCTCATGAGTCATCTTCTAGG	35000
	S L N E Q H L F U S H D H F M Q L M U D N Y S P P P T E H T M	1
	- P	57
	GATATTAGAGCACCTGATAAATGATAACATATTCTCTGCTATTGAAGGACTTATATAATCATGATATGCAATGCAAGCCAAAATAACAGAACAAACAA	35100
	Y K S C R I F S L M N E A I S P S I Y D H Y A I C A L I F L U F L	23
U25	ATAATAAATCCCTTTCCACCAATCTTCATAGGCTCTGCGAAAAAATGGTGTACTTATAAAACATTATGTCAGAAATTATTTTTTCTACCAACACTTTT	35200
	- L U N H A S N N K R G U S K	307
	Y Y I G K W C D E Y T E P F F H N Y K Y F M	1
	CCATAGTAATGGTTGTTAAATATGTTCTTTTTCTTTTCAAGTATTTCCCATGGACAGTTGATCTGCCGTGAAGCTCTTCTCCACATTTCTA	35300
	W L L P Q K F I N R K K R K C T N G W P C N I Q R S L E E E U N R	274
	ACATCGTTTGTCTTTCAACCAATACCCATGTAGTCGACGATTTTCATTAAATCGTAACAAACCGATTTTCAAAATTCAGTTATGTTATGTGCGAGAA	35400
	U D N T R E F W Y G H L R A N E N F R L C G I K L F E T I N H A L F	240
	AAATGATTTGTTTCATCATCTACCAAAAAATTTCCCATTCACATCGAATATTATCACAAGTTCAAACCACTTCCCAAAACGTTGTGTTTACACAAAA	35500
	I I Q E D D U G F I K G N U D F I I U L E F W K G F U N H K U C F	207
	AAGAATCATACAATGTTGCACGAATGACCTTTTCCACGGTGAAGGTCTTGATCAGTATAGGTGTATGGGAGTCTGCAAAATCGTGTGTATGTT	35600
	L U D U I N C R I U R K W R H L D Q D T Y P T M P L R C F A T Y T	174
	TTATAAGGACTACTTTTCAATATAAAACAAACGTTATATTTTTCATCCCTATAAATGATCATATCAGAGAAAGATTGCTATGCTCCACGATTTTGCTAC	35700
	K Y P S S K L I F C U N I N E D R Y I I M D S F S K S H E U I K S G	140
	CAGTTTCAAGTCCACGATAAATCACAATTCGTAGATGGGGTAGAAAACTTCAATCTACTAAAAAGAAATCTTGAAGTTTGTGAACATAGTA	35800
	T E F D U I F D C L E Y I P Y F F K L G U L F F D Q L N S S U Y Y	107
	AAGACTTTTGTCAAAAAACCATTTGTAGACATACAATGCCCTCTGTACCTTGTAAAGAAATGGTCTCTGCAAGTTGATTTTTTAACTGATGTAACT	35900
	L S K D F F G N Y U Y L H G R D G Q L L I P G R C T S K K U H H L	74
	ACACCAACACGATCAACGTTTTTCAACACACAGTAAGTGTTCGAATTTCTTCGATGTCTTCTTTGAAATTTCTGGGATTGTTTCAATGAGTGAA	36000
	U G U U I L T K E C C L Y T N R I E E I D E K S I E P I T E L S H F	40
	ATGTAATCGCCATTTCTTGGGAAGGCAATACGAAGATGTACCTTCTTACTTAAAGATGAATTTCTCGAGAAGAGTAAGTTTATTGACACAGCACAA	36100
	T U R W E E P F P L U F S T G E K S L I F E E L L T L K N U C C L	7
	ATTGCTAAGAAATCCATGCTTCAGTTTTAAATTTACCCAGAAAAAACAAGGCAATAATTTTCAATTTTTTTTTATTAGCACATTTAGAGCTGCA	36200
	N A L F D M	1

U26	AATTTTCTTTAGAAAAAATTACAAGCAAGCTGAACAAATAAAAAAGGTTCAACAAATCGCCTGTAATAATATCTTTTCTACCCACTGTTTTGAATTT	36300
	- F F I U F C A S C Y F L N L L D G T F I D K R G U T K S I Q	264
	GAGCAATAGAGCGCTATAACCTAAGCCAGAAAGAACTCAACAAACAAATGAAGAAGAACAAATGTTCTGTTATTACCCCTGCTAACAAACACAGAACTACT	36400
	A F L A S Y G L G L F F E F L S F F C H E T I U G A L L C L I S	231
	ACACAGAACAGTTGATATAGTTTAGTGATAACAAATTACTATGTAAAGCTGCCAGAAAAATAAATGCTGGCACTTTTTCTTGGTAATACAATTTT	36500
	C L U L Q Y L K T I F L N S H L U A L F F L H Q C S K R P L Y L K	198
	CCAAACCAACACGAGCGTTAAGGTTAAAAATTCAGCAATAAACAATAACATCTTTTATAGCCATTTGGTACGGGCCATTGGTTTATAGATCGGTT	36600
	G F W U L L T L T L F Q L L Y U I U D K I A M Q Y P G N P K Y I P K	164
	TGTATCGCTGAAGACATATGCAAACTGATGAGAGTTAACAGAACTTATAACTGGTTACATATGCGTTATCAGAACTGTAAACAGCAATCTGTA	36700
	Y R Q L C M A F Q H S N U L F K Y S T U Y P T I L F U T U L L R Y	131
	ATGAACCAATCTGATATTTTAAACCAATGGCAATAGGGTGCCGAATAAGATGCCATTGAATGCGTTGGAATATTAGCATGCATCTACAGACTATG	36800
	H U L D S I K L U I A I L T G F Y S A M S H T P F I L M C R C U I	98
	GCTCTAAGCGGATTTCAGAAAAAATAAAACGAGCAGATTACCAAAAAAATTCATCGGTCAATTTGCACACGAGTAATGATAAGTTATAATTTGA	36900
	A R L R I E S F F L F S C I U L F F E D T M Q L U L L S L T I I K L	64
	GATCGTTGAAGGACAAATAGTTAAACAATTCACCCGACGGTAGTCAATAGCAAACTCCGCTAAAGGAATATTAGCACTACTTGTTCAAACAGCGT	37000
	D N F P C Y N F L N U R R Y T L L L G G S F L F I L U U Q E F L T	31
	TTTCTTATCATAGATGGAACAGCTTTCTCCCGAATTACATTCCTTAAACAGGCCCATAGAAAACTTATCATTACATTCACATCTTTGCTTTT	37100
	K K I M L H F C S E G P I U N G L U L G M S F S I M U N W M	1
U27	- M G C R Q R K	358
	TCGAATTTGGGTATAGTCAAAATGTGCAGATCGTCACCTTCGCTGCTCTTCTTCTATTAATAAATTTGTTCTGTGCCACCATTTTATGTTGGGCAC	37200
	S N P T Y D F H A S D D S E S D E K E N F F N T G T G G N K T P U	325
	CATGTAACCTGTAATTTTGTGTTGCGTTTCTGTTTACAAAAAATTTATTTCTTCTCCACCTTGTGATTTTCTCTCTTTTCTCTGTTTGTGCT	37300
	M Y S T I K H Q T E Q K C F F N N G E E U K H N K E G K E E T K A	292
	TGACGTTCAATTTTGGGTGCTTTAACTGCTCTTGAATTAAGCTTCTACGGTCAGAAAAACATTTTATGCGATTAAATAAATTTGATTCTT	37400
	Q R E F K P D D K U Q E Q S L Y A E U T L F U N K A I L F L K Y E K	258

TGCCAGCTATTGCTCTAGAGCTACACGAAGACTTTAAACTGCACAGTACTAATGCTTGCTGTAGATTTTTGGAGAGATAGTACAGTCTCATGCATTT 37500
 G A I A R L S C S S K L U A C T S F A Q L N K S S L U L R M C K 225
 TCGCTCGTGAACACACAACTTTCCGCTATGAGCAATTTCTATTTCTGTTTAACTCGGTTAGAAATTTTATCTTGGCGGGTTAACTTGCACAACTATTTGT 37600
 A D H F U U K G S H A F E I E N L D T L F K I S P P N U Q U U I Q 192
 GCCAACGTCATTTTCATTTTATTACTGCGTTTGTCTTTGTGACCGGAGCAGGCCATTTTAAATCTCCGTTACAGTTGAATGGTCCAGTCTATTTCGAA 37700
 A L T M E N K N S R K N K T U P A L W K L I E T U T S H D L D I R L 158
 GTGCAGATTTTCCGCTTCTCTTACAATTTCTTGACCATTGACACAGGAATAGATGCTTGTGCACAAATATCTGATGCCGTGACTAAAAACCGCGTATA 37800
 A S K G S E R U I E Q G N U C P I S A Q A C I D S A T U L F R T Y 125
 GAGATCGCTATCATGTTGAATATACAGTTTGTGACATCAGGATTTGATATAATGCCCATAAACTATCAATAATGGAACAAGTTATTTATCGTTTTA 37900
 L D S D H Q I Y L K T U D P N S I I G M F S D F L P U F N N I T K 92
 GTCGAAAATGATCTGTATCGGTTATATATAACATTCTGCATGAATAATCAGCTTTAAACCAATGGTTTTTTCGAGATTGAATTATGATTGCCGGTT 38000
 T S F H D T D T I Y L C E A H I I L K L U L H N K A S Q I I I A P Q 58
 GAGGAGTAAAGTAACTGTAGTATTTTCTCGAAAAGCTTTGCAAAAGCTCTTAGAGGCTTATTGATTGTTTTCCAGTTTTTCATGTGAAAAGCCATGGT 38100
 P T F T U T T N E R L L K A F A R L P K N I T K W T K M H F A M T 25
 GGGAGGCTCTTTGGAATCTCGATGTTGCGATGATCTCGGTGACTATGGTGTCTCTGTTGCTACGATCCATGCTGCACCAAAATAGATATTACAGGA 38200
 P P E K S D R H E R H D R H S H H E R N S R D M 1

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 - Q F U H 803
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 I G T K F G N Q Y L C U L I D R M N E T K N I F F U N A Q G H D T 736
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 F P L A G U Y M N L M E N U S Y D F A N L F I T M E Q M E E E S F 703
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 L N K N U K S U D Y N U S S L Y E L H N K F R N L F L G N Y U P I Y 669
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 L T Q L E T S Y U S L D S H F U P N P H L U K I S S R K L I K N G 636
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 E I P C F S Q S C N L L D F E K S M A S G S U F T L N R L G Y K K 603
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 R Y H F M D I N T H S K Q E E S U N E U F Y S L N L A I R F A T N 436
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 F G M Q G R A R L C R C I N D L L T E T K I R A H E A T R E C E L Y K 369
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 Y I T L G T T K N T D K E U I Q L Q S L L L E M L S E A E Y H Y R T 269
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 ATTTCTCCACTAGAGGGCATTTGTGACTAACAAACTTTTTGTAATATTCGATTTTTTTTATTGACTGGCCAAATGTACACTGATTCTTAGAAAAA 40200
 I E E U L P C K H S U F S K Q L Y E I K K I Q S A L T U S I R L F I 169
 TCGTTGGATGTTTTCTCGATTCCGTTAATGAATTTGAATCTCATCGAGAAATCTCGATGCAGCTAATCTCTGGTGAACCTTCGCTCTCCAGAC 40300
 T P I N E E I G N F S N S I E D L F R S A A L U G P S F K A R W U 136

U28

ATGGATAGCTGCTTGCAGATTTTTTCAAGTTCTACTTTGGAGTCACGTACAAATTCATCAATTCTTTTTGTAAATATTTTCACTTTCTAAATAAGT 40400
H I A A Q L I K E L E U K S D R U F E I L E K Q L I N E S E L I L 103

GAGATGGAATCAAAATCCGAGCAGAGTTTGTGTTGAGATAGAACTGGCCTAACAAACGATCAACGTCGGTGCATCATGCATTGCTCCAGTGCTGAAA 40500
S I S D F E S A S N T K L Y F Q G L L R D U H P A D H M A G L A S I 69

TTATGGCATCACGTAAGCACCACATATCTAAGCCCGAATTTAAGCGCCGAGAGATTTTGAATTTTCATATACTGCTTATAAGAGAGAGTTTGTGATG 40600
I A D R L C W M D L G S N L R R L I K S I E Y L Q K Y L L T K H H 36

GAAGCGTGATAGCAAAACCGTTTTTGTATATTCATCATGACAAAGACATTTCTCAGAGAGCCCATGTTTTTATTTATGGAACCTTTATTGTTAGGA 40700
F R S Y C F R K K N Y E D H C L C K R L L G M N K N I S U K N N P 3

TCCATAATCACAGAAAATTTTTCTTTCACACAATTCGACAAAGACGCTTTTGGTCTTATAATGGTTAATGAGATACCCTGTAGTCTAAATTCCTGA 40800
D M 1

U29 - L F I K R E C L E U F U D K L R I I T L S I G Q L D L I G S 257

TTTTATGTTTTGGGTTTTACAAATGACCAATTCGTTGAAGGCTTCCAAAATAGTTTAGATTTCCATCACCGTTGATCAAAATAGTTCATAACATAAATCGT 40900
K I N Q T K C H G I R Q L S G F Y N L N G D G N I L Y N M F M F R 224

TCCTTGGAAAACCTGTTTTCTTAATAAATCTATCAATACTTCTTCATGTGTGAGCTCAGATAAAACAAATGTAGATCCCGTATTCTATTTTATTAATGCTT 41000
E K S F K N R L L D I L U E E H T L E S L U I Y I G Y E I K N F A Q 190

GCCTATAGATATAACAGAGGTAAATGTACTGAATTCGATTTTGTCTTGGTCCCAGTCAGGTCCCAATATAAATCTTTCATATGACCAATCCATATAT 41100
R Y I Y C L Y I Y Q I A N Q R P E W D P E L L L D K L I U L G Y I 157

ATTTTCTTTCTTACGTCATATACATGACCTTGCAATACACAGGATATTAGACAAATAGTCCCTTGAGAGATATATAGTTACTCCAACAAAGACACC 41200
N E K R U D Y U H G Q M U C S I L C N T G Q S I Y N T U G F L S U 124

TTTTCTTCTAAGTAGAACACTATCTAACATTTGTGTTGATCTGCAACTAATGAAGTTTATACAGATTAGCTAAGAAGTCTCTGTCGAGAAGACA 41300
K E E L Y S C S D L M T N I S D U L S T K Y L N A L S T R T C F S U 90

CATTGAAGGCATTTCATGGCTAAACCAATCACTAATCAACAAAATTTTGGACTCTCCGCGTCTGTTTCAAGTCTGAACATAAGCATTCTTAATGGTC 41400
N F A N M A L F L U S I L L F K P S E A D T E L R F M L M G L H D 57

TCGTTCAAGTCCTAAAGTTTCGAGGAGTAAACCTTCGCAAGACACACACTCTTTGGGAACACCAAAGCTAGCAAACTTCTGATCTTTTTTTTCTCA 41500
R E P G L L E C P T F S R S L U C E K P U G F A L L S R I K K K E 24

U30 M D C T N L 6

TTTTCAATGAGATATTTAAGGAAGTTTCATCAATGCTGATGTTTCTTTTGAAGCATTTCCATTGTTTCGCAAGCGAATGGATTGTACAAATTTA 41600
N E I L N N L S T E D I T Q H K R K Q L M E M 1

Q F E S I L N L L K T D U S D N T F L T I T A K I E I F S L A A E 39

CAATTTGAGTCAATATTTGAATTTACTTAAACAGATGTGTCCGATAATACATTCTTAACTATAACAGCGAAATTTGAATTTTTTCTCTGCGGCTGAAA 41700

S I T A D K I L S F A K L L P I H N Y H F N F I K N H M U F Y I L N 73

GTATCAGCAGATAGATATTTGTCATTTGCGAATTTATACCAATACCAATATATCATTTTCAACTTTATTAATAATCATATGGTGTATATATTA 41800

Y S T L G F A K R F S I A E T L C R E L K I F H R T F Q S T S K L 106

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Q N L N N A E U L Y Q F E K L I E S I Q U F K A E L A S P I G K L 139

CAAACTTAAATATGCGAGAGTCTTTATCAATTTGAAAACCTTATGAATCCATTCAAGTATTCAGGCGGAATGGCATCGCTATTGGTAAACTTC 42000

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I I F P N D N F L D R L L K M D F C Y T Y Y T A S N Q H L L S L F 239

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E Q T I D N Q I F I D P S P Y F E I N P U V Y S P E L Q F M S T F S L 273

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T T P Q K Y T D K H U S S T U L K N L C D T A Y Q S K M E T A Y E 539
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S L L P Y I T H P E F K F I F I T H Y U R P S L S L I T N L T F E E 573
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I K D N R R L L I L I F A C K L L M P S N Y L L S H Y L L L L H A 606
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F T L Q I F K U D L G H F S I I H A I T Q K I F D N I N S L T Q T 639
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I F I P K T N F L U S L L L T A Y T U H M Q T Y U N P W I Q K T I S 673
TTTTTATCCAAAAACAATTTTTTAGTCAGCCTTTTATTACAGCATACACTGTGCAATATGCAAACTTATGTGAATCCTTGGATACAAAAACAATCAG 43600

E N I A L L K E Y I D F T K K C S S T L A T T C Y L N L E N F A U 706
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N M Y F G K N K U G S T S L S A F Y A T C S K L I E E S K L F K D 739
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L Q N F I I I U E R I S S H A N T T Y Q D U L N S I D E C H F S N 806
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M Q L I Q S F K N I U Y U I D U L N T K N I F N F S L A S Q L I E 839
ATGCACTTATCCAACTCTTTAAAAACATCGTGTATGTCATTGATGTTCTGAATACTAAAAACATCTTTAATCTTCTCGCATCACAATTAATTGAAG 44100

A K K L U K K Q D T Y N Q L N U Q D D F U T U L K S H L N N L F E K 873
CGAAAAAATCTGTAAGAAACAGGACACCTATAATCAATTAATGTGCAAGATGATTTTGTCACTGTATTAAAGTCACATCTAAATATCTGTTGAAA 44200

Q K P T I N I E A R F M L E G I P D I K Q I P F L D U F D E R Y R 906
GCAGAGCCTACAATTAATATTGAAGAAGATTATGTTAGAAGGAATACCCGACATAAACAGATTCCATTCTTGATGTTTGTGATGAAGATATAGA 44300

L I P Q I E K Y L H W Y I A Y S E A A Q A D L U E P L L L K L G - 938
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U31 M R I I A G S T N Q N D P K Y G P R A G K Q C M S N C F S F L H T U 34
TGGAATCATAGCAGGAGTACAATCAAAACGATCCTAATACGGAACAGAGCGGAAGACCAATGTATGTCAAAATGTTTTCTTTCTTGCATACAGT 44500

Y L N G I N N U L N K E S I D I I M E N G A L L D N I S T T T L K 67
TTATTGAACGGAATAACAAATGTGTTAATAAGAGTCTATTGACATATCATGGAATATGGAGCATTATTGGATAATATCAGTACACACGACATTGAAA 44600

L E T G N I P E Y R F F T E I P K K I S S N F G E T I H E L S R P 100
CTCGAACTGGCAATATCCAGAAATATCGATTTTTACAGAAATCCAAAAAATTAGTTCTAATTTTGGCGAAACATACATGAATTATCTAGACCT 44700

F N G T L E S Q H I D N E U Y L G L L D F L L Y G K N K K P A F I U 134
TTAATGGTACCTTAGAATCACACATATAGATAATGAAGTTTATCTTGGACTGTAGACTTTCTATTGTATGGGAAAAATAGAAACACAGCTTTTATTGT 44800

I T I G U M A R A I F I U D E L F V L F D S H A S D T E N S A A I 167
CATCACTATAGGGTATGGCAGAGCTATATTATAGTTGATGAATGTTTTACCTTTTGAATTCACATGCATCAGACACAGAAACTCTGCAGCCATC 44900

Y I C E D I D E L Y A L L A I E N U A E F Y Y D A U F S Y F I E T 200
TATATCTGTGAGGATATTGACGAATATATGCTCTATTGGCCATAGAGATGTTGCGGAATTTTACTATGTGCAGTTTTTTCAATTTTCAATTGAACGA 45000

T D L S L E D G D A T I L I L K T Y K D P D I A L S L N D F L S M Y 234
CTGATTTATCTCTTGAGACGGAGATGCACAAATTTGATTTTAAAGACTTACAAGATCCAGATATAGCTCTTAGTTTGAATGATTTTTTATCAATGTA 45100

S S T S S T K T A E T N T L I S K Q S P S K R K Q E K T S L N S N 267
TTCATCTACATCCTCAACAAAGACAGCGGAACAAACACTTTAATTTCAAAACAATCACCAGCAAAACGCAACAGAAAAAACAGTCTAATTTCAAT 45200

S L E K K R K Q G S S L K Y Y N N E U D L U P S F Y E L R P Q F N 300
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N I L F E L S N F P I U K E N U N W T L Y I Q K F A T K S T Q P F T 334
ATATTTTATTGAGCTTTCTAATTTCCCAATTTGAAGGAAATGTAATTTGGACCTTTACATACAGAAATTTGCAACAAAGCTACACAGCCATTAC 45400

K P F I W N R U F H L F S Q U U D A L I M I K N D H W D E T Q Q Q 367
AAAACCTTTTATATGGAATAGGATTTCCATCTATTTTCTCAGTGGTTGACGCCCTTATTATGATTAACAAACGATCATTGGGATGAGACACACAGCAA 45500

K Q F F T H F L P F K E F S E E F E N A L E A C R E N N L D L I L 400
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L Y K N Y L S K T T A F K N L E R I L L T K F S A I U S P U H E K H 434
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Y T L U N T W L T N L I Q K L U K H P E D T N A F I N D Y U L K N 467
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P L N H F I C L N K K E K Q S I A L L L N K K R M S M L K D U E I 500
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E K N G F U Q L Q A F I E N I G E A P A N Y L D P E N A R K U N U E 534
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E U S E K D I P T L S T D K U S I P N E S M F T S N K K H S I E K	567
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L I H A K L K A I L S T M G Q R L T R I I Q E N Y N N I A A G F L	600
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P U N D L N N L F A Y L U K L Y F D U Y S I T I N G F U U E N E L I	634
CGGTGAACGATCTTAATAATCTGTTTGCTATTGGTCAAACTCTATTTTGATGTCTATAGCATCACCATTAACGGATTGTGGTGGAAAAACGAATTGAT	46300
K N I E Q I Y D N T Q V L R F G L T R F N M Q N L T P F T I S U R	667
AAAAATATTGAACAAATTACGCAATACGCAATATCTGAGATTGGATTGACACGCTTCAATATGCARAATTGACACCGTTTACTATATCTGTCCGC	46400
K M F L D F F L S Q K T L I D R A E E I I E N L E F K S U T P E G	700
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K Q K L A T K N M L R E Q L E Q L N A M D U D D T I N L K T D T L T	734
AACAAAAATTCGCCACAAGAAATATGCTCAGAGAACAATTAGAACAGTTGAATGCTATGGATGGATGATACAAATATCTGAARAACAGACACATTAA	46600
H Q U L F S D Q E L R M I Q D F I L Q L S I H N I P S I N F U K S	767
ACATCAGTATTATTTTACAGCCAGAAATACGCATGATACAGACTTCATTTTCAACTCTCCATTCAATATTTCCAGCATTAACTTTGTGAATCT	46700
L K L H I I L E K R P D I L L A L Q E K U Q N I L Y F Y F Q D L U	800
TTGAATACATATTATTTTGAAGAAAGACCTGATATACTATTAGCTCTACAGAAAAGTCCAGAATATTCTATATTTTATTTTCAAGATCTAGTTA	46800
N E I P A Q E N U L S T M L F I I E L F P A D S R I H L L E T G V I	834
ACGAGATACCTGCTCAGAAAAATGTTTTGCACAAATGTTATTTATAATAGAGCTTTTCCAGCCGACAGTAGAATACATCTACTAGAAACCGGATATAT	46900
S R H I U K K W L N M K S L Q D A E D L I R F I N I N K E Q L G K	867
TTCCAGACATATTGTAAGAAATGGCTAAACATGAATCATTGCAGATGCTGAGGATTAAATCGATTATAAATATTATAAAGAACAACTAGGAAAA	47000
F E H Q P F G K E I Q K L I E K I H L F Y K Q K U I E Y Q E D U W	900
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L D Q K L L I H M E N Q A K Q A M E D D K K R U A C S K I N L E R	967
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H L N D L L L L L K D R Q F A S I Q A S U L I U C E N I F K T I P	1000
CACCTGAATGATTACTGCTCTTATTGAAGACAGACATTTGCTTCCATACAGGCTCTGTTTTGATTGTGTGCGAAATATATTTAAACGATACCAG	47400
D D N L I I Q F S H A L L S U L L D I E K D L K S Y S S E I L E K I	1034
ATGATACCTAATATTCAATTTTACATGCTCTGCTTTCAGTTTACTTGACATTGAARAAGGATTTAAAGCTATTTCATCAGAAATATTAGAGAAT	47500
L I N R P L E T S R L L U F K D A Y G N L K E F L N A L K Q S L F	1067
ACTAATAAATAGGCCCTCGAARCCAGTAGATTATTAGTGTTAAGAGCGCTATGGTAATCTGAAGAGTTTTTAAACGCCTTAAACCAATCACTTTTT	47600
A T A D U Q N K A D F L I Q I L D F T Y K F R H K T N K G K L L H	1100
GCCACAGCGGATGTTCAAAACAGGCTGATTTTCTTATCCAATTTTAGATTTTACCTATAAATTTAGACATAGACAAATAAAGGTAARCTTCTACATT	47700
S I Y N E D F K L Y E E T L T E L A K K A T D A K E S L T K L F K A	1134
CCATTTATAATGAGGATTTCAAACTATACGAAGAACATTACAGAGTTAGAAAAAAGACACAGATGCAAAAGAGTCGTTAACTAACTTTTTAAGC	47800
S E Q K I E L S R T I P L K E I Y L N I E T U N F Q G Y G N U U F	1167
ATCCGAACAAAGATCGAGCTGTGCGTACGATTCCGTTAAGGAATATCACTGAACATAGAAGCTGTTAATTTCCAGGTTATGGCAACGATGTTTTT	47900
R E S A F K R A I E U E I K N Y E M K L N D L I K H F N S H L K T	1200
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K I D H M Q I L N L S F D N K W K D F U S K S K I S F P P E L T I S	1234
AAATTGACCACATGCAGATTCTTAATCTATCTTTGATACCAATGGAAGATTTTGCTCCAAGTCAAAATATCTTCCACCCAGAACTGACAAATAG	48100
S Q E L I K D P I K U I T E T L N K A S N D L A Y U I S E K I L K	1267
TTCAACAGAGTTGATCAAGGATCCCATTAAGTTATACTGAACCTTAACAAAGCCTCAACGATTTAGCGTATGTGATTAGTGAARAATATTGAAG	48200
W L I U F U K E L N T F F U A T M S E F G E U I P F D Y K H F R A	1300
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L E Y E I N S K Y I E I E N K I I C N E I I E N T D N I E K L S T L	1334
TGGAATACGAATTAATTTAAGTACATAGAGATTGAAATAAATAATCTGCAACGAATATCGAAATACTGACAAATATAGAAAACTCTCAACCTT	48400
I K Q I D P N R I A G G K Q K F Q D Y L S K I L T A E T N Q Q Q T	1367
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R Y K E Q L K K Q Y F D L L D N I A H F R F A F D F N H Q Q N L I	1400
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N F I P U E L S T U K T I P K S D I N L R M K I H T P Q T F F Q U	1500
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D S U F N T Q L I U D E K G I P U Q F Y N U F H N I U F K F F A L N 1534
ATTGAGTTTTTAATACAGTTGATAGTTGATGAGAAAGGAATTCAGTCCATTTTACAATGTTTTCCACAATATTGTTTTCAAGTTTTTGTCTCTAAA 49000

Y K K I I U P D K U L N L U S T K Y K I L T T L K S I L S U U K S 1567
TTATAAGAAATATCGTACCTGATAAGTGCTGAACCTAGTATCACCAAGTATAAGATCTTACCACATTAAAAGCATTCTGAGTGTGTAAAGGC 49100

F W K E I I N F D L T S Y F Q G K A E F T F Q N U F P I I N L K I 1600
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F I Y I I T Q A W S U T S D E T Q H S F E L P L E K F S L L I I A N 1634
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T I S D N P P K L S M D E L K I U C L D L N T W S E I T L E K Y T 1700
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F K K N S L M Q L C M G K E K F F I Y L L S A L U L P Q N F L N Y I 1734
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U I Q Y K P S C C A Q D S F Q Q L I Q D L C F E Y T H Q N H I K P 1767
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I S L N L Q E P N A L K H G E R I L S K F U L E K N A N T S L F S 1800
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L L T I R H L E N U Q Q N U D F R T I L Q S R N F D L K Y L L T Q 1867
TCTTCTACGATCCGACATTTGGAATGTCCAGCAAAACGTAGACTTTAGAACGATATTGCAATCTCGAATTTTCGATCTAAATATCTTTTAAACAAA 50000

S W T Q N U L E Q S I F H U Q L D K I I A D I K Q P Q L S L K K I 1900
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P L U L F N G D N E U U S T Y U P P E Q A S Q T E Q S F R I K N I F 1934
CACTGGTTTTGTTTAAAGGTGACAAAGAGTGTGTCACCTATGTGCCCTGAAACAGCAAGCCAGACAGAGCAGAGCTTTTCGATTAAAGATATTTT 50200

P N P U Q E Y S S K N U I L F T N Y P K N T K F L F N S P P P K T 1967
CCCAATCTGTGCAAGAGTATAGTAGCAAAATGTGATTCTTTTACGAATCTCCAAAAACACCAATTTTTATTATTAATCTCTCCACCTAAACA 50300

A A K S Y K L P D T T D D I N T E T L S S P T I Q R I P I K G L U 2000
GCGGCAAAAGTTACAACTACCAAGACTACCGATGACATAAACACGGAACATTATCAGTCCCACGATTCAAGAAATCCCTATCAAGGAGCTGTAC 50400

P K E N E I U F L P E K N T A H T D S K E T K T H L I D T F N I L S 2034
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Q T K G E I K T F S T D F D Q T I S K L K H L Y F - 2059
TCAACAAAGGTGAATCAAAACATTTTCTACGATTTTGTATCAACATTTTCCAATTAACATTTGTACTTTTAAAGATGATTCGCTAATCTTGCTA 50600
----- - S S E S U K S 84

TTAATCTATGCAAGCAAGCATGCGTAAAAATCAGTCTGAGGCTGCTTTTTCAATGTTTCCGGTATTTTGTGTTTGCATATTTTGTAGAACGCTCC 50700
N L R H L A L M R L F D L R F A R K E I N G T N Q K A Y K A L F T G 50

CTGTGACAGGGTGTGAACCATAGAGAAATGCAAGCCTAGAATATTCGTAACATTTGTTGCTTTTTCTTTTCTTCTTTTTTGAATGTTGCCAGA 50800
T U P H S G M S S H L G L I N T F M Q Q K K K E E E K K S S N G S 17

AATCTGGTTGATTTGAGCAGTGATTTTATCACCACGTGTGCGACCATGTTGCGTGCACCTAGCTAATTGAGAAATTTTACAGCCTGTACAAATTTCTCC 50900
I Q N I Q A T I E D G R T A A M 1

----- - W T D C G H Q T C K A L Q S I K C G T C I E G 455

ACAGTCTCTAGATCAAGACACGTTTCTCTGTAGATATTTTGCAATCTTGGCATTGAATTTCTGTGGAGTGAGAAATTAGTTTCAACAGTTTATTTATC 51000
C D E L D L C T E R Y I N Q C D Q C Q F E T S H S I L K L L K N I 422

GTTAGATTCTGCAGTGGATCATAGAGTAACAGTTCTGCAAGAACATGCAACATGGCATCAATTTAACACTATCGTTTAAATAGTGCAAGCGGAAT 51100
T L N Q L H I M S Y C T R C S C A U I A D F K U S D N L I T C A S N 388

TAGTTCCAATTAGCTTTCCATGATCACTTTTACTTGAATGCCTGAACACTATATTCATACATTTCTATCTTTTCAAGTGTCAAAACGTTGCC 51200
T G I I A K W S U S K U Q I G S U S Y E Y L E Y U K E L T L R Q G 355

GCCACATTAAGCAATAAAGCAATCTGTGTGCATCTGTAATAATATTTTTTCTGTCTATCTCGATAATAAACATCGAGCTTAAAGAAAGTT 51300
G C L S C Y L L D T H M S Y I I N K E Q R D R Y V F M S S L S F T 322

TGTTTCCCTTTAAGCCTCTCTTTGCGGAATTTAAACAATGTCACATTTAGAACATATCACAGTGAGATACTATCAATTTTAGCATATCTGAGACACT 51400
Q K G K L R E K G S N L G C H G C K S C I U T L Y S D I K A Y R L C K 288

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T K C F C L U P L S I I S S T L S R K L U T T L A F T L I K P L Q 255

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H K E Q K N L U I P U L N N N E L P I L F R D F S Y C Y N E I M A 222

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M A M A F I F N G C P U T L S C G H F I D Q Y T L N S A R H A Y R L 188

U32

U33

GTGTGATGTCATTACATTGTTCAAGGTTACGTAAACACAAAGAGTTCATACACAGGAATATTACATGAGTTGAATTTGGCACACATTAACCTGTTGCTGAAA 51800
T I D N C Q E F N R L C F L K M C P I N C H T S I P L M L Q Q Q F 155

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L Y Y Y L D N F S U F S P I E L L Q N L K H I P Y Q K F A E U I Q 122

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L D K S L F K K N T U F M S L U C N E S K S U D G I L F L Q L H S 22

TACGAACCATGTTTACACAGCGGAGAAATCAGCCGACAAAGCAAAATTCCTTAAGATGACATAGCATACAAATAGTAGGGCGGCAACCAAAACCACAA 52300
- U A S F D A S L A F E K F I U Y C U I L L A A U L F G C 231
Y S G H K C L P S I L R C L L N R L S S M 1

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L I N N R A R A F I P U T U P F U A A D K T N G M Y N I S R F S T M E 197

CTCTACTGACTTCAACTGTAACTCAATGGTTTTTTTATGTGCTTGCAGCTCTATGTTTCTCTAATCTTGGCGCTCTAAAAATTTTTCTTTAAGAT 52500
G U S K L Q L R L P K K I H R A A R H K E L D Q R E L F K K K L I 164

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K T L U G S S S P K I A E I D N L C U S L C E N U N L I N C E K U I 97

TGTTCTGACTTTCTGTTTTATGGGAGCGTGGAGATACAGACATGGAACAGCACCTCCCGTATTTTTAAAAATAAATCTCGCTTCTGTTTTGTCAA 52800
N Q S E Q K I P A H L Y C S M S U A G G T N K F I F R A E Q K T L 64

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D E W L S L L Y E L S Y A F D L K L L I D C L P F K P N K S F L N 31

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- T N L Y E Q H E L I G N U N L L K S L I S T L L 81

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K I K K K I I E S H S C Q N A R H H L Y K L Y T L H R Y G U M I F 48

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L L Y A H L D S S G I D S D D L N T N P N T L E N E I N S U E K T 54
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D K M W I Y D Y A L L C Y K C N A A P R T P L A U U I A T E F M Q 121
ATAAATGTGGATCTATGACTATGCTCTTTGTGTTACAAATGTAATGCTGCACCTAGAACTCCCTTGGCTGCTGAATTAATGCCACCGAATTTATGCA 53700

L I Q K H F L N I N F D G L F L N N I L S I L D F H U H F F I N R 154
GTTGATTCAAAAGCATTTCTTAACATAAATTTGATGGGTTATTTTAAACACATTTTGTCAATACTCGATTTTCATGTACACTTTTTCATAAACAGG 53800

C F S N T N D D L L H N E N I T L Y H M A I L K S L L L E D E S I 187
TGTTTCTCAACACCAACGATGATCTATTACATAATGAAACATAACCTTATATCACATGCCATATTAAATCACTTCTATTGGAGACGAATCTATAC 53900

P N I R I K K F K L K G K P T K K Q H G N A I L E K Q T L P L N T H 221
CAATATAGAATAAAGAAATTTAAATTAAGGAAACCAACGAAAAACAGCATGGAATGCTATCCTTGAACCAAACTCTCCACTTAACACGCA 54000

F T H L I F Y M W A G T N I F D R I S L T D L A I K K R Q I L K A 254
TTTTACATTTAATTTTTTATATGTGGGCTGGGACAAACATATTCGATCGCATTTCTACTACTGATCTAGCCATCAAGAACGCCAAATTTTAAAGCC 54100

I Y S T K N E L N C S A G P I L L S Q I P I S I T K N A T S S U C 287
ATTACTCTACTAAAAATGAGCTCAATGTCTGCGGACCAATCTACTATCTCAATACCGATCTCCATCACTAAGAACGCCACAGTAGCGTATGCT 54200

L L C E L M T S S Q K N F D L L Q F I Y T S U I N Y C Q N N L K M I 321
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D R I Q F U L A N L L D L A R I Y T N U K T T S D C S K I U L A N 354
TGACAGATTCATTCGTAAGTCAAAATCTTTAGATTTAGCTAGAAATATATACTAACGTTAAACCAACATCAGATTGCTCAAAATTTGATTAGCCAA 54400

E Q E F S N S D F U I D C H S F L I L K Q U G P U G L Y K H F F C 387
GAACAGAAATTTCAAACTCTGATTTTGAATTTGATGTCATAGTTTTTAATCTAAGCAGGTTGGACCTGTGGGATTATACAACATTTCTTTTGTG 54500

U34

U35

U36

D P L C I A N I K T I K P H I L F Y T T E S C I L Q D F K U A I C Y 421
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Q N E Y L N S U E K H U W L A I H F F K A F Q U S K L N H K N K T 454
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L I S D F L K D F T Q L L A D Q N F E I U D P T F T I H Y Y U - M 1
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I I ' Q S T R A L R A S S L L K K S K P Y N K E K T N L S L S L S 34
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L K E L H S U F K L F P E Y E L K F L N M M K L P I T G K E P I K I 68
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----- - L U D T L 1009
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U37

U38

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U40

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L S Q L S N M 1

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ATGTACATTTAATCCGTTAATGCTGAATCTTGTTCATTACGGATTTTGTAGAGGCTCTCTACCATCCACGTAGAATAACATATCATCCATAGTAGGC 63500
H U N L D T L H Q I K N M U S K A L P E R G D U Y F L M D D M T P 1041

TTACTATCTCTATCTTTCATCCTTCAGCTAATATGAGTAGTCTGATTTACAGAAATGGATAAATCTTCAATAATGTTGAGCACCTTTCTCGAATTA 63600
K S D R D K M U E A L I L L E P N U S N S L S E I I N L U K G R I U 1007

CTTCCACATCATAAACAATGGCTTCTCTTAACCTTTCTCACAAATATGTCACACAGTTTTGTAGCAATCACAATTTCTGACGCATAAAGCGGAATC 63700
E U D Y U I A E R K U K K U I I D C L K T A I U F K Q R M F R F D 974

TTGCAAGCCGAGGAGGAGGGGTTAATTTGCGATCTACACCACTTCCAGCTATCCAACTAATGACCAAGTGGAATAATCTCTACTAGCAACACTC 63800
Q L G S S P P N L N R D U G S G A I W G L Q G F H F Y D R S A U S 941

ACAATTTTTGATCATTAAACCAAGGTAATATAGATCTTCTGTGAAATGCTCCCAATTTGGTCTTTTGTATATGATGAGTCATAGGTTCTT 63900
U F K E I M L G F T I I S R G T F I S G F N P E K T L S A T M P E K 907

TAGTCCATTCCTACCACTTTTTTACGTCGATGACGTATCTGTCACAGAGAAATGTTGGATGTTCTTTAAGAAAATCGGAATAACATAGGGTT 64000
L G N G U L K K U H M U Y E Q U S S F T P H E K L F U P F L M P N 874

TTGAGGAAGTATTTAGAGTTAATGATGCAAACTTGTAGATAATCTCTATAACCAAGAACTGATAAATTTATTATGAAGTAATACTCGATAAAG 64100
Q P U L K S T L A H L S T L Y D R Y G L U S L L K N H F Y Y E I F 841

GATAGTAGCATTCTGGTTGAATATCTAACAAATCAATTTTCATCATATGAATTTGGTGACAGAAAGTAACCTTGATGAAGAACGCATGCTTCAACAT 64200
S L L C E P Q I D L L D I E D Y S N T U R F T F K I F S R M D E U N 807

TACCTATATCTATGTTTTTGGCATGTTATTAAAGCAAAATACGCTGCCAAATTTCTAGGCGAGGATTTTTTAATTTGGAAGAGCCGTTTCATGATATT 64300
G I D I T K P M N N L L I R Q W F E L C S I K L N P F L R E H Y K 774

AAACAGCAAAATGATAGCAACCAAGAGTGGGTTCTTTTCTGTTGACCTTTTTGAAAAAGGATTATTTGTGTGTTTTGTTGGCTTATTGAAT 64400
F L L F S L C G S L P N K K Q K U K K F F P N N Q T N K N P K N F 741

GGTCTATTTTTTACTCGAAATCTTTCAACATTGATGGAAGGGCAGAGTTTAGCTTGGATAGAGGTTTAGCATATTTACCCGATTTAAACAAT 64500
P R N K U R F D K L C Q M S L R C L K A Q I S T K A Y K G S K F L N 707

TGAATCAATGTATTTGTTCCATGTCTACATTTGAAGCTATTTTACAGTTTTCATATTTCAAAAACCTTTTTTAAATGACTGTTGTAATATGCTCCGTA 64600
F D I Y Q E M D U N S A I K U T K M N L F G K K F H S N Y F A G Y 674

GAGAGATTGGTATTGTTGCATTAAACATTTAGAAATTAAGTTTCCAGTACAGGCCTATCTACAACTAGCCCGTACCGATTATTAAGCCAGTTCTGT 64700
L S Q Y Q Q M L W K S I L N G T C P R D U U Y G T G I I L A L N Q 641

AAACAATTAGTATACTTTGTAATACGTGAACCAAGAAATGGAGAAAGGCCAAGACAGAGGTGCTGATCAATGTTGAAGATTGTAGACAGTTTT 64800
L U I L I U K Y Y T F U F F P S F A L S L P T T D I N F S Q L C N E 607

CGATTTGTTCTCTGGATGTCTCGTTTTTCTCATTTCTGAATACATTTTGAACCTGCTTCTCAATGCATTGAATTAATCATTATCATATTCACAAA 64900
I Q E R S T Q T K R M E S I C K S U A E E I C Q I L D N I M N U F 574

ATCATTTTGACTTTTAAATTTAATTTGCTTCCCGATTATGTCATCAATCAATATTTTCTTCAATATATCGTGAATCATTCTTAAGATTTGAAT 65000
D N Q S K F N L N D E G T I A D I L N N K K C Y D H I M G L F K F 541

CTATCTAGGAAGGTGGTTTGGAGTTCTTTTCATTGGATCTTTGCTTTTCATTAATCCCTTTTTCCCAAGAACCTAGAACATCTACATCTGCATAAA 65100
R D L S P T T Q A E K M P D K S E N U G K K G F S G L U D U D A Y F 507

AACGAGAAACATTGTCATAACAAATAGGTTCTTTTTTAGTCGTTTAGAATCTGAGGTAATCTGCTGTTGATTCTGATCAATGCTGTTCCGATACACGA 65200
R S F M T M U I P E K K T T K S I Q P L R S N I R I L A T G I C S 474

ATGGCAACACTTACCTTCAAAAATCACAGAGATTAGAGGAACATTTACGATGTGGTTATATATTTTCAAGATTTCCACAGTTCTGTTATAAATAGAC 65300
H C C K G E C F E C L N S S C N U I H N Y I E S N G C N N Y I S 441

ATTCTGTTCAATTTCCATATTATATGCGATAGATTTGTGGACATGTGCGACATGCGTAAGCTAGATGAAGAGCGGAAATTTATCTTCTTTACAGGTG 65400
M R N L N W I I H S L I Q P C T A C A Y A L H F A S F K D E K C P S 407

AAGAATTACACTTTTCAATTTTCTGGCATCGTTATAAAATCTTCTGTAAGAGATGACAGGAATTACAAAATCGGATTGAACGCGAGTAATGTTTCTTG 65500
S N C K I L K R A D N Y F D E N L S L S N C Y L Q I S R L L T E Q 374

AGTGATCGCAGAGTTAAAGCTTGTGTTTGTAGATATATAGGCCAATTTGTTACTGTAAGATATCGAATTCGACGCAAGACTAAGCAGCTACATGG 65600
T I A S N F A Q K T N S I Y A L K N S Y L I S N A F A F U L A A U H 341

CTAGATAGTAGGAGCTCAATTTTTTCACTTCCACGATTTTCTCTCGTGGGTTTCAAGCGATTTGATGATGGGCGCACTCTGAAAAATTCATGATTGAT 65700
S S L H L R L K L E U I K E E H T E A S K I I P W E S F N M I Q N 307

TATTTTCATAAATAGAATCAAGATACTCTGCTGTGAATCTGAAGGTTAGTTCCGTTACAGCGTCCACTAACATTAATGATCTTTTCAATCGGTGA 65800
N E Y I S D L Y E A T Y S F T L E T I U A D U L M L H D K E I P S 274

TAGTTTTTGACCAAGAAATACCGTGATATGTTTATTCGGTGCAAGCTTGACAGTTTGTTCAGTATCTTGGAATAATGTTTCAAGACCGGCTTTAATCAAT 65900
L K Q G P I G H Y T K N P A L K U T Q E T D Q I F Q K L G A K I L 241

TCCAGGGTATTATTAAATCGAAAGTCATTCCTCATGATGAAGATTAAAGTAGAACATACTTCGCTGATCTGAGGCGCATAAAGCCGTTTTCTTGAA 66000
E L T N N F R L T M G W S T F I L Y F L U E S I Q P A Y F G N E Q I 207

TGAATTCAGTGCAGATATCGATGCACAAAGTTTCTCCGATTCAACACAGGTAGCCGAATATACCGAATTTTTATTGCCAAGCATTACCAACCTGGAC 66100
F E T C T D I C L T E E S E F L T A S Y L P I K I A L C E G U Q U 174

TTGAATCTGCTCTTCTACACATGGGATTAAATATCCAGCAATAAAGTTCTTTGAACCATTCACCAACTATATGACATAGAACGTCTATGCATTT 66200
Q I Q E E U C P I L L G A F L L E K F G N G U U I H C L U D D A N 141

CTTCCAACTCTTACAGATCTTTCTATATCCACAGGCTTTGATTTCCGTTAACGACAAATCTTGTAGATTGAATTTTTCTCTGTTGTTTGCACA 66300
R G U S E C I K G I D U P K R N G N U U F E Q L N F K E R T Q K C L 107

ATTATCAGAGTTTCCATGGTCTTCTGCTCTTTTAAAAACATCTGTACCGTGGAAAAAGAGCATACAGGCATAACGATGTGATTTTGGTAATGAC 66400
K D L N G H D E A E K L F U D T G H F F F C U P M F S T I K T I U 74

TGTTCCGCCGTAATTAATATGGGTGTTTTACGGTTGGGAAGAGTCATTTTCAACCGTTAGATTAGTAACAGGGTGAGTCACTACTGATTTTCTT 66500
T G G Y N I I P T K U T P F F D N E U T L N L L L P S I U U S K R 41

TTTCCATTACGATAATGTAGTCAGATTCTATTATTTTTGTTCTTTCGGCAGATGTACAGCATGCTCGGTACATATTGGGCCCCAAACACAG 66600
K E M L S L T T L I E I L K Q E K P L I Y L W A A T C I P A S U U T 7

TTTCATTATCATCAGCCATTCTTGAACATGAGACCCCGTTTCTGCAAGGGGTGTTTCTGCTAACCTTATATATTTTAGTTGACGTACAAACTTA 66700
E N D D A M < start of fragment 1

containing origin of DNA replication
GCGTCATCATACACGGAAATTAAGTTTCTCGTTCTACTGTTTGTAGTGGGAGAACTAAAAACGATATACTGACTCGGATTGTAGTTTATGCAATT 66800

AGCGTCCACCTCACTCGTAATAGTATTTATTTTTCATGGTTTTTAAATAGAATTGCAGGCAAGGAGGATCAATGAACCTCCCACTTCCGCAAGTAAAG 66900

CAACGACCAATCAGAGTTTGCATTGCAAGTATTTAATTTGTTGCAAGCAAGCATTAGCTAGAGGACAGGCACAGAGATGCTACATATTGGGAATTAAT 67000
----- - D 516

CCGAATCATCAGATCAGTGTCTATTATGTCGGTCTCACAGTTTCTACATCTTCATAATCTAAATCCAGTTCATTTTATTATCAGAGTTTCTCTCC 67100
S D D S D T D N I D T E C T E U D E Y D L D L E M E N D S N E E G 483

ATTGTTTTCTTAATTTTTCGCTGATTTATAGAGTATCTTTTCAATAATACAAAGCGAGTTTCTCTCTGTAGAGTCTGTTGTTTCAAAATCT 67200
N N E K I K A S K M S T D N E I F U F R T E D E Q L T T N T E F D 450

ATAGAATCAACTCTTTTACTCCAGTCTTTTTTTCAGTCTGTTTTTCGGTAGTCTATTTGTTTCTGTCCTTTATTCGTTTTATCCGCAGTAAGAGCTTTT 67300
I S D U E K S W D K K L R N E R L E N T K Q G K N T K D A T L L K K end of fragment containing origin of DNA replication > 416

TACATTTGGCTTGCTTTTTGTTGTAATTCATTTGGACGGTTTGCTTAGATTGCTGTGAAGCAAGAGCTGCAGAGCGGAGTTGTAGAATATGCACATT 67400
C K A Q K K T Q L N L Q U T Q K S Q Q S A F S C S P T T S C A U N 383

AAAGCTGTTGTACTCTTTCAGGCATGTTAGGATGCAGACCAACTCCACAATTTCTTTGGGAAGATAGGTACAGAAATATAGCTTGGTTTCCAAAGTGAC 67500
F S N Y E E P M N P H L G F E U F E K P L Y T C F Y L S P K W P S 350

ATCATGCGTTGGATTCTAGTTTGACACCGATGTCTACATTGATGATTGTTAAATTTGGTCTCCGACTAATCTGGAAATCATGCCACATTGATATTGTT 67600
M N R Q I A T Q C G I D D C Q H N N F Q D G U L R S I M G C Q Y Q E 316

CACCTACAGATCTTGGTCAAATCGCGTATGAAGTGGGTTGTTAGTTTGAAGAAATACGTTCTTTTATTTGACGTAAATCCTTGCAAAAGTTACTAT 67700
S U A D Q D F D R I F Q P Q K T Q L I R E K I Q R L I R A F T U I 283

AAATGATAAGCTTGTGTGCTGGATATTGAAAGATCCAGGAGTCTGTTGCTGACTTTCATATTCGTTGTTAGGCATATCAGGTATATACCGGTTTT 67800
F S L A Q Q A P Y Q F S G P T Q Q Q U E Y E T N P M D R D Y U P K 250

CCACAAAGTTGTCTGAAATACGGTATTCTATGTCCCATGTCATTGATTAACACAAAGTTTGGCCATATTCACTTGTGAAGTATTCAA 67900
G C L Q R F I R Y E I D G H G N D N F U C C L K A M N L K N F Y E F 216

ACTTCATTATGGTAATAGTATACATAACAGATCTTGGGGTCAATAGGTAGTTGTGCACAAATGATATTTATAGTAATGCAGCTTCTCAATAAT 68000
K M I T I T Y M F L D Q P D I P L N H U F H Y K Y Y I C A E E I I 183

CGCAGAGAAATGCTAACGATGGAGAATTCTGTCATGAAAAACTCGGTCTCCGAGTATCTGTTGATGTTGTTCTCTATTGAGGGAGTTTAAAGAGTTT 68100
A L S F A L S P S N T L S F U R D G L I Q Q H Q E R N L S N L C N 150

TTATATCGTAGTACAGTCTGTTGTCATTAGTTCTTCTTTTTTCCAAATAGATTTTTTCATGATTCCGGGGAATCGATCTCGAATCCTATGAGCTGGAT 68200
K Y R L L L D T T M L E E K E L Y I K E H N R P F R D R I R H A P D 116

CTCGTGCTTACCGGAATCTTTCGTAACCAAGGGCTTCCGCGGTGTAGCTAGAGCCAAAGGTGCTGTTGGTAATTTGGGAAAAAGTCAATGCATG 68300
R A E G S Y K R L G L A E A T Y S S G F P A T P L N A F F T L A H 83

CGTCTGTGCACGCTTTTCTCTGCTTTTCTTCATGATGAGTTTTCAGCTGTTTCTAGTTTCTGTGAGACTCAAGCGCTCAATTTTGAATCATCAGCTGC 68400
T Q A R K E E Q K E E I I L K L Q E L E R L S L A D L K S E D L Q 50

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K I P I I R R H F Q K T F R S U Y K N A P K H U L T R K I T K L G Y 16

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R Q R G L U N K K U G R P Y M 1

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ACACAAATAAATAACATAAAATGTCACATATTCAAGAATCTAAACGACAGATGAATGCACTTGCTTACTATTAGATTACATTTTCGTAGTAAACAT 68800
- M N L S D L U U S S H U Q K S N S K C K T T F C 838

U42

U43

TTGCTCCATAATATTATCAAAATGCGATTGTTATCTACCTTAATTCTAAGTACACTAAGACATTTTCACGGTTTCCTTATGATTCTTGTTAACAAC	68900
K S W L I I L I R N N D U K F E L Y U L U N E R N G K H N R T L C S	804
TGAATCACTTAGTTTTCCGTTTTGCAATTTTTTAGTTGTATATTTTTGTGATCAATTTTTAGAAAAGTTACATGTTGAATTTGTGTAGCTGTTTCGTGC	69000
F D S L K G N Q L K K L Q I N K H D I K L F T U H Q F Q T A T R A	771
TTACAGTGTGGATGTTCTTTTTAACATTTGTGGCCAGGCAATTGAACGAGTAAAGTCATTAAACAATCATCAGGGAAGACAACCTGTTTCCGAA	69100
E C H Q I N K K L M Q P W A I S A T F T M L L D D R S L C S T E S	738
AAACCATGACATGTAATATTTCAACATAAAGTCTCCAGTGAACCTTGTGTTCTGTGATACAGTTGCTTAGTCTAGAATCTATAAAGAAAACCTCTG	69200
F G N U H L Y K L C L T E L S S Q K R H Y L Q K T R S D I F S F E T	704
TTGGACAGGCTTATCAAAATGCTGTAGATTATCTCTGAATGGTTGGTCTTTAGTTCCATGATGTAATAATATTATTGAGATCTAGTTGCATGCTAAC	69300
P C A K D F I S Y I I E T I T Q D K T G H H L I N N L D L Q M S U	671
GAAATCTGAAATCTTTTTCAATTTTTCCGGGACAATAAATAGGCTTCAGACGACCATACAAAATCTGTTATTCTCTTCGTCACACTTTATACATG	69400
F D Q F N K K M K E P U I F I P K L R G Y L F R N N E E D U K Y M	638
AAACCTAACCGTAACAACGTCCTGATTATAGATTCTGTATCAAAACATTACCAGGAAAAATTACCAGTTAAGAACTGCATTAAATCGTGGTTTA	69500
F G L R L C R G T G T N Y I G T D F C E G P F I U S N L I Q M L D H N L	604
GACACATTAATGATTGAATATTTTAGAAGTTGTTTTAATGGCTCACTTCCATTTATGCAGTACCTTGAGGGATTGGAATAGCAATTCGAAGACCAAT	69600
C M L H N F I K S L Q K L P E S G I I A T G Q P I P I A I R L G I	571
TTTTTTTTGCAAAACAAAAAGCTGTTTCACTTCATTGTAAACATACATTGTGGTTCAGGGGATTCTCCGATTACTACAGGTAGTTTTGAAAAAAG	69700
K K K C U C F A T T E U E N Y C U N H N L P N E P N S C T T K F F F	538
ATGGGGTAGGCGTCTTTGTCAATAACGGAATATTTTTGCCATGCATTGATCAGCACATTCGCAATCAATTTACACATAGAGAAAAATACGATTCCG	69800
I P Y A D K D I F P F I K Q W A N I L U N R M L K C M S F F L S E T	504
TTATTATAGTGAATCCTGTAATGGCAGATCTAATCACCATATATTTGTAAACGGAAGGTATTCTTAAGATTTCATGCTGGTTACGTAAACTG	69900
I I A S D Q L P L D L D G I Y N T U P L Y E N F I E H R T U Y F Q	471
TTTTTCTATTTCGTCGCTTAAAAAGGTCGTGCTCGAACCAAAATGTACTTGTAAAGATTTCAGGAATGTACTATTGGGTAAAAATGCATAACC	70000
K E I E D S L F T T D Q L W F T S T L S E D S I Y E N P L F Q M U	438
TGGTCGAACCCATATTTTGTACCACTTTCTGCACCTCCAAACAATAAGATTTTTGAAGACATTTGAACCTTAACATAGGAATGGGGTTGCTGA	70100
Q D F G M N K Y W S E A S G F C Y L N K Y S M Q U R F M P I P N S F	404
ATTGGTCATGTAGATATTGTCTCCTTGTAAACAGGTTTACCATCTATCAAAATAGATTATTAGATGCCAAATTTTAAAAATCCTTGTAAAGCTAATTT	70200
Q D H L Y Q R R T U P K G D I L I S K N S A L I K L F G Q L G L K	371
AATTGGTGAATAATACCTTCCACCGTGTATTGTCATTGTTAACCATCTTGAATTTGGTCTGAATTTATTACAGCATGATTTCTATTACTGTTT	70300
I P T F Y G E G H K N C K N U M K S I Q D S N I U L M I N R N S N	338
ATGCATAACGTAAGTGTGCAATTTGAATTTGTGTTAATCCTTTTTATTCTACATAATTTTGAATAACTGTCTTCGTTAAAGTACTGTTTCA	70400
I D Y U Y Q Q M Q F K N N L M R K I E U Y N Q F Y S D E N F Y Q K M	304
TGATTGAATGAGATCCGAGTGAAGAATTTCTAGGATGTACATATTTTCTGACATTGAGAAGTATCAGATCTGGTAGGATCATAGATGTCAAGTTG	70500
I S I L D S H L S N G L I Y M N E Q C Q S T D S R T P D Y S T L Q	271
ACTATCTTGATGAATTTATTTTTTCTAATGCTGTACTGTAGCAATGTAGATATAGTGGAACGAAACTGTTGTGAGATGCACGCTGTTTCTAAAA	70600
S Y K I F K N K E L A T S Y A I Y I Y H U R F S N T L H U S N R F	238
ATATCTATTGCTTATCAAGATAAAGAAATCTTTTGCATCTCTTATGTTTTTTGTTTTGTCATATTCAGAAAACTAACAAATTTTTCCGATAGTTAG	70700
I D I Q K D L Y L F E K R D R I N K Q K A Y E S F S U F K K R Y N S	204
ATTTCAAGTAATATTAATGAATTCAGACATGGAGGAATAGTAATACCATATCTCTAATTTATCAGTGAACACTGAACATATTTCTAGTTGTTGC	70800
K L T I N I F E S M S S Y T F U M D G L K D T F C Q U Y N K T T A	171
TATGGTGCTTTTCTGCTCTTCAATAAATAATACATCGTTAATAGTAGCATTCTTCTGTTTGACCGTATGTTGATAAAACCAAAACGGTGACGTG	70900
I T S K Q E E F L Y Y Y M T L L L M G E T Q G Y T S L F W F P S T	138
GGTAAGAGATACTATTGTTAGATGTTTAAATGATTATAGTCTTGCAAAAAAGACTAAGCTTTTAAATCTATATTTTCACTTCTTCTGGAACATGAG	71000
P L L Y K N T L H K I I I T K C F F U L S K F E I N E S G E P U H S	104
AAAGTAAAAATCTTTATACAGATTTTCTGTTTCTCCGTATTTAAACAGTGAATAATATCTCAGACTTAATGGGAATGCATTTTTTACATAATAGCT	71100
L L F D K Y L N E T E E T N L C H I I D E S K I P L A N K U Y Y S	71
GAAATCAAGATTCTGCGTCGCAACAATACCGTCTCAATCTTTTGGAAACTTGCATTTCTGTGCTGCATACAAAAATATACATTTTTTGTAGGT	71200
F N L S E A D C U F U T E I R K S F K C K Q T Q M C F Y U N K S P	38
TTATATTTAAGCATTTTGGAAAAATTAATGTTCACTAGGGTTCTTACATAGATATTTACTATCAGCTGCGCGGGTCATATCCGTTGCAACACAG	71300
K Y K U I I P F I L H E S P N K C L I N U I U H A P D Y E T A F U T	4
TAATAGTCATTGTGAATGCTTTTCAGTTTATCTTCAACAGCTTTTAAATATAAGACAATAGGAATCATGGGAATTGCTTTGTAAAAAAATCTCTTCTG	71400
I T M	1

U44	M L Y S E L S E Q E D L L D F L E T K Y T D F G I L	26
	ACATCTTCAACTCTAECTACCAGATGCTCTATTCTGAGCTCTCAGAGCAGAGGGATTTACTGGATTTTTAGAGACAAATATACAGATTTTGGAAATTTT	71500
	K T D I L N Y E R D S E T F K T L L Q U L P I Y K K T K L R Y N L	59
	AAAAACCGATATCTCACTATGAAGAGACTCCGAACATTCAAACTTTGTGCAAGTGTTACCTATCTATAAAAAACAAGCTGAGGTATAATTTG	71600
	I E A C L N N C P P H U K D A L I I E I M K A K K I L E T L D U U	92
	ATTGAACGCTGTTAATAATTTGCCCTCACGTTAAGATGCATTGATTATTGAATCATGAAGCTAAGAAAAATTTAGAGACTCTGGATGTTGTGT	71700

F M K I M I G E F T I C S D N U N Q L L N K F S I D Q T T L C D M E 126
 TCATGAARAATTATGATTGGAGAATTACAAATTTGCGAGTGACAAATGTGAATCAATTGCTCAATAAATTTCAATAGACCAACAACATTATGTGACATGGA 71800

 K I N T L I D L D E E N S K R L L T E I D P L L H Q E T G L Y Q A 159
 AAAAATAAATACTTTAATTGACTTAGACGAGAGAAATAGCAAGCGTCTTTTGACAGAGATCGATCCTTTGTTACATCAAGAACAGGCGCTGTATCAAGCG 71900

 L P N A U T D P P S E Q R A A T K K C Y E G F T K - ----- 184
 CTGCCTAATGCAGTTACGGATCCACCAAGCGACAGAGAGCGCAACTAAAAAATGTTACGAAGGATTACCAAAATAAATTTTATTCGGTGTGTACTG 72000
 ----- - E T S Y Q 375

 AAACCAAGCATCGATGTTTTATCTAARCTGCAAGCTGATTCAARCTCGATTAGGTAATAGCTTTAAATAAATGACCCGATGTGAAATGATGGTT 72100
 F W L M S T K D L U A L Q N L U R N P L L K L I F H G C T F I I T 342

 GCAATCAAAATTCCTGCTTGACAAAGATCCTCTGAGAGTGGGATTAAATCTTTACACTTGGAGTTGTGTTCTTTACAGATATTAGTTTCAACCA 72200
 A I C I G A Q U F I R Q S T P N F I K U S P T T N K L W I N T E U U 308

 CTATCCATGACAGAGAAATTTCTTTGTTGCTATTATTAAAGCTTTCAATTCATCAGGACAAATCAAAATGTAATCAAAATTTTGGATTGTGAATATT 72300
 L G H C L I E K N A I I L A K L E D P C D F M Y D F N Q I T Y N N 275

 GGATTCTACATGAATCTTTATTGGTAATTAGTGAAACTTGTATAAATTTGGAGAGGAAATTTAATAGTTTCCAGGGTTCCGGTATATAGCATGGA 72400
 S E U Y F D K N T I L S F K I F N P S P F N Y T E W P E P I Y C P 242

 AGGATGTTAATCACTAATCTATATACCCAGGTAACAACATTACTGATTCACTTGACAGGTTTATTAAAGAAATGGAGATACGTTTTCTGTTGTGATGA 72500
 L I N I U L E I D G P L L M U S E S S L N I L S I S I U N E T T I L 208

 GTTCTGTTACACATTCGCGAGAGTGTCTTAATCTGTTCCAGTCAAAATCCCAAAAGTCCGTCGGGAATGTTTAAATGACACGTTTAAATTAATAATGCG 72600
 E T U C E C L T D N U T G T L I G F L G D P I N L S U N L N F I R 175

 TACTTGTTCACAGGCACCCATATAAGTTCTCTATTACGAGTACAAATTTTATTGTTATTAGAAATACATCCGACTTTTCTCAAATGATTATT 72700
 U Q E C P U W I L E R N U L U I K N T N L I U D M R S K E F H N I 142

 AAAATGGAGTTCTGTTACTCGAGGAACATTTTCAAACCAATCTGCTAGATCTGTTTCTTGGAAAGGTGAGATATTCTTTTCATTGTCCATATGTT 72800
 L I P L E N U R P U N E F G F R S S R N R P F T L Y K K E N D M H E 108

 CTGCAAGAACTCATCGTAATTTTTTACAGGATTTGAATAAACCGTTTTGAGGAATTCAGTAAGAAATGGTCTGTGATAAACCGTCAATTCAGT 72900
 A F F E D Y I K E C S K F L G N Q P I G L L S F P R Q Y U T L E T 75

 GTTCACATATTCAATTAATTGCTTTGCATCGATTTTAGGCCATGTAAAGAGAGCTCTCTTTGTTTCGCTAAAGTCCAGATATCATCCACATCCGTTACA 73000
 N U Y E N L Q K A D I K P W T L S S E K T E S F N W I D D U D T U 42

 GTAAACAGGAAAAGTGCAAGTATCTGGACATAGGCAATTTGTTAAGTGAATTTGTTTCAGAGATTTTTTCAAGAAATATTCTTGTGTTGTTTCAGATC 73100
 T F L F F H L Y R S M P L K N L T I T E S I K E S I I K N T E S A 8

 ----- M T L Y K I U S K P I I L L R F 16
 TTCTGGAGGGTAGACTTTGCATTTTCTGTTGAAGCCTTCGGATGATTAGGAAAATGACTCTATACAGATTGTTTCCAGCCAATTATATTGCTGGCATT 73200
 R S P L S Q M 1

 F F T R U U F T N E U D G E E L F Y K P T C H S D T Y E I I L K K 49
 TTTTTCACCGAGTTGTTTTCACAAATGAAGTCGACGGGAGGAGCTGTTTATAGCCTACTTGTCATTGAGATACATATGAATTTTAAAAA 73300

 F S S I W I L U N T F I L L C S F S L F L K Y W C F K T L A K E T 82
 TTTCTTCTATTGATATTGGTCAACACATTTATTTATTATGTTTCTTTTATTTTAAAGTATTGGTGTTTAAGACTCTCGCCAAAGAACTG 73400

 U K G Y - 86
 TAAAGGGTATTAAATCTATATGAAGATGTATGAATGCCCTCAGAACTGTTTAAATGATTTTCTCCATGCATATTGACATAAATATTCTAAGC 73500

 CAAATATTTTCTCGTGATTAGTCTGCGTTACTTCTGTCAACACACTCATATTTTTCATGGTATTGTTAGAAATATCTGTGGCTTTTGCTTTCCATCATC 73600
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 AAGTATGCTTTGTACGGAGATACTCTACACTACGAAGTTATAAGTCCGTGTTTTGCTGATTATTATGCTTGTGTTACTATGGTTTGTGCGTGAAGAAGGT 73900
 ----- - T S T N S H N T T F F T 302

 CGTAGGAATGATGAAGTCTGTTGTGAAGCTTGCATGCTTGAGGTGCTCGAGTAGATGGAAGAAATTTTGTGGTTGGAAGTAACAGCGTTCCGAATT 74000
 T P F S S T Q Q S A Q M S S T G R T S P F F K T P E S T U A N P I 269

 GCTGTAGGCTTAGTAATTTGCTCTATTTTCTAAGAACATCAAGTTCCTTAAACTTTGTATTGGTGACATGATTCCTTACCAAGGAGAGTTGG 74100
 A T P K T U K T K N E L F M L N G K F S Q I P S M I G R U L S F N T 235

 TAACCAAAATGGTGTGACACATTCGCGTGTTCACAGAAATATAGAAAAATTTGAATAGAAATCTTGCATCTGTTGATGTAACAAAGTAGTA 74200
 U G F P T S U N R T N U S N Y F F K S I S N K C D T R N Y U F Y Y 202

 AATAAATTCGTAAGAAGAAAAGTTGCTCAGAAATTTTCGCGTGAATAATGAGCTTCAGTATGGTTTGGAGATCTTGGAAATGGTTTCAATCTTG 74300
 I F N T F S F L Q E S N E R S F L Q A E T H N Q L D Q F I T E I K 169

 TTTTGGCTAAGTTAATTTTAAACAAATGTGAAGCAAGTACTTCAACCGGATTTTATTGACACAGAGTCATCCATCGTTTGAATGCTAGTGTAGCAA 74400
 N Q S F N I K F L H S A L U E F P I K N U C S D D M T K F A L T A F 135

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 U L Y L F S I N D L Y U H R K R N T K T P F E F H L T W R P F N D 102

U45

U46

U47

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 TTTGAGGCAACACTTAATACAGGAGTCCATATGATCAGATACTATAAAAAAGAAAGAAATCAACGTGACACTAGCATTGAATACATTTTGTGTTTT 74800
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 - F L R F U H Y I G F L U I I I I I L Y 672
 CAGAAGAACTAACATGATTGAACCTGACTTGATTTTAGATCTAATGCGGTAAITTCGAAACAGAGCCATTTCTTAAACAAATAAATATGTGTTGCT 75200
 L L U L M I S U Q S S K L D L A T I E F U S G N R L F L L Y H T R 639
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 P N U D I F N T D P D I L K L L Q K D D M I Y U F Q I I G D I D D Y 605
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 Y F Y M 1

U48

U49

M S L E Y L P P U A R R I G Q Y N H L R I Y K K I 25
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 L L L K S N F E K L N F F L G N L F P E E L H D S K I H U Y F E U 58
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 U50 M T Q L S L F Y Q F P I Q 13
 I A K E L Q L S S T F L C N L F T K Y Q N D T U K S I L S I S N P T 192
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 N F R R A C Q K V S N L Y R G R V A T T P K L G N S K T S K R K R 225
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 E I Q K N K I L K N L L K T E L D U L Q A H U Q T E C Q K L N T N 80
 A N S K K Q D F T T K K L U K N - 239
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 U T Q U T I T O I D P A I H F T E N F R P E M I K T F Y N N T Q M W 147
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 S V T F G A W F Y K L K R A F F T D S K L K R M L K L T Y U D S L 180
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 S I T Q E L L S I S I N A L E Q I T I Y P M H D N L U S D L E A G 213
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 L C L L T A F F A S Y P G T F L T E N I K F U D U I Q N L S Q I F R 247
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 Y L N T E I L A T K N A S P Q D F Y F G F N D P D K M K Y F I P L 280
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 C K G R H Y A I N T F S N H I L I K I F I K K G U I K Q U P G D Q 313
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 M S K G H U U I E S K L T G T L T D D K L L Y W T Q I L L Q P K L G 347
 TGTGGAAGGACATGTTGAATAGAACTGAAGTTGACAGGCAGCTTAACAGATGATAAATATTATATTAGGACTCAATTTTATTGCAACCGAATTTGGG 78800

 K E U P I F U H Q Q Q Y L R S G I U A I E S L Y L L W Q I L N S E 380
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 S I F G K R T G K F Y L T T I F P H U N A E D U T E T E F S S U N 413
 AGCATTTTGGAAAGGAACTGGGAATTTTATCTAACGACAATTTCCCCATGTAATGCGAAGATGTTACAGAAACAGAAATTTCTTCTGTCAATA 79000

 I Q N F E F L M K N Y U U P T Y L A N N E S T I S T L F P G L I S I 447
 TCCAGAATTTGAGTTTCTCATGAAAACTATGTCGTCGCCACATATTAGCCAAATGAAGTACTATTCCACTTTATTTCCGGGGTTAATCAGCAT 79100

 U U N E S U R L G W D H N Q N T L T Q T N A L H S Q T K D N P F U 480
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 E Y I R S Q L E E T A E L A U L E K H D K I L F H F E N G L N U T 513
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 L S L A L P R H R L F A M A S S L F N U A D L Y D F L Y F L U L G F 547
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 I P U A T U I - 554
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 U51 M K N I D L T N W K L L A E I Y E Y L F F F S F F 25
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 F L C L L U I I U U K F N N S T U G R E Y T F S T F S G M L U Y I 58
 CTTTCTTTGCTGCTGGTAATAATAGTGGTGAATTTAATAACAGCACCGTTGGTGGAGATACACATTTAGTACTTTTTCTGGAATGTTGGTTTATATT 79700

 L L L P U K M G M L T K M W D U S T D Y C I I L M F L S D F S F I 91
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 F S S W A L T L L A L E R I N N F S F S E I K U N E T K I L K Q M S 125
 TTTGCTCTGGCGTTAAGCCTGTTGGCACTGGAACTATCAACAATTTTCTTTTCTGAGATTAGGTAACGAACAAATTTCTAAACAAATGTC 79900

 F P I I W U T S I F Q A U Q I S M K Y K K S Q M N L E D D Y C L L 158
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 A I E R S A E E A W I L L M Y T U U I P T F I U F F Y U L N K R F 191
 GCTATTGAACGCTCTCGAAGAGACCTGGATCTTATTATGTATACCGTTGTCATCCAACTTTCATTGTTTTTTCTACGTGTTAATAAGCGATTTC 80100

 L F L E R D L N S I U T H L S L F L F F G A L C F F P A S U L N E F 225
 TCTTTTGAAGAGACCTGAACTCAATGTTACACATTTAAGCTTGTTTTTTTTGGTGCTTTATGCTTTTCCCTGCTTCGGTGCTTAACGAAT 80200

	N C N R L F Y G L H E L L I U C L E L K I F Y U P T M T Y I I S C	258
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	E N Y R L A A K A F F C K C F K P C F L M P S L R K L Q Q P T K S	291
	GAGAATTATAGGCTAGCTGCCAAGCTTTTTTTTGTAAATGTTTTAAACCTTGTTTCTTGATGCCTTCGTTAAGAAAATTGCAACACCTACAAAATCTA	80400
	T Q F -	294
U52	CACAGTTTTAAATTTGTAGAGGTCGAATAGAAAACAATCTGATAAATTACACTCTGTTACTTTTGTCTTTCTCCACTATGCCACAAAAAATTTTGA	80500
	- F Q L P G I S F L D S L N C E T U K A E K E U I G C F U K F	225

	ATCATTTGATAAAAGTAATAATCCATTCCTGTGTTCTGGTTTCTGTTGACTAAAAGCACCGTGAGAATTTTGATCTTGTCAAAAAAATTAATAA	80600
	D N Q I F T F L G N R H E P K Q Q S F A G H S I K I K D F F I L Y	192
	CCAAACCACAGATGCTTACAAATTTTTCGGATAAAAGTTTCATATACCTCTTGCCCCAGAACTTGTGAATAGCGACATAATTTTAATAACGGTGAT	80700
	G F W L H K C I K R I F P E Y U E Q G W F K N F Y R C L K L L R H N	158
	TGTAGATGGCACAATAGAAAACATTATATCCCATCGTGAATAATTTACGTTGGAATTTGAATGAAGACCAATTCATCCAAAAAGAACTTTCTAT	80800
	Y I A G I S F M I N G D H I I E A P I T I S L G F E D L F F S E I	125
	GATTTGTTTACAAATTCAGTATGATGAATTTTTTCGAGAGCTGAGCTGCATTTTCTTCACTGAAGATATGTTTAAAGATTCTTGATCCAGATCTTTGT	80900
	I Q K U I G T H H L K K S L Q A A N E E S F I H K L I E S G S R Q	92
	TTAATCATGCAAAAGATCTTAACCAAAATTCATCAGGTACCTTTTCGATTGCAAGCCACTAATCACTCACTCCGATATTGTGCAAGTCTCTCTCAACA	81000
	K I M C F I K F W F E D P U K R N L U U L D S U G I N H L T E R L L	58
	GTAGATTGGATGCCGTGAGAACAATTAGGGTACACATTCGGATGATCAAAATCTCTTCTTTTAGATTAAAGTAAGATTACCCGCTTACCAA	81100
	L I Q I G H S F M L T C U N Q I I L I E E Q K L N L L S E G S U L	25
U53		
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	K K T I H L I L N S T S N N S I I Y Q G U Q T M	81200
		1
	G F L C U Y D D N D I N D N F Y L P R A T I Q E E I N S G N G L N	40
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	I P L N I N H N E N A U I G T U S S L S D L Q H G L F T U A R U Q S	74
	TTCCATTGAATATAAACCAATGAATGAAATGCCGTTATAGGCACAGTCTCTCTTTAAGTGATTACAGCAGCGTTTGTTCACGGTTGCCCGTTCATC	81400
	K E F L T I I K K I A U K S K L I T N T E E K T L P P D P E I E C	107
	AAAGGAATTCCTTACATAATTAAGAAATAGCTGTAAATCTAAGCTGATAACCAACGGAGAGAAAAAATCTGCCACCAGATCCGAATAGAGTGT	81500
	L N S I F P G L S L S N R U G G N E R D P F F K H U S I C G U G R	140
	TTAAATTCATTTTCCAGGTTTGCTATTATGACAGGGTGGTGGCAATGAAGTATCGGTTTAAACATGTCTCTATCTGTGGCGTTGGTCGTC	81600
	R P G T I A I F G R N L N W I L D R F S S I T E A E K E K I L S T D	174
	GACCTGGAAATAGCTATTTTGGACGAATTTAATTTGGATTCTGGATAGATTTCTTCTATTACAGAGCGGAAAAAGAAAGATTCTGAGCACAGA	81700
	Q S C U Q F F A E E Q F K U D L Y D L L A D S L D T S Y I K U R F	207
	TCAAGCTGTGTTGCTTTTTCGAGGAACAATTTAAGTGGATTATATGATCTGCTAGCGGATAGTTTACAGACTTCGTACATAAAGTACGTTTT	81800
	P K L Q S D K Q L S G I S K S T V I K A S E N L T A N N H T I N U	240
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	N S K U T K E T E A T D S U S Q D D C A U H A P D L I S T I C S T T	274
	ATTCAAAGTCACAAGGAGACAGAGCAACAGACAGCGTTTCACAGATGATTGCGAGTCCATGCACAGATTGATAGTACGATTGCTGCACAC	82000
	H T T H H D L U R M N G S A T G N S A S L P A P Q F S E C U F L P	307
	GCACACACGCATCAGACCTAGTCAGATGAATGGCTCAGCTACTGGCACTCAGCTAGTCTTCCCGCTCCTCAGTTTTCGAATGTGTTTTTACCG	82100
	K D T F C S L L N A T A G A Q N K N U T P A A P I F K T D E Y I T	340
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	P Y P E S L S R M D Y G N R M N Y H I P P P Y W Y P S M P G F N Y K	374
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	Y R E D D D R E L T K D K N D I K E L U D A I G M L R H E I S A L	440
	TATGAGAGATGACGATCGTGAATCTACTAAGACAAAATGATATTAAAGAACTAGTTGATGCAATAGGGATGCTGCGTCATGAATTTACGCGCTAA	82500
	K Y I R S Q S P Q R Q H C T A U D T M P T I E E K N U A S P K P S U	474
	AGTATATTGGTCTCAGTCTCTCAGAGACAGCATTTACAGCGGTAGATACAATGCCAACGATTGAAGAAAAAAGCTGGCATCACCTAAACCATCGGT	82600
	U N A S L T P G Q D R N Q N L M Q S D Q S L L S L N K K L F U E A	507
	TGTAATGCCTCGCTAATCCAGGTCAGACAGGAATCAAAATTTGATGCAAGTGATCAATCTTTATTGAGTTTGACAAAAAATTTGTTTGTAGAGCT	82700

	L N K M D N -	513
U54	TTGAATAAATGGACATTTGAATACAAATTTAGCGTTAATGTCTGTCTGTTCCCACTGGGACAGGAACCGTTTGACGCCAATGTTGCCCTCTAAAA	82800

	- H R Q R N G S P C P U T Q L G I N G E L U	434
	CAGTTAATGTGTGTTAAGGCAAGTGGTGGTAGAATGTGCAAGGTTGTCTGTTCTCATGCGATATCTGACTGGTACAGGTTGTTCTTAGCTATGTT	82900
	T L T H P L A T I P L F T R L N D T R M R Y R U P U L H E K A I N	401

TAARTGAAGAGAATTTAGATTARTAGATACGTTAGTTGCAGCTGTGATATTTGGTACTGTAGATAGTACAGGACTATCAGCGACAGGTGTTGTTTCCGAT 83000
 L H L S N L N I S U N T A A T I N P U T S L U P S D A U P T T E S 368
 CTAAGACACATTATTTGATTATTTGATTGGAATCAAAATTTCTGCTTGTCTCTGTCCAGCCAAATCTATATTTGATTGATCGTGTGTACTATTTGAC 83100
 R F U S I Q N N Q N S I L I R S T E T W G F D I N S Q D H T U I Q S 334
 TGGGTAGGAATAAGTTTCCAGTTCCTGAGAATAATCAATACGGCAGTTTTTTTTGTAGGCTCTCATGGTTACTTGAAGATGAGTTCTCTCTTTCCA 83200
 P L F I L K G L E Q S Y D I R C N K K Y A R M T U Q L H T R E K W 381
 AGTGAAAGTGTTTAATGAATCCCGTTTATTATCTCGGAATAAAAGTCTGCAATTTCTGTTTAGAATCAAAAATGTTGGAATGTACATGAGAG 83300
 T F T N L S I G N I L R P I F L G A F K Q K S D F F T P F T C S F 268
 GGGTCAGTGGTATTGCAATTAATGTTTTTGTAGAACCTACGGTTATGCATGTGCCATCGTACGTCATTACAGGTCTTGATTCTTTCCATCACATGT 83400
 P D T T N S N I N K T S G U T I C T G D Y T M U P E Q N R E M U I H 234
 GAGGAATGGTTTGGATAAAATTTACTTGGAAAAAGATGTCGTAGGAATATATCAGGATTTAAAGAGATAATGTTTTCATAGATGCTCTTATAACAG 83500
 P I T Q I F N U Q F F I D S P F N D P N L L Y N N E Y S A R I U L 281
 GATTTTTTCATGCAGCATTATTTGCTTAAATAAACATTTCTGCTGGATATAAATTCACCTTTTGCACCTGTTAAAAATTTGATCTGGTGGAGTTGTTGT 83600
 I K E H L M I Q K F Y U N R S S I F E U K A S N F I Q D P P T T Q 168
 AAATCTATCCAAATTCACACGCGTACATGTAATGCGTTGGTTCTTCGTTGTAAATCTGTCCAGCGTATTCTCTTAATATGGGCTCTTAATTTAGTTT 83700
 L D I W F E C A Y M Y H T P E E H Q L E T W A I R K I H A R L K T Q 134
 GAGATCCATAAGATAAATTGAGCAGCGCACTCTCCATGTGGAATGTAATGTGCTCCATCGCTCAACTATTTGGACAGGAAGTGATACCAATTAAT 83800
 S G Y L I F Q A R C E G H P I Y N H E M R E U I Q U P L S U L N I 101
 GCTAGGAAGAAAAAGGCAAAAGGATTAATAATTAAGGAATTTGTTTAAATCTAATCTACATCAGATATATTTTGAACAGCCAGGTTACATTGCCA 83900
 S P L F F A F L N I I L P F Q K L D L D U D S I N Q U A L T U N G 68
 CAATCTCTTAGATCGATATACGTAAGTAGGGTGTCTGTAAGCTTCCTTCATCTCTGCACATACACACAATGTTGATTGTTGCGAAGATGATGCTTAGCC 84000
 C D R L D I Y T F Y A A T F S G E D R C M C U F T S Q Q S L I S L G 34
 CTGCTCTTAAGCATCTTATTTACGAGGTTTTAAAGGATTGGTGTCTCAATTTTAGTTGTAGAAAAATGAGACACAGCCACATAACAGGATCCAT 84100
 T R L C R I E R P K L L I P A T L K L Q L F Y S S W U U Y C S E M 1
 TCTTACTTTAATCTTTTATTGTTGTAATAACTTAATAGTTGATATTACAAATGCATACGTTTGAGCGGGGTGTTATGTTCATAGAGTTATGTCTAA 84200
 - L Q M R K F R P T I N M S N H R I 411
 TGTTCCTGCTCTTGTATTTGTTTCGTAGGGAAGTCTGTCATGGGATGAACTGTCAAAATTTGGGAGAGAGTCTGAAAAAAATCGTTCCCTAAAGAT 84300
 N E T E Q I Q E Y P F D T M P H U T L I P L S D S F F D N G L F N 378
 AATTCGAATGAATTGAAGCGGCTTCAACTTTTGATTGCAATCTGCGTGTGCTGAGGATGGAAGGAATGTGGAATGTTCTCTACTGATAAGTAG 84400
 I R F S N F A A E U K S K C D A H A T P H F S H P F Q E R S I F Y 345
 ACATGACCAATTATATCATGCTCCGTACAAATGTCTCATTTCCGAGTACACGTAATTTCTAAAGTCTCACGCGGTTGCCAATGAAGGAATGAGA 84500
 U H G I I D H E T U F T E N R C Y U Y I R F T E R P Q W I F P F S L 311
 GTACATTAGATTTCTTTGGAATGAATAGCCCTACAGCAGCAGGATTCTCAAGGTTCTCGTAATGATTGTTGTGTATGTGATTAGGTGTCAGTGCAT 84600
 U N S K K P I F L G U A A P N E F T G R L N I Q T I H N P T L T M 278
 TCTTTCAGGGAATAAATTTCCATTGTTTTGAATTTCTCAGAATATTGAATACGGCATGCAATGTTAAGTGCAACTGATTGCATATTTGGTTTAGAA 84700
 R E P F Y I E M T K F E E S I N F Y P M C I N L A U S Q M N P K S 245
 AATCTTAAGCGTAAGAACACTCATCCACACAGAACGTGAATTCATTACTTTAAGATACCGTAGAAGACAATAACACCGGTGATCGATATTCATCT 84800
 F R L R L S C E D U C F R S N M U K L Y R L F U F L U P S A Y E I K 211
 TGTACACCGAARCAATTGTTGTTCTGATATCATTTCCAGCTTGCAAGATTGGCGTTGCGCTCGCGAAAAAACATTCCAAATTTGCAAGTATGTTGATTGAA 84900
 Y U S U N H E S I M E U N C I P T A S A F F U N W Y K C Y T T N F 178
 GGTGAAGATGCGATACATGGTTTCCAGTCTTTGATCATTGGAGTTTTTTCAGTAAGGTTGAATTCATTCTTTTCCCAAGTAATTTAGTTACTGTGGCA 85000
 T F I C Y M T E L R Q D N S N K L L P Q F E N K E W T I K T U T A 145
 TTTACGATCAGATCACCATTTTTCCAGGAATATAAATTTATAGGAGTTGTTCTTAACCCCTTTTCAAGATAGGCAATTTGATGAATCTAAGAGGATCCA 85100
 N U I L D G N K U S Y L I I P T T G L G K E L Y A F Q H F A L P D M 111
 TATTTTCTTTAAGTAACAATTATCTTGTATCAGCAGGGATGACGTAATGTTAAAAATTTGGCAGGGCAAAATATTGACAAAGTTTATCGATTGTATCAT 85200
 N E K F Y C N D Q I L L S S T I N F I P L A F I N U F N I S Q I M 78
 AGGAAAAACATTATTTTATCACTTTTTGTTTTTGAACGTAACCCACCAAGTTACGCAATTCGCAATGTTTTTTCAGTCCATCGGTAAATAGCAAC 85300
 P F U N I K I U K K N K L U H G U L T U C E A N N E T G D T I L L 45
 AGTACAGGTCTTTCGTGCGAAGATGACGGTAATCTCTGCGGGAGAAAAATTGAGTTCTGGCTGCAATCATTAATCCACAGTAACCTGAATTAAT 85400
 L U P R E H S L I C T I E A P S F N L E P Q L D N F D U T F Q I L Q 11
 GCGATAATTCAGAGACTGGTGTGAATTCATTTTACAAGAAACTAGATATACAATGATTCTTAATGTTTTACACGTTTTATAGAACTAGCAA 85500
 S L E S U P T S N M 1
 GCTTCTAAGGCTTTTTTAAACCGCAATCTACTTTTTGAAGGGCGGTGTTATTATATTGATCCAGATTGCAATTTTTTTTTTACGAGCGCTCCACCTT 85600
 - F R L R S K S P A H N N I N S G S Q L K K K R A S W G K 403
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 R L I L D P L D S I F I K D A L F Y L A D S E P D E S N L E I E A 378
 AGCAAACTATCCGTATAGTTGGGATCAATTTAGTTCTGAATATGCGTTGGGATAAAATAATGCTGCCTATTATGTCAATTTGTAGTCACTCTCTGC 85800
 A F S D T Y N P D F K T R L I H T P I F Y I S G I I D N T T U R Q 337

U55a

U55b

GATCTATCACTAGTCACTTTTGTGGTAAACTTGTAGTGGGAGACCAGAAAGCAATAGACTGCACCTTTGGAAATTTGGGTCTGGAACTAGAGAGCAT 85900
S R D S T U K T T F S T T P S W F S A I S Q U K S N P D P U Y L A N 303

TAGCATTAAATATAAAAGTGCCTTTAAATGAAGTTTTAGTTTCGCCCTCATCGAAAGCATCGTGTCTTGGAAAAACGTCATTTTCTTTT 86000
A N F N Y F T G K F H L K K T E G E D F L M T D Q F F U D I K R K 270

ATCGCTACAGATTTTAAAGTAATGCATATGCACAGTTAGAGAATTTTCGTTGGGATTATTTTCGTTGACAAACCAAGTTTAAAGCATGCAATCGTTTGG 86100
D S C I K F Y H M H U T L S I E N P I I E N U F G L K L M C D N P 237

ACCATATACGTGTTATTTTATGTTACCTCTGTATAACATCGAAGATAGATTTTCGAGTAGAGGAGGAGAAAGATCATTTTAAAGTACGGAACGTGTTGG 86200
U M Y T N N K T U E T Y C R L Y I E L L P P S F I M K L U S U T P D 203

CTGAATAGAAAACTTTGCACGTTGGAAATCTGAACCACTCCGAACATCGTGAACCAAAAAGGTAATTTGTTATGTTAACAGAGCAGACTGTACA 86300
S I S F U K C T P F D S G S R U D H F W F P L N N I N U S C U T C 170

TAGAGTTGTTAATGGATGGCCAGGTGTTCTTTCAATCGAACGTTGATAAGTACTTAGTTTCCATTCATGTTAAACATCGTGACGGTTATTTCTTTTACT 86400
L T T L P H G P T R E I S R Q Y T S L K W E I N F M T U T I E N U 137

TTATGTGGGTTTGCCTCACTATGACCTTTTCTGTTTTGAATCTTATCAGACTAGAAAACTCCCATCTGCTCTTGTCTTTAATCATGTTTGGGA 86500
K H P T Q T U I U K E N K F R I L S P F U G M Q E Q E K U D H N P I 103

TGATGACGATAGAGCTGTTAATTTTAAACACGGAATCCAAAAACAAGACTTTTGTATGGAATAATGTGCTATTAGATTTTAAATGTAGTTTGTAG 86600
I U I S S N I K L L P F G F F L U K S P Y I H R N L N K L H L K L 70

TTGTTGTTCTTCATTAAAGGACGAGCAGAAAAAAGGAGTCAAGATTCCTTGAATTTATTTTACGCGCTCAAAAGTAAACTGGTTCAGTTTTTATTGG 86700
Q Q E E M L P R A S F F S D S N R S N I E A S L L L U P E T K S Q 37

ACATACTCGTCAATAATATGTACATTATCTTTACCTGGAATCTCTTTGTATGGAATTTCAATCTGAACATATTTAAGATATCAGAGTTGCGA 86800
U Y E D F L L T U N D K G Q F E E K Y P I E I Q U Y K L I D S T A L 3

GAGCATGGAGCTGAATAAATCTGTTACACAGACACTATTTCAAGAAGCTTTTATTCACTCTTTAATATACAAGTTGCCAGCCTATTGTCAGCAG 86900
S M - E K F I C T A L R N D A S 1 281

AAACATCAGCCACATGAAAAACGTTTTTCTTGTGAAGGAATGATTGGTTAATCATGGTGAACACGTTTTAATTTTCTGTAATTTCTGTTTAAAT 87000
U D A U I F F T K E Q T L S N I Q N I M T F U T K I K Q L E T K I 240

TTCACTGGCCTTGAAGAACTAGGTTCTTGAGAAAAATTTTTTGTAGGAGTTCTTGACATTTAATCAATAACATAGACTGATCTTAAAGATAAT 87100
E T A K F S S P E Q S F N K K A L L E Q C K I L A M S Q D E L S L 215

CTTCTATATATGTTGAATATATCAGGAGCCATGGTGGCAATCATAGAAAAAGAAATGCATGCTGTTTTCATGGAACACGTTGGAATTTACATCATTGA 87200
R E I Y T Q U I D P A M T A I M S F S I C A T K M S F T S K C D N I 181

TAACATCTGGTAACCTAATTGTTACATCTCTGACTGCAAGTGCAGAGCTCATCTATAATTATTTGAAGTCTTCTCATATTTTCTATGTATGGAAGGAG 87300
U D P L K I T T U D R Y Q L T R L E D I I I Q U E E Y K R H I S L L 148

GCTGATGCAAAAGCATTCGCACGTTTATTTCCGTTGCGACGCTGTAGGGATCAGTAATGGCAGAACTCAGCTCCAGTTAGGTAGACAGTAATTTGTTGC 87400
S I C L M R U N I E T A U D T P I L P L I L E W N P L U L L Q Q 115

GAAGGCTTCAGAAATGGTGGCAGTAAACTCAATTGATCTCCCTTTTCCAGAGGAATGGTCCGTTATTTTGAATTTTCACTGTTGTTCCAAATTTTGGAC 87500
S P K L F P P L L S L Q D G K E L P F P G T N K I E Y Q H G I K P R 81

GTATTAAATTAATTTGTTTCTTCTATTTTGTAGAGTTGTTAACCCATTGTTTTAAGATATCCCTTATTTGAATATAATCGGTGGTTGTAGATAA 87600
I L I L Q N G E U K Q L I T L U M T K L I D R I Q I Y D T T T S L 48

GACCGTGAAGTCTTAATTTGTTGCCAATTAATGACGGTGCAGCGTATTGGGATGACGGCATTAGTGAGTTTGCATAAAGTTCCATGTCAGAA 87700
U T Y L G L N T N G I L H R H S P I P I U A N T L K C L T G I D S 15

AGAGTAAGCTTTTGTATCAAAAGTACAGTAGATTGAATCCATTTCTATAGCAGGACTCAATAATTTTGTACCGAATACACTCCCTATAGCGAAAT 87800
L T L K Q D F T C Y I S D M - L L S E I I N Q L P I C E G I A F N 1 1328

TGCAAAATGCGTTTCACTTAACTGTGTCATTCGTTCTTAGATCGACTCTCTAATAGAGCTTGGTTAGAGGAGCAATGGATTGGAACGCAATTTGTA 87900
A F H T E S L Q T M G N K S R S E L L A Q N S S C H I P F A I Q L 1295

AACTGACAGGACGATGAGTGACATCGTCTGTTCCCTCGGAACAGAACTACTGAATATCAGTGTGCTGCTGCCAGGATGTTTATGTTTTATGGAATAAT 88000
F Q C P R A H T U D D T G E S C S Y Q I D T D S D L C T K T K I S Y D 1261

CACTGATAAGTTTAAACATAAATCTATTTGCTTAAATATTTCAAGTGTCTGTGAAAAAGACTGCGTTAGGACTGTAACTTTTGGATTATATCCTAATTG 88100
S I L K F M F K N T K F I E T D T F F U A N P S Y S K P N Y G L Q 1228

ATCTCTGTGATTATATATATAGACATCAGATAAAGATCCTTCTTGAGATGCCAAGGATTTGTTGTTGCCACAAAGCGTCTGATCACTCGAGAA 88200
D R H N I N Y L U D S L S G E Q S A W P N T T A U F A D S D U R S 1195

TGATCATACAAGATTTTCTAGCTTCTGACTCATTATGGGATCGACACCATCATACAGAGCCCTTCTCTAGGATTTTATGGTGTATATAGAAAT 88300
H D Y L S K R A E S E N H P D U G M M C S A R G R P N K P T K Y F N 1161

TAATATCGAAGTCACTGGAGTAATGACAACTCGCAGATTGCTTGTGGCCATGTAAGGATTGATTGTGATTGCTTATTTATCTTACCGAAGAAAG 88400
I D S T U P T I U U E C I A Q Q G H L L I S Q S Q K N I K G F S L 1128

GATGTTTAAAGCATCGGTTTTCGGAAGGATTGGGTTTTCAATGCCAACGATGATGCCTAACCAACTATTTACAGTAGGTTGGTGTATGCGTGATTTGGA 88500
I N L A D T E S P N P K E I G U H H R U W S N U T P N T Y A H M P 1095

AAGACCGAAATAGATCTTGCACTTTACTTCCATATCAGTTTTTACCCTTTTCAATTTGCGATTGCGAGTCTGGAACATAATCCTAATCCCATATCAA 88600
F U S F L D Q U K S G M D T K U R K L N A I A T S S S F G L G M D L 1061

U56

U57

GAAAACCTTATATGCTGCGTAAGGTTATATGTGGTTGAGATGCTCTTTACTTCTGTAGATACCGTTGGGTCATCAATCATTATGGATGTTGCAGATTGGGA	88700
F S I H Q T L N Y T T S I D K U E T S U T P D D I M I S T A S K S	1028
GCTATACAGTAAGCAATTAATGTGCGAACCAATCTGTTCTTACTAAAGTCGCGACGGAACACAGGATGAATTTTTGTCTGCTTTGAGAGATGATAGCTATT	88800
S Y L L C N I D F C D T R U L T A A F G P H I K Q R S Q L I I A I	995
GGAGACAATTTGCAATGCATAGTAGCTAAAGTCATGACTTAGCAATGAATTTGAACACACAGAGCATAGACAAAGAACGGTGTCTTTGCCAATTAT	88900
P S L K C H M T A L T M I S L L S N S C C S A Y U F F P T R Q W N H	961
GGATTTCATGAGATAATGCTTGTGGTAGAGGAAACACCGTCATTTCTTTGATAGTGGGGAATATGTTTAGATAGGTTTGTACTTCAATATTTCATTAA	89000
F E H S L A Q P L P F G G D N R Q Y H P F I N L Y T Q U E I N M L	928
GCCACAATAATAGGGTCTGAGAAAAACGATTAAGGAATTGGCTTGAATACCGTTTCAACACATTAATTTGGTGATACTAAACACAGTCCATTATAT	89100
G C I I P D S F F R N F P I P K F Y R K L U N I P S U L C L G N Y	895
AAACATGTTGTAGAGATTGAGGTTTGAAGAACTACCATGCTTTTGAAGAGGATCTAAGAGAGATTCAATTTCCAAAATTTTTGTATTCTCCGTTAGGT	89200
L U H Q L S K F N S S S G H R Q S P D L S S E I E L I K T N E T L Y	861
ATAATATAGATTTAAGAGTTGTTTACCAATGCAAGATAAATCTGTGAGTGCATGTGAGGGACCAACAGCTTCAGTTATCAATTCAATCAATACATTGTT	89300
L I S K F L Q K G I C S L D T L A H S P G U A E T I L E I L U N N	828
CGTAATCGGTAAATTCGCAAAAGTTGTCATCAGGTAATATAAGGGTTCTGTGTAGAGAAATCTAGAATGAAGATTTACATCAAAACCTGCACACAC	89400
T I P L E C F N D D P L I F P E T Y F F D L I F S K U D F G A G C	795
ATCTTGTTATTTGTGCTGCTGGTAGAAGCAGAAATAAAAAATTTTCTTAAACCAATCGTTTCAAAGATGGTCTATCTACGCTGTGAATATTTCTG	89500
M K N N T L A P L F C F Y F I K S L U I T E F S P R D U D T F I E T	761
TTGAATCCAAATAATTCATTCTATTACGTCAGATACCTTATAGTTTCTTAATTTCACTGTATTTTGGGTAGGGGAGTGTTACAGCTGTGATTATTGC	89600
S D L L N M R N L D S U E Y N R L K U T N Q T L P T N G A T I I A	728
ATTGCTTCATTTTTTGGAGACTGTTTAGAATGGAGGGAATAGACGATTATCAACACAGCGTTCACAAATCCAACCAATGGTTCCCCACACAGTTGC	89700
N A E N K P L S N L F P P F L R N D F L A N U F G U L P E G C L Q	695
TCATTAAGATTTGAATAGAAATGCTCTTTTCACTAATTTAAGATTGAATATATTTTTGTATGTGTATAGCAATTCCTGGAATTGACTCATCTC	89800
E N F N S I S I T R K U L K L I S I I N K Y H T Y A I G P I S E D G	661
CAAGATAGGTTGTAAATTAACCAATCATTTCAAATATTATTGCAAAACAATAATATGTGCTTTATATTATACCAATACGTAATACATTGGCTGACACGTC	89900
L Y T T I L W I M E F N N C F L L I H K I N Y W Y T I C Q S U U D	628
TTTAAGATCTGAACGCTGTCTTATTACCATGGATGAGAGTTCTATGATATATGCTAGTTTGGGATAGCTGTGTTAGTTAAACCTTCACGACGAGT	90000
K L I Q F A T K N G H I L L E I I Y A L E P Y A T N T L S E U U L	595
TTGAGGTTGTAGTCATAATTTAAATATTTTGTCTTGGCTTGTTCGATCATTTGATTGGTCTAGCTTCATGAAGAGATGAAGGTGCTACGGCAGAGGTA	90100
K L T Y D Y N L N N T K A Q E I M Q N T R A E H F S S P A L P L P I	561
TATTGCTTACCAAAATCTTGGTGACACAAACATCAGTTGATCTGTTTTTTGAATATAGGTGAATCAAAAATGGATGATCTGTCTTTAAAGT	90200
N G L L I R P S C L U D T S R N K Q I Y T F D F F P H L E T K L T	528
AAAATTTTCAGATTATAGAATCTTCTGTGGTAAGTTCATTTTTAAGCATATTCGTCGCTTAGGTATTTCTTTTTTCATTTATATAAGTTGTATAAA	90300
F N E S K Y F D E T T L E N K L M N T T K P I E K K M E Y L N Y L	495
TTTGATAAAAGGTCGTTGGAGGTTCTTAAACAATTCACCTGACACAGTGGTTAAAGATTCCCCGTAAGGTTTGCAGCATTTTAAAAATTCGCT	90400
N S L F T S P P E R U F E U Q C L Q N F S E G T P K A A N K F I R E	461
CTGAGACACTACATCAAAAATAATTTGGATGGCACAATGATGGCAATAGATCACTATAGTCTATTCTCTGCAAAAGCTTATCCTTATTATAGAATAGAT	90500
S U S C D F I I P H C L S P L L D S Y D I R Q L L K D K N Y F Y I	428
AGATGTGGGTAGATTGTTTTCCATTGTATCATTTAGTTTAAAGCCTGCTATCCATAGTGCTAAACCACTATCCTTCAAGATGTATAAGCCATTGGGAAA	90600
S T P L N N E M T D N L K L R S D M T S F G S D K S I Y L G M P F	395
AAAAACGTCRAATCCAAATTTTGTCCAAAGGATCCTCAATGTTAGTGTTTTTATACACTTCTTTAAATGATCTAAGACACTGTTTTATCACTCAGTT	90700
F F T L E L K Q E L P D E I N T N K Y U K K L H D L U U T K D S L Q	361
GAATAATGTTTGTCTTTAGATCAGCATGTTGAGTTTGGTTTTCAAGATTTTCAGATTTTTTGTTTTGGTCTGTGTTTCAGTCGCAACGTTTTTGGTATA	90800
I I N T K L D A H Q T Q N E F I E S K K N Q D Q T E T A U N K T Y	328
ATTTGAAAAATCCGCCATAATAGCCTGGTATGCTATTGCGATACAGCATTTTCTTTCCCATACCAATGTGCCATAAGAACAGGTACAGACATTGTC	90900
N S F D A M I A Q Y A I A T U A N E K G M U F T G Y S U P U S M T	295
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M Q S I H Q S L A N S L I Q I T N P T G L L U G N I P T G D K L U Y	261
AGCTATTGGTGTATTTAAAGTCTTTTCACTGGTTGAATCAACCATTTTCAACAGATATCTGTATATAAGCTTACATTAGAAGTTCTGTTCAAAAAAAA	91100
S N T N N L I S E T T S D U M E C L Y A Y I F S U N S T R A N L F F	228
TAGGAATGATGAGTTTGTTTTTAAGTTTGAACATATTGCTTCGCTGACTTTTGAAGAGAACTGTTTACTGTTGACTTTGTTTTTCAACATGGTT	91200
L S N I L K N K F N Q F M N S R Q U K S L I Q K S N U K N E L M T	195
TTGAGGATAACTGTGGCGGTGCTTCTTAAAGATAGTTTTAATGAAGCATATTAACCTCGTTGTACCAATCAGCAGAAATTTTCAAGCATCGTA	91300
K L I F Q P P A K K L I T K I F A Y I L G R Q L S D A S N K L S R L	161
ACACCGTATGAATCGCATGATGTTGAGCATTTGATCTAAATTTGTTTTTAAAGGTGTTTTCTTAATGCGCTAACAACAGCAGCACTTAATTCACACGA	91400
U T H I A N I N L M Q D L I T N K F T N E L H A L C A A S L E F S	128
TATATTGATAGGATGCTTTTCTGAATACTTGGTAACAGTACGGTTGTTTCTTAGGCGCAGTTACGTCGTTTCTGTAGCGACTCTAGGTAAATTGTATA	91500
I N I P H K E S Y K T U L U T T E K P A T U D N G T A U R P L Q I	95

TAAACACGAATTTTTCCAGTGACATTTTGTCTAGGTCGTTGAAACGGATACATTTGCGACACCCGCTATGGACGTATGAAAAAATCTATCCATTACG 91600
Y F L I K G L S M K D L D N F R I U N A A U A I S T H F F D I W E T 61

TCCGATTACAGTAATCCCAAGTAATGCTTCGAACTTATGTTATAACGATCAGAGTCGTCACCGTAATACAATCTTAAGTTTTCAAAAAGTTGTTTCAGC 91700
R N C Y I G L L A E F S I N Y R D S D D G Y Y L R L N E F L Q E A 28

AGTTTGTGTTCTGATATCATCAACACGTTTGGAGAACATCTAGTTTTGGGAAATTTTCAGCTGTGCGCCAATTTTCCATGGTTAGTAAATATGATAGA 3
T Q T R I D D F U N P S U D L K P F I E A T R W N E M 91800 1

S I S E E T L I U K S Y T U N H C A K N U P U F I N S Y D L T A E 36
CTCAATATCTGAAGAACCTTAAATAGTAAGAGGTACACCGTTAATCACTGTGCTAAAAATGTTCCAGTGTTTATTAACCTATGATTAAACCGCAGAA 91900

U A K N E D U R L A R Q U Q I S L E K I D E U I E S I F S A S G P 69
GTGGCCAAAATGAAGACGTGCGATTAGCGGACAGTTCAAAATTTCTAGAGAAAATAGATGAAGTTATAGAATCAATTTTTCTGCGTCTGGTCTCA 92000

S U E N U K D Q A K F A L C R L L L G P U S I P C Y C E E W D U N F 103
GCGTTGAAATGTAAGATCAGGCAAGTTTGTCTTGTGTCGTTTACTGCTTGGTCTGTGAGTATTCGCTGCTACTGCGAAGATGGGATGTCAATTT 92100

Y L T K C S Y N C E G P U L Y I Y K N A S Q C C E S T Y R F S I M 136
TTATCTGACAAAATGATGTTATATTTGCGAAGGCCCGTTCTATATATCTATAAAATGCTTCTCAATGTGTGAAGCACATATCGTTTTCTATCATG 92200

T N Y H S T H I F R G L L S L Q E W N S H L S N I L C T C S N U T 169
ACTAATATCATTTCCACTCACATCTTTAGAGGATTATTATCATTACAAGATGGATAGTCATCTATCAATATCTTATGTACTTGTTCGAACGTAACAG 92300

G D K Y T A T I F P N N A S I Y L E Y V P Y F L C Y L C K H L S I I 203
GTGATAATATACTGCAACAATCTTTCCAACCAATGCTTCAATTTACTTGGATATTTATCCGATTTTCTATGCTATCTATGCAAGCATCTGTCTATCAT 92400

D I E Q C T N E L I A F L G P K T S Q R I I I H Y K L L F G F R S 236
TGATATTGAGCAATGTACTAATGAATGATAGCTTTTCTTGGTCCAAGACTTCTCAAGGATTATAATTCACATATAAATGTTATTCGGGTTTCGATCT 92500

K P M N F T U S L L E Q U F T L E I Q K L Y Y S U S K H N S T T A 269
AAACCAATGAATTTCACTGTTTCTTGTAGAACAGGTTTTCACCTTGAATCCAAAATCTACTATTCGTTAGTAGGACACACAGTACACAGCAG 92600

D F F N U I T A K F A E D K Y F U L R T F K L S A Q I T P G I Q S F 303
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C S L K F K L Q T L Y L N L K I M K N T K L S I S N S F Y H G K T 336
TTGTTCAATGAATTCAAACTCCAGACCTTATATCTAATTTGAAATTTATGAAACACAAAATTTATCCATTTCTAATAGTTTTATCATGGTAAACT 92800

L Y T L D E K Q L U W A N L L L I Y Y G Y N L K D N U K O T Q E E 369
TTATATCACTGGATGAAAGCAACTTGTGGAGAATTTATTTGTTAATTTACTATGGTTACATTTAAAGACAAATGAAACAAACACAGAAGAGA 92900

S L L S M H Y I A I L E R L S L K S F R E I N Q Q F R F E I P S Y Q 403
GTTTGTGTCGATGCATTACATACGAATATTGGAAGATTGTCTCTAAAAGTTTTCGCGAAATTAATCAACAATTTAGATTGGAATTCGAGTTACCA 93000

E K T L Q F I P G G N D F A E I T S U T H G E T T U N A F N T N R 436
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U M N U K A A L S G E I H C U L H R I P K S M T H S F U M Y K R T 469
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F K E P S L T U S T F I S N D D F T T S S L N I N I R G P Y C D F L 503
TTAAGAACCTCTTTAACAGTGAGTACCTTCATTTCAATGATGATTTCCACCACAGTTCATTGAACATTACATTCGAGGTCCCTACTGTGATTTTTT 93300

Y A L G U Y R L H U N I Q D F F L P A F U C N S N N S M D L H G L 536
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E N Q G I U R K R K K K U Y W I T N F P C M I S N S E K U N U G W 569
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F K A G T G I I P K U S G T D L K N U L L K E L I S I G E I P N I T 603
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F D M D L H A L L T L L E K R N M H Q U P F L I K Q F F M F L R L 636
TTTTGATATGGATTACATGCTTTGTTAATCTTTTGAAGAACGAATATGCATCAGGTTCCATTTCTTATTAACAATTTTTTATGTTTCTTCTGTTA 93700

G L L U G Y G R K Q E A R K U H H I M L F L I Q K G G F F D F S K A N T S 669
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U A N S K I K H A C A L U G S R L A N N U P K I L S K Q K K M K L D 703
TTGCCAACAGTAATAATTAACATGCATGCGCTAGTTGGAAGTCAGTTGCCAACAAATGTTGCTAAGCAGAAAAAATGAACCTGGA 93900

H L G R N A N A L T U L R F I U E N G Y Y K R K T I F R K L L K Y 736
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L A T T S F N A H U Q T E S N A L L L N L M H N D S K T N F S S L E 11
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D C T L Y U N N E T A T U H E I L N S D L S E L L Q L K T E F U S 44
R L Y T L R - 775
GACTGTACACTTTACGTTAACAATGAGACAGCAACTGTGCATGAATCTTGAATTCGGATTTAAGTGAACGTTACAGTTAAGACGGAATTTGTATCTA 94200

M T D L C U Y I T G C I N Q N I S S I T I Y W H A Y S E U I Y A L T 78
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U58

U59

G I I H C E K I S I E C G I K S T D N N I L Y E K P K L F L L R E 111
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 N L A P T E L R W K S L I K T K T I K S A L S P N Q N E I F P K I 144
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 CACACAAGCCGTCARTCTTTTAGAGATTGAAGAGACACCCGATTAAAGGAATGGTGTCTGATTGGAGAGTTAGTTGCCGAGAGGGGACCATTAAC 94600
 S K S E N D I U K T C K K L A E S Q R Y T L T N G T U L Q N F I L 211
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 S I H U U U K A Y Y S E H I D U S Y K I L S Y S T N M M N L F S Q 311
 ATCCATTATGATAGTAGTGAAGCATATTATTCAGAGCAGATAGATGTTTCTTACAAATTCCTTCGTACTCAACAACATGATGAACCTATTCTCTCAG 95000
 Y L N F T D L L P Y I N K H I K I D U S A S K Q D M I K F L N A C 344
 TATTTAAATTTTACAGATTATTGCCATATATAAATAGCACATTAAATTTGATGTTTCAGCATCTAAGCAAGATATGATTAATTTCTTAATGCCTGTT 95100

 L G L - 347
 TGGGACTTTAGATTTCTTTAATGAAGTTTGTTCACCTTCATGGCACATATAATAGCCATTATAATAGAATTAARAGGTATCTGAACAGGTTTGT 95200
 - I E K F S T Q K G E H C M Y I A M I I S I L L D D S C T Q K 634
 TTTGGCATTATAGGTTACGTGTTTATTATTAATTTGGTGAGATTCTTAATTTGTTCAATCAGTACTCTATTGGGTCATACGTTATTTTTATTGTA 95300
 K A N Y T U H E N I N I Q H L N K I Q E I U Y E I P D Y T I K I T 601

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 Q A I Q S Q D L T H F F T I H K Y R I U S I T Q K L I C A I K U A 534
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 S S Q N S N G E I I I K L E T F F P H L E L U A L I M H S A C E A 501
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 F L D F E I L G Q E T I L T D N U U N C L S G G M I E H K F A G E 401
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 L F L D A T K K U D A N I S I F K P K H L R Y C A C T T A N G R D N 367
 TTAGTATGTGCACATGATCTTCACAACATAAGATACTACAGTTAATTTCAAGGGGGGAATGCTTAGTTTTGTCAAGAGGAGTAGAGTGATTTCC 96100
 L I H U H D E C U Y S U U T L M E F P S N S L K T L F S T S H N G 334
 GGAATTTGTGGATGATATAAAATAATTTTAGTCGAAGATTGTGGCGAATCCAGAATTTGTGCTAAACCGCTCTTTTGTATAAATGGCTTTCATCA 96200
 S N T S S I F I I K T S S Q P L F G L I T S F A D K K I F H S E D 301

 M N G U L N D I K T E F L C N T K T 18
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 U I L L N F S Q G R I S<start of U66 exon 2 289
 D L L T L I Q K I C L N C D F I L E P U E S F P K K T E L U A U M 51
 GATCTTTTACGTTGATACAAAAATTTGCTGAACTGTGATTTCTTGAACCGGTAGAATCTTTTCTAAAAAACCGAGTTGGTTGCGGTGATGT 96400

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 Y D T L A U E I F N D L L K Y N E Q K K D G L A - 75
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 E G E C S Q M Y N L H N P L T F E M G L G N I F I C U R C F K I H F 52
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 TTGCAATATGCTAGAGACTGCACCTGATAAATCTCATGAGGATGCGGTGTTCAAAAACCGGGCTTTTTTATAACGGATGGATGCCAGCCTATTCA 96700
 H T C M E P T E E P N M E T U N U U U U L L S Y U Y S F L I Q N K 118
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 A R Y S N I I R D I I K D G K F I E Q U E N A U F C T F N K U F K N 152
 CCAGGTATTCAACATTATTCGCGACATTATAAAGATGGAAGTTTATAGAACAAGTAGAAATGCTGTTTTTGTACATTTAATAGGTGTTTAAAGAA 96900
 S T L N K L P L T T U S Q L F U Q L I I G G H A E G T I Y D N N U 185
 CTCACCTTGAATAGTTACCTCTTACTACTGTCACTCACTTTTGTTCAGTTAATTAATGGAGGCCACGGGAGGCACTATTACGATATAATGTC 97000

U66
exon 2

U62

U63

U64	I R U S R R K R E D N I L K K M R I E Y G N A L A L -	211
	M E M H L L C E T M F T C R	14
	ATTCGTGTTAGTAGAGAAGAGGGAGGATACATACCTTAATAAATGAGGATTGAATATGGAATGCACCTTGCTCTGTGAACCAATGTTTACTGCGAGA	97100
	K N N I L P U H L C I L L D D U I H K E K U K A I E G I F F Q C U	47
	AAAATAATATTTTACCGGTACATTATGTATTTTACTGGATGATGTTATACATAAGAGAAGTAAAGCTATAGAGGGATCTTTTTCAGTGTGTAT	97200
	F F K E K L U Y T E W T K I K F T Y U L H D L U I S Q I F K N A C I	81
	TTTTAAGAAAAGCTTGATATACGGATGGACAAAATAAGATTACTTATGTGTTACATGATCTTGTAAITTTCTCAATCTTTAAGATGCCTGTAT	97300
	K E U I H G A L I L S U P I N I D N L H F D T D I L I L K I I Y P	114
	TAAGAGTAAATACATGGGGCATTAAITCTTTCAGTTCACATAAATATTGATAACCTACATTTTGATACAGATATTTTAAITCTAAAAATTTATTTACCA	97400
	H F L H D D I U I K L S E I L S G A P R I Q K T U E K K Q E U E K	147
	CATTTTTTGACGATGATATTGTCATAAAATATCGGAATTTTGTCTGGAGCACCTCGCATACAAAACAGTGGAAAAAACAGAGGGTGGAAAAAC	97500
	P F F H I P A K L G D L T K E D P I S F N H H G P L E P P S T U R G	181
	CTTTTTCCATATTCTCGCAAACTTGGAGATCTCACAAGGAGAGCCCTATTTCGTTCAACCATCATGGTCCGTAGAACCTCCATCAACTGTTAGAGG	97600
	L K Q S A N U R H S H P I S R P E K A N U T F L S D S W Y S Q N L	214
	ATTAACAATATCTGCGAACGTTAGGCGATGTCATCCATATCAGGCGCTGAAGAAGCGAACGTAACTTTCTAGTGATTCTGGGTACAGCCAAAATCTA	97700
	K C D F I S D I Q Q R H U L U I F W Y E L S K G I Q M Q I K N I Q	247
	AGGTGTGACTTCTATCTGACATTCACAAGAGCATGTGCTTGTCAATTTTTGGTATGAGTTATCGAAGGGATACAAATGCAATTAATAATATTCAAA	97800
	I P P E N L F S S I T N Y L D R U N T Y L D E I A E R T F R C I T T	281
	TTCTCTCGAAATTTGTTTTCATCAATAACGAATTATTTAGATAGAGTCAACACATATCTAGACGAGATTGCTGAAGAATCTTTTCGATGTATTACTAC	97900
	N M E I Q N R H L P Q K F N S H F Q I E F N C T H L I Y G M E L A	314
	TAACATGGAATTCAGAATAGACATCTTCCACAAAAATTTAATAGTCATTTTCAATAGAGTTTAAITGTACTCACTTAATTTATGGTATGGAATTTGGCG	98000
	R D F W I L S L D R N S C U L K A M A S H F L H K K K G R S S L S	347
	AGGGATTTTTGGATTTTGTCTTTAGATAGAAATAGTTGTGTTTTAAAGCTATGGCCAGTCATTTTCTCATAAAAAAGGGAGAGCTCACTTAGTT	98100
	S N E F W A D L I D C T T G K T L Y G E K U R W Q L N S E T S L Y S	381
	CGATGAAITTTGGGCTGACTTAATTTGATTCACACCGAAAACTTATATGGAGGAAAGTACGGTGGCAATTAATTTCTGAACGAGCTTATACTC	98200
	T F R K N Q N I S W E L Q P N C Y A L Y M S E N L K L Y W U L P G	414
	CACATTCAGAAAAATCAAAACATTTTATGGGAATTCAGCCTAATTTGTTATGCACTATATATGCTGAGATTTAAGCTGTATTGGGTATTACCCGGG	98300
U65	M N F S S I G N L G C L R S F L Q N E C	20
	G F C U S G T F K L K E N D E F F F F D W Q F G M S -	439
	GGGTTCTGCGTGTCTGGAACCTTTAAATTAAGAAGAGACGATGAATTTTCTTCGATTGGCAATTTGGGATGCTCTAGGAGTTTTTACAAAATGAGTGT	98400
	N W F S U C K K K K L Y H E Y R C U A T S S P U F A U D K F K D C L	53
	AATGGTTTTCGTGTGTAAAAAAGTTGTACCACGAATATCGTTGTGTGGCAACATCTTCTCCTGTTTTCGCTGTTGATATAATTAAGATTGCTTGC	98500
	H C N I I I L K K N L D F U F S L A I N G I H A G Q F A T N S I K L	87
	ACTGTATATAATTTTAAAAAGAAATTTGGATTTTGTTTTTAGCTTGGCCATAACCGAATACATGCCGGACAGTTTGCACAAATTCATTAAACT	98600
	K K I I I T N D L U Y V I L E L G S L T U T D L H F I P K Y N S E	120
	AAAAAATATATAATAACAACGATTGGTGTACTACATATTAGAATGGGATCTTTAACGGTAACGGATTACATTTCTATTCAAAATACAAATAGTGAA	98700
	H U L N U R P I T P N L I Y D T C S I U S Y D E A K L L T U K G P	153
	CATGTGCTGAATGTGCGACCTATTACGCCAATCTAATTTATGATCTTGTTCATTTGTTAGTTATGACGAGCTAAACTTTTAACTGTTAAGGACCTG	98800
	G E N K L I P L G C G S W C L N N I G R V Y V U Y T F U L U Y D L Y L	187
	GAGAAAATAAATTAATCTTTGGGTTGTGTTCTTGGTGTCTCAACACATTGGACGTTATTATGTGTACACTTTTGCTCGGTGTACGATTATATCT	98900
	A C F E K N T L P S L S K U U F D M I S C N N K H C U F C K D H S	220
	GGCTTGCTTTGAAAAAACACTTTGCCATCATTATCTAAGTAGTTTTTGATATGATTTCTGCAATAATAAACATTGTGTTTTTTGTAAGGATCATAGT	99000
	K H U E Q T G K T U G C T D N Q E T C F C Y T P C K K K M A K I S	253
	AAACACGTAGAACAACTGGCAAAACCGTTGGATGCACGTGATAATCAGAACACATGTTTTGTTACACCCCATGCAGAAAAAATGGCTAGATTTCCA	99100
	N Q D L S S L L C D Q E L D L L D L I Y P E K P T S L S T D I N A Y	287
	ACCAAGATCTGTCTTCATTATTATGTGATCAGAGCTCGATTTACTTGTATTAATTTACCTGAAAAGCCCACTAGCTTTCACTGATATAATGCTTA	99200
	U H G H K N Q E P U U L R N T N W I L I A L D P A I S R L I L L S	320
	CGTACATGGACATAAGAACTCAAGAACCGTGGTTTTAAGGAATACAACCTGGATATTAATTCGCTTGACCCAGCAATTAGCAGATTAACTCCTTTCC	99300
U66 exon 1	C P U C K R I U S R -	330
	TGTCAGTCTGTAACGCATAGTAAGTAGGTAAGAAAAATTTGTACTTACGTGAGTGTGTGAACACTAGCAACAGTGTGCTACTTTTTATTGTTTCG	99400
	H T N Y C S A F L A T S K I T E	273

	TGTTTCGATAGTAATCACATTATCTTGACAGGTGATATCTTTTGGGGAAAAAACGCTCTACATTTAATTTCAACATCTTTCATACAAAGTGCGAACGT	99500
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	GTTTTGATGTGCAACATAACCAATGCTGATTCCTTCTAATCTTTTAATAAAAAACAATAACTGGTATCATGAACCATGTTTTACCGTGTCTTCTGGG	99600
	K Q H A U Y G I S I G E L N K L L F C I U P I M F W T K G H R A P	206
	AACTAGAAAAACACTAGCTTTCTGTTTAAAGTATGTTTACGCTGCTTTCGTTTATAAACTCTATGTCAATTTATATTTTAAAGTAATCAAGGACATGATTG	99700
	U L F U S A K Q K L I N U S S E N I F E I D F K Y K L Y D L U H N	173

GCCAGTGTGGGTAAATTCGTAACAGAGATGAAAAAATTATGTGTATAGGAATGCTCTTTTGAARATGGCTCTAGTTTAATTCCTTTTATTGGTGT 99800
A L T P L K T U S I F F I I H I L I S K Q F P E L K I A E K K N T H 139

TCTCAAAATCACCAGATCCATCTTTGAAATCTTGAATAAATTTTCGATCTGTAAAACATGGGATTTCTGTAAAACTTGTGTAGCTCTAGATG 99900
E F D G C I W R Q F D Q I F K E I Q L F M P N R Y F S T Q L E L H 106

TTTTGATATTGTACTTCTGTATTTTCTCTATGATTGCAGTAATTTGAGCTTTGACAAAGCGCAGTTCAAGGGGTCGATATTCGAATTTTAGATTTT 100000
K Q Y Q U E T N K E I I A T F K L K S L A C N L P D C I A I K S K 73

ACGTGCCGTTGGCGATCACAAGAGATATAAGGTTTAAACATGCCTGCAATATGCATGTGTAAGCCAAAGTTCTGGAGTTAATATAATAAATCGTTTTT 100100
U H R Q R D C F L Y L P K U H R C Y A H T F G L E P T L I I F R K Q 39

GGCAAAATATCGCGCTGTTTGGAAAGTTGAAGAATCTTTACGCTCTGTTTCATGTTTCCAAATTATAGACTGATACGCTTTCTGAATTGCATCTATATC 100200
C F I A S N P F T S S I K U D Q E H K W I I S Q Y A K Q I A D I D 6

U67 M D T D I A L A A I Y K E T T K L N E K D A K I F S E A U 29
GCATGATCGCAACATGGACACAGATATTGCTCTAGCTGCAATTTATAAGAAGCAGCTAATTAATGAAGAGGATGCTAAATTTTCTCGGAGGCGAGTG 100300
C S A L M 1

Q T A L T U C K A T A P N T R L K L U E T P T N N F L L U T N U U 62
CAGACCGCACTAAGTGTGTAAAGCAACCGCTCTAATACACGTCTAAACTCGTTGAACACCACTAATAACTTCTTACTAGTAACAAATGTTGTTT 100400

P S E T S K A T T E A N L N I D A A L E K L A S S F N T A U P U K S 96
CATCAGAACTTCGAAGCAGCAGCTGAGCAAACTCTTAATATTGATGCAGCGTTGGAAAACTGGCGTCTCTTTAATACAGCGGTACCTGTAATATC 100500

S K K Y L L Q N U R K M T S E N I A L T G S Y I I Y T K K H I E U 129
ATCCAAAGATATTGTTGCAAAATGTGAGAAATGACCAAGTGAACATCGCTCTAAGTGGATCATATATCATCTATACGAAAAACACATCGAGGTG 100600

A F L L D K S D F U Q D I L R Y A E T P S L L G H T D U R D L E C 162
GCGTTTCTGTAGATAGTCTGATTTTGTTCAGGATATTTCAGTTATGCTGAACACCCAGTCTTCTAGGACATACCGATGTACGTGATTAGATGTT 100700

L L W L A F C G P M S Y C Q A D N C F G L N K A G Y N A P F P I L F 196
TGTTATGGTTAGCTTTTGTGGTCTATGAGTTATTGTCAGGCTGATATTTGTTTGGACTAAATAGGCGGGGTATAACGCCCTTTCCCAATATTGTT 100800

P P C M Y E A R N M N L S U F F G L L Q I Y U F S L Y R D F S U E N 229
TCCACCATGCATGTATGAAGAATATGACCTTAGTGATTTTTTGGGTTATTGCAATTTATGTGTTCTCTTTGTATAGAGATTTTAGTGTGCAAAAT 100900

S N L Q Q G I K K R I K L U L S D L R A K E R I C E E E I G N F P 262
TCAATTTACAGCAGGTATTAAGAAGCGTATTAGTTGGTTCTGTCAGATTACGGGCCAAGAAGAATTTGTTGAGGAGAGATAGGAATTTTCCAT 101000

L A A Q I C L F C A L Y R Q N R L C M E Y A A N N L S M S U F S P I 296
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I L K D C T F M Q T T U T I T Q I L P G S K E A I I F P U Y D I G 329
AATATTAAAGGAGTGTACATTTATGCAACACAGTTACCATAACTCAATCTTGCCAGGTTCTAAGGAAGCAATATTTTCCAGTTTACGATATAGGC 101200

U68 M S L H E L I K Q T M S K N L E 16
K L L S A L U F S E N G U L L K L - 346
AAATTTATTCAGCTCTGTTTTTTCAGAGACGGGTGACTTTTGAACATATAATGTCACTGCATGAATTAATAAACAACTATGTCCAAAAATTTAGA 101300

K K H Y E L L K L K L G E D H P L S U R Q Q I H A L N Q N L U S E 49
AAAAAACATTATGAGTTGTTAAATTAACCTTGGTGAAGATCATCTCTTAGCGTTGACAGCAATTCACGCTCTCAATCAAACTCTGTATCAGAA 101400

N L E Q S Q I I T S L T K M L K D Q K L Q L K A Q R K N A A Q L E 82
AATCTGCAAGCTCCAGATAATTACTTCTTTGACAAAAATGTTAAGGATCAAAAGCTGCAGCTGAAGCGCAAGGAAAAATGCTGCTCAGCTAGAT 101500

C U D L D D I L D T A A E U K S U T D N I K E T L L A G L E S D - 114
GTGTAGATTGGATGACATTTTGGATACGGCAGCGGAGTGAATCCGTCACCGCAATATAAAGAACTTTACTGGCCGGATTAGATCAGACTAAT 101600

U69 M E Q L K T P Q N O K T R P A N M L P K K K G K E L K K R P C K U 33
ATGGAGCAGCTTAAGACACCCCAAAATCAAAAAACAGTCCAGAAATATGCTTCTAAAAAAGGAAAGAACTTAAAAAAGGCCTTGTAAAGTAA 101700

K R K L F G S E N I R P N K K I P L A S D U D N E L E K K R G S M I 67
AACGTAATTTATTTGGTTCCGAAACATCAGACCTAACAAAAATACCTCTGGCTTCAGACGTGGATAACGAATTTGAAAAAAGCGGGCTCGATGAT 101800

A K A S E T D L C P D P S U T D L L C H E S L T U S P K F E R D G 100
ACGAAACGGTCTGAGACGGACTTATGTCAGATCCATCTGTAAACAGACCTCTATGTCATGAATCTTTGACTGTATCTCCAAAGTTTGAACGAGATGGA 101900

L S A C T E F E N F M D T A K I U L S A N E K S U T D L S A H Y P 133
TTGAGTGCATGCAGGAATTTGAGATTTTATGGATACAGGAAAACTGTTTAACTGCAAAAGTCTGTGACAGATTTAAGTGACATTACCCCG 102000

U L C N L G I F E R I H S P F L F S I H I D T Q S F S U U Y U P H K 167
TTTTATGTAATCTTGAATTTTGGAGCTATTCATTCACCTTTTGTCTTCAATACACATTGATACTCAGTCATTTTCACTGTCTATGTTCCACATAA 102100

E S S C S Q F C E P E K N M A R I L G S G S Y G M U Y D L N N U A 200
GGAAAGTTCCTGTTCTCAGTTTTCGAGCCAGAAAAACATGGCAGGATTTTAGGAAGCGGATCATATGGAATGGTATATGATTTGAACAAATGTTGCA 102200

I K A S D D L E S C I S S Y U S G U U R A K A G A Q L T S R E C U 233
ATTAAGCTTCTGATGACTTAGAGAGCTGCATTTCTTCTATGTGCTGGAGTAGTTCGTGCAAAAGCCGGAGCTCAATTAACCTCAGCGAATGCGTGT 102300

F K S L L I C N S U C L N H K I S L S K T Y D T D L Y K F T D W K L 267
TAAAAAGCTTTTGTATGTAATTTGCTCTGCCTGAACATAAATCTCCCTTTCCAAACTTATGATACAGATTTATATAAATTTACAGACTGGAATTT 102400

E N U E N Y Y S I F C N L A E A U R F L N M U C K I N H C D I S L 300
GGAAACGTTGAATTAATTAATCTATTTTTCACACCTTGCAAGAGCTGTTGCTTTTTTAACATGGTGTGAATTAACCAATGATATTTCACTA 102500

A N I L I H H K E G I I L E A U L A D Y S L A E U H P Q Y N G K C 333
GCAATATTTTGTATACCCACAGGAGGTATTATTTTGGAGGCTGTGTAGCTGATTACAGTTTAGCTGAGTACCCACAGTATAATGGAAATGTG 102600

G I L R Q F D H R I Q I U P K S Y N K L C D M F N P G F R P M I A H 367
GAATCTAAGACATTTGATCATAGGATCCAGATTGTGCCTAAAGTTATAATAAATTGTGTGACATGTTTAAATCCAGGTTTCAGACCCATGATAGCTCA 102700

K I I L U E U Y A E F D G K G N P U R H C N L D L C A L A Q U F L 400
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L C U I A M L D E R G C R E A Q K Y Y E N R L F T Y S N E A C T L 433
TTATGTGTATCATGAATGTTGGATGAACGCGGATGCCGTGAGGCGCAAAATATTATGAAATCGATTGTTCCAGTACTCAATGAGGCTTGACTTTGA 102900

N P I K Y P L E Y K D A C C K U L A E H L U L F G I L F Y R E U U D 467
ATCCAATCAATACCCCTTTAGAAATATAAGATGCTTGTGCAAGTTTGTAGCTGAGCACTTAGTTTTATTGGCAITCTTTTTTATCGTGAGGTGGTGA 103000

M F E N L Y D F L H A S G D L S U R D L L E E T Y U N D S R D U R 500
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R Q P I A Y R H A Q L Q R H E I G Q I L L N D L Q Q L L S I I T I 533
AGACAACCAATCGGTATAGGACGCGCCCAATTACAAGACACGAATTTGGTCAATACTTTTAATGATCTGCACAAATGCTTTCCATTATAACTATTT 103200

U70 M A I D Y A Q I S C N L A S I I E E D 19
S D L E K D P Y S U F R U - 546
CAGATTTAGAGAGGATCCATATTCTGTATTTCCGGGTGTACATGGCAATAGATTACGCACAAATTTCTTGTAATTTGGCTTCTATTATAGAGAGGACT 103300

S U F L F L I D K L N N L D I S R R K I S F N F I R L C Y T Y Y I L 53
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I K F N S R F K D T F L A R S F I D Y M H Q N I S D F I D E N U E 86
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L S D L Y S N I Y U A R L Q D A S P K U U K N L F K I L E R E T R G 119
CTATCTGATTATATAGCAATATTATGTCCGCTTACAGATGCGAGTCCAAAGTTGTTAAGATCTATTAAATATTAGAACGAGAGACAAGAGGAC 103600

Q S T N P L W H A M R K N C I T A T K I Y D I V I S K S F S G I Q E 153
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H S Y L G D A U L Y G I K H E R I I E H L L K T F F U K K P W I S 186
GCATTTCTATTTAGGAGATCGGGTTTATATGGAATTAACATGAACGCATCATAGAACCTGTTAAGACATTCTTTGTGAAGAGCCCTGGATATCT 103800

K T L G L L L L D P S S G U F G A S I D S Y Y G I S F N D N N L I E 219
AAACACTTGGTTATTATTAGATCCTTCATCTGGAGTGTGGTGATCCATAGATTCTTATTATGGAATCTCTTTAATGACAACACCTGATAGAG 103900

U G D K U U I F E L K F R Y K Y L R E K N D L F U S E L L Q N P S E 253
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I A L A K F I L S H P I P A I E Y R E N G K M P S A R E Y L I T N 286
AATGCTTAGCTAAATTCATCTTATCACAATCAATACCAGCTATAGAGTATAGAGAAATGGAAGATGCCCTCGGCAAGAGATATTTAATCACTAAC 104100

N P L Y D S G K K A R A C L T P K N L T F D I T R L I P M N E K N 319
AATCCTCTATACGATTCTGGTAAAAACGTCGTGCTTGCTTGACTCCAAAAATTTGACGTTGACATTACAGACTAATCCCATGAACGAAAAAATG 104200

U S T A I I F D U U K D C I L N T L U A Y Q K A I F T I D A F I N P 353
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R H R Y Y F Q S I L Q Q Y U M T Q F Y I Q D H D N P E N I E K E N 386
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L P S U Y I U S A I F R K R E D D E K N C R L L I E D T E Y L E E 419
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E I P L I L L I T P I T I D A E F T S R U I K D I C C I W E N K I A 453
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U71 Q Q T N L K I W A Q S A U R Q Y M A A S S A R P K T P - 480
M G S K C C K T I H G G I F S K A E D T L U D Y K G 26
ACAACAGACAATTTAAATATGGGCTCAAGTGCTGTAGACAATACATGGCGCATCTTCAGCAGGGCCGAGACACCTTAGTAGACTATAAGGAA 104700

K Y I N L E K E F S A L S D T E S E E E E L Q L E K P L L N K Q D S S 60
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U72 U S L T Q K K L E N Q S K - 73
CGTTTCGTTARCCAGAGAACTTGAAATCAATCCAAATAACGTCATTGATTAACACCTTTTATTCATTTGCTTCTTCTAATACATCTAGGTCTT 104900
----- - E N A E E L U D L D E 336

CCACTGTTGTAGGTAATTTCTTATAATTATGATGTTTCCGCATAAAAAATCAATTAATCTGCATATAATAAGGAAGACAAACTATGGTGATCACGC 105000
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L N U I F K U T W E T K F L S D Y K L I P Y T L G L I G F L I G F 278

TGTAACCAAAATTTGAACCTTAACATACTGATGAATAATTAATCAATCCAAAGAGTATACAAAGACATAACAAAAAGGTGTTGATAGATGCGAAG 105200
H L G F Q U K U Y Q H L I L E I U L S Y U F S M U F F T N I S A F A 236

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 I I I T K Y K I T G K L K P H I R K L U F F S R E S S Q Y Q T I M 170
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 GAGGAATGATTTGAACGATTTCTATCTGTACAGCGAATTAAGAGCGTCAATCAACAGAACAACTGATATTCAGTAGAAGGTTTACATCGTGT 106300
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 S I K U H I D G D U F P I A K E K F Y A F T K M L U Q G C H F F E 459
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U74 M Q M R G C U C H L G U Y C U H N D W K N 21
S S Y I S E T G C L F Q H A D A G M C L S S G C L L R S - 787
GTTCTTATATCAGTGAACATGGTGTGCTCTCCAGCATGCAGATGCGGGGATGTTTGTCTATCTGGGTCTATTGCGTTTCATACGATTGGAAAAATA 108300
K Q Y R U P I Y Q C L F F N A E T H S L H T F L U I G N E I S E N L 55
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U75 - H L S T K E I E T M K Y E K S F A D C I A S K L F D I L Y K S D 225
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A Y U I G C L L F E T D E K L I L Y I I R A R K C Q T K S L R I E E 92
TAGCGTATCTTCGAATCAGAAGAATAATGCCAATGAGGCTAGAACCTTAATGTTTTCTCACATATGCTTTTATAGGATTTGCCATTACAAATTGTG 110800
L T D E S D L L I I G I F G L F G L T K E C I S K Y S K G N U I T 59
CCATCTTCCAAATGAACCATACATCATTTTCCAACCCGAATATCAATTAAGGTAATTTTTAATGGAACGCTGTTCCGGCGTGTGTTAGTTTAC 110900
G D E L H F W U D D N G U S I D I L P L N K I S U H E A H K N L E C 25

AGATATTCGGGACGCTTGATATATTGAATATGTCTAGAGTTTCGAATCCTTTTAAAGCTTGCTGGCAACGTCATCTTGGGATATTGAAATCTTCTGGGT 111000
 I N R U S S I N F I D L T E F G K L S A P L T M 1
 L Y E P R K I Y Q I H R S N R I R K L K S A U D D Q P Y Q F D E P N 607
 TTGTGGATCCTAARTACGGGTGCAAGTCAARTCACTTTGTTTCTGAGTATGTATTAAATGCGAAGAGCTGTTAATCTGCCGTATATAGATTAACTTTAA 111100
 T S G L D P T L T L D S Q K Q T H I L H S L E N I Q R I Y I L R L 574
 ATAATGCTTAAATTTACAGTTTGAGTACACAGCTAACATAATCTCTTTTAGAGAGAGGACAGAACTCTTCTGGGAGCAGTTCAAAATGTCTTAATTTT 111200
 Y H K I K C N S Y U A L M I E K L S L F L F E E P L L E F H R L K 541
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 L U H K M F P I L L L E L T Y N S Y S I S D E Q G Q N N U N K A L R 507
 GGAATGCTCTGTGTATTCAAGTTCCCATTAATTGATCAATTTTTTGTCTGCGTATTCAATATCTGGAATATATTGTGAAAAAACTGTTTGCCACAGC 111400
 F T R T Y E T E W L Q D I K K D A Y E I D P I Y Q S F F S N A U A 474
 TCTGGTGTCTGTTATGATACACTAGTGAATGGGAGACTTTGAACCTTTGTTTCAAGAGCTTTAGCGAGAGACAGCTTTCAATATCTGAATCTAAAGTAAG 111500
 R T D D I S U S T F P L S Q U K N L A K A L S L S E I D S D L T F 441
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 D H K S T E S L N I L S H M D K I K N E F L R N A T K L T E I E D L 407
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 Q S Q I Q E E M C K I I Q K K F I D R I D R D N N D Q G R R Q L N 374
 TCCTTTGCTGATTAAATTTATTTTGGTCAATATAGACGGCGTATGCTTTGTAACAAACCTCAATCTATCTGTTATTCCAAATTTAGATTACTA 111800
 G K S I L L K N Q D I I S P T I D Q L F G E I S D T I G I K S K S 341
 TCGGACAGTTTAAAGAACTTTATAAGACTTTTTTGCATCGCTGGTTTTTCTCTCTTTCTATAAGTTCTAGAATTTTTTGTATCAACACTGT 111900
 D S L N L L F K I L S K K A D S T K E E R E I L E L I K K N D U S N 307
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 K S T T L U K I P F T N L L Q C M K R H R H L N E H K N L E S Y L 274
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 H A L P T T F L L Q N N I F Y P A S Y U F Y E L E K N N S L C T I 241
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 T C I W D I Y K N Y I D N D L N Q L I Y N I T Q L I G E L I U Q K 141
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 T K F L L N M S S A A K U E L I U E K U A A L A D A C L E T P L P 45
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 T D W F R N I L D P E L E F N S N F E E I H S I G D E E F A Q P L P 79
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 F L P F R U L L I T G T A G A G K T S S I Q T L A A N S D C L I T 112
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 A C D I A E R A L N A A N G K A K U I P D L C E S S U I U I D E A G 212
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 E F L K H I E F G L P L K P E L I E Y U D R F U R P A T Y I R N P 345
 GAATTTTAAACATATAGAATTTGGTTTGCATTGAACCTGAATGATTGAGTATGTTGATAGGTTGTTAGACCGGCACTTATATTAGAATCCTA 113700

T N E I G M T R L F L S H Y E U K S Y F K U L H E Q U E L T N K D N 379
 CAAACGAATTGGAAATGACGCGTTTATTTTATCATTACGAAGTTAAGTCATATTTTAAAGTTTACATGAGCAGGTCGAACCTGACAAATAAGATAA 113800

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 Y E K F U E L L Q S D L F I E K T A C E Y S U H A V S F L T G L M 512
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 Y G G M Y S F C L S E F T T S E U M T E I R K I K L P N I D F L Q 545
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 C P D P F F L K Y K Q L P L T N U L T F E E I S V L Y T U F K E I 612
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 F I S R F A I L Q A H S K E M F G K S N L I T Y N R N N U S S K R 645
 TTCATTTCTAGATTTGCAATTTCTACAAAGGCACAGTAAGAATGTTCCGCAAGAGTAATTTAATCACAATATAAGGAATATGTTTCGAGCAAAAGAT 114600

 C G E I C S H U K S F Y G M L T Y A U P A N N Y T L E G V T Y D N U 679
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 I F L G T D K M L P P I I Y K R G L P K I U I K D E M G F I S I L 712
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 D N N U S K L T D T U N G N S F H I C T T I D Y A I U S K U A M T 745
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 U T K S Q G L S I Q R U A L D F G N D P K N L K L S S I Y U G M S R 779
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U79
exon 1
M I R E D R E Y G T F E S U T Q A Y Q Q I I S 23
ACTCTGAATACGTTATTTCTTTTATTGACAGAATGATTGCGGAGGATAGAGAATATGGAACGTTTGAACTCTGAACCCAGGCTTATCAGCAGATCATTAG 117800
H T L Q L R R Y E F E T G C M I M F S A N S G K C E M L S N G W I 56
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S M I S W T S E T D T A G S L T L D I C T E G G Q C K T Y S A R G 89
TCATGATTTTCATGGACTTCAGAAACCGATACGCCGGCTCATTGACATTTGGATATTTGACTGAGGGAGGGCAGTGCAAACTTACAGTGCCAGAGGTC 118000
H I L C S K N I T S I S Q K N E G K E K U L T I C H D N G K L H L T 123
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D D Y K K K A L K Q K D K R R S E Q K I L E D C D K K D E K K R M 189
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D D T E K R K L Q E D R R N E K Q D L K K R U D D T E K R K L E D D 223
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R R N E K Q D L E 232
CCGTCGAACGAAAAACAGACCTCGAAGGTTAGTTGCCCTTTTTCTAAATCACTAGTCCTAATATGACTTGTGAAATTTTGTAGTGTCTAAGGTTTT 118500
end of U79 exon 1 >

U79
exon 2
D A S K E K R M K U H H E K R H A E E Q A N E E U A S 59
TACATAACATGTTTTCTTAGATGCATCCAAAGAAAAAGGATGAAGTGATCACGAAAAACGTCATGCGGAAGAACAGCAACAGAGAGGTTGCTTC 118600
start of U79 exon 2 >

S S Q L S S R I P E G A L S P T I S I D L Q E Y Q E F E D F D K R 92
TTCAGTCACTTATCAAGTAGAATACCAGAGGGTGCCTTATCGCCCACTATTTCTATTGATCTTCAGGAATATCAAGATTTGAGGATTTTGACAGGCG 118700

U79
exon 3
I C G Q 96
ATTTGTGGGCAGGTGGGTGGAGTTTTGGGTTTATGATGCATTTTATTGCAAGTTTTTATGTGGTTAAGATGTTTCTTTCTTTAGGGGAAGATCAAG 118800
> end of U79 exon 2 start of U79 exon 3 >

D A U C K K U Q S D E S F C I N K P L E Q F R E K L I K I T H E A U 134
ACGCTGTATGCAAGAAAGTCCAAAGTGATGAAGTTTTGTATAATAAACCGTTAGAGCAGTTTAGAGAGAACTAATAAAATTTACTCATGAAGCTGT 118900

Q Q S L L Q S R G K N E D N K K D U T Q N U K F A D E N M N F A G 167
ACAAAGTCACTGTTACATCCGGGGAAAAATGAGGATAATAAAAAGATGTTACCCAAATGTAAATTCGCTGATGAATATGAATTTCCGAGGG 119000

G S K C T S K T K H I E D Q Q I Q F G A Q N R F U P I C E I K P F 200
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P I E T S E M L T U S T R S R G R S R G R P R G R G R S R N M S M 267
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R Q T P R E U E D M L P I U L D S D S D T E T L R R N E D L L A S 300
AGCAAACTCCAGAGAGGTTGAAGACATGTTACCGATTGTTTTGGACAGTGACAGTGACACGGAGACTTTAAGCGTAAAGATTTATTGGCGTCTT 119400

U81
S I L Q T L - 306
CCATATTACAGACTTTATAATCGTTTGTATGTTCCATCAATTGGACATTTGTTGTGGATTGTAAATATTTATTTGCTTTTAAAAATGACCACAAC 119500
- L D N T I N W D I P C K N H I Q L Y K N A K L F H G C G 227

CGATAAAGGTTGTTTTGATCCTTTTCTCGGAGATGGATGTGCACATTCCAAATCAAGTGTTCCTTTGAATCTATTAAAGACACGAGTTTGCAGAC 119600
I F P T K S G K T R P S P H A C E L I L H K K S D I L S U L K R A 194

CTGTGATCCCCACAACATAAAACTAAGTTTTGCATTTTTCTGATAGTTGGTTAATATTCGGTTGCTCAAACTTGCCATCCATCGCTTCATGGGAC 119700
Q S G W L M F U L N Q M K E S L Q N I R N S L U Q W G I A E H S 161

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M P U G R I U T F U T N L L L V G Q A C W S K L S G H A P A K F N E 127

CTATTGTTCTTTCAAGTTCTGCAAAATGGTTTTTAAAGATTCGGAGGGGACATCTCTCACAGTGCTGAAGCTAATCCGTGACCTCTACCATCGGG 119900
I T R E L E A F I T K L S N P P S C G R U T S F A L G H G R G D P 94

ATAAGGATCTTGGCCCACTATTATCACCTTAATCTCTCAGGCGAACATAAATACTCCAGCTGTGTACATTTCTGAGGATCGGGGTAGATAATTAATCTT 120000
Y P D Q G U I I U K I E E P S C L Y S W S H U N Q P D P Y I I L R 61

TCTCTGTCACGCTGACCAATTTGTATACATTTTGTARTGTACAATGTCAGAACTCTGATAGTTTAAACCTTAAGCCACTTCACATTGATTGAACG 120100
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 - Y T R I L L N S F E 237
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 I M N S P I N F E F G I I N E U F I N G T F K L K E Y S Y S K C U N 137
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 L L T H L Q N P N N Y L L Y F T E L F D E D I L U Q D R A S I Y P 71
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 T K M 1
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 AGCACAAATAGATCTTTTTAGTTGGGGCATTATGTACAGAGAGTAGACACCCTATTTTTCTGTGTTTGTGTTGACATTACAGGGCATCATAGCT 121600
 A C F L D K E T P A N I Y L S Y U G S N K R A H K S N U N U P M M A 225
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U82

U84

U85

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reiteration R1

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S Q Y S Q E S T E S C E E S Y K G Y D N F D E I E P P T S D S N Y 417
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L H S E L L T S S H H G N G T U Y G N R I S I S N L U T U E G T U D 383
CATATAGCTTTTCTATTTGATCACAAGCATCATTAACTATATGCAATAGTGTATCTTAATCTTTTCTATTTGCCCTGAATTTTTGTCATGAAATTC 132200
Y L K E I Q D C A D N I M H M L T I K F E K R N A R F K K C S F E 350
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K S C I U I C Q L U A A G L N K A A E I L N I C N F H I K L F T E 317

U90
exon 3

TCACACATTGACATGACATCTGATTTCATCTGTTTGGATTGCAAGTCTTTTCATAGTTTGAGCTATTCTGCTGTTTTTTCATTATTTTCAAAATTTACATT 132400
D C M S M F M Q N M Q K I A F D K M T Q A I R S N K E I I E F K C E 283
CCACACAAATCTTTTTTAATCTTATTTGTTTTATGTAGAATGCCTGATTGGAATGTTTATATCTGTTATGCTCTGTTTTTCCCATCATTATAACAT 132500
L L D K K I K N T K I Y F A Q N S I N I D T I D R N K G M M L L M 250
TGTGACATCTGTTAAGTTTCTCATTACTGCTTATAAAGTTGCCATCTTATGATCTTTTTTATACATTTGATAAATCTCTATCCATATTATTTCTC 132600
T A C R N L K E N S S I F N G M S I I K K I C K I F E R D M N N R 217
AAATCTGATAAATATTCTCTACAATCTGCAATCACTTTTTTAACAATTTTCATCAAAATTTATCACAGGCATATACAGTGATCTTGATTACACCAAGAA 132700
L D S L Y E R C D A I U K K U I E D F K D C A Y U T Y R S E C W L F 183
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F E L Q E G S L I D E Y F S I F G S S A G S I L N U N L M Q S L Q 150
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E L A L D T L M H R D N T L I G A H N I L C D E I D A K E Q D M A 117

< start of U90 exon 3

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A N U S K L I G Q I C A S I S Q A 100

< end of U90 exon 2

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A A L K I D S S A G E E U N T S Y S A N A T 78

U90
exon 2

GCAATATCATTAGATGATATTGAGTCAGGAATCAAAAGATCCAATTTCTGGAGAGAGTATTATCAAGGAAGGGTGCATTTTAAACTGCTTGCA 133200
A I D N S S I S D L F D F S D L E Q F L T N D F S P N C K L S D Q L 44

< start of U90 exon 2

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I D R I T E E U T T D P H Y 30

< end of U90 exon 1

TAAATATTTAGGTTTACCTACTCAATATGCTTTTCGTCATTCGATGCCATGGTTTCAGATGGTTGTCCACATCAACATAGGTGAAGTAGCTCCACTT 133400
E I H R E D N S D N T E S P Q G U I L N P S T A G S 4

U90
exon 1

CTTCCATAGTTTATCTGTATGTTAGCCACACCTACAATAACAACCAATCAGAATATTACCCCATTCCAACTCAATATAAGGCCAGCCTAAAAA 133500
R E M 1

< start of U90 exon 1

U91
exon 1

M V T L E Y E K R U S R P K L T Y W I I L 21
TACTTTCAAGCAGAGTTTTAAACTCTGCTTGAAGAAATGTACTCTGGAATATGAAGAACGTGTATCAGGCCAAACTTACTTATTGGATCATTTT 133600

A I L F U F L I I T G S U L I U I E T L S I Q R T T L N A Q N D K 54
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T S T U U P E L T S N S P 67
ACAAGTACTGTTGTTCCAGAAATTAACATCTAATTTCCAGGTTTGTTCAGCTATAAATGTATTGTTTAAAAAAAAGTTTGAATCTGTTAATATGA 133800

end of U91 exon 1 >

U91
exon 2

D Q T T U T N F S A S S K P T L S S D Q P G W I Q A L T 95
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start of U91 exon 2 >

T A F G I L T L F S U M N I I I T C N F W L T E K N D K T A N P R E 129
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Y Y S E D I L D Y T N P S F T E I D E D S S K U - 153
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reiteration R2

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 G Y G Y N T K I G E N C A M S Y U E Q E S U D S K Y P N K E U S I 207
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 S Y Q R N E H Y D E N L P T R E L N T D F P Q V N Q S S U L Q H T F 241
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 A N U Q S I I S Q Q S P Y Q L I G K E N S F N N Y L E T A N U D S 274
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U95

D C Q S N G G P K I G L D T D Q S U F S D E U T G A C U E N U H F 307
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P M N P K N E Y U N N I S L D U Q T E A F P U T E N P L U G E S Q A T 341
CAATGAATCCATAAATAGATATGTAATACATATCACTTGATGTACAAATGAATTTCCCTGTGACTGAGAAATCCTCTTGTAGGAGAAAGTCAGGCTAC 138400

K N K D U D S N A E U N N H S K Y R L L K R N I T P T M G N I K H 374
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L N F S C K I S T E E E R K T F F N R L S E L L K I R D D I K N T 407
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K I S S K U D F I Q S E A S T S L D I C K N T F N N H S D S S D U D 441
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T D I L A D N P L U I C E N E L I C D N N E E N I K F P P N U E K 474
CACTGATATCCTTGACAGACACCCATTAGTGATATGTGAATTAAGACTGATTGTGATACAAATGAGGAAACATCAAGTTTCCGCTAACGTTGAAAA 138800

E A U P M Q T U K R S F P E I C P E H F K K R R F I N G D U I Y E 507
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D L N S U V K U M P A S A T Y D D U R F G E U D Y Q T S S A Q T K I 541
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S N H Q L A L L P T N Y Q H M I G Q E T D I S S R D Y H N D S A Q 574
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L S K L Q Y T K E S L E A Y U L R N C N K F L D L S W P I R H K I 674
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P G R L A D R U F H T C U P G U H N A L P L D A U I K H E N N P L Y 841
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F I G Y U T T F K Q Q N D F N A N U F I A U D G N L S I Y G Y H L 874
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I S Q K T W F L A K T F S T F L K M G T R K M Y Y D Y E I P L K I 907
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- I D R N Q R K U S S K F F K K S D K S S A F U Q Q A K R E P Y 574

U100
exon 10

CGCATCTCCACAGTGGTGACGGTCGCTTCGTAATATATCAAAAAATCTTCTACTTCTAGTAGTTTTGGTGTCGGATCTTCATTGGCGCCATAATTTG 140500
R M E U T T C T A E Y I Y D F F E E U E L L K P T P D E N A G Y N S 540

< start of U100 exon 10

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N I R A A K I G E W 527

U100
exon 9

end of U100 exon 9

GAAGGCTTTGTTTAAATCAATCCAGGTCGCTTGGTGGATGTTGTTGAGTCTTTGTTAGGTTTGTGTTAGGCGTAGGTTTAAATTCATGTATGATTGTTGACTCGTA 140700
F A D N L D I W P P M P Q T K T P K N N P T P K I E H I I T T S T 493

TATATAGGAGTGACGATATGTAATACCTCCGGCTGATATATGCTGCAACGAGAAATTAAGAAATGAGTTTGTCTTAAAGCAAAAGTATTGTCCATA 140800
Y I P T C Y T I G G A Q Y I < start of U100 exon 9 479

< end of U100 exon 8

CAGTAAAAACTCACATGTTTCCGTCGTACATGTCACTTATCACATCACCGTCTGTAATCGCAAGTATTCATCACAGCAGGATTCTAGTTTAGGTAA 140900
I N G D D C T L E I U D G D T F R L Y E D C C S E L K P L 451

U100
exon 8

< start of U100 exon 8
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 Q L E S T 446
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< end of U100 exon 7
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 N C L Q A N L S K N S I L K K T T R D 427

U100
 exon 7

CATCTTTTTTAAGAAGTCAATAACAGCGTATCAATAGTGAGTAGTCTTCCGTTGTCARAACCTGTTTTGCACTGTCGGTTTTAATTTAATTGAGCT 141300
 D K K L F T L L L T D I T L L R G N D F E T K A S D T K I K I S 395

start of U100 exon 7 < end of U100 exon 6
 GGTATGAAAAAAACACATTAGTTTTCTTGTAGATTCTTATCCCCCCCCCCCCGACAGGAGAGTTTTCAATTACCAAGGTCGGAATCTTTAGA 141400
 C P G F D K S 388

U100
 exon 6

TGGTGTAGTAGTACATCGTATTGGAGATCCGTTGTAGATATCTTAGATGGAAGTCTTGCCACATAGCACTTACGATGGCTGGATCGAATCTCTAGGA 141500
 P T L L U D Y Q L D T T S I K S P F D Q W M A S U I A P D F E 357

of U100 exon 6 < end of U100 exon 5
 TGAAGAGCGAAATTAGATTATATCTAGTTTTGCTTTCTAGTTAATAATATTACATTTACCTGTTACTAAACGACTGTCGGTGGGATGTGGAAAC 141600
 R N S F S Q A H P H P F 345

U100
 exon 5

ATGCTCTGTACAGTCTTTTGTCCAAATAGTGTGGAATAGCGTTCTATTTCTAGTAGTGCTATTGGAAAAAGACTGCGAAACACAATTTATTTGCTTATTC 141700
 M D Q U T K Q G I T D F L R E I E L L A I P F L 321

< end of U100 exon 4
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 I U T T U Y N R A T T D N K P S C W 303

U100
 exon 4

< start of U100 exon 4
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 I Q G Y T S Q F 295

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U100
 exon 3

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 I D R W P E I T T E T W P H E S W R W A Y T T N E R S K N K D P C C 243

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 A D Y L P K E S T M N U K P I N F D E E K W Q S F Q M C T E W E Y 209

GCCCTTGTGCTTTTTCGGACGATTGCCAGTGATATTTGTGTCGAAGGCTATTCCGCTGTAGCTACGCATCTTTTTAAATCTGCGCGTATCTGTAAAT 142300
 G K N D K R U I A L S I Q T R F A I G S Y S A M K K F D A R I Q L 177

< start of U100 exon 3 < end of U100 exon 2
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 E 176
 C Q A S S Q T Y 169

U100
 exon 2

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 Q E R R E W R H R A P F L U L S T L I N A T N M R K U Y L L S N Q K 135

TACTTCCGAATCCTCCATTAGTAGAGATAGTGTAGCCGTGTAGTTACTGACAGACTTCAGACAGCCCTTTACTCATATTTTTTCTCTTAATCCGCG 142600
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< start of U100 exon 2
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< end of U100 exon 1
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U100
 exon 1

GTGTATTCTAACAGCTTTGTCTTTCTCGAACTTAGACCAATATATCTAGTAGAGCTTGGCTTGTGCATGTTTTCAATTATTAGTTTTCGATTATAT 142900
 T Y E L L S Q R E E S S L G I Y R T S S A N H M N E N I L N E I I D 33

CTTCTAGAGTTATTGCCGTGCGTCTTTTCAAGTGGGACCGTATTGGTACATATCTTTATGAGTAATGCGAAATATATATATGCAAGTTGCACCATTTAT 143000
 E L T I A T R A K E L P U T N T C I K I L L A F I I Y H L Q U M < 1

end of DR --->--- start of UL
 CTGCGAAGAGATTTTTTTTGCAGCGTCTTTATGTGCGAGCTTATCCCCCGTTTCGTATTCAAAATCCTAATAACCCCGGGGGTAAAAAAGGGG 143100
 start of U100 exon 1

[illegible]

DR1
exon 1

M T A A T T E H F A L R A A L N R Y W W L L L 23
TTCATCACAGACTCTGTGTTACACCACCTATGACTGCTGCARCCACAGAACATTTTGCTCTCCGCGCGGCACTCAATCGTTACTGGTGGCTGCTTCTGG 147600
> start of DR1 exon 1

G R H K L S L U C N Y U T A H R Q Q L L P L P W P E Q E F L Q L D P 57
GAGCAGACACAGCTCAGTTTGGTATGCACTACGTCACAGCTCATCGCCARACGTTACTGCCGCTGCCGTGGCCCCGACAGGAATTTCTCCAAC TTGACCC 147700

A P Y S N L R N R U A H H L H R G W P A A H N T 85
GGCCCCCTACTCCAATCTCCGACACCGTGTCGCTCACCATCTCCATCGCGGTGGCCAGCGGCACACACACATGTAGCTACCGTACATCTCTTTTACA 147800
end of DR1 exon 1 >

AACCCARGGCTCACATAGAGACAGCAGCTCGCGCAATGACATTAAACCTCCCATCATTGTCTTTCTGTGCTTTGCCGATAACGCTCTTTGCTC 147900
start of DR1

S W S C L Q Q E P U W R N C L D T R G E Q D E T E D Q E M K Q S T S 383
CTTGGTCATGTTTACGACAGAACCTGTGTGGAGGAACTGTCTAGATACGCGCGGAGAACAGGATGAGACAGAGACCAAGAGATGAACCAAGACACAG 148800
K K Q N E N K K L N T S K K H T R U S S A I P T F P L S L R E T P 416
CAAAAAGCAAAATGAGATATAAACTCAACACCTCAAAAACACACCCCGTATCGTCGGCAATTCCGACCTTTCCCTGAGTCTCCGAGAAACGCCG 148900
P E A R S P A U L A A A T Q S H K T R A I S T H N A T T T I R I P 449
CCAGAGGCCAGGAGCCAGCCGTCCTCGCCGCGCCACCCAGTCTCAAAAACCTCGAGCGATCTCGACGCAATATGCCACGACAAACATAAGAAATACCCG 149000
R L P S Y L L E A R L L S U T A I L K D T K K K K T Q P Q A - 479
GCCTTCCAGTTACCTGCTGGAAGCGCGTCTGTTGTCCGTGACAGCTATCTGAAAGACACAAAGAAAAAACCAGCCCTCAGGCGTAGCAGCTGCG 149100
ACGCTCAGCGCGGTGTCTGAAGCTCGCCAAGGTCTCGCGTAAAGAACAGATGTGAACCTCAGATGTACCAACCAATATACGGGTTCGCTATAAAA 149200
AGTGACCTCTATTCCCGTTCTTATCCCCGTTCTAACTCTTCTGTATCATACCTTGCATGTTAACCGGATCCCGTGGATCTTACACACATACACAC 149300
ACACAACTTGGTGAGGTAAACACAGAAATCTCACTAACTCATATCCCTACACGCTTACCACCACCTAAATATGGTTATGACCAAACTGGCAATAGT 149400
CTATCTTCTTTTCTTTCCATTACAGCCAAATGTGCAGTACTCGTGGGTCCACAAACAGAAAGAGACTGTAGAGACACTTCTTTAAGTAGACCTTAGA 149500

DR6
exon 1 M S A E M L R A U Q L Q P R R 15
GACACACCAATACACCCACCAAAAAAAGACAGAAACACACAAAGCCAAATGAGTGCGAAGATGCTCCGCGCTGTTACGCTCCAGCCAGAGCGCC 149600
R G H S S S P T S P P L E G E P S P K R L Q S S N S H Q G R A R G R P 49
GGGACATTCCTCATCTCCCACTTCCCTCCACTCGAAGGAGAGCCAGTCCCAAGAGACTCCAATCGAGCAACAGTCAACAGGGCGTAGAGGCAGAGC 149700
K P R A K T W S E A L S H R S F L N I V A W L S L S R G S P R K U 82
TAAACCCAGAGCTAAACATGGAGCGAAGCTTTATCCACCCGCTCTTCTCAACATTACGCGTGGCTGTCTTTGAGTCGAGGGTCTCCGCGAAAGTG 149800
Y G Y A F R H R G E L U A L P W P P N W S L E L H H D P Y R D A R 115
TACGGATATGCTTCAGGCACAGAGGAGAACTCGTAGCATTGCCATGGCCGCTAACTGGAGCCTGGAACCTTACCACGATCCCTATCGAGAGCCAGAG 149900
A Q T U W S H R W G W P A T H U T A A T U R D C 139
CACAAACCGTTTGGAGTCACCGCTGGGGATGGCTGCAACACACGTCAGACGCTCGACGGTGGGGAGTGGGTTGAGTGTAGCAGTGTGACACATTGTT 150000
end of DR6 exon 1 >
ATCGCAATTGTCTTACCGATTAACTTTTTATTATGTATTAGCACTCTTCTTACGCTGTGACTGTTGTGTTTTTTGTTGTTATCTACATCCCGGCAG 150100
start of DR6 exon 2

DR6
exon 2 A L D T H M Y U C C G R G E K L Q P U G Y U R N R A A P S D L N S L 173
CCCTCGACACGATATGTACGTGTCTGCGGACGCGGAGAAAGTTGCAGCCCGTCGGATACGTACGCAACAGAGCCGCGCCTTCAGACCTGAACCTCGTT 150200
>
R U L L I A R D G A M Y U H H M R T A R L C R L A S S U T E F A R 206
ACGCGTCTCTCATAGCCAGGAGCGGAGCAATGTATGTGCATCACATGAGACGGCGGACTGTGCCGCTAGCCAGCAGTGTGACCGAATTCCGCGCA 150300
R G L Q R E S E U Y E D D U S L P D R A U G G S A T A I H L F D U I 239
CGAGGCTGCAGCGAGAACTCCGAGGTTATGAGATGATGTTCTTCCAGACCGTCGAGTAGGTTGCGCAACGGCCATTACCTGTTTGACGTAAATTA 150400
T Q A A D U H D L L T U A G L C Q T H T G U S C Q L W Y T D H D P H 273
CCCAGGACGCGATGTCCAGACCTACTCACCGTGCGGAGTGTGTACAGCTACACCGCGCTCAGCTGCCAACTGTGGTATACAGACCAGCATCCCCA 150500
T U A G A A R F T L T U A R Q Q Y R L W P N A R R K L L Q H L H P 306
CACCGTCGCTGGGCGGACGCTTCACTGTACGGTGCACGGCAGCAGTATCGATTGTGGCAACGACGACGCAAACTGCTGCAGCACCTACATCCG 150600
D H P L G L W L L C A U L T V D A K E T N R A U P P U T P G A E T 339
GACCACCACTTGGGCTGTGGCTGTTGTGTGCGTGTCTACGTACGATCGAAAGAGACGAATCGCGCAGTGCCACCCGTAACGCCAGGGGCCGAACCG 150700
U W U I U T G R G A I L G F W P E S A K M C R L A S S M K G L W K N 373
TGTGGGTGATAGTTACTGGCAGGGGTGCCATTCTAGGATCTGCGCCAGAGAGCGCCAAATGTGCAGATTGGCCTCGTCTATGAAGGACTCTGGAAAAA 150800
G A R A L K G H W T V A A P G R H R A G E A W P L C A H Y Q S P R 406
CGGAGCGCGGCGCTAAAGGTCACTGGACATACGAGCACCCGCGCGCATAGAGCGGGAGAGGCTGGCCTTTGTGTGCACACTACCAATCTCTAGA 150900

-
TAGAACAAATATAAAGATTAAAAAAGAAAAAAGTACAGAGTGTTATCGCGAAACAGCGTGTCAAAAAAACAATCCACATACTCTAGA 151000

ACAACTGTACCCAAATATAGTCCGTGTGCAAACTGGGAAAAAATACCTTCTCGTTGCCACTAGAGGGAGTACCGAAAGTGTAGGCAGAGAG 151100
GCCACGCTGTAATGACTGTACGCTTTGGCGCTGAAACATTGCTGTTCTTGTGCTCAGGCACAACTACGTTAGATTCTTTCTGTTTCAAG 151200
TGTGCCCGGGAGGAGACATGCCCTTCTCGTGAGACATTATGAGATTTGCCTGCCAGAGAACACGTGACTTGGACTTACTTTCTGTTTCTAAGCTGC 151300
CCTTAGGCGATGAATGCTCTTAGCGTTAGCCATGAGGCTAGCGTGATCCTGTATAGTACATAAGTTTCTAAGAAATATGTTTTAACAATAATCATGTCC 151400
CAAAAAGTCGCGAGTGAATAATTCTCTGAATGAAGGCAATTAACAGGATACAGACAGTTGTGGCAGTGGTCCGTTTCTGTTTCTGTTTTC 151500
TTACGCGGCTGACGAGGTAAAGTGTCTCAGTCCATATTGTTGTCTGTGCCACCGTAGTTAGCGGTGGCATACTAAAACTCCGATAGATGCGAACAATA 151600
ACACCGAAACACCGCTGTGGAACAGACACACTTTATAAACAAACGGCCTTATCACCTGGAAAAAACAATAAATAGGCAATGATACACCTGAC 151700
TTTCCATTGGAACCTGCCGTACCTGACCACAAATCCCATGTAAATCCCTGAACACTGCCAAACGTCGCTACAGGTTTTTCCGGGATCGAGCCG 151800
CAGCAGCTTAACATGAGGTACACACGACTTTAATTACGGCAACGCACAGCTGTAGCTGCAGGAAGATACATCTGTAAGCAATGTAGTCTCAAT 151900

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