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Identification of Human Telomeric Repeat Motifs at the Genome Termini of Human Herpesvirus 7: Structural Analysis and Heterogeneity

PAOLA SECCHIERO,[1] JOHN NICHOLAS,[2] HONGYU DENG,[3] TANG XIAOPENG,[3,4] NANETTE VAN LOON,[3] VIVIAN R. RUVOLO,[2] ZWI N. BERNEMAN,[5] MARVIN S. REITZ JR.,[1] AND STEPHEN DEWHURST[3,6]*

Laboratory of Tumor Cell Biology, National Institutes of Health, Bethesda, Maryland 20892[1]; Johns Hopkins Oncology Center, Baltimore, Maryland 21231[2]; Department of Microbiology and Immunology, University of Rochester Medical Center,[3] and Cancer Center, University of Rochester,[6] Rochester, New York 14642; Second Affiliated Hospital, Hunan Medical University, Changsha, Hunan, People's Republic of China[4]; and Antwerp University Hospital, University of Antwerp, Edegem, B-2650 Belgium[5]

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Human herpesvirus 6 (HHV-6) and HHV-7 are closely related T-lymphotropic betaherpesviruses which share a common genomic organization and are composed of a single unique component (U) that is bounded by direct repeats (DR_L and DR_R). In HHV-6, *a* sequences have been identified at each end of the DR motifs, resulting in the arrangement aDR_La-U-aDR_Ra. In order to determine whether HHV-7 contains similar *a* sequences, we have sequenced the DR_L-U and U-DR_R junctions of HHV-7 strain JI, together with the $DR_R \cdot DR_L$ junction from the head-to-tail concatamer that is generated during productive virus infection. In addition, we have sequenced the genomic termini of an independent isolate of HHV-7. As in HHV-6, a $(GGGTTA)_n$ motif identical to the human telomeric repeat sequence (TRS) was identified adjacent to, but not at, the genome termini of HHV-7. The left genome terminus and the U-DR_R junction contained a homolog of the consensus herpesvirus packaging signal, *pac*-1, followed by short tandem arrays of TRSs separated by single copies of a second 6-bp repeat. This organization is similar to the arrangement found at U-DR_R in HHV-6 but differs from it in that the TRS arrays are considerably shorter in HHV-7. The right genome terminus and the DR_L-U junction contained a homolog of the consensus herpesvirus packaging signal, *pac*-2, followed by longer tandem arrays of TRSs separated by single copies of either a 6-bp or a 14-bp repeat. This arrangement is considerably more complex than the simple tandem array of TRSs that is present at the corresponding genomic location in HHV-6 and corresponds to a site of both inter- and intrastrain heterogeneity in HHV-7. The presence of TRSs in lymphotropic herpesviruses from humans (HHV-6 and HHV-7), horses (equine herpesvirus 2), and birds (Marek's disease virus) is striking and suggests that these sequences may have functional or structural significance.

Human herpesviruses 6 and 7 (HHV-6 and HHV-7) are recently discovered members of the herpesvirus family that have been isolated from peripheral blood mononuclear cells and the saliva of healthy and immunosuppressed individuals (13, 30, 41). Both viruses are ubiquitous and appear to persist throughout life following initial infection in early childhood (17, 42), with primary HHV-6 infection generally occurring at or before the age of 2 years (28) and primary HHV-7 infection occurring at a slightly later time (9, 42). Primary HHV-6 infection has been etiologically linked to exanthem subitum, a benign febrile disease of childhood (43), and HHV-6 has also been shown to be a major cause of acute febrile illness in young children, with a variety of clinical manifestations that may include febrile seizures (17, 28). The association of primary HHV-7 infection with human disease remains less certain, although HHV-7 may also be associated with at least some cases of exanthem subitum (2, 18, 27, 35), perhaps as a result of its ability to reactivate HHV-6 (14).

HHV-6 and HHV-7 share a number of biological and genetic properties, including a preferential tropism for human T lymphocytes (3, 13, 23). At the genetic level, fragments of HHV-7 DNA have been determined to exhibit 50 to 60% nucleotide identity with sequences from HHV-6 and the two viruses appear to be closely related members of the betaherpesvirus subfamily (3). The viruses also possess similar genome organizations with a single long unique sequence (U) flanked by identical direct repeats (DR_L and DR_R), yielding the arrangement DR_L-U-DR_R (5, 6, 16, 21, 26), which is unique among human herpesviruses and resembles that of channel catfish virus (11) and equine herpesvirus 2 (1, 36). In light of these similarities between HHV-7 and HHV-6, we decided to analyze the sequences present at the genomic termini of HHV-7 (the so-called *a* sequences). These sequences are found at the genomic termini of all herpesviruses and contain short conserved motifs (*pac*-1 and *pac*-2) that are required in *cis* for genome cleavage and the packaging of progeny genomes into capsids (12, 24, 25, 34, 39, 44).

In order to analyze the genome termini of HHV-7, DNA was prepared from SupT1 T cells which had been infected with either the JI strain of HHV-7 (isolated from a person with chronic fatigue syndrome [4]) or the R-2 strain of HHV-7 (isolated from the saliva of a healthy adult in Rochester, N.Y.). Nucleocapsid DNA was then prepared from HHV-7 (JI)-infected cells and used to generate recombinant λ phage libraries, which were subcloned into plasmid vectors for subsequent analysis (4, 26, 32). The regions of the HHV-7 genome which

* Corresponding author. Mailing address: Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY 14642. Phone: (716) 275-3216. Fax: (716) 473-2361. Electronic mail address: DWRT@BPHVAX.BIOPHYSICS.ROCHESTER.EDU.

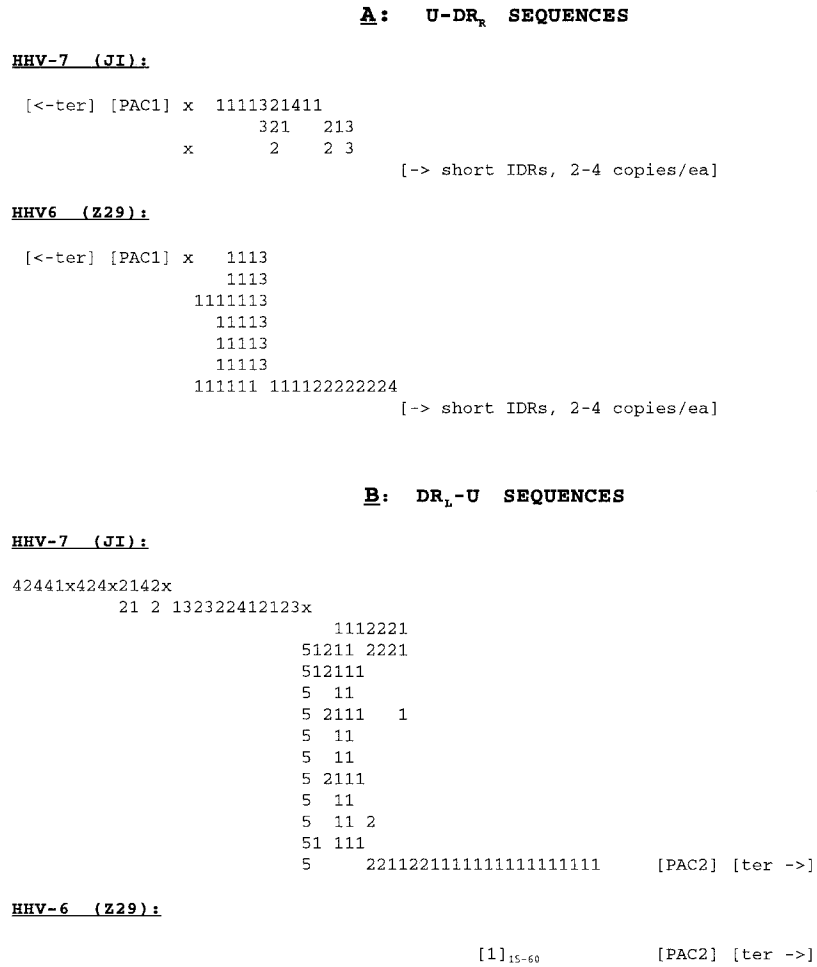

FIG. 1. Schematic representation of TRS-containing motifs in HHV-7 and comparison with a schematic representation of such motifs in HHV-6. There are up to five reiterated hexanucleotide sequence elements at the U-DR$_R$ (the equivalent of the left genome terminus) junction or the DR$_L$-U (the equivalent of the right genome terminus) junction of HHV-7, interspersed with short unique sequences. These have been represented schematically for both HHV-7 and HHV-6, with identical elements aligned; the locations of the viral genomic termini (ter) and packaging motifs (PAC) are indicated. The illustrated alignments should be read from top to bottom, left to right, starting with the uppermost line and then proceeding down one line at a time. (A) U-DR$_R$ junction (GenBank accession number L46635). Repeat motifs: 1, TAACCC (perfect TRS); 2, TRS with any single point mutation; 3, TAGCTC repeat motif (a TRS with two point mutations, which is also found in equine herpesvirus 2; in HHV-6 the corresponding sequence is TAGGTC) (37); 4, TRS with any two point mutations (other than repeat 3); x, a short intervening stretch of unique DNA (1 to 6 bp). IDRs, imperfect DR sequence motifs; ea, each. (B) DR$_L$-U junction (GenBank accession number L46634). Repeat motifs are as described above, except that 5 is a 14-bp imperfect repeat (TAGGGCTGCGGCCC, which is not found at the DR$_R$-U junction) and x is a short intervening stretch of unique DNA of 1 to 21 bp.

were selected for nucleotide sequencing included DNA fragments that were predicted to correspond to the DR$_L$-U and U-DR$_R$ junctions from HHV-7 (JI) (1.2- and 4.9-kb segments, representing *Hin*dIII and *Eco*RI fragments and designated ED132′1.2 and EZ3, respectively). Analysis of the nucleotide sequences of these fragments confirmed that they had features of DR$_L$-U and U-DR$_R$ junctions. As with HHV-6, the nucleotide sequence of the unique component of the HHV-7 genome (represented by the left end of clone EZ3) had a relatively low mean G+C content (38%), compared with that of the DR element (represented by the right end of the EZ3 clone, which had a mean G+C content of 54%).

The sequences of both the DR$_L$-U and U-DR$_R$ junctions contained reiterated hexameric repeat sequences which included both perfect and degenerate copies of a motif (GGGTTA) that is identical to the human telomeric repeat sequence (TRS) (7) (shown on the DNA strand opposite TA ACCC in Fig. 1). The overall structure of the reiterated motifs at the DR$_L$-U and U-DR$_R$ junctions is illustrated in a highly schematic form in Fig. 1; a comparison with the corresponding regions from HHV-6 (Z29) is also shown. The data in Fig. 1 clearly show that the reiterated TRS-containing domain at the U-DR$_R$ junction (the equivalent of the left genome terminus, clone EZ3) in HHV-7 is much shorter and less complex than that found at the analogous location in HHV-6. As is the case with HHV-6 (37), it is followed by a unrelated segment of repetitive DNA, which contains four short imperfect DRs, each of which is repeated from two to four times. These repeats include four distinct elements 10 (GCCCTGACTC), 21 (CCCACCCTCCGTCCCGCCCTC), 20 (TTGCCTCTGCAC TCCGCGCT), and 20 (GCCCCGCCCCTGCGCGCGCG) bp in size (not shown), which are repeated two, two, two, and four times, respectively. In contrast to the U-DR$_R$ junction, the repetitive sequence at the DR$_L$-U junction in HHV-7, which corresponds to the right genome terminus (clone ED132′1.2), is considerably longer and more complex than that found at the

LEFT GENOME TERMINUS OF HHV-7

	<terminus	<--------PAC-1 (Cn-Gn-Nn-Gn)-------->				
HHV-7	cccccgtttcgtatttcaaatcctaaataa	CCCCC	GGGGGG	TAAAAAAA	GGGGGGG	agc (taaccc)$_n$
HHV-6 Z29	tcctcgcgtttcaaaaattactttaaact	CCCC	GGGGGG	TTAAAAAAA	GGGGGG	tattaa (taaccc)$_n$
HSV-1 (KOS)	gcccgccgcccgcctttaaagggccgcgcgcga	CCCCC	GGGGGG	TGTGTTTT	GGGGGGGG	cccgt
VZV	cctctcccggggtccgccgggcgcccagaaa	CC	GGGGGGGGG	TTATTTTC	GGGGGGGGG	tccga
EBV (B95-8)	ccccatgcccccgccaacacccccccgatg	CCCCCC	GGGGG	TCTTTCCT	GGGGGG	

NOTE: HSV-1, VZV, EBV = RIGHT GENOME ENDS

RIGHT GENOME TERMINUS OF HHV-7

			<----------PAC-2 (GCn-Tn-GCn)---------->			terminus>
HHV-7	(TAACCC)$_n$	cgcccccact	GGCAGCCAATGTC	ttgtaatgccttcaaggcac	TTTTT	ctgcgagccgcgcgcagcactcagtgaaaaaca
HHV-6 Z29	(TAACCC)$_n$	atcccccaac	GCGCGCGCGCGCGC	ctctatgggaggcgccgtg	TTTTT	caccaccacgcgcgccactgcaagaggcgcgtg
HSV-1 (KOS)			GCGCCGC	ccggaccgccgcccgcc	TTTTTT	gcgcgcgcgcgcgcccgcgggggggccccgggctg
VZV			CGCCCCG	caaacgcgcggggaggtggggtcgc	TTTTTTTTTT	ctctctcgaggggccgcgagagggctggcctc
EBV (B95-8)			GGGCCGC	gggggaaggccacgcccctccac	TTTTT	ccaggaatgcgcggccccccatgcccc

NOTE: HSV-1, VZV, EBV = LEFT GENOME ENDS; underlined base = SS overhang

CONCATAMER JUNCTION CLONES

```
                                                    right terminus>  <left terminus
Ends    ggcagccaatgtcttgtaatgccttcaaggcacttttttctgcgagccgcgcgcagcactcagtgaaaaaca  ccccccgtttcgtatttcaaatcctaaataaccccccgggggtaaaaaaaggggg
        ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||  ||||||||||||||||||||||||||||||||||||||||||||
CJ712   ggcagccaatgtcttgtaatgccttcaaggcacttttttctgcgagccgcgcgcagcactcagtgaaaaacaG...ccccgtttcgtatttcaaatcctaaataaccccccgggggtaaaaaaaggggg
CJ325   ggcagccaatgtcttgtaatgccttcaaggtactttttctgcgagccgcgcgcagcactcagtgaaaaacaAT.ccccgtttcgtatttcaaatcctaaataaccccccgggggtaaaaaaaggggg
CJ7204  ggcagccaatgtctcgtaatgccttcaaggcacttttactgcgagccgcgcgcagcaccagaggaaaaacaTT..ccccgtttcgtatttcaaatcctaaataaccccccgggggtaaaaaaaggggg
CJ7105  ggcagccaatgtcttgtaatgccttcaaggcactctttctgcgagccgcgcgcagcactcagtgaaaaac...ccccccgtttcgtatttcaaatcctaaataaccccccgggggtaaaaaaaggggg
```

FIG. 2. Structure of the genomic termini of HHV-7 (R-2) and comparison with terminal sequences from HHV-6 (Z29) (37), herpes simplex virus type 1 (HSV-1) (KOS) (12), varicella-zoster virus (VZV) (10), and Epstein-Barr virus (EBV) (B95-8) (44). *pac*-1 sequences (C_n-G_n-N_n-G_n) are indicated in left-terminal sequences of HHV-7, and sequences corresponding to the *pac*-2 motif (GC_n-T_n-GC_n) are indicated in right-terminal sequences. Terminal nucleotides in HHV-7 were identified after blunt ending with T4 DNA polymerase, and any 3′ base extension was removed. The $DR_R \cdot DR_L$ junction from HHV-7 (JI) was also molecularly cloned and sequenced, following PCR amplification (see text for details), and is also shown (under concatamer junction clones). Sequences from individual concatamer junction clones (GenBank accession number L46633) are aligned with the left- and right-genome termini of HHV-7 (R-2) (vertical bars); bases in uppercase type represent bases present in junctional fragments but not in the sequences of termini isolated with T4 DNA polymerase. SS, single-stranded.

corresponding location in HHV-6 and is composed of TRS elements (both perfect and degenerate) that are interrupted by a 14-bp DR, TAGGGCTGCGGCCC (Fig. 1B, repeat motif 5). This region is centered around a long imperfect palindrome composed of TRS elements that are interrupted by the 14-bp repeat (resulting in a sequence of >340 bp with >55% self-complementarity; data not shown). In addition, sequences located at the DR_L-U junction were found to be variable in length, since plasmid clones corresponding to *Eco*RI restriction fragments from this region, which were derived from a single preparation of HHV-7 (JI) DNA, ranged in size from 1.2 kb (clone ED132′1.2) to 1.7 kb. This length heterogeneity was found to map to the TRS-containing repeats (data not shown).

In order to determine precisely the genomic location of the TRS motifs in HHV-7, the ends of the HHV-7 genome were cloned and characterized by two methods. First, virion DNA was prepared from cells infected with HHV-7 (R-2) and then treated with T4 DNA polymerase prior to digestion with *Bam*HI and subsequent cloning into *Sma*I- and *Bam*HI-digested pBluescript. This library of putative terminal DNA fragments was screened by colony hybridization with radiolabelled probes corresponding to DR_L-U and U-DR_R (clones ED132′ 1.2 and EZ3, respectively), and positive clones were subjected to DNA sequence analysis with universal sequencing primers. Terminal sequences from HHV-7 (R-2) were also cloned by a PCR method. In this case, the ligation reactions described above were used as the template DNA in PCR reactions containing one virus-specific oligonucleotide primer (H7TER2 or H7TER1; see below) plus one plasmid-specific oligonucleotide primer (T3 or T7 universal primers) to amplify junctional DNA fragments spanning the plasmid polylinker and the HHV-7 right or left genome ends. PCR products of the expected size were gel isolated, cloned into a T-overhang plasmid vector (pGEM-T; Promega Corp.), and sequenced.

All clones derived from the termini of HHV-7 strain R-2, by either of the methods employed, underwent initial blunt ending with T4 DNA polymerase, which preserved the 5′-terminal base but removed any 3′ extension. The sequences of each terminus are shown in Fig. 2; as expected, the sequences were 99% identical to regions located at the DR_L-U and U-DR_R junctions in HHV-7 (JI). Both termini were found to contain TRS elements, located at a site analogous to the position they occupy in HHV-6 (i.e., close to, but not at, the genome termini) (Fig. 2 and 3). In addition, the left genome terminus and U-DR_R junction were found to contain sequences which closely resembled the conserved *pac*-1 motif found in other herpesviruses (C_n-G_n-N_n-G_n), while the right genome terminus and DR_L-U junction contained a homolog of the second conserved cleavage-packaging motif, *pac*-2 (GC_n-T_n-GC_n) (12). The arrangement of these two motifs and their proximity to the termini in HHV-7 are consistent with those found in other herpesviruses (Fig. 2 and 3).

These findings were confirmed by PCR amplification and an analysis of HHV-7 replication intermediates (the $DR_R \cdot DR_L$ junction) with extrachromosomal DNA prepared from HHV-7 (JI)-infected SupT1 cells. Briefly, a primer oriented rightward from the right genome terminus (H7TER2, 5′ gagaattcTAAC CCTAACCCCGCCCCCACT) and a primer oriented leftward from the left terminus (H7TER1, 5′ gacctaggTTAGGGTTAG CTCCCCCCCTTT) were used to amplify DR · DR junctions

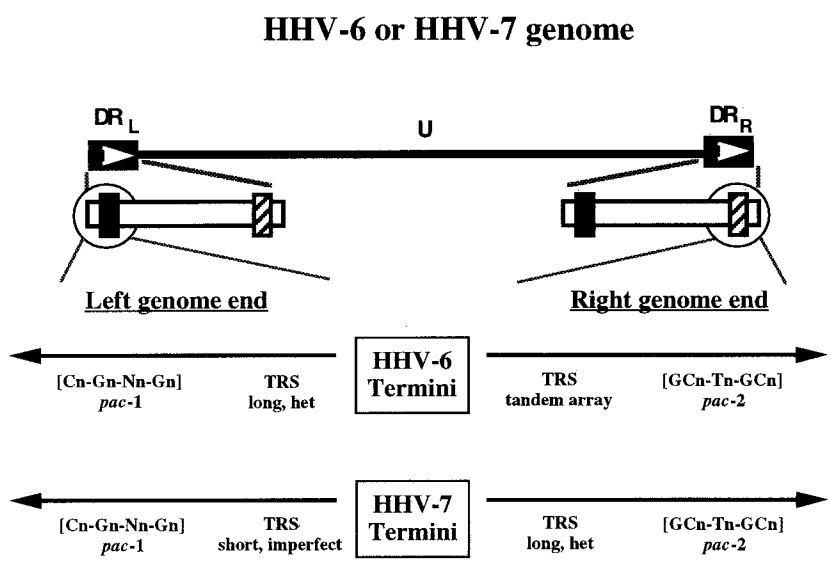

FIG. 3. Schematic comparison of sequences at the genomic termini of HHV-7 and HHV-6. Conserved sequence motifs (*pac*-1 and *pac*-2) are indicated, together with TRSs; the two distinct TRS arrays are denoted by shaded or cross-hatched rectangles. het, heterogeneous or variable sequences.

(lowercase lettering denotes nonviral sequences that were included in the primers, including synthetic restriction enzyme cleavage sites, which are underlined). PCR was carried out with 50 ng of template DNA, together with Promega *Taq* polymerase and buffer (Mg, 1.5 mM final concentration). Thirty-five cycles of amplification were performed, with sequential incubations at 94°C (1 min), 60°C (45 s), and 72°C (45 s). PCR products were then resolved by agarose gel electrophoresis, and the products of the expected size (179 bp) were gel isolated and then cloned directly into a T-overhang plasmid vector (pGEM-T; Promega) for subsequent analysis.

The sequences of the DR · DR junctions from several such clones are presented in Fig. 2 (lower panel, concatamer junction clones). As expected, the sequences correspond to a head-to-tail linkage of DR_R and DR_L with the arrangement *pac*-2 · x · *pac*-1, where x is the putative cleavage site. Each of the four junctional clones whose sequence is presented in Fig. 2 was found to be distinct. Specifically, the sequences located at the junction between the left and right genome termini were found to exhibit a degree of microheterogeneity. Thus, clone CJ712 exhibited no obvious evidence of a 3′ base extension, while the other clones had evidence of either one or two 3′ bases (Fig. 2). Similar sequence variation in terminal base composition has previously been observed in HHV-6, perhaps because of the ability of PCR to amplify rare virus subpopulations (37).

In addition to variation in the terminal nucleotide composition of HHV-7, there was also marked sequence variation at the right genome terminus (a total of six point mutations detected in 288 nucleotides of sequence), compared with the left genome terminus (zero point mutations detected in 216 nucleotides) (Fig. 2). Furthermore, an interstrain size heterogeneity was also mapped to the right terminus (DR_L-U) junction, by Southern blot analysis (data not shown). Taken together, these findings suggest that two distinct types of sequence variation (point mutations and size heterogeneity) may occur at the right genome terminus of HHV-7.

The presence of TRS motifs within HHV-7 reinforces the notion that these sequences may have biological or functional significance, and it is striking that similar elements have been detected in other lymphotropic herpesviruses, including alphaherpesviruses (Marek's disease virus), betaherpesviruses (HHV-6), and gammaherpesviruses (equine herpesvirus 2) (8, 15, 19, 20, 29, 36, 37). In most cases, these TRS motifs occur in close proximity to the viral genomic termini (e.g., in HHV-7, HHV-6, and Marek's disease virus) and are located adjacent to the *pac*-1 and *pac*-2 motifs. This arrangement suggests that the TRS motifs may have a role in the lytic-phase replication of the HHV-7 and HHV-6 genomes, perhaps because of their ability to adopt an unusual structural conformation that may promote endonucleolytic cleavage at the *pac* motifs during rolling-circle replication of the viral genome (22). In this sense, the TRS motifs can be viewed as being analogous to *a* sequences of herpes simplex virus type 1, which have previously been shown to adopt an anisomorphic conformation that is highly prone to endonucleolytic cleavage (40). Alternative functions for the TRS motifs might include roles in the regulation of viral gene expression (31), latent-phase virus replication, and/or the site-specific integration of viral DNA into the telomers of host cell chromosomes, as suggested by Torelli and colleagues (38).

In summary, this study draws attention to the high degree of similarity between HHV-7 and HHV-6, particularly in terms of genome organization. The two viruses presumably possess similar mechanisms of lytic-phase DNA replication, which may extend not only to cleavage and packaging, but also to origin function. The identification of TRS motifs in the genomes of several lymphotropic herpesviruses, including HHV-7 and HHV-6, merits further investigation. It will be of particular interest to determine what function, if any, the TRS motifs play in the replication, gene regulation, or biological properties of these viruses. Finally, the identification and analysis of *a* sequences from HHV-7 may make possible the future construction of highly defective HHV-7 amplicon vectors, which should have the ability to specifically target exogenous genes to human immunodeficiency virus type 1-susceptible $CD4^+$ cells (23, 33).

Nucleotide sequence accession number. The sequences reported here appear in the GenBank sequence database under accession numbers L46633 to L46635.

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