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Primary Structure of the *Herpesvirus Ateles* Genome†

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***Herpesvirus ateles* is an agent indigenous to spider monkeys (*Ateles* spp.) and causes fulminant lymphomas in various New World primates. Structural and genetic relatedness led to the classification of this virus as a member of the genus *Rhadinovirus*. It is most closely related to *Herpesvirus saimiri*. The 108,409-bp light DNA segment of the herpesvirus ateles strain 73 genome has two genes for U-RNA-like transcripts and 73 open reading frames, of which at least 6 show significant homologies to cellular genes (encoding complement control proteins, apoptosis-regulatory proteins, D-type cyclins, interleukin-8 receptors, and enzymes involved in nucleotide metabolism). The left terminal region of the light DNA segment bears the putative rhadinovirus oncogene *tio*.**

Herpesvirus ateles strain 810 was isolated from a primary kidney cell culture of a mature male spider monkey (*Ateles geoffroyii*) imported from Guatemala (47). This isolate, taxonomically classified as *Ateline herpesvirus 2* (AtHV-2) (49), was found to be oncogenic in marmosets (*Saguinus oedipus*) and owl monkeys (*Aotus trivirgatus*), which develop malignant lymphomas with leukemia (25, 37, 46). More AtHVs (strains 73, 87, 93, and 94) were isolated from lymphocytes of Columbian spider monkeys (*Ateles paniscus*) by cocultivation with permissive cell cultures (18). Strain 73 was classified as AtHV-3 (49). Cotton-topped and white-lipped marmosets, owl monkeys (24), and distinct rabbit strains (M. D. Daniel, R. D. Hunt, N. W. King, and J. K. Ingalls, Abstr. 3rd Int. Symp. Oncogenesis and Herpesviruses, p. 213, 1977), infected with AtHV-3 or with AtHV strain 93 or 94 developed lymphomas from which continuous cell lines can be established (18). AtHV-3 was also shown to transform T lymphocytes from *S. oedipus* and *S. fuscicollis* in vitro (16, 17, 32).

Members of the genus *Rhadinovirus* have been classified by their genetic organization. Complete genomic sequences are known for *Alcelaphine herpesvirus 1* (15), *Murine herpesvirus 68* (60), *Human herpesvirus 8* (50, 54), *Rhesus rhadinovirus* (56), and *Herpesvirus saimiri A11* (*Saimiriine herpesvirus 2* [SaHV-2]) (5), the type species of the genus. *Equine herpesvirus 2* is closely genetically related to the rhadinoviruses; however, its overall genome structure corresponds to that of betaherpesviruses (58). All of these viruses are clearly distinct from *Epstein-Barr virus*, which defines the type species of the genus *Lymphocryptovirus* within the subfamily *Gammaherpesvirinae*.

Since AtHV-2 and -3 and SaHV-2 have been proven unique in their ability to transform monkey T cells to a phenotype of permanent growth in vitro and in vivo and represent the only available model system for studying viral T-cell lymphoma induction, I explored the genetic content of AtHV-3. In this report, the genetic relationship of AtHV-3 to the family of herpesviruses is established by the presentation of the primary structure of its genome.

AtHV-3 was obtained from a frozen virus stock (18) and was propagated on owl monkey kidney cells (10) as described elsewhere (19). Viral DNA was digested with a restriction endonuclease (*Sac*I, *Eco*RI, *Pvu*II, or *Hin*dIII) and subcloned into pBluescript (Stratagene, LaJolla, Calif.) by standard procedures. Authentic clones were confirmed as such by hybridization with AtHV-3 DNA, partial sequencing, and comparison with the SaHV-2 prototype sequence (5). A set of 61 distinct overlapping clones covering the whole light DNA segment (L-DNA) as well as several individual heavy-DNA (H-DNA) repeat clones were obtained and sequenced by using a combination of the shotgun and primer walking strategies. The final AtHV-3 L-DNA sequence was generated from a total of 728,899 bases, resulting in a redundancy of 6.63 per base pair. Computer analyses were performed as described previously (5, 15). Potential open reading frames (ORFs) were defined by applying the following criteria: (i) a minimum of 60 amino acids in the derived polypeptide, (ii) a codon preference like those of unambiguously identified viral genes, (iii) the presence of a typical translational start signal, (iv) potential promoter and transcriptional terminator elements, or (v) sequence homologies to known reading frames of viral or cellular origin.

Earlier studies of the genome structure of AtHV revealed that its genomic DNA is composed of a unique DNA segment of low G+C content (L-DNA), comprising 74% of the genome, flanked by multiple copies of a tandemly repeated element of high G+C content (H-DNA) (19). This resembles the genome structure of SaHV-2 (9), the prototype of the genus *Rhadinovirus* (5). The unique L-DNA region of AtHV-3 was determined to have a total of 108,409 bp (36.6% G+C), while the prototypic H-DNA repeat unit was found to contain 1,582 bp (77.1% G+C).

Sequence analysis of the standard H-DNA repeat unit of AtHV-3 uncovered numerous internal direct and inverted repeat structures, among them an internal 154-bp direct repeat sequence whose presence has been suggested by endonuclease digestion data (19). The H-DNA of SaHV-2 and AtHV-2 and -3 had been found not to be homologous by heteroduplex analysis (19); this was confirmed here by comparison of the AtHV-3 and SaHV-2 H-DNA sequences. The only common motifs found are related to pac-1 and pac-2 sequences corresponding to genome cleavage recognition motifs conserved among herpesviruses (11) and to the cleavage-packaging site which defines the genomic termini and the junctions between

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† To the memory of my father.

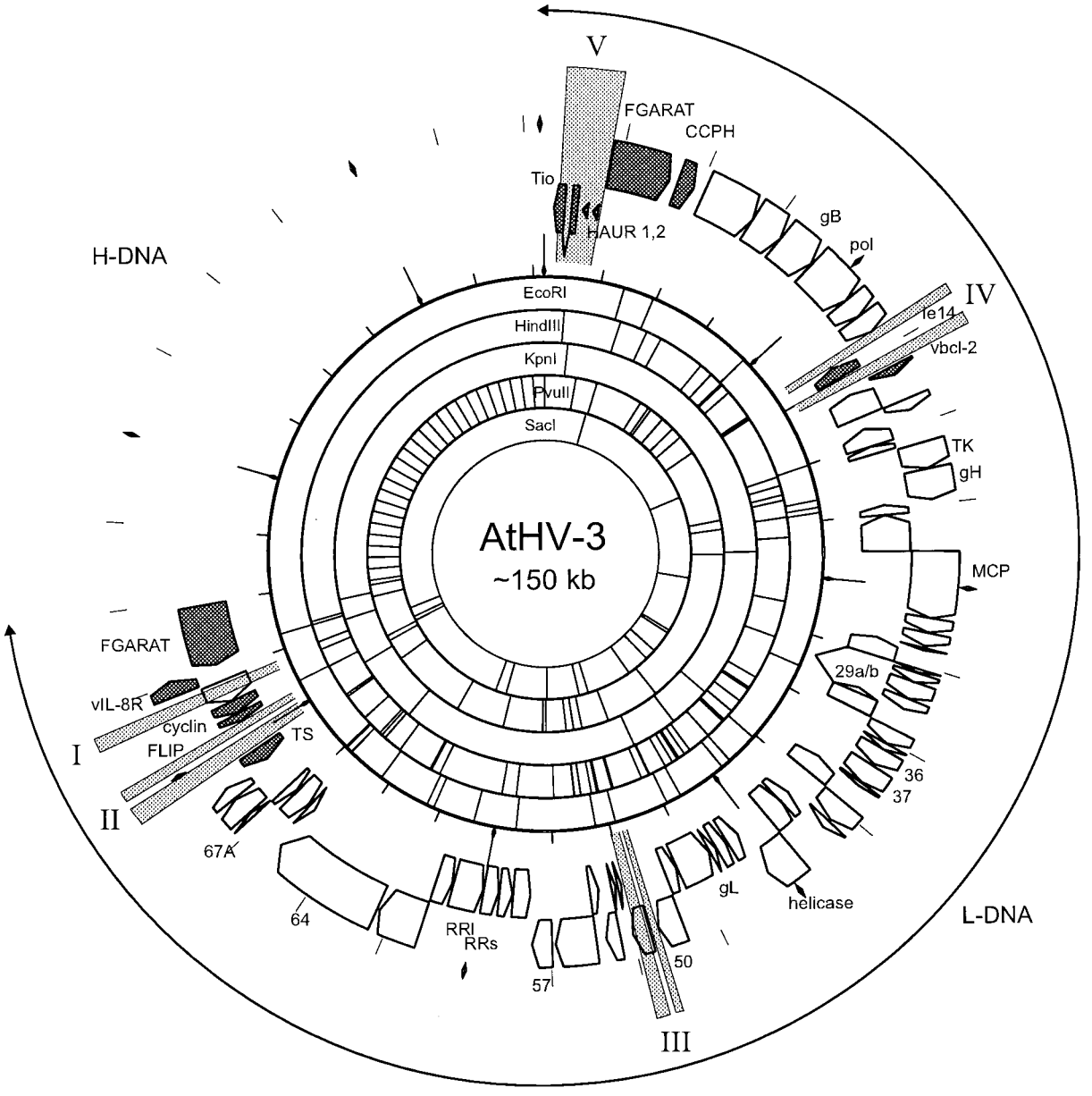

FIG. 1. Circular representation of the AtHV-3 genome. H-DNA sequences were added to L-DNA to give a total genome size of approximately 150 kbp as estimated by earlier studies. ORFs are shown as directed boxes around circular restriction maps, and cellular homologs are shaded dark gray. Areas significantly different from the SaHV-2 genome are depicted as light-gray-shaded areas I to V. The scale is 5 kbp/unit, with a diamond sign located every 20 kbp. ORF numbers are given for orientation and reference to Table 1. Abbreviations: HAUR, herpesvirus ateles U-like RNA; CCPH, complement control protein homolog; gB, glycoprotein B; pol, DNA polymerase; ie14/vsag, viral superantigen; TK, thymidine kinase; gH, glycoprotein H; MCP, major capsid protein; gL, glycoprotein L; RR, ribonucleotide reductase (l, large subunit; s, small subunit); cyclin, viral D-type cyclin; vIL-8R, viral IL-8 receptor; FGARAT, formylglycineamide ribotide amidotransferase.

H- and L-DNA sequences. These junctions, which were defined by the first nucleotide that diverges from the standard H-DNA repeat unit, can be localized to a single nucleotide of H-DNA (position 1336_H) at both ends of the L-DNA. Like in SaHV-2, the far-left terminal region of L-DNA consists of H-DNA (2, 4), which in the case of AtHV-3 is not rearranged but continuous.

Analysis of the genomic sequence of the L-DNA of AtHV-3 revealed 73 ORFs that potentially code for at least 73 proteins (Fig. 1; Table 1). Forty-eight reading frames were found to be conserved among most herpesviruses. A minimum of 14 deduced amino acid sequences are specific for the subfamily *Gammaherpesvirinae* (ORFs 3, 10, 11, 23, 27, 28, 45, 48 to 52, 58, and 75); 6 were found in rhadinoviruses only (ORFs 1, 4, 14, 71, 72, and 73), some of which appear to be restricted to specific virus species. Molecular piracy of cellular genes appears to be a common feature of rhadinovirus genomes and is most apparent in the genomes of SaHV-2 (5) and the recently isolated human Kaposi's sarcoma-associated herpesvirus (KSHV; human herpesvirus 8 [HHV-8]) (50, 54). Analysis of the entire 108.4 kbp of the AtHV-3 L-DNA also revealed a number of cellular homologs which might contribute to viral pathogenicity. These include a virus-encoded interleukin-8 receptor (IL-8R) (1), a D-type cyclin (29, 57), FLICE-inhibitory

TABLE 1. Description of AtHV-3 ORFs and comparison to SaHV-2 and HHV-8

AtHV-3 ORF	Strand[a]	Position of:		No. of amino acids encoded	Calculated molecular mass of product (kDa)	% Identity of product with:		Product description/homology[b]
		Start/exon 1	Exon 2/stop			SaHV-2	KSHV (HHV-8)	
1	c	90–730	1339–1507	269	29.2	32.8/40.0	—[c]	Tio; homologous to StpC and Tip
3		3224	6961	1,245	138.1	70.0	25.4	FGARAT
4a		7470	8552	360	40.2	73.1	28.3	mCCPH
4b		7470–8331	8525–8571	302	33.7	72.2	30.6	sCCPH
6		9205	12591	1,128	127.4	86.7	54.9	Major single-stranded-DNA binding protein
7		12598	14640	680	78.5	82.3	45.2	Transport protein
8		14627	17050	807	91.1	85.9	55.7	Glycoprotein B
9		17123	20152	1,009	114.4	87.5	60.8	DNA polymerase
10		20192	21412	406	45.4	82.0	24.0	Homologous to EBV Raji LF1/LF2 in B95-8 deletion, EHV-2 ORF10
11		21415	22632	405	45.8	75.6	28.4	Homologous to EBV Raji LF2 in B95-8 deletion, EHV-2 ORF11
14	c	23207	24028	273	30.6	47.0	—	ie14/vsag
16		25075	25599	174	19.5	65.0	19.0	bcl2 family
17	c	25629	27128	499	55.9	77.6	41.7	Protease, minor capsid scaffold protein
18		27121	27891	256	29.7	82.8	48.0	
19	c	27885	29519	544	61.2	79.7	46.2	Virion protein
20	c	29149	30060	303	34.5	67.3	41.8	Fusion protein
21		30059	31642	527	59.7	76.4	28.1	Thymidine kinase
22		31639	33789	716	83.2	87.6	34.3	Glycoprotein H
23	c	33782	34549	255	29.2	83.7	33.5	
24	c	34559	36751	730	82.5	82.1	47.4	
25		36757	40872	1,371	153.8	89.4	65.0	Major capsid protein
26		40888	41802	304	34.5	89.8	55.6	Capsid protein VP23
27		41809	42627	272	31.7	72.1	31.5	
28		42692	42916	74	7.9	56.3	36.1	
29a	c	42929	43984	351	39.0	90.6	52.3	DNA-packaging protein, terminase
30		44089	44316	75	8.3	81.3	33.3	
31		44283	44909	208	24.4	87.5	44.3	
32		44855	46180	441	51.2	71.4	29.8	
33		46173	47165	330	36.8	79.7	36.2	
29b	c	47107	48063	318	36.4	81.8	61.8	
29	c	42929–44071	47155–48063	683	77.0	87.3	58.9	DNA-packaging protein, terminase
34		48062	49012	316	36.2	87.0	44.3	
35		48999	49454	151	17.4	76.0	29.9	
36		49339	50631	430	48.4	81.4	30.2	Phosphotransferase
37		50631	52082	483	55.9	87.4	50.9	Alkaline exonuclease
38		52037	52237	66	7.7	69.7	40.0	Homologous to myristylated tegument protein in EHV-2
39	c	52263	53360	365	42.2	84.1	49.3	Integral membrane protein
40		53445	54773	442	50.7	68.6	26.9	Helicase-primase complex
41		54926	55408	160	18.5	74.4	27.5	Helicase-primase complex
42	c	55400	56197	265	29.7	80.0	37.7	
43	c	56163	57863	566	64.6	89.2	58.8	Minor capsid protein, virion protein
44		57829	60174	781	88.0	89.5	61.1	Helicase-primase complex, helicase
45	c	60214	60996	260	29.1	61.0	29.9	
46	c	61004	61762	252	29.1	82.9	59.1	Uracil DNA glycosidase
47	c	61740	62162	140	15.9	67.2	32.1	Glycoprotein L
48	c	62159	64537	792	92.6	50.7	21.6	Contains a large acidic repeat
49	c	64768	65682	304	35.8	73.9	20.2	
50		65682	67250	522	58.2	68.7	21.7	Transcriptional control; homologous to EBV Rta
51		67818	68867	349	37.0	40.5	23.9	Virus-specific glycoprotein
52	c	68906	69253	115	13.2	66.7	24.3	
53	c	69295	69564	89	10.0	61.8	25.8	
54		69636	70499	287	32.2	74.9	35.0	dUTPase
55	c	70537	71139	200	22.5	83.5	46.4	
56		71118	73625	835	96.0	81.3	44.3	Helicase-primase complex, primase
57		73782	75053	423	47.5	76.2	27.6	Transcriptional control; homologous to EBV Mta
58	c	75434	76495	353	40.7	83.3	29.3	
59	c	76504	77604	366	40.1	77.0	30.8	Processivity factor of DNA polymerase
60	c	77719	78636	305	35.3	92.5	63.0	Ribonucleotide reductase small subunit
61	c	78642	80945	767	87.0	90.0	51.9	Ribonucleotide reductase large subunit
62	c	80945	81937	330	37.5	86.1	40.1	Probable capsid assembly, DNA maturation protein
63		81944	84643	899	103.4	75.9	30.7	Tegument protein
64		84643	92058	2,471	280.0	72.0	30.5	Large tegument protein
65	c	92062	92463	133	14.4	69.7	29.3	Capsid protein
66	c	92426	93760	444	50.9	79.5	34.6	
67	c	93679	94380	233	26.5	84.1	50.6	Tegument protein
67A	c	94377	94634	85	9.7	84.0	41.6	
68		94627	95937	436	49.3	77.8	47.0	Probable major envelope protein
69		95939	96724	261	29.8	88.1	49.0	
70	c	96897	97769	290	32.9	84.8	65.5	TS
71	c	100187	100528	113	13.4	42.5	28.3	FLIP
72	c	100529	101317	262	29.6	74.8	29.6	D-type cyclin
73	c	101349	102692	447	46.5	35.0	15.0	Glycine rich, repetitive structure
74		103148	104113	321	36.6	70.6	31.5	Viral IL-8 receptor
75	c	104198	108097	1,299	143.1	73.6	36.0	FGARAT

[a] c, complementary strand.

[b] Taken in part from descriptions of other sequenced herpesvirus ORF products. Abbreviations: FGARAT, formylglycineamide ribotide amidotransferase; mCCPH and sCCPH, membrane-bound and soluble complement control protein homologs; EBV, Epstein-Barr virus; EHV-2, equine herpesvirus 2.

[c] —, not present.

protein (FLIP) (59), thymidylate synthetase (TS) (23, 53), ie14/vsag (34, 63), complement-regulatory proteins (2, 20), and two U-RNA-like transcripts (3, 39, 61) (Fig. 1; Table 1). Notably, AtHV-3 does not code for a homolog of dihydrofolate reductase, IL-17, or CD59, which are encoded by SaHV-2. Homologs for IL-6, macrophage-inhibitory protein 1-α and -β chemokines, and viral interferon-regulatory factors, all of which are encoded by HHV-8, were not identified. However, apparently all identified ORFs of AtHV-3 are conserved in SaHV-2 (Table 1), with amino acid sequence identities ranging from 30.4 to 92.5% (average, 75.1%). A gapped alignment of their complete L-DNAs revealed an average DNA sequence conservation of 76.4%.

At least five genomic loci of AtHV-3 were found to be quite distinct from those of SaHV-2 (Fig. 1). Region I corresponds to a repetitive DNA structure within ORF73 which is present in most rhadinoviruses (5, 15, 54). The function of the ORF73 protein is not known; however, a protein encoded at an analogous position in the HHV-8 genome has been demonstrated to be a nuclear antigen expressed during latency (52). Region II is characterized by variability within the 5′ noncoding region of the thymidylate synthetase (TS) gene, which has been tentatively mapped as the origin of lytic replication in SaHV-2 (55), and by the presence of an additional 168-bp repeat sequence, composed of 15.3 copies of an 11-bp unit, downstream of ORF71. Independent of this repeat insertion, ORF71 of AtHV-3 is likely to be nonfunctional due to multiple frame shifts at the 3′ end of this ORF, which encodes a FLIP in other rhadinoviruses (45, 59). This appears to be a specific feature of AtHVs, since similar results were obtained for AtHV-2 after PCR amplification and sequencing of the corresponding genomic region. Region III is composed of two insertions, of 347 and 240 bp, into the AtHV-3 genome, which affect the 3′ noncoding region of ORF50 and most of ORF51, respectively. Although no obvious sequence homology was detected, AtHV-3 ORF51 is a positional homolog of HHV-8 K8.1, murine herpesvirus 68 M7, bovine herpesvirus 4 BORFD1, alcelaphine herpesvirus 1 A8, and SaHV-2 ORF51. All of these ORFs code for a typical type I transmembrane glycoprotein with a high content of Ser and Thr residues and multiple N-linked glycosylation sites (NxT/S). Region IV of AtHV-3 has four deletions relative to the SaHV-2 genome: one of 177, affecting ORF12; one of 900 bp, in the gene encoding a viral IL-17 (5, 33); and two, of 632 and 84 bp, in the gene coding for the CD59 homologue in SaHV-2 (6).

Region V corresponds to a highly variable region of SaHV-2 (44) which has been shown to mediate the oncogenic and transforming phenotype (12–14, 31, 35, 42). The high degree of variability among different strains of SaHV-2 has led to their subdivision into three subgroups, A, B, and C (43). Group A, represented by the SaHV-2 prototype strain A11, encodes a single protein, termed StpA (for saimiri transformation-associated protein of group A), which has been demonstrated to be transforming in cell culture and in transgenic mice (30, 36). StpA has been shown to become phosphorylated by cellular Src and to bind to the Src SH2 domain by a phosphotyrosine-dependent mechanism (38). It has also been suggested that StpA interacts with the T-cell-specific Src family kinases Lck and Fyn (38). Group C viruses C484 and C488 encode two proteins, StpC and Tip, within this variable genomic region (7, 21). On the one hand, StpC has been shown to be transforming in cell culture (30) and to cause epithelial tumors in transgenic mice (48). It interacts directly with cellular Ras and competes with cellular Raf for binding to Ras, thereby affecting the signal transduction pathway of Ras (22, 26). On the other hand, Tip, a tyrosine kinase-interacting protein of SaHV-2 group C viruses, interacts with T-cell-specific kinases of the Src family, predominantly Lck (8, 41). Although its influence on Lck activity has been controversial (28, 40, 51, 62), Tip has been shown to associate with Lck by binding to the SH3 domain of Lck via its SH3 binding motif and, additionally, to the kinase domain of Lck via its CSKH motif (27, 28; U. Friedrich, unpublished data). In transformed monkey T cells, a spliced mRNA is transcribed within this variable genomic region of AtHV-3, which encodes the two-in-one protein Tio, a protein that exhibits homologies with both StpC and Tip (4). Homologous sequences were identified in AtHV-2, indicating a very close relationship between AtHV-2 and AtHV-3. AtHV-3-encoded Tio has been demonstrated to combine functions of Tip and StpA/B: Tio interacts with cellular Src family kinases by binding to their SH3 domains via an SH3 binding motif related to Tip and by binding to the SH2 domains of Lck, Src, and Fyn in a phosphotyrosine-dependent manner, like StpA (4). Sequence homology to StpC also suggests an additional function related to StpC; however, this has not yet been supported by experimental evidence. Tio appears to be the single rhadinovirus oncoprotein encoded in the entire AtHV-3 genome which is a multifunctional protein involved in signal transduction.

Nucleotide sequence accession numbers. The nucleotide sequences of the AtHV-3 unique L-DNA region, AtHV-3 H-DNA repeat unit, AtHV-2 ORF71, and AtHV-2 *tio* gene were submitted to the GenBank database and assigned accession no. AF083424, AF126541, AF133729, and AF135064, respectively.

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