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Sequence and Genetic Arrangement of the U_S Region of the Monkey B Virus (*Cercopithecine Herpesvirus 1*) Genome and Comparison with the U_S Regions of Other Primate Herpesviruses

Kazutaka Ohsawa,[1] Darla H. Black,[2] Hiroshi Sato,[1] and R. Eberle[2]*

Laboratory Animal Center for Biomedical Research, Nagasaki University School of Medicine, Nagasaki 852-8523, Japan,[1] and Department of Veterinary Pathobiology, College of Veterinary Medicine, Oklahoma State University, Stillwater, Oklahoma 74078-2007[2]

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The sequence of the unique short (U_S) region of monkey B virus (BV) was determined. The 13 genes identified are arranged in the same order and orientation as in herpes simplex virus (HSV). These results demonstrate that the BV U_S region is entirely colinear with that of HSV type 1 (HSV-1), HSV-2, and simian agent 8 virus.

Cercopithecine herpesvirus 1 (monkey B virus [BV]) is a member of the alphaherpesvirus subfamily indigenous in Asiatic macaque monkeys. The natural history of BV in macaques is similar to that of the human herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in humans, of simian agent 8 virus (SA8) in green monkeys, and of *Herpesvirus papio 2* (HVP-2) in baboons (11, 12, 38). When transmitted to nonmacaque primates, BV produces severe infections which usually involve the central nervous system and are frequently fatal (31, 37, 38). The molecular basis for the extreme neuropathology of BV in nonmacaque species is an intriguing question that remains unanswered.

While sequences for a number of genes of BV have been reported (3, 9, 23, 34, 35, 37), genomic characterization of BV has largely been limited to restriction analysis and gene mapping by hybridization with HSV gene probes (10, 16, 17). Such studies have suggested that, for the most part, the BV genome is colinear with that of HSV. However, it has been reported that the unique short (U_S) region of the BV genome may not be colinear with that of HSV (16). Here we present the sequence of the U_S region of the BV genome and its genetic layout relative to that of HSV and SA8.

The DNA sequence of the BV rhesus genotype (BVrh) strain E2490 (35) U_S region was determined by a combination of cloning restriction fragments of the genome and PCR amplification of small gaps in the sequence with genomic BV DNA as a template. The BVrh U_S region (GenBank accession no. AB 077432) is 14,447 nucleotides long, slightly longer than the 12,980 bp reported for HSV-1 strain 17 (26) but close to the 14,329-bp HSV-2 U_S region (6). The BVrh U_S sequence presented here does not include sequences aligning with the N-terminal 2 codons of the US12 open reading frame (ORF). The overall G+C content of the BVrh U_S region is 73.2%, close to the 75% G+C estimated for the entire BV genome (19). The coding sequences in the U_S region have a combined G+C content of 74.4%, a value somewhat higher than that for the noncoding intergenic regions (68.9%). BV exhibits a strong bias toward use of codons with G or C in the third position (89.6%) and Arg and Leu codons with C in the first position (93.4%). While this GC bias is strong, it is not as extreme as in the SA8 U_S region (76.8% G+C overall, 92.9% GC in the third position, 97.2% C in the first position of the Arg and Leu codons [13]).

Analysis of the BVrh U_S sequence for ORFs, homology of predicted amino acid sequences with HSV polypeptides, promoter and transcriptional initiation sites, and mRNA termination sites [consensus poly(A) signals associated with mRNA termination motifs] indicates that the genetic layout of the BVrh U_S region is very similar to those of HSV-1 and HSV-2 and is identical to that of SA8 (Fig. 1). As summarized in Table 1, 13 ORFs corresponding to HSV US1 to US12 and US8.5 are all present in BV. All ORFs occur in the same order and orientation as in HSV and SA8. This is in contrast to results reported by others (16), which indicated that while ORFs analogous to those of HSV were present in the BV cynomolgus genotype (BVcy) U_S region, they were arranged in a different order. Based on poly(A) and mRNA termination signals, the transcriptional grouping of BV US mRNAs is identical to that reported for SA8 (13) and is probably identical to those for all BV genotypes and HVP-2 as well (9, 35). Thus, mRNAs for US3/US4/US5 and US6/US7 form two 3′-coterminal transcriptional sets in all of the simian viruses, while in HSV the transcriptional groupings of these genes are US3/US4 and US5/US6/US7. Transcriptional groupings of all other BV US genes are identical to that found in HSV. Analysis of the BV U_S sequence for additional ORFs associated with transcriptional elements and/or homologous unidentified genes in SA8 did not indicate that any such unidentified genes exist.

The US1 ORF encodes the immediate-early (alpha) regulatory protein ICP22 (6, 26). The BV US1 protein is somewhat smaller than the HSV-1 and HSV-2 proteins (Fig. 2). Although

* Corresponding author. Mailing address: Department of Veterinary Pathobiology, College of Veterinary Medicine, Oklahoma State University, Stillwater, OK 74078-2007. Phone: (405) 744-8169. Fax: (405) 744-8263. E-mail: reberle@okstate.edu.

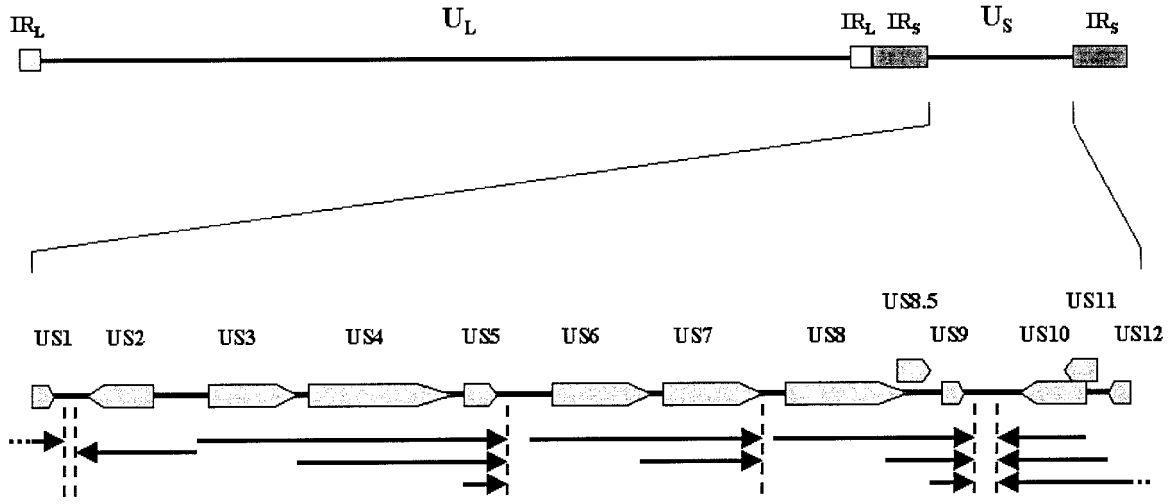

FIG. 1. Genetic organization of the BV strain E2490 U_S region. ORFs predicted to encode proteins and their orientations are indicated by large arrows. The locations of transcriptional termination signals (AATAAA, followed by GT tracts) are indicated by vertical dashed lines. The proposed mRNA transcriptional map of the region is indicated by arrows located below the ORF map. IR_L, inverted long repeat; IR_S, inverted short repeat.

the overall amino acid sequence homology is low, there are several distinct regions that are strongly conserved. Similarly, the N-terminal 70% of the US2 protein is strongly conserved among BV, HSV-1, and HSV-2, having regions of identical sequence separated by stretches of more variant sequence. This is consistent with the noted conservation of the US2 gene in mammalian and avian alphaherpesviruses (21, 28).

In HSV-1, it has been reported that a second polypeptide, designated US1.5, is synthesized from the US1 ORF by initiation at an internal in-frame Met codon (4). There is no similar Met codon in BV or HSV-2 located near this HSV-1 Met codon (Fig. 2). Given the close phylogenetic relatedness of HSV-2 and BV to HSV-1, it is curious that HSV-1 is the only one of these three viruses which appears to synthesize a US1.5 protein.

Between the US2 and US3 ORFs is an intergenic region of 556 nucleotides in which should lie the promoters for both genes. Only one potential promoter is apparent, located ca. 440 bp 5′ of the US2 start codon. This same element likely serves as the US3 promoter on the complementary strand as well. Use of this promoter would result in a fairly long 5′ untranslated region (412 bp) on the US2 mRNA which is considerably longer than the 5′ untranslated sequence predicted for all other BV US genes (50 to 200 bp) or the HSV-1 and HSV-2 US2 mRNAs (~290 bp).

The US3 proteins are serine/threonine protein kinases (25). Within the strongly conserved C-terminal 75% of the protein are the active sites for phosphorylation activity and ATP binding. Relative to the US3 proteins of HSV-1 and HSV-2, the simian virus US3 proteins are ca. 100 amino acids shorter. As for the US1 protein, ca. 80 of these "deleted" residues represent the N terminus of the polypeptide. Another 15 to 20 residues not present in the simian virus US3 polypeptide follow a 20- to 25-residue block of acidic residues located in the

TABLE 1. Properties of BVrh ORFs located in the U_S region

BVrh E2490[a]			Function of the encoded protein	% Identity/% similarity of BV proteins with homologous proteins[b] of:		
ORF	Size (aa)	Predicted MW		HSV-1	HSV-2	SA8
US1	373	40,700	Immediate-early protein ICP22	32/42 (420)	34/45 (413)	NA
US2	302	32,900	Unknown	52/58 (291)	48/57 (291)	NA
US3	379	41,600	Serine/threonine protein kinase	51/59 (481)	52/59 (481)	83/86 (377)
US4	673	67,900	Glycoprotein gG	9/12 (238)	34/44 (699)	53/61 (602)
US5	121	12,100	Glycoprotein gJ	26/36 (92)	18/30 (92)	51/58 (106)
US6	395	42,600	Glycoprotein gD	56/67 (394)	55/68 (393)	80/84 (395)
US7	401	42,000	Glycoprotein gI	43/51 (390)	46/54 (372)	66/69 (399)
US8	539	58,000	Glycoprotein gE	44/55 (550)	44/55 (545)	72/78 (540)
US8.5	122	12,600	Unknown	28/40 (159)	31/43 (146)	60/61 (102)
US9	90	9,900	Envelope phosphoprotein	57/69 (90)	57/69 (89)	75/84 (91)
US10	311	34,000	Tegument protein	36/46 (312)	42/50 (302)	84/91 (93)[c]
US11	145	16,300	RNA-binding protein	41/45 (161)	38/40 (151)	NA
US12	>78		Immediate-early protein ICP47	21/33 (88)	20/30 (86)	NA

[a] aa, amino acids; MW, molecular weight.

[b] Values are percentages of amino acid identity and percentages of amino acid similarity in pairwise alignment with the BV homologue. Numbers in parentheses represent the numbers of amino acid residues comprising the homologous viral protein. NA, sequence not available.

[c] Only a partial sequence was available.

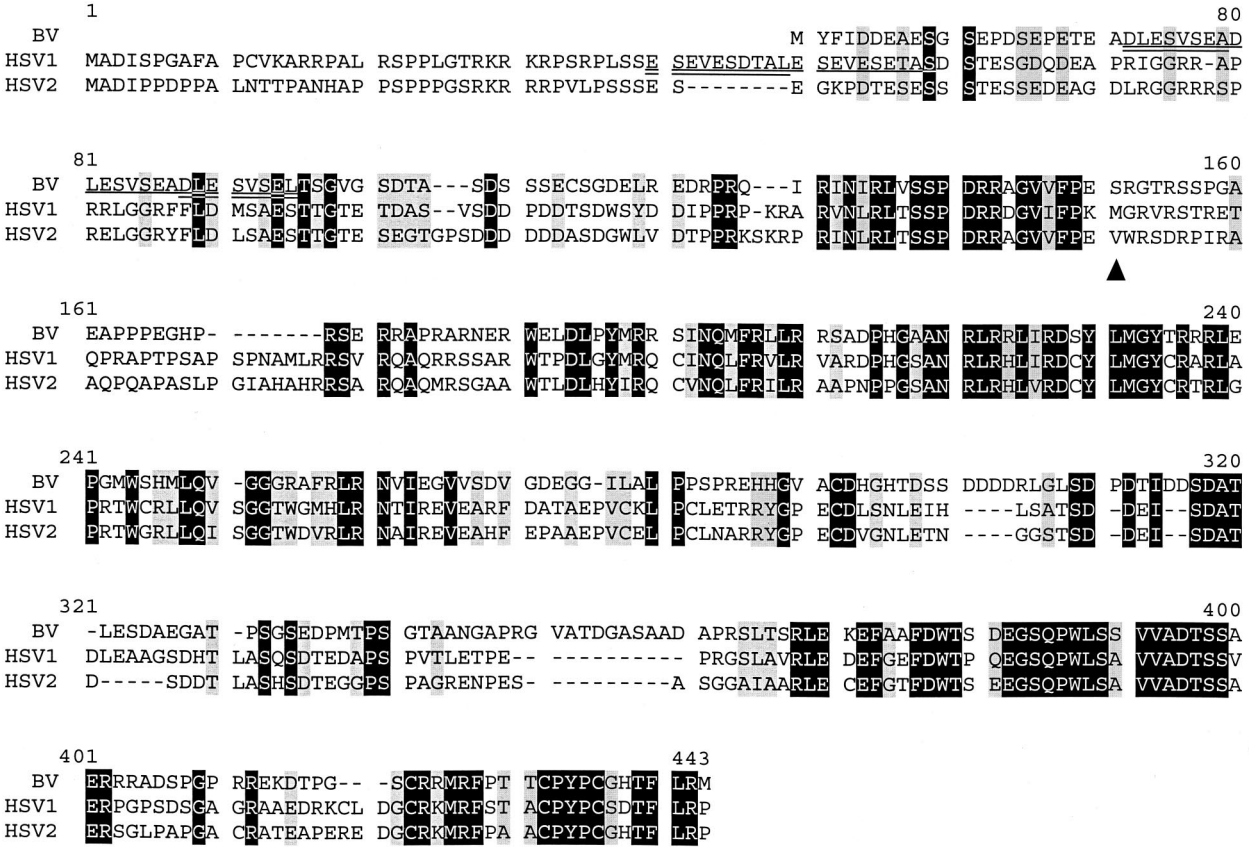

FIG. 2. Alignment of immediate-early ICP22 (US1) polypeptides. Residues which are identical in all three sequences are shown with a black background; conservative residues are with a gray background. Degenerate repeats in the BV and HSV-1 sequences are identified by underlining. The Met in the HSV-1 sequence at which the proposed US1.5 protein initiates is indicated by "▲" below the aligned sequences. Note that neither BV nor HSV-2 have a Met residue near this HSV-1 Met codon.

N-terminal region of the HSV US3 polypeptides. In this respect, the simian herpesvirus US3 polypeptides are more similar to those of varicella-zoster virus rather than to those of HSV (5, 15).

As in other primate alphaherpesviruses, US4 to US8 all encode glycoproteins. The US4 ORF encodes a glycoprotein designated gG (27), which varies considerably among these viruses. All of the simian virus gGs are more similar to the gG of HSV-2 than to that of HSV-1, having a hydrophobic N-terminal signal sequence, two distinct regions of the extracellular domain separated by a proteolytic cleavage site, a transmembrane domain, and a highly charged cytoplasmic tail (27, 36, 34). The more N-terminal of the extracellular domains is relatively conserved in sequence, with six Cys residues and one N-linked glycosylation site being positionally conserved. In contrast, the more membrane-proximal extracellular domain exhibits considerable variation in size and very little sequence identity between viruses. Nonetheless, all have a stretch of ca. 20 acidic residues located some 70 residues from the transmembrane domain, two to four additional N-glycosylation sites, and a region of high Pro, Ser, and Thr content typical of regions where O-linked carbohydrate residues are added that is located between the proteolytic cleavage site and the acidic domain.

Sequencing of the US4 gene from cynomologous, pigtail, and lion-tailed macaque BV isolates (35, 37) indicates that, in addition to the high sequence variability between gGs of different viruses, the gG polypeptide also shows considerable sequence variation among different BV genotypes. The greatest genotypic variation occurs in the same regions where sequence variation occurs between BV and other primate virus gGs. Phylogenetic analysis of the US4 coding sequences (Fig. 3) predicts a relationship among BV genotypes very similar to that previously described based primarily on analyses of intergenic and US5 coding sequences (35, 37). The BVrh sequence also contains a six-times-repeated 6-residue motif (PAPTTT) located in the high-Pro/Ser/Thr-content region of the polypeptide, much like a similar repeat sequence observed in the US7 (gI) gene of HSV-1 (26). This repeat is not present in any of the other sequenced BV gGs. PCR amplification of BVrh genomic DNA indicates that this repeat is not a cloning artifact but rather is unique to the E2490 strain of BV.

The US5 gene encodes a small glycoprotein designated gJ that has been reported to inhibit apoptosis (20, 40). Multiple alignment of 17 simian virus gJ sequences indicates that, unlike other herpesvirus glycoproteins, the two hydrophobic regions representing the signal sequence and transmembrane domain are the most conserved regions of the polypeptide. This is most evident when gJ sequences for different BV genotypes are aligned, since genotypic differences occur in the extracellular

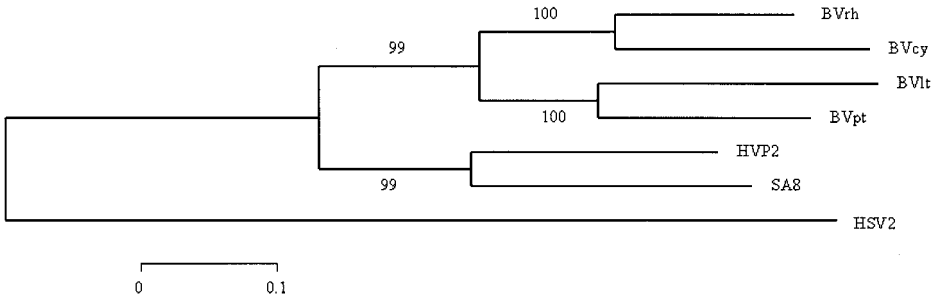

FIG. 3. Phylogenetic relationship of BV genotypes based on the US4 gG coding sequences. Predicted amino acid sequences were aligned and phylogenetic analyses performed as described previously (35). The tree shown was generated by using gamma distance estimates and neighbor-joining tree construction. Values represent bootstrap confidence intervals. BV genotypes isolated from rhesus (BVrh), cynomolgus (BVcy), lion-tailed (BVlt), and pigtailed (BVpt) macaques are indicated.

domain where two to three potential N-glycosylation sites occur. As for gG, one BVrh isolate was found to have reiterated sequences in the variable region of the extracellular domain (37).

The US6 to US8 genes encode glycoproteins gD, gI, and gE. The gD glycoprotein encoded by US6 is strongly conserved among the primate viruses and shows no significant genotypic variation among BV genotypes (3, 35, 37). The US7 gene encodes the gI glycoprotein, which complexes with the gE glycoprotein encoded by US8 to form an Fc receptor (22). Both gI and gE exhibit variable and conserved regions. In the extracellular domain of gI there is a region of highly variable sequence with a high content of Pro/Ser/Thr residues, suggesting modification by O-linked glycosylation. Although only the N-terminal 110 amino acids are available for the BVcy gI (3), only 1 amino acid difference exists between the BVrh and BVcy sequences, indicating that in this variable region there is not significant genotypic variation. A number of potential phosphorylation sites are present in the cytoplasmic tails of the BV and SA8 gI polypeptides, but only one is positionally conserved between the simian and human virus gI sequences (30). Interestingly, the domains of the gI and gE polypeptides that interact with immunoglobulin G and are involved in complexing of gI with gE (1, 2, 7) are not strongly conserved among the different primate virus gI polypeptides.

In contrast to gG, the N-terminal half of the gE extracellular domain is highly variable in sequence among the primate viruses, with the exception of a small, highly conserved stretch of 24 residues flanked by two Cys residues. Nearer the transmembrane region, the extracellular domain is more conserved, with seven of the nine conserved Cys residues being located within it. The transmembrane domain itself is fairly strongly conserved and, like the transmembrane domain of gI, has two conserved Cys residues near the cytoplasmic side. The long, highly charged cytoplasmic tail is less conserved, although both a series of basic residues adjacent to the transmembrane domain and an area rich in acidic residues are present in all of the primate virus gE polypeptides. In comparing the partial sequence for the BVcy US8 gene (23), it appears that genotypic variation does occur in the cytoplasmic tail of gE.

The function of the small protein encoded by the US8.5 gene is unknown, but it is phosphorylated and localized in the nucleoli of infected cells (14). As in SA8, the BV US8.5 ORF overlaps the 3′ end of the US8 ORF by 53 nucleotides. The N-terminal 70% of the US8.5 polypeptide is highly variable between the human and simian viruses but is fairly conserved between BV and SA8 (6). In contrast, sequence of the C-terminal region of the polypeptide is strongly conserved among all of the primate viruses. By deletion of one nucleotide that otherwise induces a frameshift, the published BVcy US8.5 sequence (23) is nearly identical to that of BVrh, suggesting that genotypic variation does not occur in US8.5.

The US9 gene encodes a small type II membrane protein found in the virion envelope and, as previously noted (23), is conserved among the primate viruses, especially in the region surrounding the tyrosine kinase phosphorylation sites (YY). Again, the BVcy and BVrh US9 sequences show little variation, being 93.3% identical and 97.8% similar to each other.

The US10 gene encodes a phosphoprotein of unknown function that is located in the virion tegument and infected cell nuclear matrix (39). The BVrh US10 protein is nearly identical to the HSV-1 US10 protein in size, but there is very little absolute sequence conservation in the N-terminal 70% of the polypeptide. In contrast, the C-terminal region of US10 is highly conserved among all of the primate viruses, including the putative zinc-finger motif (18). The amino acid sequences of the C-terminal halves of the BVrh and BVcy sequences are identical, reflecting the strong conservation of this protein.

The US11 gene encodes an RNA-binding protein which prevents phosphorylation of eukaryotic initiation factor 2 by binding to the cellular PKP kinase. The US11 ORF begins 145 nucleotides 5′ of the US10 ORF, resulting in the 3′ 65% of the US11 coding sequence overlapping the US10 ORF. The BV and HSV US11 polypeptides are strongly conserved in the C-terminal region, which contains a reiteration of 19 to 20 copies of the sequence RXP. RNA-binding activity, the nucleolar localization signal sequence, and the region responsible for association with 60S rRNA have all been mapped to this conserved region (32, 33). The 5′ portion of the gene encoding the nonoverlapping sequence shows very little conservation between BV and HSV.

The US12 gene encodes the small immediate-early (alpha) regulatory protein ICP47, which inhibits antigen presentation in infected cells by specifically binding to and blocking the transporter associated with processing (8, 24, 29). Although the start codon of the BVrh US12 ORF was not identified, what is probably the majority of the BV US12 ORF was determined. Surprisingly, alignment of the BV and HSV US12 sequences reveals very little sequence identity among these regulatory polypeptides. However, analysis of the polypeptides

for various features of secondary structure indicates that the BV and HSV ICP47 proteins are likely quite similar in structure.

In conclusion, the sequence of the U_S region of BVrh clearly demonstrates that this region of the genome is entirely colinear with the U_S regions of HSV-1, HSV-2, and SA8. Except for the US1.5 ORF, homologues of all genes detected in HSV-1 and HSV-2 are present in the BV U_S region, and the BV proteins are predicted to be similar in size to the homologous HSV-2 polypeptides. While a number of genes do exhibit substantial sequence variation, these genes also exhibit regions of highly conserved sequence. Such highly conserved regions undoubtedly represent important structural and/or functional regions of these proteins, indicating that these proteins have structures and functions similar to those of their HSV homologs. This is also consistent with the extensive antigenic cross-reactivity observed between almost all HSV, SA8, HVP-2, and BV proteins (10, 12, 17). Finally, genotypic sequence variation among BV isolates was minimal in nonglycoproteins but readily evident in the glycoproteins except for the conserved gD glycoprotein.

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