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Genome of Deerpox Virus

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Deerpox virus* (DPV), an uncharacterized and unclassified member of the *Poxviridae*, has been isolated from North American free-ranging mule deer (*Odocoileus hemionus*) exhibiting mucocutaneous disease. Here we report the genomic sequence and comparative analysis of two pathogenic DPV isolates, W-848-83 (W83) and W-1170-84 (W84). The W83 and W84 genomes are 166 and 170 kbp, containing 169 and 170 putative genes, respectively. Nucleotide identity between DPVs is 95% over the central 157 kbp. W83 and W84 share similar gene orders and code for similar replicative, structural, virulence, and host range functions. DPV open reading frames (ORFs) with putative virulence and host range functions include those similar to cytokine receptors (R), including gamma interferon receptor (IFN-γR), interleukin 1 receptor (IL-1R), and type 8 CC-chemokine receptors; cytokine binding proteins (BP), including IL-18BP, IFN-α/βBP, and tumor necrosis factor binding protein (TNFBP); serpins; and homologues of vaccinia virus (VACV) E3L, K3L, and A52R proteins. DPVs also encode distinct forms of major histocompatibility complex class I, C-type lectin-like protein, and transforming growth factor β1 (TGF-β1), a protein not previously described in a mammalian chordopoxvirus. Notably, DPV encodes homologues of cellular endothelin 2 and IL-1R antagonist, novel poxviral genes also likely involved in the manipulation of host responses. W83 and W84 differ from each other by the presence or absence of five ORFs. Specifically, homologues of a CD30 TNFR family protein, swinepox virus SPV019, and VACV E11L core protein are absent in W83, and homologues of TGF-β1 and lumpy skin disease virus LSDV023 are absent in W84. Phylogenetic analysis indicates that DPVs are genetically distinct from viruses of other characterized poxviral genera and that they likely comprise a new genus within the subfamily *Chordopoxvirinae*.

Within the subfamily *Chordopoxvirinae* of the family *Poxviridae*, eight genera are currently recognized based primarily on morphological and biological characteristics (48). Viruses from seven genera infect mammalian species (*Capripoxvirus*, *Leporipoxvirus*, *Molluscipoxvirus*, *Orthopoxvirus*, *Parapoxvirus*, *Suipoxvirus*, and *Yatapoxvirus*), and one genus infects birds (*Avipoxvirus*). Comparative genome analysis has provided a genetic basis for poxviral genus classification (31, 43). Chordopoxvirus (ChPV) genomes range from 135 to 365 kb in size and contain 130 to 328 putative genes. Complete genomic sequences have been determined for representative and often multiple viruses from each ChPV genus, including the following viruses: sheeppox, goatpox, and lumpy skin disease viruses (*Capripoxvirus*) (61, 62); myxoma and rabbit (Shope) fibroma viruses (*Leporipoxvirus*) (14, 67); molluscum contagiosum virus (*Molluscipoxvirus*) (55); monkeypox, vaccinia, camelpox, variola, and ectromelia viruses (*Orthopoxvirus*) (4, 16, 28, 32, 42, 56); orf and bovine popular stomatitis viruses (*Parapoxvirus*) (17); swinepox virus (*Suipoxvirus*) (3); Yaba monkey tumor and Yaba-like disease viruses (*Yatapoxvirus*) (12, 41); and canarypox and fowlpox viruses (*Avipoxvirus*) (2, 60). Many poxviruses are presently unclassified, however, suggesting that greater phylogenetic breadth exists within the *Chordopoxvirinae* (48).

Genomic sequences, together with extensive genetic and reverse genetic studies of model poxviruses, have demonstrated that the chordopoxviral genome is organized into a large, central region containing genes involved in basic replicative mechanisms, including multistage viral transcription, viral genome replication, and virion assembly, and into terminal regions containing genes involved in virus-host interactions (45, 46, 63). Comparative genomic analysis has revealed that while gene content and gene order in the central regions are relatively well conserved among mammalian chordopoxviruses, terminal genomic regions are more variable, with distantly related viruses having greater differences in gene order and content (31, 55).

Natural and experimentally induced poxviral diseases have been reported for members of three subfamilies of cervids, including American deer (*Odocoileinae*), alces (*Alcinae*), and reindeer and caribou (*Rangiferinae*), and include diseases which resemble infections caused by parapoxvirus orf virus (8, 24, 40, 50, 68, 71). Deerpox viruses (DPVs) are poorly characterized viruses responsible for non-orf-like infections and are presently unclassified members of the *Chordopoxvirinae.* Reports of DPV-like infections in deer include a reindeer herd in the Metropolitan Toronto Zoo (8) and two mule deer (*Odocoileus hemionus*) a year apart in Bighorn Basin, Wyoming (68). The actual prevalence of infec-

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tion and significance of DPV as a pathogen remain unknown. Clinical presentation of DPV infection includes keratoconjunctivitis and proliferative-ulcerative skin lesions on the face and feet. In the Wyoming cases, the disease was thought to be a significant factor in the death of the animals (68). Virions resembling vaccinia virus (VACV) were observed by electron microscopy upon examination of skin sections of DPV-infected animals (8, 68). Here we present genome analysis of two DPVs isolated in Wyoming. The data suggest that DPV represents a new genus within the *Chordopoxvirinae* (48).

MATERIALS AND METHODS

Virus strains, DNA isolation, cloning, sequencing, and sequence analysis. DPVs W-848-83 (W83) and W-1170-84 (W84) were isolated in Basin, Wyoming, in 1983 and in Burlington, Wyoming, in 1984, respectively, from skin lesions of free-ranging mule deer. Viral genomic DNA was isolated from uncloned stocks as previously described (65) after three passages of W83 in fetal lamb kidney cells and W84 in Vero cells. Random DNA fragments were obtained by incomplete enzymatic digestion with *Tsp509I* endonuclease (New England Biolabs, Beverly, Mass.), and DNA fragments larger than 1.0 kbp were cloned and used in dideoxy sequencing reactions as previously described (2). Reaction products were analyzed on an ABI PRISM 3700 automated DNA sequencer (Applied Biosystems, Foster City, Calif.). Sequence data were assembled with the Phrap and CAP3 software programs (22, 36), and gaps were closed as described previously (1). Final DNA consensus sequences for W83 and W84 genomes represented on average 8.6- to 9.2-fold redundancy at each base position, with Consed estimated error rates of 0.3 and 0.9 per 10 kbp, respectively (22, 23, 30), and no significant genetic heterogeneity.

Genome DNA composition, structure, repeats, and restriction enzyme patterns were analyzed as previously described (1) by using the GCG version 10 software package (18). Pairwise genomic alignments were done by using WABA (Jim Kent; http://www.cse.ucsc.edu/~kent/), and multiple genomic and protein alignments were done with DIALIGN (44) and/or CLUSTAL (58) alignment programs. Open reading frames (ORFs) longer than 30 codons were evaluated for coding potential as previously described (2). All ORFs with coding potential and ORFs greater than 60 codons were subjected to homology searches as previously described (1, 2). Based on these criteria, 172 ORFs were annotated as potential genes and numbered from left to right. Phylogenetic comparisons were performed on complete, concatenated datasets of 79 proteins encoded in conserved central core regions homologous to those located between VACV F17L and A24R. Alignment data were also manually edited with SEAVIEW to exclude ambiguously aligned gap and low-complexity regions prior to phylogenetic analysis (26). Phylogenetic analyses on unedited and edited protein alignments were done by using the PHYLO_WIN and TREE-PUZZLE version 5.2 software packages (26, 54).

Nucleotide sequence accession numbers. The genome sequences of DPVs W83 and W84 have been deposited in GenBank under accession numbers AY689436 and AY689437, respectively.

RESULTS AND DISCUSSION

DPV genome organization. Genomic sequences of DPV field isolates W83 and W84 were assembled into contiguous sequences of 166,259 and 170,560 bp, respectively, containing approximately 73% A+T. Terminal hairpin loops were not sequenced, but the assembled genome contained the putative telomeric resolution sequences at position 30 for W83 (ATTTATATACCTAAAAAAAAGATAAAAACA) and at position 122 for W84 (ATTTATATACCTTAAAAAAAAGATAAAACA), with the leftmost nucleotide of each assembled genome arbitrarily designated base 1. Like other poxviruses, DPV genomes contain a large, unique coding region (95% nucleotide identity between W83 and W84) bounded by two identical inverted terminal repeat (ITR) regions. Assembled ITRs of W83 and W84 are 5,012 and 7,061 bp, respectively, and contain significant differences in the lengths of tandem repeat regions (1.5 and 3.5 kbp, respectively). W83 contains 13 and 20 copies of a 39- and a 48-bp repeat, respectively, while W84 contains 109 and 2 copies of a 31- and a 48-bp repeat, respectively. All DPV repeats in this region share a 15-bp motif (GGGAAAG GGATAAAA).

W83 and W84 genomes contain 169 and 170 genes, respectively, coding for proteins of 53 to 1,953 amino acids and representing an approximate 96% coding density. The central DPV genomic region contains homologues of conserved poxviral genes involved in basic replicative mechanisms (including viral transcription, RNA modification, and DNA replication), virion structure, and assembly of intracellular mature and extracellular enveloped virions (Table 1) (45). DPV genomes also contain a complement of potential nucleotide metabolism genes similar to those of leporipox, capripox, swinepox, and yatapox viruses, including homologues of genes for thymidine kinase, dUTPase, and the small subunit of ribonucleotide reductase. A gene for the large subunit of ribonucleotide reductase is absent. DPV terminal genomic regions contain genes with functions likely affecting viral virulence, host range, and immune response modulation, many of which are members of gene families or have homologues in other poxviruses (Table 1).

Putative DPV virulence and host range proteins include those similar to secreted cytokine receptors (R) or binding proteins (BP), including gamma interferon receptor (IFN-γR; DPV010), interleukin-1 receptor (IL-1R; DPV015), IFN-α/βBP (DPV147), IL-18BP (DPV021), major histocompatibility complex class I (MHC-I)-like tumor necrosis factor binding protein (TNFBP; DPV008), and two TNFR-like proteins (DPV016 and DPV005). DPV016 resembles a carboxyl-terminal fragment of viral TNFR-II, proteins present in several poxviral genera, and DPV005 resembles cellular CD30, a homologue of which has been found in orthopoxviruses cowpox virus, ectromelia virus, monkeypox virus, and variola virus (Table 1). Potential membrane-bound DPV immunomodulators include ORFs similar to cellular type 8 CC-chemokine receptor (DPV013 and DPV162), CD47 (DPV139), and OX-2 (DPV153). DPV proteins that are likely to inhibit intracellular signaling involved in immunological responses and/or apoptosis include homologues of VACV E3L and K3L (DPV042 and DPV020, respectively), myxoma virus M004 and M011R (DPV004 or DPV169 and DPV022, respectively), and serpins (DPV003, DPV018, DPV167, and DPV170). Notably, serpins DPV003 and DPV170, located in the ITR, are the least similar to known poxviral serpins but do contain the Asp P1 residue similar to poxvirus serpins known to affect inflammation, apoptosis, and virulence through inhibition of caspases 1 and 8 and granzyme B (57). DPV152 and DPV157 share similarity with VACV A52R and VACV N1L, respectively, proteins which affect intracellular signaling through IL-1R/Toll-like receptors and/or TNF superfamily receptors to affect viral virulence (10, 19, 33, 38).

DPV encodes six proteins containing ankyrin repeat motifs, two kelch-like proteins, and a protein similar to rabbit fibroma virus N1R (DPV155), proteins with homologues affecting poxviral virulence, host range, immunopathology, and/or apoptosis (Table 1) (11, 27, 37, 51). Other ORFs potentially affecting

TABLE 1. Characterization of DPV ORFs

ORF number	W83 position (length)[a]	W84 position (length)[a]	% Identity[b]	Best match[c]									Description, putative function, and/or name[f]
				Accession no.[d]	Species and description[d]	% Identity	LSDV[e]		SWPV[e]		VACV[e]		
							ORF	% Identity[b]	ORF	% Identity[b]	ORF	% Identity[b]	
DPV001	2176–1715 (154)	4278–3817	95	P18387	SPPV T3A	54	LSDV001	53	SPV001	54	B15R	35	
DPV002	2754–2263 (164)	4861–4364 (166)	86				**LSDV002**	43	SPV002	38			
DPV003	4057–2975 (361)	6176–5085 (364)	88		YLDV 149R	29	LSDV149	27	SPV145	25	C12L	26	Serpin-like protein
DPV004	4788–4066 (241)	6910–6185 (242)	93				**LSDV003**	46			B9R	42	ER-localized apoptosis regulator
DPV005		7351–7043 (103)		X94355	CPXV C5L	54					A53R	31	CD30-like protein
DPV006	5312–5106 (69)	7628–7422	67	P22389	*Mus musculus* endothelin 2	39							Endothelin precursor
DPV007	6429–5365 (355)	8745–7681	91				**LSDV007**	46			C10L	35	
DPV008	7511–6492 (340)	9808–8798 (337)	79						**SPV003**	57			MHC-like TNF binding protein
DPV009	8278–7547 (244)	10575–9844	92				LSDV009	26	**SPV007**	52	C1L	26	
DPV010	9191–8376 (272)	11488–10670 (273)	86				**LSDV008**	35	SPV008	36	B8R	35	Soluble IFN-γ receptor
DPV011	9972–9253 (240)	12269–11604 (222)	95				**LSDV009**	41			N2L	30	
DPV012	10358–10017 (114)	12632–12351 (94)	97						**SPV009**	40			
DPV013	11331–10294 (346)	13629–12592	94		YLDV 7L	50	LSDV011	39	SPV146	29			CC-chemokine receptor-like protein
DPV014	12013–11387 (209)	14313–13687	93				**LSDV012**	48	SPV142	28	C19L	23	Ankyrin repeat protein
DPV015	12743–12066 (226)	15045–14365 (227)	68				**LSDV006**	32			B16R	23	IL-1 receptor-like protein
DPV016	13391–12804 (196)	15722–15126 (199)	67	AF012825	ECTV EVM008	29							Viral TNFR II-like C-terminal fragment
DPV017	14095–13418 (226)	16432–15749 (228)	86		YLDV 9L	40					M2L	29	
DPV018	15271–14126 (382)	17612–16464 (383)	94		YLDV 10L	44	LSDV149	29	SPV145	26	K2L	27	Serpin-like protein
DPV019	17220–15292 (643)	19558–17630	93		YLDV 11L	52	LSDV145	25	SPV141	24	B4R	24	Ankyrin repeat protein
DPV020	17490–17224 (89)	19828–19562	98				**LSDV014**	56			K3L	45	eIF-2α-like PKR inhibitor
DPV021	17959–17537 (141)	20299–19880 (140)	77		YLDV 14L	46	LSDV015	40	SPV011	39			IL-18 binding protein
DPV022	18518–17982 (179)	20859–20323	98		YMTV 16L	38	LSDV017	34	SPV012	32	F1L	27	Antiapoptotic membrane protein
DPV023	19002–18571 (144)	21343–20912	97				LSDV018	68	**SPV013**	71	F2L	59	dUTPase
DPV024	19424–19038 (129)	21766–21380	92		YLDV 18L	40			**SPV014**	33			
DPV025	21055–19469 (529)	23397–21811	95				LSDV019	40	**SPV015**	44	F3L	23	Kelch-like protein
DPV026	22092–21130 (321)	24434–23472	97				**LSDV020**	78	SPV016	76	F4L	76	Ribonucleotide reductase small subunit
DPV027	22407–22123 (95)	24763–24479	86		YMTV 21L	28	LSDV021	29	SPV017	31			
DPV028	22734–22459 (92)	25090–24815	91				**LSDV022**	60	SPV018	28			
DPV029	22939–22745 (65)						**LSDV023**	63					
DPV030		25381–25139 (81)							**SPV019**	46			

TABLE 1—*Continued*

ORF number	W83 position (length)[a]	W84 position (length)[a]	% Identity[b]	Best match[c]									Description, putative function, and/or name[f]
				Accession no.[d]	Species and description[d]	% Identity	LSDV[e]		SWPV[e]		VACV[e]		
							ORF	% Identity[b]	ORF	% Identity[b]	ORF	% Identity[b]	
DPV031	23655–23011 (215)	26563–25919	95				LSDV024	57	**SPV021**	60	F9L	52	
DPV032	24970–23639 (444)	27878–26547	99				LSDV025	81	**SPV022**	82	F10L	72	Serine/threonine protein kinase
DPV033	26136–24997 (380)	29047–27905 (381)	93				LSDV026	31	**SPV023**	43	F11L	32	
DPV034	28123–26168 (652)	31034–29079	95				LSDV027	50	**SPV024**	57	F12L	38	EEV maturation protein
DPV035	29289–28165 (375)	32201–31077	97				**LSDV028**	75	SPV025	72	F13L	55	Palmitylated virion envelope protein
DPV036	29523–29314 (70)	32435–32226	99	AF012825	ECTV EVM037	32			SPV026	34	F14L	32	
DPV037	30238–29795 (148)	33150–32707	97		YLDV 29L	66	LSDV029	64	SPV027	63	F15L	64	
DPV038	30964–30305 (220)	33877–33218	94				LSDV030	43	**SPV028**	49	F16L	36	
DPV039	31030–31353 (108)	33946–34266 (107)	97		YLDV 31R	72	LSDV031	70	SPV029	70	F17L	61	DNA-binding virion protein
DPV040	32765–31356 (470)	35678–34269	99				**LSDV032**	78	SPV030	76	E1L	67	Poly(A) polymerase large subunit
DPV041	34993–32798 (732)	37906–35711	98				LSDV033	53	**SPV031**	60	E2L	43	
DPV042	35662–35066 (199)	38575–37979	91				**LSDV034**	48	SPV032	46	E3L	38	dsRNA binding PKR inhibitor
DPV043	36446–35715 (244)	39359–38628	99				LSDV036	65	**SPV033**	72	E4L	55	RNA polymerase subunit RP030
DPV044	36554–37795 (414)	39467–40702 (412)	93				**LSDV035**	40			E5R	29	
DPV045	37833–39530 (566)	40740–42437	99				**LSDV037**	79	SPV034	72	E6R	62	
DPV046	39559–40359 (267)	42466–43266	98				**LSDV038**	83	SPV035	79	E8R	69	
DPV047	43395–40366 (1010)	46305–43273(1011)	99		MYXV m34L	76	LSDV039	75	SPV036	78	E9L	67	DNA polymerase
DPV048	43433–43717 (95)	46343–46627	94				LSDV040	71	**SPV037**	81	E10R	68	IMV redox protein
DPV049		47025–46630 (132)					**LSDV041**	52			E11L	46	Virion core protein
DPV050	45992–43956 (679)	49048–47015 (678)	97		YLDV 42L	49	LSDV042	46	SPV038	47	O1L	37	
DPV051	47089–46151 (313)	50148–49210	98				**LSDV043**	76	SPV039	72	I1L	71	DNA-binding virion core protein
DPV052	47321–47079 (81)	50377–50135	93				**LSDV044**	53	SPV040	54	I2L	44	
DPV053	48140–47325 (272)	51196–50381	99				LSDV045	63	**SPV041**	70	I3L	53	DNA-binding phosphoprotein
DPV054	48720–48226 (165)	51774–51283 (164)	89	AB005148	*Bos taurus* IL-1 receptor antagonist	53							IL-1 receptor antagonist
DPV055	48993–48760 (78)	52042–51809	99		YLDV 46L	78	LSDV046	64	SPV043	61	I5L	47	IMV membrane protein
DPV056	50183–49017 (389)	53226–52066 (387)	97		YMTV 47L	54	LSDV047	56	SPV044	54	I6L	51	
DPV057	51474–50179(432)	54517–53222	99				**LSDV048**	80	SPV045	78	I7L	68	Virion core protein
DPV058	51480–53528 (683)	54523–56574 (684)	97				LSDV049	65	**SPV046**	66	I8R	57	RNA helicase
DPV059	55321–53531 (597)	58367–56577	99				LSDV050	66	**SPV047**	67	G1L	56	Metalloprotease
DPV060	55647–56309 (221)	58693–59355	97				**LSDV051**	56	SPV048	53	G2R	45	Transcriptional elongation factor
DPV061	55653–55321 (111)	58699–58367	98	AF170722	SFV gp046L	68	LSDV052	58	SPV049	59	G3L	45	
DPV062	56656–56282 (125)	59702–59328	100				**LSDV053**	80	SPV050	65	G4L	52	Glutaredoxin

TABLE 1—*Continued*

ORF number	W83 position (length)[a]	W84 position (length)[a]	% Identity[b]	Best match[c]									Description, putative function, and/or name[f]
				Accession no.[d]	Species and description[d]	% Identity	LSDV[e]		SWPV[e]		VACV[e]		
							ORF	% Identity[b]	ORF	% Identity[b]	ORF	% Identity[b]	
DPV063	56659–57960 (434)	59705–61006	99				**LSDV054**	64	SPV051	63	G5R	45	
DPV064	57964–58152 (63)	61010–61198	98		YLDV 55R	85	LSDV055	86	SPV052	84	G5.5R	33	RNA polymerase subunit RPO7
DPV065	58155–58658 (168)	61201–61704	99				LSDV056	61	**SPV053**	63	G6R	45	
DPV066	59806–58682 (375)	62858–61734	98				**LSDV057**	62	SPV054	62	G7L	52	Virion core protein
DPV067	59836–60615 (260)	62888–63667	99				**LSDV058**	93	SPV055	92	G8R	84	Late transcription factor VLTF-1
DPV068	60655–61659 (335)	63707–64711	98		YLDV 59R	64	LSDV059	63	SPV056	59	G9R	52	Myristylated protein
DPV069	61663–62409 (249)	64715–65461	100				**LSDV060**	87	SPV057	84	L1R	70	Myristylated IMV envelope protein
DPV070	62457–62741 (95)	65509–65793	100				LSDV061	53	**SPV058**	56	L2R	31	
DPV071	63719–62727 (331)	66771–65779	99				**LSDV062**	72	SPV059	68	L3L	50	
DPV072	63744–64499 (252)	66796–67551	100				LSDV063	81	**SPV060**	80	L4R	64	DNA-binding virion protein VP8
DPV073	64522–64911 (130)	67574–67963	99				**LSDV064**	63	SPV061	59	L5R	53	Membrane protein
DPV074	64871–65320 (150)	67923–68372	99				**LSDV065**	72	SPV062	64	J1R	59	Virion protein
DPV075	65320–65892 (191)	68372–68944	97				**LSDV066**	67	SPV063	69	J2R	67	Thymidine kinase
DPV076	65871–66551 (227)	69008–69604(199)	96				**LSDV067**	58	SPV064	47	C7L	35	Host range protein
DPV077	66571–67611 (347)	69623–70663	99				**LSDV068**	82	SPV065	80	J3R	74	Poly(A) polymerase small subunit
DPV078	67529–68083 (185)	70581–71135	99				LSDV069	79	**SPV066**	81	J4R	69	RNA polymerase subunit RPO22
DPV079	68503–68093 (137)	71555–71145	100				**LSDV070**	73	SPV067	66	J5L	65	
DPV080	68579–72436 (1286)	71631–75488	99				LSDV071	86	**SPV068**	86	J6R	82	RNA polymerase subunit RPO147
DPV081	72974–72459 (172)	76026–75511	99	AF124517	SPPV H1L	83	LSDV072	84	SPV069	80	H1L	66	Protein-tyrosine kinase, assembly
DPV082	72990–73559 (190)	76042–76611	98				LSDV073	74	**SPV070**	73	H2R	65	
DPV083	74548–73571 (326)	77600–76623	100				**LSDV074**	61	SPV071	57	H3L	39	IMV envelope protein p35
DPV084	76948–74552 (799)	80000–77604	99				**LSDV075**	83	SPV072	82	H4L	71	RNA polymerase-associated RAP94
DPV085	77116–77691 (192)	80168–80743	99		MYXV m73R	55	LSDV076	46	SPV073	49	H5R	42	Late transcription factor VLTF-4
DPV086	77734–78675 (314)	80786–81727	99				**LSDV077**	73	SPV074	67	H6R	66	DNA topoisomerase
DPV087	78699–79136 (146)	81751–82188	99				LSDV078	62	**SPV075**	63	H7R	42	
DPV088	79187–81715 (843)	82239–84767	99				LSDV079	73	**SPV076**	72	D1R	66	mRNA capping enzyme, large subunit
DPV089	82146–82889 (248)	85198–85941	98				**LSDV081**	45	SPV078	41	D3R	36	Virion protein
DPV090	82147–81680 (156)	85199–84732	99				LSDV080	45	**SPV077**	45	D2L	39	Virion protein
DPV091	82889–83542 (218)	85941–86594	100		MYXV m79R	78	LSDV082	77	SPV079	76	D4R	68	Uracil DNA glycosylase
DPV092	83577–85934 (786)	86629–88986	100		YLDV 83R	80	LSDV083	78	SPV080	80	D5R	69	NTPase, DNA replication
DPV093	85934–87838 (635)	88986–90890	100				LSDV084	89	**SPV081**	91	D6R	82	Early transcription factor VETFs
DPV094	87872–88363 (164)	90924–91415	99				**LSDV085**	83	SPV082	80	D7R	67	RNA polymerase subunit RPO18
DPV095	88411–89043 (211)	91463–92095	99				**LSDV086**	70	SPV083	65	D9R	59	mutT motif
DPV096	89046–89795 (250)	92098–92847	99		YLDV 87R	65	LSDV087	67	SPV084	64	D10R	48	mutT motif
DPV097	91724–89820 (635)	94775–92871	100				**LSDV088**	78	SPV085	76	D11L	73	NPH-I, transcription termination factor
DPV098	92623–91763 (287)	95674–94814	100				**LSDV089**	78	**SPV086**	82	D12L	77	mRNA capping enzyme, small subunit
DPV099	94305–92656 (550)	97356–95707	100				LSDV090	80	**SPV087**	81	D13L	74	Rifampin resistance protein
DPV100	94787–94335 (151)	97838–97386	100		MYXV m89L	71	LSDV091	68	SPV088	64	A1L	64	Late transcription factor VLTF-2
DPV101	95494–94823 (224)	98545–97874	100	AB015885	YMTV Yb-B9L	87	LSDV092	88	SPV089	88	A2L	86	Late transcription factor VLTF-3
DPV102	95721–95494 (76)	98772–98545	99		MYXV m91L	75	LSDV093	71	SPV090	68	A2.5L	33	

TABLE 1—*Continued*

ORF number	W83 position (length)[a]	W84 position (length)[a]	% Identity[b]	Best match[c]									Description, putative function, and/or name[f]
				Accession no.[d]	Species and description[d]	% Identity	LSDV[e]		SWPV[e]		VACV[e]		
							ORF	% Identity[b]	ORF	% Identity[b]	ORF	% Identity[b]	
DPV103	97700–95745 (652)	100751–98796	100				LSDV094	76	**SPV091**	81	A3L	66	Virion core protein P4b
DPV104	98213–97761 (151)	101264–100812	99				**LSDV095**	47	SPV092	43	A4L	28	Virion core protein, morphogenesis
DPV105	98253–98762 (170)	101304–101810 (169)	98				**LSDV096**	68	SPV093	63	A5R	64	RNA polymerase subunit RPO19
DPV106	99892–98771 (374)	102940–101819	100				LSDV097	77	**SPV094**	76	A6L	56	
DPV107	102066–99922 (715)	105114–102970	99				**LSDV098**	81	SPV095	81	A7L	71	Early transcription factor VETF
DPV108	102126–103007 (294)	105174–106055	99		MYXV m97R	72	LSDV099	70	SPV096	70	A8R	63	Intermediate transcription factor VITF-3
DPV109	103263–103021 (81)	106311–106069	99				LSDV100	79	**SPV097**	82	A9L	71	IMV membrane protein
DPV110	106011–103267 (915)	109059–106315	99				LSDV101	71	**SPV098**	76	A10L	52	Virion core protein P4a
DPV111	106026–106976 (317)	109074–110024	99		YLDV 102R	78	LSDV102	77	**SPV099**	76	A11R	54	
DPV112	107555–106986 (190)	110603–110034	97				**LSDV103**	61	SPV100	57	A12L	49	Virion core protein
DPV113	107840–107622 (73)	110887–110669	97				**LSDV104**	63	SPV101	53	A13L	36	IMV membrane protein
DPV114	108203–107928 (92)	111246–110971	100		YLDV 105L	86	LSDV105	78	SPV102	85	A14L	54	IMV membrane protein
DPV115	108381–108223 (53)	111424–111266	100		YLDV 106L	84	LSDV106	74	SPV103	77	A14.5L	55	Virulence factor
DPV116	108655–108374 (94)	111698–111417	100	AB015885	YMTV Yb-B23L	54	LSDV107	54	SPV104	52	A15L	49	
DPV117	109781–108642 (380)	112827–111685 (381)	98				**LSDV108**	68	SPV105	66	A16L	51	Myristylated membrane protein
DPV118	110402–109812 (197)	113449–112859	98		YLDV 109L	75	LSDV109	66	SPV106	73	A17L	41	TMV membrane protein
DPV119	110417–111862 (482)	113464–114909	98				LSDV110	59	**SPV107**	64	A18R	54	DNA helicase, elongation
DPV120	112073–111849 (75)	115120–114896	100		YLDV 111L	76	LSDV111	73	SPV108	79	A19L	71	
DPV121	112420–113703 (428)	115467–116750	99				**LSDV112**	55	SPV109	55	A20R	44	DNA polymerase processivity factor
DPV122	112421–112077 (115)	115468–115124	100				**LSDV113**	64	SPV110	68	A21L	59	
DPV123	113687–114229 (181)	116734–117276	100				LSDV114	67	**SPV111**	72	A22R	72	Holliday junction resolvase
DPV124	114216–115394 (393)	117263–118441	99				**LSDV115**	65	**SPV112**	64	A23R	62	Intermediate transcription factor VITF-3
DPV125	115423–118887 (1155)	118470–121934	99				**LSDV116**	91	SPV113	89	A24R	83	RNA polymerase subunit RPO132
DPV126	119300–118890 (137)	122344–121937 (136)	95				LSDV117	47	**SPV114**	55	A27L	30	Fusion protein
DPV127	119723–119304 (140)	122767–122348	98	AF170722	SFV gp116L	70	LSDV118	69	SPV115	71	A28L	59	IMV protein
DPV128	120641–119742 (300)	123685–122786	100				**LSDV119**	69	SPV116	68	A29L	61	RNA polymerase subunit RPO35
DPV129	120837–120613 (75)	123881–123657	99	AB018404	YMTV Yb-D13L	72	LSDV120	72	SPV117	67	A30L	57	IMV, membrane
DPV130	121027–121476 (150)	124069–124527 (153)	95	AF438165	CMLV 150	47					A31R	53	
DPV131	122253–121492 (254)	125304–124543	100		MYXV m120L	88	LSDV121	88	SPV118	82	A32L	59	DNA packaging, virus assembly
DPV132	122383–122958 (192)	125433–126008	96		YLDV 122R	48	LSDV122	37	SPV119	46	A33R	28	EEV glycoprotein
DPV133	122982–123485 (168)	126032–126535	100				LSDV123	56	**SPV120**	69	A34R	51	EEV protein
DPV134	123533–124075 (181)	126583–127125	99				LSDV124	43	**SPV121**	45	A35R	37	
DPV135	124111–124971 (287)	127157–128014 (286)	98				**LSDV125**	45	**SPV122**	48			
DPV136	125031–125675 (215)	128074–128730 (219)	93				LSDV126	33	**SPV123**	46	A36R	24	EEV glycoprotein
DPV137	125741–126562 (274)	128796–129617	99				LSDV127	46	**SPV124**	49	A37R	32	
DPV138	127452–127883 (144)	130507–130938	97		YLDV 129R	50							Hypothetical protein
DPV139	127480–126584 (299)	130535–129639	98		MYXV m128L	46	LSDV128	40	SPV125	44	A38L	26	CD47-like protein
DPV140	127918–128220 (101)	130973–131317 (115)	85				LSDV129	30	SPV126	23			

TABLE 1—*Continued*

ORF number	W83 position (length)[a]	W84 position (length)[a]	% Identity[b]	Best match[c]								Description, putative function, and/or name[f]
				Accession no.[d]	Species and description[d]	% Identity	LSDV[e]		SWPV[e]		VACV[e]	
							ORF	% Identity[b]	ORF	% Identity[b]	ORF	% Identity[b]	
DPV141	128291–128536 (82)	131384–131629	99				**LSDV130**	53	SPV127	47			
DPV142	129596–128550 (349)	132691–131645	98						**SPV128**	56	A44L	46	Beta-hydroxysteroid dehydrogenase
DPV143	129652–130143 (164)	132747–133238	99				**LSDV131**	64	SPV129	62	A45R	36	Superoxide dismutase-like protein
DPV144	131047–130400 (216)	134133–133486	97	AF320596	*Mus musculus* C lectin-related protein	52					A40R	27	C-type lectin-like protein
DPV145	131243–132928 (562)	134328–136013	99				LSDV133	64	**SPV130**	67	A50R	53	DNA ligase-like protein
DPV146	133038–138896(1953)	136122–141971(1950)	96				**LSDV134**	53	SPV131	52			Variola virus B22R-like protein
DPV147a	138920–139969 (350)	142021–142308 (96)	81				LSDV135	32	**SPV132**	36	B19R	32	IFN-α/β binding protein (fragment)
DPV147b		142418–143050 (211)	89		YLDV 136R	29	LSDV135	30	SPV132	31	B19R	34	IFN-α/β binding protein fragment
DPV148	140001–140564 (188)	143082–143645	96			45	LSDV136	40	**SPV133**	46	K7R	23	
DPV149	140620–141645 (342)	143702–144727	99			47	**LSDV137**	47	SPV134	47	A51R	31	
DPV150	142576–141671 (302)	145647–144748 (300)	95	AF030894	MYXV α2,3-sialyltransferase	44							α2,3-sialyltransferase
DPV151	143540–142584 (319)	146611–145655	99	AJ010865	*Bos taurus* MHC class I antigen	27							MHC class I-like protein
DPV152	143630–144205 (192)	146701–147276	98		MYXV m139R	53			SPV135	54	A52R	34	IL-1R/TLR signaling inhibitor
DPV153	144262–144822 (187)	147333–147893	96				**LSDV138**	42			A56R	26	Ig domain OX-2-like protein
DPV154	144859–145803 (315)	147930–148874	98				**LSDV139**	66	SPV137	63	B1R	49	Serine/threonine protein kinase
DPV155	145827–146561 (245)	148898–149632	99				**LSDV140**	51	SPV138	43			N1R-like RING finger host range protein
DPV156	146642–147526 (295)	149713–150597	98				LSDV141	41	**SPV139**	53	C3L	36	EEV host range protein
DPV157	147558–147971 (138)	150629–151042	96				**LSDV142**	39			N1L	42	Virulence factor
DPV158	148004–148933 (310)	151075–152004	95				**LSDV143**	53	SPV140	54			Tyrosine protein kinase-like protein
DPV159	148966–149436 (157)	152037–152507	99				**LSDV150**	50			A52R	22	
DPV160	149486–151123 (546)	152557–154194	96				**LSDV151**	51	SPV136	30	A55R	30	Kelch-like protein
DPV161	151190–153112 (641)	154261–156183	95				LSDV145	46	**SPV141**	50	C9L	23	Ankyrin repeat protein
DPV162	153187–154434 (416)	156252–157457 (402)	68				LSDV011	36	**SPV146**	46			CC-chemokine receptor-like protein
DPV163	154548–155477 (310)			AF191297	*Cavia porcellus* TGF-β	28							TGF-β1
DPV164	155544–157046 (501)	157707–159209	93				LSDV147	44	**SPV142**	46	B4R	21	Ankyrin repeat protein

TABLE 1—*Continued*

ORF number	W83 position (length)[a]	W84 position (length)[a]	% Identity[b]	Best match[c]									Description, putative function, and/or name[f]
				Accession no.[d]	Species and description[d]	% Identity	LSDV[e]		SWPV[e]		VACV[e]		
							ORF	% Identity[b]	ORF	% Identity[b]	ORF	% Identity[b]	
DPV165	157088–158536(483)	159251–160699	94				**LSDV148**	40	SPV143	39	C9L	24	Ankyrin repeat protein
DPV166	158557–160062(502)	160752–162230(493)	96				**LSDV152**	39	SPV144	36	B4R	26	Ankyrin repeat protein
DPV167	160101–161105(335)	162261–163268(336)	92		YLDV149R	48	LSDV149	47	SPV145	42	C12L	35	Serpin-like protein
DPV168	161118–161408 (97)	163305–163586 (94)	91				LSDV153	45	**SPV147**	52			
DPV169	161472–162194(241)	163651–164376(242)	93				**LSDV154**	46			B9R	42	ER-localized apoptosis regulator
DPV170	162203–163285(361)	164385–165476(364)	88		YLDV149R	29	LSDV149	27	SPV145	25	C12L	26	Serpin-like protein
DPV171	163506–163997(164)	165700–166197(166)	86				**LSDV155**	43	SPV149	38			
DPV172	164084–164545(154)	166283–166744	95	P18387	SPPV T3A	54	LSDV156	53	SPV150	54	B15R	35	

[a] Lengths of ORFs are in codons. W84 ORF lengths are presented only if differing from that of W83.
[b] Percent amino acid identity was obtained by FASTA analysis.
[c] Best scoring matches in BLAST analysis.
[d] Accession numbers, species, and descriptions indicated are those different from lumpy skin disease virus (LSDV) and swinepox virus (SWPV). Other abbreviations are as follows: CPXV, cowpox virus; ECTV, ectromelia virus; MYXV, myxoma virus; SFV, rabbit (Shope) fibroma virus; SPPV, sheeppox virus; YLDV, Yaba-like disease virus; YMTV, yaba monkey tumor virus. GenBank database accession numbers are as follows: MYXV, AF170726; SFV, AF170722; and YLDV, AJ293568.
[e] Best-matching ORFs from LSDV (accession no. AF325528), SWPV (accession no. AF410153), and VACV strain Copenhagen (accession no. M35027 and AF516337) genomes. Highlighted ORFs indicate best overall match to W84 in similarity searches.
[f] Function was deduced from the degree of similarity to known genes and Prosite signatures. Abbreviations are as follows: IMV, intracellular mature virion; EEV, extracellular enveloped virion; eIF-2α, α subunit of eukaryotic initiation factor 2; dsRNA, double-stranded RNA.

DPV-host interaction include homologues of poxvirus β-hydroxysteroid dehydrogenase (DPV142), superoxide dismutase (DPV143), α2,3-sialyltransferase (DPV150), and Tyr protein kinase-like protein (DPV158). Although many of these terminally located genes have similarity to those found in other poxviruses, this unique complement likely underlies DPV mechanisms of virulence and host range.

Notable host range and immunomodulatory genes. DPVs contain several genes which are either completely novel within the *Poxviridae* or represent unique forms of cellular-like genes present in other poxviruses. Notably, some of these genes represent insertions in regions otherwise syntenic with other poxviruses (Table 1). These genes, likely involved in viral pathogenesis, encode proteins similar to cellular endothelin, IL-1R antagonist (IL-1Ra), transforming growth factor β1 (TGF-β1), C-type lectin-like receptors, and MHC-I.

DPV006 resembles endothelins (ETs), three potent vasoactive 21-amino-acid peptides (ET 1 to ET 3) with important roles in vascular homeostasis, and the structurally related snake venom sarafotoxins (Fig. 1A) (Table 1). ETs are synthesized as large precursors from which 40- to 90-amino-acid amino-terminal and 110- to 120-amino-acid carboxyl-terminal domains are sequentially removed by endopeptidases and endothelin-converting enzymes to yield biologically active ET peptides (49).

DPV006 encodes an ET precursor-like protein including an amino-terminal signal peptide and a highly conserved Arg/Lys-Arg-Cys tripeptide endopeptidase cleavage site (positions 47 to 49) (Fig. 1A). The lack of a carboxyl-terminal domain in DPV006 suggests that endothelin-converting enzyme-mediated cleavage is not required for activation (52). Although W83 and W84 ET-like peptides are only 52% identical, both peptides contain two predicted disulfide bonds and conserved residues which are important for ET 1 and 2 receptor binding and biological activity (Fig. 1A) (49). Upstream nucleotide sequences resembling early poxviral promoters suggest that DPV006 is expressed as an early gene.

ETs are produced primarily by endothelial cells, but also by epithelial cells and neurons, and exert their actions in a paracrine-autocrine fashion by interacting with G protein-coupled receptors expressed in vascular smooth muscle cells, endothelial cells, and, to a lesser extent, other cell types (29). Mammalian ETs have been implicated in a number of airway, pulmonary vascular, and cardiovascular disorders and in chronic and acute inflammatory diseases (5, 29, 34). ET 1 binding to smooth muscle cell receptors leads to vasoconstriction, cytokine production, cell growth, and inflammatory cell recruitment, while binding to endothelial receptors has been associated with nitric oxide release and prevention of apoptosis (5, 34). DPV ETs may have similar functions in the host, conceivably contributing to the marked proliferative and necrotizing character of DPV-induced lesions (68). Alternatively, DPV006 may function as an ET antagonist, interfering with normal host ET functions. DPV006 represents a second poxviral gene with similarity to host genes primarily associated with vascular physiology and, like parapoxvirus vascular endothelial growth factor, may have a significant role in virus virulence (53).

DPV054 is similar to cellular IL-1Ra, an IL-1-like molecule which acts as a competitive inhibitor of IL-1 and antagonizes

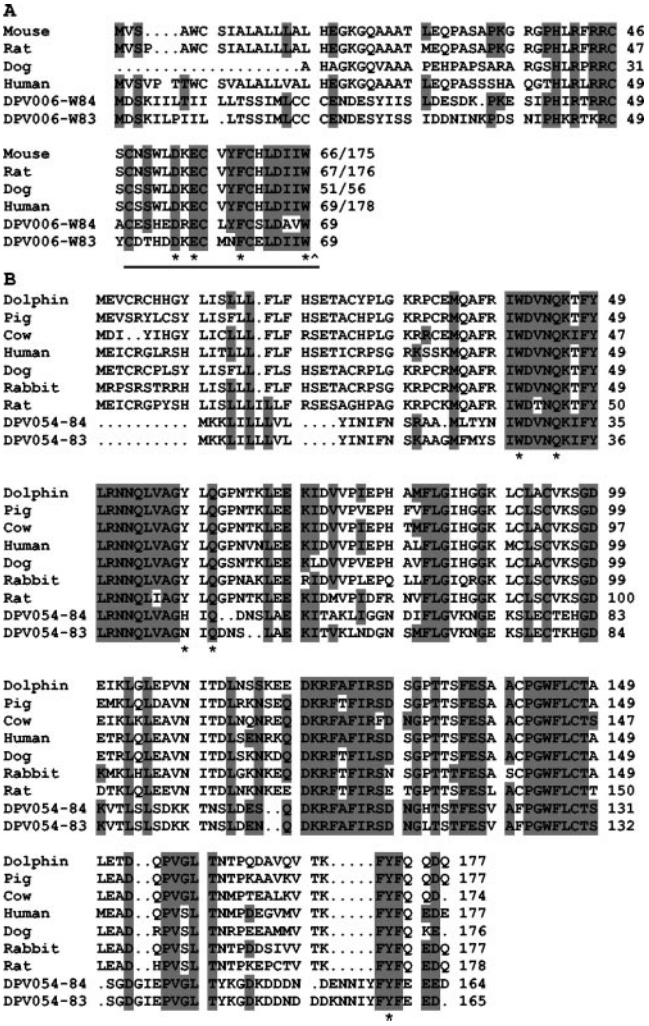

FIG. 1. Multiple amino acid alignment of DPV006 with endothelins and DPV054 with secreted IL-1Ra (isoform 1). Amino acid positions are indicated on the right; / indicates truncation of the amino acid sequence, * indicates residues critical for receptor binding, and ^ indicates cleavage sites. (A) Alignment of DPV006 to endothelin homologues. ET peptide is underlined. Accession numbers are the following: P22389, mouse; P23943, rat; P12064, dog; and P20800, human. (B) Alignment of DPV054 to IL-1Ra. Accession numbers are the following: AB038268, dolphin; L38849, pig; AB005148, cow; P18510, human; AY026462, dog; P26890, rabbit; and P25086, rat.

IL-1R signaling (Table 1) (Fig. 1B). DPV054 in W83 and W84 are 89% identical and contain a predicted amino-terminal signal peptide, indicating that DPV054, similar to mammalian secreted IL-1Ra isoforms, is secreted. Although overall identity between DPV and mammalian IL-1Ra is 41 to 53%, a region between residues 27 and 48 of DPV054 is 76 to 90% identical to mammalian IL-1Ra and contains 3 of 5 residues involved in the binding of IL-1Ra to IL-1R. A fourth residue involved in binding is also conserved in DPV054 (Tyr^{159}) (21).

The balance between IL-1 and IL-1Ra is known to influence the course of many inflammatory and viral diseases (6). For instance, elevated IL-1Ra levels relative to IL-1β levels in human immunodeficiency virus-infected patients may reflect direct stimulation of monocyte IL-1Ra production by human immunodeficiency virus (39). Correlation of increased IL-1Ra levels during rhinovirus infection with peak symptomatology and onset of clinical resolution has led to the suggestion that IL-1Ra may play a role in the resolution of this respiratory infection (70). Poxviruses inhibit proinflammatory IL-1β activity, often through multiple strategies, as evidenced in DPV, which encodes homologues of viral serpins, IL-1R, and an intracellular IL-1R/Toll-like receptor inhibitor, which affect IL-1 maturation or signaling (Table 1) (46). To our knowledge, DPV054 encodes the first viral protein with similarity to IL-1Ra, thus adding an additional poxviral strategy to block host IL-1β-mediated responses.

DPV163, present only in W83, is similar to TGF-β1 (Table 1). Although multiple copies of distantly related TGF-β homologues are present in avian poxviruses, this is the first observation of a TGF-β1-like gene in a mammalian chordopoxvirus (2). DPV163 encodes a 310-amino-acid protein that contains most of the TGF-β1 propeptide region and the TGF-β1 chain, including a TGF-β1 prosite motif and all 10 Cys residues necessary for disulfide bridge formation. As with avian poxviral TGF homologues, DPV163 is most similar to cellular TGF-β1 in the TGF-β1 chain region (50% amino acid identity between DPV163 residues 214 to 310).

DPV163 lacks features associated with the amino-terminal propeptide of eukaryotic TGF-β1, including 36 amino acids containing the predicted signal peptide, an Arg-Gly-Asp cell attachment site, and the Arg-His-Arg-Arg cleavage site (DPV163 amino acids 210 to 214) necessary for removal of the propeptide and subsequent activation of TGF-β1. Notably, DPV163 contains an Ile-Asn-Met-Pro motif (DPV163 amino acids 262 to 265) instead of the Trp-Ser-Leu-Asp motif important for the interaction of mammalian TGF-β1 with its receptor, for growth inhibition of epithelial cells, and for growth stimulation of fibroblasts (35). Divergence in the propeptide region, lack of the cleavage site needed for release of the mature peptide, and substitutions at significant sites suggest that processing or specificities of DPV163 may be distinct from cellular TGFs.

TGF-β1 suppresses multiple immune functions, including polyclonal antibody production, cytotoxic T lymphocytes, natural killer (NK) and lymphokine-activated killer cell activity, macrophage activation, and IL-1R expression (20). At the site of injury, TGF-β induces production of inflammatory cytokines IL-1, TNF, and IL-6 (20). TGF-β also affects cell growth, stimulating connective tissue cell growth and differentiation during neovascularization and wound healing while suppressing proliferation in most other cell types, including T and B lymphocytes, monocytes, and macrophages (7, 9, 15, 20, 47). DPV163 may affect similar host responses.

DPV144 encodes a protein with similarity to members of a glycoprotein gene superfamily which exhibit a C-type animal lectin domain (Table 1). DPV144 in W83 and W84 are 97% identical and are most similar to proteins encoded by the NK gene complex (NKC) and related cell receptors (40 to 60% amino acid identity). Similar to NKC proteins, DPV144 is a predicted type II integral membrane protein, containing four conserved Trp residues and two of the three Cys pairs believed to form intrachain disulfide bonds within the lectin-like do-

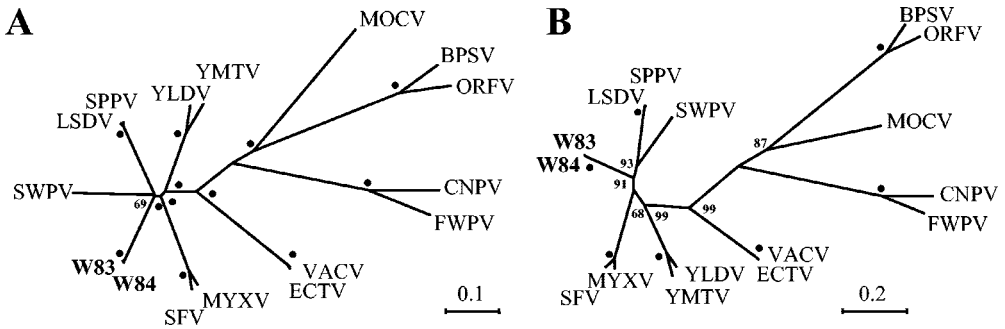

FIG. 2. Phylogenetic analysis of DPV proteins. Seventy-nine conserved ORFs between DPV039 and DPV125 were concatenated from W83 and W84 and aligned with similarly concatenated ORF sets from other ChPVs with DIALIGN. Unrooted trees were generated by neighbor-joining analysis with Poisson correction for multiple substitutions and 500 bootstrap replicates as implemented in PHYLO_WIN (A) and maximum likelihood analysis with JTT correction for multiple substitutions and 1,000 quartet puzzling steps as implemented in TREE-PUZZLE (B). Bootstrap (A) or support (B) values of 100% are marked with dots; values less than 100% are presented at appropriate nodes. Homologous protein sequences from the following viruses and accession numbers were compared: bovine popular stomatitis virus (BPSV), AY386265; canarypox virus (CNPV), AY318871; ectromelia virus (ECTV), AF012825; fowlpox virus (FWPV), AF198100; lumpy skin disease virus (LSDV), AF325528; molluscum contagiosum virus (MOCV), MCU60315; myxoma virus (MYXV), AF170726; orf virus (ORFV), AY386264; rabbit (Shope) fibroma virus (SFV), AF170722; sheeppox virus (SPPV), AY077833; swinepox virus (SWPV), AF410153; vaccinia virus (VACV), M35027; Yaba-like disease virus (YLDV), AJ293568; and Yaba monkey tumor virus (YMTV), AY386371. Similar results were obtained by using an alignment manually edited to include only unambiguously aligned sites (20,132 of 30,019 sites) and using alignments generated with CLUSTAL W (data not shown).

main (69). DPV144 also resembles viral lectin-like proteins encoded by rat cytomegalovirus (45% amino acid identity), fowlpox virus (FPV239; 36% amino acid identity), and VACV (A40R; 27% amino acid identity). These rat cytomegalovirus and VACV proteins are not essential for virus growth in vitro (64, 66), and disruption of A40R attenuates VACV strain WR following intradermal but not intranasal inoculation of mice (59, 64). Although poxviral C-type lectin-like proteins share sequence similarity to NK cell receptors, evidence for a role of these proteins in NK cell activation or modulation is lacking.

DPV151 is most similar (27% identity over 187 amino acids) to cellular HLA class I histocompatibility antigen α chain precursors, containing putative extracellular α1, α2, and α3 domains, connecting peptide, transmembrane domains, and four Cys residues necessary for disulfide bond formation (Table 1). DPV151 lacks amino-terminal signal peptide and carboxyl-terminal cytoplasmic domains homologous to cellular MHC-I, and the α 1 domain is not well conserved (data not shown). DPV151 is less similar to the MHC-I homologue from molluscum contagiosum virus (16% identity over 201 amino acids to MC080R) and to homologues of the MHC-I-like TNFBP of Tanapox virus and its homologues in DPV (DPV008), Yaba-like disease virus, and swinepox virus (21% identity over 254 amino acids to SPV003) (13). Notably, an MHC-I homologue encoded by murine cytomegalovirus (m144 gene) functions to protect against NK-mediated clearance of virus-infected cells (25). A similar function has not been demonstrated for poxviral MHC-I, but it is tempting to speculate that DPV151 could have a role in interfering with NK-mediated antiviral immunity.

Comparison of DPVs and other ChPV genera. DPVs are most similar to viruses of the capripoxvirus, suipoxvirus, leporipoxvirus, and yatapoxvirus (CSLY) genera, grouping with these viruses by phylogenetic analysis (Fig. 2). In addition, DPV and CSLY share distinctive genomic features, such as the insertion of the VACV C7L homologue (DPV076) between homologues of VACV J2R and J3R, the absence of A-type inclusion protein genes (VACV A25L/A26L), and more extensive gene colinearity (Table 1 and Fig. 2). Phylogenetic analysis also suggests that DPVs, capripoxviruses, and swinepox virus are monophyletic (Fig. 2). However, data indicate that DPV is a group as distinct as other ChPV genera are from each other (Fig. 2). Maximum likelihood analysis of whole genome sequences reveals distance estimates between DPV and other CSLY genera (0.654 to 0.754) on the same order of magnitude as those between established CSLY genera (0.505 to 0.725). Other genomic features distinguish DPV from other CSLY viruses, including the presence of DPV-specific genes and a homologue of VACV A31R, a gene otherwise present only in orthopoxviruses and avipoxviruses. Taken together, these data indicate that DPV represents a new poxvirus genus.

Despite the high degree of similarity between W83 and W84 genomes relative to other ChPV genera (Table 1 and Fig. 2), significant differences between these DPVs exist. While centrally located ORFs (DPV020 to DPV160) are the most conserved between DPVs (97% average amino acid identity), terminally located ORFs are less similar (88% average amino acid identity [Table 1]). Whole genome maximum likelihood distances between W83 and W84 (0.042) are less than distances between both sequenced viruses of the genus leporipoxvirus (0.166) but greater than distances between eight sequenced viruses of the genus capripoxvirus (0.023 to 0.034). Although W83 and W84 have similar gene orders and contents, in W84 two genes are absent (DPV030 and DPV163) and one gene is fragmented into two ORFs (DPV147a and DPV147b) by an in-frame stop, and in W83 three genes are absent (DPV005, DPV031, and DPV051). With the exception of DPV147, genomic indels of 165 to 860 bp are responsible for differences in gene content between W83 and W84. These include CD30-like, TGF-β-like, and IFN-α/βBP

genes, which conceivably could impart virus-specific host range and virulence functions to each DPV. These genomic differences suggest that W83 and W84 are distinct viruses within the genus.

Conclusions. Genome sequences of W83 and W84 provide the first view of DPV genomics. A unique complement of DPV virulence and host range genes predicts novel mechanisms underlying virus-cervid host interactions in infection and immunity. Genomic analysis indicates that DPV represents a new genus within the *Chordopoxvirinae*.

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