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The Genome of Swinepox Virus

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***Swinepox virus* (SWPV), the sole member of the *Suipoxvirus* genus of the *Poxviridae*, is the etiologic agent of a worldwide disease specific for swine. Here we report the genomic sequence of SWPV. The 146-kbp SWPV genome consists of a central coding region bounded by identical 3.7-kbp inverted terminal repeats and contains 150 putative genes. Comparison of SWPV with chordopoxviruses reveals 146 conserved genes encoding proteins involved in basic replicative functions, viral virulence, host range, and immune evasion. Notably, these include genes with similarity to genes for gamma interferon (IFN-γ) receptor, IFN resistance protein, interleukin-18 binding protein, IFN-α/β binding protein, extracellular enveloped virus host range protein, dUTPase, hydroxysteroid dehydrogenase, superoxide dismutase, serpin, herpesvirus major histocompatibility complex inhibitor, ectromelia virus macrophage host range protein, myxoma virus M011L, variola virus B22R, four ankyrin repeat proteins, three kelch-like proteins, five vaccinia virus (VV) A52R-like family proteins, and two G protein-coupled receptors. The most conserved genomic region is centrally located and corresponds to the VV region located between genes F9L and A38L. Within the terminal 13 kbp, colinearity is disrupted and multiple poxvirus gene homologues are absent or share a lower percentage of amino acid identity. Most of these differences involve genes and gene families with likely functions involving viral virulence and host range. Three open reading frames (SPV018, SPV019. and SPV020) are unique for SWPV. Phylogenetic analysis, genome organization, and amino acid identity indicate that SWPV is most closely related to the capripoxvirus lumpy skin disease virus, followed by the yatapoxvirus yaba-like disease virus and the leporipoxviruses. The gene complement of SWPV better defines *Suipoxvirus* within the *Chordopoxvirinae* subfamily and provides a basis for future genetic comparisons.**

Swinepox virus (SWPV) is the sole member of the *Suipoxvirus* genus, one of eight genera within the *Chordopoxvirinae* subfamily of the *Poxviridae*. It is responsible for swinepox, a disease that occurs worldwide and is associated with poor sanitation (18).

Swinepox is most severe in young pigs (up to 4 months of age), where morbidity may approach 100% (18, 30). Adults generally develop a mild, self-limiting form of the disease, with lesions in hairless skin areas that remain localized at the sites of entry (7, 18, 30). In adults, macroscopic cutaneous lesions pass through the characteristic stages of poxviral lesions with a very short vesicular phase that usually does not exhibit fluid exudates (9, 18, 30). SWPV infection in swine is characterized by slight fever and inflammation of local lymph nodes. Generalized infection and viremia are not observed (22). The source and the reservoir of SWPV are infected swine (18). Lice are considered the primary agents of transmission, but occasional horizontal transmission may occur through contact of nasal and oral secretions with skin abrasions (18).

SWPV infects only swine. Of several mammalian and avian species tested, only rabbits produced a nonproductive infection after intradermal inoculation (8). The host range specificity of SWPV and its ability to induce solid protective immunity have stimulated interest in using SWPV as a host range-restricted vaccine vector (14, 41, 45).

Current molecular data describing the SWPV genome consist of restriction endonuclease analysis and limited DNA sequence analysis of the terminal regions (4, 12, 25, 26, 34). Given the interest in developing more effective SWPV vaccines and expression vectors, we have sequenced and analyzed the genome of a pathogenic SWPV. These data provide a comprehensive view of the SWPV genome and further elucidate the relationship of SWPV to other chordopoxviruses (ChPVs). Furthermore, they define the gene complement that underlies the virulence and restricted host range of SWPV.

MATERIALS AND METHODS

SWPV DNA isolation, cloning, sequencing, and sequence analysis. SWPV genomic DNA was extracted from pig kidney cells infected with virus obtained from a pig litter congenitally infected during an outbreak of swinepox in Nebraska in 1999. These animals displayed foci of full-thickness epithelial necrosis distributed over the entire skin and tongue. Random DNA fragments were obtained by incomplete enzymatic digestion with *Tsp*509I endonuclease (New England Biolabs, Beverly, Mass.), and DNA fragments of 1.0 to 6.0 kbp were cloned and sequenced as previously described (2). Reaction products were run on a PRISM 3700 automated DNA sequencer (PE Biosystems, Foster City, Calif.). Sequence data were assembled with the Phrap software program and gaps were closed as described previously (1, 11), with confirmatory assemblies performed using CAP3 (19). The final DNA consensus sequence represented on average eightfold redundancy at each base position.

Genome DNA composition, structure, repeats, and restriction enzyme patterns were analyzed as previously described (1) using the Genetics Computer Group version 10 software package (10). Open reading frames (ORFs) longer than 30 codons were evaluated for coding potential as previously described (2). All potentially coding ORFs and ORFs greater than 60 codons were evaluated by

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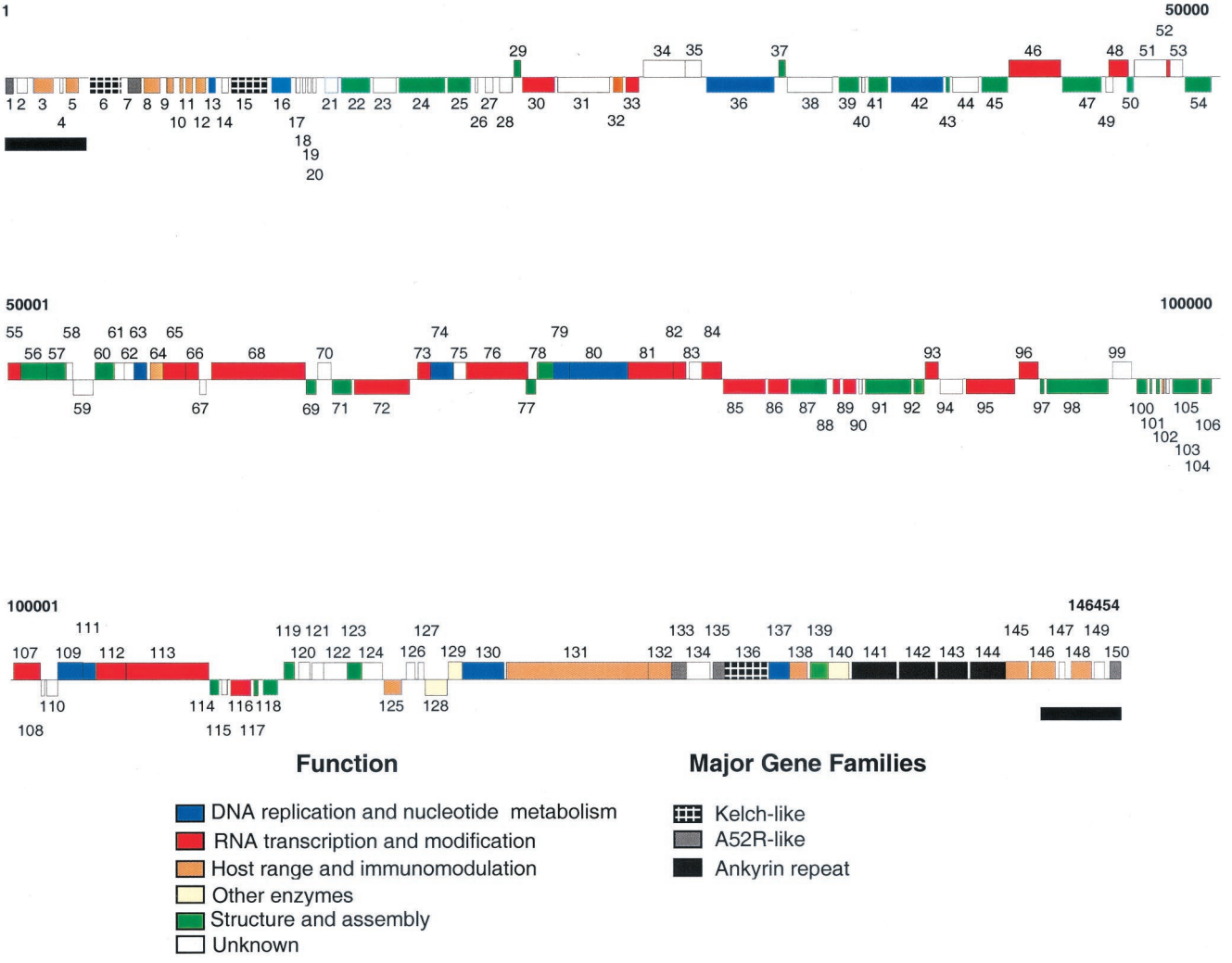

FIG. 1. Linear map of the SWPV genome. ORFs are numbered from left to right based on the position of the methionine initiation codon. ORFs transcribed to the right are located above the horizontal line; ORFs transcribed to the left are below. Genes with similar functions and members of gene families are colored as indicated. ITRs are represented as black bars below the ORF map.

homology searches as previously described (1, 2). Using these criteria, 150 ORFs were annotated as potential genes. Gene family regions were analyzed with Geanfammer (32) and promoters were analyzed with Genetics Computer Group MEME programs (10), and annotation was as previously described (1, 2). The vaccinia virus (VV) A52R-like protein family was clustered from a nonredundant peptide database of all known poxvirus sequences using the CLUS program (23) and BLASTP2 scores of greater than 115. Phylogenetic comparisons were done with the PHYLO_WIN software package (15).

Nucleotide sequence accession number. The SWPV genome sequence was assigned GenBank accession no. AF410153.

RESULTS AND DISCUSSION

Organization of the SWPV genome. SWPV genome sequences were assembled into a contiguous sequence of 146,454 bp, which agrees with a previous restriction enzyme-based size estimate of 148 to 150 kbp and previously published restriction enzyme maps (26). Because the hairpin loops were not sequenced, the leftmost nucleotide was arbitrarily designated base 1. The nucleotide composition is 72.5% A+T and is uniformly distributed. As found in other poxviruses, the SWPV genome contains a 139,023-bp central coding region bounded by two identical inverted terminal repeat (ITR) regions of 3.7 kbp (Fig. 1). The most-terminal nucleotides of the assembled sequence contain a 34-bp perfect tandem repeat which is part of a 65-bp imperfect repeat. Based on these data and published restriction digests, we estimated that heterogeneity of termini containing repeats may account for an additional 200 to 1,200 bp (26).

SWPV has a compact gene arrangement with almost no overlapping ORFs and no evidence of introns or large regions of noncoding DNA. SWPV contains 150 putative genes which encode proteins of 53 to 1,959 amino acids, of which 146 are poxvirus homologues (Fig. 1; Table 1). The conserved central core (SPV021 to SPV125), which is colinear with VV F9L to A38L, contains 106 genes, most of which are involved in basic replicative functions. In terminal genomic regions, genes are oriented toward the ends, while in the central region, genes are oriented in both directions, often grouped in clusters with identical orientation. SWPV promoters resemble other ChPV promoters (Table 1). As is found in other poxviruses, many of

TABLE 1. SWPV ORFs

ORF	Position (length, codons)	SPV accession no.[a]	Best match					Predicted structure and/or function[d]	Promoter type[e]	LSDV		YLDV		MYX		VV	
			Species	Accession no.[a]	BLASTP2 score	% Id.[j]	Length (aa)[c]			ORF[f]	% Id.[j]	ORF[g]	% Id.[j]	ORF[h]	% Id.[j]	ORF[i]	% Id.[j]
SPV001	736–287 (150)		LSDV	AF325528	498	62	145	A52R family protein		LSDV001	62	6L	41	M003.1	45	B15R	41
SPV002	1323–814 (170)		ShPV[b]	P18388	195	39	113	TM		LSDV002	39			M003.2	29		
SPV003	2452–1433 (340)	P32231	YLDV	AJ293568	539	38	335	MHC class 1 α chain-like protein, TM	E			2L	38				
SPV004	2772–2497 (92)	P32230	LSDV	AF325528	217	46	91			LSDV004	46	150R	42	M004.1	44		
SPV005	3630–2824 (269)	Q08520	Human	U45983	497	37	267	GPCR, TM		LSDV011	38	7L/145R	36				
SPV006	5285–3696 (530)	P32228	RFV	AF170722	824	33	523	Kelch-like protein		LSDV151	27	140R	28	M008L	34	A55R	29
SPV007	6038–5331 (236)	P32227	YLDV	AJ293568	444	43	217	A52R family protein		LSDV009	29	3L	43			K7R	35
SPV008	6885–6064 (274)	P32226	LSDV	AF325528	435	37	257	IFN-γ receptor, SP, TM	E	LSDV008	37			M007	25	B8R	28
SPV009	7385–6921 (155)	P32225	LSDV	AF325528	309	35	150	LAP/PHD-finger protein, TM		LSDV010	35	5L	34	M153R	36		
SPV010	7705–7448 (86)	P32224	LSDV	AF325528	248	49	85	eIF2α-like PKR inhibitor	E	LSDV014	49	12L	48	M156R	40	K3L	44
SPV011	8146–7745 (134)	P32223	LSDV	AF325528	308	44	129	IL-18 binding protein		LSDV015	44	14L	42				
SPV012	8672–8172 (167)	P32222	LSDV	AF325528	168	34	171	Integral membrane protein, apoptosis regulator	E	LSDV017	34	16L	31	M011L	27		
SPV013	9153–8728 (142)	P32208	LSDV	AF325528	505	68	141	dUTPase		LSDV018	68	17L	65	M012L	59	F2L	58
SPV014	9576–9205 (124)	P32221	YLDV	AJ293568	243	38	124		E			18L	38	M013L	36		
SPV015	11205–9604 (534)	P32206	LSDV	AF325528	1,100	40	564	Kelch-like protein		LSDV019	40	19L	38	M014L	39	F3L	28
SPV016	12243–11284 (320)	P32209	VAR	U18338	1,341	77	320	Ribonucleotide reductase (small subunit) TM	E	LSDV020	78	20L	78	M015L	74	F4L	76
SPV017	12529–12272 (86)	P32220	LSDV	AF325528	179	38	86	SP, TM		LSDV021	38	21L	33	M016L	28		
SPV018	12789–12571 (73)	P32219															
SPV019	13012–12803 (70)	P32218							E								
SPV020	13142–12942 (67)	P32217						SP, TM									
SPV021	14156–13512 (215)	P32207	LSDV	AF325528	754	64	216	TM	L	LSDV024	64	24L	50	M019L	52	F9L	45
SPV022	15462–14143 (440)	P32216	LSDV	AF325528	1,996	80	435	Ser/Thr protein kinase, virus assembly	L	LSDV025	80	25L	76	M020L	77	F10L	72
SPV023	16562–15486 (359)		VV	AF095689	448	31	351		E	LSDV026	34					F11L	31
SPV024	18530–16596 (645)		LSDV	AF325528	1,546	51	631	EEV maturation, TM	E	LSDV027	51	A26L	49	M021L	46	F12L	39
SPV025	19678–18566 (371)	AJ249689	ShPV	AF199594	1,499	76	368	EEV envelope protein, virus assembly		LSDV028	75	27L	74	M022L	73	F13L	56
SPV026	19915–19727 (63)			AL109739	72	30	53										
SPV027	20589–20146 (148)		LSDV	AF325528	514	66	148			LSDV029	66	29L	62	M024L	49	F15L	60
SPV028	21311–20661 (217)		LSDV	AF325528	502	44	218			LSDV030	44	30L	39	M025L	36	F16L	42
SPV029	21372–21680 (103)		YLDV	AJ293568	388	72	100	DNA binding virion core phosphoprotein	L	LSDV031	71	31R	72	M026L	70	F17R	62
SPV030	23092–21683 (470)		LSDV	AF325528	1,877	75	474	Poly(A) polymerase PAP		LSDV032	75	32L	71	M027L	74	E1L	65
SPV031	25324–23129 (732)		LSDV	AF325528	2,089	55	714			LSDV033	55	33L	50	M028L	53	E2L	44
SPV032	25909–25379 (177)		YLDV	AJ293568	471	50	180	PKR inhibitor, host range	E	LSDV034	49	34L	50	M029L	50	E3L	34
SPV033	26552–25938 (205)		LSDV	AF325528	795	71	199	RNA polymerase subunit RPO30	E	LSDV036	71	35L	70	M030R	68	E4L	68
SPV034	26660–28363 (568)		LSDV	AF325528	2,267	73	568		E/L	LSDV037	73	37R	68	M032R	67	E6R	60
SPV035	28370–29155 (262)		LSDV	AF325528	1,147	80	265	ER-localized protein, TM		LSDV038	80	38R	74	M033R	81	E8R	66
SPV036	32190–29167 (1008)		MYX	AF170726	4,123	75	1,008	DNA polymerase	E	LSDV039	75	39L	68	M034L	75	E9L	66
SPV037	32223–32510 (96)		MYX	AF170726	382	67	96	Potential redox protein, virus assembly		LSDV040	69	40R	71	M035R	67	E10R	66
SPV038	34587–32557 (677)		MYX	AF170726	1,521	42	678		E	LSDV042	43	42L	43	M036L	42	O1L	34
SPV039	35664–34726 (313)		LSDV	AF325528	1,187	72	314	DNA binding virion core protein, virus assembly	L	LSDV043	72	43L	67	M038L	70	I1L	66
SPV040	35892–35668 (75)		RFV	AF170722	202	53	73	TM	L	LSDV044	52	44L	53	M039L	57	12L	59
SPV041	36756–35896 (287)		LSDV	AF325528	915	65	276	DNA binding phosphoprotein		LSDV045	65	45L	61	M040L	60	I3L	53
SPV042	39041–36771 (757)		VAR	P32984	2,727	66	751	Ribonucleotide reductase (large chain)								I4L	66
SPV043	39324–39091 (78)		LSDV	AF325528	264	56	78	IMV membrane protein, SP, TM	L	LSDV046	56	46L	55	M041L	51	I5L	31
SPV044	40497–39343 (385)		LSDV	AF325528	1,181	57	394	TM		LSDV047	57	47L	50	M042L	52	I6L	51
SPV045	41791–40493 (433)		LSDV	AF325528	1,792	75	433	Virion core protein	L	LSDV048	75	48L	74	M043L	74	I7L	68
SPV046	41797–43839 (681)		LSDV	AF325528	2,315	64	681	NPH-II, RNA helicase		LSDV049	64	49R	61	M044R	62	I8R	58
SPV047	45620–43842 (593)		LSDV	AF325528	2,158	67	595	Metalloprotease, virion morphogenesis	L	LSDV050	67	50L	63	M045L	64	G1L	57
SPV048	45946–46641 (232)		LSDV	AF325528	768	63	222	Putative transcriptional elongation factor		LSDV051	63	52R	48	M047R	55	G2R	44
SPV049	45952–45620 (111)		RFV	AF170722	384	63	111	TM	L	LSDV052	58	51L	54	M046L	63	G3L	47
SPV050	46958–46584 (125)		LSDV	AF325528	488	70	124	Glutaredoxin 2, virion morphogenesis,	L	LSDV053	70	53L	64	M048L	64	G4L	43
SPV051	46963–48279 (439)		LSDV	AF325528	1,486	63	438			LSDV054	63	54R	54	M049R	52	G5R	46
SPV052	48285–48473 (63)		LSDV	AF325528	286	87	63	RNA polymerase subunit RPO7	E	LSDV055	87	55R	84	M050R	82	G5.5R	77
SPV053	48476–48994 (173)		LSDV	AF325528	539	60	169	TM		LSDV056	60	56R	55	M051R	59	G6R	43
SPV054	50144–49002 (381)		LSDV	AF325528	1,227	65	378	Virion core protein, TM	L	LSDV057	65	57L	60	M052L	54	G7L	53
SPV055	50174–50953 (260)		LSDV	AF325528	1,245	91	260	Late transcription factor VLTF-1, TM		LSDV058	91	58R	88	M053R	85	G8R	83
SPV056	50949–52016 (356)		LSDV	AF325528	1,038	58	336	Myristylated protein		LSDV059	58	59R	56	M054R	52	G9R	45
SPV057	52020–52766 (249)		LSDV	AF325528	1,111	85	245	Myristylated IMV envelope protein, TM	L	LSDV060	85	60R	81	M055R	75	L1R	67
SPV058	52799–53080 (94)		LSDV	AF325528	242	50	85	TM	E	LSDV061	50	61R	40	M056R	29	L2R	31
SPV059	54025–53066 (320)		LSDV	AF325528	1,205	70	320		L	LSDV062	70	62L	65	M057R	65	L3L	49

Continued on following page

TABLE 1—*Continued*

ORF	Position (length, codons)	SPV accession no.[a]	Best match					Predicted structure and/or function[d]	Promoter type[e]	LSDV		YLDV		MYX		VV	
			Species	Accession no.[a]	BLASTP2 score	% Id.[j]	Length (aa)[c]			ORF[f]	% Id.[j]	ORF[g]	% Id.[j]	ORF[h]	% Id.[j]	ORF[i]	% Id.[j]
SPV060	54051–54809 (253)		LSDV	AF325528	1,078	81	253	DNA-binding virion core protein VP8	L	LSDV063	81	63R	77	M058R	79	L4R	62
SPV061	54824–55210 (129)		LSDV	AF325528	412	64	126	TM	L	LSDV064	64	64R	54	M059R	52	L5R	50
SPV062	55167–55610 (148)	P23332	ShPV	P19746	451	60	148		L	LSDV065	60	65R	57	M060R	53	J1R	53
SPV063	55625–56167 (181)	M64000	ShPV	P16600	640	68	175	Thymidine kinase, SP		LSDV066	68	66R	66	M061R	67	J2R	64
SPV064	56225–56779 (185)	P23333	ShPV	P19747	467	48	187	Host range protein	E	LSDV067	48	67R	45	M062R	41	C7L	39
SPV065	56835–57833 (333)		RFV	AF170722	1,430	79	333	Poly(A) polymerase PAPs		LSDV068	77	68R	72	M065R	78	J3R	72
SPV066	57751–58305 (185)		LSDV	AF325528	816	81	185	RNA polymerase subunit RPO22		LSDV069	81	69R	75	M066R	72	J4R	66
SPV067	58715–58314 (134)		RFV	AF170722	541	68	132			LSDV070	67	70L	65	M067L	67	J5L	60
SPV068	58782–62636 (1285)		LSDV	AF325528	5,865	84	1,285	RNA polymerase subunit RPO147		LSDV071	84	71R	84	M068R	84	J6R	80
SPV069	63169–62651 (173)		ShPV	AF124517	718	78	171	Protein tyrosine phosphatase, virus assembly	L	LSDV072	78	72L	72	M069L	73	H1L	61
SPV070	63184–63753 (190)		ShPV	AF124517	789	73	190	TM		LSDV073	73	73R	67	M070R	71	H2R	65
SPV071	64742–63771 (324)		LSDV	AF325528	1,075	61	320	IMV envelope protein p35, TM	L	LSDV074	61	74L	54	M071L	54	H3L	40
SPV072	67148–64746 (801)		LSDV	AF325528	3,378	78	801	RNA polymerase-associated protein RAP94	L	LSDV075	78	75L	76	M072L	75	H4L	69
SPV073	67315–67857 (181)		YLDV	AJ293568	436	50	181	Late transcription factor VLTF-4	E	LSDV076	46	76R	50	M073R	48	H5R	37
SPV074	67896–68855 (320)		LSDV	AF325528	1,204	72	315	DNA topoisomerase		LSDV077	72	77R	61	M074R	66	H6R	61
SPV075	68867–69313 (149)		LSDV	AF325528	499	68	145		L	LSDV078	68	78R	53	M075R	55	H7R	43
SPV076	69320–71839 (840)		LSDV	AF325528	3,320	72	842	mRNA capping enzyme (large subunit)		LSDV079	72	79R	70	M076R	71	D1R	65
SPV077	72244–71807 (146)		YLDV	AJ293568	355	47	149	Virion protein		LSDV080	46	80L	47	M077L	46	D2L	40
SPV078	72249–72980 (244)		LSDV	AF325528	469	39	241	Virion protein		LSDV081	39	81R	37	M078R	37	D3R	34
SPV079	72980–73630 (217)		RFV	AF170126	926	72	216	Uracil DNA glycosylase, DNA replication		LSDV082	73	82R	73	M079R	72	D4R	69
SPV080	73663–76020 (786)		LSDV	AF325528	3,324	76	786	NTPase, DNA replication, TM	L	LSDV083	76	83R	77	M080R	76	D5R	68
SPV081	76020–77924 (635)		LSDV	AF325528	3,004	90	635	Early transcription factor $VETF_s$, TM	L	LSDV084	90	84R	87	M081R	87	D6R	81
SPV082	77952–78434 (161)		LSDV	AF325528	731	81	160	RNA polymerase subunit RPO18	L	LSDV085	81	85R	75	M082R	77	D7R	63
SPV083	78507–79145 (213)		LSDV	AF325528	744	69	213	*mutT* motif	E	LSDV086	69	86R	64	M084R	61	D9R	57
SPV084	79145–79870 (242)		RFV	P32097	709	56	237	*mutT* motif, gene expression regulator	L	LSDV087	55	87R	61	M085R	59	D10R	45
SPV085	81766–79871 (632)		LSDV	AF325528	2,606	77	632	NPH-I, transcription termination factor	L	LSDV088	77	88L	73	M086L	74	D11L	69
SPV086	82647–81787 (287)	Q08512	LSDV	AF325528	1,259	80	287	mRNA capping enzyme (small subunit), VITF	E/L	LSDV089	80	89L	82	M087L	76	D12L	77
SPV087	84330–82678 (551)	Q08517	YLDV	AJ293568	2,347	78	550	Rifampin resistance protein, IMV assembly		LSDV090	77	90L	78	M088L	76	D13L	70
SPV088	84807–84358 (150)		LSDV	AF325528	529	65	150	Late transcription factor VLTF-2	L	LSDV091	65	91L	62	M089L	64	A1L	57
SPV089	85531–84860 (224)		LSDV	AF325528	1,039	87	225	Late transcription factor VLTF-3		LSDV092	87	92L	84	M090L	85	A2L	80
SPV090	85755–85531 (75)		LSDV	AF325528	297	72	75		L	LSDV093	72	93L	56	M091L	66	8.9 kDa*	50
SPV091	87720–85765 (652)		LSDV	AF325528	2,736	78	656	Virion core protein P4b	L	LSDV094	78	94L	78	M092L	75	A3L	67
SPV092	88230–87769 (154)		LSDV	AF325528	407	52	158	Virion core protein, virion morphogenesis	L	LSDV095	52	95L	38	M093L	32	A4L	27
SPV093	88271–88756 (162)		LSDV	AF325528	542	65	170	RNA polymerase subunit RPO19	L	LSDV096	65	96R	57	M094R	65	A5R	59
SPV094	89877–88759 (373)		MYX	AF170726	1,529	77	372			LSDV097	78	97L	70	M095L	77	A6L	56
SPV095	92035–89903 (711)		LSDV	AF325528	3,027	80	714	Early transcription factor $VETF_L$		LSDV098	80	98L	77	M096L	80	A7L	71
SPV096	92097–92972 (292)		LSDV	AF325528	1,090	74	288	Intermediate transcription factor VITF-3		LSDV099	74	99R	68	M097R	70	A8R	62
SPV097	93226–92975 (84)		LSDV	AF325528	352	84	78	IMV membrane protein, morphogenesis, SP, TM	L	LSDV100	84	100L	83	M098L	80	A9L	69
SPV098	95941–93230 (904)		LSDV	AF325528	3,491	72	904	Virion core protein P4a	L	LSDV101	72	101L	68	M099L	65	A10L	51
SPV099	95956–96888 (311)		YMTV	AB015885	1,237	76	314		L	LSDV102	75	102R	77	M100R	75	A11R	53
SPV100	97433–96900 (178)		MYX	AF170726	435	66	153	Virion core protein	L	LSDV103	57	103L	62	M101L	66	A12L	52
SPV101	97657–97454 (68)		LSDV	AF325528	190	57	68	IMV membrane protein, TM	L	LSDV104	57	104L	54	M102L	48	A13L	33
SPV102	98006–97725 (94)		YLDV	AJ293568	420	87	94	IMV membrane protein, SP, TM	L	LSDV105	82	105L	87	M103L	70	A14L	55
SPV103	98184–98026 (53)		YLDV	AJ293568	235	84	52	Virulence factor, SP		LSDV106	75	106L	84	M104L	76	A14.5	56
SPV104	98458–98177 (94)		YMTV	AB015885	263	51	94		L	LSDV107	49	107L	46	M105L	50	A15L	47
SPV105	99581–98445 (379)		LSDV	AF325528	1,387	66	379	Putative myristylated membrane protein, TM	L	LSDV108	66	108L	60	M106L	60	A16L	52
SPV106	100192–99611 (194)		YLDV	AJ293568	692	69	194	Phosphorylated IMV membrane protein, TM	L	LSDV109	64	109L	69	M107L	54	A17L	42
SPV107	100207–101643 (479)		LSDV	AF325528	1,623	65	480	DNA helicase, transcriptional elongation, TM		LSDV110	65	110R	63	M108R	61	A18R	57
SPV108	101845–101630 (72)		LSDV	AF325528	292	76	72		L	LSDV111	76	111L	72	M109L	76	A19L	63
SPV109	102189–103472 (428)		LSDV	AF325528	1,266	57	427	DNA polymerase processivity factor	E	LSDV112	57	113R	48	M111R	54	A20R	46

Continued on following page

TABLE 1—*Continued*

ORF	Position (length, codons)	SPV accession no.[a]	Best match					Predicted structure and/or function[d]	Promoter type[e]	LSDV		YLDV		MYX		VV	
			Species	Accession no.[a]	BLASTP2 score	% Id.[j]	Length (aa)[c]			ORF[f]	% Id.[j]	ORF[g]	% Id.[j]	ORF[h]	% Id.[j]	ORF[i]	% Id.[j]
SPV110	102190–101849 (114)		MYX	AF170726	391	64	114	TM		LSDV113	62	112L	62	M110L	64	A21L	59
SPV111	103453–103950 (166)		VAR	X76268	653	71	164	DNA processing	E	LSDV114	64	114R	71	M112R	61	A22R	71
SPV112	103979–105124 (382)		LSDV	AF325528	1,274	66	383	Intermediate transcription factor VITF-3		LSDV115	66	115R	63	M113R	62	A23R	59
SPV113	105129–108614 (1162)		LSDV	AF325528	5,459	89	1,156	RNA polymerase subunit RPO132		LSDV116	89	116R	87	M114R	86	A24R	82
SPV114	109061–108615 (149)		LSDV	AF325528	345	48	144	Fusion protein, virus assembly	L	LSDV117	48	117L	41	M115L	52	A27L	45
SPV115	109485–109054 (144)		ShPV	P16718	539	71	139	SP, TM	L	LSDV118	71	118L	64	M116L	65	A28L	50
SPV116	110404–109499 (302)		MYX	AF170726	1,137	65	302	RNA polymerase subunit RPO35	E	LSDV119	68	119L	63	M117L	65	A29L	59
SPV117	110597–110376 (74)		YLDV	AJ293568	220	63	73	Virion protein, maturation		LSDV120	61	120L	63	M118L	57	A30L	51
SPV118	111542–110787 (252)		LSDV	AF325528	1,109	82	252	DNA packaging, virus assembly		LSDV121	82	121L	79	M120L	80	A32L	58
SPV119	111706–112260 (185)		LSDV	AF325528	356	44	179	EEV glycoprotein, TM		LSDV122	44	122R	41	M121R	38	A33R	30
SPV120	112290–112796 (169)		YLDV	AJ293568	644	64	169	EEV protein		LSDV123	58	123R	64	M122R	60	A34R	50
SPV121	112809–113363 (185)		LSDV	AF325528	444	45	177		E	LSDV124	45	124R	46	M123R	39	A35R	36
SPV122	113341–114282 (314)		LSDV	AF325528	785	53	288	TM		LSDV125	53	125R	39	M124R	44		
SPV123	114313–114909 (199)		YLDV	AJ293568	244	40	191	EEV glycoprotein, TM		LSDV126	36	126R	40	M125R	28	A36R	25
SPV124	114913–115752 (280)		LSDV	AF325528	752	51	271	TM	L	LSDV127	51	127R	40	M126R	44	A37R	28
SPV125	116661–115783 (293)		MYX	AF170726	576	38	281	CD47-like protein, SP, TM		LSDV128	31	128L	30	M128L	38	A38L	21
SPV126	116801–117178 (126)		LSDV	AF325528	128	33	112			LSDV129	33			M130R	28		
SPV127	117250–117486 (79a)		LSDV	AF325528	180	54	75			LSDV130	54	132R	40				
SPV128	118520–117489 (344)		YLDV	AJ293568	959	53	343	Hydroxysteroid dehydrogenase-like protein	E			133L	53			A44L	45
SPV129	118565–119053 (163)		LSDV	AF325528	550	64	159	Superoxide dismutase-like protein		LSDV131	64			M131R	59	A45R	31
SPV130	119089–120765 (559)		LSDV	AF325528	1,912	63	558	DNA ligase		LSDV133	63			M133R	61	A50R	50
SPV131	120870–126746 (1959)		LSDV	AF325528	5,419	56	2,007	VAR B22R homologue, TM		LSDV134	56	135R	50	M134R	50		
SPV132	126727–127758 (344)		YLDV	AJ293568	408	31	346	IFN-α/β binding protein, SP		LSDV135	32	136R	31	M135R	29	B18R	28
SPV133	127790–128326 (179)		LSDV	AF325528	358	46	156	A52R family protein		LSDV136	46	137R	30	M136R	42	K7R	25
SPV134	128372–129355 (328)		LSDV	AF325528	882	50	335		E	LSDV137	50	138R	39	M137R	39	A51R	33
SPV135	129411–129974 (188)		MYX	AF170726	539	58	187	A52R family protein		LSDV136	35	139R	45	M139R	58	A52R	38
SPV136	129994–131715 (574)		YLDV	AJ293568	1,317	44	564	Kelch-like protein, TM		LSDV151	29	140R	44	M140R	43	A55R	31
SPV137	131727–132653 (309)		LSDV	AF325528	1,069	65	297	Ser/Thr protein kinase, DNA replication		LSDV139	65	142R	55	M142R	61	B1R	46
SPV138	132666–133403 (246)		RFV	L26342	597	49	226	N1R/p28-like host range RING finger protein		LSDV140	46	143R	41	M143R	49		
SPV139	133451–134146 (232)		MYX	AF170726	497	45	215	EEV host range protein, TM		LSDV141	42	144R	44	M144R	45	C3L	34
SPV140	134184–135080 (299)		LSDV	AF325528	887	58	296	Tyrosine protein kinase-like protein		LSDV143	58			M147R	48		
SPV141	135128–137032 (635)		LSDV	AF325528	1,515	46	627	Ankyrin repeat protein		LSDV145	46	146R	29	M148R	38	B4R	26
SPV142	137100–138554 (485)		RFV	AF170722	1,183	46	484	Ankyrin repeat protein, TM		LSDV147	43	146R	38	M149R	44	B4R	24
SPV143	138662–139951 (430)		LSDV	AF325528	778	39	426	Ankyrin repeat protein	E	LSDV148	39	147R	33	M148R	29	B4R	22
SPV144	140003–141481 (493)		LSDV	AF325528	776	34	492	Ankyrin repeat protein	E	LSDV152	34	148R	28	M005	30	B4R	28
SPV145	141494–142453 (320)	L21931	LSDV	AF325528	600	41	334	Serpin	E	LSDV149	41	149R	38	M151R	33	C12L	31
SPV146	142522–143631 (370)	Q08520	Human	AY016370	589	37	343	GPCR, TM		LSDV011	37	145R/7L	38	M139R	29		
SPV147	143683–143958 (92)	P32230	LSDV	AF325528	217	46	91			LSDV153	46	150R	42	M004.1	44		
SPV148	144003–145022 (340)	P32231	YLDV	AJ293568	539	38	335	MHC class I α chain-like protein, SP, TM	E			2L	38				
SPV149	145132–145641 (170)		ShPV	P18388	195	39	113	TM		LSDV155	39			M003.2	29		
SPV150	145719–146168 (150)		LSDV	AF325528	498	62	145	A52R family protein		LSDV156	65	6L	41	M003.1	45	B15R	41

[a] Accession numbers are from the GenBank or SwissProtein database.
[b] ShPV, sheeppox virus.
[c] aa, amino acids.
[d] Function was deduced either from the degree of similarity to known genes or from the presence of Prosite signatures. TM, a *Z* score of >1.96 was used for the prediction of transmembrane (TM) domains with the MEMSAT computer program (21). SP, N-terminal signal peptide (*Z* score of >3.5 within 40 amino acids of the N terminus determined using the SIGCLEAVE computer program [ftp://ftp.ebi.ac.uk/pub/software/unix/EMBOSS/] [43]).
[e] Putative promoters (E, early; I, intermediate; L, late) were identified as previously described (2).
[f] Best-matching ORF from the LSDV genome (accession no. AF325528).
[g] Best-matching ORF from the YLDV genome (accession no. AJ293568).
[h] Best-matching ORF from the MYX genome (accession no. AF170726).
[i] Best-matching ORF from the VV Copenhagen genome (accession no. M35027), with the exception of the 8.9-kDa protein (*) (accession no. P07608), which corresponds to the VV Ankara strain.
[j] Percentage of amino acid identity in the BLASTP2 analysis.

the 30 putative early genes are members of gene families and putative host range genes, while the 45 genes containing the VV late promoter sequence (TAAATG) at the ATG codon (28) encode many of the conserved virion-associated poxviral proteins (Table 1).

Gene families and duplicated genes with probable host range functions include those for extracellular enveloped virus proteins (EEV) (SPV119 and SPV120), ankyrins (SPV141, SPV142, SPV143, and SPV144), kelch-like proteins (SPV006, SPV015, and SPV136), A52-like proteins (SPV001, SPV007,

SPV133, SPV135, and SPV150), G protein-coupled receptors (SPV005 and SPV146), major histocompatibility complex (MHC) class I α chain-like proteins (SPV003 and SPV148), and proteins of unknown function (SPV002, SPV004, SPV147, and SPV149).

Nucleic acid biogenesis, virion structure, and virion assembly. SWPV contains most of the conserved poxviral genes involved in basic replicative functions, including 26 genes encoding RNA polymerase subunits; mRNA transcription initiation, elongation, and termination factors; and enzymes which direct posttranscriptional processing of viral mRNA (28) (Table 1). Also present in SWPV are seven ChPV homologues necessary for, or potentially involved in, DNA replication (SPV036, SPV074, SPV079, SPV080, SPV109, SPV130, and SPV137) (28).

SWPV nucleotide metabolism genes are similar to those found in the capripoxviruses and leporipoxviruses, except for the addition in SWPV of the large subunit of ribonucleotide reductase (6, 42, 44). These SWPV proteins potentially include homologues of thymidine kinase, dUTP pyrophosphatase, and a large and a small subunit of ribonucleotide reductase (Table 1). Interestingly, the large subunit of ribonucleotide reductase is absent from lumpy skin disease virus (LSDV), myxoma virus (MYX), and rabbit fibroma virus (RFV), all of which are closely related viruses (Table 1 and Fig. 2).

SWPV encodes 35 homologues of conserved poxviral structural proteins and those involved in virion morphogenesis and assembly (Table 1). These include proteins present in the virion core; proteins present in the intracellular mature virus (IMV) and associated membranes; potential enzymes involved in protein modification, DNA packaging, and redox activity; and at least four VV proteins found in or associated with the release of EEV (Table 1). SWPV, like LSDV, molluscum contagiosum virus, and fowlpox virus, lacks an obvious homologue of the VV IMV membrane protein D8L, a cell surface binding protein which is present in leporipoxviruses.

Host-related functions. SWPV contains genes which likely function in modulation or evasion of host immune responses, modulation or inhibition of host cell apoptosis, or aspects of cell or tissue tropism. Many potential SWPV host range genes are homologues to genes present in other poxviruses. However, SWPV does contain a unique complement of these genes which likely dictate specific host range properties.

Some SWPV proteins are potentially secreted and are likely involved in the disruption or modulation of host immune responses as indicated by their similarity to other secreted immunomodulators and by the presence of potential signal peptide sequences. These include homologues of the gamma interferon (IFN-γ) receptor (SPV008), IFN-α/β binding protein (SPV132), and interleukin-18 (IL-18) binding protein (SPV011) (Table 1).

SWPV also contains predicted membrane-localized immunomodulatory proteins, including two homologues of G-protein coupled CC chemokine receptors (GPCR), and a CD47 homologue (6, 24, 25, 33) (Table 1). SPV005 is a truncated form of a GPCR lacking the first extracellular domain, while SPV146 resembles the complete receptor. SPV003 and SPV148 resemble cellular MHC class I α chain-like proteins, the molluscum contagiosum virus MC80R and yaba-like disease virus (YLDV) 2L gene products. These SWPV gene products have α1, -2, and -3 domains, one RGD motif, and three of the four cysteine residues required for formation of disulfide bonds. They differ from the MC80R gene product in that they lack the 50-amino-acid amino-terminal extension. SWPV MHC gene products also lack similarity to the transmembrane and cytoplasmic domains of cellular MHC homologues. In human and mouse cytomegaloviruses, another viral MHC homologue has been shown to interfere with NK cell-mediated clearance; however, the MC80R gene product appears to differ from herpesvirus homologues in the kinetics of complex formation and intracellular protein localization (36). The apparent lack of similarities in protein domains suggests that SWPV MHC-like genes may have other functions. SPV009 is similar to the leukemia-associated protein domain (LAP) and plant homeobox domain (PHD) finger protein found in LSDV, YLDV, and leporipoxviruses. Similar proteins in gammaherpesviruses are known to down-regulate expression of cellular MHC and NK cell activation ligands (20, 31, 40)

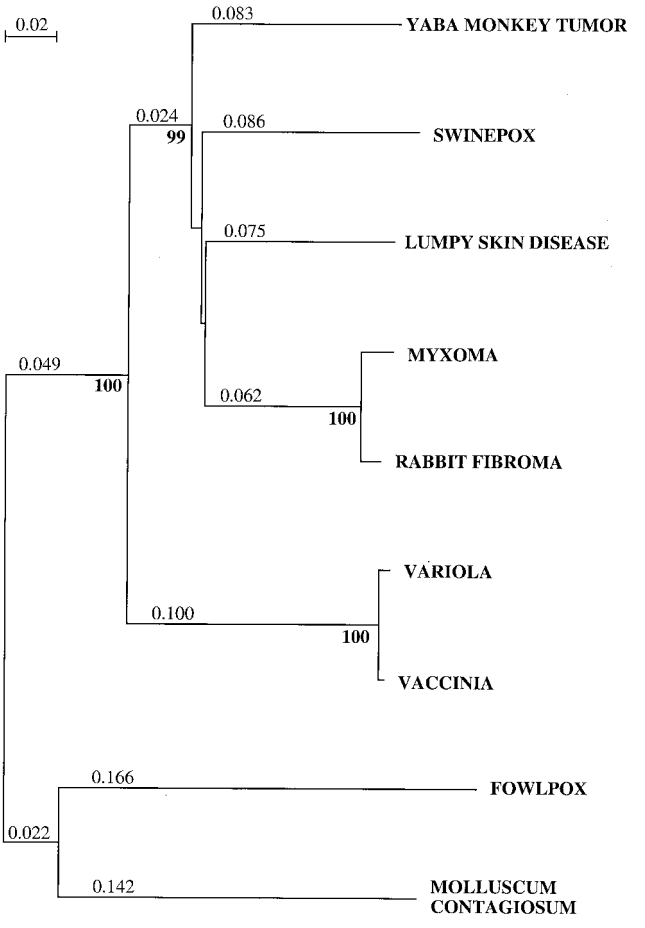

FIG. 2. Comparison of SPV068 to ChPV RNA polymerase subunit RPO147. Proteins were aligned with ClustalW. Complete amino acid sequences were used to generate the unrooted tree with *Melanoplus sanguinipes* entomopoxvirus RPO147 as the outgroup. The neighbor-joining algorithm with Poisson correction for multiple substitution and 1,000 bootstraps was used as implemented by the Phylip package (15). The figure represents the ChPV subtree. Bootstrap values greater than 80% are in boldface. The bar indicates changes per 100 amino acids. Similar results were obtaining using maximum-likelihood and maximum-parsimony analysis (data not shown).

Several SWPV proteins may have intracellular immune modulation or immune evasion functions. These include homologues of VV double-stranded RNA-dependent protein kinase inhibitors (SPV010 and SPV032) which confer resistance to the antiviral effects of IFN (Table 1). Poxviral serine proteinase inhibitors (serpins) are known to perform anti-inflammatory roles, and the single serpin encoded in SWPV (SPV145) is similar to LSDV 149, YLDV 149R, and MYX M151R (25). Notably, SPV001, SPV007, SPV133, SPV135, and SPV150 are similar to members of the poxviral gene family which includes VV A52R (family 5 [38]) (data not shown). Although the functions of most of these genes are not known, VV A52R has been shown to function as an antagonist for host cell IL-1 receptor (IL-1R) and Toll-like receptor-mediated intracellular signaling and IL-18R-mediated induction of NF-κβ activation (5). The potential for IL-1 or Toll-like receptor inhibition by a family of SWPV proteins is significant considering the role of IL-1 or Toll-like receptor signaling in induction of innate immune and inflammatory responses (13).

SWPV encodes homologues of several other poxviral proteins known to affect virus virulence, virus growth in specific cell types, and/or cellular apoptotic responses (Table 1). These include homologues of VV C7L host range (SPV064) and A14.5L virulence (SPV103) proteins, the MYX M011L apoptosis regulator protein (SPV012), a serpin homologue (SPV145), and RFV N1R (ectromelia virus p28 host range factor) (SPV138). SWPV also encodes four proteins containing ankyrin motifs (SPV141 to SPV144) (Table 1). Poxviral ankyrin genes have been associated with host range functions in MYX, cowpox virus, and VV and may inhibit virally induced apoptosis (16, 29, 39). It has been suggested that specific complements of ankyrin genes dictate poxvirus host range, and the same is probably true for SWPV (3, 37).

SWPV has homologues of poxvirus genes resembling those for cellular enzymes (Table 1). SPV128, SPV129, and SPV140 resemble hydroxysteroid dehydrogenase, copper-zinc superoxide dismutase, and tyrosine protein kinase, respectively.

SWPV encodes several homologues of poxvirus proteins of unknown function, including the VV 8.9-kDa protein (SPV090), which interacts with VV morphogenesis proteins, and the variola virus (VAR) B22R putative membrane protein (SPV131) (Table 1) (27). SPV006, SPV015, and SPV136 are similar the *Drosophila* kelch protein and other poxvirus kelch-like proteins (Table 1). SPV018, SPV019, and SPV020 lack homology to other known genes.

Comparison of SWPV to other ChPVs. SWPV is very similar to other ChPVs in overall genome structure and composition, as indicated by the presence of a central conserved core of 106 genes surrounded by regions containing many genes with apparent host range functions and the ITRs. The SWPV genome is highly colinear with the genomes of other ChPVs (Table 1) (2, 17, 35, 44). In comparison with VV, eight genes are absent in the SWPV central core. These include homologues of E11L (virion component), D8L (similar to carbonic anhydrase), A25L and A26L (A-type inclusion proteins), O2L (glutaredoxin), A31R, E5R, and E7R. A homologue of VV gene C7L (SPV064), which is believed to encode a host range factor, has been inserted between SPV063 and SPV065 (J2R and J3R homologues). Colinearity decreases toward the genome ends and disappears at the ITR. The SWPV left and right noncolinear regions contain only 44 genes and lack most VV gene homologues found in *Hin*dIII restriction fragments B, C, K, N, M, and F.

Gene colinearity is most conserved compared to LSDV, YLDV, and the leporipoxviruses (Table 1). SWPV overall amino acid identity is highest to proteins of LSDV (60% average), followed by those of YLDV (57%) and the leporipoxviruses (57%). Phylogenetic analysis of all of the SWPV genes located in the conserved central region indicates a close relationship among suipoxviruses (SWPV), capripoxviruses (LSDV), leporipoxviruses (MYX and RFV), and yatapoxviruses (Yaba monkey tumor virus [YMTV]) and a clear separation of these from other vertebrate poxvirus genera (orthopoxviruses, avipoxviruses, and molluscipoxviruses) (Fig. 2 and data not shown). These four genera also share genomic features which are different from those of orthopoxviruses, molluscipoxviruses, and avipoxviruses. Most notable is the absence of VV homologues A25L, A26L, and A31R and the insertion of one to three copies of the VV C7L homologue between J2R and J3R.

The terminal genomic regions of SWPV encode many proteins with probable functions involving host range, virulence, and immune modulation. At the amino acid level, many of these SWPV proteins are less similar to other poxvirus homologues than are viral proteins encoded in the conserved central core region. Two SWPV proteins located in terminal regions (SPV005 and SPV146) are most similar to cellular proteins (Table 1). Although closely related, SWPV contains eight genes that are absent in LSDV, including those for MHC class I proteins (two copies), ribonucleotide reductase (large subunit), hydroxysteroid dehydrogenase, and an M013L homologue and the unique SWPV genes SPV018, SPV019, and SPV020. In contrast, 13 genes present in LSDV are absent in SWPV, including those for epidermal-like growth factor, IL-10, IL-1R, VV C4/C10 like protein, endoplasmic reticulum (ER)-localized apoptosis regulator, immunoglobulin domain Ox-2 like homologue, VV E5R, E11L, K4L, F8L, and N1L and the novel LSDV genes LSDV026 and LSDV161. The absence of these genes from SWPV may explain the relatively reduced virulence and narrow host range of this virus.

Conclusions. The genome sequence of SWPV has been determined. The high degree of similarity in genomic organization, gene content, and amino acid composition to viruses from the *Suipoxvirus*, *Capripoxvirus*, *Yatapoxvirus*, and *Leporipoxvirus* genera indicates a close structural and functional relationship among these genera. Although the highest conservation occurs in genes involved in basic replicative functions, including mRNA biogenesis, DNA replication, and virion structure and assembly, significant similarities exist among genes performing other functions. A unique complement of SWPV genes in the terminal genomic regions likely function in virulence, host range, and immune evasion. The relative paucity of SWPV genes with known host range function in other poxviruses may be responsible for the low pathogenicity of this virus in swine and for its narrow host range. An improved understanding of SWPV-host interactions will permit the engineering of novel vaccine viruses and expression vectors with enhanced efficacy and greater versatility.

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