## NOTES

## Displacements of Prohead Protease Genes in the Late Operons of Double-Stranded-DNA Bacteriophages<sup>†</sup>

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Most of the known prohead maturation proteases in double-stranded-DNA bacteriophages are shown, by computational methods, to fall into two evolutionarily independent clans of serine proteases, herpesvirus assemblin-like and ClpP-like. Phylogenetic analysis suggests that these two types of phage prohead protease genes displaced each other multiple times while preserving their exact location within the late operons of the phage genomes.

Capsid maturation in double-stranded-DNA (dsDNA) bacteriophages requires proteolytic cleavage by a prohead protease. The MEROPS database (27; http://merops.sanger.ac.uk) currently places phage prohead proteases into four families, two of which exclusively consist of phage and prophage prohead proteases with uncharacterized catalytic mechanisms. They are family U9 (prohead proteases from T4-like *Myoviridae*) and family U35 (prohead proteases from HK97 and related phages of the *Siphoviridae* family). The other two, serine protease families S14 and S49, are typified by ClpP protease and *Escherichia coli* peptidase IV, respectively, and contain phage prohead proteases of *Pseudomonas aeruginosa* phage D3 (both phages are members of the *Siphoviridae*).

Prohead protease is an essential factor in phage capsid morphogenesis, as first demonstrated for phage T4 (2). The maturational cleavage of the capsid protein precursors confers stability to the nucleic acid-free prohead and triggers a conformational switch of prohead, which allows phage genomic DNA to enter and initiate the DNA packaging process. A similar capsid maturation mechanism has been reported for various dsDNA phages from the Siphoviridae family, such as HK97 (8), PVL (7), and D3 (12), suggesting that the proteolytic cleavage of structural proteins during phage capsid assembly is common in many dsDNA phages and that the prohead protease is the key enzyme in the process. The prohead protease is generally encoded next to the gene for the capsid protein that it cleaves and may be fused to it in some cases (e.g., Siphoviridae psiM2 and psiM100). Although the capsid assembly and maturation processes in phages HK97, from the lambda-like Siphoviridae group, and T4, from the Myoviridae family, are tightly regulated and share many common features,

no sequence similarity or evolutionary connection between their prohead proteases has been reported. In this study, we use computational analysis to show that virtually all known prohead proteases from dsDNA phages belong to one of the two superfamilies of serine proteases and are unrelated to each other but apparently functionally interchangeable.

To examine the evolutionary relationship between the prohead proteases from phages T4 and HK97, we searched the NCBI nonredundant protein database (7 November 2003; 1,537,641 sequences; 502,645,420 total letters) with the PSI-BLAST program (1) using members of the U9 and U35 families as queries, with the threshold for inclusion set at a BLAST E value of 0.02. Starting with the prohead protease from HK97 (gi 9634157; family U35) as a query, we collected the prohead proteases from HK97-related Siphoviridae and observed statistically significant matches to proteases from other phages. In the course of these iterative searches, members of the family U35 were found to share significant sequence similarity with herpesvirus proteases and UL26 assemblins from family S21, and they were all remote homologs of prohead proteases from T4-like Myoviridae, members of the family U9. For example, when the prohead protease from Salmonella enterica serovar Typhimurium phage ST64B (Podoviridae; gi 23505450; family U35), was used as a query after phage prohead proteases from family U9 and herpesvirus proteases from family S21 were detected, the prohead core scaffold protein and protease gp21 from phage Aeh1 (gi 33414841; family U9), a T4-like member of the Myoviridae, were found in the ninth iteration, with an E value of  $10^{-17}$  and without any false positives. In the PSI-BLAST searches that were initiated with herpesvirus proteases, a phage head maturation protease from Novosphingobium aromaticivorans (gi 23107536; COG3740) was always just below the threshold. When that protease was submitted as a query, a UL26 capsid maturation protease from meleagrid herpesvirus 1 was found in the second iteration, with an E value of  $10^{-3}$ .

In *Myovirus* P2, the internal scaffolding protein gpO is indispensable for the cleavage of capsid protein gpN (29), but it is

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FIG. 1. Structures of HCMV protease (PDB code 1CMV) and ClpP protease from *E. coli* (PDB code 1TYF). The  $\alpha$ -helices are blue, and the  $\beta$ -strands are orange. The residues in the catalytic triad are shown with balls and sticks. They are His63-Ser132-His157 in HCMV protease and Ser97-His122-Asp171 in *E. coli* ClpP protease. The structures were drawn by using the program MOLSCRIPT (19).

unknown whether gpO itself has protease activity or if the cleavage reaction is performed by a host protease. During sequence similarity searches, we found that P2 gpO shares significant sequence similarity with phage Mu putative head maturation protease gpI, and both of them are distantly related to herpesvirus assemblin UL26. For instance, when a conserved hypothetical protein from Chromobacterium violaceum ATCC 12472 (gi 34496934) served as a query in a PSI-BLAST search, gpO from P2-like Myoviridae was detected, followed by the putative head maturation protease gpI from Mu-like phages. If we included the UL26 protein from gallid herpesvirus 3 (gi 10834896), whose similarity was just below the threshold in the seventh iteration in the later round of the PSI-BLAST search, we found many UL26 proteases from herpesviruses without any false positives until no new sequences could be retrieved after the 10th iteration.

Herpesviruses are enveloped dsDNA viruses that can cause severe health problems in humans and other animals. As in dsDNA bacteriophages, the proteolytic processing of capsid protein precursor by a virus-encoded enzyme is essential for producing infectious virions (17, 20, 37-39), and several structural and mechanistic parallels between the maturation of phage heads and herpesvirus capsids have been noted (14, 31). So far, the UL26 gene products are the only known proteases encoded by herpesvirus genomes, and the three-dimensional structures of UL26 proteases from all three herpesvirus subfamilies have been determined (3, 6, 15, 25, 26, 28, 32, 35) (Fig. 1A). The central core of the enzyme is a  $\beta$ -barrel, consisting of two sheets held together at one edge by a long  $\beta$ -strand ( $\beta$ 3) passing between the sheets and forming a triple-stranded corner and at the other edge by two hydrogen bonds between strands  $\beta$ 5 and  $\beta$ 7. All residues with a direct role in catalysis, including the three members of the catalytic triad and two residues predicted to form the oxyanion hole, are located within this core. The core is surrounded by eight  $\alpha$ -helices, four of which play a role in the formation of the homodimer. The similarity between phage proteases and UL26 proteases extends along most of the  $\beta$ -strand's rich central region of the UL26 sequence, except for the middle region of the herpesvirus sequences, which consists of three  $\alpha$ -helices that appear to be lacking in phage proteases.

To further validate the sequence and structure similarities

between proteases from phages and herpesviruses, we queried the global network of independent structure prediction servers via the 3D-Jury Meta predictor (13; http://bioinfo.pl/Meta/) with prohead proteases from HK97 and ST64B. Herpesvirus proteases were ranked as the top-scoring matches, with 3D-Jury scores greater than 90, which are typical of true positives (13). We concluded that the three families are probably derived from a common ancestor and propose to group them into a single protease clan, SH.

A multiple-sequence alignment of proteases from the newly defined clan SH is shown in Fig. 2. The fully conserved serine residue in the middle of the fifth  $\beta$ -strand suggests that the phage prohead proteases from families U9 and U35 and the internal scaffolding protein gpO from P2-like phages are serine proteases. The second member of the catalytic triad, histidine, located near the C terminus of strand 2, is also universally conserved. In UL26 proteases, a histidine residue (His157 in human cytomegalovirus [HCMV] protease) at the N terminus of strand 6 is predicted to be the third triad member according to its position in the three-dimensional structure (6, 25, 32, 35). This position aligns with a well-conserved acidic residue in all phage proteases, which therefore appear to have a more conventional His-Ser-Asp(Glu) catalytic triad. Kinetic studies of HCMV protease with the His157 residue mutated to alanine (H157A) showed about a 10-fold loss in activity relative to that of the wild-type enzyme, while the H157D and H157E mutants were about three times less active than the wild type (16). It would be interesting to see whether phage prohead proteases from families U9 and U35, which all have an aspartate or glutamate in the third position, display lower activities than their herpesvirus homologs or whether evolutionary changes elsewhere in the molecule have compensated for that.

Two other recognized families of phage prohead proteases are families S14 and S49, which include proteases widely distributed in bacteria, archaea, and eukarya. The founding members of the S14 and S49 families are, respectively, ClpP protease and E. coli peptidase IV. Using lambda prohead protease gpC protein (gi 9626248) as a query and after detecting many S49 family proteases, we also retrieved ClpP proteases at the second iteration. Statistically significant matches to many members of the large crotonase superfamily were detected in later iterations, which is compatible with the observation of a distant structural similarity between ClpP protease and crotonases (11, 22). The computational fold recognition experiments further validated the sequence and structure similarities between proteases from families S14 and S49. As expected, the best match from the 3D-Jury consensus prediction (13) for lambda gpC protein is ClpP protease (PDB code 1TYF), with a score of 126.33. With an  $\alpha/\beta$  fold composed of six repeats of the  $\beta$ - $\beta$ - $\alpha$  unit (Fig. 1B) (36), ClpP is distinct from the herpesvirus protease fold. An analysis of a multiple-sequence alignment (Fig. 3) indicates that most of the enzyme catalytic core is well conserved among proteases from families S14 and S49; therefore, proteases from the two families are expected to adopt a ClpP/crotonase fold and constitute clan SK.

Herpesvirus-like proteases and ClpP-like proteases represent two distinct serine protease folds that are most likely evolutionarily independent but appear to play the same essential function in the phage life cycle. The only phage prohead protease with experimentally demonstrated activity that does

3891985 3660281 2554902 27066368 E 9632595 0 29028699 31415851 8346583 5) 9633523 9628621 9630330 4) 23505450 3) 13095847 13095723 22296526 9635718 20065968 29566751 9630537 9631144 2) 28379024 30260629 8 11513528 30044105 15865610 33414841 17975127 19548994 11863104 18249903 9634157 15801316 Ser, indicates the conservation of residues with small side chains (A, G, and S), and a white font on a black background indicates the conservation of negatively charged residues (D and E). similarities associated (A) Representatives from proteases FIG. Unclassified Myoviridae Podoviridae Siphoviridae Prophages Bacteriophage Bacteriophage , His, 5 and Asp/Glu residues in the catalytic triad are in white font on a red background, except that the His in the third position of the triad in all herpesvirus proteases is on a blue background with T4 S-PM2 Aehl phi13 HP1 K139 VZV HCMV EBV psiM2 Lp3 herpesvirus. (B) Multiple-sequence alignment of protease clan SH members. **RM378** phBC6A52 BFK20 Mu P2 phage ST64B bIL309 A2 Omega HK97 CP-933C are shown in parentheses. Consensus positions of the structural elements are shown above the alignment. Yellow shading indicates the conservation of hydrophobic residues. bIL285 phi3626 psiM100 phi-C31 LambdaBa04 phiPV83 P27 KSHV HSV-2 known three-dimensional structures are shown in bold blue font. 4 dsDNA (22) QIFEGYASVE (7) DILL---DAERMAL (6) V (30) SGEFEGYGSVE (7) DVV--PGAFTTIL (9) PJ (33) RISMEGYAKE (11) BRV--DGAGAPSI (4) V (23) RISMEGYAKE (11) BRV--DGAGAPSI (4) V (23) KRLVTGPULVE (12) BQVE--EVAXEFME (2) QC (82) QRITTGPULVE (12) BQVE--EVAXEFME (2) QC (35) TLVLEGYASTE (16) BQUD--RRAFEKTI (5) LL (36) TKVTTGYAKE (12) BVA--EVAXEFME (2) QC (24) FKTTGYAKE (11) BTIS--RRAFENTSI (3) V (24) EKIISGYAKE (11) BHDS--PHALDNVD (3) V (24) IGQIAGYALKE (11) BYIA--PIALDNVD (3) V prohead prohead (19) PIYVAGFLALY (6) (1) ALYVAGYLALY (5) (12) PVYVGGFLARY (7) (5) SVYVCGFVERP (7) (3) GLYVGGFVERP (7) phages (19) NGTFTAYASVF(7) (17) QVILDGYVNVV(15) (19) EMVIEGYALKF(11) (20) SNTLTGYVVRW (12) EKFQ--RGAFTEWL (5) (25) NRTLIGYAVKW (14) EQFK--NGAFTETL (4) (35) GKTISGYAIVW (11) EVVT--PKALDGVD (3) (31) KLYIEGIFMQS (12) KVL---QEAVTKYI (8) (36) GLYIEGIFMQA (12) RIL---EKAVKDYI (8) (22) HLYIEGVFLQS (12) SVL---EKEVSRYN (8) (4) DKTYTALIMEA (12) EAV---KKAVERMK (7) (6) (30) SGEFEGYGSVF(7) (21) PAHIIGYGSVF(11) (19) GWCQLLPAGHF family S21 with known three-dimensional structures. HSV-2, Representatives from KFFRIGVEGDT(1) DFICIATSGYT(1) DWVIVATAGTT(2) REFERENCE EEEEEEEEEEE EEEEEEE BEBEBE EEEEEEEEEE EBEBBBBBBBB β1 proteases proteases YT(1) EGRVISAQDIQEMA(9) 7T(1) EGRQITAQELHEMA(9) 7T(2) EGRVISESWINDMA(9) FT(2) EGRVISESWINDMA(9) FF(13)QGWFIDGEIAGRLV(9) 5) ELAL-DPDTVRAAL(5) LPINVDER(3) E 5) ELNI-TPEIVRSAL(5) IPINIDER(3) V 7) ELLL-PRDVVEHWL(13) LPININED(3) V 7) CLHH-DPLTVKSQL(5) LPITVELL(3) E 7) ELYL-DPDQVTPYL(5) LPITIEL(3) E ) DVVK--SGAFADTL( 5) ERIV--PKTFEKAL( 1) ETIS--RRALENTD( DVVM--SGAFAASL BIIR--PGAFDDVL ННН ннннннннннн (family (family family U35. ннннннннн ннннннн ннннннн 8 60 U35) (C) Representatives from family U9 (9) (3) (8) ) GRINLEEL (10) RYGDV- A ANLWEELR (3) NMGQV- I ALIWEELY (10) NMGEV- E VLIDYEEN (14) AAGWEN (1) D PALLWQER (3) VYATFINED (3) QNIDIMER (3) QNIDILER (3) QNIDILER (3) URLLVNEA (2) IKALVNEN (3) VRCLVDEI (3) VRALENE (3) VLALVNED (3) ALGELNHP(3) ALGELNHP(3) ALGELGHP(3) MYGELDHP(8) LPVLYGED(3) VDLLFNED(3) VRCLVDEI(3) VRGLYEND(3) QRFLWSID(3) VLMLNNID(3) PALLWOHR (3) VRALFNHD (3) нннн VAMFFNHK EEEEEE EEEEE EEEE EEEE EEEEE B2 . The left column is the gi number for each sequence followed by the blue font. Distances, in amino acid residues, from the ends of each (4) 
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A.

Herpes virus

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32.63         INTRUMENTAL         RERE	EEEE	ABEL	ABEL	ALGU	ALGUI	ADEL.	ADSVI	AL GM	ADEL	INSII	VERLO	VEELC	IDDIC.	VE EV(	IDGI	IEAV(
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Rest         Res         Rest         Rest	HHHH	EQEAT	VSEQ5	BEKA	3R-AV	EDSÕE	DYGE	DALI	EDSQE	10EAI	BOOAL	SQAV	A VEVD	BEAF	BOTAI	BREAF
32343 IMAR SEES IMPHILINGHT HIL RESE MHHHHHHHH RESE SEES IMPHILINGHT HILL HILL HILL HILL HILL HILL HILL HI	8	s	s	í4	E	ш	E4	Q	E A	S	H	F	E4	s	A	H
Bit Instruction         Exercise         Instrument information         Instrument information         Instrument information           13:065         11.0         <		AAVY	AAVF	AGLY	AGCF	AAVE	AGIF	AAVY	AAVF	ANVA	GRIF	GRIY	GRAW	GKIY	GEFW	GRVW
ESERGE HITTARLOOM	T	9	g [	g	AL		0	9	g	g	AD	AD	AD	AD	HH	P0
<ul> <li>BERGE I ARHHIMHIM HERG</li> <li>BERGE ARG (13) TI-FERGARMED-FERGA</li></ul>	HH HH	UL-DT	UL-DT	IR-ST	JK-AI	TD-TU	rd-XV	TA-MU	UT-GI	IN-XV	JK-EF	JR-EI	JR-EN	LL-KI	DEI	ME-EV
<ul> <li>Barboka SERSE HHHHHHHHH HH</li> <li>BERE BERE HHHHHHHHH</li> <li>BERE BERE HHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHH</li> <li>BERE BERE HHHHHHHHHHHHHHHHHHHHHHHHHHHHHH</li></ul>		G(5)	G(5)	G(5)	G(5)	G(5)1	G(5)	G(5)	G(5)	N(5)	G(7)	G(7)	G(7)	H(7)	R (7)	S (7)
<ul> <li>JANDA RESER LANDALTANA THAN HANNANG AND TARK (A) PURATANA NATA AND AND AND AND AND AND AND AND AND AN</li></ul>	HHHH	SAYT	SAYT	ARNR	AEAR	TYMA	ANFR	ARYT	AMFT	AESR	AA	VD	ME	AE	KT	AL
Завида         Белева         нинининин         велева         вини         нинининини         велева         вини         нининининини         велева         вини         нининининини         велева         вини         нининининини         вини         нининининини         вили         в	нннн	AQKV	PEKV	LQLI	HNLV	PERV	'VDAI	PEKV	AEKV	TGFV	VTSV'	VRVI	LDVV	VKWV	LEVU	RDKA
3234 Index (SEE) HITHHEILHI HIL SEEDE JIHTHHEILHILI DEFENDANCI (A) FUNCTOR (C) FUNCTOR	HHHH	FROMF	<b>FROME</b>	LYEME	GSEF	ARRME	SYKQF	ARKMF	ARRMF	LYATF	SYGQF	AYDEF	(FKTF	LYMDE	<b>WEHE</b>	AYQLF
32348         1ambda         688         0         1111         1111         2123         1111         1111         2123         11111         1111         1111 <th< td=""><td>НННН</td><td>RMDA7</td><td>RIDA1</td><td>EVGRI</td><td>LUVQI</td><td>RIDA</td><td>MUQN</td><td>RMDE1</td><td>RIDA</td><td>RIND?</td><td>LIDDS</td><td>LUDE</td><td>UDI</td><td>MINE</td><td>LQKQ</td><td>SAQHI</td></th<>	НННН	RMDA7	RIDA1	EVGRI	LUVQI	RIDA	MUQN	RMDE1	RIDA	RIND?	LIDDS	LUDE	UDI	MINE	LQKQ	SAQHI
3234 Indicates BERE HHHHHHHHH REBER HHHHHHHHHH REBER HHHHHHHHHH	нннн	TLQS	DFQT	- LQK	- LQA	DMQQ	-LTS	OQY-	<b>NMQQ</b>	RLQK	- LQA	- LQT	- IQK	- LQK	- IKD	LFEK
<ul> <li>BERER EIN HUHHUHHU</li> <li>BERER HUHHUHHU</li> <li>BERER HUHHUHHU</li> <li>BERER EIN HUNGLAND, THE RUDAL TO ALTAR LODAL TO ALTAR REAL TO ALTAR REAL LODAL TO ALTAR LODAL TO ALTAR LODAL TO ALTAR REAL TO ALTAR REA</li></ul>	нннн	-VRE	-VRA	SILES	ERQR	S-VRQ	SLTF	UKAD	C-VRQ	-SKE	EQSI	TUBE	EREI	EKEY	DLKI	EEAE
<ul> <li>BERER IMHHHHHH HUNG</li> <li>BERER IMHHHHHHH ER</li> <li>BALHHHHHHH ER</li> <li>BALH STALODA</li></ul>	HHH	IL PDD	(LPED	MTSE	ILSDD	LPAE	LSDQ	<b>TPES</b>	LPAE	ISEE	LLPE	VTDE	LKPE	MTKE	DINK	PLKF
Застав         внининини         всеме		-PYSE	- PYER	- PHEF	PHKV	-QFEP	- PHEF	- PSQF	QFEP-	SPFQP	FDRE	SQTRE	DWRG	SPFRI	PFKE	SAEEF
32233         100         55255         11111         1111         1211         <	HHH	NO	VIDGN	NDEN	ADFS-	VIDGN	- LIEN	PDLT-	VDGN-	- GMG	-DILS	-DILLS	-DMG	-DIG	-SVLI	-BLLO
32334         Lambda         RERE         LERE         RERE         LERE         RERE         LERE         LERE <thline< th=""> <thline< th=""> <thline< th=""> <th< td=""><td>H</td><td>GSHK</td><td>GDHK</td><td>GSRK</td><td>GDYK</td><td>GAHK</td><td>GDHK</td><td>GAHK</td><td>GAHK</td><td>GEFK</td><td>GPYK</td><td>GPYK</td><td>GPYK</td><td>GKYK</td><td>GRONK</td><td>GKYA</td></th<></thline<></thline<></thline<>	H	GSHK	GDHK	GSRK	GDYK	GAHK	GDHK	GAHK	GAHK	GEFK	GPYK	GPYK	GPYK	GKYK	GRONK	GKYA
32348 Lambda RESEB INHUHHUHHU HERES HUHHUHHUHHUH RESEB RUHHUHUHHUHHUH RESE RUHHUHUHHUH RESE REPRES AND ADDRATE	EE EE	STI-	SYI-L	C-IFA	1-V-S	SYI-L	S-VFA	SY1-L	SYI-L	- IKA	-IKS	I-FKS	7-FKT	-IKA	I-YTE	I-ISR
32234         Lambda         ESERE (HILHHUHH)         LERES (HILH)         LERES (HILH) <thleres (HILH)         LERES (HILH)</thleres 	EEF	3) ITI	ISN(E	S) YTT	3) IAV	3) ITI	3) VTS	3) ITI	3) ITI	NNI (8	3) FK	3) FNJ	3) VEV	LLA (8	3) RRV	3) KET
32.5246         Immedia         BEREE         Immediation         BEREE         Immediation         BEREE         Immediation         BEREE         Immediation         BEREE         Immediation         BEREE         Immediation         BEREE	EE	AE (1	AH (1	SH (1.	GR (1.	SH (1.	NE (1	AH (1.	SH (1.	VE (1.	RG (1.	1) SQ	V田(1	DL (1	SG (1.	AR (1.
322348         LHHUHHUHH         HHH         HHHUHHUHH         HHH         HHHUHHUHH         HHH         HHHUHHUHHU         HEBER           30466         N15         (9) GTDS (14) NGTTARLQOA         (5) LLDDDTPGGMOTGARD         (4) PWALADDMPGGGGLIASSAS (1) RLDDT (1)           30468         N15         (9) GTDS (14) NGTTARLQOA         (5) LLDDDTPGGMOTGARD         (4) PWALADDMPGGGGLIASSAS (1) RLDDT (1)           30416         (7) GTDS (14) NGTTARLQOA         (5) LLDDDTPGGMOTGARD         (4) PWALADDMPGGGGLIASSAS (1) RLDTD (1)           311111         VIML         (7) GGLA         (4) PWALADDMPGGGGLIASSAS (1) RLDTD (1)           32046         (7) TTVS (14) NGTTARLQOA         (5) LLDDDTGGGGOLIASSAS (1) RLDTD (1)         (7) PWALADDMPGGGGLIASSAS (1) RLDTD (1)           32046         (7) TTVS (14) GLA         (7) PWALADDTGGGGLIASSAS (1) RLDTD (1)         (7) PWALADDTGGGGLIASSAS (1) RLDTD (1)           32046         (7) TTVS (14) GLA         (7) TTVS (14) GLA         (7) PWALADDTGGGGLIASSAS (1) RLDTD (1)           32046         (7) TTVS (14) GLA         (7) TTVS (14) GLA         (7) PWALADDTGGGGLIASSAS (1) RLDTD (1)           321410         (7) GLA         (7) TTVS (14) GLA         (7) PWALADDTGGGGLIASSAS (1) RLDTD (1)           321410         (7) TTVS (14) GLA         (7) TTVS (14) GLA         (7) PWALADDTGGGGLIASSAS (1) RLDTD (1)           321410         <	EEE	GVMM	GVMM	GUIA	GVIC	GVMM	GVIA	MUVD	GVMM	GUIM	GVIL	GUIM	GVIY	GURM	GVVS	GUVT
32234         Jambda         REERER         HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH	E	0(7)	0 (7)	S(8)	T(8)	(8) L	S(8)	T(8)	T(8)	S(8)	N(8)	(8) H	D(8)	E(8)	AL (8)	E(8)
ЗСЕЗАВ         ПИНИНИНИИ         НИН           22232         ОП         ПИНИНИНИНИ         НИНИНИНИНИНИ           22323         ОП	EEF	RLVJ	RLVJ	KUFN	QVFI	RRLV	KVIV	HRLV	RRLV	EIL	HIMI	KIY	KIIM	AIVE	RIYA	AIVIA
22234         1ambda         REREM         HHHHHHHH         HH           2331         1ambda         (8)         711VS         714         714         714           2311         101         (3)         (111VS)         (14)         711         714         714         714           2311         111         VIM         (3)         (111VS)         714 <td></td> <td>Ξ</td> <td>H</td> <td></td>		Ξ	H													
22.214         Lambda         REBER         HHHHHHHHH         HH         REBER         HHHHHHHHH           22.215         NO         533         TUNC 141, NUCLIAR/COQASD-(5)         LLIDHOTTGGR/AGERPO/RELEAR(4)         PWALABNING 56AD           23.215         NO         533         TUNC 141, NUCLIAR/COQASD-(5)         LLIDHOTTGGR/AGERPO/RELEAR(4)         PWALABNING 56AD           23.113         VIML         (7)         66LAH (4)         PWALABNING 56AD           23.114         VIML         (7)         66LAH (4)         PWALABNIC 56AD           23.115         (4)         (7)         (7)         PWALABNIC 56AD           25.256         G1 (7)         (7)         (7)         PWALABNIC 56AD           27.5536         G1 (7)         (7)         (7)         PWALABNIC 55AD           27.5536         G1 (7)         (7)         (7)         PWALABNIC 55AD	H	AS	AS	BE	9	S	AS	CS	CS	B	G	AT	DA	DA	8	AN
322328         Lambda         REBER         HHHHHHHH         RHH         REPER         HHHHHHHHHHHHHHHHHHHHHHHHHHH         REPER         RHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH	НННН	LASAAS	IASSAS (	IASSAD	LACCCD	LASACS	IAAAAS	LAAACS	LASACS	LASSAD	IAMGCP	ISAPAT	TACGAD	<b>NSAPAD</b>	<b>ILACSGD</b>	MAMAAN
326264         Lambda         GB TUPX (14) NUTLARLOQA	ннннннн	AGQLLASAAS	AGQLIASSAS (	MAYAIASSAB	AAYALACCCD	AAMLLASACS	GGYLIAAAS	AAMLLAAACS	AAMLLASACS	MAYALASSAD	GGVYIAMGCP	GGYYISAPAT	GGYYIACGAD	GAYMVSAPAD	GGYWLACSGD	GGYYMAMAAN
ЗС2646         Панийса         ВЕВЕЕ         Ининининини         III           3046         N3         (4) NOT TAR LOOM	ннннннннн	MNCBAGQLLASAAS	MNCSAGQLIASSAS (	UDAY SAAYAIAS SAD	SCYSAAYALACCCD	DTACSAAMLLASACS	SAFSGGYLIAAAAS	STACSAAMLLAAACS	OTAC SAAMLLASACS	SFACSAAYALASSAD	II SASGGVYIAMGCP	IMAASGYYI SAPAT	SYAT SGGYYIACGAD	BLDASGAYMVSAPAD	MAASGGYWLACSGD	OVAASGGYYMAMAAN
22234         Jambda         REREE         HHHHHHHH         HERE         HHHHHHHHHHHHHHHHHHHHHH           23234         Jambda         (68) TTSK (14) NGTTARLODASED-(5) LILDPOTPGSAYGABBOCA         TTARV           23231         (90) GTOS (14) NGTTARLODASED-(5) LILDPOTPGSAYGABBOCA         TTARV         (11) TARV           23231         (90) GTOS (14) NGTTARLODA	нннннннннн ээээ	ALANDMNCSAGOLLASAAS	ALANDMNCSAGQLIASSAS (	AIANDDAYSAAYAIASSAB	S LENES CY SAA YALAC CCD	ALCNDTACSAAMLLASACS	AIVNFSAFSGGYLIAAAS	ALANETACSAAMLLAAACS	ALCNDTACSAAMLLASACS	AYUDEFACSAAYALASSAB	ASFGNI SASGGVYIAMGCP	V SMGNMAASGGYYISAPAT	AYISGYATSGGYYIACGAD	VYVEGLDASGAYMVSAPAD	SFIEDMAASGGYWLACSGD	ASMSDVAASGGYYMAMAAN
32.2348         Lambda         BERER         HIHHHHHHHH           3.3045         NL         CUMP (1) NGL TARLOOMSD-(5) LLDPOTTPG9N/SGRED OF TLAN           3.3045         NL         (90) GTUS (14) NGL TARLOOMSD-(5) LLDPOTTPG9N/SGRED OF TLAN           3.3045         NL         (90) GTUS (14) NGL TARLOOMSD-(5) LLDPOTTPG9N/SGRED OF TLAN           3.3111         (11) GGGA (14) NGL TARLOOMSD-(5) LLDPOTTPG9N/SGRED OF TLAN           3.3111         (11) GGGA (14) NGL TARLOOMSD-(5) LLDPOTTPG9N/SGRED OF TLAN           3.3111         (11) GGGA (14) NGL TARLOOMSD-(5) LLDPOTTPG9N/SGRED OF TLAN           3.3111         (11) GGGA (14) NGL TARLOOMSD-(5) LLDPOTTPG9N/SGRED OF TLAN           3.3111         (31) GGGA (14) NGL TARLOOMND-(5) LLDDOTTPG9N/SGRED OF TLAN           3.3111         (31) GGGA (14) NGL TARLOOMND-(5) LLDDOTTPG9N/SGRED OF TLAN           755305         (23) GLUY (14) DGLAROLOMND-(5) LLDDOTTPG9N/SGRED OF TLAN           755305         (24) GLUY (14) DGLAROLOMND-(5) LLDDOTSPG3N/SGRED OF DUDLING           755305         (24) GLUY (14) DGLAROLOMND-(5) LLDDOTSPG3N/SGRED OF DUDLINC	ннннннннн ддддд	PUWALANDMNCSAGQLLASAAS	PIWALANDMNCSAGQLIASSAS (	RITAIANDDAYSAAYAIASSAB	TRVS LENES CYSAAYALACCOD	PUWALCNDTACSAAMLLASACS	PITAIVNFSAFSGGYLIAAAAS	PUWALANETAC SAAMLLAAACS	PVWALCNDTACSAAMLLASACS	KIIAYVDEFACSAAYALASSAE	KUVASFGNI SASGGVYI AMGCP	PVYV SMGNMAASGGYYISAPAT	PIVAYISGYATSGGYYIACGAD	PVVVYVEGLDASGAYMVSAPAD	KIYSFIEDMAASGGYWLACSGD	PUIASMSDVAASGGYYMAMAAN
32.2348         Lambda         REREE         HHHHHHHH         HH         LERE         HHHHHHHH           3.0463         N13         NG1	ни вееес ининини	V(4) PUWALANDMNCEAGQLLASAAS	M(4) PIWALANDMNCSAGQLIASSAS(	CS(4) RIIAIANDDAYSAAYAIASSAB	A(7) TRVSLENESCYSAAYALACCC	KL (4) PUWALCNDTACSAAMLLASACS	A (4) PITAIVNFSAFSGYLIAAAAS	KM(4) PUWALANETACSAAMLLAAACS	<pre>kL(4) PVWALCNDTACSAAMLLASACS</pre>	AS (4) KIIAYVDEFACSAAYALASSAE	(4) KVVASFGNISASGVYIAMGCP	CI (6) PVYVSMGNMAASGGYYISAPAT	CL(4) PIVAYISGYATSGYYIACGAD	CL(4) PVVVYVEGLDASGAYMVSAPAD	0L(6) KIYSFIEDMAASGGYWLACSGD	JL(4) PVIASMSDVAASGGYYMAMAAN
22.244         Lambda         REREES         HHHH         REREES         HHH           22.22.48         Lambda         (86) FTLMS (14) NGTLARLQQASID-(5) LLDMDTFGGMYGRA           22.22.29         WO         (53) GLTMS (14) NGTLARLQQASID-(5) LLDMDTFGGMYGRA           22.22.29         WO         (53) GLTMS (14) NGTLARLQQAASD-(5) LLDMDTFGGMYGRA           23.21.111         (11) DLDMGTFGGMYGRA         (11) DLDMGTFGGMYGRA           27.55         (53) GLTMS (14) NGTLARLQQAADD-(5) LLDMDTFGGMYGRA           27.51         (64) GTMS (14) SUCQARLAQAMD-(6) HEDLTMTGGGAGAAGA           27.55         (24) SUCMARLQQAADD-(5) TUDDTGSGGAAGA           27.55         (24) SUCMARLQQAVSD-(5) TUDDTGSGGAAGA           27.55         (24) SUCMARLQQAVSD-(5) TUDDTGSGGAAGA           27.55         (24) SUCMARLQQA	ннннннннн ввеве	IIARV(4) PVWALANDMNCSAGQLLASAAS	IIARM(4) PIWALANDMNCSAGQLIASSAS(	FIYES(4) RIIAIANDDAYSAAYAIASSAB	SLLSA(7) TRVSLENESCYSAAYALACCCD	MIYRL(4) PUWALCNDTACSAAMLLASACS	DIRAA(4) PITAIVNFSAFSGGYLIAAAAS	MIYRM(4) PUWALANETACSAAMLLAAACS	MIYRL(4) PUWALCNDTACSAAMLLASACS	KHIMAS(4) KIIAYVDEFACSAAYALASSAB	KLKQL(4) KVVASFGNISASGVYIAMGCP	(QVEEI (6) PVYVSMGNMAASGGYYISAPAT	(EVKEL (4) PIVAYISGYATSGYATSGAL	UKVEEL (4) PVVVYVEGLDASGAYMVSAPAD	(RIRDL(6) KIYSFIEDMAASGCYWLACSCD	REIKLL(4) PVIASMSDVAASGGYYMAMAAN
326248         Lambda         (88) 570% (14) NGLTARLQQA	нининини вееес	DCALLIARV (4) PVWALANDMNCSAGOLLASAAS	DCADIIARM(4) PIWALANDMNCSAGQLIASSAS	FDLARFIYES(4) RIIAIANDDAYSAAYAIASSAB	ZDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	PDCAMMIYRL(4) PVWALCNDTACSAAMLLASACS	FELADIRAA(4) PITAIVNFSAFSGYLIAAAAS	FDCARMIYRM(4) PUWALANETACSAAMLLAAACS	FDCADMIYRL(4) PVWALCNDTACSAAMLLASACS	FELARHIMAS(4) KIIAYVDEFACSAAYALASSAB	DELYTKLKQL(4) KVVASFGNISASGGVYIAMGCP	AEIHKQVEEI (6) PVYVSMGNMAASGGYYISAPAT	RAIYKEVKEL(4) PIVAYISGYATSGYYIACGA	EKLARKVEEL(4) PVVVYVEGLDASGAYMVSAPAD	ELIAKRIRDL(6) KIYSFIEDMAASGGYWLACSCD	OLMWREIKLL(4) PUIASMSDVAASSCYYMAMAAN
22246         Lambda         REBER         HHHHHHH         HH         REBER           23234         Lambda         (8)         GTUS (14) NGTTARLQQASD-(5)         LUDDB3           23232         PO         GTUS (14) NGTTARLQQASD-(5)         LUDDB3           231119         VHM         (2)         GTUS (14) NGTTARLQQASD-(5)         LUDDB3           23232         PO         GTUS (14) NGTTARLQQASD-(5)         LUDDB3           2936         CIVA         GO         GTUS (14) SUCCASA	нинининини векк	VAGAFDCALITARV (4) PUWALANDMNCSAGQLLASAAS	VSGAFDCADIIARM(4) PIWALANDMNCSAGQLIASSAS(	VNGIFDLAEFIYES (4) RIIAIANDDAYSAAYAIASSAB	AAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	AAGAFDCAMMIYRL(4) PUWALCNDTACSAAMLLASACS	ATCAFELADDIRAA(4) PITAIVNFSAFSGYLIAAAAS	AAGAFDCAEMIYRM(4) PUWALANETACSAAMLLAAACS	AAGAFDCAUMIYRL(4) PVWALCNDTACSAAMLLASACS	ASGCFELARHIMAS(4) KIIAYVDEFACSAAYALASSAB	VVDSQEIYTKLKQL(4) KVVASFGNISASGVYIAMGCP	VLESAEIHKQVEEI(6) PVYVSMGNMAASGCYYISAPAT	ICPVRALYKEVKEL(4) PIVAYISGYATEGGAE	VIASEKLARKVEEL(4) PVVVYVEGLDASGAYMVSAPAD	PVOSELIAKRIRDL(6) KIYSFIEDMAASGGYWLACSGD	ALASDLMWREIKLL(4) PVIASMSDVAASGCYYMAMAAN
22.2.14         Lambda         (BS BTT/NS (14) NGTT/RALQDAASD(S) TILL           23.2.2.3         NO         (S) GTT/NS (14) NGTT/RALQDAASD(S) TILL           23.1.1.1.1         (S) GTT/NS (14) NGTT/RALQDAASD(S) TILL           23.1.1.2         (S) GTT/NS (14) NGTT/RALQDAASD(S) TILL           23.1.1.2         (S) GTT/NS (14) NGTT/RALQDAASD(S) TILL           23.1.1.2         (T) GGLAH (14) BL/RADT/TA	ннинининин веевс	PGGMVAGAFDCALITARV (4) PVWALANDMNCSAGQLLASAAS	PGGMVSGAFDCALITARM(4) PIWALANDMNCSAGQLIASSAS(	PGGEVNGIFDLAEFIYES (4) RIIAIANDDAYSAAYAIASSAB	GGGEAAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	PGGQAAGAFDCAMMIYRL(4) PUWALCNDTACSAAMLLASACS	NGGSATGAFELADIRAA(4) PITAIVNFSAFSGGYLIAAAAS	PGGQAAGAFDCAEMIYRM(4) PVWALANETACSAAMLLAAACS	PGGQAAGAFDCADMIYRL(4) PVWALCNDTACSAAMLLASACS	GGGEASGCFELARHIMAS (4) KIIAYVDEFACSAAYALASSAB	PGGTVVDSQEIYTKLKQL(4) KVVASFGNISASGGVYIAMGCP	PGGGVLESAEIHKQVEEI (6) PVYVSMGNMAASGGYYISAPAT	PGGYIGPVRALYKEVKEL(4) PIVAYISGYATEGGYYIACGAL	PGGEVIASEKLARKVEEL(4) PVVVYVEGLDASGAYMVSAPAD	PGGSPVQSELIAKRIRDL(6) KIYSFIEDMAASGYWLACSGD	PGGDALASDLMWREIKLL(4) PVIASMSDVAASGYYMAMAAN
223248         Lambda         REBER         IHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH	зеве нинининин вееве ининининин	DMDTPGGMVAGAFDCABIIARV(4) PVWALANDMNCSAGQLLASAAS	DMDTPGGMVSGAFDCADILARM(4) PIWALANDMNCSAGQLIASSAS(	DIDSPGGEVNGIFDLARFIYES (4) RIIAIANDDAYSAAYAIASSAB	BDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	DIDSPGGQAAGAFDCAMMIYRL(4) PVWALCNDTACSAAMLLASACS	DIDSNGGSATGAFELADIRAA(4) PITAIVNFSAFSGGYLIAAAAS	UDIDSPGGQAAGAFDCAEMIYRM(4) PVWALANETACSAAMLLAAACS	DIDSPGGQAAGAFDCAUMIYRL(4) PVWALCNDTACSAAMLLASACS	LHIDSGGGEASGCFELARHIMAS (4) KIIAYVDEFACSAAYALASSAE	IRIDSPGGTVVDSQEIYTKLKQL(4) KVVASFGNISASGGVYIAMGCP	QUNTPGGGVLESAEIHKQVEEI (6) PVYVSMGNMAASGGYYISAPAT	UNIDSPGGYIGPVRALYKEVKEL(4) PIVAYISGYATSGYYIACGAD	UVVNSPGGEVIASEKLARKVEEL(4) PVVVYVEGLDASGAYMVSAPAD	LIINSPGGSPVQSELIAKRIRDL(6) KIYSFIEDMAASGCYWLACSGD	RIDSPGGDALASDLMWREIKLL(4) PVIASMSDVAAGGGYYMAMAAN
22348         Lambda         REBER         HHHHHHH         HH           23248         Lambda         (e8) GTUS (14) NGLTARLQQALS         232311           231119         VHL         (73) GTUS (14) NGLTARLQQALS           231119         VHL         (73) GTUS (14) NGLTARLQQALS           290         GTUS (14) NGLTARLQQALS         290           291516         PLI         PLIAPDYTANS           29535         PLIAPDYTANS         297           275595         CHINS (14) GUUSCHERANS         275           275595         CHINS (14) GUUSCHERANS         275           275595         CHINS (14) GUUSCHERANS         275           215760         PH         (14) GUUSCHOOAVS           215760         BH         (29) GUUSCH        S           215760         PH         (14) GUUSCHOOAVS           215760         PH         (29) GUUSCHS           215760         BH         (29) GUUSCHS           215760         PH         (29) GUUSCHS           215760         SH         (29) GUUSCHS           215761         SH         (29) GUUSCHS           215761         SH         (29) GUUSCHS	вееес инининини вееес инининини	5) ILLIDMDTPGGMVAGAFDCALITARV (4) PVWALANDMNCSAGQLLASAAS	5) ILLDMDTPGGMVSGAFDCADILARM(4) PIWALANDMNCSAGQLIASSAS(	5) ILLDIDSPGGEVNGIFDLALFIYES (4) RIIAIANDDAYSAAYAIASSAD	5) RHGDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	5) VLLDIDSPGGOAGGAFDCAMMIYRL(4) PVWALCNDTACSAAMLLASACS	5) IVLDIDSNGGSATGAFELAEDIRAA(4) PITAIVNFSAFSGGYLIAAAAS	5) ILLDIDSPGGQAAGAFDCAEMIYRM(4) PVWALANETACSAAMLLAAACS	5) VLLDIDSPGGQAGGFDCAMMIYRL(4) PVWALCNDTACSAMLLASACS	5) IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDEFACSAAYALASSAE	5) LLVRIDSPGGTVVDSQEIYTKLKQL (4) KVVASFGNISASGVYIAMGCP	5) IILQVNTPGGGVLESAEIHKQVEEI (6) PVYVSMGNMAAGGYYISAPAT	5) VLLWIDSPGGYIGPVRALYKEVKEL (4) PIVAYISGYATSGYYIACGAL	5) VLLVVNSPGGEVIASEKLARKVEEL (4) PVVVYVEGLDASGAYMVSAPAD	5) LCLIINSPGGSPVQSELIAKRIRDL(6) KIYSFIEDMAASGYWLACSGI	5) ALIRIDSPGGDALASDLMWREIKLL (4) PVIASMSDVAASGGYYMAMAAN
326368         Пантиска 130680         Пантиска 130680         Пантиска 13060         Пантиска 1306	Н БЕЕЕЕ ИННИНИНИНИ БЕЕЕЕ ИНИНИНИИ	D(5) ILLDMDTPGGMVAGAFDCALITARV(4) PVWALANDMNCBAGQLLASAAS	D(5) ILLDMDTPGGMVSGAFDCADILARM(4) PIWALANDMNCSAGQLIASSAS(	N(5)ILLDIDSPGGEVNGIFDLAEFIYES(4) RIIAIANDDAYSAANAIASSAD	D(6) RHGDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	D(5) VLLDIDSPGGQAAGAFDCAMMIYRL(4) PVWALCNDTACSAAMLLASACS	D(5) IVLDIDSNGGSATGAFELADDIRAA(4) PITAIVNFSAFSGYLIAAAAS	D(5) ILLDIDSPGGQAAGAFDCAEMIYRM(4) PVWALANETACSAAMLLAAACS	D(5)VLLDIDSPGGQAAGAFDCAUMIYRL(4) PVWALCNDTACSAAMLLASACS	D(5) IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDEFACSAAYALASSAE	E (5) LLVRIDSPGGTVVDSQEIYTKLKQL (4) KVVASFGNISASGVYIAMGCP	D(5) IILQUNTPGGGVLESAEIHKQVEEI(6) PVYVSMGNMAASGGYYISAPAT	D(5) VLLWIDSPGGYIGPVRAIYKEVKEL(4) PIVAYISGYATSGYATACGAL	D(5) VLLVVNSPGGEVIASEKLARKVEEL(4) PVVVYVEGLDASGAYMVSAPAD	I(5) LCLIINSPGGSPVQSELIAKRIRDL(6) KIYSFIEDMAASGGYWLACSGD	S (5) AIIRIDSPGSDALASDLMMREIKLL (4) PUIASMSDVAAGSSYYMAMAAN
22248         lambda         REREER HHHHHH           222248         lambda         (86) TTMS (14) NGTTARLOC           22329         NIS         (90) GTMS (14) NGTTARLOC           2311131         VIML         (53) GTMS (14) NGTTARLOC           2926         P21         (90) GTMS (14) NGTTARLOC           2926         P21         (91) GTMS (14) NGTTARLOC           2926         P21         (91) GTMS (14) NGTTARLOC           2925         P21         (91) GTMS (14) GTMS	нин веве ининининин веве ининини	ASD(5)ILLDMDTPGGMVAGAFDCABIIARV(4) PVWALANDMNCBAGQLLASAAS	ISD(5)ILLDMDTPGGMVSGAFDCADILARM(4) PIWALANDMNCSAGQLIASSAS(	LSN(5)ILLDIDSPGGEVNGIFDLAEFIYES(4) RIIAIANDDAYSAAYAIASSA5	LND (6) RHGDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	MAD(5) VLLDIDSPGGQAAGAFDCAMMIYRL(4) PVWALCNDIACSAAMLLASACS	VAD(5)IVLDIDSNGGSATGAFELADDIRAA(4) PITAIVNFSAFSGGYLIAAAAS	VSD(5)ILLDIDSPGGQAAGAFDCAEMIYRM(4) PVWALANETACSAAMLLAAACS	MAD(5) VLLDIDSPGGQAAGAFDCAUMIYRL(4) PVWALCNDTACSAMLLASACS	LAD(5) IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDEFACSAAYALASSAE	VEE(5) LLVRIDSPGGTVVDSQEIYTKLKQL(4) KVVASFGNISASGGVYIAMGCP	GED(5)IILQVNTPGGGVLESAEIHKQVEEI(6) PVYVSMGNMAASGGYYISAPAT	KSD(5) VLLWIDSPGGYIGPVRALYKEVKEL(4) PIVAYISGYATSGGYYIACGAL	EKD(5) VLLIVVNSPGGEVIASEKLARKVEEL (4) PVVVYVEGLDASCAYMVSAPAD	FKI(5)LCLIINSPGGSPVOSELIAKRIRDL(6) KIYSFIEDMAASGGYWLACSGD	RES(5)AIIRIDSPGGDALASDLMWREIKLL(4) PVIASMSDVAASGGYYMAMAAN
262248         lambda         (e) CTUS (14) NGL1           130659         NIS         (e) CTUS (14) NGL1           131121         UHH         (f) NGL1           131121         (f) NGL1         (f) NGL1           131121         (f) NGL1         (f) NGL1           131121         (f) NGL1         (f) NGL1           131122         (f) CUVH (14) DUVH         (f) NGL1           1755326         G157-1         (f) QUVH (14) DUVH           175532         Pelix01         (f) QUVH (14) DUVH           1776         (f) QUVH (14) DUVH         (f) DUVH           1776         (f) QUVH         (f) DUVH           1776 <td< td=""><td>ни ни вевее ининининини вевее ининини</td><td>)AASD(5)ILLDMDTPGGMVAGAFDCALTIARV(4) PVWALANDMNCSAGQLLASAAS</td><td>)AISD(5)ILLDMDTPGGMVSGAFDCARTIARM(4) PIWALANDMNC9AGQLIASSAS(</td><td>2ALSN(5)ILLDIDSPGGEVNGIFDLAFFIYES(4) RIIAIANDDAYSAAYAIASSAE</td><td>RALND(6) RHGDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD</td><td>)AMAD(5) VLLDIDSPGGQAGGPDCAUMIYRL(4) PVWALCNDTACEAAMLLASACS</td><td>DAVAD(5) IVLDIDSNGGSATGAFELADDIRAA(4) PITAIVNFSAFSGGYLIAAAAS</td><td>)AVSD(5) ILLDIDSPGGQAAGAFDCAEMIYRM(4) PVWALANETACSAAMLLAAACS</td><td>)AMAD(5) VLLDIDSPGGQAAGAFDCAUMIYRL(4) PVWALCNDTACSAAMLLASACS</td><td>2ALAD(5)IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDEFACSAAYALASSAE</td><td>CTVEE (5) LLVRIDSPGGTVVDSQEIYTKLKQL (4) KVVASFGNISASGVYIAMGCP</td><td>CAGED(5)IILQVNTPGGGVLESAEIHKQVEEI(6) PVYVSMGNMAASGGYYISAPAT</td><td>TIKSD (5) VLLWIDSPGGYIGPVRAIYKEVKEL (4) PIVAYISGYATSGGYYIACGAD</td><td>0LEKD(5) VLLIVVNSPGGEVIASEKLARKVEEL (4) PVVVYVEGLDAGAYMVSAPAL</td><td>CAFKI(5)LCLIINSPGGSPVQSELIAKRIRDL(6) KIYSFIEDMAASGGYWLACSGI</td><td>VVRES(5)AIIRIDSPGGDALASDLMWREIKLL(4) PUIASMSDVAASGYYMAMAAN</td></td<>	ни ни вевее ининининини вевее ининини	)AASD(5)ILLDMDTPGGMVAGAFDCALTIARV(4) PVWALANDMNCSAGQLLASAAS	)AISD(5)ILLDMDTPGGMVSGAFDCARTIARM(4) PIWALANDMNC9AGQLIASSAS(	2ALSN(5)ILLDIDSPGGEVNGIFDLAFFIYES(4) RIIAIANDDAYSAAYAIASSAE	RALND(6) RHGDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYSAAYALACCCD	)AMAD(5) VLLDIDSPGGQAGGPDCAUMIYRL(4) PVWALCNDTACEAAMLLASACS	DAVAD(5) IVLDIDSNGGSATGAFELADDIRAA(4) PITAIVNFSAFSGGYLIAAAAS	)AVSD(5) ILLDIDSPGGQAAGAFDCAEMIYRM(4) PVWALANETACSAAMLLAAACS	)AMAD(5) VLLDIDSPGGQAAGAFDCAUMIYRL(4) PVWALCNDTACSAAMLLASACS	2ALAD(5)IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDEFACSAAYALASSAE	CTVEE (5) LLVRIDSPGGTVVDSQEIYTKLKQL (4) KVVASFGNISASGVYIAMGCP	CAGED(5)IILQVNTPGGGVLESAEIHKQVEEI(6) PVYVSMGNMAASGGYYISAPAT	TIKSD (5) VLLWIDSPGGYIGPVRAIYKEVKEL (4) PIVAYISGYATSGGYYIACGAD	0LEKD(5) VLLIVVNSPGGEVIASEKLARKVEEL (4) PVVVYVEGLDAGAYMVSAPAL	CAFKI(5)LCLIINSPGGSPVQSELIAKRIRDL(6) KIYSFIEDMAASGGYWLACSGI	VVRES(5)AIIRIDSPGGDALASDLMWREIKLL(4) PUIASMSDVAASGYYMAMAAN
262748         lambda         (88) 67105 (14)           222229         WD         (53) 617105 (14)           222229         WD         (53) 617105 (14)           272129         VHM         (71) 664.04 (14)           2711         VHM         (71) 664.04 (14)           2712         (84) 67105 (14)         (71) 664.04 (14)           2713         (94) 67105 (14)         (71) 964.04 (14)           2715         (84) 67104 (14)         (71) 964.04 (14)           2715         (84) 67104 (14)         (71) 964.04 (14)           2715         (84) 67104 (14)         (71) 964.04 (14)           2715         (84) 67104 (14)         (71) 964.04 (14)           2714         (71) (64) 671.04 (14)         (71) 971.05 (14)           2714         (71) (64) 661.06 (17)         (71) 971.05 (13)           2714         (71) (71) (64) 96.01.07 (14)         (71) 971.05 (13)           2714         (71) (71) (71) (71) (71)         (71) 971.05 (13)           2714         (73) 971.05 (17) (75) 971.07 (15)         (71) 971.05 (15)           2714         (73) 971.07 (15) (83) 671.07 (15)         (71) 971.05 (15)           2714         (73) 971.07 (16) (83) 671.07 (15)         (71) 971.05 (15)           2715         (71) 971.05 (15) (71)	ниннин вееее ининининини вееее инининини	ARLQQAASD(5)ILLDMDTPGGMVAGAFDCAEIIARV(4) PVWALANDMNCSAGQLLASAAS	ARLQQAISD(5)ILLDMDTPGGMVSGAFDCABILARM(4) PIWALANDMNCEAGQLIASSAS(	SEIEEALSN(5)ILLDIDSPGGEVNGIFDLAUEIYES(4) RIIAIANDDAYEAAYAIASSAE	IDYDTALND(6)RHGDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYEAAGCCU	<pre>ACLQQAMAD(5) VLLDIDSPGGQAAGAFDCAMMIYRL(4) PVWALCNDTACSAAMLLASACS</pre>	<pre>SAVNQAVaD(5)IVLDIDSNGGSATGAFELAEDIRAA(4) PITAIVNFSAFSGGYLIAAAAS</pre>	ARLQQAVSD(5)ILLDIDSPGGQAGAFDCAEMIYRM(4) PVWALANETACEAAMLLAAACS	<pre>ACLQQAMAD(5)VLLDIDSPGGQAGGAFDCAEMIYRL(4) PVWALCNDTACEAMILLASACS</pre>	<pre>KGFDEALAD(5)IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDEFACEAYAYLASSAE</pre>	CAL-KTVEE(5)LLVRIDSPGGTVVDSQEIYTKLKQL(4) KVVASFGNISASGGVYIAMGCP	<pre>DE-KAGED(5)IILQUNTPGGGULESAEIHKQVEEI(6) PVVVSMGNMAABGGYYISAPAT</pre>	<pre>CLE-VIKSD(5)VLLWIDSPGGYIGPVRAIYKEVKEL(4) PIVAYISGYATBGGYYIACGAB</pre>	ILIDDLEKD(5)VLLVVNSPGGEVIASEKLARKVEEL(4) PVVVYVEGLDAGGAYMVSAPAL	ALIEKAFKI(5)LCLIINSPGGSPVQSELIAKRIRDL(6) KIYSFIEDMAASGGYWLACSGI	KIRSVRES(5)AIIR <mark>I</mark> DSPGGDALASDLMMRE <mark>I</mark> KL <mark>L</mark> (4) PVIASMSDVAA <mark>G</mark> GGYYMAMAAN
222248 lambda (8) 670% 310469 N15 (90) 671% 311131 VIML (9) 671% 311131 VIML (9) 671% 311131 VIML (9) 6711/0 311131 VIML (9) 611/0 975166 (91 64) 717/0 975526 (61 64) 717/0 97552 (61 64) 717/0 49702 (64) 60/1 66 8632 (9) (9) 91/1 66 8632 M) (9) 91/1 892468 Rc (9) 10.108 892468 Rc (9) 10.108 892468 Rc (9) 10.108 892468 Rc (9) 31.018 892468 Rc (9) 31.018 89248 Rc (9) 31.018 80248 Rc (9	нниннин зазая ниннининин зазая нин ниннинин	VGIIARLQQAASD(5)ILLDMDTPGS#VAGAFDCABILARV(4) PVWALANDMNCSAGQLLASAAS	NGTIARLQQAISD(5)ILLDMDTPGGMVSGAFDCARIIARM(4) PIWALANDMNCSAGQLIASSAS(	ZKIQEEIEEALSN(5)ILLDIDSPGGEVNGIFDLAEFIYES(4) RIIAIANDDAYSAAYAIASSAE	LIRHDYDTALND(6)RHGDLTHGGGEAAGCYDLAPSLLSA(7) TRVSLENESCYGAAYALACCU	CIVACLOOAMAD(5) VLLDIDSPGGQAGAFAFDCAEMIYRL(4) PVWALCNDIACSAAMLLASACS	ZGLRSAVNQAVAD(5)IVLDIDSNGGSATGAFELAQDIRAA(4) PITAIVNFSAFSGYLIAAAAS	JGVTARLQQAVSD(5)ILLDIDSPGGQAAGAFDCAAMIXRM(4) PVWALANETACSAMLLAAACS	VGIVACLQQAMAD(5)VLLDIDSPGGQAAGAFDCAAMIYKL(4) PVWALCNDTACSAAMLLASACS	GLRRGFDEALAD(5)IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDEFACGAAYALASSA	KAVLKAL-KTVEE(5) LLVRIDSPGGTVVDSQEIYTKLKQL(4) KVVASFGNISAEGVYIAMGCP	TELKQLE-KAGED(5)IILQUNTPGGGVLESAEIHKQVEEI(6) PVYVSMGNMAASGGYYISAPAT	VVRGLE-VIKSD(5)VLLMIDSPGGYIGPVRAIYKEVKEL(4) PIVAYISGYATSGGYYIACGAE	RYINLLDDLEKD(5)VLLVVNSPGGEVIASEKLARKVEEL(4) PVVVYVEGLDAGGAYMVSAPAL	SCINALIEKAFKI(5) LCLIINSPGSSPVOSELIAKRIRDL(6) KIYSFIEDMAASGYWLACSG	BOLIEKIRSVRES(5)AIIRIDSPGGDALASDLMWREIKLU(4) PUIASMSDVAABGGYYMAMAAN
222248         lambda         (89)           130469         N15         (20)           13104         N15         (20)           13119         VHML         (21)           13119         VHML         (71)           13119         VHML         (71)           131119         VHML         (71)           195516         pilitzl         (84)           1755926         Lifey-1         (84)           19712         Felixol1         (84)           19702         Pelixol1         (84)           977955         Pf         (71)           977955         Pf         (77)           979555         Pf         (77)           979563         Ac         (93)           979553         Pf         (93)           979553         Pf         (93)           979533         Ac         (93)           979533         Ac         (93)           979533	ниннинин вевее инниннинин вевее инниннинин	(14)NGTIARLQQAASD(5)ILLDMDTPGGMVAGAFDCALIIARV(4) PVWALANDMNCGAGQLLASAAS	(14)NGIIARLQQAISD(5)ILLDMDTPGGWVSGAFDCAUIIARM(4) PIWALANDMNCSAGQLIASSAS(	(14) <u>EKIQEEIEEAL</u> SN(5) ILLDIDSPGGEVNGIFDLA <mark>E</mark> FIYES(4) RIIAIANDDAY <mark>S</mark> AAYAIASSAE	(14) <b>DLIRHDYDTALND</b> (6) <b>RHGDLTHGGEBAAGCVDLAPSLLSA</b> (7) T <b>RVSLENSCYSAAYALACCU</b>	(114) BeIVACLOOAMAD(5) VLLDIDSPGGOAAGAPDCAEMIYRL(4) PVWALGNDTACEAMILLASACS	(14) BGLRSAVNQAVAD(5) IVLDIDSNGGSATGAFELABDIRAA(4) PITAIVNFSAFBGGYLIAAAAS	(14) DGVTARLQQAVSD(5) ILLDIDSPGGQAGAFDCAEMIYRM(4) PVWALANFTACEAAMLLAAACS	(14) DGIVACLQQAMAD(5) VLLDIDSPGGQAAGAFDCAEMIYRL(4) PVWALCNDTACEAAMLLASACS	(14) BGLRRGFDEALAD(5) IVLHIDSGGGEASGCFELARHIMAS(4) KIIAYVDFFACSAAYALASSA	(3) KAULKAL-KTVEE(5) LLVRIDSPGCTUVDSQEIYIKLKQL(4) KUVASFGNISASGUYIAMGCP	(1) DFLKQLE-KAGED(5) IILQUNTPGGGVLESAEIHKQVEEI(6) PVYVSMGNMAAGGGYYISAPAT	(4) EVVKKLE-VIKSD(5)VLLWIDSPGGYIGPVRAIYKEVKEL(4) PIVAYISGYATEGGYIACGAE	(5) RYINLLDDLEKD(5)VLLVVNSPGEVIASEKLARKVEEL(4) PVVVYVEGLDAGAYMVSAPAL	(11) ESINALIEKAFKI(5) LCLIINSPGGSPVOSELIAKRIRDL(6) KIYSFIEDMAAGGYWLACSOL	(14) BOLIEKIRSVRES(5) ALIRIDSPGGDALASDLMMREIKLL(4) PVIASMSDVAASGGYYMAMAAN
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FIG. 3. Multiple-sequence alignment of protease clan SK members. Designations are as described in the legend to Fig. 2. Species abbreviations: Ec, *E. coli*; Bs, *Bacillus subilis*; Lp, *Lactobacillus plantarum*; At, *Arabidopsis thaliana*; Sco, *Streptomyces coelicolor* A3(2); Sy, *Synechocystis* sp. strain PCC 6803; Bh, *Bacillus halodurans*; Pf, *Pyrococcus furiosus* DSM 3638, Mi, *Methanococcus jannaschii*; Rc, Rickettsia conorii.



FIG. 4. Phylogenetic tree constructed by using the sequence alignment of phage portal proteins. Sequences of the portal proteins from phages and prophages were aligned by using the T-Coffee (23) and CLUSTAL\_X (34) programs, followed by manual validation and the removal of poorly aligned regions. The phylogenetic tree was constructed by using the neighbor-joining method as implemented in the NEIGHBOR program, and subsets of the data were used to rebuild the tree multiple times. The root was set to midpoint by the RETREE program of the PHYLIP package (10), and the consensus tree was subsequently reviewed by TreeView (24). Bootstrap values were estimated by resampling the set of the alignment 100 times (see the supplemental material). The level of bootstrap support is marked by small circles in the following colors: red (90 to 100%), yellow (80 to 90%), green (70 to 80%), and blue (50 to 70%). The nodes with <40% support are unlabeled. Phages that encode prohead protease belonging to clan SK are shaded in pink, and those that encode prohead protease belonging to clan SK are shaded in gray.

not seem to belong to these two classes and lacks similarity to any other proteins is the product of *orf13* in pneumococcal phage Cp-1 (21). While ClpP-like proteases are found in both prokaryotic and eukaryotic organisms, a striking feature of clan SH is that its members are found only in the dsDNA viruses of bacteria and eukaryotes. Sensitive probabilistic searches of sequence databases, such as with the HMMER package (9) and Wise2 package (http://www.ebi.ac.uk/Wise2/), as well as searches of the databases of unfinished prokaryotic and eukaryotic genomes and expressed sequence tags, failed to reveal clan SH members in any other viruses or cellular organisms. All significant matches to bacterial genomes turned out to be in the recently integrated prophages, which typically possess the full complement of structural components of the virions (data not shown).

Mechanistic similarities between the maturation of phage heads and herpesvirus capsids are quite remarkable. Both procapsids are assembled on an asymmetric  $\alpha$ -helical scaffold, which is cut into fragments by viral protease and leaves behind an empty head shell. In both cases, replicated virus genome is packaged into this shell until the associated virus-encoded terminase enzyme cleaves genomic DNA. Concomitant with DNA packaging, the capsid changes from nearly spherical to a much more stable icosahedral form. These parallel relationships remained an evolutionary puzzle without direct evidence for sequence relationships between individual components. It has been noted, however, that the orders of structural components and factors of their assembly in virus genomes were similar and that large subunits of phage and herpesvirus terminases are related ATP-hydrolyzing enzymes (5, 14, 31). Statistically significant sequence similarity between the SH-type proteases from phages and herpesviruses strengthens the argument that the complement of genes encoding capsid components and maturation factors in bacteriophages and herpesviruses has evolved from a common ancestor.

In phages, the prohead protease gene is always located between genes that encode the portal protein and the major capsid protein. Since these three gene products interact intimately with each other during the phage capsid assembly and maturation process, the tandem arrangement appears to be under a selective constraint. Strikingly, however, the type of the maturation protease is not correlated with the extent of sequence similarity between the neighboring structural proteins. One such example is presented by phages Xp10, D3, and *Pseudomonas putida* prophage; their genes coding for the portal protein and the major capsid protein are closely related and must have diverged very recently (Fig. 4 and data not shown), yet in phages Xp10 and D3, the protease belongs to clan SK, and the gene in exactly the same location in *P. putida* prophage codes for a clan SH member (40).

A prohead protease gene can thus be replaced in evolution by a functionally equivalent gene coding for a structurally unrelated protease. Such nonorthologous gene displacement is thought to be common in the genomes of cellular life forms (18) and has been noted to occur in some other phage genes, such as integrase (33) and lysozyme (4). In order to trace the history of the mutual displacement of prohead proteases, we built a phylogenetic tree of dsDNA phages based on the similarity of their portal proteins and labeled the leaves of the resulting consensus tree by the type of prohead protease observed in each lineage. Analysis of the resulting tree (Fig. 4) indicates that the SK-type protease may be a derived characteristic, with the possessors of this protease typically being nested within a group of phages with the SH-type protease. All of the deepest branches of the tree, or all clades but one with bootstrap support of more than 50%, are inferred to have the SH-type protease at the root (Fig. 4 and data not shown). Thus, the SH-type protease may be evolutionarily ancient, predating the common ancestor of present-day DNA phages, and several in situ gene replacements by the ClpP-like protease may have occurred in different evolutionary lineages. Interestingly, at lease in one case, such SH-to-SK displacement appears to have been followed by a reverse displacement, from SK to SH, in the *P. putida* prophage (Fig. 4).

The phage phylogeny shown in Fig. 4 is inferred on the basis of a single gene, albeit one that has strong functional links to prohead protease. We also examined the distribution of two classes of portal proteases in a phylogenetic tree built on the basis of a whole-genome approach (30). There are topological differences between that phage proteomic tree and our singlegene tree, but remarkably, the pattern of incongruity between the protease type and the whole-genome phylogeny still holds, with phages with the SK-type protease typically nested within a group of phages with the SH-type protease (details are available from the authors upon request).

To conclude, the proteolytic cleavage of the scaffold during the assembly of capsids in dsDNA bacteriophages appears to be a virus-specific function provided by the proteolytic enzymes from at least two distinct families and folds. One of these folds, which is perhaps evolutionarily more ancient, is shared with the functionally very similar protease of herpesviruses. Phylogenetic analysis suggests that the two types of head maturation proteases in dsDNA bacteriophages have displaced each other on multiple occasions.

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