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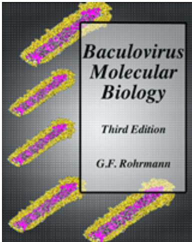

12. The AcMNPV genome: Gene content, conservation, and function

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The *Autographa californica* nucleopolyhedrovirus (AcMNPV) was originally described in the early 1970s (1) and research on its genetics began later in that decade. This was stimulated by the facility with which the virus replicated in cells from *Spodoptera frugiperda* (2) and *Trichoplusia ni* (3). Subsequently, this led to the development of technology for the deletion of genes (4, 5), and allowed for targeted studies on the function of specific genes, particularly if the deletion or mutation of the target gene was not lethal to the virus. The publication of the genome sequence of AcMNPV (6) was a landmark in the investigation of this virus because it put all previous and future investigations into context. It also revealed genes that are shared with other organisms, and provided the basis for understanding baculovirus diversity. Subsequently, the development of the bacmid system, which allowed for the production of recombinants via transposition of recombinant plasmids into the AcMNPV genome incorporated into a bacterial artificial chromosome, allowed for manipulation of the whole AcMNPV genome in bacteria (7). The adaptation of this technology to making targeted deletions provided a method for constructing baculovirus gene knockouts in bacteria that could then be investigated via transfection into insect cell lines (8). The modification of this technology using a lambda *red* recombinant system (9) allowed for the more efficient production of knockouts (10). This has resulted in a proliferation of studies on AcMNPV essential genes that were previously difficult to investigate because knockouts were lethal and they could not be readily generated without the production of complementary cell lines. With bacmid knockouts, the function of the target gene can be inferred from the examination of cells transfected with DNA of the mutant. The adaptation of similar bacmid systems for other baculovirus genomes has allowed for parallel studies on these viruses. Concomitant with the development of techniques for investigating gene function has been a proliferation of complete genome sequence data for many baculoviruses. Because of the widespread use of AcMNPV, not only for fundamental investigations on gene function, but also because of its use as an expression vector, I have attempted to annotate the AcMNPV genome in terms of understanding the function of each of the genes.

Adjustments to the AcMNPV genome sequence: There are approximately 150 orfs

Several regions of the genome of the AcMNPV C-6 strain have been resequenced by one or more laboratories. This, in combination with genome sequences of variants of AcMNPV that have become available, has revealed revisions that should be incorporated into the sequence. The following summarizes the physical corrections to the AcMNPV genome that have been described. The original orfs Ac20/21, 58/59, 106/107 and 112/113 (6) should be combined into single orfs. Ac20/21 was resequenced when it was implicated in actin rearrangement (11), and all four of these regions were resequenced as a comparison of the AcMNPV and RoMNPV genomes

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(12). In addition, resequencing also indicated that Ac17, 52, 131, and 143 are longer than originally reported (12). The total number of orfs reported for AcMNPV was originally calculated to be 154; this adjustment reduces it by 4. However, the discovery of lef-10 (Ac53a), which was missed in the original annotation because of its significant overlap with the 5' region of an adjacent gene (Ac54) (13), adds an additional orf. Therefore, there appear to be 151 orfs present in the genome based on the original criteria of an orf comprising 50 amino acids. However, Ac85 (53 aa) is only found in two other NPVs that are variants of AcMNPV (PlxyNPV) (14) and RoMNPV (12). Two orfs, Ac97 (56 aa) and Ac140 (60 aa), are only present in AcMNPV. Of these three orfs, only Ac97 was predicted to be preceded by transcriptional regulatory sequences (6). Although these three orfs may not be valid, others may be present that have not yet been detected. Therefore, it would appear that there are 'about' 150 orfs in the AcMNPV genome.

In this review, I have attempted to include pertinent information on the function of all the orfs present in the AcMNPV genome. This is not an exhaustive review, but an attempt to infer function from either actual experimentation on the AcMNPV gene or to homology from related viruses. A significant proportion of the data included comes from the *Bombyx mori* NPV (BmNPV). It is closely related to AcMNPV and is the second most studied NPV and a complete study based on the generation of BmNPV bacmid knockouts of all its open reading frames has been described (15).

Table 1 lists all the genes that have been named in the AcMNPV genome followed by the orf number. It cannot be emphasized enough how important it is to incorporate both orf numbers and the AcMNPV homolog (if present) into any description of a baculovirus gene no matter which baculovirus it is from. Without this reference, it is difficult, if not impossible, to put reports into any sort of perspective. Following the index is a review of what I could find regarding all the genes in the AcMNPV genome. This is not a complete review of these genes but focuses particularly on AcMNPV. When a report of the homolog from another virus is relevant, that material is also included.

Table 1. Index to named AcMNPV genes/gene products

ARIF1 (Actin rearranging factor1)	**Ac20/21**
Alkaline nuclease	**Ac133**
BRO (Baculovirus repeated orf)	**Ac2**
BV/ODV-E26	**Ac16**
BV/ODV-C42	**Ac101**
Calyx, polyhedron envelope	**Ac131**
Cathepsin	**Ac127**
ChaB homolog	**Ac59**
ChaB homolog	**Ac60**
Cg30	**Ac88**
C42	**Ac102**
Chitinase	**Ac126**
Conotoxin like (Ctl)	**Ac3**
Desmoplakin-like	**Ac66**
DBP (DNA binding protein)	**Ac25**
DnaJ domain protein	**Ac51**
DNA polymerase	**Ac65**
EGT	**Ac15**

Table 1. continued from previous page.

ETL (PCNA)	**Ac49**
ETM	**Ac48**
ETS	**Ac47**
Exon-0	**Ac141**
F (fusion protein homolog)	**Ac23**
FGF (fibroblast growth factor)	**Ac32**
FP (few polyhedra)	**Ac61**
Fusolin (gp37)	**Ac64**
GP16	**Ac130**
GP37	**Ac64**
GP41	**Ac80**
GP64	**Ac128**
Gta (global transactivator)	**Ac42**
Hcf-1 (host cell factor 1)	**Ac70**
Helicase, p143	**Ac95**
He65	**Ac105**
Homologous regions	**Hrs** (see end of chapter)
Iap-1	**Ac27**
Iap-2	**Ac71**
Ie1	**Ac147**
Ie0	**Ac147-0**
Ie2	**Ac151**
J domain	**Ac51**
Lef1	**Ac14**
Lef2	**Ac6**
Lef3	**Ac67**
Lef4	**Ac90**
Lef5	**Ac99**
Lef6	**Ac28**
Lef7	**Ac125**
Lef8	**Ac50**
Lef9	**Ac62**
Lef10	**Ac53a**
Lef11	**Ac37**
Lef12	**Ac41**
Me53	**Ac139**
MTase (methyl transferase)	**Ac69**
Nudix	**Ac38**

Table 1. continued from previous page.

ODV-E18	**Ac143**
ODV-E25, p25, 25k	**Ac94**
ODV-EC27	**Ac144**
ODV-E56	**Ac148**
ODV-E66	**Ac46**
P6.9	**Ac100**
P10	**Ac137**
P11	**Ac145**
P12	**Ac102**
P15	**Ac87**
P18	**Ac93**
P24	**Ac129**
P26	**Ac136**
P33 (sulfhydryl oxidase)	**Ac92**
P35	**Ac135**
P40	**Ac102**
P43	**Ac39**
P45, p48	**Ac103**
P47	**Ac40**
P49	**Ac142**
P74, pif	**Ac138**
P94	**Ac134**
P143 (helicase)	**Ac95**
PCNA	**Ac49**
Pe38	**Ac153**
PEP polyhedron envelope protein	**Ac131**
Pif-1	**Ac119**
Pif-2	**Ac22**
Pif-3	**Ac115**
Pif-4	**Ac96**
Pif-5	**Ac148**
Pif-6	**Ac68**
PK1 (Protein kinase 1)	**Ac10**
PK2 (Protein kinase 2)	**Ac123**
PKIP (Protein kinase interacting factor)	**Ac24**
PNK polynucleotide kinase	**Ac33**

Table 1. continued from previous page.

PNK/PNL polynucleotide kinase/ ligase	**Ac86**
Polyhedrin	**Ac8**
Pp31;39K	**Ac36**
Pp34, polyhedron envelope	**Ac131**
Pp78/83;orf1629	**Ac9**
Protein tyrosine phosphatase (ptp)	**Ac1**
SOD superoxide dismutase	**Ac31**
Sulfhydryl oxidiase, sox	**Ac92**
TLP telokin-like	**Ac82**
TRAX-like	**Ac47**
Ubiquitin	**Ac35**
VLF-1 very late factor 1	**Ac77**
Vp39, capsid	**Ac89**
Vp80, vp87	**Ac104**
Vp91	**Ac83**
Vp1054	**Ac54**
19K	**Ac96**
38K	**Ac98**
49K	**Ac142**

Annotation of the AcMNPV genome

Below is an annotation of the orfs in the AcMNPV genome based on their orf number from (6). An asterisk (*) indicates a core gene with homologs found in all sequenced baculovirus genomes. The orf size in amino acids, followed by the molecular mass in kDa is indicated after each orf as reported by (6, 12). The same information is also included for the BmNPV (16) and *Heliocoverpa armigera* (HaSNPV) (17) orthologs of these genes. Both AcMNPV and BmNPV are Group I alphabaculoviruses whereas HaSNPV is a group II alphabaculovirus and lacks some of the genes found in AcMNPV and BmNPV but also has some additional genes. The distribution of the genes is from analyses completed in early 2008; therefore, the viral distribution reflects the genomes available at that time. The survey of information regarding each gene was updated in late 2013.

Ac1 (168aa:19.3kDa), (Bm130:168aa:19.3kDa), (protein tyrosine phosphatase (ptp); baculovirus phophatase (bvp)).

Ac1 homologs are present in the genomes of all lepidopteran Group I NPVs, but not those of other baculoviruses. Closely related orfs are found in a variety of invertebrates, e.g., *Drosophila* (E = 7e-30) and vertebrates, e.g., human (E = 2e-27). It is expressed from a late promoter (18). It was originally identified because of its relatedness to protein tyrosine phosphatases and its ability to dephosphorylate proteins at ser, thr and tyr residues (19). However, it was later found that Ac1 is an RNA 5'-triphosphatase and hydrolyzes the gamma phosphate of triphosphate-terminated poly(A) and also hydrolyzes ATP to ADP and GTP to GDP (20, 21). The crystal structure has been determined (22). Ac1 is predicted to have one of the same enzymatic activities of LEF-4 (Ac90) that is involved in preparing RNA for cap formation. Although deletion is not lethal, mutants are

partially defective in occluded virus production in Sf-21, but not Tn-368 cells (23). During the final larval stages many Lepidoptera disperse (wander) probably as an evolutionary mechanism to spread the population, reduce predation, and find an optimal location for pupation. Baculovirus infection appears to be capable of enhancing this behavior possibly as a mechanism of spreading the virus. It was found that BmNPV deleted for the tyrosine phosphatase gene failed to undergo this enhanced wandering behavior (24). It is not clear whether the enzymatic activity of this protein is related to this observation. One report indicated that it was not required for BmNPV infected *B. mori* larvae (25), whereas the other suggested that it was required for the in AcMNPV infected *S. exigua* larvae (26). Although not reported to be associated with ODV by proteomic analysis, it was found in BV preparations (27).

Ac2 (328aa:38.8kDa), (Bm131:349aa:40.1kDa, Bm22:317aa:35.4kDa, Bm80:239:27.5kDa, Bm81:318aa:35.9kDa, Bm132:241aa:27.8kDa), (Ha59:244aa:28.2,Ha60:527aa:59.7kDa,Ha105:501aa:58.3kDa) (Baculovirus repeated orf—BRO).

Derivation: In American inner-city dialect 'bro' means 'brother', but not necessarily a close relationship.

Homologs of Ac2 have a widespread distribution in lepidopteran NPVs and GVs and are also found in the dipteran, but not hymenopteran NPV genomes. Related orfs are also found in double-stranded DNA phage, prokaryotic class II transposons, and a variety of DNA viruses pathogenic for insects, including entomopox viruses, iridoviruses and ascoviruses (28). Twenty-three copies of *bro* genes have been reported in a *Heliothis virescens* ascovirus genome sequence (29). Although there is only one copy of the *bro* gene in AcMNPV, the number can vary in different baculoviruses from none in the closely related *Rachiplusia ou* MNPV — its orfs are 96% identical in sequence to AcMNPV (12), two in the more closely related PlxyNPV (14) (orfs are 98.5% identical to AcMNPV), to up to 16 copies in LdMNPV (30). AcMNPV Ac 2 deletion mutants are viable, but some differences in polyhedron production in infected cells were noted (28). One of the major differences in gene content between BmNPV and AcMNPV is the presence of 3-5 copies of *bro* genes in BmNPV vs. a single copy in AcMNPV (16). The BmNPV *bro* genes are present in three locations with duplicate genes in two of the locations. In contrast, another BmNPV strain only shows 3 copies of the gene, one at each of the three locations (31, 32). This suggests that duplication/loss of these genes might be common. In the strain with five genes, individual mutants of four of the genes were isolated in BmNPV, but a mutant of one gene (*bro-d*) could not be isolated. Also, a double mutant of *bro-a* and *bro-c* could not be produced, suggesting that they complement an essential function and that *bro-d* has a unique essential function (33). BmNPV BRO proteins have DNA binding activity (34), and all the BmNPV *bro* genes appeared to be expressed as early genes and are distributed in both the nucleus and cytoplasm (33). One of the *bro* gene products was found to interact with laminin, a glycoprotein that is a major constituent of the basal lamina and is involved in cell attachment (35).

Ac3 (53aa:5.6kDa) (Conotoxin-like (*ctl*) genes).

Conotoxins are small disulfide-rich ion channel antagonists isolated from snails (genus *Conus)* (36). Homologs of *ctl* are found in about half of the sequenced Group I and Group II lepidopteran NPV genomes and two GVs (Xcni- and HaGV). Although in AcMNPV a single *ctl* gene is present, several other viruses, e.g., OpMNPV and LdMNPV, encode two *ctl* genes of different lineages (*ctl-1* and *ctl-2*). Homologs are found in the *Amsacta moori* entomopoxvirus (E = 0.006), a few mosquito species, a funnel web spider, a wasp, and a bacterium. The EPV (*A. moori* gene falls within the baculovirus *ctl-2* lineage. In a study examining the AcMNPV *ctl* (*ctl*-1) gene, no differences in mortality, motility, or weight gain were observed when either neonate or late instar *Spodoptera frugiperda* larvae were infected with an AcMNPV mutant deleted for *ctl-1*, compared with infection with wt virus (37).

Ac4 (151aa:17.6kDa), (Bm133:151aa:17.7kDa).

Homologs of Ac4 are found in all Group I, three group II, and two GV genomes, but not in other lineages. Ac4/Bm133 is likely to be nonessential because when it was deleted the virus appeared normal (15, 38, 39).

Ac 5 (109aa:12.4kDa), (Bm134:109aa:12.4kDa).

Homologs of Ac5 are found in the genomes all Group I (except AnpeNPV) NPV genomes. It is associated with the AcMNPV PIF complex (40). Ac5/Bm134 is likely to be nonessential because when Bm134 was deleted, the virus appeared normal (15, 24).

*Ac6 (210aa:23.9kDa), (Bm135:210aa:23.8kDa) (Ha117:241aa:27.8kDa)(Lef-2).

LEF-2 is a DNA primase accessory factor and is encoded by all baculovirus genomes. It interacts with LEF-1 (41), the baculovirus DNA primase. It has homology to the large subunit of DNA primase in several archaea. It is required for transient DNA replication (42, 43). Based on limited amounts of DNA synthesis by a *lef-2* bacmid knockout in transfected cells, it was suggested that Lef-2 is not required for the initiation of DNA replication. This was in contrast to a bacmid with the helicase gene deleted that showed no synthesis (44). However, the transfected DNA is likely nicked and therefore the ends of the nicks could act as primers, resulting in limited amounts of leading strand DNA synthesis in the absence of an active primase complex. Elution profiles of LEF-1 and LEF-2 from ssDNA cellulose and DEAE resin, suggested that LEF-2 may bind to both DNA and LEF-1 (45). LEF-2 mutants have been characterized that appear to affect very late transcription, indicating that it may have roles in both replication and transcription (46). In addition, BmNPV LEF-2 was shown to activate late transcription (47). It is an essential gene as AcMNPV or BmNPV bacmids deleted for *lef-2* were unable to produce infectious virus (15, 44).

Ac7 (201aa:23.6kDa) (Orf 603).

This gene is only found in three baculovirus genomes in addition to AcMNPV, including ClbiNPV, PlxyNPV and RoMNPV. Deletion from AcMNPV did not affect replication in cell culture or in *T. ni* larvae (48).

Ac8 (245aa:28.6kDa), (Bm1:245aa:28.8kDa) (Ha1:245aa: 26.7kDa) (polyhedrin, occlusion body protein).

Homologs of polyhedrin are found in all baculovirus genomes, except for that of the dipteran virus (CuniNPV). Surprisingly, CuniNPV has an occlusion body protein unrelated and about three times as large as polyhedrin of other baculoviruses (49, 50). Because of unexpected patterns of phylogeny of AcMNPV polyhedrin, it has been suggested that it is a chimera derived from both Group I and II sequences (51). It is generally thought that polyhedrin serves to stabilize baculovirus virions in the environment allowing them to persist indefinitely. The polyhedrin gene is nonessential in cell culture, and occlusion-positive and negative plaques can be readily be distinguished. This, in combination with the strength of the polyhedrin promoter, led to the use of the polyhedrin locus as the site for the production of recombinant baculoviruses (4, 5). The crystal structure of AcMNPV polyhedra has been described (52).

Ac9 (543aa:60.7kDa), (Bm2:542aa:60.9kDa) (Ha9:413aa:45.9kDa), (pp78/83, Orf1629).

Homologs of pp78/83 are found in all lepidopteran NPV (I and II) genomes. It is an essential gene. Because it is located adjacent to the polyhedrin gene, it was originally manipulated via complementation to elevate the frequency of obtaining recombinant baculoviruses at the polyhedrin locus (53). It is phosphorylated (54) and is

a structural protein located at one end of nucleocapsids (54, 55). Ac9 is a Wiskott-Aldrich syndrome protein (WASP)-like protein involved in nuclear actin assembly during the baculovirus infection that leads to movement of virions through the cytoplasm of the infected cell (56, 57).

Ac10 (272aa:32kDa), (Bm3:275aa:32.4kDa) (Ha10:267aa:31.5kDa), (Protein kinase-1 (PK-1)).

Homologs of pk-1 are found in lepidopteran NPV and GV genomes, but not in other lineages. AcMNPV PK-1 shows significant relatedness to some insect orfs, e.g., *Anopheles gambiae* (E = 3e-18). Purified PK-1 was able to phosphorylate histone substrates (58). A bacmid with a knockout of pk-1 produced no viral progeny, although DNA replication was unaffected. It was also found that the kinase catalytic domain was required for infectivity. Cells transfected with the mutant bacmids showed extensive arrays of tubular structures that appeared to lack DNA suggesting that the phosphorylation of one or more proteins was required for capsid morphogenesis (59). Ts mutants characterized for defects in very late gene expression contained mutations in *pk-1* (60). In addition, inactivation of pk-1 mRNA using DNAzyme technology caused a reduction in the expression from the polyhedrin promoter (61). PK-1 also may be associated with a very late transcription complex and be involved in the phosphorylation of LEF-8 (62). Purified PK1 of SpltNPV-I was found to bind to the polyhedrin promoter, suggesting that it might act as a very late gene transcription factor (63).

Ac11 (340aa:40.1kDa), (Bm4:340aa:39.8kDa).

Homologs of Ac11 are found in all lepidopteran Group I NPV and in one Group II (LdMNPV) genomes, but not in other lineages. Ac11/Bm4 is likely to be nonessential because when Bm4 was deleted, the virus appeared normal (15).

Ac12 (217aa:25.4kDa).

Homologs of Ac12 are found in only three additional lepidopteran NPVs, including PlxyNPV, RoMNPV and LdMNPV. Analysis by HHpred (64) predicts that it contains an F-box domain that is involved in a ubiquitin pathway. It shows limited similarity to the tryptophan repeat gene family proteins of *Amsacta moorei* entomopoxvirus (E = 0.12) (see also Ac30).

Ac13 (327aa:38.7kDa), (Bm5:331aa:39.3kDa)(Ha123:385aa:44.5kDa).

Homologs of Ac13 are found in all Group I, II, and GV genomes, but not in other lineages. Analysis by HHpred (64) predicts that it contains coiled-coil regions and has some structural similarity to fibrinogen and borealin, a chromosomal passenger protein that is involved in the stability of mitotic spindles. Ac13/Bm5 is likely to be nonessential because when Bm5 was deleted, the virus appeared normal (15). In addition Bm5 appears to encode a late expressed protein not associated with BV or ODV (65).

*Ac14 (266aa:30.8kDa), (Bm6:270aa:31.1kDa), (Ha124:245aa:29kDa) (Lef-1, DNA primase).

LEF-1 is a core gene present in all baculovirus genomes. Purified LEF-1 has DNA primase activity (45). It interacts with Ac6 (LEF-2) (41), the baculovirus DNA primase accessory factor and is required for transient DNA replication (42, 43). Lef-1 is likely an essential gene as a deletion/insertion mutant in the BmNPV homolog (Bm6) could not be isolated (15, 66).

Ac15 (506aa:57kDa), (Bm7:506aa:57.0kDa), (Ha126:515:58.9kDa), EGT.

Ac15 encodes ecdysteroid UDP-glucosyltransferase (67) and homologs are found in all Group I, II, and most GV genomes, but not in other lineages. Homologs are found in a variety of insects, e.g., *B. mori* (E = 3e-50). The

function of EGT is to block molting and pupation in infected larvae by catalyzing the transfer of glucose from UDP-glucose to ecdysteroids, thereby inactivating these insect molting hormones (68, 69). This is thought to prolong the feeding stage of infected larvae, thereby allowing the virus to replicate over a longer period in larger larvae, resulting in a higher yield of virus. AcMNPV and BmNPV mutants in which the *egt* gene is inactivated are viable (69) but their survival time is reduced (39, 70). Spontaneous deletions of the *egt* gene commonly occur in cell culture (71).

Ac16 (225aa:25.9kDa), (Bm8:229aa:26.2kDa) (BV/ODV-E26).

Homologs of Ac16 are found in all lepidopteran Group I NPV genomes, but not in other lineages. Ac16 interacts with fp25 (Ac61), forms a complex with cellular actin (72) and is palmitoylated (73). It was found to be associated with the envelopes of both BV and ODV and was called BV/ODV-E26, and was also identified as being associated with ODV by mass spectrometry analysis (74). However, in BmNPV, the homolog of AcMNPV Ac16 (Bm8) was not identified as a virion structural protein (75). It was suggested that the difference in the results was due to the source of the antibody (76). In BmNPV, Bm8 directly interacts with IE-1 (77). Similar observations were made in AcMNPV with Ac16 interacting with both IE-1 and IE-0 (78). In addition, Bm8 was found to interact with cellular membrane-bound proteins or secreted proteins (79). A mutant, in which AcMNPV orf16 (called DA26) was insertionally inactivated was viable and showed no difference from wt in *T. ni* or *S. frugiperda* cells or larvae (80). Initial attempts at isolation of null mutants of BmNPV (Bm8) were not successful, but a C-terminal deletion mutant was viable (75), although this mutant was unable to produce BV titers as high as wt. However, a bacmid deleted for Bm8 was viable (15). It was also found that Bm8 appears to inhibit occlusion body production in middle silk glands and its deletion accelerated the death of infected insects (39). In AcMNPV, deletion of Ac16 resulted in a delay in full levels of DNA synthesis and BV production in one study (81), but had lesser effects in another (78). Analysis by HHpred (64) predicts that it contains a coiled-coil region.

Ac17 (209aa:23.9kDa), (Bm9:210aa:24.1kDa), (Ha128:266aa:30.4kDa).

Homologs of Ac17 are found in all Group I and II (except TnSNPV and ChchNPV) NPV genomes. It is an early expressed gene with a product of about 19 kDa that localizes to the cytoplasm (82). A homolog of Ac17 in HearNPV (He128) is expressed late and was found in the cytoplasm (83). Deletion of Ac17 did not affect DNA synthesis, although BV production was reduced by up to a factor of 10 to 100 (81). Deletion of both Ac16 and Ac17 was similar to the Ac17 deletion although there were more significant delays for DNA replication and BV titers to reach levels similar to the Ac17 deletion alone (81). Similar results were reported for a BmNPV bacmid knock out. In addition, the mutant BmNPV took significantly longer to kill larvae and required higher titers BV to achieve an LD_{50} (84). The predicted size of Ac17 is longer than previously reported (12).

Ac18 (353aa:40.9kDa), (Bm10:356aa:41.5kDa).

Homologs of Ac18 are found in all Group I and II NPV genomes. An AcMNPV bacmid deleted for Ac18 was infectious with an LD50 in *T. ni* larvae similar to wt, but took somewhat longer to kill larvae than wt (85).

Ac19 (108aa:12.2kDa), (Bm11:110aa:12.5kDa), (Ha115:129aa:15.3kDa).

Homologs of Ac19 are found in all Group I and most group II NPVs. Ac19 is likely to be nonessential because when it a BmNPV Bm11 deletion was viable (15, 39).

Ac20/21 (417aa:47.7kDa), (Bm12:440aa:50.0kDa), (Ha131: 265aaa:30.4kDa)(arif-1).

This region has been resequenced in AcMNPV strains C6 and also in strains E, E2, and L1, and in all cases it was found that Ac20 and 21 are a single orf (11), see also (12). In addition, these two orfs are combined as a single orf in several closely related viruses. Homologs of arif-1 are present in all Group I and most Group II genomes. AcMNPV orf20/21 is called actin-rearrangement-inducing factors (arif-1). It is expressed as an early gene and transfection of a plasmid containing this gene into Tn-368 cells is able to induce actin rearrangement (86). Arif-1 was found to colocalize with F-actin at the plasma membrane and deletion mutants showed a loss of actin concentration at the plasma membrane. Deletions of the C-terminal half of the gene or insertion of the LacZ gene near the center of the orf resulted in constructs that showed no significant loss of infectivity in Tn-368 or Sf cells (11). Analysis by HHpred (64) predicts that Ac21 has an extensive region that resembles structures found in the largest subunit of RNA polymerase II, fibrinogen, and rhodopsin.

*Ac22 (382aa:43.8kDa), (Bm13:382aa:43.8kDa), (Ha132:383:44.5kDa) (PIF-2).

This gene is a member of the per os infectivity factor (87) gene group. These genes can be deleted and the mutant are still infectious for cultured cells, but are not orally infectious for insects (88). It is present in all baculovirus genomes and is also present in a nudivirus genome (89). For more information see Ac138 (p74) and Chapter 3.

Ac23 (690aa:79.9kDa), (Bm14:673aa:78.0kDa), (Ha133:677aa:78.2kDa), F (Fusion) protein.

Ac23 is a homolog of the predicted fusion protein (F) of Group II lepidopteran NPVs, GVs, and the dipteran virus (CuniNPV). Homologs are found in all baculoviruses except the hymenopteran viruses. In Group II viruses such as LdMNPV and HaSNPV, Ac23 homologs (*ld130, Ha133*) encode low pH-activated fusion proteins. In Group I viruses, they appear to be inactive as fusion proteins and have been replaced by *gp64*, which is not found in the Group II viruses, GVs, or hymenopteran or dipteran viruses. Orthologs of the F gene are also found as the env gene of insect retroviruses (90), and are also present in some insect genomes (91). They also appear to be related to the fusion (F) proteins of the paramyxoviridae (see Chapter 2). Although inactive in Group I viruses, the Acorf23 homolog is glycosylated and associated with the envelope of BV and with the membranes of OpMNPV-infected cells (92). In AcMNPV, Ac23 is also associated with BV membranes and its deletion from the genome results in infectious virus, but the time to kill larvae was somewhat extended (10). Ac23 was found to be associated with ODV as was the homolog in CuniNPV (74, 93).

Ac24 (169aa:19.2kDa), (Bm15:169aa:19.4kDa), Protein kinase interacting protein (PKIP).

Homologs are found in all Group I and II NPV genomes. This gene product was found to interact with AcMNPV protein kinase I (see Ac10) in a yeast two-hybrid assay. It stimulates PK-1 activity in vitro. PKIP appears to be essential as attempts to isolate a deletion mutant were unsuccessful (94). Ts mutants in PKIP are defective in very late transcription (95). BmNPV bacmids deleted for Bm15 were viable, but the infection spread slower than wt in cultured cells (15).

Ac25 (316aa:36.6kDa), (Bm16:317aa:36.7kDa),(Ha25:324aa:37.6kDa), DNA binding protein (DBP).

Ac25 encodes a single-stranded DNA binding protein called DBP. Homologs are found in all sequenced baculovirus genomes, except that of the dipteran (CuniNPV) (although an orf is present with ~50% identity over

22 aa) and in some instances multiple copies of the *dbp* gene are present. It has properties similar to the other baculovirus SSB, LEF-3 (Ac67), in that it interacts with itself and is capable of both unwinding and annealing DNA (96). It is an essential gene, as bacmids lacking Ac25 are noninfectious and appear to produce defective nucleocapsids. Although not a virion structural protein, DBP exhibits a tight association with subnuclear structures, suggesting that it is a component of the virogenic stroma (96), and when DBP was deleted from an AcMNPV bacmid, cells transfected with this construct appeared to lack a virogenic stroma. This suggested that *dbp* is required for the production of nucleocapsids and the virogenic stroma (97).

Ac26 (129aa:14.6kDa), (Bm17:129aa:14.5kDa), Ha26:133aa:15kDa).

Homologs of Ac26 are found in the genomes all Group I, and most Group II NPV genomes. Bm17 is expressed as a late gene and is localized to both the nucleus and cytoplasm (98). When Bm17 was deleted from a BmNPV bacmid, the virus was viable, but the infection spread slowly in cell culture (15).

Ac27 (286aa:33.3kDa), (Bm18:292aa:34.0kDa), iap-1.

Ac27 is a member of the inhibitor of apoptosis (*iap*) gene family. Up to 5 *iap* homologs are found in baculovirus genomes (99), however AcMNPV has two copies, *iap-1* and *-2*. Unlike *iap-2*, which is found in both Group I and II NPVs, *iap-1* appears to be confined to Group I lepidopteran NPVs and is a member of a lineage distinct from the other iap homologs. Deletion mutants of *iap-1* were similar to wt in their replication in cells lines and larvae of *T. ni* and *S. frugiperda*. However, when they were co-infected with wt virus in Tn-368 (but not Sf-21) cells, the mutants appeared to out compete wt virus (100). Evidence suggested that transfection of AcMNPV iap-1 into T. ni cells suppressed apoptosis by HearNPV infections, although a recombinant HearNPV expressing iap-1 also suppressed apoptosis, BV production was not rescued (101). In another investigation in EppoMNPV, The iap-1 gene was able to delay apoptosis onset caused by inducing agents such as actinomycin but was not able to prevent apoptosis upon prolonged exposure of the cells to the inducer (102). In another study, transient expression of iap-1 form a variety of viruses induced apoptosis and it was suggested that this might facilitate dissemination of the virus (103).

Ac28 (173aa:20.4kDa), (Bm19:173aa:20.3kDa), (Ha24:187aa:22.2kDa), Lef-6.

Homologs of lef-6 are found in the genomes of all lepidopteran NPVs and GVs. It was originally identified because it was required for transient transcription of late genes (104). A bacmid deleted for lef-6 was infectious, but the virus was severely compromised. The major effect appeared to be reflected in a delay in the onset of late transcription (105). Using the HHpred program (64), AcMNPV LEF-6 showed a 68% probability of being related to the RNA binding domain of the mRNA export factor TAP (106).

Ac29 (71aa:8.6kDa), (Bm20:71aa:8.6kDa), (Ha23:67aa:8.3kDa).

Homologs of Ac29 are found in all Group I and most Group II and GV genomes. A BmNPV bacmid deleted for Bm20 was viable (15).

Ac30 (463aa:54.7kDa), (Bm21:472aa:55.8kDa).

Homologs of Ac30 are present in the genomes of all Group 1 NPVs. It has homology to a family of genes that encode tryptophan repeat gene family proteins (see also Ac12) that are also found in entomopox viruses. e.g., *Melanoplus sanguinipes* entomopoxvirus (E = 1e-11). These proteins contain 3 to 12 copies of a 23-amino acid sequence containing tryptophan, leucine and isoleucine residues (107). Ac30 is likely to be nonessential because when the ortholog (Bm21) was interrupted by insertional/deletion mutagenesis in BmNPV, the virus appeared

to be normal, although it resulted in a longer survival time suggesting that the mutant was less virulent that wt (108).

Ac31 (151aa:16.2kDa), (Bm23:151aa:16.3kDa), SOD.

Ac31 has homology to super oxide dismutase (109). Homologs are found in the genomes of almost all lepidopteran baculovirus genomes (it appears to be absent only in EppoNPV, a member of Group II, and SpliGV). It has a high degree of similarity to SOD from a variety of insects, including *B. mori* (E = 8E-49). Insect hemocytes are phagocytic cells similar to neutrophils and can destroy invading pathogens by the production of superoxide (110). Superoxide can be inactivated by SOD by converting it to hydrogen peroxide, which is also toxic, but can itself be inactivated with catalase yielding water and O_2. Many baculoviruses may infect hemocytes and in this manner can spread an infection throughout an insect. The expression of viral SOD might mitigate the effects of superoxide production by hemocytes. An enzymatic activity could not be confirmed for AcMNPV SOD and AcMNPV deleted for *sod* replicated normally in cultured cells and insect larvae. The *sod*-deleted viruses showed no reduction in replication when grown in the presence of paraquat, a superoxide anion inducer (109). In one study, deletion of the *sod* gene from BmNPV (Bm23) indicated that it was essential for replication in BmN cells (111), however, another report indicated that a Bm23-deleted bacmid was viable (15).

Ac32 (181aa:20.6kDa), (Bm24:182aa:20.8kDa), (Ha113:301aa:34.4kDa) fgf.

Ac32 has homology to fibroblast growth factor (FGF). Orthologs are found in the genomes of all lepidopteran baculoviruses and may reflect several independent lineages. AcMNPV *fgf* is most closely related to a non-baculovirus gene in *D. melanogaster* called *branchless* (E = 3e-24). In contrast, a Group II *fgf* homolog from LdMNPV is less closely related to the insect homologs (e.g. *D. melanogaster* branchless E = 2e-10) and the GV homologs show only limited similarity to NPV *fgf* homologs (e.g., AcMNPV vs CpGV FGFs = ~10% identity). It has been suggested all of the NPV *fgf*s are monophyletic, however the possibility of at least two capture events of fgf in the GVs has not been ruled out (112). AcMNPV FGF is a secreted protein that stimulates insect cell motility (113). In BmNPV, the FGF homolog is glycosylated, which is essential for its (114, 115) and binds to an insect receptor of FGF/*branchless* called *breathless* (114). Although the deletion of *fgf* in AcMNPV showed no differences from wt on cultured cells (116), the time of death was delayed when fed to two insect species (117). Similar results were observed for a BmNPV *fgf* deletion (118). It has been suggested that FGF may play a role in dissemination of the virus within the host insect (117). Recent evidence suggests that vFGF initiates a cascade of events that may accelerate the establishment of systemic infections. This involves two processes. vFGF from virus infected midgut cells diffuse through the basal lamina and attract tracheal cells so that they are adjacent to infected midgut cells but separated by the basal lamina. vFGF then activates FGF receptors located on the tips of tracheal cells. This leads to the activation of matrix metalloproteases located in the same subcellular region via a MAP kinase or NFkB pathway. Matrix metalloproteases subsequently activate effector caspases that move extracellularly so that they are positioned for the degradation of the basal lamina by digestion of the laminin component. The delaminated tracheal cells are then susceptible to virus infection. This allows the transit of the virus through tracheal cells to other tissues and results in the systemic infection (119). This theory is supported by evidence for the activation of matrix metalloproteinases, the activation of effector caspases, and the degradation of laminin after the per os infection of midgut cells.

Ac33 (182aa:20.8kDa) (polynucleotide kinase (PNK)).

Orthologs of Ac33 are found in most Group II and a few Group I and GV genomes. Homology searches indicate that it has significant similarity to polynucleotide kinase-3'-phosphatase of *Apis mellifera* (E = 9e-36) and somewhat lesser to the human homolog (E = 1e-28). In other organisms this enzyme has functions similar to T4 PNK. It is predicted to have structural similarity to Chain B of a DNA repair enzyme, polynucleotide kinase with

an E value of 1.0e-^{32} (120). As previously suggested, Ac33 also has structural similarity to histidinol-phosphatase (an enzyme in the histidine biosynthesis pathway) (121). Orthologs are not present in BmNPV (16) or HaSNPV (17).

Ac34 (215aa:24.9kDa), (Bm25:215aa:24.8kDa), (Ha27:255aa:29.5kDa).

Orthologs of Ac34 are found in Group I and II NPV genomes. Ac34 localizes to both the nuclei and cytoplasm of infected cells but does not appear to be a structural protein. Deletion of Ac34 from an AcMNPV bacmid resulted a delay in late gene expression, a100-fold reduction the viral titer, but did not appear to affect DNA replication. This mutant was unable to establish a fatal infection in the larvae of *T. ni* via *per os* exposure (122). In another study, deletion of Ac34 resulted in no BV production, but reduction of Ac34 expression by RNAi, elevated the expression of a heterologous gene expressed from the polyhedrin promoter (123). Deletion of Bm25 also resulted in a compromised virus (15).

Ac35 (77aa:8.7kDa), (Bm26:77aa:8.7kDa),(Ha28:83aa:9.2kDa), ubiquitin-like protein.

Orthologs of ubiquitin have been found in the genomes of all alpha and beta baculoviruses, but are not present in hymenopteran or dipteran baculoviruses (124). Ac35 is expressed from both early and late promoter elements (125, 126). It was observed that late in infection recombinant virus expressing GFP fusions of ubiquitin from BmNPV localized throughout the nuclei with a few concentrated foci in the cytoplasm, whereas that of HaSNPV localized mostly to the peripheral regions of nuclei (127). The phylogenetic tree indicates that, whereas the ubiquitin of most eukaryotes is almost invariant, the baculovirus tree shows a higher degree of phylogenetic diversity, particularly between GVs and NPVs, suggesting that it may have been independently incorporated into a viral genome more than once. It is highly conserved among different NPVs showing at least 76% amino acid sequence identity. The most closely related non-baculovirus homologs of Ac35 are from vertebrates, e.g., rat (E = 2e-28). It is BV associated (27) and appears to be present on the inner surface of viral envelopes (128). A viral mutant with a frameshift of Ac35 is viable, but a 5–10-fold reduction in BV was observed (129). It has been suggested that viral ubiquitin may inhibit steps in the host degradative pathway to stabilize what would otherwise be a short-lived viral protein (130). The *Spodoptera litura* NPV genome was found to contain a gene that is a fusion of *ubiquitin* and *gp37* (=Ac64). In addition, it was noted that unfused homologs of both these proteins are found in entomopox viruses (131). Although the significance of the linkage of these two proteins is not known, other such proteins have been termed 'rosetta stone' proteins because they reveal proteins that interact with one another and participate in the same molecular pathways. Consequently, when a mutation event occurs that leads to the fusion of two proteins that normally function together, the mutation is preserved because such a linkage is a normal feature of the two proteins. The presence of homologs of both these proteins in two disparate families of viruses along with the presence of a fused orf in the SlNPV genome, suggests that these orfs may participate in the same pathway, possibly as participants in a ubiquitin pathway or in ubiquitin inhibition.

Ac36 (275aa:31.3kDa), (Bm27:277aa:31.5kDa), (Ha31:311aa:35.2kDa), 39K;pp31.

Pp31 was originally identified because it contains an early promoter that is stimulated by IE-1 (132). Homologs are found in all lepidopteran NPV and GV genomes. It is phosphorylated and localized to the virogenic stroma of infected cells, and is capable of binding to DNA but is not a virion structural protein (133), although it was reported to be BV associated in a proteomic study (27). Purified PP31 was found to bind to single-stranded and double-stranded DNA with equal affinities and inhibited transcription in vitro (134). Phosphorylation of pp31 appeared to be a dynamic process (135). Several basic regions were identified that may be involved in nuclear localization or DNA binding (136). Pp31 stimulates late gene expression in a transient transcription assay (137).

Deletion of the *pp31* homolog in BmNPV (Bm27) resulted in virus that, although viable, showed a reduction in late gene transcription, a 100 fold reduction in BV production, and improper formation of the virogenic stroma (66). Similar results were obtained for an AcMNPV bacmid deleted for *pp31* and it was observed that the deletion resulted in a significant decrease of the transcription of six late genes (138).

Ac 37 (112aa:13.1kDa), (Bm28:112aa:13.1kDa), (Ha32:127aa:14.6 kDa), Lef-11.

Lef-11 is present in all baculovirus genomes, except the dipteran CuniNPV. It was identified as being stimulatory for late gene expression in a transient transcription assay (43). An AcMNPV bacmid deleted for *lef-11* failed to replicate and no DNA synthesis or late gene transcription were evident, indicating that it is an essential gene. Although LEF-11 localizes to nuclei of infected cells and appears to be essential for DNA replication, no domains associated with other factors involved in DNA replication have been reported and its role in DNA replication is not known (105).

Ac38 (216aa:25.3kDa), (Bm29:217aa:25.5kDa), (Ha33:238aa:28.4kDa), Nudix, ADP-ribose pyrophosphatase (ADPRase).

Homologs of Ac38 are found in all lepidopteran NPVs and GVs. It contains a conserved Nudix (nucleotide diphosphate X) motif ($GX_5EX_7REUXEEXGU$; X= any aa, U represents l, L, or V) (139) and has a homology to ADPRase, a subfamily of Nudix pyrophosphatases. Ac38 was shown to have ADPRase activity and a deletion mutant was severely compromised and produced BV at 1% the level of wt (140). Proteins of the nudix superfamily are common in all organisms and have been reported in other viruses including T4 bacteriophage, African swine fever virus (ASFV), and poxviruses. A vaccinia virus nudix protein may negatively regulate viral gene expression by acting as a decapping enzyme (141). Deletion of the gene in vaccinia resulted in smaller plaque and low virus yield (142), similar to the *Ac38*-deleted AcMNPV. Ha33 of the *Heliocoverpa armigera* NPV is a homolog Ac38 and was found to be associated with the envelope of budded virions (143).

Ac39 (363aa:43.5kDa), (Bm30:362aa:43.4kDa).

Homologs of Ac39 are found in a few Group I NPV closely related to AcMNPV and at least two Group II (Adho- and ClbiNPV) genomes. Deletion showed no effects on growth curves or virus production (144).

*Ac40 (401aa:47.5kDa), (Bm31:399aa:47.3kDa), (Ha35:3590aa:39kDa), P47, a subunit of the baculovirus polymerase.

P47 homologs are found in all baculovirus genomes. P47 was originally identified as the site of a ts mutation that caused a defect in late gene expression (145, 146). P47 was found to be required for transient late gene transcription (137) and to be a component of the baculovirus late polymerase complex (147). It is likely an essential gene as a deletion/insertion mutant in the BmNPV *lef-8* homolog (Bm31) could not be isolated (15, 66).

Ac41 (181aa:21.1kDa), (Bm32:183aa:21.1kDa), (Ha36:223aa:25.8kDa), Lef-12.

Lef-12 is found in about one-half the Group I and Group II NPV genomes sequenced. Although 18 genes were originally identified as being involved in transient expression from a late promoter (137), when individually cloned, the genes failed to support late transcription. Because of its close proximity to Ac 40 (p47), Ac41 (lef-12) had not been identified in the initial screen. It was subsequently demonstrated to be required for transient late gene transcription in *S. frugiperda* cells (148, 149), but not in *T. ni* cells (148). Mutants with *lef-12* interrupted by insertional mutagenesis or by mutation of the ATG translation initiation codon were viable in both *S. frugiperda* and *T. ni* cells, although reduced yields of BV were observed (20-40% or wt) in both cell lines and the infection

cycle appeared to be slowed (150). Although expressed as an (aphidicolin sensitive) late gene, initiation of *lef-12* mRNA did not appear to occur at conventional late (or early) promoter elements. It was suggested that *lef-12* may be functionally redundant in the AcMNPV genome and, therefore, it is not essential for late transcription when the rest of the virus genome is present (150).

Ac42 (506aa:59.1kDa), (Bm33:506aa:59.2kDa), gta.

Ac42 has homology to 'global transactivator,' the DEAD-like helicase superfamily that are enzymes involved in ATP-dependent unwinding of DNA or RNA. They contain an SNF2 family N-terminal domain that is present in proteins involved in some processes, such as regulation of transcription, DNA recombination and repair, chromatin unwinding, and other functions. Homologs of this gene are found in all Group I NPV genomes. It has significant similarity to a wide variety of orfs from bacteria to marsupials, e.g., (E = 9e-61). Deletion of the Ac43 homolog from BmNPV (Bm33) did not cause any defects in BV or ODV production in BmN cells. Assays in *B. mori* larvae showed that the mutant, although similar in infectivity to the wt, took about 15 hr longer to kill when administered either by injection or per os (151).

Ac43 (77aa:8.8kDa), (Bm34:78aa:9.0kDa), (Ha37:80aa:9.5).

Homologs of Ac43 are found in all Group I and most Group II NPV genomes. It appears to be involved in late and very late gene expression as deletion of BmNPV Bm34 resulted in a reduction in occlusion body production and a lengthening of the time to death in larvae. These effects were attributed to a down regulation of *vlf-1* which is required for very late gene expression along with the reduction expression of the *fp25k* (=Ac61) gene (152). A knockout of Ac43 did not appear to affect BV production, but resulted in reduced expression of polyhedrin, but those present were larger than normal. They appeared contain more singly enveloped nucleocapsids than wt (153).

Ac44 (131aa:15kDa), (Bm35:131aa:15.0kDa).

Homologs of Ac44 are found in all of Group I and one Group II (SeMNPV) lepidopteran NPVs. Ac44 is 131 amino acids and shows homology to a 64.2 kDa inhibitor of apoptosis/RING-finger protein in the genome of *Spodoptera frugiperda* ascovirus 1a (E = 1e-04). The SeMNPV homolog is more closely related to the ascovirus 1a orf (E = 2e-55) than to its Group I baculovirus homologs. Ac44 may be nonessential as a BmNPV bacmid with a Bm35 knock out appeared to be normal (15).

Ac45 (192aa:22.7kDa), (Bm36:193aa:22.5kDa).

Homologs of Ac45 are found in four close relatives of AcMNPV (PlxyNPV, BmNPV, RoMNPV, and MaviMNPV). Sequences located within Ac45 appeared to be required for Ac41 expression in a transient late transcription assay (149). Ac45 may be nonessential as a BmNPV bacmid with a Bm36 knock out appeared to be normal (15).

Ac46 (704aa:79.1kDa). (Bm37:702aa:79.2kDa), (Ha96:672aa:76kDa), ODV-E66.

Ac46 is a component of ODV envelopes (154). Homologs of this gene are found in the genomes of all Group I NPVs, GVs, and most Group II NPVs, but not in hymenopteran or dipteran viruses. Two copies of the gene are present in some genomes (e.g., SeMNPV). When the N-terminal 23 amino acids of ODV-E66 are fused to a reporter gene, it is targeted to the nucleus (155). Ac46 shows 100% probability of being related to hyaluronidase of *Streptococcus pneumonia* using the HHpred program (64) and has been shown to have hyaluronan lyase activity that is capable of digesting hyaluronan, a polysaccharide that is a major component of the extracellular matrix (156). Subsequently it was shown that a truncated form lacking the N-terminal 66 amino acids was

secreted into the medium by infected cells and had chondroitinase activity. Chondroitinases have been shown to regulate cytokine and growth factors and can influence a variety of processes including development, inflammation, and organ morphogenesis. Its activity as a hyaluronan lyase was minimal (157). The crystal structure has been determined (158). A peptide of about 12 aa that was similar to the AcMNPV ODV-E66 sequence was observed to bind to the epithelium of guts *Heliothis virescens* and inhibited infection by AcMNPV (159). When the homolog of ODV-E66 was inactivated in BmNPV (Bm37), the mutant, although viable, took more time to kill insect larvae (160). In a study of AcMNPV, an ODV-E66 deletion was observed to kill *Plutella xylostella* larvae as efficiently as wt, however when infected per os the LD50 was1000 fold greater for the mutant than wt virus. Therefore it was suggested that ODV-E66 is a per os infectivity factor (PIF) (161). For more information on PIFs see Chapters 2 and 3.

Ac47 (88aa:10.5kDa), (Bm38:89aa:10.5kDa), TRAX-like.

Ac 47 homologs are found in 5 Group I lepidopteran NPVs closely related to AcMNPV. It shows 27% identity to homologs of a protein called translin-associated factor X (Trax). Although TRAX interacts with translin, which may be involved in responses to DNA damage, transport of RNA, and control of translation, its function is not known (162). Ac47 may be nonessential as a BmNPV bacmid with a Bm38 knock out appeared to be normal (15). In AcMNPV his gene was referred to as ETS and transcriptional data for Ac47 in relation to PCNA has been described (163).

Ac48 (113aa:12.9kDa).

Ac48 homologs are found in the genomes of most Group I lepidopteran NPVs. A homolog of Ac48 is not present in the BmNPV genome (16). This gene was referred to as ETM (the mid-sized orf in the EcoRI T fragment) and transcriptional data for Ac48 in relation to PCNA has been described (163).

Ac49 (285aa:32.1kDa) (PCNA).

Ac 49 has homology to proliferating cell nuclear antigen (PCNA). PCNA homologs have been found in a few Group I and Group II alphabaculovirus genomes. The Group I PCNA homologs appear to be insect-derived and show a high degree of similarity to insect PCNAs, e.g., *S. frugiperda* (E = 6e-65). In contrast, the PCNA homologs of two Group II viruses (TnSNPV and ChchNPV) belong to a different lineage and do not show such a close relationship to insect PCNAs, e.g., *S. frugiperda* (E = 7e-20) and are even more distantly related to the Group I baculovirus PCNAs than to those of insects. Although eukaryotic PCNA lacks an enzymatic function, it plays a role in DNA synthesis, DNA repair, and cell cycle progression. It functions as a sliding circular clamp that mediates protein interactions with DNA and is required for the coordinated synthesis of both leading and lagging strands at the replication fork during DNA replication (164). In AcMNPV it is not an essential gene (163, 165, 166) and did not appear to elevate DNA replication in transient replication assays (42). A homolog of PCNA is not present in the genome of BmNPV (16).

*Ac50 (876aa:101.8kDa), (Bm39:877aa:101.8kDa), (Ha38:901aa:105 kDa), Lef-8, baculovirus RNA polymerase subunit.

Lef-8 was originally identified as a gene required for transient late gene expression (167). Homologs are found in all baculoviruses and are also in nudiviruses. LEF-8 contains a conserved motif found in other RNA polymerases and it is thought that this is part of the catalytic site (167, 168). It is a component of the baculovirus late RNA polymerase complex (147, 169). It is likely an essential gene; in BmNPV a ts mutant located in lef-8 (A542V) was defective for BV production at the non permissive temperature (170). In addition, a deletion mutant in the BmNPV lef-8 homolog (Bm39) was not viable (15). Also a ts mutation L531S in Ac50 abolished very late transcription at 33 ° C (171).

Ac51 (318aa:37.5kDa), (Bm40:319aa:37.8kDa), (Ha39 :194aa :22.5kDa), DnaJ domain protein.

Homologs of Ac51 are found in all Group I and II lepidopteran NPV genomes. It is a DNA J domain protein and shows homology to a variety of bacterial proteins. In *E. coli*, DnaJ has been demonstrated to have chaperone activity and aids in folding of other proteins (172). The homolog of Ac51 in HearNPV (ha39) has an RNA recognition motif, localizes to the cytoplasm and is associated with BV (27, 173). It may be an essential gene as a BmNPV bacmid with Bm40 deleted was defective for viral spread (15).

Ac52 (194aa:123.2kDa), (Bm41:194aa:23.3kDa), (Ha42:180aa:21.3kDa).

Homologs of Ac52 are found in about one-half the Group I and II lepidopteran NPV genomes. Deletion of Bm41 resulted in reduction in BV production by 1000-fold and appeared to disrupt normal nucleocapsid envelopment and polyhedron formation in infected nuclei and resulted in a 14-fold elevation of LD_{50} in larvae and an increase in time to death (174). The predicted size of Ac52 is longer (194 vs 123 aa) than previously reported (12).

*Ac53 (139aa:17kDa), (Bm42:139aa:16.9kDa), (Ha43:136aa:16.4kDa).

Homologs of Ac53 are found in all baculoviruses. Deletion of Ac53 indicated that it was an essential gene. The mutant bacmid was able to replicate DNA, but the virions were defective and appear to lack the nucleoprotein core (175). Ac53 is predicted to contain domains structurally similar to the U-box/RING-like domains found in the E3 ubiquitin ligase family (124).

Ac53a (78aa:8.6kDa), (Bm42a:78aa:8.6kDa), (Ha46:71aa:7.7kDa), Lef-10.

This orf was named Ac53a because it was not identified in the original AcMNPV genome sequence because it is a small orf encoding 78 aa and about half the 3' coding region overlaps the 5' region of Ac54. Homologs of lef-10 are found in the genomes of all Group I and most Group II NPV and GV genomes. Lef-10 was originally identified because it was required for late gene expression (13). When Bm42a was deleted from a BmNPV bacmid, the bacmid was not viable (15).

*Ac54 (365aa:42.1kDa), (Bm43:365aa:42.0kDa), (Ha47:351aa:41.7kDa), Capsid protein, (vp1054).

Homologs of Ac54 are found in all baculovirus genomes. It encodes a protein required for nucleocapsid assembly. A ts mutant failed to produce nucleocapsids at the nonpermissive temperature, indicating that it is an essential gene and it was associated with both BV and ODV (176). It interacts with 38K (Ac98) (177). When the vp1054 gene was deleted from a bacmid, the bacmid did not appear to be viable and nucleocapsids appeared to be replaced with tube-like structures. It was suggested that vp1054 may be related to a cellular protein called PURa that binds to purine-rich sequences and may be involved in DNA packaging. Ac54 was shown to bind to single stranded DNA or RNA sequences that contained runs of GGN (178).

Ac55 (73aa:8.2kDa), (Bm44:77aa:8.6kDa), (Ha48:68aa:8.0kDa).

Homologs of Ac55 are found in the genomes of all Group I and most of the Group II NPVs. It appears to be nonessential because a BmNPV mutant deleted for this gene appeared to be normal (15).

Ac56 (84aa:9.9kDa), (Bm45:84aa:9.9kDa), (Ha49:64aa:7.4kDa).

Homologs of this orf are found in genomes of all Group I and most Group II NPVs. It appears to be nonessential because a BmNPV mutant deleted for this gene appeared to be normal (15).

Ac57 (161aa:19kDa), (Bm46:161aa:20.2kDa), (Ha50:171aa:20.7kDa).

Homologs of this orf are found in most Group I and II NPVs. It appears to be nonessential because a BmNPV mutant deleted for this gene appeared to be normal (15). It also appeared to be non essential for HearSNPV (179).

Ac58/59 (172aa:20.3kDa), (Bm47:171aa:37.8kDa), (Ha51:160aa:19.0kDa), ChaB-like.

These two orfs are likely a single gene, as homologs are fused in other baculoviruses and they were also found to be joined when the region was resequenced in the C-6 strain (12). This results in an orf predicted to encode 172 amino acids. Homologs of this orf are found in the genomes of all Group I and all but one (LeseNPV) Group II NPVs. It has a ChaB domain. In *E. coli*, ChaB is thought to regulate ChaA, a cation transporter protein. It was found to localize to nuclei of infected cells (180) and was associated with AcMNPV ODV (74). It is also BV associated (27). It appears to be nonessential because a BmNPV mutant deleted for this gene appeared to be normal (15).

Ac60 (87aa:10.1kDa), Bm48:83aa:9.7kDa), (Ha52:88aa:10.2kDa), (ChaB-like).

Homologs of Ac60 are found in the genomes of all Group I and II NPVs and most GVs. Similar to Ac58/59, Ac60 also has a ChaB domain. It is surprising that Ac58/59 and Ac60 are both predicted to encode ChaB domains as they do not show much sequence similarity. Alignment of the sequences resulted in an amino acid sequence identity of 15%; however, it required the insertion of several gaps, so the significant of the relatedness is not clear. In SpliNPV, two adjacent ChaB homologs were also identified. Evidence suggests that they may be DNA binding proteins (181). It appears to be nonessential because a BmNPV mutant deleted for this gene appeared to be normal (15).

Ac61 (214aa:25.2kDa), (Bm49:214aa:25.3kDa), (Ha53:217aa:25.4kDa), Few polyhedra (fp, fp-25).

Orthologs of Ac61 have been found in the genomes of all alpha, beta, and gamma baculoviruses (124). AC61 has been shown to be BV associated (27). Deletion is not lethal, but results in a 'few polyhedra phenotype' (182, 183). FP mutants are defective in virion occlusion and nucleocapsid envelopment in nuclei and release two- to fivefold more infectious BV than wt in infected Sf9 cells (183, 184). The nonlethal, but readily distinguishable phenotype has facilitated investigations on this gene. FP mutations often result from the insertion of host DNA into the fp gene (182, 185). They can also be the result of errors in DNA replication (186). Mutations in the *fp* gene result in a reduction in polyhedrin gene (but not *p10*) transcription (183). Mutations also appear to affect the levels and nuclear transport of Ac46 (ODV-E66), an ODV envelope protein (187, 188). In BmNPV *fp* mutants, the few virions that were occluded appear to lack envelopes (189). A combination of reduction in the level of polyhedrin and an ODV envelope protein could contribute to the FP phenotype. The defect in occlusion and in the ODV envelope could lead to the availability of more virions for budding. A reduced level of liquefaction of larvae was also noted with an fp mutant in BmNPV (189). This was attributed to the involvement of Bm49 in the regulation of v-cathepsin expression (190). In *T. ni* cells, double *p35* (see Ac135) and *fp* mutants underwent apoptosis, whereas p35 mutants alone did not, suggesting that the *fp* gene may have pro-apoptotic properties in this cell line (191). In contrast, in BmNPV infected BmN cells, deletion of fp25k did not affect apoptosis induced by a

virus with p35 deleted (192). Fp25k mutants of AcMNPV produce virions that are occluded with different efficiencies depending on the cell line or insect. When replicated in Sf cells or insects the efficiency was lower than in *T. ni* Hi F cells or larvae (193). The fp25k gene was also found to contain two hypermutable sequences of 7 adenine residues and the mutant 25k genes expressed different amounts of polyhedrin mRNA and protein depending on the cell line (194).

*Ac62 (516aa:59.3kDa), (Bm50:490aa:56.4kDa), (Ha55:519aa:60.0kDa), Lef-9, baculovirus RNA polymerase subunit.

Lef-9 homologs are present in all baculovirus and also nudivirus genomes. It was found to be required for transient late gene expression (13) and subsequently shown to be a subunit of the baculovirus RNA polymerase (147). It contains a 7-amino acid motif (NTDCDGD or NRDCDGD except NADFDGD in the dipteran virus) similar to the Mg++ binding sequence (NADFDGD) found in the catalytic center in large RNA polymerase subunits of a few DNA-dependent RNA polymerases (13). The D residues bind Mg++ and are conserved in all these sequences. It is likely an essential gene as an insertion/deletion mutant in the BmNPV homolog (Bm50) could not be isolated (66) or did not replicate (15).

Ac63 (155aa:18.5kDa), (Bm51:155aa:18.5kDa), (Ha121:154aa:18.5kDa).

Homologs of Ac63 are found in five Group I and six Group II lepidopteran NPVs. A homolog in a nudivirus has been reported (195). It appears to be associated with BV envelopes (196). It appears to be nonessential because a BmNPV mutant deleted for this gene appeared to be normal (15).

Ac64 (302aa:34.8kDa), (Bm52:294aa:33.8kDa), (Ha58:279aa:32.1kDa), (GP37/P34.8, spindlin, fusolin, spheroidin-like protein).

The terminology of Ac64 has a confusing history and in addition to gp37 has been referred to as p34.8, spindlin, fusolin, or spheroidin-like protein because of homology with an entomopox virus gene (197, 198). Evidence suggests that it is not a spheroidin-like homolog (199). Orthologs of gp37 have been found in the genomes of all alpha and beta baculoviruses (124). In AcMNPV it is expressed as a late gene (200). In addition to entomopox, it is related to orfs in a variety of eubacteria, e.g., *Vibrio alginolyticus* (E = 5e-27). It has been suggested that the granulovirus gp37 lineage is more closely related to the entompox lineage than to gp37s from NPVs (201). A homolog of Ac64 is referred to as chitinase B in the marine bacterium *Pseudoalteromonas* sp. and was found to bind to, but not digest chitin (202). The gp37 homolog in SpltNPV has been reported to contain chitin binding domains and is capable of binding to chitin (203). The gp37 of CpGV also bound chitin and was able to enhance per os infections (204). Insect proteins, such as the coagulation protein hemolectin, also have chitin-binding domains (205). Whether gp37 somehow inhibits or redirects such pathways remains to be determined. GP37 was reported to be polyhedron associated in AcMNPV and to be N-glycosylated (198). It was also found to be BV associated (27). In OpMNPV infected *L. dispar* cells, GP37 was found to be an N-glycosylated protein located in cytoplasmic occlusions late in infection (206). The *gp37* gene is nonessential for replication in cell culture or *T. ni* larvae (197). Similar results were observed for the BmNPV homolog (Bm52) (15). The *Spodoptera litura* NPV genome was found to contain a gene that is a fusion of ubiquitin and gp37 (for discussion, see *Ac35, ubiquitin*) and the protein was associated with the envelopes of BV and ODV (131) .

*Ac65 (984aa:114.3kDa), (Bm53:986aa:114.4kDa), (Ha67:1020aa:119.3kDa) (DNA polymerase).

Homologs are found in all baculoviruses. The nonbaculovirus homologs showing the highest level of similarity are found in herpesviruses, e.g., human herpes virus 7 (E = 1e-25), several protozoans, and archae. A DNA

polymerase homolog was originally identified in the AcMNPV genome by hybridization with degenerate primers designed based on a highly conserved domain in other DNA polymerases (207). A 3'→5' exonuclease activity specific for single-stranded DNA was shown to be associated with the DNA polymerase from *Bombyx mori* NPV (BmNPV) (208) and AcMNPV (209), suggesting that a proofreading activity was associated with this enzyme. A purified DNA polymerase from AcMNPV was characterized as being active on singly primed M13 templates (210). The polymerase is highly processive on poly (dA)-oligo dT (209). Mutations of AcMNPV DNA polymerase resistant to a variety of inhibitors have been described (211). DNA polymerase is an essential gene because deletion is lethal in AcMNPV (212) and BmNPV (15, 66).

*Ac66 (808aa:94kDa), (Bm54:805aa:93.3kDa), (Ha66:785aa:88.9kDa).

Homologs of *Ac66* appear to be present in all baculoviruses. Many viruses appear to have two copies Ac66 of homologs, and some may have three copies (99). Ac66 is closely related to a variety of proteins including a predicted orf in the protozoan *Trichomonas vaginalis* (E = 6e-20), an actin binding protein in *Dictyostelium discoideum* (E = 1e-14), rabbit myosin heavy chain (E = 2e-14), and centromere protein E of *Canis familiaris* (E = 2e-14). It has a few conserved domains, including Smc, which is a chromosome segregation ATPase involved in cell division and chromosome partitioning, desmoplakin, the main adhesive junction protein in epithelia and cardiac muscle, and a domain in a chromosome segregation protein. It was found to be associated with AcMNPV (74) and HearNPV (Ha66) (213) ODV and AcMNPV BV (27). Ac66 is oriented in the opposite direction of DNA polymerase (Ac65) and its promoter region overlaps with the 5' region of the DNA pol orf. This orientation is conserved in many, if not all baculoviruses. Although the orfs adjacent to DNA polymerase in *Neodiprion* (e.g., NeSeNPV) and CuniNPVs show little homology to Ac66, they and Ac66 show homology to the same proteins, i.e., they both show almost 100% probability of being related to colicin 1a and myosin using the HHpred program (64). Consequently, it is likely that Ac66 is conserved throughout the baculoviruses. Ac66 is transcribed as a late gene and its expression does not affect the expression of DNA pol (214). An AcMNPV bacmid deleted for Ac66 was severely compromised and BV titers derived from transfected cells were reduced by over 99% compared with wt. In addition, at low titers the mutant BV appeared to infect single cells and was unable to spread to other cells. Although the nucleocapsids appeared to be normal and had an electron dense core, suggesting that they contained DNA, they appeared to be trapped in the virogenic stroma, suggesting that Ac66 was required for the efficient egress of virions from nuclei. The deletion did not affect the levels of DNA replication or polyhedrin transcription, but the production of occlusion bodies was eliminated (215). This suggests that Ac66 is required both for egress of virions from nuclei and also may be involved in the ennucleation of polyhedra. For additional discussion, see Chapter 5. A bacmid deleted from Bm54 produced non-infectious BV and appeared to be properly assembled. Polyhedron formation also appeared to be affected (216).

Ac67 (385aa:44.6kDa), (Bm55:385aa:44.9kDa), (Ha65:379aa:44.0kDa), LEF-3.

Lef-3 was originally found to be essential for DNA replication in transient assays (42, 43). Homologs of *lef-3* are found in the genomes of lepidopteran NPVs and GVs, but not those of hymenopteran or the dipteran NPVs. LEF-3 is a single-stranded DNA binding protein (SSB) (217) and interacts with itself as a homo-oligomer (218). It also binds to helicase (219) and facilitates its transport into the nucleus (220). It can also drive nuclear transport into mammalian cells (221). It also may have a function in DNA replication in addition to its requirement as a helicase transport factor (222, 223). LEF-3 also interacts with alkaline nuclease and may regulate the function of this enzyme (224, 225); it is capable of both unwinding and annealing DNA depending on its concentration or redox state (226, 227); and it can facilitate the production of structures resembling recombination intermediates via strand exchange between donor and recipient molecules in vitro (228). The lack of conservation of LEF-3 in baculoviruses might not be unexpected because, although homologs of alkaline nuclease are present in many organisms (see *Ac133*) and many have been reported to interact with an SSB (e.g.,

herpesvirus, ICP8 and lambda phage, red-beta), clear sequence relationships between the various SSBs are not evident (229). Insertion/deletion mutants of *lef-3* are lethal (66, 223). In another report a bacmid deleted for LEF-3 showed some evidence for limited amounts of DNA replication and late gene expression, and some infectious virus was observed although over100,000 times less than wt (230).

*Ac68 (192aa:22.3kDa), (Bm56:134aa:15.8kDa), (Ha64:133aa:15.6kDa).

Homologs of Ac68 are present in all baculoviruses. A frame shift in this gene did not affect transient late gene expression (149) and a deletion of Ac68 resulted in no major effects on AcMNPV production and TCID50, and no differences in the number, size, and shape of polyhedra were noted, although the lethal time was longer in T. in larvae (231). In contrast, another report suggested that Ac68 was a per os infectivity factor (PIF-6) as a deletion mutant, although producing normal appearing polyhedra, failed to kill *T. ni* larvae (230). In addition, it is reported to be associated with the AcMNPV PIF complex (40). When the homolog in BmNPV (Bm56) was deleted in a bacmid, no effects on titers in cultured cells or in BV-injected larvae were detected, although the lethal time in larvae was longer. Although enveloped ODV were present, the polyhedra produced by the mutant bacmid were abnormal and lacked virions, suggesting that Bm56 is involved in polyhedron morphogenesis (232).

Ac69 (262aa:30.4kDa), (Bm57:262aa:30.4kDa), (Ha63:274aa:31.6kDa), (MTase).

Ac69 encodes a methyltransferase and orthologs are found in the genomes of all Group I NPVs, except OpMNPV and about one-half of Group II NPVs and one hymenopteran NPV. The homolog present in the hymenopteran NPV (NeseNPV) falls within an insect, rather than a baculovirus lineage. Homologs are found in a nudivirus (Hz-1) and a variety of insects, e.g., *Anopheles gambiae* (E = 8e-18) and other invertebrates and vertebrates. Ac69 was found to stimulate late gene transcription in a transient assay (149). The gene encodes a protein with RNA Cap (Nucleoside-2′-O)-Methyltransferase activity. AcMNPV, with a null mutation of the gene, replicated normally in cell culture (233). Similar results were observed for a knockout of the homolog (Bm57) in BmNPV (15).

Ac70 (290aa:34.4kDa), host cell-specific factor-1 (hcf-1).

Homologs are present in only three other baculoviruses; two are close relatives of AcMNPV and their HCF-1 orfs are 99% (PlxyNPV) and 84% (RoMNPV) identical to that of AcMNPV, whereas the homolog in ClbiNPV is more distantly related (21% identical). HCF-1 was found to be required for transient expression of a late promoter-reporter gene by a late expression factor library in *T. ni* cells, but not SF-21 cells (234). AcMNPV with null mutations in hcf-1 were found to replicate normally in both Sf-21 cells and *S. frugiperda* larvae. However, in *T. ni* cells replication was impaired and in *T. ni* larvae the mutant showed a significantly reduced infectivity by intrahemocelic injection. Although oral infectivity was relatively normal in *T. ni* larvae, the insects died more slowly than when infected with wt (235). It was suggested that HCF-1 is a RING finger-containing protein that is dependent upon self-association and gene repression for its activity (236).

Ac71 (249aa:28.6kDa), (Bm58:249aa:28.7kDa), (Ha62:250aa:29.3kDa), iap-2.

Ac71 encodes an inhibitor of apoptosis-2 (*iap-2*) gene. Homologs of *iap-2* are found in the genomes of all Group I and most Group II NPVs, and as with all *iap* genes more distant relatives are found in many organisms. It is BV associated in AcMNPV (27). Deletion of *iap-2* had no effect on viral replication in cell culture; however, this may have been due to the presence of another apoptotic suppressor, *p35* (237). In contrast, deletion of *iap-2* (bm58) from the BmNPV genome indicated that it was required for replication in BmN cells (111). Evidence suggested

that transfection of AcMNPV iap-2 into *T. ni* cells suppressed apoptosis by HearNPV infections, and although a recombinant HearNPV expressing iap-2 also suppressed apoptosis, BV production was not rescued (101). In *Epiphyas postvittana* NPV, the *iap-2* homolog was found to have anti apoptotic activity when expressed from a CMV promoter in *S. frugiperda* cells (102). However, it was observed that *ipa-2* of *Lymantria dispar* MNPV induced apoptosis when transfected into Ld652Y cells. However, it was suggested apoptosis was suppressed by the virus because of the presence of the apoptotic repressor, *apsup* in LdMNPV (238).

Ac72 (60aa:7.1kDa), (Bm58a,60aa,7.1kDa).

Homologs of Ac72 are found in the genomes of all sequenced Group I NPVs, but not in other viruses. In BmNPV, deletion of this orf caused no observable changes from wt (15)

Ac73 (99aa:11.5kDa), (Bm59:99aa:11.5kDa).

Homologs of Ac73 are found in the genomes of all sequenced Group I NPVs, but not in other viruses. It is BV associated in AcMNPV (27). In BmNPV this gene appears to be essential (15).

Ac74 (265aa:30.6kDa), (Bm60:268aa:31.0kDa), (Ha68:152aa:17.6kDa).

Homologs of Ac74 are found in the genomes of all Group I and about half Group II NPVs, but is not present in hymenopteran or dipteran NPVs or GVs. It is BV associated in AcMNPV (27). Bm60 was found to be expressed as a late gene and was localized to both the cytoplasm and nucleus of infected cells (239). It was found to be associated with AcMNPV ODV (74), but not in HearNPV ODV (213). Deletion of Bm60 from BmNPV resulted in a reduction and delay in DNA synthesis, a reduction in BV production by about 10-fold, and a lengthening of the time to kill larvae (240).

Ac75 (133aa:15.5kDa), (Bm61:133aa:15.5kDa), (Ha69:127aa:14.9kDa).

Homologs of Ac75 are present in all lepidopteran NPV, GV and hymenopteran NPV genomes, but not in the dipteran virus genome. It was found to be associated with both BV and ODV of BmNPV and localized to the ring zone of infected cells (241). In BmNPV it appears to be essential because when deleted, no BV were detected and the virions appeared to be retained in the nuclei (242).

Ac76 (84aa:9.4kDa), (Bm62:85aa:9.6kDa) (Ha70:85aa:10.0kDa).

Homologs of Ac76 are present in the genomes of all lepidopteran NPVs, GVs, and hymenopteran NPVs, but have not been reported in the dipteran virus genome. Ac76 localized to the ring zone late in infection. It is an essential gene, as deletion of ac76 resulted in a mutant bacmid able to produce DNA to normal levels, but was deficient in intra nuclear microvesicles and was unable to produce BV (243). Ac76 appears to be present as a stable dimer that is resistant to denaturation and functions as a type II integral membrane protein in which the C-terminus is located in the ER lumen and the N-terminus interacts with the cytosol (244).

*Ac77 (379aa:44.4kDa), (Bm63:379aa:44.3.0kDa), (Ha71:412aa:47.9kDa), Very late factor-1 (Vlf-1).

Homologs are found in all baculoviruses. The most closely related nonbaculovirus homologs are found in a number of eubacterial species, e.g., *Caldicellulosiruptor saccharolyticus* (E = 1e-06). Homologs are also reported in nudiviruses (195). VLF-1 is a member of the lambda integrase (245) family of proteins. Integrases are a large group of site-specific DNA recombinases that catalyze DNA rearrangements and are involved in the integration and excision of viral genomes and decatenation of newly replicated chromosomes. A feature of these enzymes is that a conserved tyrosine forms a covalent link with DNA during the cleavage process. VLF-1 was originally identified because it influences the hyperexpression of very late genes (245). It was found to bind near the

regulatory region of very late genes (246). Whereas mutations to the region that affected very late gene transcription were not lethal, other mutations, including mutation of the conserved tyrosine, appeared to be lethal to the virus (247). VLF-1 appears to be a structural protein present in both BV and ODV (247) and localizes to the ends of nucleocapsids, suggesting that it is a structural protein (248) and is required for the production of nucleocapsids. Although *vlf-1* is an essential gene, an AcMNPV bacmid with *vlf-1* knocked out (248-250) was able to synthesize viral DNA at levels similar to control bacmids. However, the mutant produces tube-like capsids that appear to lack DNA. Characterization of a mutant of the conserved tyrosine indicated the nucleocapsids were unable to be released from the virogenic stroma, suggesting that the protein may be involved in a final step in the maturation of DNA (248). VLF-1 showed structure-dependent binding to DNA substrates with the highest binding affinity to cruciform DNA that mimics a structure common to recombination intermediates (251). See also Chapters 5 and 6.

*Ac78 (109aa:12.5kDa), (Bm64:110aa:12.7kDa), (Ha72:110aa:12.7kDa).

Ac78 is a core gene (124); the ortholog in HearNPV is associated with the ODV envelopes (252) and in BmNPV, the gene appeared to be essential (15). When deleted from AcMNPV, DNA replication appeared to be unaffected, nucleocapsids appeared to be confined to the nucleus, infectious BV were not produced, and polyhedra lacked occluded virions. Ac78 also appeared to be envelope associated in both BV and ODV (253). The homolog of Ac78 in HearNPV was found to be essential for production of infectious viruses and interacted with the baculovirus sulfhydryl oxidase, p33 (254).

Ac79 (104aa:12.2kDa), (Bm65:104aa:12.2kDa).

Homologs are present in all Group I, about half the Group II NPV and GV genomes. It was found to be associated with AcMNPV ODV(74). It has homology to ascovirus orfs from *T. ni* (E = 1e-18) and *S. frugiperda* (2e-11), Chilo iridescent virus (E = 3e-10), and orfs from a variety of *Yersinia* sp (e.g., E = 2e-10), *Serratia* sp., and other bacteria. It is predicted to be homologous to an endonuclease in a number of these organisms. It has been suggested that Ac79 is a member of the UvrC superfamily of endonucleases that are involved in DNA repair (255). It shows a high degree of similarity both in sequence and predicted structure to EF2693 from *E. faecalis* (256). Bacmids deleted for Ac79 resulted in reduced BV production and smaller plaque size, and showed some tube-like structures that may be aberrant capsids. Point mutations in conserved motifs shared by Ac79 and the endonuclease superfamily failed to cause production of the tube-like structures but one of the mutations caused a reduction in BV production (257). One study of BmNPV suggested that Bm65 is an essential gene (258), whereas another study indicated that it produced BV and could spread between cells but with reduced efficiency (15).

*Ac80 (409aa:45.4kDa), (Bm66:403aa:44.9kDa), (Ha73:322aa:36.6kDa), GP41, tegument protein.

GP41 is a tegument protein modified with O-linked N-acetylglucosamine, located between the virion envelope and capsid (259, 260). It was found to be associated with ODV by mass spectrometry (74, 213). Homologs are present in all baculovirus genomes. Based on the characterization of a ts mutant, Ac80 is an essential gene required for the egress of nucleocapsids from the nucleus (261). A deletion mutant of the homologous gene in BmNPV (Bm66) indicated that it produced BV and could spread between cells but with reduced efficiency (15).

*Ac81 (233aa:26.9kDa), (Bm67:234aa:27.0kDa), (Ha74:241aa:27.7kDa),.

Homologs of this orf appear to be present in all baculovirus genomes. A homolog has also been reported in nudiviruses (195). The BmNPV homolog (Bm67) appears to be a late expressed nonstructural gene that localizes

to the cytoplasm (262). When put through the HHpred program (64) that compares predicted proteins to known structures, Ac81 and its ortholog from NeseNPV showed relatedness to the HIV TAT protein with a probability of greater than 80%. It may be essential because a deletion mutant of the homologous gene in BmNPV (Bm67) was severely compromised and did not appear to produce BV (15).

Ac82 (180aa:19.8kDa), (Bm68:181aa:20.1kDa), (Ha75:225aa:24.9kDa), Telokin-like protein (TLP).

Telokin-like protein is not like telokin! Homologs of Ac82 are found in the genomes of all lepidopteran NPVs and GVs. A protein called telokin is identical to 157 C-terminal amino acids of the myosin light chain kinase (MLCK), but is expressed independently. Telokin is the myosin binding fragment of myosin light chain kinase and is involved in muscle contraction. A polyclonal antibody prepared against smooth muscle telokin reacted with a protein from cell extracts of AcMNPV-infected Sf9 cells. This protein was called telokin-like protein. Clones that reacted with the antibody were isolated from a cDNA library of AcMNPV infected sf9 cells (263). The clones showed no sequence homology to telokin but when expressed in a pET vector, the product reacted with the telokin polyclonal antiserum. The AcMNPV sequence that produced the reactive protein contains portions of Ac82. The crystal structure of AcMNPV TLP was determined, but showed no similarity to telokin or any other characterized protein (264). Therefore, although this protein has been called telokin-like protein, its resemblance to telokin appears to be an artifact of the polyclonal antiserum. Consequently, information on a function for one of the few baculovirus specific proteins for which a crystal structure has been determined is still lacking. It is likely to be nonessential because when it was deleted in BmNPV (Bm68) the virus appeared to be normal, but production of BV and DNA replication was somewhat delayed. Although it showed nuclear localization and did not concentrate at the plasma cell membrane, it was found to be associated with the envelope/tegument of budded virions (265). In AcMNPV a TS mutant appeared to cause a major reduction in BV production (171).

*Ac83 (847aa:96.2kDa), (Bm69:839aa:95.8kDa), (Ha76:816aa:93.5kDa), VP91.

Ac83 encodes a virion capsid protein called VP91 that was originally characterized in OpMNPV (266). It has also been shown to be ODV associated in AcMNPV, CuniNPV, and HaSNPV by mass spectrometry (74, 93, 267) and was found as a component of the per os infectivity factor (PIF) complex (40). Homologs are encoded by all baculovirus and are also found in nudiviruses (195) and possibly in several insect genomes, e.g., *Anopheles gambiae* (E = 5e-04). Ac83 is predicted to contain a chitin binding domain and has a high degree of predicted structural similarity by HHpred (64) to Tachycitin, a 73aa antimicrobial peptide (268). When the ac83 deleted from an AcMNPV bacmid, the bacmid was non infectious. However when just the chitin domain was deleted, the virus was unable to infect larvae via the midgut, but could infect via intrahaemocoelic injection, indicating that Ac83 is a per os infectivity factor and that chitin binding plays a major role in the ability of the virus to initiate midgut infection (269). This suggests that ac83 likely plays two or more roles in virus infection. A deletion mutant of this gene in BmNPV (Bm69) did not produce BV and results in the production of tubular structures (270).

Ac84 (188aa:21.7kDa).

This orf is only found in a few other NPVs: PlxyNPV, ChchNPV, and RoMNPV, and TnSNPV. A homolog is also found in ascoviruses, e.g., *T. ni* ascovirus (E = 3e-10). It is not found in the BmNPV or the HaSNPV genomes.

Ac85 (53aa:6.4kDa).

This small orf encoding 53 aa is only found in two other NPVs that are AcMNPV variants: PlxyNPV and RoMNPV. This gene is not found in the BmNPV or HaSNPV genomes.

Ac86 (684aa:80.8kDa) (PNK/PNL).

This gene encodes a protein with RNA ligase, polynucleotide 5'-kinase, and polynucleotide 3'-phosphatase activities and may be part of an RNA repair pathway (271). Homologs are only found in 5 baculovirus genomes, three are closely related to AcMNPV including AgMNPV, ApNPV, and RoMNPV, whereas the other is in a GV, SpliGV. A closely related orf is also found in a *T. ni* ascovirus (E = 2e-125). Ac86 appears to be a nonessential gene expressed early in infection (272). This gene is not found in the BmNPV or HaSNPV genomes.

Ac87 (126aa:15kDa), (Bm70:126aa:15.1kDa).

This gene appears to be present in most Group I lepidopteran NPV genomes. It was suggested that the homolog in BmNPV (Bm70) might encode a capsid protein called p15 (273). It is likely nonessential, as a deletion mutant in BmNPV (Bm70) appeared normal (15).

Ac88 (264aa:30.1kDa), (Bm71:267aa:30.7kDa), (Ha77:283aa:32.3kDa), CG30.

Homologs of Ac88 appear to be present in the genomes of most Group I and II NPVs, and also may be present in a single GV (SpliGV). An orf in *Clostridium perfringens* showed significant similarity (E = 2e-06). Ac88 contains predicted zinc finger and leucine finger domains (274). It was found to be associated with AcMNPV (74), but not in HearNPV ODV (213). Deletion of this gene from AcMNPV resulted in only subtle differences from wt (275). However, deletion of the gene from BmNPV (Bm71) resulted in a 10 to 100 fold reduction in titer and showed a longer lethal time (276). In another study of Bm71, a deletion and two RING finger mutants were constructed. The deletion mutant produced fewer BV and fewer occlusion bodies were released into the hemolymph of infected larvae. The RING finger mutants released fewer OBs into larval hemolymph. They also noted that cg30 localized to nuclei of infected cells (277).

*Ac89 (347aa:39kDa), (Bm72:350aa:39.3kDa), (Ha78:293aa:33.4kDa), VP39.

This gene encodes the major capsid protein VP39. It is present in all baculovirus genomes. It was originally characterized in OpMNPV (278) and AcMNPV (279). It interacts with 38K (Ac98) (177). Deletion of Bm72 from BmNPV resulted in no apparent BV production (15). It has been observed that VP39 interacts with a conserved domain of kinesin 1 and it has been suggestion that this interaction is involved in the transport of nucleocapsids destined to become BV to the cell membrane after their assembly in nuclei (280).

*Ac90 (464aa:53.9kDa), (Bm73:465aa:54.0kDa), (Ha79:3461aa:54.0kDa), LEF-4.

LEF-4 is an enzyme involved in RNA capping and is a component of the late baculovirus RNA polymerase (147). It is present in all baculovirus genomes and is also present in nudivirus genomes (195). This gene was originally identified as being essential for late transcription (137). LEF-4 was subsequently found to be an RNA capping enzyme (281, 282). The addition of an mRNA 5' cap structure involves the hydrolysis of the gamma phosphate of the 5'-triphosphate of the first nucleotide of pre-mRNA and the capping reaction that involves the transfer of GMP from GTP. The two reactions involve two different enzymatic activities: an RNA 5' triphosphatase to remove the terminal gamma phosphate and the addition of GMP by guanylyltransferase. These two activities are present on a single protein located at the N- and C-termini, respectively, in metazoans and plants. Although having similar activity, LEF-4 is unrelated to this category of capping enzyme, but is a member of metal dependent group of capping enzymes found in fungi and protozoa (281, 283, 284). The 5' cap structure appears to serve two roles. It protects the 5' end of the mRNA from degradation by exonucleases and it interacts with translation initiation factors, thereby facilitating the initiation of translation. Capping in eukaryotes involves an

enzyme that associates with the highly repetitive carboxy terminal domain (CTD) of the β' subunit of RNA polymerase II. Because the baculovirus polymerase lacks a similar domain, it is likely that it evolved to include the enzyme as part of the RNA polymerase complex. However, assuming these reactions are free from exonuclease, it is not clear why LEF-4 is required for transcription in in vitro assays. These assays monitor RNA transcripts that would not need to be capped in order to be detected. This suggests that LEF-4 may play a structural role in the organization of the polymerase subunits, or it may have some other function. LEF-4 is an essential gene and could not be deleted (285). For more information see Chapter 6.

Ac91 (224aa:24.1kDa), (Bm74:154aa:17.3kDa).

Homologs of this gene are found in genomes of all Group I lepidopteran NPV and two GV (CpGV and PlxyGV) genomes. It has an unusual predicted amino acid sequence: 31% proline and 18% ser/thr residues. In HearNPV the Ac91 homolog (ha80) was expressed first cytoplasmically and then in nuclei, but did not appear to be a structural protein of BV or ODV (286). Deletion of Bm74 causes few differences from wt and repair viruses in DNA synthesis or BV titers. However, the lethal time in larvae was longer by 14.7 hr (287).

*Ac92 (259aa:30.9kDa), (Bm75:259aa:30.9kDa), (Ha80:254aa:30.8kDa), p33, sulfhydryloxidase (sox).

Ac92 is a flavin adenine dinucleotide (FAD)-linked sulfhydryl oxidase (288) (289). Proteins with sulfhydryl oxidase activity have been implicated in the protection of cells from oxidative stress caused by apoptosis (290) (291). Orthologs of Ac92 are present in all sequenced baculovirus genomes, it is associated with BV and ODV, and it is an essential gene as viable recombinants deleted for this gene have not been isolated (289) (292). Ac92 is able to form a stable complex with the human tumor suppressor gene p53 when it was expressed in a baculovirus system. When expressed by itself, p33 shows diffuse cytoplasmic staining and punctate staining of nuclei. However, when co-expressed with p53, it exclusively localizes to nuclei. Expression of human p53 in Sf cells causes apoptosis that can be blocked by co-expression of baculovirus anti-apoptotic suppressors p35 or OpIAP. However, co-expression of p53 with p33 elevated the induction of apoptosis about two fold. By proteomic analysis, p33 appears to be an ODV-associated protein in AcMNPV (74) and HearNPV (213, 267). The crystal structure of Ac92 was described as a novel dimer composed of two pseudodimers (293). The structure of Bm75 has also been reported (294). An ortholog of P53 has been described for *S. frugiperda* (295) and similar to human p53, Sfp53 was found to interact with Ac92 (296). It interacts with the Sfp53 DNA binding domain and a point mutation in Sfp53 that inactivated DNA binding also inactivated binding of Ac92 to Sfp53. Ac92 was also shown to oxidize Sfp53 in vitro. However, despite the ability of p33 to interact with and oxidize Sfp53 in cultured cells, no effects on Sfp53-mediated apoptosis or virus replication were observed (296). Effects on other cell types or in whole insects was not ruled out by these studies.

*Ac93 (161aa:18.4kDa), (Bm76:161aa:18.4kDa) (Ha81:162aa:19.1kDa).

This gene appears to be present in all baculovirus genomes (297). An Ac93 knockout did not produce infectious BV and may be involved in the formation of intranuclear microvesicles, (297). In addition, a BmNPV bacmid deleted for Bm76 did not produce BV (15).

*Ac94 (228aa:25.5kDa), (Bm77:228aa:25.6kDa), (Ha82:230aa:25.9kDa), ODV-E25 (p25, 25k).

Ac94 appears to be encoded by all baculovirus genomes (297). The protein encoded by this gene was originally identified in OpMNPV, and immunogold staining with a specific antibody against Ac94 was localized to ODV envelopes (298). It has also been shown to be associated with BV and ODV of AcMNPV and HearNPV (27, 74, 213, 267). The hydrophobic N-terminal 24 aa of AcMNPV ODV-E25 appears to be a nuclear targeting signal (155). Deletion of Ac94 resulted in a 100 fold reduction in infectious BV. In addition, ODV were not evident and

although polyhedra were produced, they lacked virions (299). It has been reported that when ODV-E25 is expressed as an early gene under the IE-1 promoter, it accumulated on the cytoplasmic side of the nuclear membrane rather than within nuclei, and budded virus production was severely reduced. This suggests that it might play a role in the shift from BV to ODV virions. In addition, expression from the very late polyhedrin or p10 promoter reduced and delayed occlusion body formation suggesting that it may play a role in virion occlusion (300) (301). Subsequently it was found that the open reading frame of ODV-E25 encodes a microRNA that down regulates ODV-E25 expression. It was suggested that this might result in a reduction in infectious virus production and be involved in the shift to occluded virus production (302).

*Ac95 (1221aa:143kDa), (Bm78:1222aa:143.6kDa), (Ha84:1253aa:146.0kDa), DNA helicase (p143).

Homologs of DNA helicase are present in all baculovirus genomes. This gene was initially identified as a ts mutant that was unable to synthesize DNA at 33° (303). The defect was localized to a homolog of DNA helicase with a predicted mass of 143 kDa (304). P143 is required for transient DNA replication (42, 43) and shows ATPase activity and is able to unwind a DNA primer annealed to a larger DNA molecule in an ATPase-dependent manner (305). Helicase is dependent on an interaction with LEF-3 for transport to the nucleus (see Ac67, LEF-3) (220). Mutations in this gene have been implicated in affecting viral host range (306, 307). Deletion is probably lethal as deletion/insertion mutants of this gene in BmNPV (Bm84) could not be isolated (66).

*Ac96 (173aa:19.8kDa), (Bm79:182aa:21.0kDa), (Ha85:173aa:19.8kDa) PIF-4.

This orf appears to be present in all baculoviruses and homologs also appear to be present in nudiviruses (195). The homolog in BmNPV (Bm79) is an ODV envelope associated protein (308) and was also found associated with the envelopes of BV (309). Deletion of Ac96 from a bacmid construct resulted in a virus that could replicate in cell lines, but not insects. Consequently it was concluded that Ac96 is a per os infectivity factor, the 4th such protein identified in the AcMNPV genome (309).

Ac97 (56aa:6.5kDa).

This is a small orf (56 aa) and appears to be present only in AcMNPV. There is no homolog in BmNPV and it is positioned at the location of the apparent insertion of two bro (Ac2) homologs (see Ac2). The lack of this orf in closely related viruses may indicate that it is not a functional orf.

*Ac98 (320aa:38kDa), (Bm82:320aa:38.0kDa), (Ha86:321aa:37.9kDa), 38K.

Ac98 encodes a predicted protein of 38k and orthologs are present in all baculovirus genomes. AcMNPV Ac98 interacts with itself, VP1054 (Ac54), VP39 (Ac89), and VP80 (Ac104) and is associated with BV and ODV nucleocapsids (177). In HearNPV it interacted with itself, ODV-E56,GP41, PIF-2 and PEF-3 (310). An AcMNPV bacmid deletion construct, although unable to produce infectious virions, was capable of DNA synthesis, but nucleocapsid formation was disrupted. Tube-like structures that appeared to lack DNA, but stained with an anti-vp39 antibody were observed (311). It has also been suggested that Ac98 is capable of stimulating transcription in a transient transcription assay (312). When put through the HHpred program (64) that compares predicted proteins to known structures (see Chapter 6), Ac98 showed relatedness to a set of enzymes including CTD phosphatases with a probability of almost 100%. Dephosphorylation of the CTD can negatively regulate RNA polymerase II by inhibiting RNA elongation (313, 314). Although it is required for nucleocapsid formation, it does not appear to be a structural component of ODV as determined by proteomic analysis (74, 213). However, it was detected in CuniNPV ODV (93).

*Ac99 (265aa:31kDa), (Bm83:265aa:31.1kDa), (Ha87:315aa:37.0kDa), (LEF-5).

Homologs of lef-5 are found in all baculoviruses and are also present in nudiviruses (195). LEF-5 was originally identified as being required for transient late gene expression (315). It was demonstrated to interact with itself and to contain a domain similar to that of the RNA polymerase II elongation factor TFIIS (316). Subsequent investigations indicated that LEF-5 did not enable the baculovirus polymerase to transit pause sites, and it was concluded that it functions as an initiation factor, rather than an elongation factor (317). A lef-5 knockout bacmid appeared to express early genes and replicate DNA normally, but was defective in late gene transcription, and did not yield any detectable virus when transfected in to Sf9 cells. (318).

*Ac100 (55aa:6.9kDa), (Bm84:65aa: 8.1kDa), (Ha88:109aa:11.5kDa),p6.9.

P6.9 is a small (55 aa) arginine/serine/threonine-rich DNA binding protein (319). Homologs appear to be found in all baculoviruses, but are apparently difficult to detect because of their small size and repetitive amino acid content (320). It was originally shown to be a DNA binding protein in a GV (321), and the homolog was isolated from AcMNPV (319). The high concentration of arginine and ser/thr residues is similar to protamines that are present in sperm nuclei of many higher eukaryotes and are involved in the production of highly condensed DNA. Protamines are also small molecules of 44-65 amino acids (322, 323). Arginine is positively charged, and the polyarginine tracts in protamines neutralize the phosphodiester backbone, whereas the ser and thr residues interact with other protamine molecules, thereby yielding a neutral, highly compact complex that is biochemically inert. P6.9 localizes to the nuclear matrix during infection (324). It was found to elevate virus transcription at 12-24 hpi, but did not appear to be involved in basal levels of virus transcription. It was also found to co-localize with viral DNA during this same time frame and to fractionate with RNA polymerase II at 24 hpi (325). P6.9 appears to be phosphorylated immediately upon synthesis and dephosphorylated when complexed with DNA (326). Some localizes to the virogenic stroma but the majority was found near the inner nuclear membrane throughout the infection. It shows distinct patterns of phosphorylation with multiple forms present in association with ODV, however, only the dephosphorylated form was associated with BV (327). It is not clear whether the phosphorylated form of p6.9 is present within the ODV virions bound to DNA, or possibly a contaminant of the exterior. With BV, contaminating phosphorylated p6.9 would likely be stripped off as the virions are transported through the cytoplasm. Using an AcMNPV bacmid deleted for p6.9, nucleocapsids were not produced although tube-like structures similar to those associated with the deletion of VLF-1 and Ac98 (see above) were observed. The mutant appeared to synthesize normal amounts of DNA, but did not produce infectious virus (328).

*Ac101 (361aa:41.5kDa), (Bm85:362aa:41.6kDa), (Ha89:369aa:42.6kDa), BV/ODV-C42.

Ac101 encodes a capsid-associated protein of both BV and ODV (74). Homologs have been identified in all sequenced baculovirus genomes (124). It was reported to interact in a yeast two-hybrid assay and by native gel electrophoresis (329) with pp78/83 (Ac8) that has been shown to localize to the basal end region of nucleocapsids (54, 55). Evidence suggests that it binds to PP78/83 and transports it into nuclei (330) and is involved in actin polymerization (331). It also interacts with FP25 (Ac61) and Ac141 (332). Deletion of Ac101 from an AcMNPV bacmid appeared to affect nucleocapsid formation but, although lethal, did not appear to affect DNA synthesis (333). Deletion/mutation of Ac101 was also reported to be lethal by others (330, 334).

Ac102 (122aa:13.3kDa), (Bm86:123aa:13.5kDa), (Ha90:122aa:13.8kDa), p12.

Homologs of Ac102 are found in all lepidopteran NPV, and GV genomes, but not in hymenopteran or dipteran viruses. It appears to encode an ODV-associated protein (74) in AcMNPV and HearNPV (267). It is involved in the nuclear localization of G-actin (38, 335). Deletion is lethal as insertion/deletion mutants of this gene could not be isolated in AcMNPV (38, 334) and viral spread to other cells was not observed with a BmNPV (Bm86) knockout (15).

*Ac103 (387aa:45.3kDa), (Bm87:387aa:45.4kDa), (Ha91:377aa:44.0kDa), p45.

Homologs of Ac103 are present in all baculovirus genomes (124). Deletion of Ac103 was lethal, no viable BV were detected, and the constructs appeared to be deficient in the envelopment of ODV and their incorporation into occlusion bodies (336).

Ac104 (691aa:79.9kDa), (Bm88:692aa:79.9kDa), (Ha92:605aa:69.7kDa), vp80 capsid, vp87.

Homologs of Ac104 are found in all Group I and II lepidopteran NPV genomes, but not in those of GVs or hymenopteran or dipteran NPVs. It is capsid associated in both OpMNPV (337) and AcMNPV (74, 338, 339) and interacts with 38K (Ac98) (177). Deletion of Vp80 showed that it is an essential gene and resulted in nucleocapsids that were unable to move from the virogenic stroma (340). It appears to localize in nuclei near actin scaffolds that connect the virogenic stroma to the nuclear envelope. In addition, it co-immunoprecipitates with actin. It also appears to localize to one end of nucleocapsids and contains sequences similar to paramysin motifs that may be involved in the transport of virions to the periphery of nuclei (338). It forms dimers, contains a C-terminal region that was predicted to contain a basic helix-loop-helix domain, and binds to DNA (341).

Ac105 (553aa:65.6kDa), (Bm89:289aa:34.3kDa), He65.

Homologs of Ac105 are found in the genomes of most Group I, about one-half the Group II and three GVs (Agse-, Ha-, and XecnGV). It is a member of a distinct family of ligases that includes editing ligases of trypanosomes, putative RNA ligases of many species of archaea, and also baculoviruses and an entomopoxviruses (342). It is an early-transcribed gene (343). It may be involved in the nuclear localization of G-actin (335). It appears to be a non essential gene in AcMNPV (38) and BmNPV (15).

Ac106/107 (243aa:28.3kDa), (Bm90:249aa:28.9kDa) (Ha101:253aa:29.0kDa).

These two orfs are likely a single gene as homologs are fused in many baculoviruses and were found to be joined when the region was resequenced in the C-6 strain (12). Homologs are found in all Group I and II lepidopteran NPV, GV and hymenopteran NPV genomes, but not in that of the dipteran NPV. Deletion of Bm90 resulted in a mutant that was unable to spread between cells indicating that it is an essential gene (15).

Ac108 (105aa:11.8kDa), (Bm91:105aa:11.8kDa) (Ha95:94aa:11.0kDa).

Orthologs of Ac108 have been found in the genomes of all alpha, beta, and gamma baculoviruses (124). Although Ac108 was not found to be ODV-associated in AcMNPV (74) or HearNPV (213), the homolog in the *Antheraea pernyi* nucleopolyhedrovirus (p11) was found to be associated with ODV (344). In addition, it was present in the PIF complex of AcMNPV in another report (40). Furthermore, the ortholog in *Spodoptera frugiperda* MNPV (sf58) appeared to be a per os infectivity factor (PIF) as mutant BV were infectious by

injection of larvae, but mutant ODV were not infectious when fed to larvae (345). In BmNPV, Bm91 was ODV associated, but appeared to be non essential (15, 346).

*Ac109 (390aa:44.8kDa), (Bm92:391aa:45.0kDa), (Ha94:361aa:41.5kDa).

Homologs of Ac109 are present in all baculovirus genomes. Evidence suggests that it is ODV-associated in AcMNPV (74) and *Helicoverpa armigera* NPV (Ha94-ODV-EC43) (213, 347) and also is BV-associated in AcMNPV (27, 348). Four studies have examined deletions of Ac109 and demonstrate that it is an essential gene and when deleted, DNA replication is not affected. One study reported that deletion of Ac109 resulted in a block in nucleocapsid and polyhedron formation (349). However, the other reports described different results. One indicated that polyhedra and virions were produced by Ac109 deletions, but the virus was not infectious (348). Another study found similar results but also showed that the nucleocapsids had defects in envelopment and the polyhedra lacked virions (350). A fourth report also described similar findings but indicated that the BV produced by a Ac109 knockout could enter the cytoplasm, but not nuclei and also noted that the occlusion bodies lacked virions (351).

Ac110 (56aa:6.8kDa), (Bm92a), (Ha93:58aa:6.9kDa).

Homologs of Ac110 are present in all lepidopteran baculovirus genomes. Deletion of Bm92a had no effects on virus replication (15).

Ac111 (67aa:8.2kDa), (Bm93:67aa: 8.2kDa), (Ha116:71aa:8.2kDa).

Homologs of Ac111 are present in genomes of all Group I, four Group II (Hear-, Heze-, Ld-, and LeseNPV) and two GVs (SpliGV and XecnGV). Deletion of Bm93 had no effects on virus replication (15).

Ac112/113 (258aa:30.9kDa).

These two orfs are likely a single gene as homologs are fused in many baculoviruses and were found to be joined when the region was resequenced in the C-6 strain (12). Homologs are present in three Group I variants of AcMNPV (Ac-, Plxy-, and RoMNPV), one Group II NPV (LdMNPV) and three GV (Spli- Hear-, and XecnGV) genomes. It shows highly significant homology to FPV217, a hypothetical protein of fowlpox virus (E = 8e-28). BLAST searches with FP217 only picks out baculovirus Ac112 homologs. A related orf is not present in BmNPV (16). The ortholog of this orf in LdMNPV (ld109) is a suppressor of apoptosis called *apsup*. They show about 30% amino acid sequence identity, but Ac112/113 did not show any apoptotic activity (352).

Ac114 (424aa:49.3kDa), (Bm94:424aa:49.4kDa).

Homologs of Ac114 are found in all Group I NPV genomes. It shows some homology to a hypothetical orf of *Plasmodium falciparum* 3D7 (E = 5e-04). In AcMNPV it appears to be an ODV (74, 353) and BV associated protein (27). It is likely to be nonessential, as a BmNPV bacmid deleted for this gene (Bm94) appeared similar to wt (15).

*Ac115 (204aa:23kDa), (Bm95:204aa:23.0kDa), (Ha90:199aa:22.4kDa), pif-3.

Homologs of *pif-3* appear to be present in all baculovirus genomes. It is also present in nudivirus genomes (195). Like other *pif* genes, *pif-3* is required for oral infectivity of insect but not for infection of cultured cells (88). It forms a complex with PIF-1 and PIF-2 (310). For more information see Ac138 (p74).

Ac116 (56aa:6.4kDa), (Bm95a).

Homologs of Ac116 are found only in four Group I NPVs (Ac-, Ro-, Bm-, and PlxyNPV). Deletion Bm95a and Bm96 showed no defects as did deletion of Bm96 alone, therefore Bm95 appears to be non essential (15).

Ac117 (95aa:11kDa), (Bm96:95aa:10.9kDa), (Ha110:88aa:10.1kDa).

Homologs of Ac117 are found in the genomes of all Group I and seven group II NPVs. It is likely to be nonessential, as insertion/deletion mutants of this gene in BmNPV (Bm96) were similar to wt, although a slight effect on the motility of infected larvae was noted (15, 160).

Ac118 (157aa:18.7kDa).

Homologs are only found in three Group I NPVs (Ac-, Ro- and PlxyNPV) genomes. A related orf is not present in BmNPV.

*Ac119 (530aa:59.8kDa), (Bm97:527aa:59.8kDa), (Ha111:528aa:60.3kDa), pif-1.

Homologs of *pif-1* are present in all baculovirus genomes and are also present in nudivirus genomes (195). This gene can be deleted and the mutant is still infectious for cultured cells, but is not orally infectious for insects (88). It forms a complex with PIF-2 and PIF-3 (310). For more information see Ac138 (p74).

Ac120 (82aa:9.5kDa), (Bm98:82aa:9.5kDa).

Homologs of Ac120 are found in all Group I and most Group II genomes. It is likely to be nonessential, as an insertion/deletion mutation of this gene in BmNPV (Bm98) had no apparent effect on infectivity (15).

Ac121 (58aa:6.7kDa), (Bm98a).

Homologs of Ac121 are only found in the genomes of Bm- and PlxyNPV. It may be a transcriptional activator of some early genes, including IE1 and pp31 (354). However, it does not appear to activate late gene expression (149). In BmNPV, it appeared to be non essential (15).

Ac122 (62aa:7.2kDa), (Bm99:61aa:7.1kDa).

Homologs of Ac122 are present in all sequenced Group I genomes except EppoNPV. It is likely to be nonessential, as an insertion mutation of this gene in BmNPV (Bm99) had no apparent effect on infectivity (15).

Ac123 (215aa:25kDa), (Bm100:225aa:26.0kDa), Protein kinase 2 (PK2).

Homologs of Ac123 are found only in BmNPV, PlxyNPV and RoMNPV and they are all over 98% identical to AcPK2. PK2 is closely related to translation initiation factor eIF 2α kinase (e.g., B. mori (E = 2e-20)), and the homology appears to be focused on the C-terminal region of the kinase domain (355). An AcMNPV mutant deleted for *pk2* displayed no differences from wt in its infectivity to cultured cells and insect larvae (355). In contrast, PK2 (Bm100) from BmNPV was found to be required for replication in BmN cells (111). In addition, novel eIF-2alpha kinase called BeK was identified from B. mori. It has a distinct N-terminal requlatory region not shared by other eIF-2alpha kinases. BmPK2 was found to be capable of inhibiting the enzymatic activity of BeK (356). AcMNPV PK2 was found to inhibit yeast and human eIF2α kinases (357). Insect cells infected with wt showed reduced eIF2α phosphorylation and increased translational activity that was not observed in cells infected with the *pk2* deletion mutant. It was suggested that this gene could be involved in a mechanism for inactivating a host stress response to virus infection (357). Sf9 cell infection by AcMNPV deleted for PK2 or by wt virus both encoding the p35 anti-apoptotic gene was found to induce the expression of BiP. BiP is a stress

marker of the endoplasmic reticulum and a chaperone. It was observed, however, that the UV induction of eIF2alpha phosphorylation and the activation of caspase were mitigated more effectively by the wt virus than the mutant virus that lacks pK2, which is an eIF2alpha kinase inhibitor (358).

Ac124 (247aa:28.5kDa), (Bm101:244aa:28.1kDa).

Homologs of Ac124 are present in the genomes of all sequenced Group I lepidopteran NPVs. It has been shown to be BV associated (27). In BmNPV, it appeared to be a non essential gene (15).

Ac125 (226aa:26.6kDa), (Bm102:227aa:26.6kDa), lef-7.

Homologs of lef-7 are present in the genomes of all Group I, three Group II (Se-, Sf- and MacoNPV A) and two GVs (Ha- and XecnGV). Lef-7 is stimulatory for transient DNA replication (43, 359). When deleted, infection was unaffected in Tn368 cells, but in Sf21 and Se1c cells DNA replication was 10% of wt (360). Deletion of BmNPV lef-7 also caused a reduction in BmNPV DNA synthesis (66). LEF-7 was found to be involved in the regulation of the DNA damage response (DDR). It appears to be an F-box protein that interacts with host S-phase kinase-associated protein 1 (SKP1). SKP1 is a component of a complex that interacts with and targets proteins for polyubiquitination. Deletion of *lef-7* from the AcMNPV genome resulted in the accumulation of phosphorylated H2AX and activation of the DDR that led to a major reduction in late gene expression and reduced infectious virus production by 100 fold. It was suggested that LEF-7 may interfere with the phosphorylation of H2AX thereby diverting host DDR proteins from cellular chromatin, so that they can be exploited for viral DNA replication (361).

Ac126 (551aa:61.4kDa), (Bm103:552aa:61.8kDa), (Ha41:570aa:65.5kDa), chitinase.

As of 2008, homologs of chitinase were reported in genomes of all Group I (except AgMNPV), all Group II (except AdhoNPV) and four GVs (Agse, Cp-, Ha-, and XecnGV) and is phylogenetically clustered with a number of lepidopteran chitinases, i.e., it shows 63% aa sequence identity to *B. mori* chitinase. Comparison of BmNPV and *B. mori* chitinases indicated that, although closely related, they have different properties; the viral chitinase is retained in the cell and functions under alkaline conditions, whereas the host enzyme is secreted and has reduced activity at higher pH (362). Phylogenetic studies indicate that it is more closely related to the chitinase of proteobacteria that employ the enzyme to degrade fungal chitins (363). It has a mode of action similar to *Serratia marcescens* chitinase to which it is 60.5% identical and processively hydrolyzes beta-chitin (364). In conjunction with Ac127 (cathepsin), chitinase participates in the liquefaction of insects late in infection. It is a late expressed gene and its product is localized to the cytoplasm (365) and also is BV associated (27). When it is deleted along with Ac127 (cathepsin), insects remained intact for several days after death (366). Chitinase is localized to the endoplasmic reticulum in infected cells by KEDL, an endoplasmic reticulum retention motif (367, 368). The retention in the ER may prevent the premature death and liquefaction of infected insects, allowing the virus to continue to replicate. It is thought that the presence of chitinase and cathepsin assists in the dissemination of the virus by degrading the insect upon its death. The facility with which a virus (*Anticarsia gemmatalis* NPV) can be processed for use as a biocontrol agent has been attributed to its lack of these two genes, thereby allowing collection of the virus from intact rather than disintegrated insects (369).

Ac127 (323aa:36.9kDa), (Bm104:323aa:36.9kDa), (Ha56:365aa:42.0kDa), cathepsin, vcath, a metalloprotease.

Homologs of Ac127, cathepsin, have a similar distribution to Ac126 (chitinase) and are present in the genomes of all Group I (except AgMNPV), all Group II and four GVs (Agse-, Cp-, Crle-, and XecnGV). The baculovirus genes are closely related to insect cathepsins, i.e. Ac127 is 39% identical to an *Apis mellifera* cathepsin. The baculovirus cathepsin appears to participate along with chitinase in the liquefaction of infected insects (see

Ac126) (370). When it is deleted along with Ac126 (chitinase), insects remained intact for several days after death (366). It has been suggested that Ac127 is synthesized in an inactive form that is activated upon death of the insect by lysosomal proteinases (371). It was subsequently demonstrated that AcMNPV and CfMNPV cathepsins are expressed as pre-proenzymes that are cleaved in infected cells (372). Viral chitinase (see above) is apparently synthesized before cathepsin to facilitate cathepsins retention in the ER. Cathepsin is synthesized as an inactive precursor (preproV-CATH) and upon translation the N-terminal 22 amino acids encompassing the signal peptide causes the localization to the ER during which the signal peptide is cleaved. Within the ER the viral chitinase appears to interact with the proV-CATH and assists in the proper folding and causes its retention in the ER (373). Upon death of the host proV-CATH is cleaved and activated and released from the ER along with chitinase to facilitate the degradation of the insect and release of the virus.

Ac128 (530aa:60.6kDa), (Bm105:530aa:60.6kDa), gp64, gp67.

gp64 encodes a low pH activated envelope fusion protein, and homologs are present in all Group I genomes. It is one of the major distinguishing features of these viruses. It is thought that all Group I viruses use GP64 for the entry of BV into cells, whereas all other baculoviruses lack a *gp64* homolog and use the F protein (ac23 homolog) except for hymenopteran NPVs which lack both genes. In addition to the Group I NPVs, homologs of *gp64* are also found in thogotoviruses, which are members of the Orthomyxoviridae (374). GP64 (375-377) is a fatty acid acylated glycoprotein (378). Deletion of gp64 is lethal and results in viruses that replicate in a single cell, but cannot bud out and infect surrounding cells (379, 380). The postfusion structure of GP64 has been described (381).

Ac129 (198aa:22.1kDa), (Bm106:195aa:21.8kDa), (Ha118:248aa:28.4kDa), p24-capsid.

Homologs of Ac129 are present in the genomes of all Group I /II and GV genomes. Ac129 (p24) is associated with both BV and ODV of AcMNPV and OpMNPV (27, 382). Its presence in AcMNPV ODV was confirmed, however, the HearNPV homolog, He118, was not found associated with ODV (213). It is likely to be nonessential, as interruption of this gene with a transposable element in a strain of AcMNPV has been reported (383, 384). In addition, insertion/deletion mutations of this gene in BmNPV (Bm106), although viable, took slightly longer to kill insects than wt (160). Also, LdMNPV, the original strain sequenced, lacked this gene, whereas it is present in other strains (385).

Ac130 (106aa:12.1kDa), (Bm107:106aa:12.1kDa), (Ha119:94aa:10.7kDa), gp16.

Homologs of Ac130 are present in the genomes of all Group I, all Group II except (LdMNPV and LeseNPV), but are not present in those of GVs. In OpMNPV, the homolog (Op128) is glycosylated and localized near the nuclear membrane in the cytoplasm. Although it appeared to be associated with envelopes of nucleocapsids in the cytoplasm, it was not associated with either ODV or BV (386). It appears to be a non essential gene in BmNPV (15).

Ac131 (322aa:36.4kDa), (Bm108:315aa:35.4kDa), (Ha120:340aa:39.1kDa), calyx, polyhedron envelope (PE) protein, pp34.

Orthologs of Ac131 have been found in the genomes of all alpha, beta, and gamma baculoviruses (124)(173). In addition, domains of PE may be present as fusion with segments of p10 in some GVs (see below). The calyx/polyhedron envelope was originally found to be composed of carbohydrate (387); subsequently a phosphorylated protein component was identified (388) and was shown to be associated with the calyx/PE (389). Similar results were obtained for OpMNPV and it was also found to be associated with p10 fibrillar structures (390-393). In addition, in some viral genomes, genes are present that appear to be fusions of both PE and p10

protein domains (394, 395). The Ac131 encoded protein appears to be an integral component of the calyx/PE, and when the gene is deleted, polyhedra lack an intact calyx/PE, and have a rough surface showing cavities where virions have apparently been dislodged (396). It has also been reported to be BV associated (27) although what role it may play in this phenotype is not clear. The function of the calyx/PE appears to be to encase the occlusion body in order to enhance its stability. See Chapter 2 for additional information. The predicted size of Ac131 is longer (322 vs 252 aa) than previously reported (12).

Ac132 (219aa:25.1kDa), (Bm109:220aa:25.2kDa).

Homologs of Ac132 are present in all sequenced Group I genomes. Ac132 was identified as being associated with AcMNPV ODV(74) and BV (27). Bm109 was also reported to be ODV associated (397). In BmNPV, it appear to be an essential gene (15).

*Ac133 (419aa:48.3kDa), (Bm110:420aa:48.5kDa), (Ha114:428aa:49.4kDa), Alkaline nuclease (AN).

Homologs of alkaline nuclease (AN) are found in all baculovirus genomes. They are also found in a variety of other viruses such as lambda phage and herpes viruses. In these viruses, the AN homolog associates with an SSB and has an exonuclease activity which generates 3' single-strand DNA ends that can participate in DNA recombination. In AcMNPV, AN interacts and co-purifies with the SSB LEF-3 and has both a 5'→3' exonuclease and an endonuclease activity (224, 225, 398). Deletion of Ac133 is lethal (399, 400). It is thought that AN is involved in DNA recombination. Homologs are also present in nudiviruses and hytrosaviruses. In *Epinotia aporema* granulovirus (EpapGV), the ortholog of Ac133 is fused with an ortholog of helicase 2 (401) (see Chapter 13) suggesting that they might act together possibly for the maturation of Okazaki intermediates. Ac133 may act as Fen nuclease in this process as its endonuclease and the single strand specific 5' to 3' exonuclease could be involved in the digestion of the primer overhangs generated by helicases.

Ac134 (Bm111:803aa:94.5kDa) (p94).

Homologs of Ac134 are present in the genomes of most Group I, three Group II (MacoA- MacoB-, Se- and SfMNPV), and three GVs (Agse-, Hear- and XecnGV). Homologs are found in several polydnaviruses, e.g., *Cotesia congregata* bracovirus (E = 7e-40) and entomopox viruses, e.g., *Melanoplus sanguinipes* entomopoxvirus (E = 1e-04), and several protozoa, some of which are insect-associated, e.g., the acetyl-CoA carboxylase 1 precursor of *Plasmodium yoelii* (E = 2e-05). The disruption of the p94 gene showed no effect on the ability of AcMNPV to infect *S. frugiperda* larvae by either the oral or intrahaemocelic route (402).

Ac135 (299aa:34.8kDa), (Bm112:299aa:34.5kDa), p35.

P35 is an inhibitor of apoptosis, and homologs are limited to a few Group I NPVs closely related to AcMNPV. A homolog has also been reported in a GV of *Choristoneura occidentalis* (ChocGV) (394), and a variant (p49) is found in a Group II NPV (SpliNPV) genome (403, 404). Furthermore, a homolog most closely related to SpliNPV p49 has also been identified in an entomopox virus genome (405). P35 is able to block apoptosis in *S. frugiperda* cells caused by AcMNPV infection (406). Although deletion mutants are viable, they are severely compromised in BV production in Sf cells (406, 407). The crystal structure of p35 has been described (408) (409). For additional information, see Chapter 7.

Ac136 (240aa:27.3kDa), (Bm113:240aa:27.3kDa), (Ha22:267aa:30.5kDa), p26.

Homologs of p26 are present in the genomes of all Group I, all Group II except (SpliNPV), but are not present in those of GVs. Multiple copies of the gene may be present. Homologs are also found in the genomes of numerous

pox viruses, e.g., Vaccinia (E = 0.15, 25% identity over 201 aa). Ac126 forms homodimers and is primarily a cytoplasmic protein (410). The examination of an AcMNPV deleted for p26 revealed no differences from wt in the cells and larvae tested (411). However, a deletion of p26 along with p10 and p74 resulted in polyhedra lacking virions (412).

Ac137 (94aa:10.3kDa), (Bm114:70aa:7.5kDa), (Ha21:87aa:9.3kDa), p10.

Homologs of p10 are found in the genomes of all Group I and II NPVs and most GVs, in some instances in multiple copies (413). They are also present in all hymenopteran NPV genomes. A p10 homolog has been characterized in an entomopox virus (414). P10 was originally identified as a very late hyperexpressed gene (415) and therefore the p10 promoter has been used in expression vectors (416). P10 interacts with tubulin (417) and forms two different types of structures; microtubule-associated filaments, and tube-like structures that surround the nucleus (418). As noted above, p10 appears to be associated with the PE protein (Ac131) and in some viral genomes, genes are present that appear to be fusions of both PE and p10 protein domains (394, 395). Deletions of P10 result in polyhedra that resemble those produced by mutants lacking the calyx/polyhedron envelope protein (Ac131); they are fragile, have a rough surface showing cavities where virions have apparently been dislodged, and often show an incomplete calyx/polyhedron envelope (396, 419, 420). For more information, see Chapter 2.

*Ac138 (645aa:73.9kDa), (Bm115:645aa:74.0kDa), (Ha20:688aa:78.4kDa), p74-pif.

P74 was the first member to be identified of proteins called per os infectivity factors that are required for oral infection of insects, but are dispensable for infection of cultured cells. Homologs of *p74* along with the other *pif* genes, *pif*-1 (*ac119*), -2 (*ac22*), and -3 (*ac115*) are present in all baculovirus genomes and are also found in genomes of nudiviruses (195). P74 was the first such protein identified and characterized (87, 421-424). Three other *pif* genes were identified in BmNPV (425) and subsequently their homologs were characterized in AcMNPV. AcMNPV deleted for *pif-1, -2,* or *-3* are not orally infectious for *T. ni* or *S. exigua* larvae based on feeding of 10,000 PIB of the deleted virus. They are also not orally infectious for *H. virescens*, except for the *pif-2* mutant that shows limited infectivity. In contrast, injection of 1 pfu, of the three deletion mutants, into third instar larvae of the three insect species caused over 80% mortality. In addition, PIF1, PIF2, and p74 mediate specific binding of occlusion derived virus to midgut cells, suggesting that they are directly involved in virus cell interaction as an initial step in infection (88). Although PIF-3 appears to be an ODV associated protein (426), it does not appear to be involved in specific binding and its function is not known. Both P74 (421) and a homolog of PIF-1 from *Spodoptera littoralis* NPV (427) also appear to be components of the ODV envelope. Co-infection with a wt- and a *p74*-deleted virus expressing *gfp* resulted in per os infection by the *gfp* expressing virus, suggesting the p74 did not have to be directly associated with a virus to facilitate per os infection. In addition, a 35-kDa binding partner for AcMNPV P74 was detected in extracts of brush border membrane vesicles from host larvae (*Spodoptera exigua*), but not from a nonhost (*Helicoverpa armigera* larvae) (424). The identity of this host protein has not been determined. By proteomic analysis, P74 was found associated with AcMNPV, HearNPV and CuniNPV ODV (74, 213) (93); however, the other PIF proteins showed differing associations,e.g., CuniNPV (PIF-1,2,3), AcMNPV (PIF-2) and HearNPV (PIF-1). Ac145 and Ac150 also may be *pif* genes (see below). P74 appears to be cleaved into two fragments by a protease associated with occlusion bodies produced in insects. This cleavage does not occur in polyhedra produced in cell culture. The significance of the cleavage is not clear because cell culture and insect produced polyhedra appear to be equally infectious (428).

Ac 139 (449aa:52.6kDa), (Bm116:451aa:52.6kDa), (Ha16:284aa:33.6kDa),ME53.

Homologs of *ac139* are present in the genomes of all the lepidopteran NPVs and GVs, but have not been reported in hymenopteran or diperan baculovirus genomes. It is BV and ODV associated (429). One study indicated that AcMNPV deleted for this gene is not viable and fails to replicate its DNA and does not produce nucleocapsids. However, cells transfected with DNA from the mutant showed early stages of cpe, including nuclear enlargement and the formation of granular material in the nucleus (430). This suggests that the mutant is blocked in an early gene function. This is consistent with its original characterization as a major early gene (431). However, another study showed that deletion of Ac139 did not alter DNA replication, but results in a 1000-fold reduction in BV titer. In addition, it was found that it appears to be required both early and late in infection (429). ME53 fused to GFP localized mostly to the cytoplasm early and to nuclei late in infection. However, foci of ME53 were also noted at the cell periphery late in infection and co-localized with gp64 and VP39-capsid and was capsid associated in BV. It was suggested that it may provide a connection between the nucleocapsid and the viral envelope (432).

Ac140 (60aa:7.1kDa).

This orf encodes 60 aa and is only found in AcMNPV.

Ac141 (261aa:30.1kDa), (Bm117:261aa:30.1kDa), (Ha8:285aa:33.2kDa), exon0.

Homologs of Ac141 are found in all lepidopteran NPVs, and orfs with low homology are also found in GV genomes. In AcMNPV it is associated with both BV and ODV nucleocapsids (27, 433) and interacts with BV/ODV-C42 (Ac101) and FP25 (Ac61) (332). Ac141 contains a predicted RING finger domain (434) that is a type of zinc finger comprising 40-60 residues that binds two zinc atoms and may be involved in protein-protein interactions. Deletion of Ac141 severely compromises BV production and results in virus that appear to be restricted to cells initially infected, suggesting that Ac141 may be required for efficient egress of BV (433, 434). It appears to both co-localize with and co-purifiy with β-tubulin, and inhibitors of microtubules reduced BV production by over 85% (435). It has also been shown to interact with a conserved domain of kinesin 1, a motor protein involved in transporting cargo along microtubules to the periphery of the cell further supporting a role for microtubules in the transport of virions to the cell surface (280). Therefore, it has been suggested that the interaction of Ac141 with microtubules might be involved in the egress of BV.

*Ac142 (477aa:55.4kDa), (Bm118:476aa:55.5kDa), (Ha9:468aa:55.3kDa), p49.

Homologs of Ac142 have been identified in all sequenced baculovirus genomes. Ac142 is associated with both BV and ODV virions, and deletion of Ac142 appeared to affect nucleocapsid formation but, although lethal, did not appear to affect DNA synthesis (333). Another study describing a different bacmid construct that deleted less of the Ac142 gene showed similar results except that some nucleocapsids appeared to be fully formed, but were un-enveloped in the nucleus and were not occluded (436). It is unclear whether the difference in the two studies was due to the removal of a 3' processing signal for the upstream Ac141 gene in the former investigation, or to the presence of a significant portion of the Ac142 orf in the latter study. A BmNPV deleted for Bm118 failed to produce BV and produced polyhedra lacking virions. There appeared to be a defect in nucleocapsid formation as elongated capsid-like particles apparently devoid of DNA were observed (437). Mass spectrometry also suggests that Ac142 is ODV-associated in three different viruses (74, 93, 213).

*Ac143 (90aa:9.7kDa), (Bm119:101aa:10.4kDa), (Ha10:81aa:8.8kDa), ODV-E18.

Homologs of Ac143 are present in the genomes of all baculoviruses. An antibody generated against an Ac143-GST fusion reacted with a protein of 18 kDa in the ODV envelope fraction, and Ac143 was named ODV-E18 (438). Ac143 and its HearNPV homolog were found in surveys of ODV-associated proteins by mass spectrometry (74, 213). No BV is produced when Ac143 is deleted (439). Ac143 was found to be BV associated in a proteomic analysis (27).The predicted size of Ac143 is longer than previously reported (90 vs 62aa) (12).

*Ac144 (290aa:33.5kDa), (Bm120:290aa:33.5kDa), (Ha11:284aa:33.3kDa).

Homologs of Ac144 are present in all sequenced baculovirus genomes. Ac144 was named ODV-EC27; however, other data suggests that it is present in both BV and ODV and has a molecular weight of 33.5 kDa (see below). Mass spectrometry also suggests that Ac144 is ODV-associated in three different viruses (74, 93, 213). A variety of investigations have been conducted on Ac144. Initially, it was confirmed that its transcript initiates at a late promoter element (438). Later, it was suggested that it is a multifunctional cyclin and may be involved in regulating the cell cycle during virus infection (440). It was reported to interact in a yeast two-hybrid assay with Ac101 described above (also named C42) and with both Ac101 and p78/83 (Ac9) in native gel electrophoresis assays (329). Although this orf was designated as ODV-EC27, another investigation using an HA-tagged Ac144 recombinant virus and anti-HA monoclonal antibodies found that Ac144 was expressed as an ~ 33.5 kDa protein which conforms to the predicted MW (333). In addition, it was found to be BV associated (27, 333). It was also found that deletion of Ac144 appeared to affect nucleocapsid formation but, although lethal, did not appear to affect DNA synthesis (333).

Ac145 (97.0aa:8.9kDa), (Bm121:95aa:11.0kDa), (Ha12:92aa:10.8kDa), (pif?).

Ac145 and Ac150 encode small proteins (~9 and 11 kDa, respectively) that are related to one another (23% aa sequence identity) and are also related to a gene encoding an 11-kDa protein in an entomopox virus of *Heliothis armigera*. Close relatives of Ac145 are found in all baculovirus genomes including lepidopteran NPVs and GVs, and hymenopteran NPVs, but not the dipteran NPV. In contrast to Ac145, close relatives of Ac150 are only found in a few NPVs closely related to AcMNPV. However, it shows significant homology ($E = \sim 10^{-3}$) to predicted proteins from several dipteran insects. Ac145 and 150 are predicted to encode a domain thought to bind to chitin (441). In one study (442), deletion of Ac145 led to a sixfold drop in infectivity in *T. ni,* but not *H. virescens* larvae. An effect of deletion of Ac150 was not detected. Deletion of both genes causes a major (39-fold) reduction of infectivity for *H. virescens*. Injection of BV of the double mutant intrahemocoelically was as infectious as wt suggesting that these genes play a role in oral infection. These properties suggest that Ac145 and Ac150 are pif genes. Products of *ac145* and *ac150* were found to be associated with both BV and ODV. In another study (443), occluded virions deleted for Ac150 were found to be significantly less virulent when administered per os than the wt virus in *Heliothis virescens*, *S. exigua* and *T. ni* larvae. Evidence suggested that the mutant had a reduction in its ability to establish primary infections in midgut cells. The Ac145 homolog in HearSNPV was found to bind to chitin (444). For related genes see Ac138 (p74). The predicted size of Ac145 is longer (97 vs 77 aa) than previously reported (12).

Ac146 (201aa:22.9kDa), (Bm122:201aa:22.9kDa), (Ha13:203aa:22.9kDa).

Homologs of Ac146 are present in the genomes of all lepidopteran NPV and GV genomes, but are not present in those of hymenopteran or dipteran. When Bm122 was fused with gfp, nuclear localization was observed (445).

Ac146 is expressed at late times pi. Deletion resulted in a defective virus that did not produce BV. A HA-tagged Ac146 bacmid construct indicated that Ac146 was associated with both BV nucleocapsids, but not envelopes and ODV suggesting that it may be a structural protein. In BV it appeared as a polypeptide of 23kDa that conforms to its predicted mass, whereas in ODV, there were two sizes, one of 23kDa and the other of 34kDa. It is likely an essential gene, as infectious BV was not produced by an mutant deleted for Ac146 (446).

Ac147 (582aa:66.9kDa), (Bm123:584aa:66.9kDa), (Ha14:655aa:76.0kDa), immediate early gene-1 (IE-1).

Homologs of IE-1 have been identified in all Group I and II genomes sequenced. They also appear to be present in all GV genomes, but the homology is very low, e.g., XcGVorf9 vs. Ac147 show about 10% amino acid sequence identity. However, the orientation and position of XcGV orf9 relative to more conserved orfs is similar to Ac147, suggesting that the limited homology might be real. In addition, the limited identity is located in conserved regions that are identified by other more convincing alignments, e.g., Ac-Ie1 vs. Ld-Ie1 (23% identity). Part of the IE-1 population is called IE-0 and is translated from a larger spliced mRNA, which is the only major spliced transcript described for baculoviruses (see below Ac147-0). IE-1 was originally identified because of its ability to transactivate early promoters of AcMNPV (132). The ability of IE-1 to transactivate transcription is greatly enhanced when the activated gene is linked to *hr* sequences (447). It also may participate in the negative regulation of some genes (448). IE-1 is required for transient DNA replication (42, 43). Whereas deletions of either IE-1 or IE-0 can support infectious virus production, inactivation/deletion of both these genes is lethal (449). Similar results were reported for BmNPV (66).

Ac147-0 (636aa:72kDa) (ie-0).

Part of the IE-1 population is called IE-0 and is translated from a larger spliced mRNA, which is the only major spliced transcript described for baculoviruses and in AcMNPV results in an additional 54 amino acids at the N-terminus of IE-1 for a total of 636 amino acids (450). AcMNPV IE-1 is present as a homodimer but also can form a heterodimer with IE-0, and either IE-1 or IE-0 can support infectious virus production; however, there were subtle differences in timing of events and production of BV and polyhedra, depending on which gene is being expressed, suggesting that both *ie-0* and *ie-1* are required for wt levels of infection. As described above, *ie-0* can be eliminated, as long as IE-1 is being produced (449). In contrast, in LdMNPV only the spliced form is able to transactivate transient transcription and DNA replication (451).

*Ac148 (376aa:40.9kDa), (Bm124:375aa:41.3kDa), (Ha15:354aa:38.9kDa), odv-e56, PIF-5.

Homologs of odv-e56 are present in the genomes of all baculovirus and are also present in nudivirus genomes (195). ODV-E56 localizes to the envelopes of occluded virions (452) in AcMNPV and other baculoviruses (453) and has also been reported to be associated with AcMNPV BV (27). An insertion mutant, in which the lacZ gene was placed in frame at about amino acid 139 (out of 376) was viable (452). Ac148 and its homologs in HearNPV and CuniNPV were found to be ODV associated (74, 93, 213). Deletion of Ac148 from a bacmid construct resulted in a virus that could replicate in cell lines, but not insects. Consequently it was concluded that Ac148 is a per os infectivity factor, the 5th such protein identified in the AcMNPV genome (454, 455). Similar conclusions were drawn for a BmNPV deletion of Bm124 (456).

Ac149 (107aa:12.4kDa), (Bm125:106aa:12.3kDa).

Homologs of Ac149 are present in 4 other Group I viruses closely related to AcMNPV (Bm-, Mavi-, Plxy-, and RoNPV). It is likely to be nonessential as BmNPV with insertion/deletion mutations of this gene (Bm125) appeared normal (15).

Ac150 (99aa:11.2kDa), (Bm126:115aa:13.4kDa), pif?.

Ac150 is related to Ac145. In contrast to Ac145 homologs that are found in lepidopteran NPV and GV and hymenopteran NPV genomes, Ac150 is only found in a few group I NPVs closely related to AcMNPV. in AcMNPV, deletion results in less infectivity by occluded virions for larvae (443). In BmNPV, deletion resulted in no apparent difference in BV production of mean lethal dose by occlusion bodies although the lethal time was extended somewhat (457). For more information, see Ac145 and Ac138 (p74).

Ac151 (408aa:47kDa), (Bm127:422aa:48.8kDa), ie-2/ie-n.

Homologs of *ie-2* are limited to the genomes of all Group I lepidopteran NPVs. IE-2 contains a predicted RING finger domain and shows significant levels of similarity to a protein of *Trichomonas vaginalis* (E = 1e-06), an anaerobic, parasitic flagellated protozoan. IE-2 was found to augment activation by IE-1 (458-460). BmNPV IE-2 interacts with itself (461). IE-2 was required for optimal origin specific plasmid DNA replication in Sf-21 cells, but had little effect in Tn-368 cells (234). *Ie-2* deletion mutants behaved differently in Sf-21 cells in which the infection was delayed vs. Tn-5B1-4 cells, in which the infection was not delayed. In insect larvae, the mutant viruses were significantly less infectious than wt, which appeared to be due to a lack of virions in the occlusion bodies (462). IE-2 may also be involved in cell cycle regulation (463).

Ac152 (92aa:10.8kDa).

Homologs of Ac152 are present in the genomes of four Group I NPVs closely related to AcMNPV, and three Group II NPVs. It is associated with the nuclear localization of G-actin (335). Deletion resulted in reduced BV titers (38). Orthologs are not found in the BmNPV or HaSNPV genomes.

Ac153 (321aa:37.4kDa), (Bm128:309aa:36.1kDa), pe38.

Ac153 homologs have an unusual distribution being found in all Group I NPV and four GV genomes. Duplicate copies appear to be present in some of the genomes. Ac153 was originally identified because of its early transcription profile and the presence of predicted zinc finger and leucine zipper motifs (464). However,in OpMNPV it was shown to be expressed as full length (34 kda) and truncated (20 kda) forms with the larger variant functioning as a transcriptional transactivator of an early promoter (465). In addition, it appears to activate DNA replication in transient assays (42). Deletion of *pe38* results in a reduction in the expression of several genes, a delay in DNA replication, a 99% reduction in BV production, and reduced levels of DNA synthesis and was less orally infectious in larvae (466, 467).

Ac154 (81aa:9.4kDa), (Bm129:77aa:8.9kDa).

Homologs of Ac154 are present in 4 other Group I viruses closely related to AcMNPV (Bm-, Mavi-, Plxy-, and RoNPV). It is likely to be nonessential, as an insertion mutation of this gene in BmNPV (Bm129) had no apparent effect on infectivity (15).

Hrs (homologous regions).

In AcMNPV, *hrs* are comprised of repeated units of about 70-bp with an imperfect 30-bp palindrome near their center. They are repeated at eight locations in the genome with 2 to 8 repeats at each site. They are highly variable, and although they are closely related within a genome, they may show very limited homology between different viruses. For example, in the CpGV genome, tandem repeated sequences are not evident, although a 75-bp imperfect palindrome is present at 13 different locations on the genome (468). In addition, in the TnSNPV (Group II) and several other genomes, *hrs* were not found (469), reviewed in (470). *Hrs* have been implicated both as transcriptional enhancers and origins of DNA replication for several baculoviruses (447, 471-475). They bind the transcriptional activator IE-1 (Ac147) (476-478) and this binding may cause IE-1 to localize into foci

which may be a prelude to replication loci (479). *Hrs* contain a high concentration of cAMP and TPA response elements (CRE and TRE) that bind cellular transcription factors and stimulate RNA polymerase II dependent transcription and enhance activation by IE-1 (480). It has been shown that deletion of individual *hrs* or combinations of two *hrs* does not appear to affect virus replication in cultured cells (481).

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