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Nudivirus Genomics: Diversity and Classification*

Yong-jie Wang[1], John P. Burand[2] and Johannes A. Jehle[1**]

(1. *Laboratory for Biotechnological Crop Protection, Department of Phytopathology, Agricultural Service Center Palatinate (DLR Rheinpfalz), Breitenweg 71, 67435 Neustadt an der Weinstrasse, Germany;* 2. *Plant, Soil and Insect Sciences, University of Massachusetts, Amherst, USA)*

Abstract: Nudiviruses represent a diverse group of arthropod specific, rod-shaped and dsDNA viruses. Due to similarities in pathology and morphology to members of the family *Baculoviridae*, they have been previously classified as the so-called "non-occluded" baculoviruses. However, presently they are taxonomically orphaned and are not assigned to any virus family because of the lack of genetic relatedness to *Baculoviridae*,. Here, we report on recent progress in the genomic analysis of *Heliothis zea* nudivirus 1 (HzNV-1), *Oryctes rhinoceros* nudivirus (OrNV), *Gryllus bimaculatus* nudivirus (GbNV) and *Heliotis zea* nudivirus 2 (HzNV-2). Gene content comparison and phylogenetic analyses indicated that the viruses share 15 core genes with baculoviruses and form a monophyletic sister group to them. Consequences of the genetic relationship are discussed for the classification of nudiviruses.

Key words: Nudiviruses; Baculoviruses; Diversity; Genomics; Phylogeny; Classification

DISCOVERY AND DIVERSITY

Nudiviruses are a large and a diverse group of nuclear rod-shaped, enveloped, and circular dsDNA viruses of arthropods, particularly of insects. Given that they share similar structural and replication aspects with baculoviruses of insects, nudiviruses were previously classified as the so-called "non-occluded baculoviruses" (NOBs). Due to the lack of convincing genetic data, they were later removed from the family *Baculoviridae* (36). Nudiv-iruses have been also referred to as intranuclear bacilliform viruses (IBVs) (17). Notably, unlike baculoviruses, nudiviruses generally lack occlusion bodies (OBs). Thus far, a variety of nudiviruses and nudivirus-like viruses have been reported from various host species belonging to Lepidoptera, Trichoptera, Diptera, Siphonaptera, Hymenoptera, Neuroptera, Coleoptera, Homoptera, Thysanura, Orthoptera, Acarina, Araneina, and Crustacea (27). A brief summary of these viruses is given in Tables 1 and 2. However, most of these viruses were classified solely based on morphological and very limited biological data. Accordingly, it remains unclear whether they are evolutionarily monophyletic or polyphyletic groups, and whether they are genetically related to each other and to the baculoviruses.

GENOMIC COMPARISON

Among the various nudiviruses, *Heliothis zea* nudivirus 1 (HzNV-1), *Oryctes rhinoceros* nudivirus (OrNV), *Gryllus bimaculatus* nudivirus (GbNV) and

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** Corresponding author. Tel.: +49-632-167-1482, Fax: +49-632-167-1222, E-mail: Johannes.Jehle@dlr.rlp.de

Helicoverpa (=*Heliothis*) *zea* nudivirus 2 (HzNV-2) have been the well studied examples (Table 3) and have been reviewed previously with respect to viral origin, host range, pathology, virus structure and composition, persistence, and some biochemical and molecular biological properties (8, 27). Herein, we mainly focus on the recent genomic progresses on these viruses.

HzNV-1

HzNV-1, known as Hz-1 virus, was originally identified as a persistent viral infection in the IMC-Hz-1 cell line isolated from the adult ovarian tissues of the corn earworm *Heliothis zea* (20). It can also persistently infect several other lepidopterous cell lines, e.g. IPLB-1075 (*H. zea*), IPLB-SF-21 (*Spodoptera frugiperda*), IPLB-65Z (*Lymantria dispar*) and TN-368 (*Trichoplusia ni*) (20, 31, 45). In contrast, clear infections have not been observed when the virus was inoculated into larvae of *H. zea*, *H. armigera*, *Estigmene acrea*, *S. frugiperda*, and S. littoralis（20, 31）. HzNV-1 is a rod-shaped and enveloped virus containing a circular dsDNA genome (11,20,24). The complete genome sequence of HzNV-1 was determined recently. It is 228, 089 bp in length and poten-

Table 1. The putative nudiviruses of insects and other arthropods. Modified from (27)

Host		Host stage and/or tissue tropism	Size (nm)		Molecular Data	Refe-rences
			Virus particles	Nucleocapsids		
Insects	Chaoborus crystallinus (Diptera: Chaoboridae)	Larvae; midgut	260–300×75–600	210–226×38–43	–	(34)
	Chaoborus astictopus (Diptera: Chaoboridae)	Larvae; midgut	220×90	150×60		(18)
	Pulex simulans (Siphonaptera: Pulicidae)	Midgut	120×50	90×30	–	(4)
	Microplitis croceipes (Hymenoptera: Braconidae)	Larvae and adults; fat body, midgut and hemocytes				(23)
	Gyrinus natator (Cleoptera: Gyrinidae)	Adults; midgut	ca. 160×75	150×35	DNA	(19)
	Diabrotica undecimpunctata (Coleoptera: Chrysomelidae)	Adults; hemocytes	ca. 295×95	230×52	–	(32)
	Aphis sp. Pentalonia nigronervosa (Homoptera: Aphidae)	Fat body and muscle cells	200–300×50–60	180–200×40–50	–	(33)
	Bacillus rossius (Orthoptera: Phasmidae)	Midgut	250–300×100	210×50–60	DNA	(50)
	Acheta domesticus (Orthoptera: Gryllidae)	Hemocytes (?)	–	223×57	–	(21)
	Gryllus rubens (Orthoptera: Gryllidae)	Nymphs; fat body	154×91	127×55	circular dsDNA, 87 kb; 6 major and 11 minor polypeptides	(7)
Other arthropods	Panonychus ulmi (Acarina: Tetranychidae)	Fat body	200×90	150×38	–	(5)
	Panonychus citri (Acarina: Tetranychidae)	Midgut and hindgut	266×111	194×58		(47)
	Penaeus japonicus (Decapoda: Penaeidae)	Adults; gill, epidermal tissues, head soft tissues and hemoly mph	322–378×130–159	316–350×65–66	4 structural proteins, ca. 183 kb of genome	(38, 49)
	Crangon crangon (Decapoda: Crangonidae)	Hepatopancreas and midgut	280×72	215×40		(51)
	Carcinus maenas (Decapoda: Portunidae)	Hemocytes and connective tissues	300–320×90–100			(3)
	Callinectes sapidus (Decapoda: Portunidae)	Hemocytes and hepatopancreas		300×50		(29, 30)

Table 2. The putative nudivirus–like viruses of insects with filamentous or elongated nucleocapsids. Modified from (27)

Host	Host stage and/or tissue tropism	Size (nm)		Molecular Data	References
		Virus particles (shape)	Nucleocapsids		
Musca domestica (Diptera: Muscidae)	Adults; salivary gland	–	–	dsDNA, ca. 137 kb; 10 polypeptides	(14)
Glossina pallidipes (Diptera: Muscidae)	Adults; salivary gland	869×57 (Elongated); 1175×57 (Filamentous)	–	dsDNA, ca. 180 kb; 12 polypeptides	(6, 39)
Merodon equestris (Diptera: Syrphidae)	Pupae, adults; salivary gland	650–700×65 (Elongated) 700×60 (Elongated)	650×35	DNA	(1)
Apis mellifera (Hymenoptera: Apidae)	Adults; fat body	400–450×100–150 (Ellipsoidal)	ca. 3000×40–60	dsDNA, M_r, ~30×10^6, 12 polypeptides	(2, 13)
Tenebrio molitor (Coleoptera: Tenebrionidae)	Adults; midgut	ca. 450×200 (ovoidal)	500×25	Probably DNA	(16, 52)
Diabrotica undecimlineata (Coleoptera: hrysomelidae)	Adults; salivary gland	>1000×60 (filamentous)	2000×25	–	(32)

Table 3. The well studied nudiviruses

Virus	Host	Host stage and/or tissue tropism	Size (nm)		Genome		
			Virus particles	Nucleocapsids	Size (kb)#	AT%	ORFs
HzNV-1	*Heliothis zea* (?) (Lepidoptera: Noctuidae)	–	384–444×77–83	–	228/228,089	58	154
HzNV-2	*Heliothis zea* (Lepidoptera: Noctuidae)	Larvae and adults; reproductive tissues	415×80	500×25	225/231.621	58	113‡
OrNV	*Oryctes rhinoceros* (Coleoptera: Dynastidae)	Larvae and adults; midgut and fat body	200–235×100–120	160–180×50–65	130/36,951†	57	40
GbNV	*Gryllus bimaculatus* (Orthoptera: Gryllidae)	Nymphs and adults; fat body	145–240×80–100	162×66	95/96,944	72	98

Predicted/sequenced genomic DNA size. † Partial genomic sequences obtained. ‡ Burand, unpubl.

tially contains 154 methionine-initiated open reading frames (ORFs) of 50 or more amino acids and minimal overlap with adjacent ORFs (12). The AT content of HzNV-1 genome sequence is 58.2% (12). Twentyfour HzNV-1 ORFs are homologous to baculovirus genes, including 16 baculovirus core genes, e.g. *dnapol*, *helicase*, *lef-5*, *lef-4*, *lef-9*, *lef-8*, *vp91*, *p74*, *pif-1*, *pif-2*, *pif-3*, *odv-e56*, *vlf-1*, *19kda*, *ac81*, *38K*, and 7 non-conserved genes, e.g. *iap-3*, *dnaligase*, *helicase 2*, *rr1*, *rr2*, *dutpase*, *mt* (Table 4) (12, 54); 10 HzNV-1 ORFs are homologues of cellular proteins, histidine kinase, dihydrofolate reductase, dUTP pyrophosphatase, matrix metalloproteinase, deoxynucleoside kinase, glycine hydroxymethyl-transferase, ribonucleotide reductase small subunit, thymidylate synthase, alt1, and carboxylesterase(12). Unlike baculoviruses, homologous repeat regions (*hrs*) were not identified in the HzNV-1 genome. However, many tandem repeat sequences of 21 to 75 bp were distributed throughout the HzNV-1 genome(12). Gene content and phylogenetic analyses suggested that HzNV-1 is indeed genetically related, albeit distantly, to the Baculoviridae (12, 54).

OrNV

The Oryctes rhinoceros nudivirus (OrNV), known as OrV, was discovered in the 1960s in Malaysia and has been widely used to control rhinoceros beetle (*O. rhinoceros*) in coconut and oil palm in Southeast Asia and the Pacific until the present day (25, 28). It is a classical example of successful inoculation and long-term control of an insect pest.

It is an enveloped rod-shaped virion and replicates in the nucleus of infected midgut and fat body cells (25, 40, 41). OrNV contains a circular double-stranded

Table 4. Homologous genes present in baculoviruses, HzNV-1, HzNV-2, GbNV, and OrNV. The 16 baculovirus core gene homologues are in bold.

Baculovirus genes	HzNV-1	HzNV-2	GbNV	OrNV
38K	Hz1V010	Hz2V108	1	?
vp91	Hz1V046	Hz2V089	2	?
pif-3	Hz1V088	Hz2V053	3	?
odv-e56	Hz1V076	Hz2V062	5	?
dnapol	Hz1V131	Hz2V018	12	C17
ac81	Hz1V033	Hz2V096	14	C14
lef-9	Hz1V075	Hz2V063	24	?
p74	Hz1V011	Hz2V106	45	+
lef-8	Hz1V090	Hz2V051	49	?
pif-1	Hz1V055	Hz2V082	52	?
pif-2	Hz1V123	Hz2V026	66	C2
vlf-1	Hz1V121	Hz2V028	80	?
lef-5	Hz1V101	Hz2V040	85	D7
19kda	Hz1V103	Hz2V039	87	?
lef-4	Hz1V098	Hz2V043	96	D16
helicase	Hz1V104	Hz2V038	–	?
dnaligase	Hz1V036	Hz2V094	38	?
helicase 2	Hz1V060	Hz2V076	46	?
rr2	Hz1V073	Hz2V065	63	?
desmoplakin	–	–	77	?
rr1	Hz1V095	Hz2V047	82	D8
iap-3	Hz1V138	Hz2V012	98	?
	Hz1V135	Hz2V015		
dutpase	Hz1V069	Hz2V069	–	?
mt	Hz1V037	Hz2V093	–	?
odv-e66	–	–	–	C6
–	Hz1V013	Hz2V104	7	?
–	–	–	13	C15
–	Hz1V051	Hz2V085	17	C20
–	–	–	19	D11
–	–	–	22	D12
–	–	–	23	D13
–	Hz1V111	Hz2V034	34	?
–	Hz1V115	Hz2V032	44	?
–	Hz1V144	Hz2V008	57(*integrase*)	?
–	Hz1V143	Hz2V009	58	?
–	–	–	64	C4
–	Hz1V068	Hz2V070	65	C3
–	–	–	83	D5
–	–	–	84	D6
–	Hz1V104	Hz2V038	88	?
–	–	–	93	D19
–	–	–	94	D18
–	Hz1V124	Hz2V025	95	D17
–	–	–	97	D14
–	Hz1V109 (*ts*)	Hz2V035	–	C12

DNA genome of about 130 kilobase (kb) pairs (15). Genetic variation exists as evidenced by restriction fragment length polymorphism of OrNV field isolates (46). A segment of 4 kb was sequenced to design PCR primers for the detection of OrNV (48). It bears no significant similarity to the published databases.

Currently, *Pst*I fragments C (*Pst*I-C) and D (*Pst*I-D) of OrNV DNA were completely sequenced and are 19, 805 and 17, 146 bp in size, respectively (54). This is in good agreement with the originally predicted sizes of 20.1 (*Pst*I-C) and 17.7 kb (*Pst*I-D), as determined in agarose gels (15). So far, these are the largest genome sequence fragments known for OrNV and represent almost 30% of the 130 kb genomic DNA. The AT contents of the *Pst*I-C and-D are 58.6 and 58.0%, respectively. The AT content of the OrNV genome was estimated to be 57% (40), which is in close agreement with the sequence data. A total of 40 ORFs were detected in the two fragments (54). Predicted proteins from 15 ORFs showed significant identity (21 to 51%) to proteins from other dsDNA viruses and/or cellular organisms (54). Out of the 15 ORFs, ten had significant similarities to those of HzNV-1, including 3 homologues of HzNV-1 ORFs with unknown functions as well as 5 homologues of baculovirus core genes, *lef-4*, *lef-5*, *pif-2*, *dnapol*, and *ac81* (Table 4). In addition, a homologue of baculovirus core gene *p74* was detected in a 3.3 kb of *Hin*dIII fragment Q of OrNV genome DNA, which reveals higher sequence similarity to that of GbNV and HzNV-1 (Y. Wang, unpubl.). ORF D8 is homologous to baculovirus *rr1* (54). A baculovirus *odv-e66* homologue is also present in OrNV (54). Five ORFs encode proteins homologous to cellular thymidylate synthase (TS), patatin-like phospholipase, mitochondrial carrier protein, ser/thr protein phosphatase, and serine protease, respectively (54). OrNV TS is phylogenetically related to those of eukarya and nucleocytoplasmic large dsDNA viruses (54). A hemopexin domain was detected in OrNV ORF D1. ORF D11 contains an esterase catalytic domain, suggesting hydrolytic activity of the putative protein. A PIN domain (PilT N terminus) was identified in ORF C3. While its

function remains unknown, a role in signaling appears to be possible (37). ORF C5 contains a tubulin chaperone cofactor A signature.

A double repeat of 18 bp with a palindromic core sequence and a short direct repeat sequence (14 bp) were detected within the PstI-D fragment of OrNV DNA (54). No hrs and/or tandem repeat regions were found in fragment *Pst*I-C. No sequence homology between these OrNV repeats and those of baculoviruses and other dsDNA viruses was observed. The 37 kb of OrNV partial genomic sequence provides evidence that OrNV is related to HzNV-1.

GbNV

The cricket nudivirus GbNV infects nymphs and adults of several field crickets, Gryllus bimaculatus, G. campestris, Teleogryllus oceanicus and T. commodus (26). It is a rod-shaped and enveloped virus with circular dsDNA genome, and replicates in the nuclei of the infected fat body cells (26).

The complete genome DNA of GbNV was cloned and sequenced. It is 96, 944 bp in length and potentially contains 98 ORFs (53). The AT content of the GbNV genome is 72%, which is one of the highest compared with any sequenced dsDNA virus isolated from insects. 41 ORFs of GbNV share sequence similarities with ORFs in OrNV, HzNV-1, baculoviruses and bacteria. Most notably, 15 GbNV ORFs are homologous to the core baculovirus genes, which are associated with transcription (lef-8, lef-9, lef-4, vlf-1, and lef-5), replication (dnapol), structural proteins (p74, pif-1, pif-2, pif-3, vp91, and odv-e56), and unknown function proteins (38K, ac81, and 19kda), and have been predicted in HzNV-1 as well (Table 4). Six GbNV ORFs are homologous to non-conserved baculovirus genes, dnaligase, helicase 2, rr1, rr2, iap-3, and desmoplakin (Table 4). Except for desmoplakin, the other 5 gene homologues are also present in HzNV-1 (Table 4). Additionally, nine other GbNV ORFs are homologous to those of HzNV-1 (Table 4). In total, there are 29 genes shared between GbNV and HzNV-1, and 20 ORFs between GbNV and the partial genomic sequence of OrNV (Table 4). However, the remaining 57 ORFs revealed no homology or poor similarities to current gene databases. Instead of hrs, fourteen short direct repeat regions (drs) were detected in GbNV, which account for 0.6% of the GbNV genome and are distributed throughout the genome. GbNV drs were up to 96% AT rich and contained two or three copies of tandemly arranged repeat sequences, ranging from 11 to 42 bp in size.

The arrangement of orthologous genes in the GbNV genome was compared to those of OrNV, HzNV-1 and baculovirus genomes. No organizationally similar region was detected between GbNV and baculoviruses, OrNV and HzNV-1 genomes, respectively. Only two GbNV gene clusters have a collinear ORF arrangement in the HzNV-1 genome (Fig. 1), whereas five regions with collinearly arranged ORFs were found in the partial genome of OrNV (Fig. 1). More regions of collinear gene arrangement are expected to be identified when the entire OrNV genome is sequenced. The observed patterns of conserved gene arrangements also support the conclusion that GbNV and OrNV are more closely related to each other than either is to HzNV-1 as it was suggested by gene content analyses.

HzNV-2

Heliothis zea nudivirus 2, known as gonad-specific virus (GSV), Heliothis zea reproductive virus and Hz-2V, was first observed in the gonads of adult corn earworm Heliothis zea (42). It causes deformities of

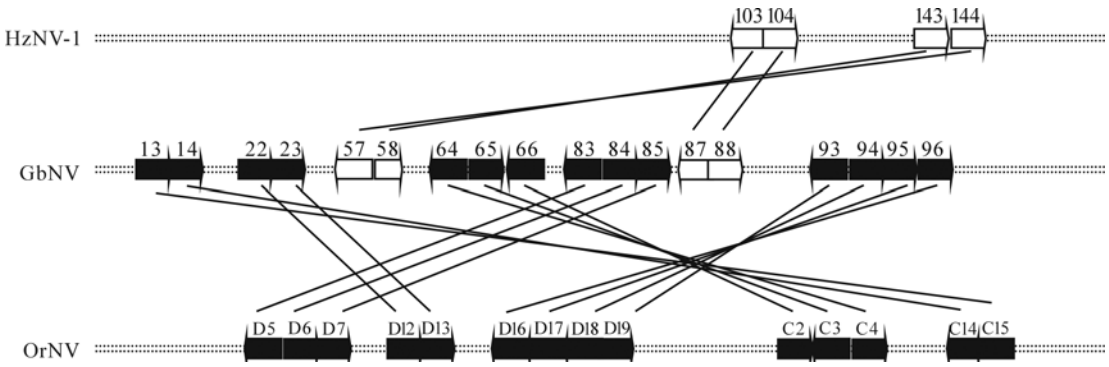

Fig. 1. A schematic diagram showing the spatial distribution of the gene clusters shared between HzNV-1 and GbNV, and between GbNV and OrNV. The sizes of genomes and ORFs as well as the location of the ORFs are not drawn in ratio. ORFs and transcriptional direction are indicated as arrows.

the reproductive organs of insect hosts, which in turn lead to sterility in both females and males (10, 22, 42, 43). The virus is able to infect other Noctuid species and to replicate in two lepidopteran insect cell lines (Tn-368 and Ld652Y) derived from ovarian tissues (9, 35, 44).

The HzNV-2 virion comprises an enveloped rod-shaped nucleocapsid containing a circular dsDNA genome (8, 43). The genome of HzNV-2 is 231, 621 bp in length (Burand, unpubished data), which is in close agreement with the predicted 225 kb (43) and is very similar to the size of 228 kb of HzNV-1. The AT content of HzNV-2 genomic DNA is 58.1% and is identical to that of HzNV-1. It was predicted that HzNV-2 has 113 ORFs. The global sequence similarity between HzNV-1 and HzNV-2 is 93.5%. Like HzNV-1, 16 ORFs of HzNV-2 are homologous to core baculovirus genes (Table 4). So far, only 3, 422 bp of two fragments of HzNV-2 genomic DNA has been deposited in GenBank (43). The 2, 295 bp fragment contains two partial ORFs, which are highly similar (>97% nt sequence identity) to HzNV-1 ORFs Hz1V058 and Hz1V059, respectively (Fig.2). The 1, 127 bp fragm- ent is actually identical to HzNV-1 sequence (identity, >99%). It contains a homologue of Hz1V134 as well as of Hz1V135 which is similar to a baculovirus iap-3 gene (Fig.2). The high identities of homologous genes as well as the conserved gene orders suggest that HzNV-2 is a very closely related virus of HzNV-1. This is also suggested by a phylogenetic analysis of the concatenated amino acid sequences of the five core baculovirus gene homologues (Fig. 3).

CLASSIFICATION AND NOMENCLATURE

Gene content (see above) and phylogenetic analyses (Fig. 3) suggest that the nudiviruses form a monophyletic group of non-occluded dsDNA viruses. They diverged from a common ancestor of the baculoviruses lineages before this radiated into dipteran, hymenopteran and lepidopteran specific clades. They

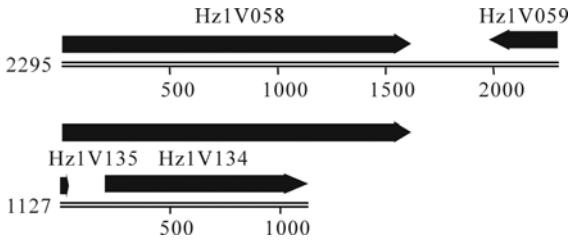

Fig.2. A linear map showing the predicted ORFs in the two sequenced genomic fragments of HzNV-2. ORFs and transcriptional direction are indicated as arrows.

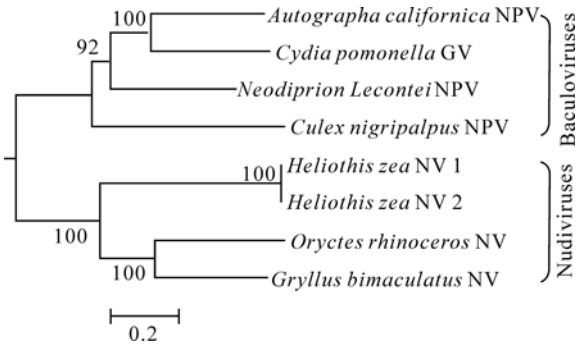

Fig. 3. The midpoint rooted neighbour-joining (NJ) phylogenetic tree based on 1789 sites of concatenated amino acid sequences of the *lef-4*, *lef-5*, *dnapol* and *ac81* genes from GbNV, OrNV, HzNV-1, HzNV-2 and 4 selected baculoviruses. Gaps and missing data are excluded for the analyses. The robustness of the tree was tested using bootstrap analyses (1000 replicates) and the percent values (NJ) are given next to the nodes. Minimal evolution (ME) and maximum parsimony (MP) analyses revealed the similar tree topology. The groups of baculoviruses and nudiviruses are indicated on the tree. The scale bar represents a distance of 20%.

represent a highly diverse and phylogenetically ancient sister group of the baculoviruses, and have evolved into a variety of highly divergent host orders.

Whether nudiviruses should taxonomically be reconsidered as a subfamily within the family of *Baculoviridae* or whether a new family together with baculoviruses may form in a distinct order, needs to be re-evaluated based on the genomic data presented here as well as on further biological characters. Presently, to classify nudiviruses, a new viral genus Nudivirus was proposed (54). Based on the currently available morphological and molecular data, we propose following demarcation criteria for classification of a candidate virus into the genus Nudivirus (Table 5): 1. Genome: large circular dsDNA; 2. Genome organization and replication: a set of conserved core genes shared among members; propagation in the nuclei of infected host cells; 3. Morphology: rod-shaped and enveloped virion; 4. Biologic properties: transmission

Table 5. The demarcation criteria of the baculoviruses and the nudiviruses

Demarcation criteria	Baculoviruses	Nudiviruses
Rod-shaped virion	+	+
Circular dsDNA genome	+	+
Replication in nucleus	+	+
Nucleus hypertrophy	+	+
Host range		
Holometabolous	+	+
Hemimetabolous	–	+
Host stage infected		
Larvae	+	+
Adults	–	+
Horizontal transmission		
parenteral	–	+
peroral	+	+
Vertical transmission	+/–	+/–
Occlusion body	+	–

via per oral and/or per parenteral route; infection of larvae and/or adults; diverse tissue and cell tropisms. Clearly, these demarcation criteria need to be updated in the future, when more biological properties, such as virion properties, infection and replication strategies, as well as host range and virus ecology, become available. However, given that facts that nudiviruses are currently of high diversity and that the lack of a defined classification system for these viruses, the proposed criteria are of particular value and should be considered as the guide lines to assign a virus to the Nudiviruses.

To name a Nudivirus species, we suggest following the nomenclature for other large eukaryotic dsDNA viruses-host name with the suffix name of nudi-virus-as we named these nudiviruses, e.g. HzNV-1, HzNV-2, OrNV, and GbNV.

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