

Fish herpesvirus diseases: a short review of current knowledge

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Abstract

Fish herpesviruses can cause significant economic losses in aquaculture, and some of these viruses are oncogenic. The virion morphology and genome organization of fish herpesviruses are generally similar to those of higher vertebrates, but the phylogenetic connections between herpesvirus families are tenuous. In accordance with new taxonomy, fish herpesviruses belong to the family Alloherpesviridae in the order Herpesvirales. Fish herpesviruses can induce diseases ranging from mild, inapparent infections to serious ones that cause mass mortality. The aim of this work was to summarize the present knowledge about fish herpesvirus diseases.

Alloherpesviridae, CyHV-3, CyHV-2, CyHV-1, IcHV-1, AngHV-1

Herpesviruses comprise a numerous group of large DNA viruses with common virion structure and biological properties (McGeoch et al. 2008; Mattenleiter et al. 2008). They are host-specific pathogens. Apart from three herpesviruses found recently in invertebrate species, all known herpesviruses infect vertebrates, from fish to mammals (Davison et al. 2005a; Savin et al. 2010). According to a new classification accepted by the International Committee on Taxonomy of Viruses (<http://ictvonline.org>), all herpesviruses have been incorporated into a new order named Herpesvirales, which has been split into three families. The revised family Herpesviridae contains mammalian, avian, and reptilian viruses; the newly-created family Alloherpesviridae contains herpesviruses of fish and amphibians, and the new family Malacoherpesviridae comprises single invertebrate herpesvirus (*Ostreid herpesvirus*). The current taxonomy of fish herpesviruses, including most known and unassigned virus species, is shown in Table 1.

The virion of herpesviruses comprises four morphologically distinct parts: a core consisting of linear dsDNA; an icosahedral capsid; a proteinaceous tegument; a host-derived lipid envelope with viral proteins embedded in it (Davison et al. 2005b).

Although the specific virion architecture is common among all herpesviruses, the genetic relationships between three families of Herpesvirales are very tenuous. The only sequence-based evidence for a common ancestor for all herpesviruses is the gene encoding the ATPase subunit of the terminase, a protein complex which is responsible for DNA packaging into the procapsid (Davison 2002; McGeoch et al. 2006).

The family of Alloherpesviridae is a highly diverse group with a genome size ranging from 134 kbp of channel catfish virus (the smallest sequenced genome) to 295 kbp of cyprinid herpesvirus-3, which is the largest known genome among the order Herpesvirales (McGeoch et al. 2006; Davison 2010). The phylogenetic studies of Waltzek et al. (2009) revealed two major clades within the family Alloherpesviridae: the first comprises viruses from cyprinid and anguillid hosts, and the second comprises ictalurid, salmonid, acipenserid, and ranid taxa.

Genus *Cyprinivirus*

Cyprinid herpesvirus 1, also known as a carp pox virus, causes benign papillomatous lesions in the epithelium of common carp, *Cyprinus carpio*, and its ornamental form koi (Plumb and Hanson 2011a). Fish pox virus was found in fish in most European countries,

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Table 1. The current taxonomy of fish herpesviruses including most known unassigned virus species (according to: Crockford et al. 2005, Davison 2010, Jakob et al. 2010, Shlapobersky et al. 2010, Marcos-Lopez et al. 2012).

Taxon name	Common name	Abbreviation	Host species
Order: Herpesvirales (wt)			
Family: Alloherpesviridae			
Genus: <i>Cyprinivirus</i>			
<i>Cyprinid herpesvirus-1</i>	Carp pox herpesvirus	CyHV-1	<i>Cyprinus carpio</i>
<i>Cyprinid herpesvirus-2</i>	Goldfish haematopoietic necrosis virus	CyHV-2	<i>Carassius auratus</i>
<i>Cyprinid herpesvirus-3</i>	Koi herpesvirus	CyHV-3	<i>Cyprinus carpio</i>
<i>Anguillid herpesvirus 1</i>	Eel herpesvirus	AngHV-1	<i>Anguilla anguilla</i> <i>Anguilla japonica</i>
Genus <i>Ictalurivirus</i>			
<i>Ictalurid herpesvirus 1</i>	Channel catfish virus	IcHV-1	<i>Ictalurus punctatus</i>
<i>Ictalurid herpesvirus 2</i>	Black bullhead herpesvirus	IcHV-2	<i>Ameiurus melas</i>
<i>Acipenserid herpesvirus 2</i>	White sturgeon herpesvirus 2	AciHV-2	<i>Acipenser transmontanus</i>
Genus: <i>Salmonivirus</i>			
<i>Salmonid herpesvirus 1</i>	-	SalHV-1	<i>Oncorhynchus mykiss</i>
<i>Salmonid herpesvirus 2</i>	Oncorhynchus masou herpesvirus	SalHV-2	<i>Oncorhynchus nerka</i> <i>Oncorhynchus masou</i>
<i>Salmonid herpesvirus 3</i>	Epizootic epitheliotropic disease virus	SalHV-3	<i>Salvelinus namaycush</i>
Unassigned fish herpesviruses			
<i>Acipenserid herpesvirus 1</i>	White sturgeon herpesvirus 1	AciHV-1	<i>Acipenser transmontanus</i>
<i>Percid herpesvirus 1</i>	Walleye epidermal hyperplasia herpesvirus	PeHV-1	<i>Sander vitreus</i>
<i>Esocid herpesvirus 1</i>	Northern pike herpesvirus	EsHV-1	<i>Esox lucius</i>
<i>Pleuronectid herpesvirus 1</i>	Turbot herpesvirus	PIHV-1	<i>Scophthalmus maximus</i>
<i>Osmerus eperlanus herpesvirus 1</i>	Comet herpesvirus of smelt	HVOE-1	<i>Osmerus eperlanus</i>
N.N.	Tilapia larvae encephalitis virus	TLEV	<i>Oreochromis aureus</i>
N.N.	Pilchard herpesvirus	PHV	<i>Sardinops sagax neopilchardus</i>
<i>Gadid herpesvirus 1</i>	Atlantic cod herpesvirus	GaHV-1	<i>Gadus morhua</i>

N.N. - non nominata

the United States, Israel, Russia, and in some Asian regions (China, Japan, Korea, Malaysia). Tumours found in fish are white to gray and can cover large areas of the body surface including the head and fins. Adult infected fish show no distinct behavioral or clinical signs; however, in juveniles, CyHV-1 infection results in clinical disease and high mortality. Infected juvenile carp may develop appetite loss, distended abdomens, exophthalmia, haemorrhages on the operculum and abdomen, and darkened skin pigmentation (Plumb and Hanson 2011a). The disease is seasonal and lesions usually develop when water temperature is lower than 15 °C, and it regresses when water temperature increases (Palmeiro and Scott Weber III 2010). Sano et al. (1993) demonstrated that CyHV-1 genome is present in nervous and subcutaneous tissues after disease regression, suggesting that the virus becomes latent, which might explain the recurrence of lesions.

Cyprinid herpesvirus 2 (CyHV-2) causes herpesvirus haematopoietic necrosis in goldfish (*Carassius auratus*). The affected fish present no characteristic external signs except for apathy and pale gills. Histopathological investigations showed discoloration and necrosis in the spleen and kidney, and hypertrophy and hyperplasia in the gill epithelium (Jung and Miyazaki 1995; Groff et al. 1998). Disease outbreaks depend on water temperature and occur between 15–25 °C with 50–100% mortality (Groff et al. 1998). Rapid detection of CyHV-2 is usually done with PCR techniques (Goodwin et al. 2006; Waltzek et al. 2009).

Cyprinid herpesvirus 3 (CyHV-3, also named koi herpesvirus), first reported in 1998 (Ariav et al. 1998), is responsible for severe epizootic disease and mass mortality among *Cyprinus carpio*, causing enormous economic losses in carp industries worldwide (Hedrick et al. 2000; Ilouze et al. 2006). The disease affects common carp and its varieties (koi carp, ghost carp) and has spread around the world except for Australia and South America (Manual of Diagnostic Tests for Aquatic Animals 2010). Outbreaks appear seasonally when the water temperature is 18–28 °C (Perelberg et al. 2003). Affected fish exhibit apathy, gill epithelium necrosis, pale patches on the skin, pale and irregularly colored gills, increased mucus production, and enophthalmia (Hedrick et al. 2000; Pokorova et al. 2005). The study by Perelberg et al. (2003) found fry to be more susceptible to infection than mature fish. Further experimental trials conducted in Japan indicated that carp larvae (3–4 days post hatch) are resistant to CyHV-3 infection, although the same fish died when exposed to virus two months later (Ito et al. 2007). The latest research using bioluminescence imaging showed that skin is the major portal of entry for CyHV-3 in carp (Costes et al. 2009). It has been demonstrated that the virus is transmitted horizontally through fish excrement (Dishon et al. 2005) and viral particle secretion into the water (Perelberg et al. 2003). Ilouze et al. (2011) suggested that the virus might be transferred by birds moving sick fish from pond to pond. There are no data indicating that CyHV-3 is transmitted vertically. Most herpesviruses have been demonstrated to persist in the host as a latent virus, and there is some evidence suggesting that CyHV-3 can remain latent in clinically healthy fish, and that the infection can be reactivated by temperature stress (Gilad et al. 2004; Eide et al. 2011). Nested PCR, real-time PCR, and semi-nested PCR seem to be the most useful and sensitive techniques for detecting CyHV-3 (Bergmann et al. 2010). Since koi herpesvirus seems to pose the greatest threat to world carp population, most investigations are currently focused on developing efficient prophylaxis and control methods for CyHV-3 disease.

Anguillid herpesvirus 1 (AngHV-1) frequently causes disease in cultured and wild eels (Sano et al. 1990; Haenen et al. 2002). Van Beurden et al. (2010) sequenced the complete genome of the virus and confirmed that AngHV-1 is a new virus species within the family Alloherpesviridae. Although the AngHV-1 infects eels rather than cyprinid species, phylogenetic studies have shown that AngHV-1 is most closely related to the cyprinid herpesviruses (van Beurden et al. 2010). Thus, in the newest ICTV (International Committee on Taxonomy of Viruses) classification, AngHV-1 is assigned to the genus *Cyprinovirus*. AngHV-1 was isolated from farmed European eel (*Anguilla anguilla*) and Japanese eel (*Anguilla japonica*) in Japan (Sano et al. 1990), from Japanese eel in Taiwan (Ueno et al. 1992), and from European eel in many European countries (Davidse et al. 1999; Haenen et al. 2002; van Ginneken et al. 2004; Jakob et al. 2009). The virus was also found in wild eel populations in the Netherlands (van Ginneken et al. 2004) and Germany (Jakob et al. 2009). While clinical signs can vary among and within outbreaks, apathy, haemorrhages in the skin, fins, and gills, congested gill epithelium, and pale liver are the most frequent symptoms. Mortality ranges from 1 to 10% (Sano et al. 1990; Haenen et al. 2002). Diagnosis is usually made by virus isolation in cell culture (Sano et al. 1990; Haenen et al. 2002) or AngHV-1-specific PCR (Rijsewijk et al. 2005). Although the mortality rates are not very high, the control of disease outbreaks can be difficult because the virus is present in wild eel populations and has the ability to remain latent in apparently healthy fish (van Nieuwstadt et al. 2001).

Genus *Ictalurivirus*

Ictalurid herpesvirus 1 (IcHV-1) causes an acute haemorrhagic disease in cultured juvenile channel catfish, *Ictalurus punctatus*. Epizootics usually involve high mortality occurring in

southern United States on commercial fish farms. Outbreaks of ICHV-1 disease have yet to be observed in wild populations suggesting that intensive fish farming may be a predictive factor. The disease occurs in the summer months, and mortality rates can reach 100% at 28 °C (Kucuktas and Brady 1999; Davison 2008). Clinical signs of ICHV-1 disease include erratic or spiral swimming, exophthalmia, swollen abdomen, pale or haemorrhagic gills, and haemorrhages at the fin bases and throughout the skin. Internal signs include yellowish fluid in the peritoneal cavity, dark, enlarged spleen, and extensive haemorrhages in the liver and kidneys (Smail and Munro 2001; Davison 2008; Plumb and Hanson 2011b). Transmission of the virus occurs by two routes: horizontally through the water and by direct contact; and also vertically (Kucuktas and Brady 1999). There is some evidence suggesting that survivors can be a reservoir for latent virus, which could cause disease reactivation and transmission (Davison 2008). Although ICHV-1 can cause significant losses on farms because of high mortality among young fish, its overall significance in the channel catfish industry is not very high (Plumb and Hanson 2011b).

Ictalurid herpesvirus 2 (ICHV-2), also named black bullhead herpesvirus and Ameiurine herpesvirus 1, is associated with disease causing mass mortality among black bullhead, *Ameiurus melas*, in Italy (Hedrick et al. 2003). The virus causes clinical signs similar to those of ICHV-1 in channel catfish, including spiral swimming and haemorrhages in the skin and internal organs, and at the bases of fins (Hedrick et al. 2003; Plumb and Hanson 2011b). Hedrick et al. showed that ICHV-2 is also pathogenic for channel catfish fry and fingerlings, which poses a potential danger to the channel catfish industry (Hedrick et al. 2003).

Acipenserid herpesvirus 2 (AciHV-2), commonly named white sturgeon herpesvirus 2 (WSHV-2), is associated with the disease of cultured and wild white sturgeon, *Acipenser transmontanus*, in North America and Italy. Affected fish display pale lesions on the body surface, lethargy, appetite loss, and erratic swimming. Mortality in adult fish is less than 10%. Experimental studies revealed that pallid sturgeon and shovelnose sturgeon are also susceptible to AciHV-2 infection. Phylogenetic research showed that AciHV-2 is more closely related to ICHV-1 than to AciHV-1, and, according to current taxonomy of fish herpesviruses, is assigned to the genus *Ictalurivirus* (Hua and Wang 2005; Plumb and Hanson 2011c).

Genus *Salmonivirus*

Salmonid herpesvirus 1 (SalHV-1) is a causative agent of mild disease in rainbow and steelhead trout and was reported in the USA. Disease outbreaks occur when the water temperature is 10 °C or less. It causes darkened pigmentation, apathy, pale gills, exophthalmia, and distended abdomen. In experimental trials, the virus was also pathogenic for chum salmon and chinook salmon, while brook trout, brown trout, Atlantic salmon, and coho salmon were not susceptible to SalHV-1 infection (Plumb and Hanson 2011d). Sequence analysis by Davison (1998) indicated that SalHV-1 is closely related to SalHV-2.

Salmonid herpesvirus 2 (SalHV-2), more commonly known as *Oncorhynchus masou* virus, causes significant economic losses of farmed and wild salmonid fish in Japan. The susceptible fish species include masu, coho, sockeye, chum salmon, and rainbow trout. Clinical signs of the disease depend on fish age. In juveniles, the virus causes acute infection with apathy, exophthalmia, and skin ulcers, and cumulative mortality can be as high as 100% (in 1-month-old sockeye salmon). Four months to one year post infection, 12–100% of surviving fish develop tumours, located mainly around the mouth and head. SalHV-2 is transmitted horizontally through the water and vertically via ovarian fluids (Plumb and Hanson 2011d). The disease is successfully controlled in hatcheries by disinfection with iodophore of all collected eggs after fertilization and again at the early-eyed stage (Yoshimizu and Nomura 2001).

Salmonid herpesvirus 3 (SalHV-3) was originally found in cultured juvenile lake trout, and it causes acute disease with mortality approaching 100%. Clinical signs are nonspecific and include lethargy interspersed with periods of hyperexcitability, spiral swimming, haemorrhages in the eyes and mouth and at the base of the fins. Histopathologically, affected fish exhibit hyperplasia, hypertrophy, and necrosis of epidermal cells. Transmission experiments showed that only lake trout and hybrids of lake and brown trout are susceptible to the disease (Bradley et al. 1989; McAllister and Herman 1989). The disease is known to appear only in the region of Great Lakes in North America when water temperatures are 6–15 °C (Plumb and Hanson 2011d). Salmonid herpesvirus 3 is transmitted horizontally by waterborne contact (McAllister and Herman 1989), and some data suggest that it can also be transmitted vertically (Kurobe et al. 2009). Survivors of SalHV-3 infection might become long-term virus carriers (McAllister 1991).

Unassigned fish herpesviruses

Acipenserid herpesvirus 1 (AciHV-1), also known as a white sturgeon herpesvirus 1, was initially isolated from cultured juvenile white sturgeon, *Acipenser transmontanus*, in California (USA) hatcheries. Experimental infection resulted in a 35% mortality rate with no specific external signs. Histopathologically, the virus causes epidermal lesions and diffused dermatitis. AciHV-1 appears to be less virulent under experimental conditions than is AciHV-2 (Plumb and Hanson 2011c).

In conclusion, the number of identified fish herpesviruses is increasing every year. Most fish herpesviruses cause mild infections in the natural environment, but under aquaculture conditions these viruses can cause severe, clinical diseases with high rates of mortality. Most of discovered alloherpesviruses are epitheliotropic, and some might be oncogenic.

These viruses are a highly diverse group, with two apparent major classes; the first includes viruses that have large genomes (anguillid and cyprinid species), while the second includes viruses that appear to possess smaller genomes like IchV1. Although the phylogenetic connections among all herpesviruses are tenuous, fish herpesviruses share at least several structural and biological properties with other herpesvirus families: similar virion structure, many fish herpesviruses can cause persistent, life-long infections (latency), and a high level of host specificity, although there is some evidence to suggest that interspecies transmission of fish herpesviruses does exist (Waltzek et al. 2009; Bandín and Dopazo 2011).

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