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## A review on DNA viral diseases of fish

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### Abstract

Aquatic animal species are cultured in high stocking density in various water bodies where they become more susceptible to new diseases. The number of viruses isolated from fish grew steadily over the last couple of decades. Both DNA and RNA viruses causing high mortality among commercially important cultivable fishes have been studied last two decades. Most of the viruses described are considered to be serious pathogens and hence are economically important in the aquaculture systems. Viral infections with dermatologic manifestations are common in many tropical countries of the world. Some of the DNA virus groups including herpesviruses, adenovirus, polyomavirus, poxvirus and iridoviruses cause disease resulting in important economic losses of aquaculture production. The present review was based on DNA genome containing virus diseases are one of the major challenges that are threatening a sustainable growth of fish farming and wild populations.

**Keywords:** aquaculture, fish, DNA viruses, infectious disease

### 1. Introduction

Fish viral diseases account for a large scale mortality in farmed fish and are very difficult to treat directly. Avoidance has been suggested as one of the best control measures of viral infections. Usually, viruses can be easily transmitted from one culture system to another through handling or improper management and hence require easy and early diagnostic methods to detect infections.

Viruses are unique, they are exceedingly small, often made up of a nucleic acid molecule within a protein shell and when they are entering a cell, they parasitize the cellular machinery to produce thousands of progeny. The objective of research in virology is to understand how viruses enter individual cells, replicate and assemble as a new infectious particle. There are a number of viral diseases that attack fishes attack cultured fishes. Seed production of ornamental fishes, similar to many other fishes has been extremely vulnerable by mass mortality due to viral infections. Viral diseases are sometimes hard to diagnose properly. Viral studies are usually carried out with cell cultures rather than with animals because cell culture provides a much simpler and more homogenous experimental system. Fish cell lines are important tools for studying viruses in fishes [1] and are also essential for isolating and identifying fish viruses. A cell line will also allow further study of viruses isolated in disease outbreaks. The aim of the present review was to analyse DNA DNA genomic viral diseases in fish aquaculture.

### 2. DNA viral diseases

Periodic outbreaks of viral diseases have resulted in catastrophic losses to fish farmers globally [2]. In general, RNA viruses by far cause severe diseases in fish aquaculture and hence become economically important universally. IHN, IPN and VHS are major viral diseases in salmon and trout [3]. Several DNA viruses have also been isolated from different fishes including channel catfish virus (CCV) [4], salmonid herpesvirus 2 (SHV-2) [5], koi herpesvirus (KHV) [6], carp edema virus (CEV) [7], infectious spleen and kidney necrosis virus (ISKNV) [8], largemouth bass (*Micropterus salmoides*) virus (LMBV) [9], Tilapia lake virus (TiLV) [10], dwarf gourami *Colisa lalia* iridovirus (DGIV) [11], rock bream *Oplegnathus fasciatus* iridovirus (RBIV) [12], grouper *Cromileptes altivelis* sleepy disease virus (GSDIV) [13] and Santee-Cooper ranavirus [14]. Systemic iridovirus-like infection have been reported from several exotic ornamental fish including *Etroplus maculatus* from Singapore into Canada [15]; in dwarf gourami *Colisa lalia* imported from South East Asia to Australia [16]; and in guppy *Poecilia reticulata* and doctor

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fish *Labroides dimidetus* in USA, both from South East Asian imports [17].

## 2.1. Herpesviruses

*Herpesviridae* is the name of a family of enveloped, double-stranded DNA viruses with relatively large complex genomes. Surrounding the core is an icosahedral capsid with a 100 nm diameter constructed of 162 capsomeres. Herpesviruses are host specific pathogens and caused systemic diseases in channel catfish (*Ictalurus punctatus*) and goldfish (*Carassius auratus*). A herpesvirus has been isolated for the first time from a population of European eels (*Anguilla anguilla*) cultured in a recirculated culture system in Taiwan [18]. Several herpes-like viruses have been detected from different fishes but only a few are sufficiently characterized. Herpesvirus infection has been reported in three adult angelfish (*Pterophyllum altum*) [19] in Denmark. The diseased fish displayed many of the nonspecific signs of a systemic infection such as loss of equilibrium, spiral swimming movements and skin haemorrhages.

### 2.1.1. Channel catfish virus (CCV)

Channel catfish virus disease (CCVD) has been listed as a notifiable or significant disease by OIE. CCV is a herpesvirus responsible for serious infection in fry and fingerlings of channel catfish (*Ictalurus punctatus*) [20]. CCV has been reported in most areas of the United States where channel catfish are grown. It has also been isolated from fry shipped from the United States to Honduras, Central America [20]. Channel catfish herpesvirus (CHV) is causing serious economic losses of channel catfish (*Ictalurus punctatus*). The infection is most common during summer months. Channel catfish virus (CCV) has a size of about 100 nm and replicates in the nucleus and grows well in channel cat fish ovary (CCO) cells. Channel catfish viral infection induces behavioral symptoms like spiral swimming and vertical hanging. Plumb [21] reported that experimental infection of channel catfish fingerlings with CCV leads to a haemorrhagic, oedematous and anaemic disease and mortality. CCV infection could be diagnosed by IFAT, neutralization tests ELISA or PCR.

Other herpesviruses reported from finfish include salmonid herpesvirus 1-*Herpesvirus salmonis* reported from salmon [22]; *Onchorhynchus masou* virus reported from *Onchorhynchus masou* [23]; Cyprinids herpesvirus reported from carps [24]; Yamame tumor virus [25] and herpesvirus isolated from moribund Japanese eel and European eel using eel kidney cell line (EK-1) [26, 25].

### 2.1.2. Salmonid herpesvirus 2 (SHV-2)

*Oncorhynchus masou* virus disease (OMVD) is an economically significant disease of farmed salmonid fish (salmon and rainbow trout) in Japan. The virus was isolated from the ovarian fluid and tumor tissues of masou salmon, (*Oncorhynchus masou*) [27]. SHV-2 experimentally infected salmon fry exhibited necrosis and hyperplasia of haematopoietic tissues [28]. The SHV-2 related herpesviruses, the yamame tumour virus (YTV) reported in the mandibular tumour of masou salmon (*O. masou*) and nerka tumour virus (NeVTA) reported in kokanee salmon (*O. kisutch*) are the two other herpesviruses of salmonid fishes described in Japan [28]. All Japanese salmonid herpesviruses were clearly distinguishable from the North American herpesvirus strains [29].

### 2.1.3. Koi herpesvirus (KHV)

The cyprinid herpesvirus-3 (CyHV-3) has been described as a

causative agent of koi herpesvirus disease [30]. In 1990, KHV has been described as a highly virulent disease to common carp (*Cyprinus carpio*) in Israel. KHV has been reported in US and many other Asian and European countries [31, 32, 33] and also in Indonesia, Japan, Israel, Singapore, Philippines, Hong Kong, Thailand and Korea [34, 35]. Cyprinid herpesvirus-3 has been differentiated from Cyprinid herpesvirus-1 (CyHV-1) which causes carp pox, and Cyprinid herpes virus-2 (CyHV-2) by clinical signs, host range, antigen properties, growth characteristics, CPE in cell culture and DNA sequence [36]. KHV disease attacks common carp and koi carp of all ages. CyHV-3 has been reported in gold fish (*Carrassius auratus auratus*) and crasian carp (*Carrassius carrassius*) [37-39]. Clinical signs of KHV infection in fish include erratic swimming, disorientation, gasping at the surface and high mortality. Generally, KHV infected fish exhibit severe gill necrosis, pale gill and skin and haemorrhages on the skin. KHV disease progression depends on different environmental conditions, which is very fast in summer and slows in the winter season [40].

## 2.2. Adenovirus

The adenoviruses coming under the family *Adenoviridae* are characterized by non-enveloped icosahedral particles measuring 70-90 nm in diameter have an inner core surrounded by a capsid with fibres [41]. Virions contain one single linear molecule of double stranded DNA and about 40 proteins. Adenoviruses replicate in the nucleus. In fish, the adenovirus causes hyperplasia in the epidermis and in some cases it causes tumors. Adenovirus can cause mortality rates up to 50% in white sturgeon (*Acipenser transmontanus*). Adenovirus infection can be identified by ultrastructural or molecular methods in fish and this virus has been isolated from at least 40 vertebrate species [42, 43].

## 2.3. Polyomavirus

Viruses of the family *Polyomaviridae* (previously termed *Papovaviridae*) comprise the genus *Papillomavirus*. The family *Polyomaviridae* has been characterized by the lack of an envelope and icosahedral symmetry with the capsid composed of 72 capsomeres [44]. Virions, measuring 40 nm in diameter, contain one molecule of circular double standard DNA and 5-10 proteins. Polyoma-like viruses of lower vertebrates are not included in the present taxonomy of viruses [45]. Polyoma-like viruses were discovered in some fishes like hybrids of swordtail fish (*Xiphophorus* sp.) associated with melanomas and winter flounder (*Pseudopleuronectes americanus*) with epidermal hyperplasia.

## 2.4. Poxvirus

### 2.4.1. Carp edema virus (CEV)

Koi sleepy disease (KSD), also known as carp edema virus (CEV), was first reported from juvenile colour carp in Japan in the 1970s [46]. Carp edema virus is a large, double-stranded DNA virus thought to belong to the poxvirus family of viruses (family *Poxviridae*) [47]. The disease has spread to various countries including England, France, the Netherlands, Germany, Italy, the Czech Republic, Austria, Poland, and India. Outbreaks of CEV have been reported in common carp in England. KSD/CEV is an emerging infectious disease characterized by a typical sleepy behaviour, enophthalmia, generalized oedematous condition and gill necrosis, leading to hypoxia. High mortality, of up to 80-100%, has found in

juvenile koi collected from infected ponds [46]. The histopathological examination of the affected fish revealed necrotic changes in gills and virus particles were demonstrated in the cytoplasm of gill epithelial cells in transmission electron microscopy. Swaminathan *et al.* [48] have reported that no cytopathic effect is found in six fish cell lines following inoculation of filtered tissue homogenate prepared from gills of affected fish. Temperature is an important factor affecting carp morbidity and mortality in CEV infection [49].

## 2.5. Iridoviruses

Iridoviruses are large-genome DNA viruses infecting only invertebrates and poikilothermic vertebrate hosts including fish, amphibians, reptiles, crustaceans, molluscs and insects [50, 51, 52]. The family *Iridoviridae* is subdivided into five genera, *Iridovirus* and *Chloriridovirus* genera, which infect insects, the *Lymphocystivirus* and *Megalocytivirus* genera, which infect fish species and the *Ranavirus* that infect amphibians, fish and reptiles [51].

### 2.5.1. Iridovirus

Significant economic losses in cultured fish worldwide have been attributed to outbreaks of iridovirus infections in aquaculture in recent years. *Iridovirus* is double stranded DNA virus, enveloped or non-enveloped and icosahedral. Iridovirus are large icosahedral viruses 120-300 nm in diameter. The exact size measurement highly dependent on the method of measurement and on the isolate; fish isolates tend to be large, 200-300 nm, than the amphibian or the other invertebrate viruses (120-200 nm) [50]. The seventh report of the ICTV have described, the nucleic acid of virion core contains a single linear dsDNA molecule of 140–303 kbp, a value that includes both unique and terminally redundant sequences. Iridoviruses are structurally complex, and up to 36 polypeptides, ranging from about 5 to 250 kDa, have been detected by two-dimensional PAGE of virus particles. Non-enveloped particles contain 5–17% lipid, predominantly as the phospholipid [45].

Iridovirus genes can be classified into four categories: genes directly involved in virus replication, genes involved in immune evasion, genes homologous to those seen in other iridoviruses but not homologous to other genes in the database and genes with no known homology [53]. Earlier workers have reported that the genera *Ranavirus*, *Iridovirus* and lymphocystis virus (which is a large virus in this family) include structurally related viruses, all of them are composed of similar protein units which contribute to the icosahedral outline structure [54].

Iridovirus has been reported as the most important pathogens infecting grouper in the last decade [55]. Iridovirus infections of fish have been reported in wild and cultured fish species in Asia, Australia, Europe, North America, China, Japan, Korea, and Taiwan. Iridovirus has been reported to infect some commercially important aquatic animals, such as rainbow trout, sheatfish, grouper, and catfish [56, 57]. There are several iridoviruses described in economically important marine species that include seabass, *Lateolabrax* sp. [58], various species of grouper, *Epinephelus* spp. [59, 60], red drum, (*Sciaenops ocellata*) [56], large yellow croaker, (*Larimichthys crocea*) [61], striped beakperch, (*Oplegnathus fasciatus*) [62] and turbot, (*Scophthalmus maximus*) [63]. Several iridovirus infections have been reported in Taiwan. The first one was reported in grouper, with diagnostic evidence provided by

electron microscopy observations [64]. Large yellow croaker iridovirus (LYCIV) was first isolated from large yellow croaker, *Pseudosciaena crocea*, an economically important fish species in China in 2001 [65].

Iridovirus infections can cause wide-range of clinical signs depending on the species infected [66, 17]. Systemic iridovirus-like infections have been reported from several exotic ornamental fish: in the cichlid *Eutroplus maculatus* imported from Singapore into Canada [15]; in dwarf gourami *Colisa lalia* imported from Southeast Asia to Australia [16]. An iridovirus has been described in freshwater angelfish (*Pterophyllum scalare*) showing signs of systemic disease [11]. A systemic viral infection in both gourami *Trichogaster* spp. and swordtail *Xiphophorus hellerii* and an outbreak of lymphocystis in scalare *Pterophyllum scalarae* and gourami are reported to have occurred in fish reared in ornamental fish farms in Israel [67].

### 2.5.2. Ranavirus

There are six viral species described within the genus *Ranavirus* (Ambystoma tigrinum virus; Bohle iridovirus; Epizootic hematopoietic necrosis virus; European catfish virus; Frog virus 3; Santee-Cooper ranavirus with Frog virus 3 being the type species. Ranaviruses have been reported in healthy or diseased frogs, salamanders and reptiles in America, Europe and Australia [51, 68, 69]. Ranaviruses are characterized by large (150–180 nm), icosahedral virions, a double-stranded DNA genome of 150–170 kb with replication in both nucleus and cytoplasm with cytoplasmic assembly [70].

#### 2.5.2.1. Epizootic hematopoietic necrosis virus (EHNV)

EHNV is a member of the genus *Ranavirus* in the family *Iridoviridae*. Iridoviruses infecting fish with severe necrosis of the haematopoietic tissue causing epizootics have been recognized as epizootic haematopoietic necrosis virus (EHNV) in perch (*Perca fluviatilis*) and rainbow trout (*Oncorhynchus mykiss*) in Australia [71, 45], European sheatfish virus (ESV) in sheatfish (*Silurus glanis*) in Germany [72] and European catfish virus (ECV) in European catfish (*Ictalurus melas*) in France [66]. Whittington and Reddacliff [71] reported that the virus could be experimentally transmitted to fry and young fishes inducing high mortalities within few days. EHNV has been characterized as a large icosahedral virus, approximately of 175 nm size with a double-stranded DNA genome of 127 kb [73]. The infected fish show clinical signs like distended abdomen, darkened skin, petechial, haemorrhages at base of fin and in gill [74]. EHNV can cause multifocal necrosis of spleen and renal hematopoietic tissue and liver. In addition, hyperplasia and multifocal necrosis of gill epithelial cell, necrosis of atrial trabeculae and gastrointestinal epithelial cells focal pancreatic necrosis, necrosis of circulating haematopoietic cells and degeneration of vascular epithelial cells in many organs [69].

#### 2.5.2.2. Santee-Cooper ranavirus (SCRV)

SCRV has been reported to be very similar to iridoviruses, including largemouth bass iridovirus (LMBV), doctor fish virus (DFV-16) and guppy virus (GV-6) [14]. During 1997-1998, LMBV were detected in the wild largemouth bass in south-eastern USA. Juvenile largemouth bass (*Micropterus salmoides*) and striped bass (*Morone saxatilis*) are prone to LMBV. LMBV caused mortality in the wild largemouth bass (*Micropterus salmoides*) and it was isolated from the swimbladder and liver of infected fish [75]. LMBV has been

shown to transmit horizontally (Plumb *et al.*, 1996). Doctor fish (*Labroides dimidatus*) virus (DFV-6) and guppy fish (*Poecilia reticulata*) virus (GV-6) were isolated from fish imported from South East Asia which had low pathogenicity to rainbow trout and chinook salmon [177].

### 2.5.2.3. Largemouth Bass Virus (LMBV)

LMBV has been detected in the Santee-Cooper Reservoir (South Carolina, USA) in 1996. It has been found in largemouth bass in most southeastern and many Midwestern states. LMBV has been shown to be present in the South-eastern United States, as far north as Michigan, and as far west as Texas [76, 77]. LMBV was responsible for the mortality of adult largemouth bass (*Micropterus salmoides*), sub clinically infected fish have been detected in some lakes [78, 79]. In 1995, largemouth bass virus (LMBV) was identified as the putative etiological agent by electron microscopy, polymerase chain reaction, and indirect antibody fluorescent assay [80]. Goldberg *et al.* [42] reported that experimentally infected largemouth bass juveniles LMBV exhibit differences in pathogenicity and virulence. Those viruses which show sequence similarity with LMBV within the MCP gene are described as SCR strains [14].

### 2.5.2.4. Koi ranavirus (KIRV)

Santee-Cooper Ranavirus-like agent has been detected and isolated from infected koi (*Cyprinus carpio koi*) in India [81]. The virus was isolated, propagated and infectivity assays have been reported in SNKD2a cell lines developed from snakehead kidney. KIRV was associated with mass mortalities of koi experienced in South Indian fish farms. Infected fish suffered continuous mortality exhibiting swimming abnormalities, intermittent surfacing and skin darkening. KIRV showed characteristics such as icosahedral symmetry, 100 to 120 nm size, produced virions by budding from the cell membrane. Sequence analysis of the major capsid protein gene showed an identity of 99.9% to that of largemouth bass virus (LMBV) isolated from North America [81].

### 2.5.2.5. Singapore grouper iridovirus (SGIV)

Singapore grouper iridovirus (SGIV) was first isolated from the diseased brown-spotted grouper, *Epinephelus tauvina*. SGIV was characterized as a novel member of the genus *Ranavirus*, family *Iridoviridae* [58, 82]. The size of the intracellular nucleocapsid is 154 nm between the opposite sides or 176 nm between the opposite vertices with an inner electron-dense core of 93 nm. The size of the virus particle is 200 nm in diameter. SDS-PAGE of the purified virus has 20 structural protein bands and a major capsid protein (MCP) of 49 kDa. SGIV is able to cause serious systemic disease capable of killing 96% of grouper fry [58].

### 2.5.3. Megalocytivirus

Megalocytiviruses have been isolated and reported in more than twenty species of marine fish [83]. Different megalocytiviruses described are red seabream iridovirus (RSIV), rock bream iridovirus (RBIV) and infectious spleen and kidney necrosis virus (ISKNV) (type species), which infect most of the marine fish in Southeast Asia, including economically important species in aquaculture [84].

#### 2.5.3.1 Infectious spleen and kidney necrosis

ISKNV cause high mortality both freshwater and marine fish.

The disease has been reported in a large number of marine fish species including the order Perciformes, Pleuronectiformes, Clupeiformes, Tertrodontiformes, Myctophyiformes, and Mugiliformes in China [39]. In China, a molecular epidemiology study indicated that over 50 species of cultured and wild seawater fish were infected by infectious spleen and kidney necrosis virus-like (ISKNV-like) viruses [85]. Xu *et al.* [86] reported hypertrophied cells in spleen, kidney, liver, gill, esophagus, gut and muscle of zebrafish infected with ISKNV.

#### 2.5.3.2. Red sea bream iridovirus (RSIV)

Red sea bream iridovirus (RSIV) was first isolated in 1990 in Japan, which causes mortality in cultured juvenile red sea bream (*Pagrus major*) [87, 88]. In Japan, red sea bream iridoviral disease (RSIVD) has been documented in 31 cultured seawater fishes [89]. RSIV has been reported to infect 25 fish species of the orders *Perciformes*, *Pleuronectiformes* and *Tetradontiformes* [90]. Infected fish by RSIV exhibit severe anaemia, petechia of the gills and enlargement of the spleen [90]. RSIV has been reported in brown-spotted grouper (*Epinephelus tauvina*) in Thailand [91]. The mortality rates may be ranging between 0% and 100% depending on host fish species, fish size, fish age, water temperature, and other culture conditions. The principal mode of transmission of RSIV is horizontal mainly through the water. Vertical transmission of RSIV has not yet been investigated. RSIV was isolated from the kidney and spleen of infected fish using fish cell cultures [87] and the agent was identified by IFAT or PCR amplification and sequencing [92, 93].

#### 2.5.3.3. White sturgeon iridovirus group (WSIV)

White sturgeon iridovirus (WSIV) was first reported among hatchery-raised white sturgeon (*Acipenser transmontanus*) in North America and also among Russian sturgeon (*A. guldenstadi*) in northern Europe [94, 95]. Other sturgeon species have also been experimentally infected by WSIV [96]. WSIV have been detected in white sturgeon originating from wild-caught adults in California, Oregon, Washington, and Idaho [94] and pallid sturgeon (*Scaphirhynchus albus*) and shovelnose sturgeon (*S. platyrhynchus*) that suffered from high levels of mortality in North and South Dakota [97]. WSIV mainly infects juvenile sturgeon younger than one year old [98]. WSIV is an epitheliotropic virus, which can infect the skin, gills and the upper alimentary tract inducing mortality [94]. Sturgeon cell lines have been used for WSIV isolation and propagation. Siberian sturgeon (*Acipenser baeri*) and lake sturgeon (*Acipenser fulvescens*) were also found susceptible to the virus [96, 95].

### 2.5.4. Lymphocystis virus

Lymphocystis disease virus (LCDV) is an iridovirus that affects a wide variety of fish species, including more than 25 marine fish species [99]. Lymphocystis virus has been genetically classified into two different species; LCDV-1, which occurs in flounder (*Platichthys flesus*) and plaice (*Pleuronectes platessa*), whereas LCDV-2 is usually found in dab (*Limanda limanda*) lesions [100, 101, 102]. Lymphocystis viruses cause severe disease, mortality and economic loss in farmed fish and ornamental fish in wild as well as hatcheries. Kitamura *et al.* [103] reported that the first iridovirus disease that described in fish as lymphocystis disease virus (LCDV) which infects fresh water and marine species.

Lymphocystis disease virus is the type virus of the genus

*Lymphocystis* <sup>[104, 105]</sup>. LDV is double stranded DNA virus showing icosahedral symmetry with approximately 200-300 nm in diameter, which replicates only in the cytoplasm. The infected fish shows a number of nodular lesions on the skin surface of the fish. It is also present in internal organs of freshwater, brackish water and marine fish species. This virus can be easily transmitted from one fish to another fish through skin aberration. Lymphocystis disease virus was first reported in an aquarium-held freshwater ornamental fish (*Macropodus* sp.) in 1927. Paperna *et al.* <sup>[106]</sup> reported LDV infection in a gourami (*Trichogaster pectoralis*) imported to Israel.

### 3. Conclusion

Several factors such as increasing global population, increasing demand for seafood and limitations on production from capture fisheries are inevitably leading the continued global expansion of aquaculture. However, aquaculture with high stocking density is associated with risks of disease emergence and spread. These infectious diseases are very difficult to control by treating with antibiotics or therapeutic agents. Particularly viral diseases are major constraints to the aquaculture sectors. Prophylactic health management against infectious diseases is one of the essential requirements that are encouraged and practiced in aquaculture. Prevention and controlling of viral disease outbreaks is depending on various factors such as host susceptibility, environment, properties of disease causing organism, mode of disease transmission, pathogenicity of virus etc. RNA viruses cause severe diseases in aquaculture while some DNA viruses also induce diseases such as koi herpes virus disease, channel catfish herpesvirus disease and epizootic haematopoietic necrosis resulting in economic losses in farmed fish. However, vaccination principles have proved as the effective method to reduce the prevalence and their impact on cultured fishes. Moreover, considerable efforts of further research in terms of the development of effective vaccines and immunostimulants are needed for successful fish aquaculture production. In addition, good biosecurity measures are more essential to avoid the risk of introduction of disease causing organism particularly virus pathogen which would help to achieve prosperous aquaculture production.

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