A proposed disease classification system for duck viral hepatitis

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ABSTRACT The nomenclature of duck viral hepatitis (DVH) was historically not a problem. However, 14 hepatotropic viruses among 10 different genera are associated with the same disease name, DVH. Therefore, the disease name increasingly lacks clarity and may no longer fit the scientific description of the disease. Because one disease should not be attributed to 10 genera of viruses, this almost certainly causes misunderstanding regarding the disease-virus relationship. Herein, we revisited the problem and proposed an update to DVH disease classification. This classification is based on the nomenclature of human viral hepatitis and the key principle of Koch’s postulates (“one microbe and one disease”). In total, 10 types of disease names have been proposed. These names were literately matched with hepatitis-related viruses. We envision that this intuitive nomenclature system will facilitate scientific communication and consistent interpretation in this field, especially in the Asian veterinary community, where these diseases are most commonly reported.

Key words: duck viral hepatitis, nomenclature

2022 Poultry Science 101:102042
https://doi.org/10.1016/j.psj.2022.102042

THE COMPLEXITY AND IRRATIONALITY OF THE DISEASE NAME OF DUCK VIRUS HEPATITIS

Since 1950, both classical and new duck hepatotropic viruses have been identified that cause a disease that was historically named duck hepatitis (DH) or duck viral hepatitis (DVH) (Stoute et al., 2020). Recently, we noticed 14 prototypes of viruses implicated in this disease, including 6 prototypes in the Picornaviridae family, 3 prototypes in the Astroviridae family, 2 prototypes in the Flaviviridae family, and 1 prototype each in the Hepadnaviridae family, the Kolmoviridae family, and the Hepeviridae family. In total, they belong to 10 genera among 6 viral families. It is generally not recommended to define a disease caused by more than one genus of viruses. In this regard, this irrationality of the disease classification system challenges the key principle of Koch’s postulates and Pasteur’s conception. The disease-pathogen relationship is not followed by the principle of “one microbe and one disease” (Falkow, 1988). For example, although the viral names of duck hepatitis A virus (DHAV) and duck hepatitis B virus (DHBV) are different, they are both linked to the same disease name, DVH. There is no distinctive disease name specified by a defined hepatitis-related virus. This remains the main issue of the current disease naming compilation. To facilitate scientific communication and consistent interpretation, we revisited the historical definition of DVH and the corresponding causative viruses and proposed an intuitive classification system.

THE DISCOVERY AND HISTORICAL DEFINITION OF DUCK VIRAL HEPATITIS

In 1950, infectious viral hepatitis in ducklings was first described but not well defined by Levine and Fabricant.
in Long Island, USA (Macpherson and Avery et al., 1957). In 1954, Asplin and McLauchlan also reported the same disease and first coined the term “duck virus hepatitis”, as the gross lesions were limited to the liver (Asplin and McLauchlan, 1954). Two years later (1956), the disease was transmitted to British Columbia, Canada (Macpherson and Avery et al., 1957). In 1971, this disease was further spread into Germany and Europe (Ulbrich, 1971), later into China (Wen et al., 2018), into Korea in 1985 (Kim et al., 2007), and recently into Egypt (Yehia et al., 2021). The disease was severe and caused sequential catastrophes in the duck industry. Then, researchers tried to isolate the causative virus by culturing it in duck embryos, chicken embryos, or corresponding primary cells (Pollard and Starr, 1960). After successful isolation of the duck hepatitis virus and subsequent observation by electron microscopy (Richter et al., 1964), the virus was designated duck hepatitis virus (DHV). This virus is identical to historically classical type I DHV and is now renamed duck hepatitis A virus (DHAV) (Kaeberle et al., 1961). However, certain early studies before 2019 also used duck hepatitis virus type 1 (or I) to describe DHAV or used those 2 names interchangeably (Kim et al., 2007; Liu and Kong, 2019). The nomenclature DHAV was almost consistently used in later literature (Ou et al., 2017; Sui et al., 2022). DHAV was formerly classified as a member of the genus Enterovirus in the Picornaviridae family (Kim et al., 2006) and has historically been suggested to be a new genus that is genetically related to the genus Parechovirus (Ding and Zhang, 2007). It has now been classified into a new genus Avihepatovirus of the Picornaviridae family based on genetic evidence and International Committee on Taxonomy of Viruses (ICTV) classification (Zell et al., 2017). In addition, DHAV has been further divided into 3 different genotypes that are genetically and geographically different: the classically and globally distributed DHAV-1 and DHAV-2 in Taiwan and DHAV-3 in South Korea and China (Wen et al., 2014). This definition of DHAV genotypes was previously and is currently well recognized (Tseng et al., 2007; Liu et al., 2021). However, from 2012 to 2014, some literature used genotypes of DHAV-A, DHAV-B and, in particular, DHAV-C instead of genotypes DHAV-1, DHAV-2, and DHAV-3 (Zhang et al., 2012; Li et al., 2014). According to sequence appending information from the NCBI virus database, DHAV-1 and DHAV-3 were the main prevalent genotypes distributed...
in Vietnam, Hungary, South Korea, and China, particularly Eastern China (Figures 1A–1F). The infected host species vary and are mainly limited to the Anatidae family (Figures 1C and 1F). With the isolated virus, a chicken embryo attenuated vaccine was developed by Aspin and provided 100% protection in ducklings (Aspin, 1965). However, a virus that was serologically and antigenically unrelated to “DHV” emerged in 1969, as vaccination of the chicken embryo attenuated vaccine did not provide complete immune protection (Toth, 1969). The emerging virus was subsequently proven to be duck astrovirus. In line with this observation, R E Gough 1985 reported an outbreak of type II DVHs, despite early descriptions by Mansi et al. in 1964 and Aspin in 1965 (Gough et al., 1985). During that time, Haider and Calnek (1979) also showed evidence of the occurrence of type III DVH, as the causative virus was antigenically unrelated to either type I or type II DHV. As reported, this virus has recently reemerged in China in 2021 (Wei et al., 2021). Type III DHV was previously suggested to be a member of the Picornaviridae family (Haider and Calnek, 1979). Of note, the causative virus of type II and III DVH is different from that of classical type I DVH. The genomic sequences of type II and III DHVs were different from those of type I DHVs with high evolutionary distance. Therefore, the original type II and III DVHs have been renamed duck astrovirus type-1 (DAstV-1) and duck astrovirus type-2 (DAstV-2), respectively, and they have both been classified into the Avastroviridae family (Fu et al., 2009). In 1980, DHBV was first discovered in Peking ducks, and its genome is DNA covered by a capsid and lipid envelope. However, early literature used the term “DHV” to describe DHBV, which caused misunderstanding regarding the causative virus itself because “DHV” remains an RNA virus and is not enveloped (Robinson, 1980). In addition, DHBV belongs to the genus Avihepadnavirus of the Hepadnaviridae family, while DHAV belongs to the genus Avihepadnavirus of the Picornaviridae family (Zell et al., 2017). The misunderstanding was resolved 2 yr later, and since then, the term DHBV has been recognized and continually used in the hepatitis research community (Mason et al., 1983). Moreover, other names of DHBV-related viruses isolated from other host species in the Anatidae family have been also suggested, such as snow goose hepatitis B virus (literately named SGHBV) (Chang et al., 1999). The geographical distribution and host spectrum of DHBV are similar to those of DHAV (Figures 1H–1J). Since then, 2 genera (Avihepadnavirus and Avastrovirus) of RNA viruses (i.e., DHBV and DAstV) and one genus (Avihepadnavirus) of DNA viruses (i.e., DHBV) have been well recognized and linked to the same disease, DVH, which has made the virus-disease relationship in this regard unclear to some extent.

There are some neglected hepatitis-related viruses in ducks that cause only a minimal disease burden. These viruses were only tentatively named, as they generally did not cause a fatal outcome. The names of these viruses and their associated disease have not been clearly defined. Thus, the disease caused by these neglected viruses was described as being identical to “DVH”. The disease name may inevitably be misused and may cause confusion to some extent in certain studies. For example, A Ponzetto in 1987 reported hepatitis delta virus (HDV) in Peking ducks that were coinfected with DHBV (Ponzetto et al., 1987). Coinfection between HDV and HBV commonly exists in humans, as HDV is a defective RNA virus that requires HBV to complete its life cycle (Miao et al., 2020). The nomenclature of duck-derived HDV, as well as the corresponding disease name, was not well recognized or defined (Wille et al., 2018). In 1990, Chun-Hsien Tseng reported an outbreak of a DHAV-­resembling virus that had a relatively large genome size (8,351 nt vs. 7,761 nt). This virus was originally suggested to be named “Avian sapelovirus” and was recently classified into the genus Anativirus of the Picornaviridae family (Tseng et al., 2007). Lili Chu in 2019 identified the first hepacivirus-like flavivirus in ducks and tentatively named it duck hepavivirus-like virus (DuHV) (Chu et al., 2019). Xiaoyan Wang in 2014 reported a virus closely related to DHAV but with low protein identity and, thus, suggested the tentative name ‘Aalivirus’, with ‘Aalivirus A’ as the type species (Wang et al., 2014). Qinfeng Liao in 2014 reported megivirus-related viruses in ducks. Based on protein identities and genomic organization, duck-derived megiviruses, thus named duck megiviruses, and a new genus, Megivirus, were suggested and were recently accepted by ICTV (Liao et al., 2014). Baoyuan Liu in 2018 reported infection of ducks by hepatitis E virus (HEV) by antibody evidence and RNA detection (Liu et al., 2018). In addition, human hepatitis G virus (also known as human pegivirus) is the causative agent of hepatitis G. It is possible that ducks can be infected by this type of pegivirus (tentatively DHGV), because we have recently identified this virus in geese, and geese and ducks belong to the same family Anatidae (Wu et al., 2020). Collectively, there are 14 prototypes of hepatitis-related viruses distributed in 10 genera of 6 families that are implicated in this disease, DVH (see Table 1).

### A Newly Proposed Classification System for Duck Viral Hepatitis and Its Causative Virus(es)

Human viral hepatitis diseases have been well defined by members of viruses in a defined genus, such as the disease-virus relationship between hepatitis A virus (HAV) and hepatitis A, as well as hepatitis B virus (HBV) and hepatitis B (Liao et al., 1991; Huang et al., 2016; Li et al., 2019; Miao et al., 2019). In total, 7 types of human viral hepatitis have now been indexed from hepatitis A to hepatitis G, named according to the alphabet of the hepatitis viruses (Table 1). Based on Koch’s postulates and the conception of the human viral hepatitis classification system, we attempt to address
the naming complexity of DVH via a newly proposed classification system.

In our newly proposed system, 10 types of DVH-related disease names that are caused by (possibly) 10 virus genera have been proposed. The redundancy of the causative viruses is attributed to multiple genotypes, such as genotypes of the genus Avihepatovirus and the genus Avastrovirus (Table 2). For example, we proposed that duck hepatitis A (DHA) was attributed to 3 genotypes of DHAV. Based on evolutionary analysis, 4 of 10 genera are closely related to members of the Picornaviridae family, while the remaining 6 genera in 5 different viral families have high evolutionary distance and less sequence coverage, except the genera Avihepacivirus and Pegivirus in the Flaviviridae family (Figure 2). To make a literal association between the disease names and all corresponding causative viruses (although some fit the standard), an intuitive disease-virus mapping system has been proposed, including DHAV and duck hepatitis A (DHA), DHBV and duck hepatitis B (DHB) (Jilbert and Kotlarski, 2000), duck hepatitis C virus (DHCV) and duck hepatitis C (DHC) (Simmonds et al., 2005; Chu et al., 2019), duck hepatitis D virus (DHDV) and duck hepatitis D (DHD) (Miao et al., 2019), duck hepatitis E virus (DHEV) and duck hepatitis E (DHE) (Huang et al., 2016), duck hepatitis G virus (DHGV) and duck hepatitis G (DHG) (Wu et al., 2020), Aalivirus and duck hepatitis Aa (DHAa) (Wang et al., 2014), Avian anativirus 1 (AAV-1) and duck hepatitis Aa (DHAa) (Tseng et al., 2007), DAsV and duck hepatitis As (DAs) (Fu et al., 2009; Chen et al., 2012; Liu et al., 2014), and duck megrivirus (DuMV) and duck hepatitis M (DHM) (Liao et al., 2014). Given that many Asian researchers focus on these diseases, the disease name in Chinese has accordingly been proposed by the order of the sexagenary cycle (ganzhi, “干支”), which is a traditional Chinese calendar used for reckoning time. This supplementary Chinese nomenclature system also obeys the same naming conception that is accepted by the Chinese hepatitis research community (Table 1).

Table 1. Classification of human viral hepatitis and proposed nomenclature for duck viral hepatitis.

| Virus | Disease | Chinese disease name | Virus | Disease | Chinese disease name |
|-------|---------|----------------------|-------|---------|----------------------|
| HAV   | Hepatitis A | 甲型肝炎 | DHAV | Duck Hepatitis A | 鸭甲型肝炎 |
| HBV   | Hepatitis B | 乙型肝炎 | DHBV | Duck Hepatitis B | 鸭乙型肝炎 |
| HCV   | Hepatitis C | 丙型肝炎 | DHCV | Duck Hepatitis C | 鸭丙型肝炎 |
| HDV   | Hepatitis D | 丁型肝炎 | DHDV | Duck Hepatitis D | 鸭丁型肝炎 |
| HEV   | Hepatitis E | 戊型肝炎 | DHEV | Duck Hepatitis E | 鸭戊型肝炎 |
| HGV   | Hepatitis G | 己型肝炎 | DHGV | Duck Hepatitis G | 鸭己型肝炎 |
| HDV   | | | DhAa | Duck Hepatitis Aa | 鸭辛型肝炎 |
| HDV   | | | AA1-1 | Duck Hepatitis A1 | 鸭壬型肝炎 |
| HDV   | | | DAsV | Duck hepatitis A | 鸭甲型肝炎 |
| HDV   | | | DAsV | Duck hepatitis A | 鸭乙型肝炎 |
| HDV   | | | DAsV | Duck hepatitis A | 鸭丙型肝炎 |
| HDV   | | | DAsV | Duck hepatitis A | 鸭丁型肝炎 |

Table 2. List of hepatitis-related viruses and proposed disease names.

| Family | Genus | Species | Prototype | Tax ID. | Seq No. | Original disease name | Proposed disease name | 中文病名 |
|--------|-------|---------|-----------|---------|---------|----------------------|----------------------|----------|
| Picornaviridae | Avihepatovirus | Avihepatovirus A | DHAV-gt1 | 1000601 | 226 | DH or DVH | DHA? | 鸭甲型肝炎 |
| | | | DHAV-gt2 | 1000602 | 2 | DH or DVH | DHA? | 鸭甲型肝炎 |
| | | | DHAV-gt3 | 1000603 | 227 | DH or DVH | DHA? | 鸭甲型肝炎 |
| | Aalivirus | Aalivirus | AAV-1 (Past avian sapelovirus) | 216995 | 3 | DH or DVH | DHAa? | 鸭辛型肝炎 |
| | Anativirus (Past Avian sapelovirus) | Anativirus A | AAV-1 (Past avian sapelovirus 1) | 2759419 | 1 | DH or DVH | DHAa? | 鸭辛型肝炎 |
| Hepadnaviridae | Megivirus | Megivirus A | DuMV | 1330609 | 19 | DH or DVH | DMM? | 鸭甲型肝炎 |
| | | | DHBV | 12639 | 109 | DH or DVH | DHB? | 鸭乙型肝炎 |
| | | | duck hepaticvirus (DHCV) | 2509636 | 4 | Unclassified | DHC? | 鸭丙型肝炎 |
| Astroviridae | Pegasus | Unclassified | DHGV? | 2830620 | 2 | Unclassified | DHG? | 鸭戊型肝炎 |
| | | | DHDV? | 2364132 | 1 | Unclassified | DHD? | 鸭丁型肝炎 |
| | | | DAsV-1 | 2907992 | 2 | Unclassified | DAs? | 鸭戊型肝炎 |
| | | | DAsV-2 | 1239441 | 24 | DH or DVH | DAs? | 鸭戊型肝炎 |
| | | | DAsV-3? | 2830620 | 24 | DH or DVH | DAs? | 鸭戊型肝炎 |

Tax ID.: NCBI virus database.
Abbreviations: Aalivirus, Avihepatovirus/Avistivirus-like virus; AAV-1, Avian anativirus 1; DHAV-gt1, duck hepatitis A virus genotype 1; DHV-1, duck hepatitis virus type 1; DHA, duck hepatitis A; DH, duck hepatitis; DVH, duck viral hepatitis; DHAa, duck hepatitis Aa; DHC, duck hepatitis C; DHE, duck hepatitis C virus; DHC, duck hepatitis C; DHDV, duck hepatitis D virus; DHD, duck hepatitis D; DHEV, duck hepatitis E virus; DHE, duck hepatitis E; 中文病名, Chinese disease name; ?, Proposed name.
For emerging DVH-related viruses, we suggested assigning the name of the causative virus by the format of “duck hepatitis X virus, shortly DHXV”, in which the X represents the first or the first 2 letter(s) of the causative viruses. When X overlaps or lacks identity, we suggest taking 2 letters to assign a distinct name for the disease and the causative virus, such as duck hepatitis A (DHA) and duck Aalivirus (DHAa) (Table 2). The corresponding disease name should be in the format of “duck hepatitis X, shortly DHX”. However, in humans, the hepatitis F virus is a hypothetical virus and has not yet been substantiated (Deka et al., 1994). This deduction is attributed to the exclusion of any of the known hepatitis viruses. Thus, we suspended the disease name (i.e., duck hepatitis F, 鸭己型肝炎) in ducks that may be caused by possible “duck hepatitis F virus”. The possibility of this disease awaits further verification by epidemiological and experimental evidence. In conclusion, we have proposed an intuitive disease classification system for explicitly indicating the disease and the causative virus, as well as the Chinese disease name. We hope this nomenclature system will facilitate scientific communication and consistent interpretation in this field, particularly in the Asian veterinary community.

ACKNOWLEDGMENTS

The Program Sichuan Veterinary Medicine and Drug Innovation Group of China Agricultural Research System (SCCXTD-2021-18), the earmarked fund for China Agriculture Research System (CARS-42-17), Science and Technology Program of Sichuan Province (2020YJ0396), and the National Natural Science Foundation of China (32102706) supported this work.

Availability of data and materials: The data that support the findings of this study are available in this manuscript.

DISCLOSURES

The authors declare no conflicts of interest that pertain to this study.
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