Infection, Genetics and Evolution 75 (2019) 103928

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Research paper

Genetic characterization of fowl adenovirus serotype 4 isolates in Southern China reveals potential cross-species transmission

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ARTICLE INFO

Keywords:
Hepatitis-hydropericardium syndrome
Fowl adenovirus 4
Hexon
Mandarin duck
Cross-species transmission

ABSTRACT

Increasing numbers of hepatitis-hydropericardium syndrome (HHS) outbreaks associated with *Fowl adenovirus 4* (FAdV-4) have been confirmed in several provinces of China since 2015, mainly affecting 3–5-week-old broiler chicks, resulting in significant losses to the poultry industry. However, little is currently known regarding the molecular epidemiology and host specificity of FAdV-4 associated with HHS in Southern China. In the present study, we isolated 37 FAdV-4 strains from 52 suspected cases of HHS (33 from broilers, one from a layer, two from ducks, and one from a mandarin duck) from Guangdong province during 2016 to 2017. All 37 FAdV-4 strains obtained showed 100% identity of hexon genes at the nucleotide level, and also showed 100% nucleotide sequence identities with strains obtained from other provinces such as Shandong, Zhejiang, and Anhui, which grouped into a FAdV-C cluster. To our knowledge, this represents the first report of an FAdV-4 strain (GZ1) from a mandarin duck with HHS. Experimental infection of the GZ1 strain via intramuscular injection led to a 100% mortality rate in 21-day-old specific pathogen-free chickens. These data indicate the possibility of the cross-species transmission of FAdV-4, highlighting the need for implementing strict biosecurity measures to avoid the mixing of different bird species.

1. Introduction

Fowl adenoviruses (FAdVs), members of the family *Adenoviridae*, are non-enveloped double-stranded DNA viruses (Shah et al., 2017). FAdVs are classified into five species (A–E) based on genomic differences, and are further divided into 12 serotypes (1–8a and 8b to 11) on the basis of cross-neutralization assays (Hess, 2000). The genome of FAdV is 25–46 kb long, encoding three major structural proteins—hexon, penton, and the fiber protein—as well as numerous non-structural proteins (Griffin and Nagy, 2011). Since the main neutralizing epitopes were confirmed in hexon protein, the hexon gene has been widely selected for taxonomic and antigenic property analyses of FAdVs (Marek et al., 2010; Pichla-Gollon et al., 2007).

FAdV infection can trigger inclusion body hepatitis (IBH), hepatitis-hydropericardium syndrome (HHS), and gizzard erosion (GE) in chickens (Schachner et al., 2018). Most studies have shown that FAdV-4 is the causative agent of HHS, resulting in an acute infectious disease of chickens characterized by high morbidity and mortality rates (Li et al., 2016b; Liu et al., 2016). Since the first outbreak of HHS was reported in Pakistan in 1987, HHS has been documented in many countries such as Japan (Abe et al., 1998), Korea (Park et al., 2017), China (Ye et al., 2016), India (Kumar et al., 1997), Germany, Canada (Ojkic et al., 2008), Poland (Niczyporuk, 2016), Hungary (Kajan et al., 2013), and Peru (Marek et al., 2010; Toro et al., 1999).

Before 2015, outbreaks of IBH and HHS were sporadically reported in China. However, the number of clinical cases of HHS in chicken flocks suddenly increased after 2015 in most provinces of China, including Shandong, Henan, Hebei, Anhui, Heilongjiang, Sichuan, and Jiangsu (Fig. 1a), characterized by a clear or colored liquid in the pericardial sac, with a swollen and friable liver showing small multifocal areas of necrosis (Guan et al., 2018; Li et al., 2018). Epidemiological data indicate that the majority of FAdV-4 infections occurs during the hot and humid season. Guangdong province, located in southern China, hosts the largest poultry industry in China, along with a

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https://doi.org/10.1016/j.meegid.2019.103928
Received 3 April 2019; Received in revised form 10 June 2019
Available online 18 June 2019

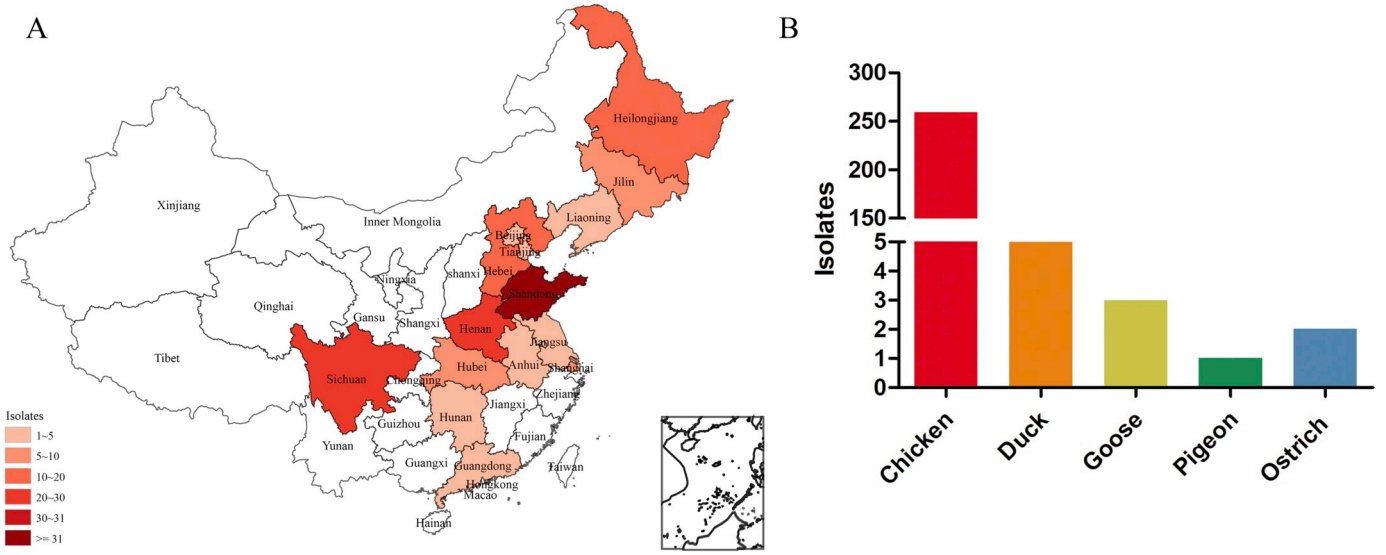

Fig. 1. Epidemiology of FAdVs associated with hepatitis-hydropericardium syndrome (HHS) in China. (a) Distribution of FAdVs associated with HHS in China. (b) Isolation rate of FAdV-4 strains from different birds. All data are from the NCBI (http://www.ncbi.nlm.nih.gov/GenBank/) up until October 20, 2018.

large number of live poultry markets as well as numerous small backyard poultry farms with poor biosecurity. Moreover, the hot and humid climate of Guangdong province is beneficial for the outbreak of FAdV-4. However, little information is available regarding the molecular epidemiology of FAdVs associated with HHS in birds in southern China.

Most of FAdV-4 isolated from chickens (Fig. 1b), and HHS is associated with high mortality in 3–5-week-old broilers, causing great economic losses to the poultry industry. Previous studies have demonstrated that FAdV-4 can infect birds via both vertical and horizontal transmission (Chandra et al., 2000; Toro et al., 2001). In addition, FAdV-4 infection in ducks [2], geese [3] and ostriches (Li et al., 2016a) has been associated with HHS, suggesting the possibility of cross-species transmission. In the present study, we investigated the presence of FAdV-4 in different bird species of southern China during 2016–2017, and selected one representative isolate for evaluation of its pathogenicity in an experimental infection of specific pathogen-free (SPF) chickens.

2. Materials and methods

2.1. Ethics statement

The study design was reviewed and approved by the South China Agricultural University Experimental Animal Welfare Ethics Committee (Guangzhou, China). All animal experiments were performed strictly in accordance with these approved guidelines.

2.2. Sample collection and virus isolation

A total of 52 liver samples from various bird species, including chickens, ducks, and Mandarin duck, showing clinical signs and symptoms of HHS were collected from Guangdong province, Southern China, from 2016 to 2017. The samples were homogenized and freeze-thawed three times, and centrifuged at 8000 × *g* for 15 min at 4 °C. The supernatant was filtered using 0.22-μm membrane filters, and then inoculated onto confluent primary-cultured chicken liver hepatocellular (LMH) cells (provided by the University of Pennsylvania), as described previously (Ruan et al., 2018). After 3 days of culture, the culture supernatants were collected as the virus stocks.

2.3. DNA extraction and polymerase chain reaction (PCR)

Viral DNA was extracted from the supernatants using HiPure Viral DNA/RNA Kits (Qiagen, Hilden, Germany) according to the manufacturer instructions, and stored at −20 °C for further use. To detect FAdV, a PCR assay was performed to amplify the hexon gene using primers designed based the published reference sequences in GenBank (KU569296, GU188428.1, HE608152.1, KM096544.1, KP295475.1, KU24554-0.1, KU342001.1, KU558760.1, KU558762.1, KU569296.1, KU587519.1, KU991797.1, KX061750.1, KX090424.1, NC_015323.1) that were synthesized by Sango Biotech (Shanghai, China). The PCRs were carried out under the following protocol: 94 °C for 150 s; followed by 35 cycles of 94 °C for 30 s, 55 °C for 30 s, and 72 °C for 90 s; and a final elongation step at 72 °C for 300 s. All PCR products were analyzed by 1% agarose gel electrophoresis. The positive products were purified using a gel extraction kit (Omega, Norcross, GA, USA), cloned into the plasmid vector pMD 19-T (Takara, Dalian, China) and then introduced into *E.coli* DH5α competent cells (Takara) for sequencing.

2.4. Sequence alignment and phylogenetic analysis

Complete nucleotide sequences of the hexon genes were aligned with available FAdV-4 hexon genome sequences from GenBank using the MegAlign program of the DNAStar software suite, version 5.01 (DNASTAR, Madison, WI, USA). A phylogenetic tree based on the hexon genes was reconstructed by the maximum-likelihood method implemented in IQ-TREE 1.6.8, under the TIM3 + F + I nucleotide substitution model, and visualized in FigTree v. 1.4.2.

2.5. Pathogenicity of the GZ1 strain in SPF chickens

To determine the pathogenicity of a newly isolated strain (designated GZ1), groups of 10–21-day-old SPF chickens (Guangdong Wens Dahuanong Biotechnology Co., Ltd., Yunfu, China) were inoculated with $10^{5.8}$ $TCID_{50}$/0.1 mL of the GZ1 strain via oral or intramuscular injection. The other 10 chickens received the same volume of phosphate buffered saline as the control group. All chickens were monitored for clinical symptoms, morbidity, and mortality for 21 days.

Table 1
Surveillance statistics for *Fowl adenovirus* field strains in Guangdong Province, southern China, during 2016–2017.

Location	Year	Host	Number screened	Positive	Positive rate	Serotype
Heyuan	2016	Broiler	5	5	100%	4
Qingyuan	2016	Broiler	5	5	100%	4
Guangzhou	2016	Mandarin duck	1	1	100%	4
Huizhou	2016	Broiler	1	1	100%	4
Yunfu	2016	Broiler	1	1	100%	4
Dongguan	2016	Duck	4	2	60%	4
Jiangmen	2016	Layer	3	1	40%	4
Huizhou	2017	Broiler	18	18	100%	4
Jiangmen	2017	Broiler	2	0	0	/
Qingyuan	2017	Broiler	1	1	100%	4
Heyuan	2017	Broiler	4	1	25%	4
Yunfu	2017	Broiler	7	1	14.3%	4
Total			52	37	75.8%	4

3. Results

3.1. FAdV epidemiology in southern China during 2016–2017

To investigate the epidemiology of FAdVs in southern China, we collected 52 clinical samples from birds suspected to have HHS during 2016 to 2017. The results showed that 37 of the 52 samples were positive for FAdV, including 33 of 44 samples from broilers, and 1 of 3 samples from layers (Table 1). As shown in Fig. 2, a total of 100% (19/19) and 100% (6/6) FAdV-4 were identified in Huizhou and Qingyuan, respectively, during 2016 to 2017. Notably, all 37 FAdV strains were identified as FAdV-4. Moreover, FAdV-4 infection was confirmed in ducks and in the mandarin duck in 2016.

3.2. Characterization of the FAdV-4

All 37 of the isolated FAdV-4 strains obtained in the current study showed 100% identity with the hexon gene sequence of the FAdV-4 reference strain at the nucleotide level. Moreover, the hexon genes of these 37 strains also showed 100% nucleotide sequence identities with strain SD0828 isolated from Shandong province, ZJ2015 isolated from Zhejiang province, SCnj1601 isolated from Sichuan province, AH712 isolated from Anhui province, and HLJ/160826 isolated from Heilongjiang province. Phylogenetic analysis based on hexon amino acid sequences demonstrated that all 37 isolates obtained in this study grouped into the FAdV-C cluster (Fig. 3).

3.3. Pathogenicity of the GZ1 strain in SPF chicken

No significant clinical symptoms were observed in the control group or in the chickens inoculated orally with the GZ1 strain. However, the chickens inoculated with the GZ1 strain via intramuscular injection showed depression and diarrhea at 2 days post-inoculation (*dpi*), exhibiting a mortality of 100% with a mean death time of 3.7 days (Fig. 4). Necroscopy demonstrated that the livers of infected chickens were swollen and friable with multifocal necrosis lesions, and the pericardial sac showed accumulation of an amber-colored and jelly-like fluid.

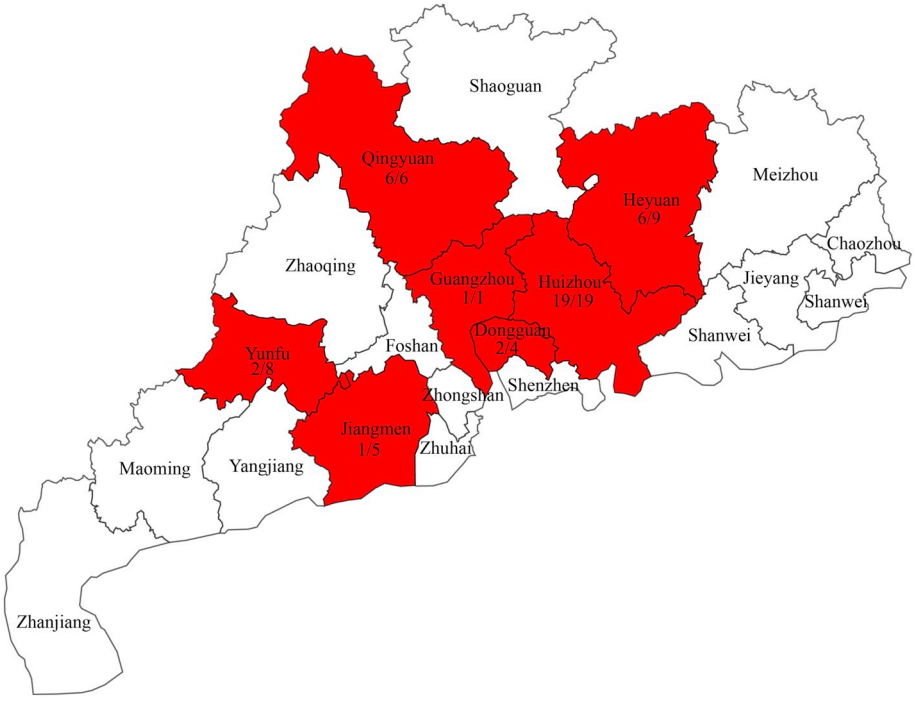

Fig. 2. Sample collection sites in Guangdong Province. Sampled cities are indicated in red. FAdV-positives of total positive samples are indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

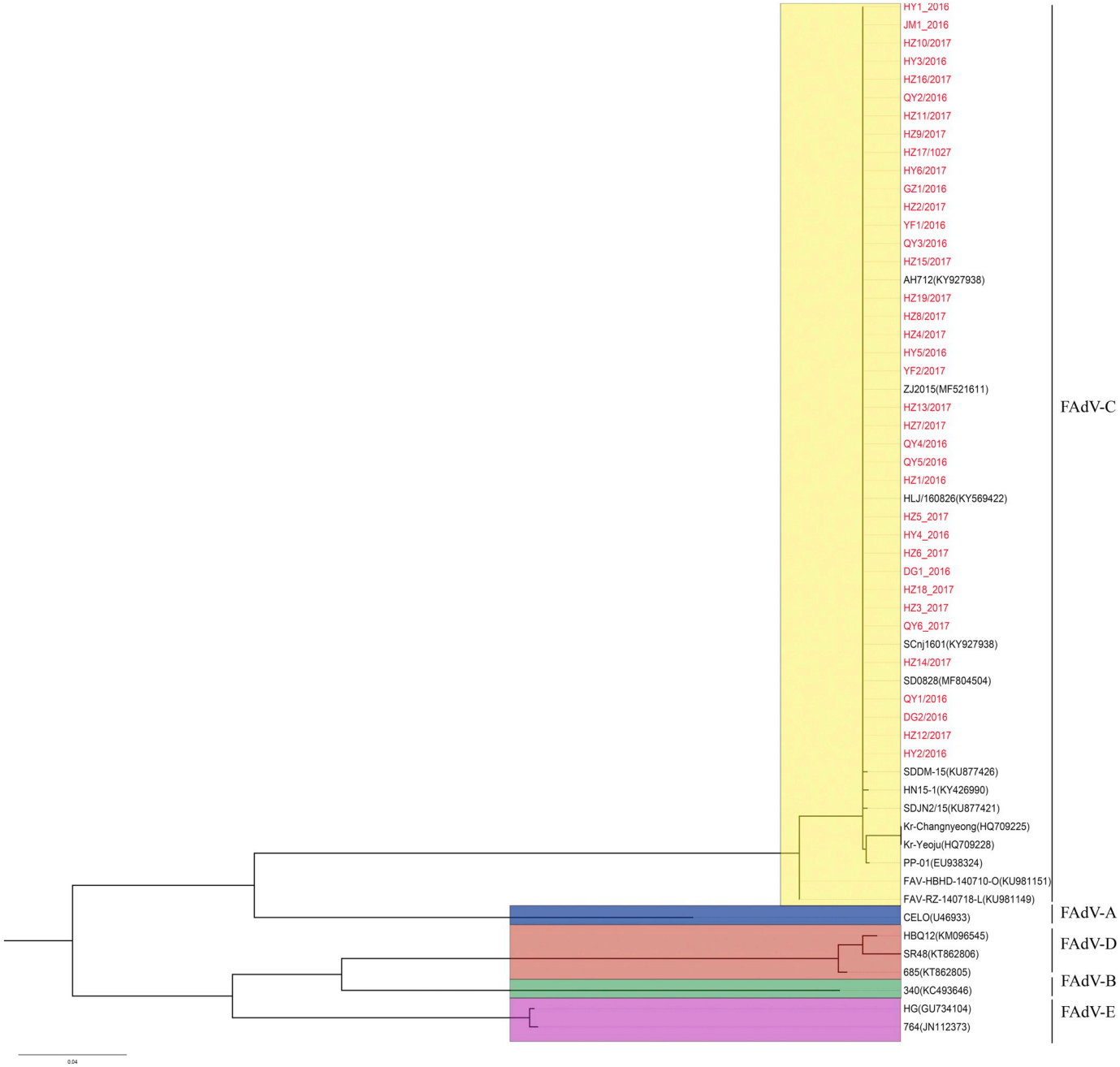

Fig. 3. Phylogenetic tree based on hexon gene sequences of FAdV. The ML tree was generated by the IQ-TREE 1.6.8, under the TIM3 + F + I nucleotide substitution model, and visualized in FigTree v1.4.2. Isolates in this study are shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

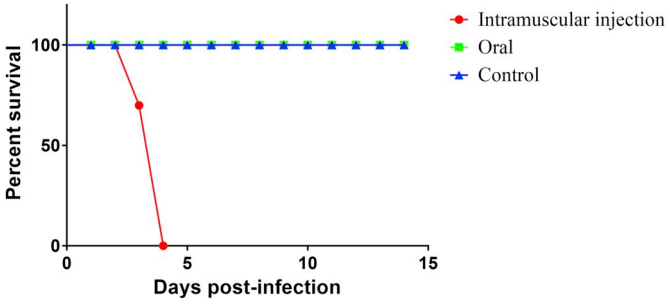

Fig. 4. Survival of 3-week-old SPF chickens after inoculated with FAdV-4 strain GZ1 from mandarin duck.

4. Discussion

FAdVs are common infectious pathogens of poultry and wild birds. Previous studies have demonstrated that IBH was associated with all 12 serotypes of FAdVs, whereas HHS was mainly caused by FAdV-4 (Domanska-Blicharz et al., 2011; Liu et al., 2016; Zadravec et al., 2013). HHS was first reported in broilers in Jiangsu Province of eastern China during 2012 to 2013, but the disease did not become widespread at that time, however it is suddenly increased after 2015 in most provinces of China(Niu et al., 2016). Zhang et al. (Zhang et al., 2016) reported that all 12 liver samples of chickens with HHS were related to FAdV-4 but no other FAdVs serotypes were found in central China. However, Niu et al. (Niu et al., 2018) reported that no less than three FAdV species, FAdV-C, FAdV-D, and FAdV-E, responsible for HHS, were circulating in five

provinces of China during 2015 to 2016, with FAdV-C strains being predominant. Consistently, in the present study, all FAdV strains isolated from birds of southern China with suspected HHS were FAdV-4, clustered into the FAdV-C group and showed 100% sequence similarity with FAdV-4 strains isolated from other provinces, including Shandong, Zhejiang, Sichuan, Anhui, and Heilongjiang. Guangdong province is one of the most highly developed economic regions with a high population density. Moreover, people in this region prefer to consume live poultry rather than chilled products. To satisfy the huge consumer demand, a large number of live poultries have been introduced into Guangdong province from more highly developed economic regions. Therefore, FAdV-4 might have been brought to southern China from other regions of the country through the live poultry trade.

In general, FAdV-4 causes disease in broilers at 3–5 weeks of age. In addition, FAdV-4 has been isolated from sick ducks (Chen et al., 2017; Yu et al., 2018), geese (Ivanics et al., 2010), and ostriches (Li et al., 2016a) that showed similar symptoms of HHS in chickens, such as enlarged liver and kidneys, but the mortality was significantly different. Ducks could be a reservoir of the FAdV-4 without clinical signs (Pan et al., 2017a, 2017b, 2017c). However, obvious gross and histopathological lesions were observed in Muscovy Ducks (Yu et al., 2018). (Pan et al., 2017a, 2017b, 2017c) reported that the FAdV-4 in ducks is far more likely to have been transmitted from chickens to ducks than from ducks to ducks. Moreover, early research also showed that latent infection with FAdVs can occur in several breeds of chickens (Grgic et al., 2006; Li et al., 2019). However, to our knowledge, the present study represents the first confirmation of an FAdV-4 infection in Mandarin duck, who was evaluated from Guangzhou Zoo in 2016 as it appeared to be suffering from diarrhea, ataxia, and depression, and showed a swollen and friable liver, this result is consistent with previous reports and indicate the possibility of cross-species transmission among different bird species. There are a large number of small backyard farms in Guangdong province, the majority of which harbor multiple bird species with poor biosecurity, thereby providing a perfect hotbed for cross-host transmission of the virus. Therefore, it is necessary to reduce the possibility of contact among different bird species.

Previous studies have demonstrated that the pathogenicity of FAdV-4 strains varied from subclinical infections to severe diseases in chickens, and was significantly influenced by the route of inoculation (Grgic et al., 2013; Li et al., 2017; Li et al., 2018). Pan et al. (Pan et al., 2017a) reported that the FAdV-4 strain HLJFAd15 could induce mortality in 76.9% and 100% of chickens infected via the oral and intramuscular injection route, respectively. Moreover, Guan et al. (Guan et al., 2018) showed that the FAdV-4 strain SC-Neijiang led to the death of 80% of chickens infected via an intramuscular injection route, whereas only 5% mortality was observed when infection was performed via the nasal route. No obvious clinical signs or death was observed in chickens infected with strain HB1501 via the oral route, while the mortality rate was 100% for chickens infected by intramuscular injection (Ruan et al., 2018). In addition, the inoculated subcutaneously group's overall mortality was 86.7%, but no obvious pathological changes were observed in the chickens of the airborne group (strain SDDM-4/15). (Li et al., 2019).Consistently, in the present study, the chickens inoculated with strain GZ01 via the oral route showed no obvious clinical symptoms throughout the experiment; however, those inoculated via intramuscular injection showed significant clinical signs of HHS and succumbed to the infections within 4 *dpi*. In a recent study, the mixed infection of a *Newcastle disease virus* live vaccine, FAdV-4, and infectious *Chicken anemia virus* was shown to play an important role in outbreaks of HHS with high mortality in some flocks(Su et al., 2018; Su et al., 2019). Therefore, the pathogenicity of the FAdV-4 strains depends on the infection route and requires further analysis.

In conclusion, the 37 FAdVs isolated from birds of Guangdong province, southern China, were all identified as FAdV-4, and are closely related with strains isolated from other provinces. Moreover, this is the first isolation of an FAdV-4 strain from Mandarin duck associated with HHS. To better control FAdV-4 infection, it is necessary to pay attention to the possibility of cross-transmission between different bird species. Thus, further studies are required to characterize the pathogenic mechanism of FAdV-4 in different bird species and investigate molecular epidemiology in different bird species.

Acknowledgements

This work was supported by the National Key Research and Development Program of China (No. 2017YFD0500701-4), the Pilot Trial and Industrialization of Bivalent Inactivated Novel-H9 Subtype Avian Influenza Vaccine (No. 201704020017), China Agriculture Research System (No. CARS-41-G16), and the National Key Research and Development Program of China (No. 2015BAD12B05).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2019.103928.

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