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Investigation on Fowl Adenovirus Outbreaks in some Broiler and Broiler Breeders' Flocks in Egypt

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Abstract

Egypt's poultry industry has been adversely impacted by multiple outbreaks of inclusion body hepatitis (IBH) and hepatitis hydropericardium syndrome (HPS) in recent years, resulting in significant economic losses. So, this research aimed to identify and characterize IBH and HPS in broiler and broiler breeders' flocks across the country for three years (2020-2022). Clinical cases of fowl adenovirus (FAdVs) infection in 835 flocks (10,000–20,000 birds in each flock) were investigated from 11 Egyptian provinces for identifying and genotyping FAdVs. The examined flocks showed variant symptoms of diarrhea, anemia, and general weakness. An enlarged, yellowish, and friable liver with necrotic foci was observed at necropsy, along with hydropericardium effusions, an enlarged, mottled spleen, enteritis, severe pancreatitis, and an inflamed bursa. DNA extracted from suspected isolates was analyzed by conventional polymerase chain reaction (PCR) and sequencing targeting the loop L1 of the hexon gene. The sequences were analyzed using BLAST and compared to adenovirus available in the GenBank database NCBI. FAdVs were detected in 22.4% (146/650) of broiler flock samples and 32.9% (61/185) of broiler breeders' flocks. Additionally, the hexon gene was subjected to phylogenetic analysis, which revealed that FAdVs can be classified into four genotypes. (FAdVs B-E) were detected from 34 represented samples (n= 34), 1 out of 34 FAdV-B, 3 out of 34 FAdV-C, 22 out of 34 FAdV-D, and 8 out of 34 FAdV-E (4 with 8a and 4 with 8b), FAdV-D was the most predominant. This investigation revealed the existence of infectious FADVs of various genotypes, and it is critical to design an effective vaccination program and comprehensive epidemic prevention in both broiler and broiler breeders' flocks in Egypt.

KEYWORDS
Fowl adenovirus FAdVs, Hepatitis-hydropericardium syndrome, Hexon gene, Phylogenetic analysis.

INTRODUCTION

FAdVs are members of the Adenoviridae family, which consists of medium-sized, icosahedral, double-stranded DNA viruses with no envelope (Berk, 2007; Harrach *et al*., 2019).

Inclusion body hepatitis (IBH), hepatitis hydropericardium syndrome (HHS), and adenoviral gizzard erosion (AGE) are all related to outbreaks of fowl adenoviruses (FAdVs) identified in many regions worldwide during the previous decade (Schachner *et al*., 2018; Harrach *et al*., 2019). FAdVs spread primarily through vertical and horizontal transmission (Fadly and Winterfield, 1973; Hess, 2013). The virus reacts to a group of pattern recognition receptors inside the cells specially toll like receptor group (Elfeil *et al*., 2016). Field reports of IBH and HHS have mostly come from commercial broiler flocks, where greater mortality and poor flock performance have resulted in significant economic losses (Hess, 2013). Generally, broilers are more susceptible to the disease between the ages of 21 and 28 days and may associate with failure to vaccination programs during this age (Ayoub *et al*., 2019). Depending on the virulence of the virus and coexisting diseases specially Newcastle disease, Gumboro, mortality can reach 80% (Sedeik *et al*., 2018; Talat *et al*., 2020; Fawzy *et al*., 2020). Nevertheless, the disease has been documented in birds from one week to 20 weeks (Howell *et al*., 1970; Pan *et al*., 2017). The infected broilers had an enlarged, pale, and friable liver, accompanied by ecchymotic hemorrhages, and the pericardium exhibited the presence of fluids of straw color that had been collected (Schachner *et al*., 2018).

Sequencing the hexon gene allows field isolates to be grouped into five species (FAdVs-A to E) based on their genetic composition. The cross-neutralization test further classifies it into 12 serotypes (Hess, 2000; Balamurugan and Kataria, 2004; Harrach *et al*., 2011). FAdV-1 is primarily responsible for gizzard erosion and ulceration (GE), FAdV-2, 8a, 8b, and 11 for inclusion body hepatitis (IBH), and FAdV-4 for hydropericardium hepatitis syndrome (HPS) (McFerran and Smyth, 2000; Balamurugan and Kataria, 2004; Harrach *et al*., 2019). Highly pathogenic FAdV-4 (species C) appears to have a more significant effect than species (E and D) associated with IBH and HHS and is responsible for high mortality rates (20%-80%) (Asthana *et al*., 2013).

Because maternal antibodies are so crucial, effective control strategies are frequently introduced through breeder immunization programs. While inactivated vaccinations are still the gold standard, recent interest has been focused on subunit vaccines (Schachner *et al*., 2014). Scanty studies have been conducted in Egypt (El-Tholoth and Abou El-Azm, 2019; Radwan *et al*., 2019;

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Elbestawy *et al*., 2020; El-Basrey *et al*., 2020; Adel *et al*., 2021; Lebdah *et al*., 2022; Safwat, 2022), that way the goal of the current study was to distinguish the avian adenovirus strains in broiler and broiler breeders' flocks in some governorates, detect their pathogenicity, as well as their disease forms and molecular characterization from the epidemiological point of view, which was taken into account for the development of a vaccine program in Egypt.

MATERIALS AND METHODS

Ethics statement

All institutional and national guidelines for the care and use of birds were carried out and were approved by the Institutional Animal Care and Use Committee (IACUC) of the Faculty of Veterinary Medicine, Suez Canal University.

Samples collection and processing

A total of 835 broiler and broiler breeders' flocks (10000–20000 birds were in each flock); 650 samples from broiler flocks, and 185 samples from broiler breeder flocks were collected from 11 Egyptian provinces (Giza, Qalyobia, Sharqia, Menofia, Gharbia, Al Behira, Suez Canal area, Alexandria, Kafr-El Sheikh, Fayoum, and Beni-Suef). Birds showed lethargy, huddling with ruffled feathers, loss of appetite, and mucoid yellow feces of varying ages were selected for the study. A post-mortem examination was carried out.

From freshly died or euthanized birds, cloacal samples and organs of suspected cases (liver, spleen, bursa, cecal tonsil, and heart) were collected, the samples were placed in sterile, dry containers filled with phosphate-buffered saline (PBS) and afterward transported to the laboratory using an ice box, and preserved at a temperature of -20°C until they were utilized for the identification of FAdVs using the polymerase chain reaction (PCR) technique, The supernatant was collected and filtered through 0.2 m syringe filters following 10 minutes of centrifugation at 700 xg (El-Tholoth and Abou El-Azm, 2019).

Nucleic acid extraction

The DNA extraction procedure was conducted using the WizPrep ® Viral DNA / RNA Mini Kit (Wizbiosolutions Inc., Korea) in accordance with the instructions provided by the manufacturer. The purified DNA samples were stored at a temperature of -20°C in order to facilitate their subsequent use in polymerase chain reaction (PCR) and sequencing.

Conventional PCR

The loop L1 region of the FAdVs hexon gene was analyzed and amplified by PCR using in-house primers from Metabion (Germany). The anticipated size of the product was 700 bp, and the nucleotide sequences of the primers were adeno-F- 5-ACATGGGAGCGACCTACTTCGACA-3 and adeno-R- 5-TCGGCGAGCATGTACTGGTAAC-3, Emerald Amp Max PCR Master Mix (Takara, Japan) was utilized. PCR reactions were carried out using a Biometra T3000 thermal cycler (Adel *et al*., 2021).

Sequencing L1 region of the hexon gene

34 samples were chosen for sequencing the L1 region of the hexon gene using forward and reverse primers in two reactions with the purified DNA fragment (Adel *et al*., 2021).

Phylogenetic analysis

In order to discover reference viruses that are related, the analysis of each sequence was conducted using BLAST, accessed at http://www.ncbi.nlm.nih.gov/BLAST. The nucleotide sequences were subjected to analysis using the Clustal W alignment technique applied in the BIOEDIT program. The sequences obtained in this investigation were matched with adenovirus field and reference strain sequences from different countries accessible in the GenBank NCBI database. The construction of phylogenetic trees was carried out via MEGA 6 software and employing the neighbor likelihood technique (Elbestawy *et al*., 2020).

RESULTS

The observed clinical manifestations in the possibly affected broiler flocks were lethargy, gathering behavior accompanied by ruffled feathers, reduced food intake, and the presence of mucoid yellow feces. Decreases in weight gains led to a poor feed conversion ratio. Additionally, at the advanced phases of infection, the chicks exhibited signs of lethargy, depression, and reduced mobility. The individuals tended to cluster in corners, leading to a mortality rate ranging from 5% to 40%. This mortality rate reached its highest point between days three and four

Table 1. Molecular detection of Fowl adenoviruses (FAdVs) in 11 provinces in Egypt.

Governorate		Broiler flocks			Broiler breeders' flocks		
		Number of Flocks	PCR Positive Flocks	% of positive flocks/ Total positive	Number of Flocks	PCR Positive Flocks	% of positive flocks/ Total positive
1	Giza	315	53	36.30%	46	23	37.70%
2	Qaliobeya	33	13	8.90%	15	10	16.40%
3	Sharqia	49	11	7.50%	23	5	8.20%
4	Menofia	71	18	12.30%	17	3	4.90%
5	Gharbia	41	5	3.40%	11	2	3.30%
6	Al Behira	23	7	4.80%	16	7	11.50%
7	Kafr El-Sheikh	24	7	4.80%	5	1	1.60%
8	Fayoum	27	8	5.50%	6	1	1.60%
9	Beni-Suef	27	5	3.40%	12	4	6.60%
10	Alexandria	16	9	6.20%	10	0	0.00%
11	Suez Canal area	24	10	6.80%	24	5	8.20%
Total	11	650	146	22.40%	185	61	32.90%

and usually stopped by day five. The poor performance of the flock has had a notable impact, resulting in significant economic losses. The breeders' flock did not exhibit any clinical signs or mortality. Moreover, the egg production and hatchability were within the normal range.

On necropsy, Lesions have been identified in vital organs such as the liver, heart, kidneys, and lungs. The liver exhibited signs of enlargement and pale, friable, and yellow discoloration, accompanied by regions of necrotic foci and pinpoint hemorrhages. Hydropericarditis, characterized by the accumulation of hydropericardium effusions containing up to 20 mL of transparent, straw-colored fluid within the pericardial sac, results in a distended, balloon-shaped appearance. Furthermore, most dead birds exhibited an enlarged mottled spleen and pancreatitis. The kidneys exhibit a pale appearance and signs of edema and inflammation (Figures 1, 2 and 3).

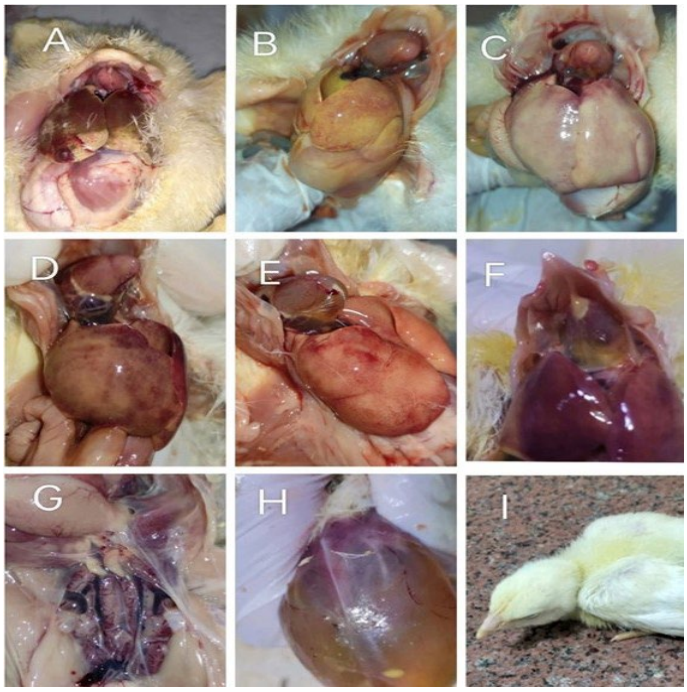

Figure 1. Gross lesions in the liver and heart from dead 1–14-day-old chicks. (A, B, C, D, E) shows swollen and friable livers with multifocal areas of necrosis with hydro pericardium. (D, E) Heart with straw-colored fluid accumulated in the pericardial sac. (F) kidneys with nephritis, enlargement, and tubules prominent (H) chick with ascites (I). Chicks suffer from poor performance, apathy, and prostration.

Suspected samples were tested: 650 from broiler flocks and 185 from broiler breeder flocks. The results indicated that 146/650 (22.4%) samples from broiler flocks and 61/185 (32.9%) samples from broiler breeders' flocks were positive for FAdVs. There were 146 positive samples from broiler flocks out of 207 positive flocks (70.5%) and 61 positive samples from broiler breeder flocks (29.5%) (Table 1).

Thirty-four samples were chosen for sequencing the L1 region of the hexon gene, revealing 1 of 34 FAdV-B, 3 of 34 FAdV-C, 22 of 34 FAdV-D, and 8 of 34 FAdV-E (4 with 8a and 4 with 8b). FAdV-D was the most prevalent virus (Table 2).

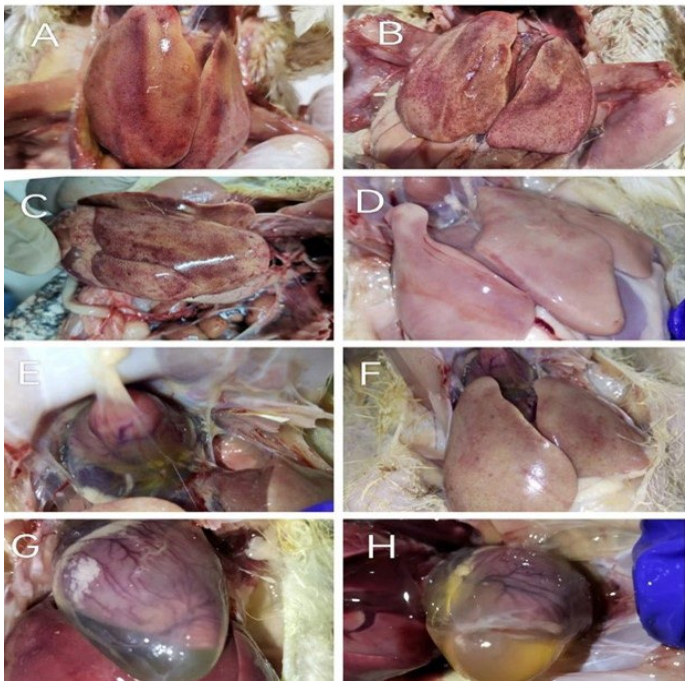

Figure 2. Gross lesions in liver and heart from dead 21–35-day old chicks. (A, B, C, D, F) Swollen and friable liver with multifocal areas of necrosis and petechial hemorrhage. (E, G, H) misshapen and flabby heart with the accumulation of clear, watery, or jelly-like fluid in the pericardial sac.

DISCUSSION

The poultry sector in Egypt's governorates is large; most of the tested and positive samples were collected from Giza, Qalyobia, Sharqia, Menofia, Gharbia, Al Behira, Suez Canal area, Alexandria, Kafr-El Sheikh, Fayoum, and Beni-Suef (Table 1). Broiler flocks were more affected than broiler breeder's flocks as the results revealed 146 positive samples from broiler flocks out of 207 positive flocks (70.5%) and 61 positive samples from broiler breeder flocks (29.5%). FAdVs isolated from the appropriate organ confirm that it is the etiological agent of the disease from both apparently healthy and diseased chicks (Niczyporuk, 2016; Adel *et al*., 2021).

Clinical cases of FAdV infections occurred at various ages (1-35 days old). These findings suggest horizontal and vertical transmissions, which were confirmed by virus isolation and similar findings were described by Schachner *et al.* (2018). Observing that broiler flocks exhibit varying strains at different times and ages suggests the introduction of a novel virus during later phases of the cycle. Broiler flocks may receive day-old chicks

Table 2. Fowl adenovirus serotypes were isolated and characterized in the positive flocks in relation to age in the present study.

Phylogenetic group	No.34	Age range	Type	% Percentage	
Serotype 5/B	1	35wks	Breeder	2.94%	2.94%
Serotype 4/C	3	21-30 Days	Broiler	8.82%	97.06%
Serotype 2/11/D	5	1-6days		64.71%	
	4	6- 12 days			
	7	12- 21 days			
	6	21-35days			
Serotype 8a/E	4	20-25 days		11.76%	
Serotype 8b/E	2	1-6 days		11.76%	
	2	12-21days			

Table 3. Pairwise identity matrix of nucleotide and amino acid sequences

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Fowl adenovirus 1-A- strain CELO	1		66%	67%	66%	66%	65%	67%	68%	61%	61%	60%	66%	66%	71%	65%	63%	67%	68%	58%
Fowl adenovirus 5 strain TR22	2	70%		61%	68%	69%	69%	72%	71%	65%	65%	64%	69%	69%	66%	68%	69%	70%	71%	61%
HQ897593-Fowl adenovirus 4	3	69%	66%		61%	61%	62%	62%	63%	62%	63%	61%	61%	61%	93%	61%	59%	62%	63%	56%
Fowl aviadenovirus D Sin-2	4	69%	78%	63%		100%	96%	72%	74%	69%	69%	67%	96%	97%	64%	98%	95%	73%	74%	62%
Fowl aviadenovirus D IS/3116/2020	5	69%	79%	63%	100%		97%	72%	75%	68%	68%	67%	96%	98%	64%	98%	95%	74%	74%	62%
Fowl adenovirus 2 ATCC VR-827	6	69%	78%	62%	96%	96%		71%	75%	69%	68%	66%	99%	96%	64%	95%	92%	73%	74%	62%
Fowl adenovirus 3 ATCC VR-828	7	71%	76%	62%	76%	77%	77%		74%	68%	67%	66%	72%	71%	66%	71%	69%	73%	73%	88%
Fowl aviadenovirus E IS/3343/2020	8	70%	80%	63%	85%	85%	85%	78%		79%	92%	79%	75%	74%	67%	75%	72%	88%	100%	63%
Fowl adenovirus 6 CR119.	9	62%	73%	60%	78%	78%	78%	72%	83%		85%	85%	69%	68%	60%	68%	67%	78%	79%	64%
Fowl adenovirus 8a TR59.	10	62%	73%	62%	79%	79%	78%	70%	92%	90%		85%	68%	68%	60%	68%	67%	80%	92%	63%
Fowl adenovirus 8b HeB20.	11	61%	70%	59%	77%	76%	76%	70%	81%	89%	88%		66%	67%	58%	66%	65%	89%	79%	61%
Fowl aviadenovirus 2 Elfeil-Gurbia	12	69%	78%	62%	96%	97%	100%	77%	85%	78%	78%	76%		96%	64%	95%	92%	73%	74%	62%
Fowl aviadenovirus D 11/D.F.G/Elfeil/Bekeiera/20	13	69%	79%	63%	98%	98%	95%	78%	85%	78%	78%	76%	95%		64%	97%	94%	73%	74%	61%
Fowl aviadenovirus C 4/C/F.G/Elfeil/Bekeria/21	14	74%	70%	93%	66%	66%	66%	65%	67%	58%	60%	57%	66%	66%		64%	61%	65%	66%	57%
FADV-D-ES-FG/GIZA-5006-2022	15	68%	78%	62%	98%	99%	95%	76%	84%	77%	78%	75%	95%	97%	65%		95%	73%	74%	61%
FADV-D-ES-FG/GIZA-4-2022	16	63%	73%	58%	93%	93%	90%	71%	79%	73%	74%	72%	91%	92%	61%	93%		71%	72%	59%
FADV-ES-FG/GIZA-24-8B-2022	17	69%	78%	61%	83%	83%	83%	77%	90%	82%	83%	80%	83%	83%	66%	82%	77%		88%	62%
FADV-ES-FG/GIZA-36-8A-2022	18	69%	80%	62%	84%	85%	84%	77%	99%	84%	93%	81%	84%	84%	66%	84%	79%	90%		63%
FADV-ES-FG/GIZA-17-B-2022	19	58%	64%	54%	65%	65%	65%	87%	66%	67%	65%	65%	65%	66%	55%	64%	60%	65%	66%	

Nucleotide and amino acid identities of the L1 hexone gene sequenced compared to other selected reference strains available on the gene bank revealed high similarity among the samples of each species.

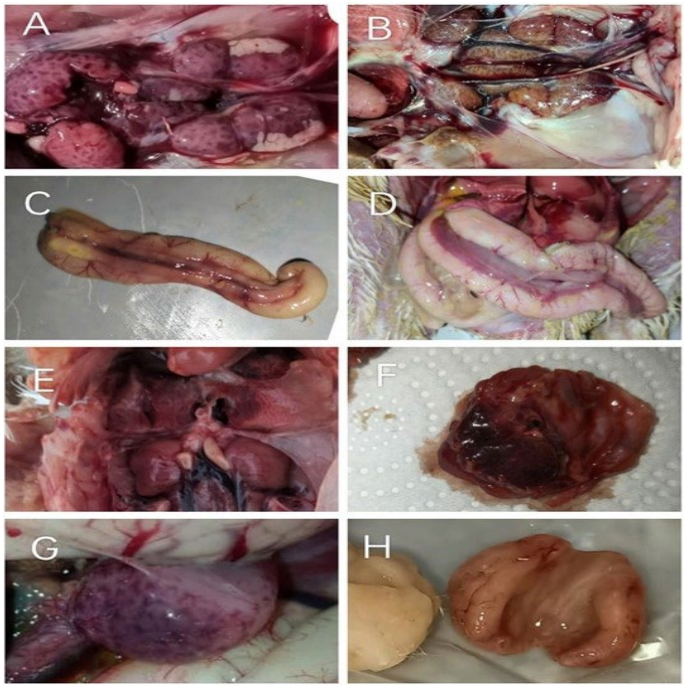

Figure 3. Gross lesions in the kidney, Lung, pancreas, and bursa from dead 21-35-day-old chicks. (A, B) kidneys with nephritis and enlargement and tubules prominent (C, D) shows severe pancreatitis (E, F) Lung with congestion and edema (G) Congested spleen with (H) Inflammation and hemorrhage in the bursa and some were atrophied.

from up to a dozen breeding farms. Finally, it is impossible to exclude the possibility of egg contamination at the hatchery. There is a significant exchange of adenovirus serotypes during the loss of maternal antibody. Adenoviruses can be isolated from every flock during this time, regardless of whether the birds got the disease. All of this evidence indicates that the biosecurity measures are ineffective. The examination of necropsy findings on broilers yielded a diverse array of pathological lesions, such as a pale, fragile, and enlarged liver with little white foci. Additionally, petechial or ecchymotic hemorrhages were observed. Abnormalities are typically characterized by enlarged, hemorrhagic kidneys with dilated tubules. The spleen is pale and enlarged, the pancreas is inflamed, and widespread necrosis has been detected as a result of the severe metabolic imbalance and extensive pancreatic and liver damage, similar results reported by Mase *et al.* (2012); Ahamad *et al.* (2016); Matos *et al.* (2016) and Niu *et al.* (2016), Hydropericardium is the accumulation of a transparent straw-colored fluid within the pericardial sac (Nakamura *et al.*, 2011). Pulmonary edema, ascites, and necropsies of the liver and spleen of dead chicken revealed lesions typical for IBH (Kim *et al.*, 2008; Benkő *et al.*, 2002).

The findings from the PCR analysis indicate that there may be variations in the pathogenicity of adenovirus strains belonging to the same serotype (Absalón *et al.*, 2017).

The molecular characterization of the new FAdV isolates using PCR and sequencing has provided confirmation of the existence of four FAdV species in Egypt. The finding aligns with the outcomes of a preceding investigation (Adel *et al.*, 2021).

Through phylogenetic analysis, it was discovered that one isolate was classified under species B and had a genetic identity with high sequence homology, sharing 97% similarity with isolates from Japan that were isolated in 2021 and had accession numbers (LC637578.1_LC604652.1_LC637582.1). Three isolates had a 99% sequence similarity with species C strains that were isolated in China from 2019-2020 and had an accession number (MG856954.1_ MN604721.1_MK629523.1) and one from Pakistan in 2008 (OQ291173.1). From 34 virus sequences in the study, 22 clustered with species D. Two had a high sequence homology of 98-99% with the FAdVs strain GB528 isolate, which was isolated in 2001 and had an accession number of (AF339915.1). The remaining isolates had a high sequence homology of 98-99% with FAdVs 2/11 Egyptian strains bst11 and kom3 and Sin-4 that were isolated in 2019-2021 and had accession numbers (MH782423.1_ MH782425.1_OK634392.1) and IS/3116/2020 strain and IS/3114/2020 and IS/3346/2020 that were isolated from Israel in 2020 (MT380197.1_ MT380196.1). Four isolates exhibited similarity to viruses belonging to serotype 8a, For instance, the IS/3343/2020 strain isolated from Israel in 2020 and strain TR59 from Japan in 2016 (MT759841.1_ KT862810.1). Four isolates had a 98-99% similarity with FADV-8B-D4 and FADV-8B-B2/5 isolated from Iran in 2017 with an accession number of (MT459118.1_ MT459114.1) and FADV11/TUR/TYPEE HEXON from Turkey in 2018 (MN717240.1) and Egyptian isolate AD15 in 2021 (MW712888.1).

According to the current study, Egypt is home to all FAdV species (B to E) linked to diseases in broilers and broiler breeders. Our study is part of an ongoing global FAdV screening effort, and we anticipate that the findings will help with FAdV infection research or FAdV vaccine development.

CONCLUSION

The current investigation conclude that, there are several types of Fowl Adenovirus emerged and circulating in Egypt including FAD type-B (serotype-5), type-C (serotype-4), type-E (serotype-8a and 8b) and type-D (serotype-2 and 11), and those types did not show cross protection against each other, thus require developing multivalent vaccine to cover the different circulating fowl adenovirus in the region for proper implementation

to the control strategy.

CONFLICT OF INTEREST

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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