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Meta-analysis of genetic diversity of the VP1 gene among the circulating O, A, and SAT2 serotypes and vaccine strains of FMD virus in Egypt

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Abstract

Introduction: Three strains of the FMD virus (A, O, and SAT 2) were recognised as causes of the FMD circulating in Egypt. The aims of this study were to trace the FMDV isolates from outbreaks in Egypt to understand their epidemiology and evolution and to understand the situation of the vaccine strains compared with the circulating serotypes. **Material and Methods:** A meta-analysis was carried out by using the data available for FMD outbreaks in Egypt from GenBank and the World Reference Laboratory for Foot-and-Mouth Disease (WRLFMD); a comparison was done with both data sets for the three serotypes. MEGA-X was used for the evolution analysis, through constructions of phylogenetic trees for all sequences recorded in GenBank for each serotype in different Egyptian outbreaks in different years and also within the same year. Additionally, nucleotide substitution rate, molecular clock, and mean evolutionary rates were estimated for the three serotypes to understand and compare their evolution. **Results:** Absence of some records of certain serotype outbreaks from the WRLFMD database was noted as were subsequent missing appropriate vaccine programmes. Genetic variation was recorded among the virus isolates within the same years and also the vaccine strain was associated with up to 26 amino acid substitutions. The evolution rate of the SAT2 strain was the highest of the circulating strains. SAT2 had high amino acid substitution per year at an important immunogenic site (130–170), serotype A had less, and serotype O the least. **Conclusion:** The need for different strategies for vaccine serotype selection is indicated.

Keywords: foot-and-mouth, disease, serotypes A, O, and SAT2, vaccine, VP1.

Introduction

Foot-and-mouth disease (FMD) is a highly contagious, economically important disease of cloven-hoofed animals (3). The causative agent, foot-and-mouth disease virus (FMDV), belongs to the *Aphtovirus* genus in the *Picornaviridae* family. There are seven serotypes of FMDV: A, O, C, Asia 1, and SAT1–3, and other various subtypes with indicative genetic variations (6, 14, 20). At present, FMD is endemic in different African and Asian countries, with serotype O having the highest prevalence, followed by serotype A (7, 14, 29, 33). The World Reference Laboratory for Foot-and-Mouth Disease (WRLFMD) indicated Egypt as being in multiple pools, as it has evidence of FMDV originating from two or more in the past four years. Three strains of the virus (A, O and SAT2) were recognised as causes of the FMD circulating in Egypt (1, 2). The main circulating serotype was O from 1961 to 2000, sporadic outbreaks of serotype A having been reported in 1958, 1957, and 1972 (41). SAT2 caused a severe outbreak across Egypt with recorded mortalities in many cattle and buffalo herds in 2012 (1, 39).

Although vaccines for FMD have been available for seven decades, disease outbreaks have still occurred in many regions of the world (30). One of the main problems in controlling FMD is the broad genetic diversity of the virus, which makes the prevention of the disease difficult (32). Within each FMDV serotype there are multiple antigenic variants. No cross-protection between the serotypes was recorded for vaccines and also within the same serotype vaccine-derived protection can be limited (13).

Understanding the FMDV molecular epidemiology lineage is mainly dependent on the phylogenetic relationship of different mutations of VP1, which is a highly variable capsid protein accommodating the relevant antigenic domains (22, 23). VP1 phylogeny determines the serotype, topotypes, and sub-lineages of the virus based on the percentage of sequence identity between different iterations of this gene, which determines the genetic distances and the phylogenetic clustering of the viruses (9, 15, 16, 24, 27, 38).

FMD virus has a quasispecies nature; its evolutionary change rate is high, and it proceeds through natural selection rapidly as it is associated with high mutation and substitution rates and deficient repair mechanisms, which leads to new strains of viruses arising that differ completely from the circulating strain and render the vaccine strains ineffective. Estimates of the mutation rates of the virus and the nucleotide substitutions in the VP1 gene between closely related FMDV isolates are important not only for understanding the virus' evolution and estimation of the interval between isolates but also for selection of the appropriate vaccine (10, 28, 32, 40).

In Egypt, routine prophylactic vaccination for FMD is usually conducted with local serotypes of the newly emerging strains, and recently a trivalent vaccine (A, O, and SAT2) was used as reported in the WRLFMD-Egypt database. The aim of the study was to trace the different FMDV outbreaks in Egypt to understand their epidemiology and evolution and to understand the situation of the vaccine strains compared with the circulating serotypes by using the data available on Egyptian FMD outbreaks from GenBank and WRLFMD.

Material and Methods

A meta-analysis was conducted on VP1 sequence datasets of A, O, and SAT2 circulating in Egypt. The data was obtained from GenBank from 2006–2018 (supplementary Table 1), and complemented only by one sequence for serotype O identified in 1993 (Eu553840.1 FMD-O/EGY/3/93). The short sequences were excluded, the nucleotide sequences were manually adjusted to equal numbers to avoid any variation arising from different nucleotide numbers, and they were also adjusted to the coding frame. The sequences used numbered 45 for serotype O (390 nucleotides starting from amino acid 1), 14 for serotype A (408 nucleotides starting from amino acid 79) and 25 for SAT2 (504 nucleotides starting from amino acid 49). The data of different outbreaks in Egypt were obtained from the WRLFMD report for Egypt and include the vaccine strains used (for which data were recorded from 2012) (supplementary Table 1).

The VP1 sequences of FMDV were aligned using MUSCLE in MEGA X (19) on translated sequences, and amino acids were aligned and substituted using this application. An unrooted maximum likelihood phylogenetic tree including four rate categories was constructed using MEGA X, the robustness of the tree topology was assessed with 1,000 bootstrap replicates, and all parameters were estimated from the data. Gamma distribution with invariant sites (G+I) was used to model evolutionary rate differences among sites. The phylogeny and molecular evolution were simultaneously estimated also using MEGA X. The GTR model of nucleotide substitution was applied with gamma-distributed rates among sites and a proportion of invariant sites.

Results

Year distribution of FMD serotypes. Year distributions of the three serotypes in Egypt revealed the presence of more than one serotype per year. Serotypes O and A were detected in 2006, 2007, 2010, 2011, and 2015. Furthermore, all three serotypes were detected in 2009, 2012–2014, and 2016–2018.

A comparison of the GenBank database and that of the WRL revealed the absence of the SAT2 serotype in 2009 and serotype O in 2010 from the WRL database and its inclusion in GenBank. Similarly, in 2013 serotypes SAT2 and O were only reported in GenBank. Also, in 2015, serotype A was only reported in GenBank and serotype O only in the WRL records, and no vaccine strain was recorded (Table 1, supplementary Table 1).

Phylogenetic study of the three serotypes. Comparison of VP1 sequences of serotype O from 2006–2018 and an additional sequence recorded in 1993 revealed great diversity among them. They are classified into four main clusters, the first of which includes the 2016 and 2017 sequences, which are subdivided into two sub-clusters, one for VP1 records unique to 2016, and the other for records from 2016 and 2017. The second main cluster placed 2013 and 2014 sequences together, and the third comprises those recorded in 2009 and 2012. Interestingly, the fourth cluster contains some accessions of 2009, those of 2010 and 2011, and a single 1993 accession (Fig. 1). The tree also recorded some virus strains which were used for vaccination in subsequent outbreaks of the virus within the same year or in the next year. The vaccine strain of 2014 (KX258003.1) in the phylogenetic tree is located far from the other virus strains of that year (Fig. 1).

Virus strains recorded within the same year also varied genetically as Fig. 1 shows; the overall distance among FMD serotype O VP1 sequences of 2009 is 0.1, there are 22 amino acid substitutions among them, and they include two subclades. In the 2014 sequences, the distance is 0.01, five amino acid substitutions are evident, and they comprise two subclades separating the vaccine strain from the circulating virus strains. In 2016, the distance between them is 0.01 and 10 amino acid differences are apparent, and they devolve into two subclades. In 2017, the distance is 0.01 with five amino

acid differences among them. Interestingly, no repeats occur in the substituted amino acids among the circulating viruses except for amino acid 59 in 2009 and 2017 and amino acid 107 in 2009 and 2014.

Diversity was also seen in serotype A VP1 sequences as Fig. 2 diagrammatises; although the number of sequences included in the tree is small and the overall distance among the virus genotypes circulating from 2013 to 2018 is 0.03, amino acid substitutions within the same year were recorded. These were especially prevalent in 2015 outbreak strains, where 18 amino acid substitutions were noted, and there were four in 2018, two in 2014, and only one in 2016 sequences.

The SAT2 strain VP1 gene also showed itself to be varied, and Fig. 3 presents its diversity. The overall distance between the virus genotypes from 2012 to 2018 is 0.02; two major clusters exist for SAT2 separating the viruses of 2012 from those of 2014 and indicating great genetic variation among the circulating virus strains within the same year. The location of one vaccine strain (JX570617.1FMD-SAT2-EGY/2/2012) is far from the circulating virus and is placed in a different subclade. The number of amino acid substitutions among the viruses in 2012 is 25, and in 2014 it is 26.

Comparison of the evolution rate among serotypes O, A, and SAT2. Comparison of the evolution rate of the different isolates of the three serotypes revealed for serotype O that the overall distance between its genotypes was 0.1 (45 sequences from 1993–2018). Regarding serotype A, the distance was 0.03 between the genotypes from 2009 to 2018. The farthest distance was observed among the isolates of SAT2 and it was 0.02 in the period from 2012 to 2018. This longest separation between the isolates of the SAT2 serotype over six years was also reflected in higher transitional substitution (Table 2), mean evolution rate (Table 3), and more numerous amino acid substitutions (Fig. 3).

Table 1. Year distribution of O, A, and SAT2 serotypes of FMDV and vaccine strains in Egypt based on the data in GenBank and WRLFMD

	SAT2		O		A		Vaccine
	GenBank	WRL	GenBank	WRL	GenBank	WRL	
2006	0	0	0	1	0	5	
2007	0	0	0	8	0	3	
2008	0	0	0	5	0	0	
2009	5*	0	6	19	0	9	
2010	0	0	2*	0	0	3	
2011	0	0	0	3	1	4	
2012	17	19	1	12	0	4	O, A, SAT2
2013	2*	0	1*	0	2	10	A
2014	1	6	4	21	3	4	O, A, SAT2
							O, SAT2
2015	0	0	0	6	3*	0	No vaccine
2016	0	1	9	12	3	1	O
							O, A, SAT2
2017	0	1	19	22	0	1	O, A
2018	0	6	0	1	2	2	O, A, SAT2

* – the serotype recorded in GenBank and missing in WRL

Table 2. Maximum likelihood estimate of substitution matrix-A among O, A, and SAT2 serotypes circulating in Egypt

	O serotype				A serotype				SAT2 serotype			
	A	**T/U**	**C**	G	A	T/U	C	G	A	T/U	C	G
A	-				-				-			
T/U	*3.47*	-			*4.69*	-			*3.16*	-		
C	*3.47*	**18.06**	-		*4.69*	**15.62**	-		*3.16*	**18.67**	-	
G	**18.06**	*3.47*	*3.47*	-	**15.62**	*4.69*	*4.69*	-	**18.67**	*3.16*	*3.16*	-

Bold letters indicate transitional substitutions, *italics* indicate transversional substitutions
N.B. The substitution matrix covered the virus isolates from 1993 to 2018 for the O serotype, from 2009 to 2018 for the A serotype, and from 2012 to 2018 for the SAT2 serotype

Table 3. Mean evolutionary rates of the O, A, and SAT2 serotypes

	O				A				SAT2			
From/To	A	T	C	G	A	T	C	G	A	T	C	G
Mean evolutionary rates	0.03	0.25	0.82	2.90	0.01	0.11	0.61	3.28	-	3.16	3.16	18.67

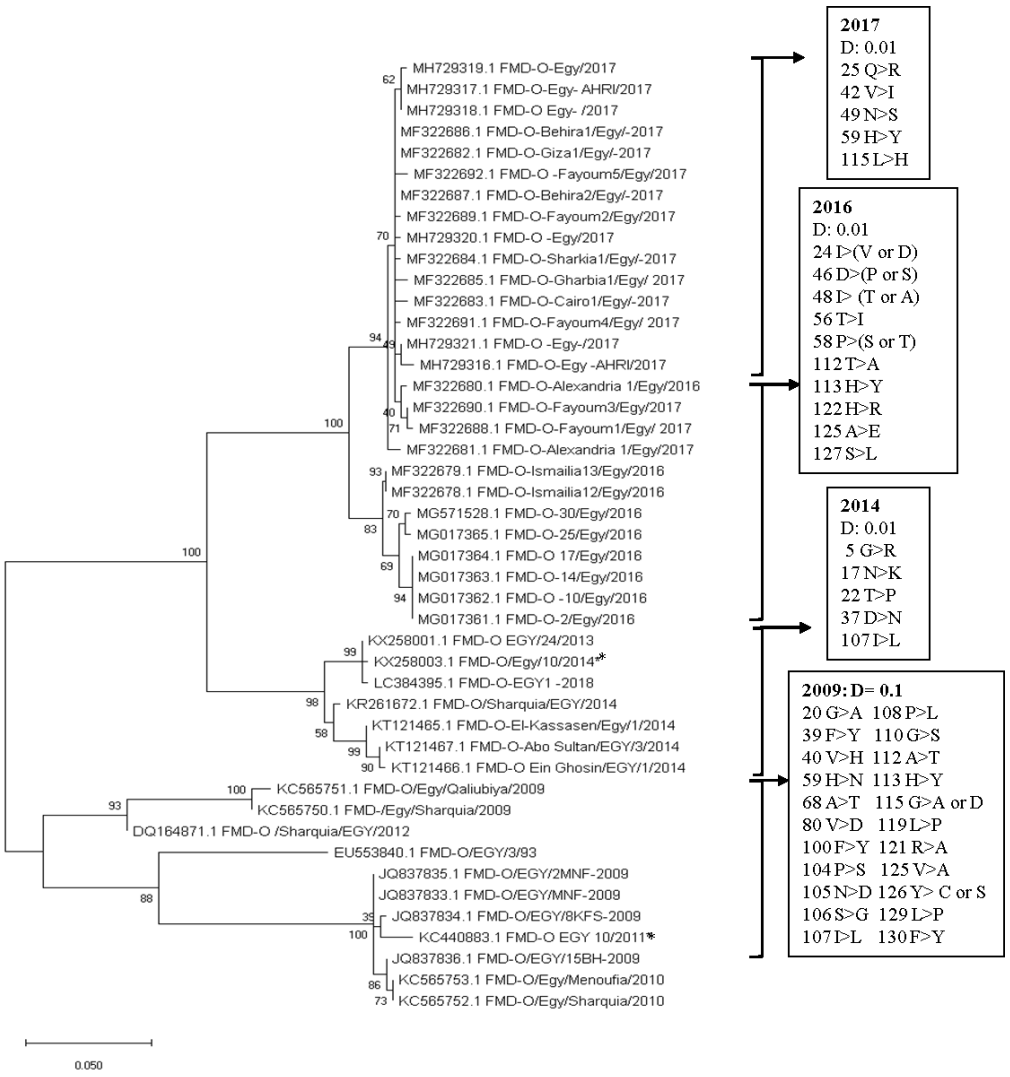

Fig. 1. Maximum likelihood phylogenetic tree of the VP1 gene nucleotide sequences of FMDV serotype O genotypes circulating in Egypt from 1993 to 2018. Numbers at nodes indicate the bootstrap values based on the maximum likelihood analysis of 1,000 replicates. The scale bar (0.05) represents substitutions per nucleotide position. * – Vaccine strains. The rectangles contain the amino acid substitutions per year

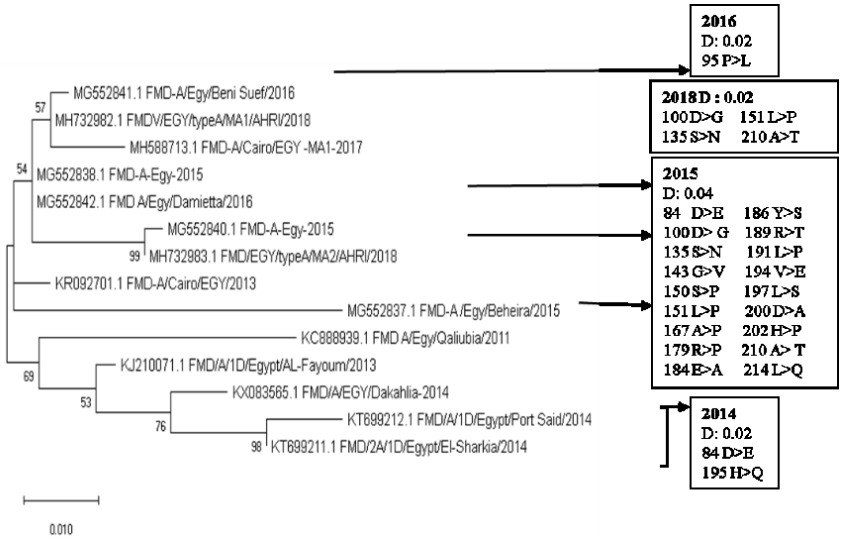

Fig. 2. Maximum likelihood phylogenetic tree of the VP1 gene nucleotide sequences of FMDV serotype A genotypes circulating in Egypt from 2011 to 2018. Numbers at nodes indicate the bootstrap values based on the maximum likelihood analysis of 1,000 replicates. The scale bar (0.01) represents substitutions per nucleotide position. The rectangles contain the amino acid substitutions per year

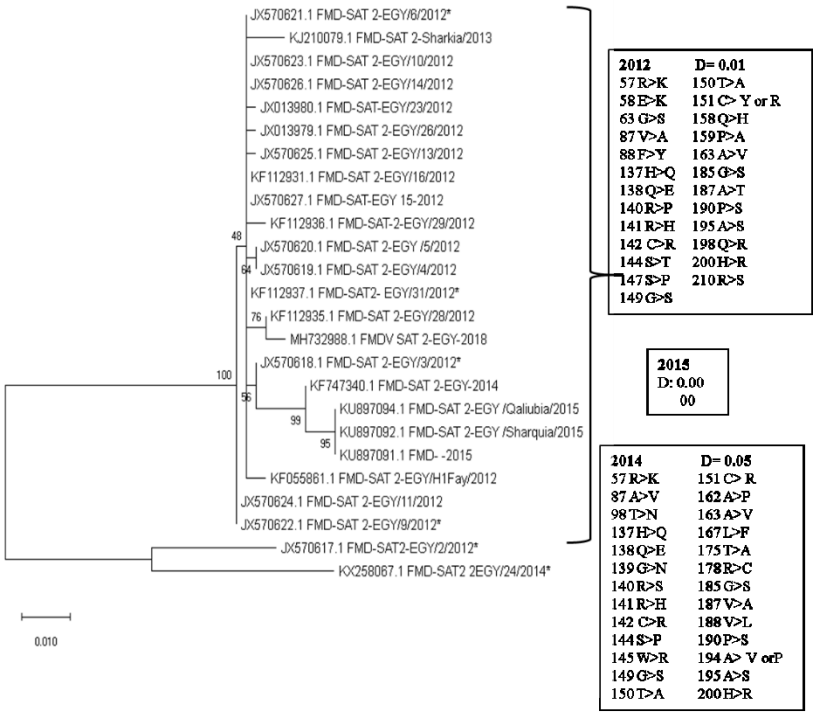

Fig. 3. Maximum likelihood phylogenetic tree of the VP1 gene nucleotide sequences of FMDV serotypes SAT2 genotypes circulating in Egypt from 2012 to 2018. Numbers at nodes indicate the bootstrap values based on the maximum likelihood analysis of 1,000 replicates. The scale bar (0.01) represents substitutions per nucleotide position. *– Vaccine strains. The rectangles contain the amino acid substitutions per year

Discussion

For successful control of FMD in developing countries many challenges must be overcome. There is always a variable gap between the actual state of the disease and countries' announcements to the World Organisation for Animal Health (OIE), members of which most countries are (33). Discrepancy between the Egyptian FMD data WRL and GenBank in some years caused the actual vaccine serotypes to be missed, as observed in 2013 and 2015 (supplementary Table 1), and subsequent more extensive virus dissemination led to infection of more varied hosts or reservoirs, the emergence of new variants of the virus and ensuing difficulty in the control of the disease, as described by Parthiban *et al.* (25) and Singh *et al*. (31). In our study, the combined assessment of the quantitative FMD data available in GenBank and WRL from several years provides a better view of the prevalence of the three serotypes. The phylogenetic tree of VP1 of the three serotypes gives better understanding of the current virus situation compared with the previous outbreaks and also compares circulating strains with the vaccine strain. While research such as this can see historical examples of suboptimal vaccine strain choice, missed diagnosis of a circulating virus serotype can also occur at the present time and bring new vaccine strain unsuitability problems. This hampers control of the disease, and therefore a national strategy is needed for this which will require collaboration between all veterinary agencies and institutions across the country on one side and the OIE on the other to avoid failures of serotype identification.

The sequence coding for VP1 is 627–657 nucleotides (according to the serotype) and this has been used in molecular epidemiology and investigation of the evolution of FMDV. The virus has a high mutation rate of between one and eight nucleotides per replication. Within the VP1 gene, there is a highly variable nucleotide sequence with a higher mutation rate that varies among the subtypes (codons 130–171); this region called the G-H loop represents an important immunogenic site of the virus (42). In our study, SAT2 has the highest amino acid substitution per year at this site, serotype A having less, and serotype O the least. Similarly, Lycett *et al.* (21) demonstrated genetic diversity between the topotype clades of SAT2 in sub-Saharan African isolates indicated by a large number of amino acid substitutions and large average pairwise distances between sequences from one topotype to another. Ullah *et al.* (37) suggested that eight amino acid substitutions in the G-H loop of VP1 of the locally circulating FMDV Asia1 serotype may be a cause of vaccination failure. Also, Fernandez-Sainz *et al.* (12) demonstrated that nucleotide substitution at the G-H loop of VP1 cannot be undergone without a loss of immunogenicity.

The maximum likelihood estimate of the substitution matrix of VP1-coding segments is highest in serotype SAT2 and lowest in serotype O. The number of mutations accumulate over one year with altered amino acid residues, especially at the immunogenic site, which

leads to diversity of serotype and antigenic shift. This shift could be associated with a widening host range and an ability of the virus to infect animals with a small dose, and could lead to invalid vaccination as described by Kitching (3). Consequently, a different strategy is required for selection of the vaccine strain of the three circulating serotypes. Strategy formulation is a contributor to the difficulty of FMD outbreak control when the virus remains in circulation in the vaccinated population (31).

The study of the evolutionary history and dynamics of FMD viruses along boundaries, in different countries or at continent level is important for better understanding of the basic epidemiological aspects of the virus and the geographical basis of the functional divergence of the virus serotypes (3, 14, 17, 18, 21, 35, 36). However, with recovery of live virus 28 days after acute infection and the persistence of FMDV in cattle in the oropharynx for years (3, 26), local strains of the viruses evolve with different immunological identity. Additionally, Arzt *et al.* (5) demonstrated the evolution of a super-swarm of FMDV virus in cattle due to multiple shifts of dominant viral haplotype occurring at the early and transitional phases of infection. Therefore, elucidation of the structure of different local FMDV serotypes is very important for an appropriate national strategy for controlling this serious disease.

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