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Genetic Analysis of Familial Mediterranean Fever among Egyptian Patients

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Abstract

Background: Familial Mediterranean fever (FMF) is an autoinflammatory genetic disorder that associated with different genetic mutations. Frequency of clinical manifestation differs according to age group, geographic region and ethnic population. **Objectives:** To study the clinical manifestation of FMF in relation to genotype (M680I, M694V, M694I and V726A). **Result:** The main presentation of studied group was abdominal pain 65.9% (203), followed by fever 60.4% (186) patients. (Mutation M694V) was the commonest 47.6% (297), followed by (Mutation V726A) in 32.8% (169%), then (Mutation M6802) in 23.4% (121) lastly (Mutation M6941) was in 22.1% (114) patients. Fever was highly associated with mutation (V729A) and it was statistically significant (*p value 0.047). **Conclusion:** Abdominal pain and fever were the most common manifestation of FMF patients. (Mutation M694V), (Mutation V726A) were the most detected mutation. Third age group; fever was associated with genetic mutation (V726A), abdominal pain with (M6941).

Keywords

Familial Mediterranean Fever (FMF), MEFV Gene, Mutation (M680I, M694V, M694I and V726A), Fever, Abdominal Pain, Autoinflammatory

1. Background

Familial Mediterranean fever (FMF) is an autoinflammatory genetic disorder that causes recurrent fevers and serosal inflammation of the abdomen, lungs, and joints leading to severe pain [1].

More than 300 sequence variations in MEFV gene were found to be associated

with FMF phenotype. Five of the most found mutations; M680I, M694V, M694I and V726A, and E148Q account for 65-95% of the cases [2].

Frequency of type of FMF manifestations differs between studies according to the enrolled age group, geographic region and ethnic population [3]. Association of clinical presentation to racial or underlying specific genotype is area of research to prove its relation so the aim of the current research is to study the clinical presentation in relation to certain genetic tests.

2. Subject and Method

A total of (516) patients were studied in the current work retrospectively during 2 year period 2020-2022. Data were retrieved from patients' medical records in Mansoura University children's Hospital and Mansoura University Hospital (MUH).

These inclusion criteria are paediatric or adult patients, who met the clinical presentation of FMF and had been subjected to genetic studies. Patients with FMF diagnosed according to Livneh *et al.*, 1997 diagnostic criteria [4].

Exclusion criteria:

- any paediatric or adult does not fulfil previous mentioned diagnostic criteria.
- any paediatric or adult not undergo genetic study.

Genetic characteristics: genetic analysis was done using the CE/IVD-labeled FMF Strip Assay (Vienna Lab Diagnostics, Vienna, Austria), and it included Mutation V726A, Mutation M694, Mutation M694V and Mutation M6801; that available in our laboratory during the study.

The age of studied subject in the current work was taken at the time of diagnosis. Age group was divided into 3 tertials; first tertials (I) = age group less than 11 years, second tertials (II) = age group (11 - 16) years, third tertials (III) = age group more than 16 years.

Assessment of different clinical presentation of FMF patients such as fever, abdominal pain, GIT symptoms (bloating, distension, indigestion), others (Myalgia, arthralgia, Headache, Dizziness, Skin rash, …) or combined presentation; patient who present with more than one symptom during the attack and correlation these clinical presentation with different FMF mutation.

Statistical analysis:

After the collection of data, they were analyzed using the statistical package of social science (SPSS, IBM) software version 24. Categorical data were expressed as numbers and percentages and were analyzed by Chi-square and Fisher-exact tests. Scale data were expressed as means ± SD or medians (IQR) as appropriate. Normality was tested using Shapiro Wilkinson or Kolmogorov-Simiranov tests, as appropriate. Non-parametric data were analyzed using Mann-Whitneys. P value was considered significant if it was <0.05.

3. Result

Our study recruited 516 FMF patients with slightly higher incidence of male 265

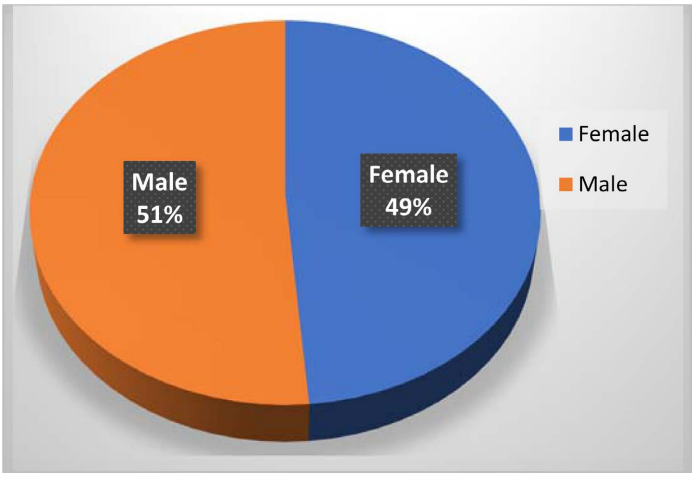

Figure 1. Gender distribution of FMF studied group.

(51.4%) than female 251 (48.6%) as show in Figure 1.

The main presentation of studied group; was abdominal pain 65.9% (203), followed by fever 60.4% (186), while 53.9% (166) patient presented with both abdominal pain and fever. GIT symptoms (bloating, distension, indigestion) was 36.7% (113) patients. More than 50% (166) of studied group presented with combination of two symptoms (abdominal pain, fever, GIT symptom), while 23.4% (72) patients only had more than two symptoms as show in Table 1.

Genetic mutation of studied group; (Mutation M694V) was the commonest 57.6% (297), followed by (Mutation V726A) in 32.8% (169%), then (Mutation M6802) in 23.4% (121) lastly (Mutation M6941) was in 22.1% (114) patients as Figure 2.

Median age of studied group; 9 (4.5 - 13) years was statistically significantly lower in patients with mutation (M6802) than without mutation.

Association of different genetic mutation with clinical presentation

Fever was highly associated with mutation **(V729A)** and it was statistically significant (p value 0.047), with no statistically significant with other FMF manifestation, while abdominal pain (*p value 0.885), GIT symptoms (*p value 0.505) weren't associated (Table 2).

Mutation (M6941) was highly associated with different symptoms (Myalgia, arthralgia, Headache, dizziness, Skin rash…) and it was statistically significant (*p value 0.034), with no association with abdominal pain (*p value 0.089) nor fever (*p value 0.978) nor GIT symptoms (*p value 0.051) Table 3.

Abdominal pain and GIT symptoms were statistically significantly associated with mutation (M694V) (*p value 0.025), (*p value 0.038) respectively, without association with fever (*p value 0.217) Table 4.

Unlike other studied genetic mutation, genetic mutation (M6802) wasn't associated with different FMF manifestation; fever (*p value 0.107), abdominal pain (*p value 0.231), GIT symptoms (*p value 0.092) Table 5.

Frequency of FMF genetic mutation among different age groups: Table 6.

Mutation (M694V) was higher in third age group (62.5%), followed by first

Table 1. Descriptive statistics of the selected cases.

Age (years)		**N**	**274**
		Mean ± SD	13.87 ± 11.03
		Median (Q1 - Q3)	11 (6 - 18)
		n	**%**
Sex	Female	251	48.6
	Male	265	51.4
Fever	No	122	39.6
	Yes	186	60.4
GIT Symptoms	No	195	63.3
	Yes	113	36.7
Other pain types	No	200	64.9
	Yes	108	35.1
Abdominal pain	No	105	34.1
	Yes	203	65.9
Presented by two symptoms	No	142	46.1
	Yes	166	53.9
Presented by more than two symptoms	No	236	76.6
	Yes	72	23.4
Mutation V726A	Negative	347	67.2
	Positive	169	32.8
Mutation M6941	Negative	402	77.9
	Positive	114	22.1
Mutation M694V	Negative	219	42.4
	Positive	297	57.6
Mutation M6802	Negative	395	76.6
	Positive	121	23.4

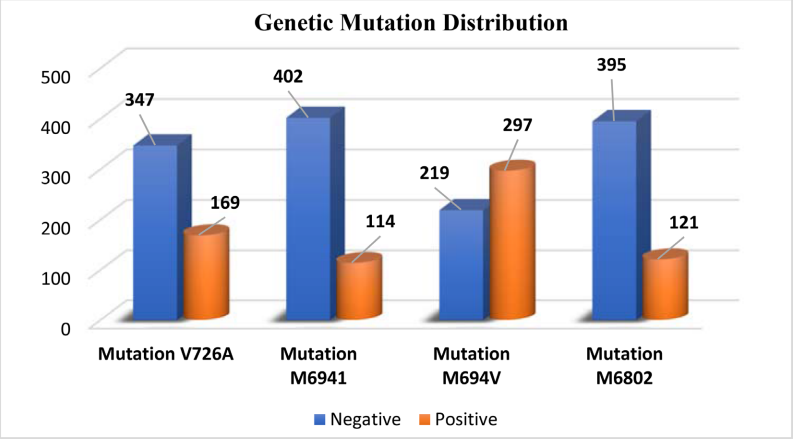

Figure 2. Genetic mutation distribution of studied group.

Table 2. Comparison between mutation in mutation V726A and different parameters.

		Mutation V726A				p
		Negative		Positive		
		n	%	n	%	
Sex	Female	169	48.7%	82	48.5%	0.969
	Male	178	51.3%	87	51.5%	
Abdominal Pain	No	64	34.4%	41	33.6%	0.885
	Yes	122	65.6%	81	66.4%	
Fever	No	82	44.1%	40	32.8%	0.047
	Yes	104	55.9%	82	67.2%	
Other Pain Types	No	127	68.3%	73	59.8%	0.129
	Yes	59	31.7%	49	40.2%	
GIT Symptoms	No	115	61.8%	80	65.6%	0.505
	Yes	71	38.2%	42	34.4%	
Presented by two Symptoms	No	87	46.8%	55	45.1%	0.771
	Yes	99	53.2%	67	54.9%	
Presented by more than two Symptoms	No	147	79.0%	89	73.0%	0.217
	Yes	39	21.0%	33	27.0%	

P value was measured using Chi-square test.

Table 3. Comparison between mutation in mutation M6941 and different parameters.

		Mutation M6941				P
		Negative		Positive		
		n	%	n	%	
Sex	Female	202	50.2%	49	43.0%	0.171
	Male	200	49.8%	65	57.0%	
Abdominal Pain	No	73	31.5%	32	42.1%	0.089
	Yes	159	68.5%	44	57.9%	
Fever	No	92	39.7%	30	39.5%	0.978
	Yes	140	60.3%	46	60.5%	
Other Pain Types	No	143	61.6%	57	75.0%	0.034
	Yes	89	38.4%	19	25.0%	
GIT Symptoms	No	154	66.4%	41	53.9%	0.051
	Yes	78	33.6%	35	46.1%	
Presented by two Symptoms	No	103	44.4%	39	51.3%	0.294
	Yes	129	55.6%	37	48.7%	
Presented by more than two Symptoms	No	176	75.9%	60	78.9%	0.581
	Yes	56	24.1%	16	21.1%	

P value was measured using Chi-square test.

Table 4. Comparison between mutation in mutation M694V and different parameters.

		Mutation M694V				p
		Negative		Positive		
		Negative	%	n	%	
Sex	Female	101	46.1%	150	50.5%	0.324
	Male	118	53.9%	147	49.5%	
Abdominal Pain	No	56	40.9%	49	28.7%	0.025
	Yes	81	59.1%	122	71.3%	
Fever	No	49	35.8%	73	42.7%	0.217
	Yes	88	64.2%	98	57.3%	
Other Pain Types	No	96	70.1%	104	60.8%	0.091
	Yes	41	29.9%	67	39.2%	
GIT Symptoms	No	78	56.9%	117	68.4%	0.038
	Yes	59	43.1%	54	31.6%	
Presented by two Symptoms	No	68	49.6%	74	43.3%	0.266
	Yes	69	50.4%	97	56.7%	
Presented by more than two Symptoms	No	102	74.5%	134	78.4%	0.42
	Yes	35	25.5%	37	21.6%	

P value was measured using Chi-square test.

Table 5. Comparison between mutation in mutation M6802 and different parameters.

		Mutation M6802				p
		Negative		Positive		
		n	%	n	%	
Sex	Female	190	48.1%	61	50.4%	0.656
	Male	205	51.9%	60	49.6%	
Abdominal Pain	No	73	32.2%	32	39.5%	0.231
	Yes	154	67.8%	49	60.5%	
Fever	No	96	42.3%	26	32.1%	0.107
	Yes	131	57.7%	55	67.9%	
Other Pain Types	No	146	64.3%	54	66.7%	0.704
	Yes	81	35.7%	27	33.3%	
GIT Symptoms	No	150	66.1%	45	55.6%	0.092
	Yes	77	33.9%	36	44.4%	
Presented by two Symptoms	No	102	44.9%	40	49.4%	0.49
	Yes	125	55.1%	41	50.6%	
Presented by more than two Symptoms	No	179	78.9%	57	70.4%	0.121
	Yes	48	21.1%	24	29.6%	

P value was measured using Chi-square test.

Table 6. Show Frequency of FMF mutation among different age groups.

		Age group						P*
		First group		Second group		Third group		
		n	%	n	%	n	%	
Mutation V726A	Negative	54	65.9%	56	58.3%	62	64.6%	0.528
	Positive	28	34.1%	40	41.7%	34	35.4%	
Mutation M6941	Negative	61	74.4%	69	71.9%	74	77.1%	0.71
	Positive	21	25.6%	27	28.1%	22	22.9%	
Mutation M694V	Negative	34	41.5%	54	56.3%	36	37.5%	0.024
	Positive	48	58.5%	42	43.8%	60	62.5%	
Mutation M6802	Negative	55	67.1%	65	67.7%	79	82.3%	0.031
	Positive	27	33%	31	32.3%	17	17.7%	

*p value was measured using chi-square test.

age group (58.5%), lastly second age group (43.8%) and it was statistically significant (*p value 0.024).

Mutation (M6802) was higher in first age group (33%), then second age group (32.3%), finally third age group (17.7%) and it was statistically significant (*p value 0.031).

Mutation (V726A) was higher in second age group (41.7%), followed by third age group (35.4%), then first age group (34.1%), but it was statistically insignificant (*p value 0.528).

Mutation (M6941) was higher in the second group (28.1%), followed by first group (25.6%), lastly third group (22.9%), but it was statistically insignificant (*p value 0.71).

Regarding third group;

Fever was statistically significantly higher in patients with genetic mutation (V726A) (*p value 0.025) than those without.

Abdominal pain was statistically significantly higher in patients with genetic mutation (M6941) (*p value 0.049) than those without.

Patients presented more than two symptoms were statistically significantly higher in patients in patients with genetic mutation (M6802) (*p value 0.047) than those without this genetic mutation.

4. Discussion

Familial Mediterranean fever (FMF) is an autoinflammatory genetic disorder, that causes recurrent fevers and serosal inflammation of the abdomen, lungs, and joints leading to severe pain [1]. Different genetic mutation was commonly found (M680I, M694V, M694I and V726A, and E148Q) [2].

The correlation of different genetic mutation to clinical manifestation of FMF is interesting part to be study as may guide the physician in predicting the course

of disease and long-term prognosis.

Our study showed that male was slightly higher incidence 265 (51.4%) than female 251 (48.6%), while previous studies conducted by (*G. Grateau et al.*; 2000) [5] who concluded that higher frequency of female sex among FMF Italians and Arabs population, and (*Özgür AL. et al.*; 2020) [6] who concluded that no significant difference was found between sex of FMF patients. Discrepancies in May due to different sample size, different Ethnic race and type of mutation studied.

In this study; (Mutation M694V) was the commonest 47.6% (297) genetic mutation in studied group. Consistent with other research conducted with (*Touitou I et al.;* 2001) [7] stated that "the most frequent of FMF genetic mutations are M694V, M694I, V726A, and E148Q". Thus, genetic mutation (M694V) may be the most common mutation in different races.

Previous research, that studied 1387 FMF patients in Alexandria, (*Amal R. Mansour; et al.* 2019) declared that that E148Q mutant allele was the most common genetic mutation [8], however our work detected; (Mutation V726A) 32.8% (169) of patients was the second common genetic mutation followed by (Mutation M6802) 23.4% (121) of cases while (Mutation M6941) 22.1% (114) of patients was the least genetic mutation in studied patients. This can be explained by two factors; 1) small sample size, 516 FMF patients were studied. 2) limited genetic study, only four available genetic mutations were studied.

It was noteworthy that, consistent with the results of (*H. A. Majeed; et al.* 2005) who concluded that the most commonly encountered alleles in Jordan population in descending order of frequency were M694V, V726A, and M680I accounting for 38%, 26%, and 10% of cases, respectively [9], This can be explained by high prevalent of FMF in population originating from the Eastern Mediterranean region.

Abdominal pain was the most common clinical presentation in 65.9% (203) FMF studied patients, As reported by (*Tunca M et al.*; 2005) who stated that Abdominal pain is the most encountered type of episode in FMF, thus FMF genetic study is highly recommended in refractory abdominal pain [10].

Fever was the second presenting symptom after abdominal pain in 60.4% (186) studied FMF patients, However, this finding conflicts with the results of (*Shohat M. et al.*; 2011) who declared that "fever may be the only symptoms during childhood" [11]. This can be explained by our study targeted different age group, both children and adult were included.

More than fifty of studied FMF patients were presented with dual symptoms (abdominal pain and fever) that in agreement with (*N. Cekin. et al.*; 2017) who concluded that abdominal pain (76%) and fever (58%) were the two most manifestations of FMF Turkish patients followed by arthritis (28%) and chest pain (19%) [12]. Although racial variation, different sample size and limited genetic study in our work, still abdominal pain and fever were the main presentation of FMF.

Regard correlation of genetic mutation with clinical presentation: our study concluded that:

Fever was highly associated with mutation (V729A) and it was statistically significant (*p value 0.047), this contrasted with (*Kilic et al.;* 2015) who stated that fever, arthritis, and arthralgia were common associated with E148Q genetic mutation [13]. This explained by limited genetic study in our work (four genetic mutation) and different sample size.

Abdominal pain and GIT symptoms were statistically significantly associated with mutation (M694V) (*p value 0.025), (*p value 0.038) respectively. This consistent with the results of (*Özelkaya et al*.; 2011) who stated that fever and abdominal pain were commonly associated with M694V homozygote mutations [14].

It was observed that other common presentation (Myalgia, arthralgia, Headache, dizziness, Skin rash…) were highly associated with mutation (M6941) and it was statistically significant (*p value 0.034). *By contrast*, *the* study conducted by (*Olgun A*, *et al*.; 2005) declared that these clinical findings were accompanied by M694V homozygote, because of different sample size, age group and racial variation [15].

Our study noticed that in third group (age group more than 16 years.); fever and abdominal pain were statistically significantly higher in patients with genetic mutation (V726A), (M6941) respectively. As observed with (*Padeh et al*.; 2010) who stated that fever and serositis may develop later in disease course [16].

It is peculiar of our study: to correlate the genetic mutation with age group.

Genetic mutation (M694V) was higher in third age group (62.5%), followed by first age group (58.5%).

Genetic mutation (M6802) was higher in first age group (33%), then second age group (32.3%).

While Mutation (V726A) and Mutation (M6941) was higher in the second age group (41.7%), (28.1%) respectively.

This research has some unavoidable limitations. First, because of limited genetic study in our laboratory, only four genetic mutations were studied, might have led to missing patients who could have different genetic mutation other than studied. Second, because the study was conducted in single centre, Mansoura government, this may have interfered with the burden of disease.

5. Conclusions

Abdominal pain and fever were the most common manifestation of FMF patients, followed by GIT symptoms and more than half of participants presented with dual symptoms.

(Mutation M694V), (Mutation V726A), (Mutation M6802) and (Mutation M6941) were the most common FMF genetic mutation detected in descending order.

Third age group has special characteristics. Fever was higher in patients with

genetic mutation (V726A) and abdominal pain was higher in patients with genetic mutation (M6941) than those without, while genetic mutation (M6802) was associated with more than two presentations.

The second group was highly associated with genetic mutation (V726A) then genetic mutation (M6941) and lastly (M6802) genetic mutation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

Familial Mediterranean fever	(FMF)
Mansoura University Hospital	(MUH).