http:// ijp.mums.ac.ir
Original Article (Pages: 8935-8940)

Genotype Pattern of Pediatric Familial Mediterranean Fever in Jordan: A Single Center Experience

*Raed Alzyoud[1], Motasem Alsweiti[1], Hiba Maittah[1], Boshra Adayleh[1], Mohammad Alnobani[1], Adel Alwahadneh[1], Mohammed Abu-Shukair[1]

[1]Pediatric Immunology, Allergy, and Rheumatology Division, Queen Rania Children's Hospital, King Hussein Medical Center, Amman, Jordan.

Abstract

Background

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder caused by mutations in the MEFV gene. The disease is especially common among Mediterranean ancestry, mostly Armenian, Turkish, Jewish and Arab populations. We aimed to describe genotype pattern of FMF in the Jordanian children and to compare it with other populations.

Materials and Methods

A retrospective analysis of MEFV mutations in pediatric patients, who were below 14 years of age, diagnosed as FMF and followed up at Queen Rania Children's Hospital in Jordan between 2014 and 2017.

Results

A total of 196 pediatric patients were diagnosed with FMF; 54% Females and 46% males. The mean age of patients was 7.8 ± 3.1 years; mean age at disease onset was 4.9 ± 2.3 years old. MEFV gene mutations were homozygous in 47(24%) patients, heterozygous in 87(44.4%) patients, compound heterozygous in 55(28.1%), and negative genotype in 7(3.6%) patients. Five mutations were the most frequent; M694V, E148Q, M680I, M694I, respectively.

Conclusion

The five-founder FMF mutations were the most detected in Jordanian children but in different order than what had been reported.

Key Words: Children, Familial Mediterranean fever, Jordan, MEFV Genotype.

*Please cite this article as: Alzyoud R, Alsweiti M, Maittah H, Adayleh B, Alnobani M, Alwahadneh A, Abu-Shukair M. Genotype Pattern of Pediatric Familial Mediterranean Fever in Jordan: A Single Center Experience. Int J Pediatr 2019; 7(2): 8935-40. DOI: **10.22038/ijp.2018.34530.3037**

Corresponding Author:

Raed Alzyoud (MD), Pediatric Immunology, Allergy, and Rheumatology Division, Queen Rania Children's Hospital, Amman-Jordan, PO Box: 855122.

Email: raedalzyoud@gmail.com

Received date: Jul.25, 2018; Accepted date: Aug.22, 2018

1- INTRODUCTION

Familial Mediterranean fever (FMF) is one of the most common hereditary autoinflammatory syndromes; which are a group of disorders characterized by recurrent episodes of generalized inflammation in the absence of infectious or autoimmune causes (1). FMF is an autosomal recessive inherited disease that occurs as a result of point mutation in the Mediterranean Fever (MEFV) gene, on the short arm of chromosome 16 which encodes the protein called pyrin, and frequently occurs among ethnic groups living around the Mediterranean basin; Turks, Armenians, Jews and Arabs (2).

The MEFV gene is composed of 10 exons, most of FMF mutations occur in exon 10, four of them are the most frequently identified in FMF patients: M694 V, V726A, M680I and M694I variants, and to date, more than 310 MEFV sequence variants have been reported (3). The order and percentage of MEFV gene mutations are different among each ethnic group, in this study we aimed to describe the pattern of MEFV gene mutations which had been identified in a clinically correlated FMF pediatric patients in Jordanian population.

2- MATERIALS AND METHODS

A retrospective analysis was performed on medical records of 196 pediatric patients aged from 0-14 years, who were diagnosed as FMF at Queen Rania Children's Hospital (the only children's Hospital in Jordan) from 2014 through 2017. Inclusion criteria of the study population were: patients who met validated Diagnostic Criteria of FMF in Childhood which had designed by a group of Turkish pediatric rheumatologists in 2009, Jordanian and Arab ancestry, and were receiving colchicine for at least six months. Patients who missed follow up or had an alternating diagnosis were excluded from the study. This study was approved by the Jordanian Royal Medical Services Ethics committee number 8/5/2018, and informed consents were obtained from the patients legal guardians. All patients were tested for 12 mutations of MEFV gene, using the FMF STRIP ASSAY TM.VIENNA LAB DIAGNOSTICS GmbH, baseline tests were performed: complete blood count, kidney function test, liver function test, routine urine analysis urine culture and abdominal ultrasound. C-reactive protein, erythrocytes sedimentation rate, white blood cells count, and urine analysis were performed during attacks. All data were collected, tabulated and analyzed using Microsoft Excel sheet 2013.

3- RESULTS

A total of 196 pediatric patients were diagnosed as FMF from January 2014 till June 2017; 106 (54%) were females, 90 (46%) were males, all patients were Jordanian; Arab ethnicity. The mean age of patients was 7.8 ± 3.1 years, mean age at disease onset was 4.9 ± 2.3 years, the youngest patient at time of diagnosis was 6 months old, and the oldest was 14 years old. The distribution of FMF mutations in 196 patients is listed in **Table.1**, patients were classified into four categories based on FMF genotype: the most common pattern was heterozygous genotype in 87(44.4%) patients followed by compound heterozygous in 55(28.1%), homozygous in 47(24%), and negative genotype in 7(3.6%) patients. The most frequent genotypes in each category were: M694V in 34 (17.3%) patients as heterozygous, M694V-M694V in 32 (16.3%) patients as homozygous, and M694V-V726A in 15 (7.7%) patients as compound heterozygous. The frequencies of mutant genotypes are shown in **Figure.1**, the most frequent five mutations had been detected: M694V, V726A, E148Q, M680I, M694I in 49.7%, 21.3%, 19.3%, 15.7%, and 9.6%, respectively.

Table-1: MEFV mutations in Jordanian FMF children (n=196).

Mutation	Genotype	NO.	%
Heterozygous	M694V	34	17.3
	E148Q	21	10.7
	V726A	10	5.1
	M680I	10	5.1
	P369S	4	2.0
	A744S	3	1.5
	M694I	3	1.5
	P479L	1	0.5
	F479L	1	0.5
	Total	87	44.4
Homozygous	M694V-M694V	32	16.3
	V726A-V726A	6	3.1
	M680I-M680I	7	3.6
	E148Q-E148Q	1	0.5
	M694I-M694I	1	0.5
	Total	47	24.0
Compound heterozygous	M694V-V726A	15	7.7
	E148Q-M694V	6	3.1
	M694V-M694I	6	3.1
	E148Q-V726A	6	3.1
	M694I-M680I	6	3.1
	M680I-V726A	4	2
	M680I-M694V	3	1.5
	E148Q-A744S	3	1.5
	M694I- V726A	3	1.5
	R761H-M694V	1	0.5
	M694V-R761H	1	0.5
	M680I-E148Q	1	0.5
	Total	55	28.1
Negative genotype		7	3.6

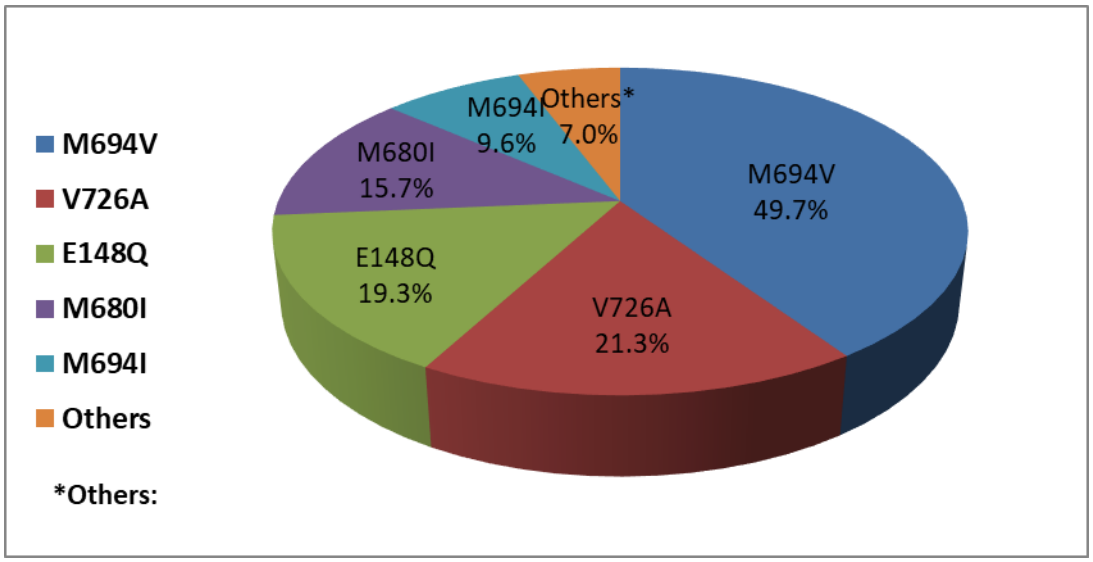

Fig.1: The frequencies of mutant genotypes in Jordanian Children (n=196).

4- DISCUSSION

We aimed in our study to describe the pattern of MEFV gene mutations in Jordanian children who had been diagnosed as FMF, and to compare it with other published data of different ethnic groups and populations. We abled to make a diagnosis of FMF in 196 children; 54% Females and 46% males, with a relatively high MEFV gene mutation positivity rate (96.4%). FMF is the most common monogenic autoinflmmatory disease in children, and its diagnosis is still challenging, to provide a diagnostic tool for children, a European initiative called Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) was launched to optimize diagnosis and management of FMF in pediatric age group (4). SHARE emphasized on the role of genetics in supporting the diagnosis but not excluding FMF, also FMF genotype can partly explain clinical variability of the disease, for instance, M694V mutant patient is at risk of developing a severe phenotype. The distribution of MEFV mutations is quite similar in the Eastern Mediterranean populations where FMF is common, on the other hand MEFV mutations have different distribution in populations where FMF is rare like Japan (5). In our cohort the distribution of FMF mutations was in heterozygous pattern in 44.4%, followed by compound heterozygous in 28.0%, homozygous in 24%, and none had a complex alleles, this order is similar to what other pediatric studies had reported, but what was remarkable for our cohort a higher rate of mutation detection (96.4%) in comparison with reports from Egypt, Syria and the Eurofever Registry (85.7%, 71.8%, 87.4%, respectively) (6, 7, 8). Hasan A. Majeed and coworkers (2005) studied a 407 adult and pediatric FMF Arabic patients most of them were Jordanian, they reported 59% with positive genotype, the most common pattern was homozygous in 38% while compound heterozygous was reported only in 22%, this could be explained by, they test only for five mutations for their cohort (9). The five founder FMF mutations, M694V, M680I, M694I, V726A (in exon 10), and E148Q (in exon 2) account for approximate 70% of FMF cases (10). In our cohort the five founder mutations order was: M694V, V726A, E148Q, M680I,M694I in 49.7%, 21.3%, 19.3%, 15.7%, 9.6% respectively (Figure.1), a comparison of this result with different studies in different ethnic groups is listed

in **Table.2**. All studies reported that the five founder mutations were the most common, M694V mutation was in the first order, while others had different orders (7, 9, 11-13). The point that was remarkable in our cohort, the higher rate of E148Q mutation (19.3%) in comparison with other reports in Arabs and non-Arabs ethnic groups. Evren Gumus had studied FMF patients, both Turkish and Syrian in South-Eastern Region of Turkey after Syrian Civil war, he reported a different FMF mutations frequency and order: R202Q (24%), M694V (17%), E148Q (16%), M680I (10 %), and R761H (8%), than previously reported before the war, were the most frequent mutations were: R202Q (33.3%), M694V (22.6%), E148Q (22%),V726A (7.5%), and R761H (4.3%), also the author detected E148Q in 25% of Syrian patients which was higher than in Turkish patients (14). FMF clinical phenotype and genotype in Japanese patients were different from Mediterranean populations disease phenotypes, the most frequently detected FMF mutation was E148Q, its frequency approximate 40%, the diversity of mutations in Japanese patients suggested the difference in the clinical phenotypes from Mediterranean populations (15).

Table-2: Comparison of the most frequent FMF mutations in different populations.

FMF studies (Reference)	Number of Patients	Study Population	Country/ Ethnicity	Mutations frequencies (%)				
				M694V	V726A	M680I	M694I	E148Q
Rami A. Jarjour et al. (7)	103	Pediatric	Syria Syrian	36.4	10.7	14	11.6	14.9
Hasan A. Majeed et al. (9)	239	Adult and pediatrics	Jordan Arab	38	15	1	10	8.3
Kenan Barut et al. (11)	708	Pediatric	Turkey Turkish	53.8	7.8	12.8	--	7.5
M. Medlej-Hashim et al. (12)	640	Adult and pediatrics	Lebanon Lebanese	30.3	19.4	7.4	12.8	8.3
Farhad Salehzadeh (13)	403	Adult and pediatrics	Iran Iranian	20.9	12.7	10.3	2.1	10.7
Current study	196	Pediatric	Jordan Jordanian	49.7	21.3	15.7	9.6	19.3

5- CONCLUSION

Our study showed that the five founder FMF mutations were the most detected in Jordanian children, the highest frequency was M694V, and a higher frequency of the E148Q mutation was seen than other reports among Arabs.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Gayane Manukyan, Rustam Aminov. Update on Pyrin Functions and Mechanisms of Familial Mediterranean fever. Front Microbiol. 2016; 7: 456. Published online 2016 Mar 31. doi: 10.3389/fmicb.2016.00456

2. İsmail Sarı, Merih Birlik, Timuçin Kasifoğlu. Familial Mediterranean fever: An updated review. Eur J Rheumatol. 2014; 1(1): 21–33. Published online 2014 Mar 1. doi: 10.5152/eurjrheum.2014.006.

3. Padeh S, Berkun Y. Familial Mediterranean fever. Curr Opin Rheumatol. 2016 Sep; 28(5):523-9. doi: 10.1097/BOR.0000000000000315.

4. Giancane G, Ter Haar NM, Wulffraat N, Vastert SJ, Barron K, Hentgen V, et al. Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever. Ann

Rheum Dis. 2015; 74(4):635-41. doi: 10.1136/annrheumdis-2014-206844. Epub 2015 Jan 27.

5. Özen S, Batu ED, Demir S. Familial Mediterranean fever: Recent Developments in Pathogenesis and New Recommendations for Management. Front Immunol. 2017; 8: 253. doi: 10.3389/fimmu.2017.00253. eCollection 2017.

6. Talaat HS, Mohamed MF, El Rifai NM, Gomaa MA. The expanded clinical profile and the efficacy of colchicine therapy in Egyptian children suffering from familial Mediterranean fever: a descriptive study. Ital J Pediatr. 2012; 38: 66. doi: 10.1186/1824-7288-38-66.

7. Jarjour RA, Al-Berrawi S. Familial Mediterranean fever in Syrian children: phenotype-genotype correlation. Rheumatol Int. 2015; 35(4): 629-34. doi: 10.1007/s00296-014-3116-x. Epub 2014 Aug 24.

8. Demirkaya E, Saglam C, Turker T, Koné-Paut I, Woo P, Doglio M, et al. Paediatric Rheumatology International Trials Organisations (PRINTO); Eurofever Project. Performance of Different Diagnostic Criteria for Familial Mediterranean fever in Children with Periodic Fevers: Results from a Multicenter International Registry. J Rheumatol. 2016; 43(1):154-60. doi: 10.3899/jrheum.141249.

9. Majeed HA, El-Khateeb M, El-Shanti H, Rabaiha ZA, Tayeh M, Najib D. The spectrum of familial Mediterranean fever gene mutations in Arabs: report of a large series. Semin Arthritis Rheum. 2005; 34(6):813-8.

10. Fujikura K. Global epidemiology of Familial Mediterranean fever mutations using population exome sequences. Mol Genet Genomic Med. 2015; 3(4):272-82. doi: 10.1002/mgg3.140. Epub 2015 Apr 5.

11. Barut K, Sahin S, Adrovic A, Sinoplu AB, Yucel G, Pamuk G, et al. Familial Mediterranean fever in childhood: a single-center experience. Rheumatol Int. 2018; 38(1):67-74. doi: 10.1007/s00296-017-3796-0. Epub 2017 Aug 21.

12. Medlej-Hashim M, Serre JL, Corbani S, Saab O, Jalkh N, Delague V, et al. Familial Mediterranean fever (FMF) in Lebanon and Jordan: a population genetics study and report of three novel mutations. Eur J Med Genet. 2005; 48(4):412-20. Epub 2005 Jun 20.

13. Salehzadeh F. Familial Mediterranean fever in Iran: A Report from FMF Registration Center. Int J Rheumatol. 2015; 2015:912137. doi: 10.1155/2015/912137.

14. Gumus E. The Frequency of MEFV Gene Mutations and Genotypes in Sanliurfa Province, South-Eastern Region of Turkey, after the Syrian Civil War by Using Next Generation Sequencing and Report of a Novel Exon 4 Mutation (I423T). J Clin Med. 2018; 7(5): pii: E105. doi: 10.3390/jcm7050105.

15. Kishida D, Nakamura A, Yazaki M, Tsuchiya-Suzuki A, Matsuda M, Ikeda S. Genotype-phenotype correlation in Japanese patients with familial Mediterranean fever: differences in genotype and clinical features between Japanese and Mediterranean populations. Arthritis Res Ther. 2014; 16(5):439. doi: 10.1186/s13075-014-0439-7.