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Common MEFV Mutations in Palestinian Patients with Familial Mediterranean Fever

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Abstract: Familial Mediterranean fever (FMF) is an autosomal recessive inflammatory disorder caused by mutations in the MEFV gene that encodes the pyrin protein. The disease is relatively common among people originating from the Mediterranean areas. The aim of this study was to determine the common MEFV gene mutations in 270 Palestinian patients diagnosed with FMF. The patients were screened for four common MEFV gene mutations namely, p.M694V, p.M694I, p.V726A, and p.E148Q using allele-specific polymerase chain reaction (AS-PCR). The results revealed that around 22% of the patients harbored two MEFV mutations, with the compound heterozygous forms being more prevalent than the homozygous ones. The most frequently encountered mutant allele was p.M694V which existed in around 12% of the tested chromosomes. The p.M694I, p.V226A and p.E148Q mutations were observed in around 9, 9 and 7% of the tested chromosomes, respectively. In about 29% of the patients only one mutant allele could be detected and around 49% of the patients did not show any of the investigated mutations. In conclusion, the four tested MEFV gene mutations have a significant contribution to FMF in the Palestinian population of Gaza strip. Screening for those mutations should be offered to FMF patients to confirm diagnosis and effect timely treatment. Further mutations analysis the MEFV gene should be conducted in this population in order to document additional MEFV mutations.

Keywords: FMF, MEFV Gene, Mutation, AS-PCR, Gaza Strip-Palestine

1. Introduction

Familial Mediterranean fever (FMF; OMIM: 249100) is an autosomal recessive inflammatory disorder characterized by recurrent, self-limiting, episodes of fever and abdominal pain. If left untreated, amyloidosis and subsequent renal failure can occur in a significant fraction of the patients (Livneh et al., 1999).

Through analyses of MEFV gene three forms of FMF have been suggested. Patients with typical clinical features are defined as type I. Patients who present with renal amyloidosis without typical attacks of the disease have been defined as type II (Balci et al., 2002). Individuals who do not have any symptoms related to FMF but have at least two MEFV mutations are considered type III (Yigit et al., 2008).

The disease is relatively common among people of Mediterranean origin especially, North African Jews, Armenians, Turks, and Arabs (Ben-Chetrit and Touitou, 2009) with a carrier frequency reaching up to 39% in certain populations (Booty et al., 2009).

FMF is the result of mutations in MEFV gene which codes for the protein pyrin. The gene is located on chromosome 16p13.3 and comprises 10 exons. MEFV is expressed predominantly in the granulocytes and its product, pyrin, participates in the inflammatory response (Shohat and Halpern, 2011).

Over 30 disease-associated mutations have been identified in the MEFV, with the majority of mutations being missense changes clustering in exons 2 and 10 (Touitou et al., 2004). Molecular diagnosis of patients with FMF is usually initiated by targeted-mutation analysis through screening for the common mutations that are frequently observed in FMF cases (e.g., p.M694V, p.M694I, p.V726A, p.M680I, and p.E148Q). In most individuals suffering from FMF, analysis of those common mutations confirms the diagnosis (Kishida et al., 2014).

The Gaza strip is a small area (365 km2) located in the south-western part of Palestine. It lies at the Mediterranean southeast coast. The strip is inhabited by around 1.9 million people.

This study was carried out to screen FMF-diagnosed Palestinian patients for the four common MEFV gene mutations: p.M694V, p.M694I, p.V726A and p.E148Q.

2. Materials and Methods

2.1. Patients

The population of this descriptive study consisted of 270 patients with an initial diagnosis of FMF type I. The patients were referred to our Genetic diagnosis unit by general pediatricians and internists from all over Gaza Strip. Clinical phenotypes are assigned according to the Tel-Hashomer criteria for diagnosis of FMF (Sari et al., 2014). The patients consisted of 150 males and 120 females. The age of the patients ranged from 5 to 15 years.

2.2. Mutation Analysis

Anticoagulated venous blood (~2 ml) was collected from each patient. Genomic DNA was prepared from peripheral blood lymphocytes using Wizard Genomic DNA Purification Kit (Promega, USA) according to the manufacturer's protocol. Extracted DNA was used in screening for the four selected mutations. Allele-specific PCR (AS-PCR) was employed for detecting the four mutations as previously described by other investigators (Ayesh et al., 2005; Mohammadnejad and Farajnia, 2013). PCR products were analyzed by electrophoresis in a 2% agarose gel containing ethidium bromide, and the results were documented using a gel documentation system.

All the DNA samples were screened for p.M694V, p.M694I, p.V726A, and p.E148Q mutations. The rationale behind selecting those mutations is based on their common presence in FMF patients of Mediterranean origins.

3. Results

This study investigated four common MEFV gene mutations in 270 patients living in the Gaza strip region of Palestine. Among the FMF diagnosed patients, 150 (55.56%) were males and 120 (44.44%) were females. The age of the patients ranged from 5 to 15 years.

Genotyping results showed that p.M694V was the most frequently encountered mutation where 64 (11.85%) of the tested 540 chromosomes harbored this mutation. The other three mutations; p.M694I, p.V726A, and p.E148Q, existed in 9.07, 8.9 and 6.85% of the chromosomes, respectively (Table 1).

Around 49% (132/270) of the patients did not show any of the tested mutations, 78 (28.9%) had one mutation and 60 (22.2%) had two mutations, of whom 24 were homozygous and 36 were compound heterozygous (Table 2).

4. Discussion

This work investigated four MEFV mutations in Gaza strip Palestinian patients with the initial diagnosis of FMF. The results revealed that the MEFV mutations, in one or two copies, were evident in about half of the patients. This mutation detection rate is comparable to that reported in other MEFV targeted mutation studies (e.g., Balci et al., 2002; Medlej-Hashim et al., 2005; Belmahi et al., 2012).

The four tested mutations showed a trend, in terms of the frequency of mutant alleles, comparable to that reported in other Mediterranean populations (Touitou, 2001). Additionally, mutation p.M694V was the most frequent mutation and represented about 32% of the mutant alleles (Table 1). This mutation is also the most frequently seen mutation in FMF patients belonging to the four major Mediterranean (Armenians, Jews, Arabs and Turks) populations (e.g., Aksentijevich et al., 1999; Solak et al., 2008; Belmahi et al., 2012). These observations indicate that common MEFV mutations are actually old and had descended from ancestors (founders) common to the four populations.

Table 1. *Distribution of MEFV mutations in tested patients.*

Mutation	No. of chromosomes	(%)	% among the mutant alleles
p.M694V	64	11.85	32.32
p.M694I	49	9.07	24.75
p.V726A	48	8.90	24.24
p.E148Q	37	6.85	18.69
Unknown	342	63.33	-
Total	540	100	

Table 2. *Genotypes distribution in the patients.*

Genotype	No. of patients	%	Sub-total No. (%)
p.M694I/p.M694I	12	4.44	
p.V726A/p.V726A	6	2.22	24 (8.88)
p.E148Q/p.E148Q	5	1.85	
p.M694V/ p.M694V	1	0.37	
p.M694V/ p.V726A	11	4.07	
p.M694V/p.E148Q	8	2.96	
p.M694I/p.V726A	7	2.59	36 (13.33)
p.M694V/p.M694I	4	1.48	
p.M694I/p.E148Q	3	1.11	
p.V726A/p.E148Q	3	1.11	
p.M694V/X*	39	14.44	
p.V726A/X	15	5.60	78 (28.90)
p.E148Q/X	13	4.80	
p.M694I/X	11	4.07	
X/X	132	48.89	132 (48.89)
Total	270	100	270 (100)

* X = Unknown

Apart from importance in confirming the diagnosis, identification of MEFV mutations in FMF patients is essential for justifying colchicine treatment and predicting disease phenotype. Colchicine is the mainstay of treatment- it prevents attacks and relieves symptoms. Colchicine is also important in delaying the development of amyloidosis (Ozen, 2004). Genotype-phenotype correlation studies have shown that mutation type is associated with clinical characteristics of the disease. The presence of p.M694V mutation, in either homozygous or heterozygous form, is usually associated with severe disease presentation (Majeed et al., 2002; Mohammadnejad and Farajnia, 2013; Ece et al., 2014; Uluca

et al., 2015). Likewise, p.V726A/p.V726A genotype predicts a poor clinical outcome (Majeed et al., 2002). On the other hand, p.M694I/p.M694I and p.E148Q/p.148Q genotypes are associated with milder disease forms (Majeed et al., 2002; Uluca et al., 2015).

Assuming correct FMF diagnosis, observing patients with only one mutant MEFV allele and others without any detectable MEFV mutation, is suggestive for the presence of other MEFV mutations. Therefore, analysis of those samples for other known mutations and sequencing of the MEFV mutation-prone exons, such as exons 1,2,3,5, and 10 (Kishida et al., 2014), should be conducted in this population in order to identify additional MEFV mutations.

It is important, however, to note that researchers have shown that about 25% of the patients carry only one MEFV mutation (Ozen, 2009), and up to 20% harbor no MEFV mutation at all (Booty et al., 2009; Touitou, 2013).

In conclusion, the four tested MEFV mutations accounted for about 37% of FMF chromosomes in the Palestinian FMF-diagnosed patients. Screening FMF-diagnosed patients for those mutations should constitute part of the standard screening for the investigated population. Testing for MEFV p.M680I mutation and sequencing the MEFV mutation-prone exons will identify additional mutations.

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