Frequency of MEFV gene 12 mutations in Egyptian Patients with Familial Mediterranean Fever Disease In Relation To Disease Presentation

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BY

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Contents

List of Abbreviations

AS	:	Ankylosing spondylitis
ASO	:	Antistreptolysin O
BD	:	Behcet Disease
CV	:	Cardiovascular
ELE	:	Erysipelas-like erythema
EMG	:	Electromyography
FMF	:	Familial Mediterranean Fever
GFR	:	Glomerular filtration rate
GN	:	Glomerulonephritis
HSP	:	Henoch-Schönlein purpura
IBD	:	Inflammatory bowel disease
MEFV	:	Mediterranean fever gene
MRI	:	Magnetic resonance imaging
NASH	:	Non-alcoholic steatohepatitis
PAN	:	Polyarteritis nodosa
PFM	:	Protracted febrile myalgia
SpA	:	Spondyloarthropathy

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Abstract

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease that results from point mutations in the Mediterranean Fever (MEFV) gene on the short arm of chromosome 16. To date, more than 310 MEFV sequence variants have been reported including the most common M694V, V726A, M680I and M694I mutations. The wide clinical variability in FMF is partly explained by genetic heterogeneity.

The aim: of this present study was to assess the distribution of MEFV gene mutations in Egyptian patients with FMF, to find certain genotype-phenotype correlation and to relate these findings to disease onset, chronicity and Colchicine administration.

Patients and Methods: This was a cross-sectional study on one hundred fifty eight patients who were diagnosed primarily on clinical basis to have FMF then to be genetically tested for the most common 12 mutations in the MEFV gene in the Medical Genetics Unit; Paediatrics Hospital; Ain Shams University. A blood sample was withdrawn from each FMF patient for Molecular genetics study using DNA isolation followed by PCR amplification followed by hybridization. Urine was tested for Microalbuminuria

Results: The study revealed that E148Q, M694I, V726A, M680I and M694V are the most common mutations of MEFV gene and that M691V, F479L and I692deI mutations did not appear in our study population. The common heterozygous mutations observed in this study were E148Q, M694I and V726A, while, the common homozygous mutations were M694I and M680I and the common compound mutations wereM694I/V726A and M680I/V726A. Abdominal pain, arthralgia and combined presentations are significantly higher in heterozygous than in compound. On the other hand; chest pain was significantly higher in compound than heterozygous of E148Q mutation. The combined and arthralgia phenotyping were significantly high (87% and 74% respectively) in E148Q mutation in comparison to the other mutations. Non-abdominal surgeries are almost 2.75 times more common than that of abdominal surgeries in the 5 common FMF mutations. The most sensitive symptoms that predict the mutations are; vomiting for V726A,

Weakness, Fatigue & Maylgia for M680I, Arthralgia & Vomiting for E148Q and Vomiting for M694I. Meanwhile, the most sensitive symptoms that predict the zygosity are; FH & Arthralgia for Compound heterozygous, FH & Vomiting for Heterozygous and Arthralgia & Abdominal Pain for Homozygous.

In conclusion: FMF in our study population did show great diversity in terms of age of onset, presentation, severity and response to treatment. This could be attributed to the heterogeneity of the disease; multiplicity of the mutations and that every mutation could present as heterozygous, homozygous and compound heterozygous.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent acute attacks of fever accompanied by abdominal pain, arthritis, and pleurisy. The most severe complication is the development of renal amyloidosis, which can be prevented by the daily and life-long administration of colchicine therapy **(El Shanti et al., 2006).**

In FMF, loss of appetite, decrease in physical activity during attacks, and the presence of persistent subclinical inflammation may affect the growth. Although it was reported again in some studies that growth hormone and insulin-like growth factor axis might be affected by the inflammation enduring during the period with no attacks, pathogenesis of the possible growth retardation in these patients could not be explained sufficiently **(Pozo and Argente, 2002 & Mor et al., 2005).**

FMF primarily affects populations surrounding the Mediterranean basin: Sephardic Jews, Armenians, Turks, Arabs, Greeks, Druze, and Ashkenazi Jews. The gene responsible for this disease is MEFV gene that was identified in 1997. It is located on chromosome 16p13.3 **(International FMF Consortium, 1997).**

The MEFV gene encodes pyrin, a protein expressed in neutrophils, eosinophils, monocytes, dendritic cells, and fibroblasts. In monocytes, pyrin co-localized with the microtubule system. This fact may contribute to the therapeutic effect of colchicine, which destabilizes the cytoskeleton. The exact role for pyrin and the mechanisms by which MEFV mutations (more than 300 variants; mutations and polymorphisms) exert their pathogenic effects are inadequately understood **(Padeh, 2005).**

By this means, the twelve common mutations E148Q in exon 2, P369S in exon 3, F479L in exon 5 and M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H in exon 10 were determined.

In all ethnic groups, M694V was the most common mutation. M680I was the second most common mutation among the Turks, whereas V726A was the second mutation among the Jews, Armenians, Arabs, and Iranian-Azeri. While M6941 is common among Arabs and least frequent among Jews, it displayed a higher rate among the Iranian-Azeri **(Salehzadeh, 2015).**

Many diagnostic criteria for FMF were initially developed for adults (Tel-Hashomer criteria and Livneh criteria **(Livneh et al., 1997)**) and then for children (Yalcinkaya criteria **(Yalçinkaya et al., 2009)**). All criteria have high sensitivity, but low specificity; particularly in the pediatric age group where recurrent fever attacks are more common than in adults. Since the identification of the MEFV gene, considerable progress has been made in the understanding of FMF. Gene analysis test is a valuable diagnostic tool, but is still unable to confirm diagnosis in all patients. Consequently, more attention should be given to the clinical diagnostic criteria **(Koné-Paut, 2011).**

While identifying MEFV gene mutations determines the definitive diagnosis of FMF, clinical manifestations of the disease is much more sensitive and specific to diagnosis, especially in practice. It should be kept in mind that failure to find mutations in the MEFV gene does not rule out the disease **(Padeh, 2005).**

The onset of the disease occurs before the age of 5 years in more than 60% of cases and before 20 in 90%. An onset as early as 6 month has been reported **(Zeinab, 2004).**

Aim of the Study

The aim of this present study is to assess the distribution of MEFV gene mutations in Egyptian patients of familial Mediterranean fever, to find certain genotype-phenotype correlation and to relate these findings to disease onset and chronicity.

Chapter I
Familial Mediterranean fever

Familial Mediterranean fever (FMF) is the most commonly seen fever syndrome and is significantly associated with ethnicity. Although it has been known about for a long time, it was first mentioned in the literature in 1908 by Janeway and Mosenthal, who reported recurrent fever and abdominal pain in a 6 year-old Jewish girl (Sohar et al., 1967). Its first definition as a disease was based on a case report, published under the title "benign paroxysmal peritonitis" by the allergy specialist Siegal from New York, as a compilation of Jewish patients with similar complaints. The periodical fever definition was first used by Reimann in 1948, and Sohar et al (1967) defined the disease as FMF in 1955. Prior to the use of colchicine, the disease was fatal, but a new era in the treatment of FMF began with the introduction of colchicine in 1972. In a number of studies, it has been shown that this drug not only has an effect on the symptoms, but also affects the development of amyloidosis (Ozcakar, 2006). In 1992, it was reported that the abnormality associated with FMF is found on chromosome 16, and the gene responsible for the disease was identified in 1997 (International FMF Consortium, 1997). The disease is accompanied by a marked decrease in quality of life due to the effects of attacks and subclinical inflammation in the period between attacks (Ozcakar, 2006). Untreated or inadequately treated patients run the risk of amyloidosis, which is an important cause of morbidity and mortality ***(Livneh, 1996).***

Epidemiology

Familial Mediterranean fever shows a marked ethnic distribution. The disease is most frequently observed in Turkish, Armenian, Jewish and Arabic communities.