PHENOTYPE-HETEROZYGOUS GENOTYPE CORRELATIONS IN CHILDERN SUFFERING FROM FAMILIAL MEDITERRANEAN FEVER

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ABSTRACT

The present study was not only to review clinical and demographic features of Familial Mediterranean Fever patients but also to investigate whether there is a phenotype–genotype correlations in the same patient population. Medical records of 65 patients from Rheumatology clinic at specialized Cairo University Pediatric Hospital were retrospectively reviewed and classified into two groups according to mutations: homozygous and heterozygous groups. Our data indicate that presentation with severe phenotype in heterozygous patients should be further analyzed for less common second MEFV mutation using gene sequencing.

Key words:

Familial Mediterranean Fever

Clinical presentations

Phenotype-Genotype correlation

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List of Abbreviations

AA	Amyloid A
AML	Acute myelogenous leukemia
ANCAs	Anti-neutrophil cytoplasmic antibody
ASBO	Adhesive small bowel obstruction
ASO	Antistreptolysin O
BD	Behcet Disease
C5a	Complement 5a
CAPS	Cryopyrin associated periodic syndrome
CIAS1	Chronic infantile, neurological, cutaneous,articular syndrome
CRP	C- reactive protein
CT	Computed tomography
ELA2	Mutations in the human neutrophil elastase gene
ESR	Erythocyte sedimentation rate
FMF	Familial Mediterranean fever
HIDS	Hyperimmunoglobulinemia D and periodic fever syndrome
HLA	Human leukocyte antigen
HSP	Henoch-Schonlein Purpura

Ig	Immunoglobulin
IL	Interleukin
JRA	Juvenile rheumatoid arthritis
MDS	Myelodysplasia
MEFV	MEditerranean FeVer
MRI	Magnetic resonance imaging
NK	Natural killer
NSAIDS	Non-steroidal anti-inflammatory drug
PAN	Polyarteritis nodosa
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome
PFMS	Protracted febrile myalgia syndrome
PID	Pelvic inflammatory disease
PUO	Pyrexia of Unknown Origin
SAA1	Serum amyliod A1
SLE	Systemic lupus erythematosus
TNF	Tumor necrosis factor
TRAPS	Tumour necrosis factor receptor-associated periodic syndrome

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INTRODUCTION

Familial Mediterranean Fever (FMF), is an autosomal recessive disease that affects commonly populations of Armenian, Arab, Sephardic Jewish or Turkish origin and it is not uncommon in other Mediterranean populations, such as Italians, Spanish, Portuguese, French, and Greeks. The historic trace-back of the shared haplotype and common mutations suggests a common ancestor at least 2000 years ago, when most of these populations were living together in the eastern Mediterranean basin ***(Kastner et al., 2005).***

Although an unexplained clinical heterogeneity is not uncommon, the diagnosis of the disease, which is based on various sets of clinical criteria**,** can be confirmed by molecular means that provides the only objective diagnostic criterion in the absence of functional test ***(Livneh et al., 1997)***.

In 1997 the gene linked to FMF, called MEFV, was cloned from to chromosome 16p using positional cloning and some of the mutations associated with the disease were identified ***(Ben-Chetrit and Levy, 1998).***

The gene comprises 10 exons, spanning approximately 15 kb of genomic DNA and encodes a 781 amino acid-long protein. All four of the initial FMF-associated mutations in MEFV were in exon 10, and even now, with over 166 mutations having been identified **(Milhavet et al., 2008*).***

Livneh et al. (1997) referres to that exon 10 remains the major site of mutations with a smaller cluster in exon 2 .

Nearly all of the known FMF-associated mutations encode conservative missense changes. The most frequent mutations (M680I, M694V, V726A, M694I and E148Q) are found in more than two thirds of cases ***(Yilmaz et al., 2001).***

The incomplete penetrance and the varying expression of FMF suggest the presence of other, possibly genetic, factors that could influence the expression of illness (***Medlej-Hashim et al., 2005***).

Colchicine is the preferred drug for FMF ***(Samuels et al., 1998).***

Genotype-phenotype correlation, thoroughly studied over the past few years, suggested that mutations located within the mutational hotspots in codons 680 and 694 are associated with severe disease, early onset, high frequency of attacks, the necessity of a high dose of colchicine to control attacks, and frequent occurrence of amyloidosis in untreated patients ***(Langevitz et al., 2001).***

AIM OF THE WORK

- To study variable clinical presentations of FMF patients.
- To correlate the various genotypes of FMF to the clinical presentation.
- To detect phenotype-heterozygous genotype correlations.

FAMILIAL MEDITERRANEAN FEVER

Definition:

Familial Mediterranean Fever (FMF), is an autosomal recessive condition, affects more than 100,000 people worldwide, and as such, is the most common of the hereditary periodic fevers. The disease is most prevalent among non-Ashkenazi Jews, Arabs, Turks and Armenians, with carrier frequencies of 1:5 to 1:16, 1:5, 1:5, and 1:7, respectively. Yet, it is observed worldwide due to the extensive population movements of the 20th century ***(Kastner et al., 2005).***

The disease course can be complicated by development of amyloid deposition and organ failure which can be fatal ***(Medlej-Hashim et al.,2004)***

History:

The affected population began to appear after the 2nd world war. They were discussed under a variety of names in publication since the early 1900's. The 1st case reported was a description by **Janway and Mosenthal**, 1908 of a 16 year old Jewish girl suffering from recurrent episodes of fever, leucocytosis and abdominal pain where they termed it "unusual paroxysmal syndrome". It was only documented by **Siegal** in 1945 as a new clinical entity when he drew attention to the recurrent abdominal attacks of these patients and discussed 10 cases of "benign paroxysmal peritonitis". **Reimmann** in 1951 used the term "periodic disease" .The extensive studies of **Heller et al**, in 1955 and 1958 and **Sohar et al**, in 1967 followed by

Schwabe et al, in 1974 used the term "Familial Mediterranean Fever" another term recurrent polyserositis was used in 1961 to describe the disease by **Ehrenfeld and Eliakim**. The effect of Colchicine on the symptoms was reported by **Goldfinger** in 1972 and **Eliakim and Linch** in 1973 ***(Eliakim,1996: Mijatovic et al.,2003).***

Racial distribution:

Although FMF is common among people of Mediterranean ancestry, clinical symptoms have been well documented in people who lack any Mediterranean background ***(Takahashi et al., 1992)***

It is a worldwide disease due to widespread inter-continental travel in 20th century ***(Touito et al., 2001).***

Etiology and pathogenesis:

Numerous hypothesis and pathogenic mechanisms considering the etiology of FMF have been suggested since fever and inflammation are the major signs of the disease of an infectious etiology such as Brucella and Tuberculous bacilli, have been implicated as a causative agent in FMF. But no infectious agents were detected in many extensive studies for FMF cases ***(Wolff , 1992).***

More studies proved that physical and emotional stress and a high fat diet may trigger the attacks and affect the frequency and severity of the attacks ***(Wolff, 1992).***

The etiology of FMF was expected to be linked to its prevalence in distinct ethnic groups, mode of inheritance and clinical

picture as an inborn error of metabolism was a cause. However, there was no evidence to support this hypothesis ***(Heller et al.,1958)***.

Some of the earlier reports suggested that FMF could be explained by an allergic process but no data has been supported that hypothesis ***(Majeed and Barakat , 1998).***

An autoimmune pathogenecity was studied as FMF has clinical manifestations resembling SLE (fever, arthritis and serositis) however, no autoantibodies were detected and the disease didn't respond to corticosteriods and other immunosuppressive. These finding suggested that it is highly unlikely that FMF belongs to the family of the autoimmune collagen disease ***(Swissa et al., 1991)***

Some laboratories have studied the abnormalities in the immune system seen in patients with FMF however, these changes are now considered secondary to and not the primary defect in the pathophysiology of FMF ***(Ehrenfeld et al.,1997)***

Of special interest are the studies that showed evidence of C5a inhibitor deficiency in peritoneal and synovial fluids of patients with FMF ***(Matzner et al ., 1990)***.

Patients with FMF have been found to have higher amounts of natural killer (NK) cells, decreased numbers of helper and suppressor T-cells and produce elevated levels of inerleukin-1 (IL-1) and lower levels of IL-2 as compared to normal controls ***(Melamed et al.,1991).***