Familial Mediterranean Fever Gene

**Alternative Names**
- MEFV
- Pyrin
- Marenosrin

**Record Category**
- Gene locus

**WHO-ICD**
- N/A to gene loci

**OMIM Number**
- 608107

**Mode of Inheritance**
- Autosomal recessive

**Gene Map Locus**
- 16p13

**Description**
MEFV is the gene responsible for familial Mediterranean fever, an autosomal recessive condition mostly seen in Jews, Armenians, Arabs, and Turks, characterized by recurrent episodes of painful inflammation in the abdomen, chest, and/or joints. The gene expresses itself mostly in peripheral blood leukocytes, particularly in mature granulocytes and their precursors. The expressed protein, pyrin, is involved in down-regulation of the inflammatory response to a stimulus, when the inflammatory response is no longer needed. This is accomplished by the regulation of caspase-1 activation and interleukin-1 production. Mutations in the gene lead to faulty pyrin production, and a prolonged inflammatory response caused by loss of control on inflammation. The inflammation may also lead to excess production of amyloid A protein and its accumulation in the kidneys, resulting in kidney failure.

**Molecular Genetics**
The MEFV gene is located on chromosome 16p13.3, and consists of 10 exons. The pyrin protein is 781 amino acids long. More than 80 mutations in the gene have been identified so far; at least 17 of them from the Mediterranean populations. The most common of them is a M694V mutation, which has been shown to be associated with an increased risk for developing amyloidosis.

**Epidemiology in the Arab World**

**Algeria**
Belmahi et al. (2006) described the frequencies of the MEFV mutation spectrum among 209 North African Arab patients, clinically diagnosed with FMF. The studied group included 85 Algerian patients. Exons 5 and 10 of the MEFV gene were amplified by PCR and sequenced, while the E148Q mutation on exon 2 was detected by PCR-RFLP using Ava I. In 34% of the cases, the disease could be confirmed by the presence of two MEFV mutations, while in 12% only one mutation could be detected. The M694I mutation was the most common in this population (80%), whereas the M694V mutation was detected in only 5% of the patients. Belmahi et al. (2006) hypothesized that the M694I mutation is an old mutation and is localized to the region populated by Arabs who were originally Berbers. Rare alleles detected included M680I, E148Q, V726A, and A744S. Belmahi et al. (2006) tried to estimate the MEFV mutation carrier frequency rate among a control group of 113 normal individuals, including 31 Algerians. Not a single M694V mutation could be detected, arguing against a heterozygote advantage in this population [See also: Morocco, Tunisia > Belmahi et al., 2006].

**Iraq**
Similarly, Kogan et al. (2001) investigated the carrier rate of the most common MEFV mutations among different Jewish groups. Screening for the E148Q, V726A, and M694V mutations was performed in 300 Ashkenazi, 101 Iraqi, and 120 Moroccan Jews, with a resulting overall carrier frequency in the 3 ethnic groups, respectively, of 14%, 29%, and 21%. The frequency of subjects with 2 MEFV mutations who did not express FMF, the so-called phenotype III, was 1 in 300 in Ashkenazi Jews and 1 in 25 in Iraqi Jews, exceeding the reported rate of overt FMF in these ethnic groups by 40- to 240-fold.

[See also: Morocco > Gershoni-Baruch et al., 2001]

**Jordan**

Medlej-Hasim et al. (2005) undertook a study among a group of 55 Jordanian FMF patients in order to determine the frequencies of MEFV mutations. Restriction enzyme analysis was used to identify 14 MEFV mutations in the patients, followed by single strand conformation analysis. Of the patients, 29% did not have any mutation, and 71% were homozygous or compound heterozygous mutants. M694V was the most frequent allele in the patients with mutations (34.6%), followed by V726A (19.2%), M680I (12.8%), E148Q (6.4%), and M694I (2.6%). Although homozygotes were found in excess in the population, once the inbred homozygotes were removed from the data, no such excess was observed. A few patients showed the rare mutations such as: A744S, T267I, and F479L.

[See also: Lebanon > Medlej-Hashim et al., 2001 and 2004].

**Lebanon**

Mansour et al. (2001) undertook a study to determine the spectrum of MEFV mutations in different communities in Lebanon and to analyze their genotype-phenotype relationships. Seventy nine Lebanese patients, suffering from familial Mediterranean fever, and belonging to Moslem (Sunnite, Shiite and Druze) and Christian (Maronites, Greek orthodox, Greek catholic, Syriac, and Armenian) communities, were studied. Consanguinity was seen in 33% of the patients, and 37% had a positive family history of the disease. It was seen that Muslim patients had an earlier onset and higher frequency of arthritis. Only patients belonging to the Druze, Shiite, or Armenian groups showed amyloidosis. PCR-restriction digestion, DGGE, and sequencing were performed. Of the 143 alleles tested, 67% were positive for one of the 15 mutations tested; the remaining 33% were negative. The most frequent mutation, overall, was found to be the M694V mutation, followed by V726A, M694I, E148Q, and M680I. However, different communities showed different mutation profiles. The M694V was present in 50% and 83% of the alleles in the Shiites and Armenians, respectively, but was totally absent in the Druzes, Greek orthodox, Greek Catholics, and Maronites. The M694V allele was also seen to be associated with the most severe phenotype. In fact, association between a mutation at position 694 and development of amyloidosis was found to be statistically significant, with all patients with amyloidosis carrying two mutations in the codon (either M694V or M694I). Armenians, Shiites, and Druzes, with the highest frequencies of M694V and M694I alleles showed the most severe phenotypes. However, two patients with M694V/M694V and M694I/M694I genotype showed no signs of amyloidosis, indicating the existence of a second genetic factor providing a predisposition to the development of amyloidosis.

Delague et al. (2004) compared the specificity, sensitivity, and throughput capacity of conventional fluorescent cycle sequencing, with multiplex DNA amplification and reverse hybridization technique for detection of MEFV mutations. DNA from 100 Lebanese patients diagnosed with FMF was analyzed for mutations in exons 2, 3, 5, and 10; both by DNA sequencing, as well as by using the reverse hybridization dependent FMFStripAssay for simultaneous detection of 12 MEFV mutations. A total of 15 different mutations were identified in the patients. Sequencing identified 71% of the 200 tested alleles; 97% of these were identified by the reverse hybridization method too. Three additional mutations could be identified only by sequencing. Mutations in close proximity, such as M680I(G/C) and M680I(G/A), M694V and M694I, could also be distinguished by the FMFStripAssay.

Medlej-Hashim et al. (2001) attempted a genotype-phenotype correlation in FMF. They studied 147 unrelated Lebanese and Jordanian FMF patients and correlated IgD plasma level with specific phenotypic characteristics. The IgD plasma distribution in patients was similar to that of healthy subjects, which was not in favor of a direct effect of MEFV mutations on serum IgD levels. However, homozygote status for the M694V mutation (odds ratio, 6.25) and to a lesser extent V726A (OR, 2.2) increased the risk of higher IgD level when compared to other genotypes. Patients with higher IgD levels were more likely to suffer...
Three years later, Medlej-Hashim et al. (2004) studied a group of 30 Lebanese and Jordanian FMF patients from 24 families, to understand the correlation between the MEFV genotype and occurrence of amyloidosis. The patients were compared to a control group of 40 non-amyloidotic FMF patients. Consanguinity was seen in 50% of the amyloidotic, and in only 20% of the non-amyloidotic patients, suggesting a recessive modifying aspect of the phenotype. The individuals were screened for 14 MEFV mutations known to be present in the Lebanese population. SAA1 (serum amyloid A1) and MICA (major histocompatibility complex class I chain-related gene A) gene polymorphisms were also tested. A group of six siblings in the group with amyloidosis showed homozygous M694V genotype. M694V was the most frequent allele in this group (67%), followed by V726A (12%), and M964I (8%). In the group without amyloidosis, the same mutations showed frequencies of 25%, 39%, and 15% respectively. The M694V mutation, therefore, was shown to be significantly associated with development of amyloidosis in FMF patients. Medlej-Hasim et al. (2004) were also able to demonstrate the association of the SAA1-alpha allele with the severe phenotype, SAA1-beta and gamma alleles with FMF without amyloidosis, and the lack of any significant association of amyloidosis with the MICA alleles.

A group of 558 Lebanese FMF patients were studied by Medlej-Hasim et al. (2005) in order to determine the frequencies of MEFV mutations. The control group consisted of 200 normal individuals. Restriction enzyme analysis was used to identify 14 MEFV mutations in the patients, followed by single strand conformation analysis. Of the patients, 41% did not have any mutation, 19% had one mutation, while the remaining 40% were homozygous or compound heterozygous mutants. Homozygotes were found in excess in the population, which remained even when the inbred homozygotes were removed from the analysis. M694V was the most frequent allele in the patients with mutations (30.3%; absent in controls), followed by V726A (19.4%; 4% in controls), M694I (12.8%; absent in controls), E148Q (8.3%; 5% in controls), and M680I (7.4%; 0.5% in controls). Medlej-Hasim et al. (2005) were of the opinion that the excess of homozygotes and the higher frequency of severe alleles in the patients could be due to a selection bias in the census of the patients. They also hypothesized that the severity of the phenotype of individuals with mutations affecting codon 694 could be due to protein dimerization defects. A few patients showed the A744S, R653H, and L692del mutations in the heterozygous state. Three new mutations were also identified in this population- T1771 (T530C-T), S108R (C322A-C), and E474K (A1420G-A). None of the controls showed the presence of these mutations, indicating their pathogenicity.

Morocco
Gershoni-Baruch et al. (2001) examined 146 unrelated FMF patients of Jewish and Arab descent for for 5 common MEFV gene mutations (M694V, M680I, E148Q, V726A, and M694I). The mutations accounted for 91% of FMF chromosomes. The overall carrier rates for the 4 most common FMF mutations (M680I, M694V, V726A, and E148Q) were 1:4.5 in 407 Ashkenazi Jews, 1:4.7 in 243 Moroccan Jews, 1:3.5 in 205 Iraqi Jews, and 1:4.3 in 318 Muslim Arabs. The overall frequency of low-penetrant mutations E148Q and V726A indicated that most individuals who have a genetic diagnosis of FMF remain asymptomatic.

Belmahi et al. (2006) described the frequencies of the MEFV mutation spectrum among 209 North African Arab patients, clinically diagnosed with FMF. The studied group included 87 Moroccans. In 38% of the Moroccan patients, FMF could be confirmed by the presence of two mutant alleles, while only one mutation could be detected in 10% of the patients. Unlike among the Algerian population, the most prominent mutation in this population was M694V (49%) followed by M694I (37%). Rare alleles detected in this population included M680I, E148Q, and M680L. Among the controls, which included 50 Moroccans, only one was found to be heterozygous for the M694V mutation [See also: Algeria, Tunisia > Belmahi et al., 2006].

[See also: Iraq > Kogan et al., 2001].

Tunisia
Belmahi et al. (2006) described the frequencies of the MEFV mutation spectrum among 209 North African Arab patients, clinically diagnosed with FMF. The studied group included 37 Tunisians. The FMF could be confirmed in 19% of the patients as caused due to two detectable mutations, FMF, while only one mutation could be detected in 16% of the patients. Just like among the Moroccan population, the most prominent mutation in this population was M694V (10%) followed by M694I (5%). Belmahi et al. (2006) proposed that the M694V mutation arrived to the Maghreb region with migrations from the Middle
East. Rare alleles detected in this population included M680I, E148Q, and A744S [See also: Algeria, Morocco > Belmahi et al., 2006].

References


Related CTGA Records
Familial Mediterranean Fever

External Links
http://www.genecards.org/cgi-bin/carddisp.pl?gene=MEFV&search=mefv
http://www.genetests.org/profiles/fmf
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=342

Contributors
Pratibha Nair: 24.4.2007
Ghazi O. Tadmouri: 10.1.2007
Pratibha Nair: 10.7.2006