Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent episodes of fever, peritonitis, pleuritis, synovitis, and complications of amyloidosis. This autosomal recessive condition is usually caused by mutations in both alleles of MEFV gene. Correlation between genotype and phenotype in individuals affected by the (FMF) has long been a subject of discussion. Studies from different populations have suggested significant variance in symptoms and pathogenicity of the disease with regards to corresponding mutations. Over thirty mutations in MEFV gene, which codes for a protein called Pyrin, have been attributed to causing FMF. The most prevalent and common mutations in different populations are M694V, V726A, M680I, E148Q, R761H, and M694I. The symptoms and severity of the inflammation varies depending on type and the quantity of the mutation. A good example of high penetrance is M694V mutation, which causes the most frequent attacks and amyloidosis.

Prevalence

FMF in the Mediterranean Populations

The frequencies of known MEFV mutations among patients with FMF are increasing on a daily basis among four major ethnic groups of Mediterranean region, Armenians, Jews, Arabs, and Turks. Also residents of South European countries such as Italy, Greece, Spain, and France have been shown to suffer from the FMF.

In the past decade genetic testing has allowed us to identify the mutations responsible for FMF and cure the disease as well as prevent future complications. Table 1 shows the results of FMF mutation studies four major ethnic groups, their symptoms, and risks if remain undiagnosed.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Ethnic group</th>
<th>Phenotype assessed</th>
<th>Relation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M694V/M694V</td>
<td>Non-Ashkenazi Jews</td>
<td>Arthritis and pleuritis, Amyloidosis</td>
<td>Increased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>Armenians</td>
<td>Arthritis, Amyloidosis</td>
<td>Increased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>Non-Ashkenazi Jews, Arabs</td>
<td>Severity (no specific index), Amyloidosis</td>
<td>Increased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>North African Jews, Armenians, and Turks</td>
<td>Amyloidosis</td>
<td>Increased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>Non-Ashkenazi Jews</td>
<td>Amyloidosis</td>
<td>Increased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>Mixed Jewish</td>
<td>Tel Hashomer severity score</td>
<td>Increased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>Mixed Jewish</td>
<td>Protracted febrile myalgia</td>
<td>Increased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>Turks</td>
<td>Severity (12 variables), Amyloidosis</td>
<td>No relation</td>
</tr>
<tr>
<td>M680I/M680I</td>
<td>Turks</td>
<td>Arthritis</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>M694V/M694V</td>
<td>Arabs</td>
<td>Amyloidosis</td>
<td>Increased risk</td>
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</tr>
</tbody>
</table>
A major study investigated the rate of the most common MEFV mutations among all ethnic groups suffering from the FMF (Figure 2).
Criteria for Testing

Family History
Fever
Abdominal pain
Skin eruption
Chest pain
Joint pain
Amyloidosis
Painful breathing
Myalgia
Upper back/shoulder pain

FMF diagnosis:
Prevents unnecessary surgeries such as appendectomy
Provides simple treatments for all FMF symptoms (Colchicine)
Prevents future complications such as amyloidosis and renal failure

The spectrum of MEFV mutations

Figure 4 The spectrum of MEFV mutations. The MEFV gene is composed of 10 exons. Twenty-nine disease-associated mutations have been recorded so far. The five most frequent mutations are underlined. Mutations in hot spots are in bold letters. Deletions are with italics letters. The sole nonsense mutation is boxed (reference 6).
DNA Sequencing is the technique to decode the patients’ DNA and print them on paper (Figure 5). In normal individual the peak for nucleotide Guanine (G) is a single black peak, on the other hand in heterozygous carrier there are two peaks on the same level hence the nucleotide shows an N. In homozygous patients there is one peak but it is not a Guanine, it is mutated to Cytosine (C).

We at Makgene.com take great pride in being the first Genetic Testing service to offer complete sequence and analysis of the mutations responsible for FMF. Please do not hesitate to contact us with any questions regarding medical genetic testing.

Morava Inc.
Makgene.com
Tel: (818)244-7000
info@makgene.com

Prepared by: Mike M Moradian, Ph.D., CLS

CONCLUSIONS

- Molecular analysis of more than 5350 patients has demonstrated direct correlation between the clinical severity and spectrum of MEFV mutations, including development of renal amyloidosis.

- Frequency of the mutations of MEFV gene is high in all affected ethnic groups, genetic testing is recommended for all siblings of FMF patients and if any symptoms present.

References