

# Familial Mediterranean Fever

## **Disease characteristics**

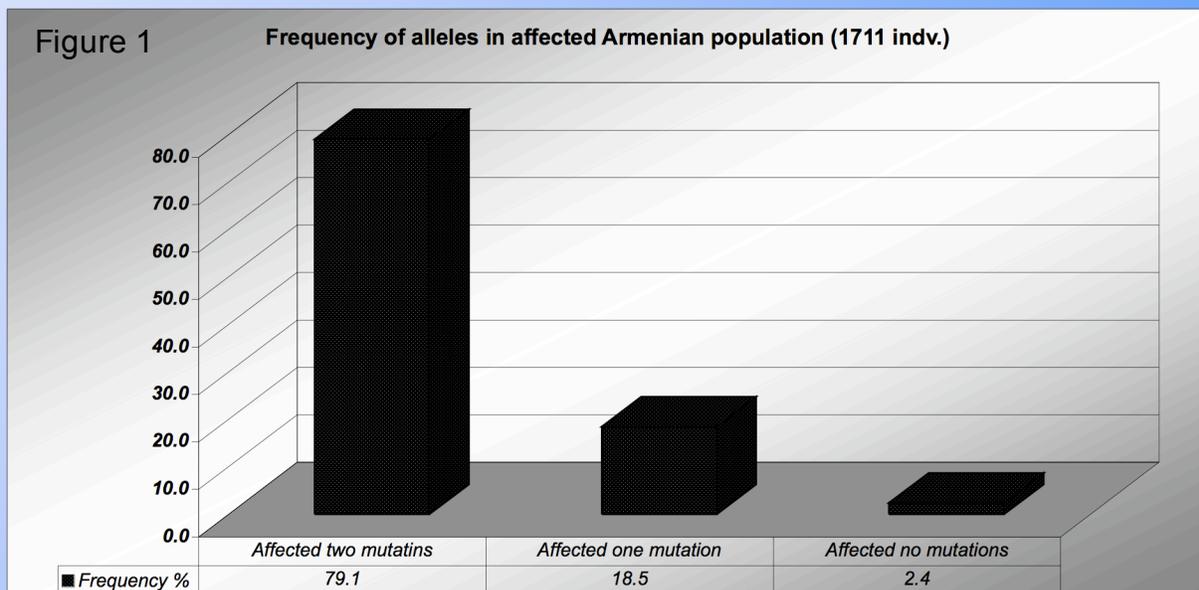
Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent episodes of fever, peritonitis, pleuritis, synovitis, and complications of amyloidosis.<sup>1</sup> This autosomal recessive condition is usually caused by mutations in both alleles of MEFV gene.<sup>2,3</sup> 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.<sup>4,5</sup> 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.<sup>6</sup> 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.<sup>4</sup>

## Prevalence

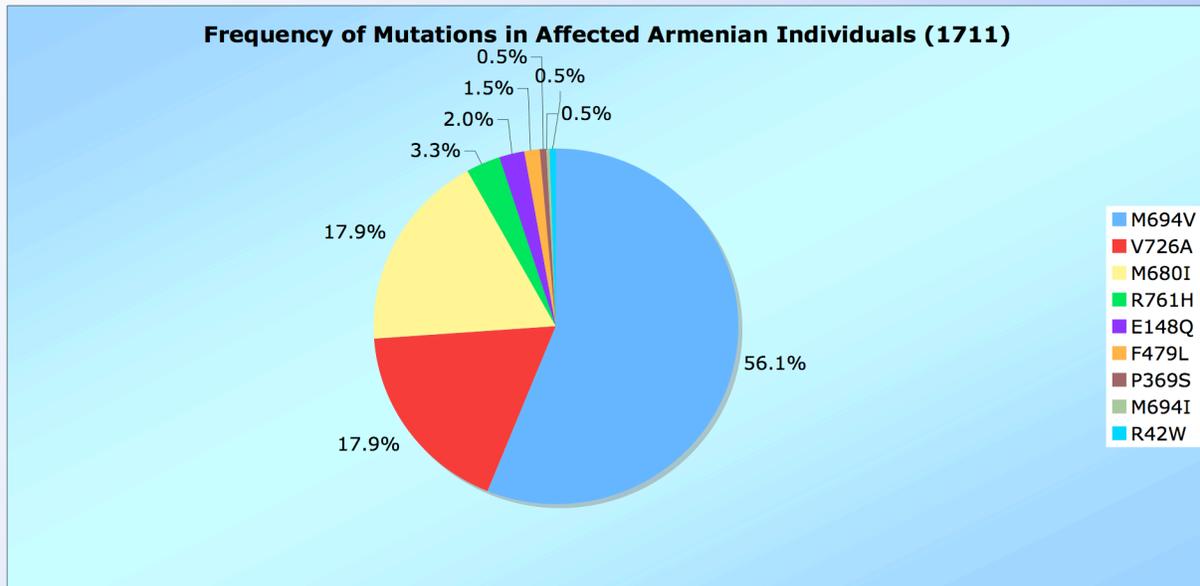
### *FMF in the Armenian Population*

The frequencies of known MEFV mutations among the Armenian patients with FMF represents a substantial percentage of the referrals to the Medical Genetics Center in Yerevan. Figure 1 shows the results of FMF mutation studies in 1711 Armenian patients from a pool of over 6000 known FMF cases. On average there are over 10 new cases per day that are referred to the center for genetic screening.

The overall carrier frequency calculated from mutation frequencies was about 31%, more than twice the previous estimates. Also, 20% of the affected FMF cases are known to have one of the mutations and basically are considered heterozygous (Figure 1).

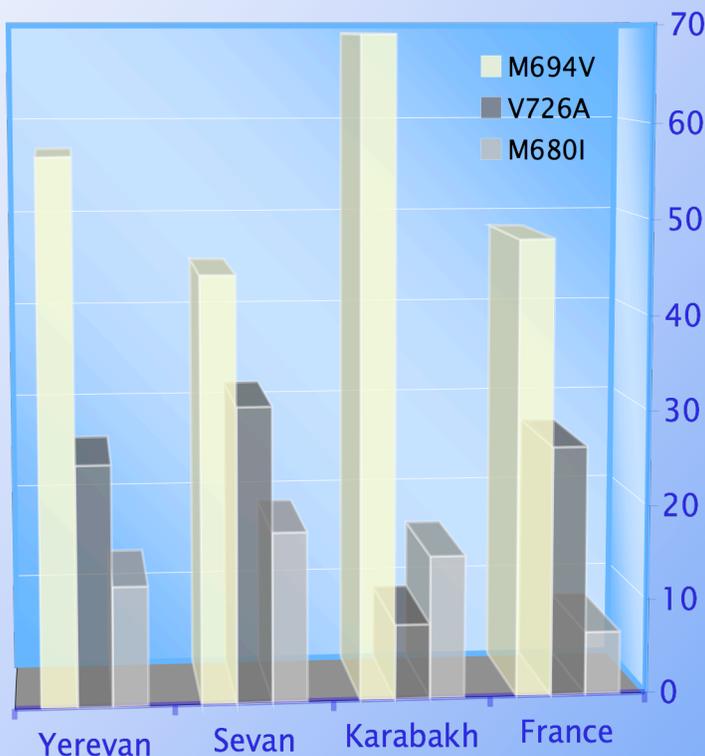


A major study investigated the rate of the most common MEFV mutations among Armenians (Figure 2). From 1711 patients who were screened for 9 most common mutations more than half were M694V genotypes, which is considered the most pathogenic mutations in FMF. The other two major groups, V726A and M680I, were evenly frequent followed by the fourth group R761H. These four groups were the only mutations, which were present in homozygous forms suggesting a significant correlation between the phenotype and mutation frequency.



Source: Center for Medical Genetics in Yerevan, Armenia.

### Percentage of FMF Mutations in Different Regions



High carrier rates result in higher FMF cases.

Figure 3- Higher than expected carrier rates for familial Mediterranean fever in various Armenian groups

FMF is known as Armenian disease where individuals of Armenian ancestry regardless of their birthplace are equally likely to be affected as individuals from Armenia. These mutations originated thousands of years ago and are present in all original and migratory Mediterranean populations.

# 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

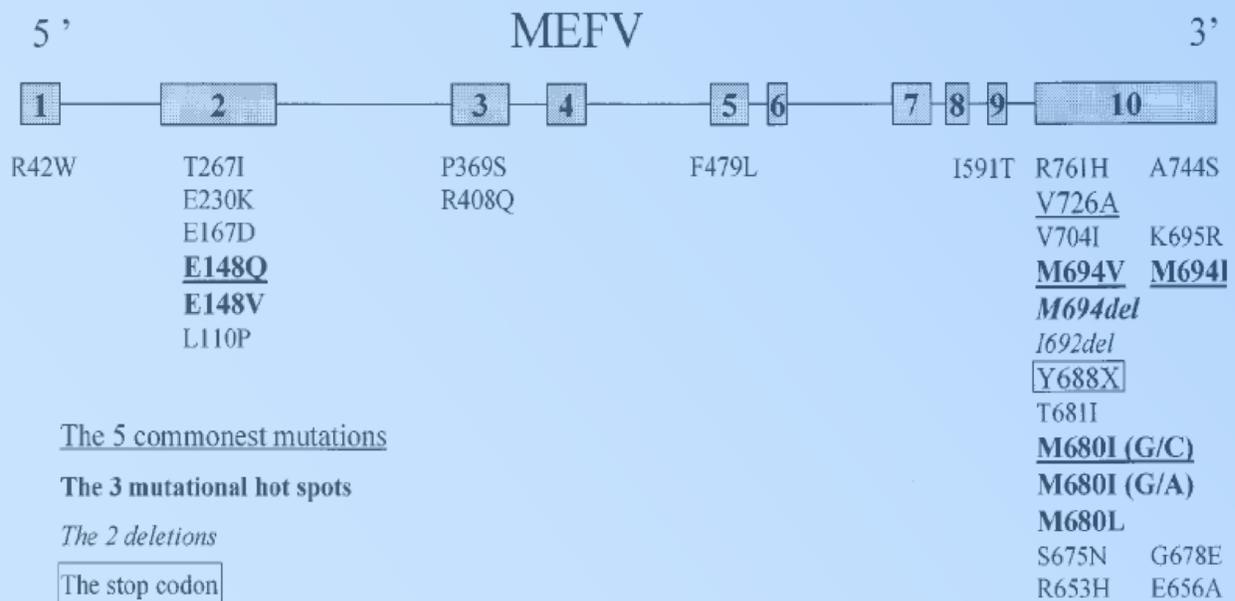
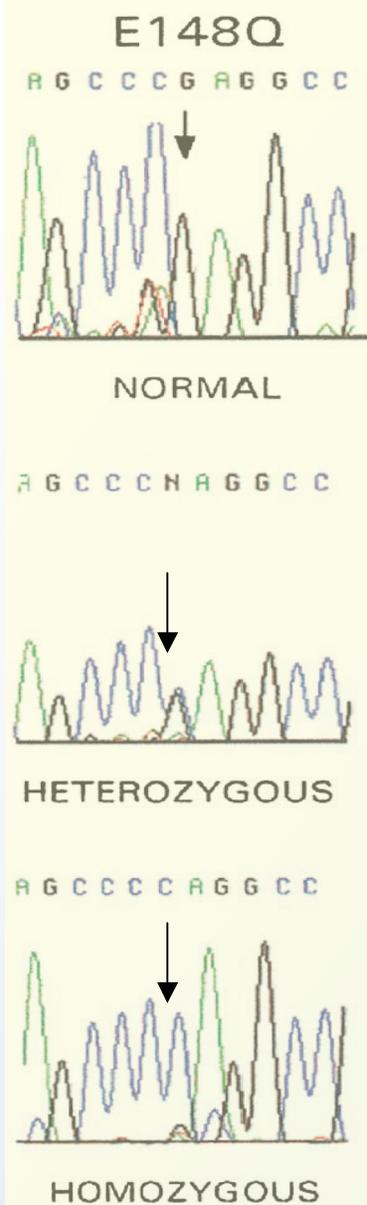


Figure 4 The spectrum of MEFV mutations. The MEFV gene is composed of 10 exons. Twenty-nine disease-associated mutations have been recorded so far. The five most frequent mutations are underlined. Mutations in hot spots are in bold letters. Deletions are with italics letters. The sole nonsense mutation is boxed (reference 6)

Figure 5



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.

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## 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 extremely high in Armenians, genetic testing is recommended for all siblings of FMF patients and if any symptoms present.

### References

- 1 Sohar E, Gafni J, Pras M, Heller H: Familial Mediterranean fever. A survey of 470 patients. *Am J Med* 1967; **43**: 227-253.
- 2 The International FMF Consortium: Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; **90**: 797-807.
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- 4 Cazeneuve C, Sarkisian T, Pecheux C *et al* Therapeutic Implications. *Am. J. Hum. Genet.* 1999; **65**: 88-97.
- 5 Aksentjevich I, Torosyan Y, Samuels J *et al*: Mutations and haplotype studies of familial Mediterranean fever reveal new ancestral relationships and evidence for a high carrier frequency with reduced penetrance in the Ashkenazi Jewish population. *Am J Hum Genet* 1999; **64**:949-962.
- 6 Touitou I: The spectrum of Familial Mediterranean Fever (FMF) mutations. *Eur J Hum Genet* 2001; **9**: 473-483.