

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.¹ This autosomal recessive condition is usually caused by mutations in both alleles of MEFV gene.^{2,3} 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.^{4,5} 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.⁶ 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.⁴

Prevalence

FMF in the Mediterranean Populations

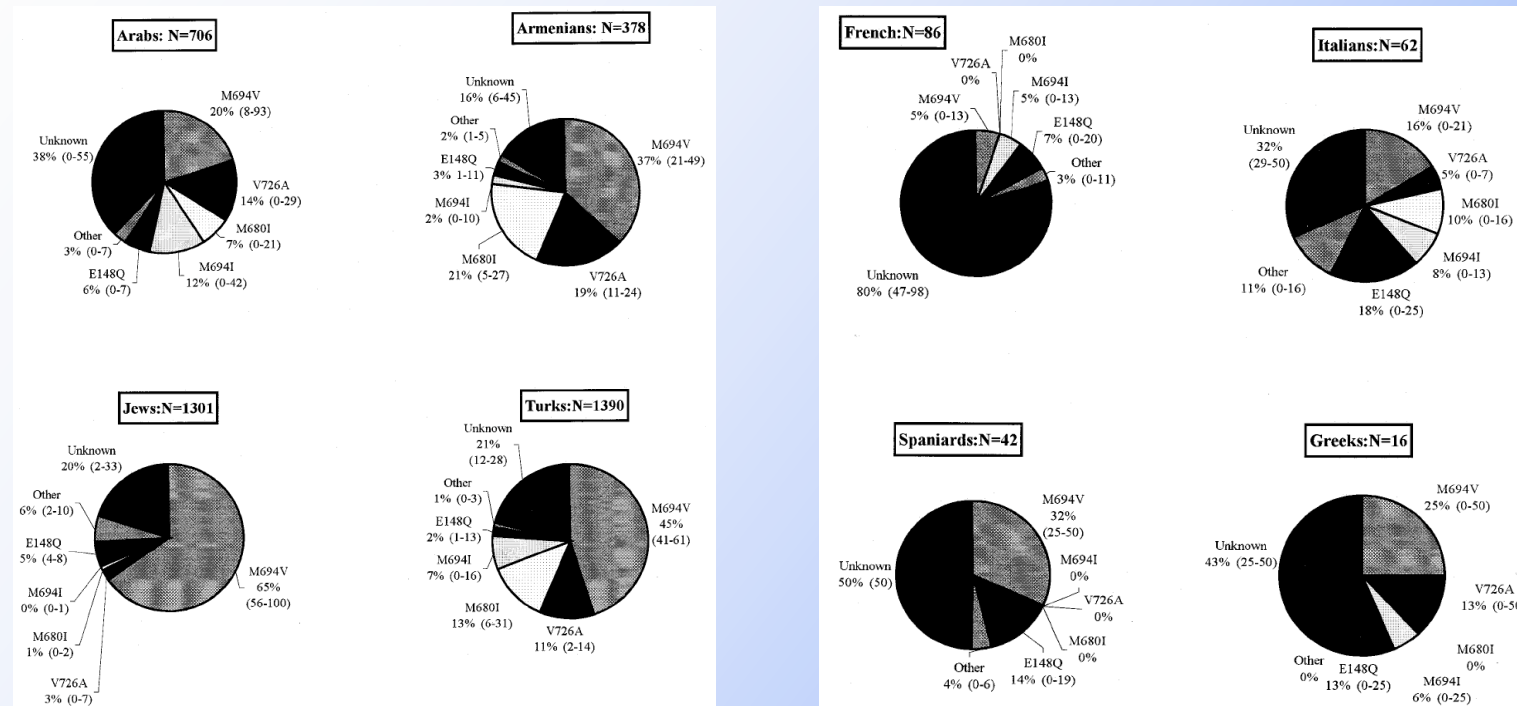
The frequencies of known MEFV mutations among patients with FMF are increasing on a daily basis among four major ethnic groups of Mediterranean region, Armenians, Jews, Arabs, and Turks. Also residents of South European countries such as Italy, Greece, Spain, and France have been shown to suffer from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

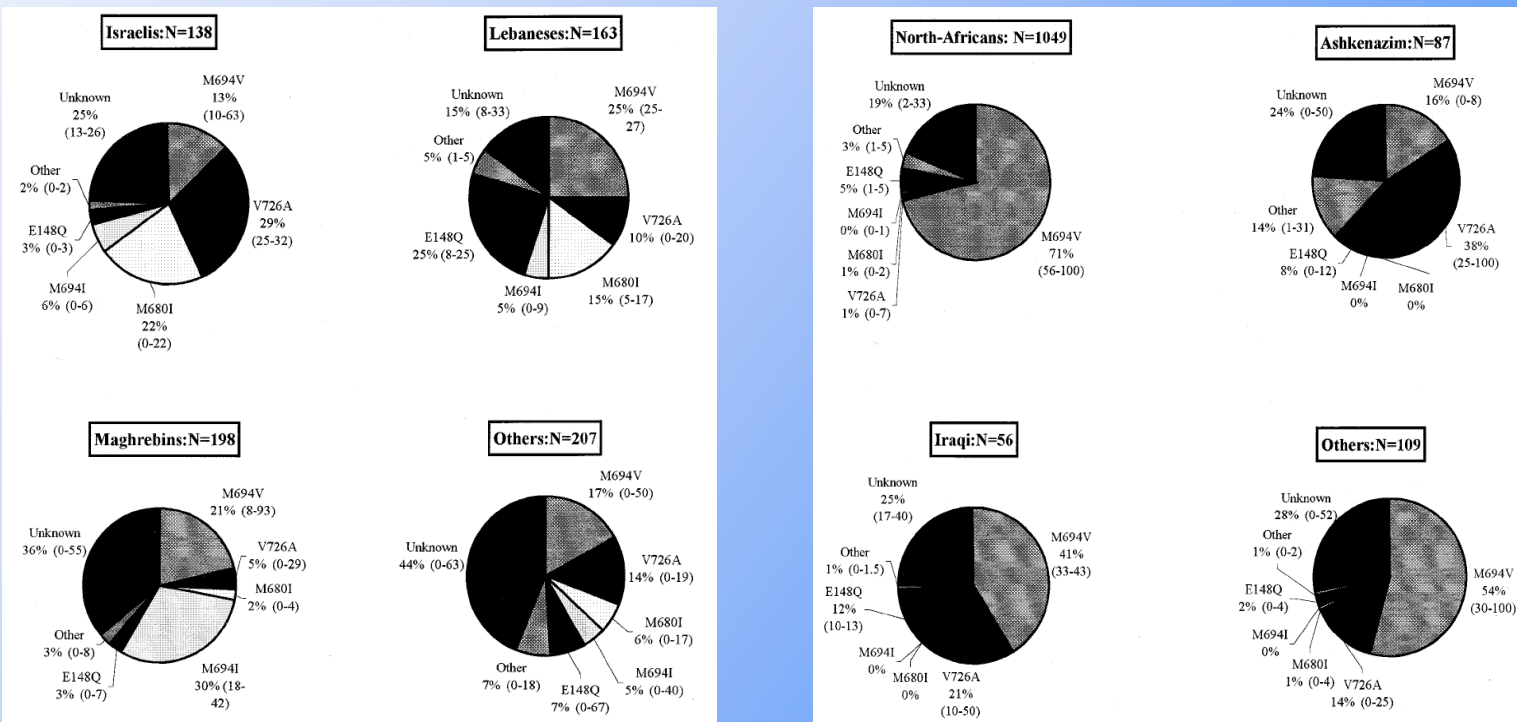
Table 1

Mutation	Ethnic group	Phenotype assessed	Relation
M694V/M694V	Non-Ashkenazi Jews	Arthritis and pleuritis	Increased risk
		Amyloidosis	Increased risk
M694V/M694V	Armenians	Arthritis	Increased risk
		Amyloidosis	Increased risk
M694V/M694V	Non-Ashkenazi Jews, Arabs	Severity (no specific index)	Increased risk
		Amyloidosis	Increased risk
M694V/M694V	North African Jews, Others	Amyloidosis	Increased risk
	Armenians, and Turks	Severity	No relation
M694V/M694V	Non-Ashkenazi Jews	Amyloidosis	Increased risk
M694V/M694V	Mixed Jewish	Tel Hashomer severity score	Increased risk
M694V/M694V	Mixed Jewish	Protracted febrile myalgia	Increased risk
M694V/M694V	Turks	Severity (12 variables)	No relation
M694V/M694V		Amyloidosis	No relation
M680I/M680I		Arthritis	Decreased risk
M694V/M694V	Arabs	Amyloidosis	Increased risk
M694I/M694I		Amyloidosis	Increased risk
M694V/M694I		Amyloidosis	Increased risk
M694V/M694V	Arabs	Severity (modified score)	Increased risk

A major study⁶ investigated the rate of the most common MEFV mutations among all ethnic groups suffering from the FMF (Figure 2).



High carrier rates result in higher FMF cases



Subgroups of Arabs

Subgroups of Jews

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

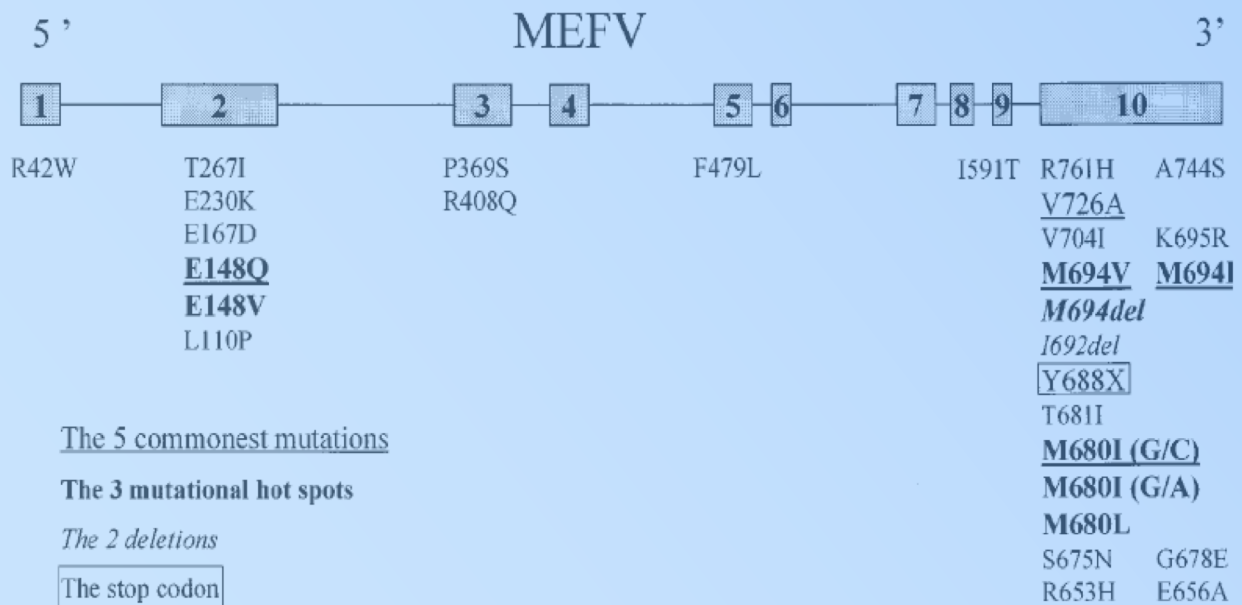
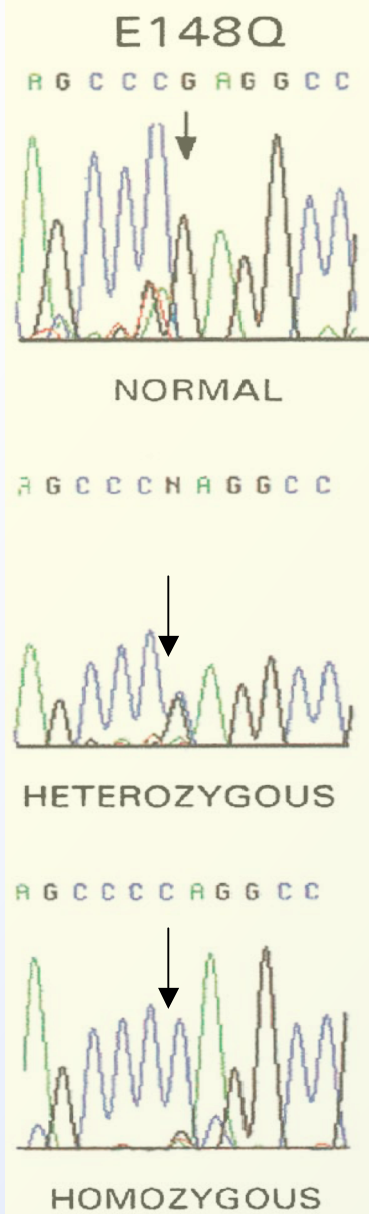


Figure 4 The spectrum of MEFV mutations. The MEFV gene is composed of 10 exons. Twenty-nine disease-associated mutations have been recorded so far. The five most frequent mutations are underlined. Mutations in hot spots are in bold letters. Deletions are with italics letters. The sole nonsense mutation 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 high in all affected ethnic groups, 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.