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 Ashkenazi Jewish Population

The frequencies of known MEFV mutations among the Ashkenazi Jewish patients with FMF represents a substantial percentage of the referrals to the New York University Medical Center. Table 1 shows the results of FMF mutation studies in a cohort of Ashkenazi Jews undergoing carrier screening for other genetic disorders at the NYU Medical Center[7].

The overall carrier frequency calculated from mutation frequencies was 21%, more than twice the 9% estimated from the frequency of FMF in the first cousins of affected probands and more than ***25 times*** a recent estimate calculated on the basis of total numbers of Ashkenazi patients with FMF in Israel[8].

Table 1- MEFV Mutation Frequencies in the U.S. Ashkenazi Jewish Population

Mutation	Positives	Total Scored	Gene Freq.	Carrierm Freq.
E148Q	23	420	0.055	0.104
E167D	0	172	0	0
P369S	10	426	0.023	0.045
M680I	0	225	0	0
M694V	0	420	0	0
M694I	0	122	0	0
K695R	6	402	0.015	0.03
V726A	9	400	0.022	0.043
A744S	1	146	0.007	0.014
R761H	0	105	0	0
Total	49	»400	0.122	0.214

Another major study[8] investigated the carrier rate of the most common MEFV mutations among different Jewish ethnic groups in Israel (Table 2). Further, an attempt was made to elucidate the possible biological advantage that the heterozygote state may confer. Three hundred Ashkenazi, 101 Iraqi, and 12 Moroccan Jews were screened for the E148Q, V726A, and M694V mutations (at least two most commor mutations per group), with a resulting overall carrier frequency in the respective ethnic group of 14%, 29 and 21%. No difference in morbidity between Ashkenazi carriers and non-carriers of MEFV mutations wa discerned, although an excess of febrile episodes in carriers of the V726A and in carriers of either V726 or E148Q was evident (P<0.02 and P<0.05, respectively).

Table 2- Relation of various diseases/conditionsof FMF gene carriage in Ashkenazi subjects

Disease or condition	Affected non carriers	Affected carriers according to genotype			
		E148Q/E148Q according	E148Q/0 to	V726A/0 genotype mutation	Any mutation
Tuberculosis (TB)	3	0	0	0	0
Family history of TB	7	0	1	1	2
Chronic lung disease	15	0	1	2	3
Febrile episodes/ year					
<2	165	1	8	18	27
2±4	17	0	2	1	3
>4	6	0	1	3	4
Malignancy	30	0	1	5	6
Ischemic heart disease	73	1	4	11	16
Diabetes	18	0	2	3	5
Pneumonia	39	0	1	5	6
Stroke	18	0	2	0	2
Hypertension	59	0	5	7	12
Urinary tract disease	11	0	1	1	2
Peptic disease	9	0	1	1	2
Autoimmune disease	9	0	0	0	0
Holocaust survisor	48	1	3	8	12
Total number of subjects	233	1	14	25	40

Source: Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine Tel Aviv University, Tel Aviv, Israel.[8]

High carrier rates result in higher FMF cases.

Table 3- **Higher than expected carrier rates for familial Mediterranean fever in various Jewish ethnic groups** (reference 9).

Table 3- Frequency of the four most common MEFV mutations among healthy individuals of Jewish ancestry

	M694V	V726A	M680I	E148Q	Mutation Frequency	Carrier Rate
North African Jews (n=200)	16/200 (0.05–0.13)	2/200 (0.00–0.03)	0 (0–0.02)	10/200 (0.02–0.09)	28/200 (0.09–0.19)	22/100 (0.14–0.31)
Iraqi Jews (n=200)	11/200 (0.03–0.10)	10/200 (0.02–0.09)	1/200 (0.0001–0.03)	23/200 (0.07–0.17)	45/200 (0.17–0.29)	39/100 (0.29–0.49)
Iranian Jews (n=200)	1/200 (0.00–0.03)	0 (0.00–0.02)	0 (0.00–0.02)	5/200 (0.01–0.06)	6/200 (0.01–0.06)	6/100 (0.02–0.13)
Ashkenazi Jews (n=200)	1/200 (0.00–0.03)	4/200 (0.01–0.05)	1/200 (0.0001–0.03)	15/200 (0.04–0.08)	21/200 (0.07–0.16)	21/100 (0.13–0.30)
Total (n=800)	29/800 (0.024–0.052)	16/800 (0.011–0.03)	2/800 (0.00–0.01)	53/800 (0.05–0.86)	100/800 (0.10–0.15)	88/400 (0.18–0.26)

95% confidence interval (CI)

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

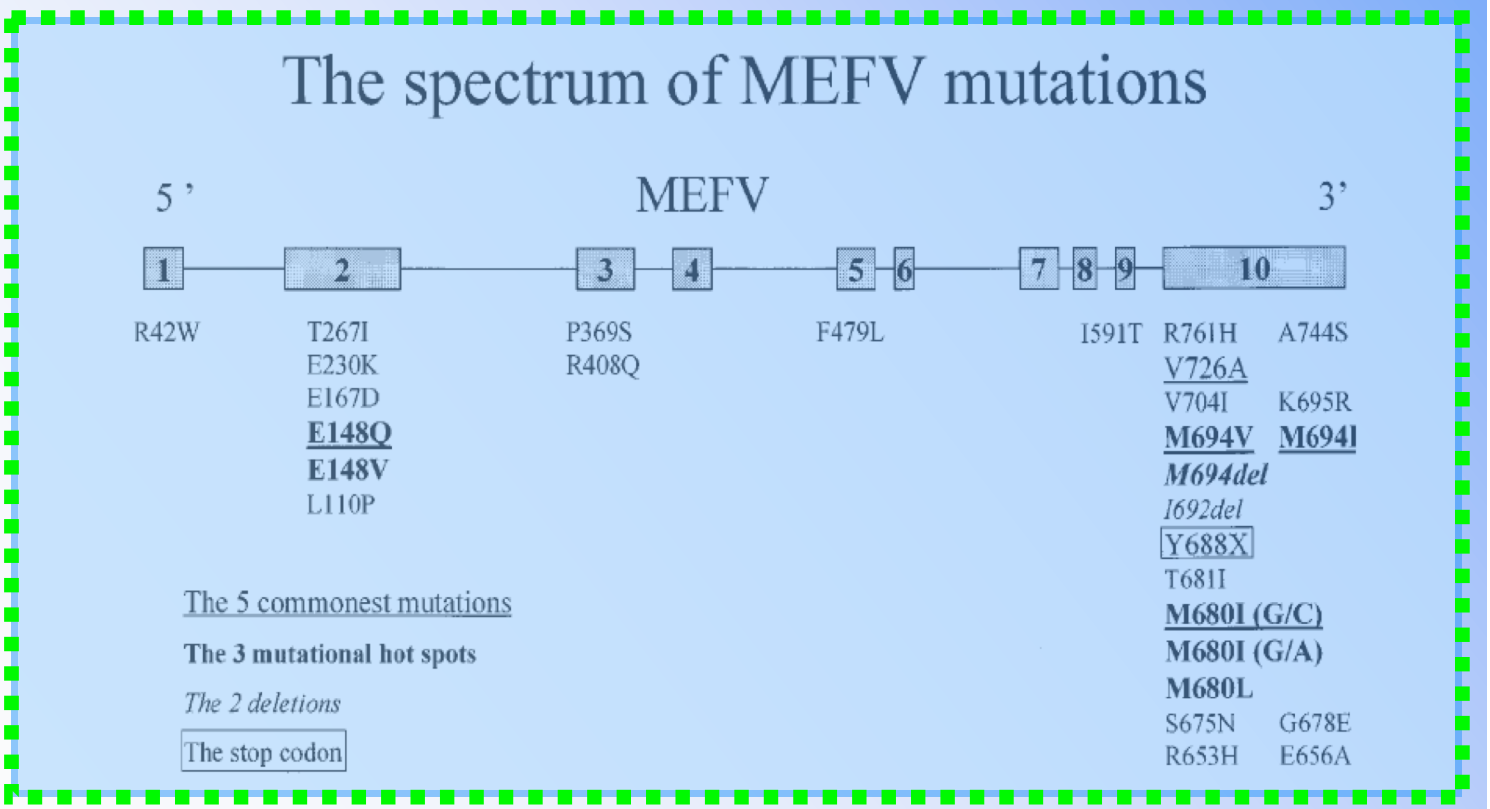

Figure 1 The spectrum of MEFV mutations. The MEFV gene is composed of 10 exons. Twenty-nine disease-associated mutations have been recorded so far. The five most frequent mutations are underlined. Mutations in hot spots are in bold letters. Deletions are with italics letters. The sole nonsense mutation is boxed (reference 6).

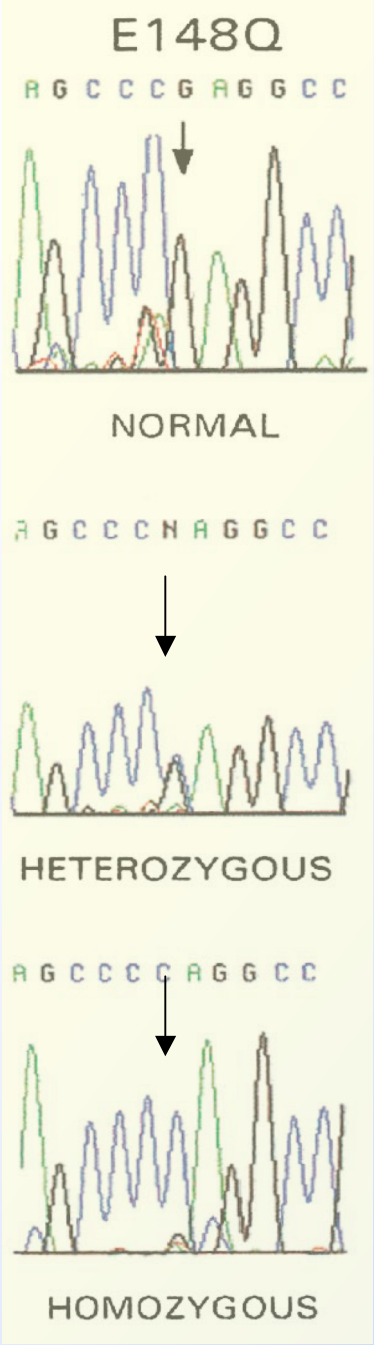

Figure 2

DNA Sequencing is the technique to decode the patients' DNA and print them on paper (Figure 2). 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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