MEFV Mutations and Phenotype-Genotype Correlations in North African Jews and Armenians with Familial Mediterranean Fever

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Abstract

Background: Familial Mediterranean fever is a genetic disease in which some characteristic gene mutations have been found.

Objectives: To analyze the phenotype-genotype correlations in North African Jews and Armenians with FMF.

Methods: We studied MEFV gene mutations and phenotype-genotype correlations in North African Jews and Armenians with Familial Mediterranean Fever living in France.

Results: M694V mutation was the most common mutation in Jews and in Armenians. Patients with M680I homozygosity or M680I/M694V compound heterozygosity had a phenotype as severe as patients with M694V homozygosity.

Conclusions: This study characterizes the phenotype-genotype in specific ethnic groups of patients with FMF.

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Familial Mediterranean fever is an autosomal recessive disorder characterized by recurring attacks of fever and serositis. Daily and life-long administration of colchicine reduces the frequency and severity of attacks and prevents amyloidosis. Amyloidosis in FMF patients is very rare in France. FMF affects primarily non-Ashkenazi Jews, Armenians, Turks and Arabs [1].

The gene responsible for FMF (MEFV) is located on the short arm of chromosome 16. More than 20 conservative missense mutations have been described [2,3]. The disease phenotypes described in affected ethnic groups and in different countries vary, raising the possibility that genetic but also environmental factors contribute to the severity of the disease.

The purpose of this study was to analyze the phenotype-genotype correlations in North African Jews and Armenians suffering from FMF. The patients were followed by two physicians (D.C., M.D) working together since 1975 in the same center.

FMF = familial Mediterranean fever

Materials and Methods

The study group comprised 106 patients with FMF (59 North African Jews belonging to 40 families and 47 Armenians belonging to 36 families). All of them were living, and most had been born, in France. We utilized the Tel-Hashomer diagnosis criteria [4] and severity score, taking into account the age at onset, the frequency of attacks, the dosage of colchicine necessary to control attacks, and the presence of arthritis (acute and protracted), erysipelas-like erythema, and amyloidosis (severity index 1 to 18) [5]. Mutations in the MEFV gene were assessed by amplifying genomic DNA of exons 10, 2, 3, and 5, followed by automatic sequencing (exon 10), restriction analysis (exons 2 and 3) and denaturing gradient gel electrophoresis (exon 5).

The statistical significance of differences between groups was calculated by the chi-square test for categorized data, and by variance analysis followed by Student's *t*-test for quantitative data.

Results

The distribution of genotypes among North African Jews and Armenians is shown in Table 1. M694V was the more frequent mutation (80% of independent alleles in North African Jews versus 35% in Armenians).

The percentage of patients with arthritis attacks, erysipelas-like erythema, splenomegaly before treatment, and colchicine requirement of more than 1 mg/day, was slightly higher among North African Jews than among Armenians. The severity score was also slightly higher among the former group. In Armenians, thoracic attacks were slightly more frequent. However, none of these differences were statistically significant. Amyloidosis was observed in two North African Jewish patients.

Table 1. The distribution of genotypes among North African Jews (n = 59) and Armenians (n = 47) with FMF

	M694V	V726A	M680I	M694I	E148Q	R761H	K695R	F479L	?
M694V	43/4	0/13	0/7		5/3	0/4	1/0		6/1
V726A		0/1	0/7			0/1		0/1	
M680I			0/2	0/1					0/1
E148Q									1/0
?									3/1

Disease parameters were compared between the 47 patients homozygous for the M694V mutation and all other patients (n = 59). In patients homozygous for the M694V mutation, the disease was significantly more severe (severity score: mean 9.2, range 3–14 vs. 6.3, range 1–13; $P = 0.00003$). Significant differences between the two groups were found for age at onset under age 6 years ($P = 0.002$), percentage of patients with arthritis attacks ($P = 0.0001$), erysipelas-like erythema ($P = 0.0009$), splenomegaly prior to treatment ($P = 0.04$), and colchicine dosage more than 1 mg/day to control attacks ($P = 0.003$).

Homozygosity for the M694V mutation was indeed more frequent in North African Jews than in Armenians (43/59 vs. 4/47). However, the severity score was not different in the two populations. Two explanations for this phenomenon could be proposed. The first is the existence of some severe genotypes that are frequent in Armenians and rare in Jews. Among the Armenian patients nine who were M680I homozygous or M680I/M694V compound heterozygous showed similar clinical data and severity score to M694V homozygous patients (mean severity score 8.9, range 7–11 vs. 9.2, range 3–14; $P = 0.45$). The second explanation is the existence of some mild genotype frequent in Jews and rare in Armenians. Among the Jewish patients 11 who were M694V/E148Q compound heterozygous or with a single M694V mutation had a very low severity score (5.6, range 3–9 vs. 5.6, range 1–10 respectively). Only four patients with these genotypes were found among the Armenians. These 15 patients had definite clinical FMF, with a long follow-up (14 years, range 0.3–34 vs. 22 years, range 19–35 respectively). Moreover, in M694V/E148Q patients, the two mutations were found by family studies not to be on the same MEFV allele.

Discussion

As already known, M694V was found to be the most common MEFV mutation in North African Jews and Armenians. The present study, which was performed in the same center, confirms that homozygosity for the M694V mutation frequently observed in North African Jews is associated with a severe form of the disease. The study further shows that a group of patients with M680I homozygosity or M680I/M694V compound heterozygosity also had a very high severity score. Moreover, genotyping was not contributory to the diagnosis (no mutation or simple heterozygosity) in 12% of patients (13/106) clinically classified as FMF, suggesting the existence of still unknown mutations or of genetic heterogeneity.

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