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Original article

Familial Mediterranean fever in a large Lebanese family: Multiple *MEFV* mutations and evidence for a Founder effect of the p.[M694I] mutation

Myrna Medlej-Hashim [a,b], Eliane Chouery [a], Nabiha Salem [a], Valérie Delague [a,c], Gérard Lefranc [d], Jacques Loiselet [a], André Mégarbané [a,*]

[a] Unité de Génétique Médicale et Laboratoire Associé INSERM à l'Unité UMR_S 910, Faculté de Médecine, Université Saint Joseph, Beirut, Lebanon
[b] Department of Life and Earth Sciences, Faculty of Sciences, Branch II, Lebanese University, Fanar, Lebanon
[c] INSERM UMR_S 910, Génétique Médicale et Développement, Faculté de Médecine de la Timone, Marseille, France
[d] Institut de Génétique Humaine, CNRS UPR 1142 et Université Montpellier 2, Montpellier, France

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ABSTRACT

Familial Mediterranean fever (FMF) is an autoinflammatory autosomal recessive disease characterized by recurrent fever crises and serous inflammation. The *MEFV* gene responsible for the disease was identified on chromosome 16, and 5 of the mutations discovered so far in the gene are most frequently encountered in FMF patients: p.[M694V], p.[V726A], p.[M680I] and p.[M694I] in exon 10, and p.[E148Q] in exon 2. The present work describes multiple *MEFV* mutations and the corresponding haplotypes for 31 FMF patients as well as 32 "healthy" individuals of a large consanguineous Lebanese family. The DNAs were screened for *MEFV* mutations, and determination of the corresponding haplotypes was performed for all individuals by genotyping 4 microsatellites surrounding the gene. Five different mutations were detected in this one family, which is unexpected in such a genetic isolate. A phenotypic variability was also observed. The haplotype carrying the p.[M694I] allele, detected in all the family branches, was well conserved and therefore seems to be the ancestral one.

1. Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory autosomal recessive disease characterized by serous inflammation leading to abdominal, articular and/or pleural pain, and often fever. The most severe complication of the disease is renal amyloidosis that develops in some patients. The *MEFV* gene responsible for the disease was identified on chromosome 16p13.3 and consists of 10 exons, covering around 14 kilobases of genomic DNA (Fig. 1) [12,13]. More than 80 *MEFV* mutations have been reported so far in FMF patients [5], but 5 of them are most frequently encountered: p.[M694V], p.[V726A], p.[M680I] and p.[M694I] in exon 10, and p.[E148Q] in exon 2 [11].

FMF is frequent in countries of the eastern Mediterranean coast, particularly among Armenians, Jews, Arabs and Turks [12,13]. Lebanon is an Arab country where the FMF carrier rate is around 17% [7]. The frequency, however, varies from one Lebanese region to the other along with the rate of consanguinity which is responsible for increased frequencies of autosomal recessive diseases. We investigated the FMF disease in a village where all inhabitants belong to only one large consanguineous family and are descendants of 4 brothers who settled in the village around 500 years ago.

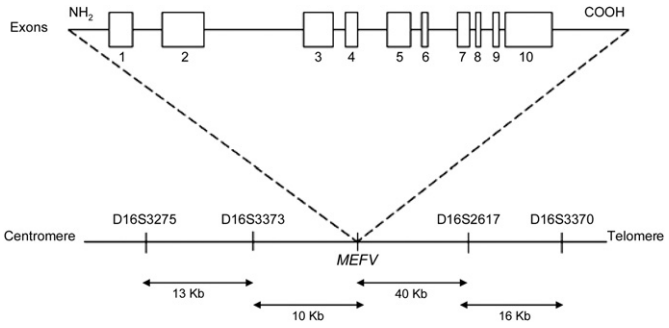

Fig. 1. The microsatellites surrounding the *MEFV* gene, on chromosome 16p13.3. Arrows show approximate distances between markers and the *MEFV* gene.

* Corresponding author. Unité de Génétique Médicale, Faculté de Médecine, Université Saint-Joseph, 42, rue de Grenelle, 75007 Paris, France. Tel: +961 1 421 252; fax: +961 1 421 021.
E-mail addresses: myrnahachem@ul.edu.lb (M. Medlej-Hashim), eliane.chouery@usj.edu.lb (E. Chouery), nabiha.salem@usj.edu.lb (N. Salem), valerie.delague@medecine.univ-mrs.fr (V. Delague), glefranc@univ-montp2.fr (G. Lefranc), jacques.loiselet@usj.edu.lb (J. Loiselet), megarbane@usj.edu.lb (A. Mégarbané).

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The present work describes multiple *MEFV* mutations and the corresponding haplotypes for 31 patients as well as 32 "healthy" individuals of this family that do not complain of any FMF clinical sign.

2. Materials and methods

The study was run on 31 FMF patients and 32 healthy individuals out of the 461 family members represented in the pedigree (Fig. 2). Clinical information and social status were investigated. Further subjects could not be included to the study since they were inaccessible or did not want to participate. The blood samples from the individuals were collected after the informed written consent was obtained. DNA was extracted from blood samples and the 5 most frequent *MEFV* mutations were investigated by Restriction Enzyme Analysis (REA) or Amplification Refractory Mutation System (ARMS), as previously described [6]. Sequencing of exon 10 of the *MEFV* gene was undertaken for the individuals who showed only one or none of the 5 mutations. Further sequencing of exons 2, 3 and 5 of the *MEFV* gene was performed for the individuals who still had one missing mutation.

The haplotypes for the mutant alleles were constructed by genotyping of the four microsatellites surrounding the *MEFV* gene (Fig. 1): D16S3275, D16S3373, D16S2617 and D16S3370, on an ABI genetic analyzer. The sequences of the related primers were determined by the Genome Database (GDB).

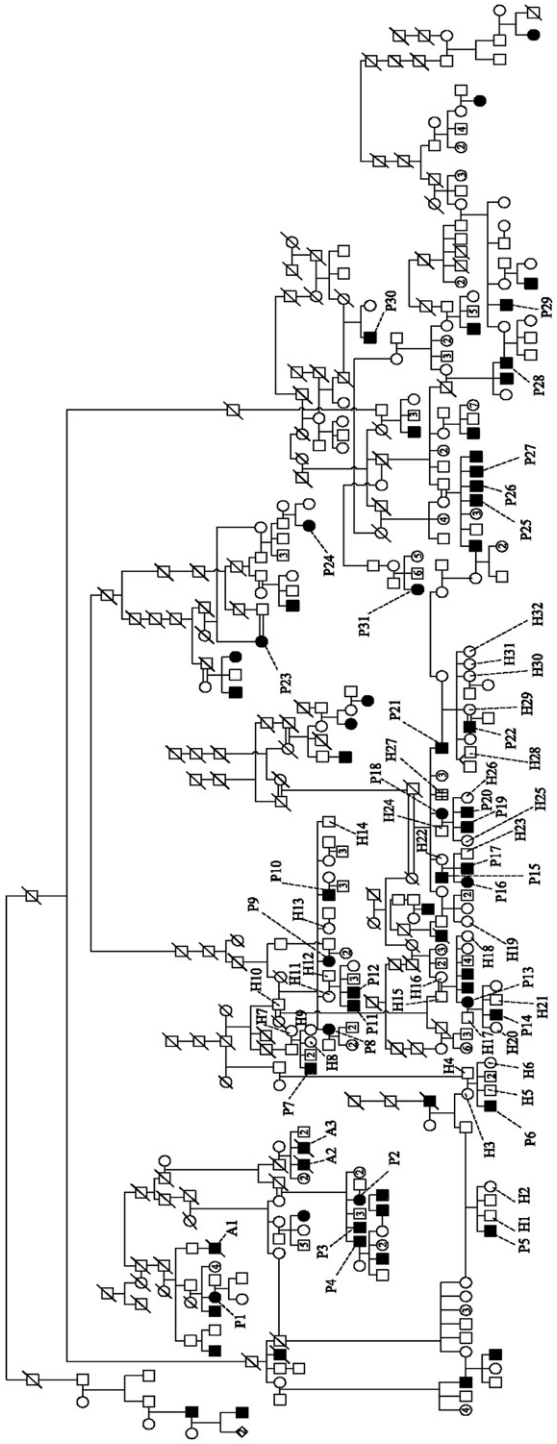

Fig. 2. Pedigree of the large Lebanese studied family. ■,●: Familial Mediterranean fever (FMF) patients; ■: Behcet disease affected patient; P: FMF patient; A: patient with renal amyloidosis; and H: healthy individual.

3. Results

The *MEFV* genotypes observed are grouped in Table 1, and the corresponding haplotypes are shown on the family pedigree (Fig. 2). The patients tested were designated by a number following the letter "P", and the healthy ones by a number following the letter "H". Five different mutations were identified in this family. Three of them (p.[M694I], p.[M694V] and p.[V726A]) were frequently observed, while p.[R761H] was only detected at the heterozygous state in 2 patients, and p.[E148Q] at the heterozygous state in 2 patients and 2 healthy individuals.

Clinical information obtained from the patients showed phenotypic variability when compared in view of the genotypic data. All the patients had 2 mutations, except 2 who were heterozygous for only one: p.[V726A]. The molecular genetic test in the available parents showed that the mutations detected in compound heterozygous patients were carried by different alleles. Three family members designated A1, A2 and A3 in the pedigree died prior to the study, following the development of renal amyloidosis.

Seven of the "healthy", not showing any clinical symptoms of FMF, individuals tested were found to be compound heterozygotes. H5, aged 13, carries the same 2 mutations as his brother P6, aged 19. It is noteworthy that the age of onset of FMF clinical signs was seven years for P6. H7, mother of P7, and her 2 daughters H8 and H9 are compound heterozygous. The genotype of H8 who is 15 years old is identical to that of her brother P7. The latter is 21 years old and had his first symptoms at 16 years (Figs. 3 and 4). H18 who is 40 years

Table 1
Observed *MEFV* genotypes among patients and individuals with no FMF clinical sign in the Lebanese village under study.

MEFV genotypes	Patients	Healthy individuals (with no clinical FMF sign)
p.[M694I]+[V726A]	14	2
p.[M694V]+[V726A]	4	1
p.[M694V]+[M694I]	3	0
p.[M694V]+[=]	2	0
p.[M694I]+[E148Q]	2	2
p.[M694I]+[=]	1	1
p.[V726A] +[=]	1	0
p.[V726A]+[R761H]	1	0
p.[V726A]+[R761H]	1	0
p.[V726A]+[E148Q]	0	1
p.[V726A] +[?]	2	11
p.[M694I]+[?]	0	9
p.[M694V]+[?]	0	3
p.[E148Q]+[?]	0	1
[?]+[?]	0	1
Total	31	32