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SHORT REPORT

Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases in Maronites, Greek orthodoxes, Greek catholics, Syriacs and Chiites and for an association between amyloidosis and M694V and M694I mutations

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Seventy-nine unrelated Lebanese patients were tested for 15 mutations in the *MEFV* gene: A761H, A744S, V726A, K695R, M694V, M694I, M694del, M6801 (G C), M680I (G A) in exon 10, F479L in exon 5, P369S in exon 3, T267I, E167D and E148Q in exon 2, using PCR digestion, ARMS, DGGE and/or sequencing. Mutations were detected in patients belonging to all communities, most interestingly the Maronite, Greek orthodox, Greek catholic, Syriac and Chiite communities. The most frequent mutations are M694V and V726A (27% and 20% of the total alleles respectively). M694I, E148Q and M680I mutations account respectively for 9%, 8% and 5%. Each of the K695R, E167D and F479L mutations was observed once and all the remaining mutations were not encountered. Of the alleles 33% do not carry any of the studied mutations. The mutation spectra, clinical features and severity of the disease differed among the Lebanese communities. The genotype–phenotype analysis showed a significant association ($P < 0.001$) between amyloidosis and the presence of mutations at codon 694 in exon 10 (both M694V and M694I). None of the patients carrying other mutations developed amyloidosis. *European Journal of Human Genetics* (2001) **9**, 51–55.

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Introduction

Familial Mediterrannean fever (FMF) is an autosomal recessive disorder characterised by recurrent attacks of fever of (38–40°C) and painful episodes of sterile serositis that involves typically the peritoneum, pleura and/or synovia.[1–4] Patients may also develop erysipelas-like erythema and less frequently amyloidosis that may affect several organs, particularly the kidney, leading to end-stage renal failure.[1,2]

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The gene is responsible for the disease (*MEFV*) is located on the short arm of chromosome 16[5,6] and is made up of 10 exons. Up to the present, 17 mutations that affect the *MEFV* gene have been found in Mediterranean populations, mainly Jews, Armenians, Turks, Arabs and Italians.[3,7–19] A few patients have been also reported outside the Mediterranean region.[1,3,13,16,18,20] The distribution of mutations is variable among populations but the M694V, V726A, M694I and M680I, account for over 80% of mutations.[1,5,8,12,20,21]

Since the early 1950s, FMF patients have been reported in the Lebanese population,[12] which is a mosaic of 18 religious communities, mainly Maronite, Sunnite, Chiite, Druze, Greek orthodox, Greek catholics, Syriac and Armenian.

The *MEFV* gene mutations had never been assessed in patients belonging to these communities. The aim of the present study is to determine the spectrum of *MEFV* mutations, compare their distribution in the different communities and analyse the phenotype–genotype relationship.

Subjects and methods

Patients

Seventy-nine individuals from unrelated Lebanese families have been analysed. The diagnosis of FMF was made according to established clinical criteria (Sohar and Livneh classifications).[22,23] Diseases sharing clinical features with FMF were ruled out as follows:

(1) Rheumatoid arthritis by the lack of joint deformity and the short and spontaneous resolution of the joint findings,

(2) Behçet's disease according to the criteria of the Japanese Research Committee,[24] and

(3) the hyperimmunoglobunemia syndrome by IgD titration lower than 100 U/ml.

The severity scores were evaluated referring to the Tel Hashomer classification.[23] However, a high number of patients was diagnosed recently or was non-compliant to the colchicine treatment. For this reason, we calculated the severity score, without taking into consideration the colchicine dosage.

Patients belonged to both Moslem and Christian communities; Moslems were Sunnite, Shiite or Druze, and Christians were Maronite, Greek orthodox, Greek catholic, Syriac or Armenian.

IgD measurement

The IgD blood levels were determined using a new sensitive ELISA method as described elsewhere.[25]

Mutation analysis

As a first step, the PCR restriction-digestion, DGGE and sequencing methods were used sequentially on only 30 patients. Four different mutations were detected by these three methods (M694V, M694I, M680I, V726A). For sequencing, exon 10 was amplified using the 5'-GAGGTGGAGGTTGGAGACAA-3' and 5'-AGAGCAGCTGGCGAATGTAT-3' primers and analysed on an ABI 377 sequencer (Perkin Elmer, Applied Biosystems, Foster City, CA, USA). Sequencing was performed in both reverse and forward directions. Using DGGE, we studied fragment 10A of exon 10 as described earlier.[17] Next, the PCR restriction-digestion method was exclusively used for all patients and was extended to the other mutations: M694V, M680I, V726A, R761H, P369S, T267I, E167D and E148Q. The A744S, K695R and F479L mutations were detected by the ARMS method. The deltaI692 and deltaM694 were detected by a PCR-electrophoresis assay. Primers, restriction enzymes and DNA fragments used for mutation analysis are listed in Table 1.

Data analysis

The frequency of mutation was estimated relatively to the total number of alleles. Only one allele was counted in patients homozygous by descent. The genotype–phenotype correlation was calculated by the χ^2 test with Yates's correction. Exact *P* values were corrected to avoid a type I error. The statistical significance was determined by a *P* value < 0.01. The M694V/M694V, M694V/M694I and M694I/M694I genotypes were correlated to clinical features separately then compared among them. These three genotypes were also considered as one group homozygous for a mutation at the 694 codon of exon 10.

Results

Mutations were detected in patients belonging to heterogeneous religious origins. Of the patients 37% have a positive family history for the disease and consanguinity was observed for 33% of the patients; 96% of patients had fever, 94% abdominal pain, 54% thoracic pain, 46% arthritis, 10% skin involvement and 8% amyloidosis. The mean onset of the disease was relatively high (17 years), and the sex ratio male/female was calculated at 1.5. Comparison of the frequencies among the different communities showed that Moslem patients had an earlier onset and frequency of arthritis twice as high as FMF-Christian patients, and that patients with amyloidosis belong exclusively to the Druze, Chiite and Armenian groups.

Mutation analysis showed that the 15 tested mutations account for 67% of the total alleles ($n = 143$), and 45 alleles (33%) were tested negative. The M694V mutation is the most frequent, followed by the V726A, M694I, E148Q and M680I mutations (Table 2). However, a high heterogeneity was observed when the distribution was analysed by religious groups. The most significant differences concerned the frequencies of alleles testing negative for all mutations, and alleles positive for the M694V and M694I mutations. Whereas in Druze and Syriac patients all alleles were mutation positive, 75% of alleles (12/16) in Maronites tested negative. The M694V mutation accounts for 50% and 83% in Chiites and Armenians respectively, but was absent in Druzes, the Greek orthodox, Greek catholics and Maronites. The M694I mutation accounts for 56% in Druzes but was absent in Sunnites, Greek catholics and Syriacs.

When the genotype was correlated to clinical features, we observed that the highest severity scores were observed in patients carrying the M694V mutation. The mean severity score, without the colchicine dosage criteria, was found to be equal to 8 in M694V homozygous patients and is at least 2 points higher than the scores observed among FMF patients homozygous for the other mutations (Table 3). A higher mean score was also observed among M694V/M694I heterozygous (Table 3). The statistical analysis showed that only the

Table 1 Primers, restriction enzymes and DNA fragment profiles used for mutation analysis

Mutation	*Primers*	*Restriction enzymes*	*Profile (in base pairs)* *Normal*	*Mutant*
M694V	Forward 5'-GAGGTGGAGGTTGGAGACAA-3' Reverse: 5'-AGAGCAGCTGGCGAATGTAT-3'	*HpH*1	166–109	157–109–9
V726A	Forward: 5'-TATCATTGTTCTGGGCTC-3' Reverse: 5'-CTCCGTACTTCCTCCTCT-3'	*Alu* I	315–154–129–67	257–154–129–67–58
M680I	Forward: 5'-TATCATTGTTCTGGGCTC-3' Reverse: 5'-CTCCGTACTTCCTCCTCT-3'	*Hinf* I	541–123	664
E148Q	Forward: 5'-AACTTTAATATCCAAGGGGATTC-3' Reverse: 5'-TTCTCTGCAGCCGATATAAAGTA-3'	*Ava* I	221-190-128-121-69-42	290–190–128–121–42
E167D	Forward: 5' AACTTTAATATCCAAGGGGATTC-3' Reverse: 5'-TTCTCTGCAGCCGATATAAAGTA-3'	*Dra* II	268–202–179–83–47	447–202–83–47
T267I	Forward: 5'-AACTTTAATATCCAAGGGGATTC-3' Reverse: 5'-TTCTCTGCAGCCGATATAAAGTA-3'	*MspA*1I	453–184–155	453–339
R761H	Forward: 5'-TATCATTGTTCTGGGCTC-3' Reverse: 5'-CTCCGTACTTCCTCCTCT-3'	*Nla* III	482–78–42–28–24–18	244–238–78–42–28–24–18
P369S	Forward: 5'-GAAGAGCCCGGGAAGCCTGAGC-3' Reverse: 5'-TTGGGAAAATGAAGTAAGGCCC-3'	*Sac* I	252	228–24
I692del& M694del	Forward: 5'-GAGGTGGAGGTTGGAGACAA-3' Reverse: 5'-GACGCCTGGTACTCATTTT-3'	No digestion	135	132
M694I	Common: 5'-TATCATTGTTCTGGGCTC-3' Normal: 5'-CTGGTACTCATTTTCCTTC-3' Mutant: 5'-CTGGTACTCATTTTCCTTT-3'	No digestion	Amplification with normal primer	Amplification with mutant primer
A744S	Common: 5'-GAGGTGGAGGTTGGAGACAA-3' Normal: 5'-CCAGAGAAAGAGCAGCTGGC-3' Mutant: 5'-CCAGAGAAAGAGCAGCTGGA-3'	No digestion	Amplification with normal primer	Amplification with mutant primer
F479L	Common: 5'-CCACCTCTTATCCACCTCC-3' Normal: 5'-CCTCCAGTGAGGCCACAAAG-3' Mutant: 5'-CCTCCAGTGAGGCCAGAAAC-3'	No digestion	Amplification with normal primer	Amplification with mutant primer
K695R	Common: 5'-TTAGACTTGGAACAAGTGGGAGAGGCTGC-3' Normal: 5'-TCGGGGGAACGCTGGACGCCTGGTACTCATTTTCCT-3' Mutant: 5'-TCGGGGGAACGCTGGACGCCTGGTACTCATTTTCCC-3'	No digestion	Amplification with normal primer	Amplification with mutant primer

Table 2 Allele frequency[1] among the Lebanese communities

		M694V %	*V726A %*	*M694I %*	*E148Q %*	*M680I %*	*None %*
Total alleles	*n* = 143	27	20	9	8	5	33
Total Moslem[2]	*n* = 75	32	19	12	9	5	25
Total Christian[2]	*n* = 64	22	22	6	5	5	41
Druze[2]	*n* = 9	0	11	56	33	0	0
Chiite[2]	*n* = 28	50	11	14	0	4	21
Sunnite[2]	*n* = 36	25	22	0	8	8	36
Amenian[2]	*n* = 12	83	0	0	0	8	8
Maronite[2]	*n* = 16	0	13	6	0	6	75
Greek Orthodox[2]	*n* = 8	0	25	37	13	0	25
Greek Catholic[2]	*n* = 6	0	50	0	0	17	33
Syriac[2]	*n* = 6	33	67	0	0	0	0

[1]Only one of the allele was counted in patients homozygous by descent. The E167D and F479L mutations were found in one patient showing the V726A/E167D/F479L genotype but alleles were not determined. The K695R was also found in one patient; [2]Patients with parents of different origins are not shown.

association between the presence of a mutation at codon 694 and amyloidosis was statistically significant ($P < 0.001$). Patients with amyloidosis showed three genotypes: M694V/M694V, M694V/M694I and M694I/M694I (Table 3).

Alleles in *cis* position were found in two patients: one was homozygous for the V726A-E148Q complex allele, and a second showed the V726A/E167D/F479L genotype but the alleles could not be determined.

Discussion

The *MEFV* gene assessment in the Lebanese population revealed the presence of mutations in communities that had never been reported before. At present, 18 religious communities compose the Lebanese population. The Sunnite, Chiite, Druze, Maronite, Greek orthodox, Greek catholic, Syriac and Armenian communities are numerically the most important. This heterogeneity has been the consequence of the situation of Lebanon as a crossroads between Asia, Africa, and Europe. In the first century AD, the greater part of the population was Syriac-speaking Christian, a part of whom followed the Greek rites in the fifth century. Next, a Maronite community moved from Syria to Lebanon. During the Arab conquests, a portion of the population was converted to Islam (Sunnites). In the seventh century, the Moslem Chiite branch took place and a Chiite population migrated to Lebanon. In the eleventh century, the Moslem Druze community was formed and a portion settled in the central Lebanese mountains. More recently, the Christian Syriac, Armenian, Assyrian and Chaldean communities were pushed into Lebanon following regional political difficulties. Other smaller groups, notably, Protestant, Jewish, and Alawit completed the Lebanese mosaic population.

We observed a heterogeneous mutation spectrum (Table 2), whereas in other populations, notably, Jews, Armenians and Turks, usually one mutation predominates.[5,6,8,14,17,21,26] Interestingly, mutations were detected in patients belonging to all Lebanese communities, particularly, Maronites, Chiites, the Greek orthodox, Greek catholic and Syriacs and the mutation spectra were different among these communities (Table 2).

Sixteen patients tested negative, of whom six belonged to the homogeneous Maronite population, and showed typical clinical FMF features. The etiopathology in these patients could be attributed to several mechanisms, including:

(1) unknown common FMF mutation,

(2) a new familial periodic fever syndrome,

(3) hyperimmunoglobulinemia-D syndrome (HIDS), and

(4) TNF-receptor associated periodic syndrome (TRAPS).

Unfortunately, we could not test the first two hypotheses due to the refusal of informative families to participate in the study. The HIDS and TRAPS are less likely since the patients tested showed an IgD level lower than 100 U/ml and a recessive inheritance of the disease. Nevertheless, these two periodic fevers will be taken into consideration for further investigations.

The spectrum of mutated alleles also differed among the religious groups that have not been known to mix throughout history due to geographic isolation and social marriage customs. A founder effect and the homogeneity of these groups are most probably at the origin of a skewing toward one particular FMF mutation.

The prevalence of the M694V mutation among Armenians is in accordance with already published data.[5,6] However, the frequencies in the Lebanese Druze group are different from those reported among non-Lebanese Druze, most probably due to the founder effect. In fact, the V726A, which is usually frequent in non-Lebanese Druzes,[5,6,8] accounts for only 11% (1/9 alleles) and the M694I accounts for 56% (5/9 alleles).

Table 3 The mean severity score and clinical feature frequencies in function of the genotype

		Severity score (mean)	*Thoracic pain* $n = 43$	*Arthritis* $n = 36$	*Skin* $n = 8$	*Amyloidosis* $n = 6$
M694V/M694V	$n = 10$	8	5 (50%)	6 (60%)	2 (20%)	4 (40%)
V726A/V726A	$n = 4$	5	3 (75%)	3 (75%)	1 (25%)	–
M694I/M694I	$n = 4$	5	2 (50%)	1 (25%)	–	1 (25%)
E148Q/E148Q	$n = 2$	5	2 (100%)	1 (50%)	–	–
M680I/M680I	$n = 1$	6	1 (100%)	–	–	–
M694V/V726A	$n = 8$	5	7 (87%)	7 (87%)	1 (25%)	–
M694V/M694I	$n = 3$	7	3 (100%)	3 (100%)	–	1 (33%)
M694V/M680I	$n = 2$	5	1 (50%)	–	–	–
V726A/M694I	$n = 2$	5	2 (100%)	–	–	–
V726A/E148Q	$n = 1$	1	1 (100%)	–	–	–
V726A/M680I	$n = 3$	3	2 (67%)	1 (33%)	–	–
M694I/E148Q	$n = 2$	3	1 (50%)	1 (50%)	–	–
M694V/–	$n = 7$	4	3 (43%)	4 (57%)	1 (14%)	–
V726A/–	$n = 9$	3	3 (33%)	1 (11%)	1 (11%)	–
E148Q/–	$n = 5$	4	1 (20%)	2 (40%)	1 (20%)	–
M680I/–	$n = 1$	5	1 (100%)	–	–	–
–/–	$n = 16$	4	5 (31%)	6 (37%)	1 (6%)	–

The presence of FMF patients in many different homogeneous Lebanese groups parallels the presence of patients in different Mediterranean populations. Although we have not conducted yet a study to determine the FMF carrier frequency in the Lebanese population, the present heterogeneous cohort of patients re-emphasis the hypothesis of a selective advantage for the FMF carrier chromosomes in the Mediterranean region.

Assessment of the phenotype–genotype correlation revealed that the Armenian, Chiite and Druze groups showed the highest severity scores and frequencies of M694V or M694I mutations (Table 2), and that patients with amyloidosis belong exclusively to these three communities. In parallel, all patients with amyloidosis carry two mutations in codon 694 of exon 10 (four M694V homozygous, one M694I homozygous and one M694V/M694I heterozygous) (Table 3). It is noteworthy that these patients had never received colchicine treatment. The statistical analysis showed that the association between the presence of mutations at codon 694 in exon 10 and amyloidosis is the only significant correlation ($P < 0.001$) in the present cohort.

Two patients aged 43 and 60 who have never been treated with colchicine and have not developed amyloidosis showed the M694V/M694V and M694I/M694I genotypes, respectively. Neither patients reported positive FMF family history or consanguinity, whereas all the other patients with amyloidosis reported positive family history and/or consanguinity. These two cases suggest that, in addition to the *MEFV* mutations, there exists a second genetic factor that predisposes to the development of amyloidosis.

In conclusion, this study allowed us to detect *MEFV* gene mutations in the Maronite, Greek orthodox, Greek catholic, Syriac and Chiite communities and to establish the mutation spectrum among the Lebanese FMF patients. The most important features are the heterogeneity of mutations and the high number of chromosomes who tested negative for all the mutations. This provides important tools for adapting a molecular diagnostic test for the Lebanese population and further investigations. The genotype–phenotype analysis also indicates that both M694V and M694I mutations are associated with amyloidosis.

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