ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Clinical and genetic heterogeneity in a large cohort of Armenian patients with late-onset familial Mediterranean fever

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Purpose: This work aimed at investigating demographic, clinical, and genetic characteristics of individuals experiencing their first familial Mediterranean fever (FMF) attack at age ≥ 40 years in a very large cohort of Armenian FMF patients.

Methods: In total, 10,370 Armenian patients diagnosed with FMF based on the Tel Hashomer criteria and carrying at least one *MEFV* mutant allele were included in this study.

Results: A total of 354 (3.40%) patients had late-onset FMF. Of these, 194 (54.80%) were female and 160 (45.20%) were male. The following genotypes were significantly associated with the late-onset variant: M680I/E148Q ($P = 0.004$), M694V/E148Q ($P < 0.001$), and V726A/V726A ($P < 0.001$). Of note, 12/354 (3.40%) patients were found to be homozygous for the M694V mutation. Individuals with late-onset FMF had a milder disease phenotype presenting significantly less frequent fever, skin manifestation, and chest pain compared to individuals with a disease onset before 40 years of age. Abdominal pain was found more often in the late-onset FMF group, whereas arthritis, proteinuria, and amyloidosis did not differ significantly between the two groups.

Conclusion: Our data suggest that late-onset FMF is more prevalent in women and is of greater clinical as well as genetic heterogeneity than previously reported.

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Key Words: disease phenotype; familial Mediterranean fever; late onset; *MEFV* mutation

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive inherited autoinflammatory disorder that is characterized by recurrent febrile episodes, accompanied by pain in the abdomen (peritonitis), chest (pleuritis), or joints (arthritis), and erysipelas-like skin erythema.[1] The disease is observed primarily in Armenians, Turks, Arabs, and North African Jews.[2]

FMF is caused by several mutations within the Mediterranean fever (*MEFV*) gene, which is localized on chromosome 16p13.3. This gene is composed of 10 exons, which encode a 781–amino acid protein known as pyrin.[3,4] Four (M694V, M694I, M680I, V726A) and one (E148Q) missense mutations in exon 10 and exon 2, respectively, are the most frequently reported *MEVF* variants in ethnic groups at risk of FMF.[3,5,6] With an estimated 20%, the overall *MEFV* carrier rate in the Armenian population is extremely high, resulting in an FMF prevalence of approximately 3%.[7,8]

In general, FMF diagnosis is based on clinical findings, which can be backed up but never replaced by genetic testing.[9] Moreover, diagnosing FMF may be extremely difficult in individuals with nonspecific symptoms, with late-onset disease, or with an absence of family history. In such cases, mutational analysis is crucial to enable an early diagnosis.[10,11]

The age of onset of FMF varies with about 60 and 90% of patients experiencing their first attack before the age of 10 and 20 years, respectively.[12] Hence, FMF with the first attack occurring at the age of ≥ 40 years is rare and only a few small studies have investigated the clinical and molecular genetic characteristics of FMF patients with late-onset disease.[12–15]

Therefore, the present study was conducted to better define the subset of late-onset disease in 10,370 Armenian FMF patients by matching *MEFV* mutational spectra and resulting genotypes against the clinicodemographic profiles collected for these patients between 2005 and 2016.

MATERIALS AND METHODS

Ethical approval

The study was approved by the local ethics committee of the Yerevan State Medical University, Yerevan, Armenia, and is in accordance with the latest version of the Declaration of Helsinki. All patients provided written informed consent.

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FMF patients

A cohort of 10,370 Armenian patients diagnosed with FMF based on the Tel Hashomer criteria and carrying at least one *MEFV* mutant allele who visited the Center of Medical Genetics and Primary Health Care in Yerevan between 2005 and 2016 were included in this study. Personal and medical data, including age, sex, age of disease onset, fever, abdominal pain (peritonitis), chest pain (pleuritis), arthritis, skin involvement (erysipelas-like erythema), proteinuria, and amyloidosis were recorded. Disease severity was determined by the use of a scoring system suggested by Pras et al.[16] Patients also suffering from non-FMF-related inflammation or chronic disease were excluded from the study.

MEFV mutational analysis

DNA was isolated from anticoagulated blood using the GenXtract DNA extraction system (ViennaLab Diagnostics, Vienna, Austria). Twelve common *MEFV* mutations including E148Q (c.442G > C) in exon 2; P369S (c.1105C > T) in exon 3; F479L (c.1437C > G) in exon 5; and M680I G/C (c.2040G > C), M680I G/A (c.2040G > A), I692del (c.2076_2078del), M694V (c.2080A > G), M694I (c.2082G > A), K695R (c.2084A > G), V726A (c.2177T > C), A744S (c.2230G > T), and R761H (c.2282G > A; RefSeq NG_007871.1) in exon 10 were simultaneously analyzed using a test strip–based reverse-hybridization assay (FMF StripAssay, ViennaLab Diagnostics). The operators were blinded to the patient's disease status.

Statistical analysis

For subgroup comparison of categorical variables, the chi-square test ($n \times k$ table) and the Fisher's exact test (2×2 tables) were calculated. For subgroup comparison of continuous variables in the case of normal distribution (verified by the Kolmogorov–Smirnov test with Lilliefors significance correction) and variance homogeneity (verified by the Levene test) the two-sample independent Student's *t*-test was used. In the case of variance heterogeneity Welch's test was used. In the case of nonnormality the exact Mann–Whitney U test was calculated. All statistical tests were used in an explorative way. Therefore no correction of the type I error (two-sided, 5%) was made. For all calculations the open-source statistical program package R version 3.2.3. (R Foundation for Statistical Computing, Vienna, Austria) was used.

RESULTS

Baseline characteristics

In total, 10,370 individuals with a clinical diagnosis of FMF were included, of whom 4,881 were female (47.10%), and 5,489 (52.90%) were male. The mean age was 27.91 ± 15.98 years. Of all participants, 3,520 (33.90%) could be identified with a family history of FMF. Concerning the age of disease onset, 10,016 (96.60%) and 354 (3.40%) patients experienced their first attack before the age of 40 years and at or after the age of 40 years (i.e., late-onset FMF), respectively.

MEFV mutational spectrum and genotypes

As listed in **Table 1**, 59 different genotypes could be distinguished, comprising 2,627 (25.33%) heterozygous, 6,042 (58.26%) compound heterozygous, and 1,685 (16.25%) homozygous mutations. Sixteen (0.16%) individuals had a complex genotype incorporating three mutations. In about 90% of our cohort, four mutations were most prevalent: M694V (41.34%), V726A (27.62%), M680I (18.18%), and

Table 1 Genotype distribution found in 10,370 familial Mediterranean fever patients

Mutation (*n*, %)	Genotype	Patients	
		n	%
Heterozygous (*n* = 2,627, 25.33%)	M694V/-	1,247	12.02
	V726A/-	567	5.47
	E148Q/-	310	2.99
	M680I/-	297	2.86
	R761H/-	68	0.65
	F479L/-	53	0.51
	P369S/-	35	0.34
	A744S/-	30	0.29
	K695R/-	12	0.12
	M694I/-	8	0.08
	Subtotal	2,627	25.33
Compound heterozygous (*n* = 6,042, 58.26%)	M694V/V726A	2,097	20.22
	V726A/M680I	1,215	11.72
	M694V/M680I	1,057	10.19
	M694V/E148Q	388	3.74
	V726A/F479L	336	3.24
	M694V/R761H	275	2.65
	M680I/R761H	150	1.45
	V726A/R761H	99	0.95
	M680I/E148Q	92	0.89
	V726A/E148Q	77	0.74
	E148Q/P369S	48	0.46
	M694V/F479L	44	0.42
	M694V/M694I	27	0.26
	M694V/A744S	25	0.24
	V726A/M694I	23	0.22
	M680I/F479L	17	0.16
	M680I/M694I	16	0.15
	E148Q/R761H	12	0.12
	M694V/K695R	11	0.11
	M680I/A744S	6	0.06
	V726A/P369S	5	0.05
	E148Q/M694I	5	0.05
	M694V/P369S	3	0.03
	V726A/A744S	2	0.02
	F479L/E148Q	2	0.02
	M680I/P369S	2	0.02
	E148Q/A744S	2	0.02
	F479L/P369S	2	0.02

Table 1 Continued

Mutation (*n*, %)	Genotype	Patients	
		n	%
	E148Q/K695R	1	0.01
	M680I/K695R	1	0.01
	R761H/K695R	1	0.01
	F479L/R761H	1	0.01
	Subtotal	6,042	58.26
Homozygous (*n* = 1,685, 16.25%)	M694V/M694V	1,153	11.12
	V726A/V726A	288	2.77
	M680I/M680I	220	2.12
	E148Q/E148Q	8	0.08
	R761H/R761H	8	0.08
	F479L/F479L	7	0.07
	A744S/A744S	1	0.01
	Subtotal	1,685	16.25
Complex (*n* = 16, 0.16%)	M694V/M694V/E148Q	4	0.04
	M694V/V726A/E148Q	2	0.02
	V726A/V726A/E148Q	2	0.02
	V726A/M680I/E148Q	2	0.02
	M694V/V726A/M680I	1	0.01
	M694V/E148Q/P369S	1	0.01
	V726A/F479L/E148Q	1	0.01
	M694V/M694V/P369S	1	0.01
	E148Q/E148Q/P369S	1	0.01
	V726A/E148Q/R761H	1	0.01
	Subtotal	16	0.16
Total		10,370	100.00

E148Q (5.34%). Six other mutations (R761H, F479L, P369S, A744S, M694I, and K695R) were found with a distinctly lower frequency (**Table 2**).

The mutational spectrum obtained for 10,016 (96.60%) and 354 (3.40%) FMF patients with an age of onset <40 and ≥40 years is illustrated in **Table 3**. Genotypes M680I/E148Q ($P = 0.004$), M694V/E148Q ($P < 0.001$), and V726A/V726A ($P < 0.001$) were significantly associated with the late-onset variant whereas genotypes M694V/M694V ($P < 0.001$), V726A/F479L ($P = 0.005$), and V726A/M680I ($P = 0.023$) were more frequently observed in patients with a disease onset <40 years. Of note, 12/354 (3.39%) patients with late-onset FMF were found to be homozygous for the M694V mutation.

Table 2 *MEFV* allele frequencies found in 10,370 familial Mediterranean fever patients

Allele	Number of alleles	Frequency (%)
M694V	7,494	41.34
V726A	5,008	27.62
M680I	3,296	18.18
E148Q	968	5.34
R761H	623	3.44
F479L	470	2.59
P369S	98	0.54
M694I	79	0.44
A744S	67	0.37
K695R	26	0.14
Total	18,129	100.00

Clinical aspects of the late-onset disease

The demographic aspects and clinical manifestations of FMF patients with age of onset <40 and ≥40 years are presented in **Table 4**. In the late-onset FMF group ($n = 354$) the mean age (female, 194 (54.80%); male, 160 (45.20%)) was 56.97 ± 7.82 years. For those patients with a disease onset before 40 years of age the mean age at onset of disease was 11.86 ± 9.66 years.

The frequencies of FMF-related clinical manifestations were significantly different between the two groups except for arthritis, proteinuria, and amyloidosis. Patients with disease onset ≥40 years of age showed a milder disease phenotype ($P < 0.001$) presenting significantly less frequent fever (89.55 vs. 92.46%, $P = 0.048$), skin manifestation (9.89 vs. 14.99%, $P = 0.009$), and chest pain (43.22 vs. 48.66%, $P = 0.046$) compared to individuals with a disease onset before 40 years of age. However, abdominal pain was significantly more frequent in patients with late-onset disease (90.40 vs. 86.42%, $P = 0.035$).

DISCUSSION

In this study, *MEFV* mutational spectra and resulting genotypes were matched against the clinicodemographic profiles of 10,370 FMF patients including 354 (3.40%) individuals with late-onset disease. The most frequently observed mutations were M694V (41.34%), V726A (27.62%), and M680I (18.18%), whereas all other mutations were found with distinctly lower frequencies. These findings are in line with two earlier Armenian studies that observed M694V (50.60 and 56.10%), V726A (22.30 and 17.90%), and M680I (18.70 and 17.90%) to be most common including 3,000 and 1,299 FMF patients, respectively.[7,17]

With respect to the genotype distribution among FMF patients, we found the following genotypes to be most frequent: M694V/V726A (20.22%), M694V/- (12.02%), M680I/V726A (11.72%), M694V/M694V (11.12%), M694V/M680I (10.19%), V726A/- (5.47%), and M694V/E148Q (3.74%). In contrast, a previous Armenian study comprising 3,000 FMF patients found a divergent order: M694V/M694V (20.90%), M694V/V726A (18.00%), M694V/M680I (12.70%),

Table 3 Mutation frequencies found in familial Mediterranean fever patients according to age of onset

	Total	<40 years		≥40 years		*P* value
		n	%	*n*	%	
A744S/-	30	27	0.27	3	0.85	0.081
A744S/A744S	1	1	0.01	0	0.00	—
E148Q/-	310	301	3.01	9	2.54	0.751
E148Q/A744S	2	2	0.02	0	0.00	—
E148Q/E148Q	8	7	0.07	1	0.28	0.243
E148Q/M694I	5	4	0.04	1	0.28	0.159
E148Q/E148Q/P369S	1	1	0.01	0	0.00	—
E148Q/K695R	1	1	0.01	0	0.00	—
E148Q/P369S	48	48	0.48	0	0.00	—
E148Q/R761H	12	11	0.11	1	0.28	0.341
F479L/-	53	51	0.51	2	0.56	0.703
F479L/E148Q	2	2	0.02	0	0.00	—
F479L/F479L	7	7	0.07	0	0.00	—
F479L/P369S	2	2	0.02	0	0.00	—
F479L/R761H	1	1	0.01	0	0.00	—
K695R/-	12	12	0.12	0	0.00	—
M680I/-	297	283	2.83	14	3.95	0.195
M680I/A744S	6	6	0.06	0	0.00	—
M680I/E148Q	92	83	0.83	9	2.54	0.004
M680I/F479L	17	15	0.15	2	0.56	0.113
M680I/K695R	1	1	0.01	0	0.00	—
M680I/M680I	220	214	2.14	6	1.69	0.708
M680I/M694I	16	15	0.15	1	0.28	0.427
M680I/P369S	2	2	0.02	0	0.00	—
M680I/R761H	150	143	1.43	7	1.98	0.361
M694I/-	8	7	0.07	1	0.28	0.243
M694V/-	1,247	1,197	11.95	50	14.12	0.212
M694V/A744S	25	24	0.24	1	0.28	0.581
M694V/E148Q	388	361	3.60	27	7.63	<0.001
M694V/E148Q/P369S	1	1	0.01	0	0.00	—
M694V/F479L	44	42	0.42	2	0.56	0.662
M694V/K695R	11	10	0.10	1	0.28	0.318
M694V/M680I	1,057	1,028	10.26	29	8.19	0.244
M694V/M694I	27	26	0.26	1	0.28	0.609
M694V/M694V	1,153	1,141	11.39	12	3.39	<0.001
M694V/M694V/E148Q	4	4	0.04	0	0.00	—
M694V/M694V/P369S	1	1	0.01	0	0.00	—
M694V/P369S	3	3	0.03	0	0.00	—
M694V/R761H	275	264	2.64	11	3.11	0.611
M694V/V726A	2,097	2,013	20.10	84	23.73	0.106
M694V/V726A/E148Q	2	2	0.02	0	0.00	—
M694V/V726A/M680I	1	1	0.01	0	0.00	—
P369S/-	35	32	0.32	3	0.85	0.116
R761H/-	68	66	0.66	2	0.56	>0.999
R761H/K695R	1	1	0.01	0	0.00	—
R761H/R761H	8	8	0.08	0	0.00	—
V726A/-	567	553	5.52	14	3.95	0.234
V726A/A744S	2	2	0.02	0	0.00	—
V726A/E148Q	77	74	0.74	3	0.85	0.747
V726A/E148Q/R761H	1	1	0.01	0	0.00	—
V726A/F479L	336	333	3.32	3	0.85	0.005
V726A/F479L/E148Q	1	1	0.01	0	0.00	—
V726A/M680I	1,215	1,187	11.85	28	7.91	0.023
V726A/M680I/E148Q	2	2	0.02	0	0.00	—
V726A/M694I	23	21	0.21	2	0.56	0.172
V726A/P369S	5	5	0.05	0	0.00	—
V726A/R761H	99	98	0.98	1	0.28	0.266
V726A/V726A	288	265	2.65	23	6.50	<0.001
V726A/V726A/E148Q	2	2	0.02	0	0.00	—
Total	10,370	10,016	100	354	100	

Table 4 Clinicodemographic profiles of familial Mediterranean fever patients with age of onset <40 and ≥40 years

	<40 years	≥40 years	*P* value
	n = 10,016	*n* = 354	
Mean age, years	26.89 ± 15.20	56.97 ± 7.82	<0.001
Mean age of onset, years	11.86 ± 9.66	46.02 ± 5.57	—
Gender			
Male	5,329 (53.20%)	160 (45.20%)	0.003
Female	4,687 (46.80%)	194 (54.80%)	
Family history of FMF	3,414 (34.09%)	106 (29.94%)	0.111
Fever (≥38 °C)	9,261 (92.46%)	317 (89.55%)	0.048
Arthritis	1,690 (16.87%)	62 (17.51%)	0.778
Skin rash (erysipelas-like erythema)	1,501 (14.99%)	35 (9.89%)	0.009
Abdominal pain	8,656 (86.42%)	320 (90.40%)	0.035
Chest pain	4,874 (48.66%)	153 (43.22%)	0.046
Proteinuria	142 (1.42%)	7 (1.98%)	0.359
Amyloidosis	61 (0.61%)	2 (0.56%)	>0.999
Pras			
Mild	4,579 (45.72%)	238 (67.23%)	<0.001
Moderate	4,936 (49.28%)	115 (32.49%)	
Severe	501 (5.00%)	1 (0.28%)	

FMF, familial Mediterranean fever.

M680I/V726A (9.80%), M680I/M680I (3.40%), V726A/V726A (2.80%), and M694V/R761H (2.80%). Additionally, we identified a lower rate of FMF patients with complex alleles (0.16 vs. 0.70%).[7]

Here, we found 354 (3.40%) of 10,370 patients who experienced their first FMF attack at an age of ≥40 years and were more often of female gender (female, 194 (54.80%); male, 160 (45.20%)). An earlier study on late-onset FMF in

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Israel has reported different results indicating a lower rate of late-onset disease (20/4,000 individuals (0.5%)) and a predominant male gender among late-onset FMF patients (female, 4 (20%); male, 16 (80%)).[12] Moreover, we observed different frequencies for the following genotypes: M694V/M694V (12/354 (3.39%) vs. 0/14 (0.00%)), M694V/V726A (84/354 (23.73%) vs. 2/14 (14.0%), V726A/V726A (23/354 (6.50%) vs. 3/14 (21.40%)), V726A/E148Q (3/354 (0.85%) vs. 0/14 (0.00%), and E148Q/E148Q (1/354 (0.28%) vs. 0/14 (0.00%)). While amyloidosis has been described in patients with a disease onset after age 40,[15] this is, to the best of our knowledge, the first report on M694V homozygosity in late-onset FMF patients. This finding is of special interest because several studies have associated M694V homozygosity with an earlier age of onset and a more severe disease phenotype.[17–23] Corroborating previous data,[12] none of our late-onset FMF patients carried the complex allele V726A-E148Q, which is known to be present in individuals with a severe disease phenotype.[22,23]

In the current study, genotypes M680I/E148Q ($P = 0.004$), M694V/E148Q ($P < 0.001$), and V726A/V726A ($P < 0.001$) were significantly associated with the late-onset variant. While genotypes M694V/E148Q and V726A/V726A have already been described in FMF patients with late-onset and/or milder disease,[12,23] this is the first report to correlate genotype M680I/E148Q with the late-onset variant, supporting the observation that both mutations M680I and E148Q associate with a less severe disease activity.[7,12,23] Furthermore, mutation E148Q has been shown to predispose to a prolonged disease onset.[17]

Small study populations comprising small percentages of late-onset patients only are the major limitations of studies published so far.[12–15] For example, based on their findings in 20 late-onset FMF patients Tamir et al.[12] suggested a milder disease course without proteinuria and amyloidosis presenting significantly less arthritis, chest pain, fever, and skin manifestations and a nonsignificant difference in abdominal pain compared to patients with an age of onset before 40 years of age.

The results of this study support the concept of late-onset FMF as being a less symptomatic disease variant. Patients with an age of onset before 40 years had significantly more frequent fever ($P = 0.048$), skin involvement ($P = 0.009$), chest pain ($P = 0.046$), and a more severe disease phenotype ($P < 0.001$) compared to the group of patients with an age of onset ≥ 40 years. Interestingly, abdominal pain was found more often in the late-onset FMF group ($P = 0.035$), whereas arthritis, proteinuria, and amyloidosis did not differ significantly between the two groups.

The main strength of this retrospective study is its sample size, which enables the clinical and genetic characterization of 354 patients with late-onset FMF. However, it is limited by the fact that genetic analysis was performed for the 12 most common *MEFV* mutations only, thus neglecting less frequent ones. Another limitation of this work is the lack of information regarding response and compliance to colchicine treatment.

Our data suggest that late-onset FMF is more prevalent in women and is of greater clinical as well as genetic heterogeneity than previously reported. Therefore physicians should include FMF in their differential diagnosis list even when evaluating older patients with a relevant ethnic background. Moreover, further studies including late-onset FMF patients homozygous for *MEFV* mutation M694V may lead to the identification of novel disease-modifying mechanisms.

DISCLOSURE

The authors declare no conflict of interest

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