# Editorial

# Familial Mediterranean fever in Armenia in 2015: some interesting lessons

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## Introduction

Armenia is a relatively small country consisting of 29,000 square kilometers with 2.9 million citizens. In the 6th-7th centuries it was a large kingdom named Urartu which included most of the Anatolian heights (Turkey today) and the southern part of Caucasia. Therefore, it is conceivable that part of the population in these regions of Turkey and Caucasia has Armenian ancestry and thus their genetic background would resemble that of the Armenian population.

Over the years, the Armenian people remained a genetically pure population since they did not mix with neighboring communities, probably due to their different religion and culture. Analysis of diseases such as familial Mediterranean fever (FMF) among Armenians may give us more precise information regarding the relative role and contribution of genetics to the prevalence and characteristics of this disease.

Armenia is the country with the highest prevalence of FMF in the world (1). Among 2.9 million people there are more than 20,000 patients suffering from FMF, indicating a prevalence of 1:150. The carrier rate of *MEFV* mutations is about 1:3. In the Armenian Centre of Medical Genetics and Primary Health Care in Yerevan, there is a registry with more than 14,500 FMF patients. This is the largest FMF data base in the world and as such it allows a thorough analysis of the Armenian FMF patients, their genetics and their clinical characteristics. In this paper we focus on some unique observations regarding FMF in Armenia as derived from the analysis of this large registry.

## Patients carrying a single mutation (heterozygotes) *versus* patients carrying more than a single mutation (homozygotes or compound heterozygotes)

About 80% of the FMF patients in Armenia carry 2 or more mutations (Tables I-II). Only 19% of the patients with FMF are heterozygotes. The rate of FMF patients in whom no mutation was found is close to zero. This observation is in contrast to the situation in Israel – another country where FMF is relatively common – where only 66% of FMF patients carry 2 or more mutations and third of them carries a single mutation (2). About 3–6% of FMF patients in Israel do not carry any detectable *MEFV* mutation. Among 116 Japanese FMF patients, 2 (1.7%) were homozygous, 67 (57.8%) were compound heterozygous, and 47 (40.5%) were heterozygous for *MEFV* mutations (3). Furthermore, additional Japanese study reported that the rate of FMF patients in whom no mutation was detected was close to 13% (4). As expected, these data show that the higher the carrier rate, the lower the number of FMF patients who are heterozygotes or without any *MEFV* mutation. This observation raises the question as to the validity of the diagnosis of FMF in countries with a low carrier rate, especially in patients with no detected *MEFV* mutations.

Another question that was raised is whether patients with 2 or more mutations display a more severe disease than those with a single or no *MEFV* mutation. The clinical manifestations of the heterozygote FMF patients in the Armenian cohort are summarised in Figure 1. When these features were compared between homozygote and heterozygote patients carrying the same muta-

**Table I.** MEFV Genotype segregation among Armenian FMF patients (%)*.

| Genotypes | % |
|---|---|
| M694V/V726A | 21.3 |
| M694V/M694V | 14.1 |
| V762A/M680I | 11.9 |
| M694V/M680I | 11.6 |
| M694V/E148Q | 3.7 |
| M694V/R761H | 3.0 |
| V726A/F479L | 3.0 |
| V726A/V762A | 2.8 |
| M680I/M680I | 2.5 |
| M694V/- | 9.9 |
| V726A/- | 4.5 |
| M680I/- | 1.5 |
| E148Q/- | 0.5 |

*In addition: 44 cases – 3 mutations in *MEFV* gene; 1 case – 4 mutations in *MEFV* gene.

tion (M694V/M694V and M694V/-, V726A/V726A and V726A/-, etc.) it was found that the heterozygotes had a milder disease with a lower rate of occurrence of the above clinical manifestations. Of special note is the observation of extremely low percentage of fever (about 70% only) among the heterozygotes patients. However, when homozygotes for E148Q and heterozygotes carrying this mutation were compared, there was no difference in the above-mentioned clinical features, suggesting that this mutation may not have an actual role in FMF presentation and manifestation. These observations are in accord with previous reports from Israel and Turkey (5-7).

In the Japanese population, FMF is milder no matter the patient genotype (carrying a single of more mutations) suggesting that the severity of the disease is influenced by additional non genetic factors (3, 4).

**FMF patients with complex alleles**

An additional observation from the Armenian cohort is the relatively high rate of FMF patients with complex alleles. In several series from Israel and Turkey it was quite rare to find FMF patients carrying more than two mutations. However, in Armenia about 0.4% of the FMF patients carry 3 or 4 mutations. In 32 out of 116 (28%) Japanese FMF patients, 3 or more mutations were detected (3). In both populations (Armenians and Japanese), most of the mutations in complex alleles were on exons 2 or 3. This may suggest that areas of exons 2 and 3 on the MEVF gene are unstable and may create mutations in cis position – a matter which should be further investigated (Table II). The extremely high prevalence of complex alleles among the Japanese FMF population also deserves an explanation apart from the fact that it may reflect a "founder effect".

As a matter of fact, complex alleles were found even in asymptomatic patients in a relatively high rate (Table II). Of the 65 patients with complex alleles

**Table II.** Genotypes of individuals with complex alleles in the Armenian cohort.

| Genotype | FMF | Non FMF |
|---|---|---|
| M694V/M694V/M680I | 2 | |
| M694V/M694V/E148Q | 5 | 2 |
| M694V/M694V/P369S | 1 | 1 |
| M694V/M680I/M680I | 2 | |
| M694V/V726A/M680I | 4 | |
| M694V/V726A/E148Q | 3 | |
| M694V/V726A/P369S | | 3 |
| M694V/M680I/E148Q | 1 | |
| M694V/M680I/P369S | | 1 |
| M694V/M680I/F479L | 1 | |
| M694V/F479L/E148Q | | 1 |
| M694V/F479L/P369S | | 1 |
| M694V/F479L/R761H | 1 | |
| M694V/E148Q/P369S | 3 | 3 |
| M694V/E148Q/R761H | 1 | 1 |
| M694I/R408Q/P369S | | 1 |
| V726A/V726A/E148Q | 3 | |
| V726A/V726A/P369S | | 1 |
| V726A/M680I/M680I | 1 | |
| V726A/F479L/F479L | 5 | |
| V726A/F479L/E148Q | 2 | |
| V726A/M680I/E148Q | 2 | |
| V726A/E148Q/P369S | | 3 |
| M680I/F479L/F479L | 1 | |
| M680I/E148Q/P369S | 3 | |
| M680I/E148Q/M694I | 1 | |
| F479L/E148Q/P369S | | 1 |
| E148Q/R761H/R761H | 1 | |
| E148Q/R761H/P369S | | 1 |
| E148Q/E148Q/P369S | 1 | |
| M694V/V726A/M680I/M680I | 1 | |
| TOTAL | 45 | 20 |

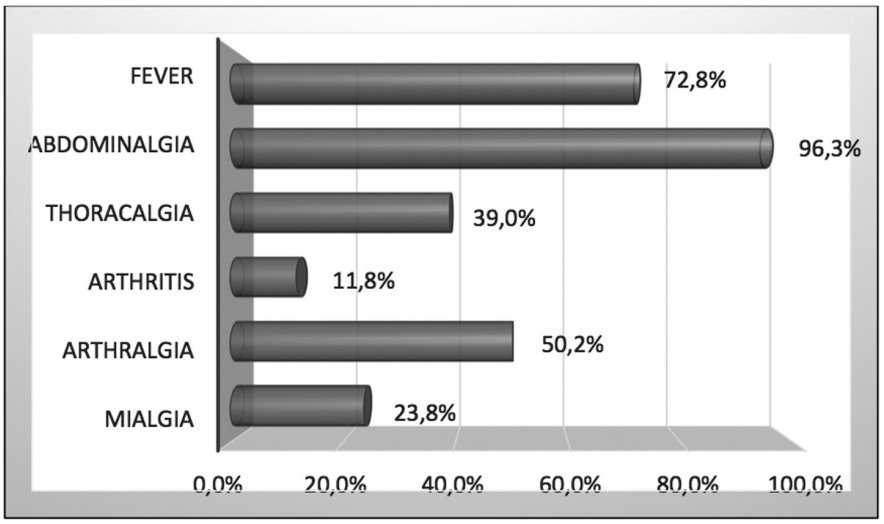


**Fig. 1.** Clinical manifestations of heterozygotes with FMF.

**Table III.** Genotype analysis in FMF patients with amyloidosis.

| | | | |
|---|---|---|---|
| M694V/M694V | 56 | M680I/R761H | 3 |
| M694V/M680I | 25 | M694V/R761H | 2 |
| M694V/V726A | 21 | F479L/- | 2 |
| V726A/M680I | 7 | M694V/F479L | 1 |
| M680I/M680I | 6 | M680I/M694I | 1 |
| M694V/- | 6 | V726A/E148Q | 1 |
| V726A/- | 4 | V726A/R761H | 1 |
| E148Q/- | 4 | V726A/F479L | 1 |
| M680I/- | 4 | R761H/- | 1 |

45 had symptomatic FMF whereas the rest 20 individuals were asymptomatic. When one looks at the cases where there were only "non FMF" individuals with complex alleles, the common denominator is the carriage of mutation 369 in most of them. It is tempting to speculate that the presence of this mutation within a complex allele serves as a "protective" factor from expressing the clinical manifestation of FMF. However, the clinical manifestations of the FMF patients with complex alleles (3 or 4 mutations) did not differ from those with two mutations.

**Amyloidosis**

Previous studies reported that the rate of amyloidosis in Armenia was relatively high - about 20–30% (8). In the current cohort of 14,495 patients with FMF, amyloidosis was documented in only 146 (1%). Since the main cause or major risk factor for amyloidosis is the *country of residence*, one may wonder what the explanation is for this improvement since the country of residence of the patients remained the same (9). It seems that this observation reflects the progress made in Armenia over the last years regarding early diagnosis of FMF and improved availability of colchicine treatment. This further emphasizes the importance of colchicine treatment as the main measure for preventing amyloidosis. Moreover, colchicine treatment can alter the tendency to develop amyloidosis and overcome any risk factor for this complication existing in these countries.

In Israel as well as in Turkey, most patients who develop amyloidosis carry two or more mutations, especially on exon 10 (M694V, M680I) (10-12). In the current Armenian cohort it is interesting to note that 21 out of the 146 (15%) FMF patients with amyloidosis carried only a single mutation (Table III). Moreover, some patients carry the mutations V726A and F479L, which are considered as genetic variants causing mild disease. This observation may further support the role of additional genetic and environmental factors in the process of developing amyloidosis. Recently, it was suggested that since heterozygote FMF patients display mild disease, usually without the occurrence of amyloidosis, discontinuing colchicine treatment once the patient is asymptomatic for about 5 years or so should be considered (13). The fact that even heterozygote FMF patients may develop amyloidosis poses a serious question regarding the adoption of this approach.

An analysis of the group of patients who developed amyloidosis discloses that the M694V was the most frequent mutation associated with this complication (in 51% of the cases) where 14.4% were associated with M680I and only 8.6% with V726A. In the study of the largest cohort in Turkey, the authors did not find a correlation between M694V mutation and amyloidosis (14). However, additional studies from Turkey and Israel have reported a higher risk for amyloidosis in FMF patients who are homozygous for the M694V mutation in the MEFV gene (15-17). Kaşifoğlu *et al*. performed a study conducted on 2246 patients and reported that FMF patients who are M694V homozygotes carry a 6-fold risk for amyloidosis compared with FMF patients carrying other MEFV gene mutations (18). The observation from the Armenian cohort again confirms this association. Moreover, the Armenian cohort shows that almost all the patients with amyloidosis carried mutations on exon 10, reflecting the association between this portion of the gene and a more severe disease.

In the current Armenian cohort, analysis of 52 FMF patients with amyloidosis for their SAA polymorphism revealed that most of them (41 cases) bore either α/α subtype (18 patients) or were heterozygotes for α subtype (23 patients). Still, some patients with amyloidosis carried β/β subtype, suggesting that the α - SAA polymorphism is not necessarily an obligatory risk factor for amyloidosis although its presence may increase the risk for developing this complication.

**Spread of FMF disease – which direction?**

Studies from the Balkan states showed that the closer a country is to Turkey, the higher the rate of MEFV carrier state among its population. The most plausible explanation is the previous rule of the Ottoman Empire in these countries (19). Since Armenia is a neighbor of Turkey a question is raised as to the direction of spread of FMF – is it from Turkey to Armenia or vice versa?

Since the Ottoman Empire also ruled in the region of Armenia, one may conclude that the case of the Balkan states also applies to this country. However, this possibility is less plausible because FMF is a relatively ancient disease and it is probable that its spread occurred much earlier than during the Ottoman Empire era.

In 2005, the Turkish FMF study group described the largest series of patients with FMF reported from one country (14). The cohort was composed of 2838 FMF patients. Ninety-four percent of the patients were recruited from centers within central-western parts of the country. However, when the parental or maternal origins were considered, over 70% of the cases originated from central and eastern Anatolia and inner Black Sea regions.

The rate of carrier state and the repertoire of mutations in the Anatolian heights are almost similar to those of Armenia. Since we know that ancient Armenia in the 6$^{th}$-7$^{th}$ centuries included the eastern part of the Anatolian heights, one can speculate that the

source of FMF in this region is the Armenian population. It is more plausible that the disease was spread to Turkey in the era of the Armenian kingdom of Urartu rather than during the relatively recent period of the Ottoman Empire's rule over Armenia.

## Key points

- Armenia is the country with the highest prevalence of FMF in the world.
- FMF patients carrying 2 or more mutations display a more severe disease than those carrying a single mutation.
- Most of the mutations in complex alleles (3 or more mutations) were on exons 2 or 3. Their clinical features resemble those of FMF patients carrying only 2 mutations.
- Amyloidosis may be developed even in heterozygotes FMF patients carrying mutations supposed to cause a mild disease.
- It is probable that FMF was spread from Armenia to Turkey rather than the other way around.

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