Familial Mediterranean Fever in the World

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever accompanied by peritonitis, pleuritis, arthritis, or erysipelas-like erythema (1,2). A typical FMF attack lasts approximately 3 days. The frequency of episodes varies from once every week to several times a year. One of the devastating complications of FMF is the development of serum amyloid A (SAA) amyloidosis, which mainly affects the kidneys but may involve other organs. Since 1972, colchicine has been the treatment of choice for FMF (3). It controls the acute attacks and prevents the development of amyloidosis.

The disease is prevalent among populations surrounding the Mediterranean Sea. However, in recent years, more and more cases have been reported in countries not related or close to this area, such as the US and Japan. This observation raised the question as to the real prevalence of FMF in countries other than those around the Mediterranean basin and to its clinical characteristics in these countries. Furthermore, it poses a challenge to find out the ethnic origin of these patients and to study whether their disease behaves similarly to that in the countries commonly associated with FMF. FMF may display a different clinical picture among various populations, and these differences reflect the change in the repertoire of mutations among the specific populations.

In this review, we will try to look for and explain the origin of FMF in countries far from the Mediterranean and Middle East regions. We will also compare the nature of the disease in these countries and find out whether they differ from the FMF manifestations, treatment, and prognosis in patients surrounding the Mediterranean Sea.

Prevalence of FMF in the world

FMF is almost always restricted to Turks, Armenians, Arabs, and non-Ashkenazi Jews. It is quite a rare disease in the rest of the world, although patients with FMF have been reported in European countries such as France, Germany, Italy, and Spain, as well as in the US and Australia (2,4). The exact frequency of FMF among the various populations is not always available because formal epidemiologic studies have not been done. Nevertheless, a rough estimate regarding the prevalence of the disease can be obtained by gathering details from different studies and sources (Figure 1). Turkey is probably the country with the highest number of FMF patients in the world. Since the prevalence of FMF is approximately 1:400 to 1:1,000 (highest in the areas of Anatolia) and the population is approximately 70 million, it is estimated that Turkey has more than 100,000 patients with FMF (4–6). In Israel, the prevalence is slightly more than 1:1,000 (depending on the ethnic group), and since the population is approximately 7 million, it is estimated that there are approximately 10,000 patients (7). Armenia is probably the next country with widespread FMF. It is estimated that the prevalence of FMF is approximately 1:500 and with a population of 3 million, the total number of patients is approximately 6,000 (8). Other countries in the Middle East such as Jordan, Syria, and Lebanon have many FMF patients, but their exact number is not known (9,10).

In addition to the above countries, FMF is found in significant numbers in North African countries, Greece, Crete, France, Germany, Italy, and the US (11–14). In recent years, approximately 100 cases have been reported in Japan (15, 16, and Tsuchiya-Suzuki A, et al: unpublished observations). On the other hand, there are countries where FMF has not been found or reported. These include sub-Saharan African countries, Ethiopia, Yemen, and Scandinavian states, as well as South Asian and Far Eastern countries such as India and Thailand.

The identification of the MEFV gene associated with FMF and the prevalence of its mutations in the different ethnic groups allowed some hypotheses on the phylogeny of the disease (12).

Distribution of MEFV mutations in FMF patients around the world

The 4 main mutations found in the studies that identified the MEFV gene responsible for FMF were p.M680I,
Figure 1. World map showing the countries where familial Mediterranean fever (FMF) is relatively common. Circle size is proportional to the size of the FMF community in that country. Arrows show the possible ways of spreading the disease. Red arrows show the migration of the MEFV mutations in the ancient world. The yellow arrow corresponds to the Silk Road, while black arrows denote the migration of the disease in the new world.

p.M694V, p.M694I, and p.V726A on exon 10 (17,18). Subsequently, the p.E148Q sequence alteration was identified on exon 2 (19). These were found to be the most common mutations among the populations of the countries where FMF is prevalent. Several studies have pointed out that these 5 mutations are responsible for more than 85% of FMF patients in the Middle Eastern area (1).

Many other sequence alterations (more than 180) have already been recorded in Infevers, an online database for autoinflammatory mutations (online at http://fmf.igh.cnrs.fr/ISSAID/infevers). However, most of them are relatively rare and do not have a clinical phenotype, and many are found exclusively in populations where FMF is uncommon (20). For example, sequence alterations p.H478Y and p.E163A are mainly found among Spanish patients (21).

When the repertoire of mutations was analyzed in different populations (Table 1), an interesting picture was drawn that could shed some light on the possible ways these mutations spread. In Israel, Jews of Middle Eastern origin (e.g., Iraq, Syria) carry many kinds of mutations similar to those in Arabs, Armenians, and Turks. However, Jews of North African origin have only the mutations p.M694V and p.E148Q, whereas Ashkenazi Jews carry only the mutations p.E148Q and p.V726A. It seems that these 3 mutations are very ancient and appeared in the Middle East (Mesopotamia) more than 2,500 years ago (22). Mutation p.M694V migrated to Spain and North Africa either in the early days via sailors (Phoenicians) who crossed the Mediterranean Sea from the Middle East or later (in the 8th century) via land migration westward during the Muslim conquest of North Africa and Spain (Figure 1). Mutation p.V726A migrated to Europe either by sea or by land (1). In both cases, these reflect the consequences of the immigration of a few families carrying these mutations and spreading them in their new location, leading to a founder effect. An interesting observation among the “Chuetas” community in Palma de Mallorca can further support this hypothesis (21,23,24). The “Chuetas” are descendants of converted Jews who were expelled from Spain to Palma de Mallorca in the 11th century. They comprise approximately 18 families in whom more than 60 FMF patients have been diagnosed. An analysis of their FMF clinical manifestations and their haplotypes disclosed great similarity to FMF in North African Jews, who are descendants of those expelled from Spain in the 16th century. This suggests that the founder of both of these populations lived in Spain, probably arriving with the Muslims who came from the Middle East in the 8th century. Because Armenia has a direct land connection with Turkey, it is most likely that neighboring interactions brought FMF from Asia Minor to Armenia. A less plausible explanation, although a more interesting one, would be the migration of Jews from the Middle East to the Caspian Sea in the 8th century to the kingdom of the Khazars, who converted to Judaism. This interaction could have also brought FMF to this area of Caucasus.

Most FMF patients in France are of North African origin, and most of those who live in Germany are of Turkish origin. Most FMF patients in Italy are located in the central and southern parts of the peninsula. Their origin is probably composed of Greeks, Turks, and Phoenicians who came by way of the sea (14). FMF migrated from the Middle East (to Europe) in ancient times and reached the “new world” (the US) in modern times. In the US, there are FMF patients in communities originating from Armenia (mainly in California) and from North African and Middle Eastern countries (on the east coast). In South America, most FMF patients are immigrants from the Middle East and North Africa, although it has also been proposed that Spanish ancestors brought the disease when Spain conquered this continent.

A recent case report described a Gypsy woman with FMF in Hungary (25). Since the origin of the Gypsies is in India, where the disease has not been reported, it is assumed that intermarriage with local Balkan or Turkish citizens is responsible for this unexpected finding.

An interesting question is raised regarding the presence of FMF in Japan. The possibility that the Silk Road was also the route for spreading FMF, as is the case with Behçet’s disease (BD), is quite plausible. Supporting this

| Table 1. Most frequent mutations according to various ethnic groups and countries |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
view are the studies claiming that FMF is more prevalent among patients with BD than in the control populations, and that patients with BD carry \textit{MEFV} mutations more than controls (26,27). However, such a possibility would predict a larger repertoire of mutations in Japan (similar to that found among Turkish and Armenian patients). Furthermore, one would expect to find more FMF cases in Japan resembling the high prevalence of BD. The fact that the number of mutations in Japan is relatively restricted, consisting mainly of p.M694I, p.E148Q, and p.[E148Q; L110P] in cis, calls for the possibility of a founder effect. Indeed, the presence of this complex allele was reported for the first time in Turkish families where the p.M694I mutation is also prevalent, further supporting the notion of Turkish origin through the Silk Road (20). However, the possibility of de novo appearance of the mutations cannot be ruled out. This is supported by the fact that these mutations are on exons 2 and 10, which contain a large area of hot spots for sequence alterations (Table 2).

### Clinical manifestations of FMF in various populations

The typical manifestations of FMF include fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema. In different individuals, the disease may present differently or may change its course over the patient’s lifetime. Similarly, different manifestations of FMF have been observed among populations of various ethnic origins. Comparison of different populations showed that fever and peritonitis were present in more than 90% of the patients (Table 3). In the group of patients from Crete, the rates of these manifestations were somehow lower and no explanation was offered (12). In most populations, joint involvement is the next common symptom of FMF. However, in Armenians and Japanese, pleuritis is more prevalent than arthritis. The prevalence of skin rash (erysipelas-like erythema) is much lower in all of the FMF populations studied (Table 3). Joint involvement (arthritis) was much more common among non-Ashkenazi Jews than in Turks, Arabs, Armenians, or Japanese. The question is: what are the reasons for these differences?

Following the isolation of the \textit{MEFV} gene and mutations, numerous studies tested the genotype–phenotype correlations in FMF patients in different countries. When FMF was first discovered, it was shown that homozygosity for p.M694V was associated with more severe disease, including early onset, more frequent attacks, significantly more joint disease, a higher dose of colchicine needed to control attacks, and a higher rate of amyloidosis among patients not adequately treated (28). These results were confirmed in further studies performed in Israel, France (with Armenian patients), and in Middle Eastern countries (Jordan and Lebanon) (22–24). However, some studies from Turkey were not in agreement with these results, but many recent studies from this country do show similar results (5,29–31).

The various manifestations of FMF in different populations reflect the change in repertoire of mutations in the specific populations. Usually, p.V726A causes a relatively mild disease. When mutations are on exon 2 (such as p.E148Q), the disease is milder with less arthritis and there may be more pleuritis and almost no amyloidosis. The p.E148Q mutation leads to FMF expression almost exclusively when associated with other mutations. Fifty percent of homozygotes for E148Q are asymptomatic, suggesting that this sequence variant is expressed only under certain circumstances, genetic backgrounds, or environmental factors (32).

Patients carrying p.M694V, p.M694I, or p.M680I mutations are prone to have a more severe disease, more joint

### Table 2. \textit{MEFV} mutations associated at least once with typical presentation of familial Mediterranean fever

<table>
<thead>
<tr>
<th>Exon 1</th>
<th>Exon 2</th>
<th>Exon 3</th>
<th>Exon 5</th>
<th>Exon 9</th>
<th>Exon 10</th>
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<tr>
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<td>V469L</td>
<td>I591T</td>
<td>D661N</td>
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<td>R354W</td>
<td>H478Y</td>
<td>M690L</td>
<td>M680LG</td>
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<td>F479L</td>
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</tr>
<tr>
<td>E148Q</td>
<td>I692DEL</td>
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<td>T681I</td>
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<td>R151S</td>
<td>M694I</td>
<td>M694I</td>
<td>M694I</td>
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</tr>
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<td>M694I</td>
<td>M694I</td>
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</tr>
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<tr>
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</tr>
<tr>
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<tr>
<td>P283L</td>
<td>A744S</td>
<td>A744S</td>
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<tr>
<td>A289V</td>
<td>R761H</td>
<td>R761H</td>
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<td>R761H</td>
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* Note the numerous mutations, especially in exons 2 and 10 (adapted from Infevers). Only the usual names are shown.

### Table 3. Main familial Mediterranean fever manifestations in various countries and populations

<table>
<thead>
<tr>
<th></th>
<th>Armenia</th>
<th>Turkey</th>
<th>Israel</th>
<th>Arabs</th>
<th>Italy</th>
<th>Crete</th>
<th>Japan</th>
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<tr>
<td>No. of patients</td>
<td>335</td>
<td>2,838</td>
<td>576</td>
<td>175</td>
<td>71</td>
<td>71</td>
<td>80</td>
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<tr>
<td>Fever, %</td>
<td>94</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td>92</td>
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<td>98</td>
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<td>Peritonitis, %</td>
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<td>93</td>
<td>96</td>
<td>93</td>
<td>91</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>Pleuritis, %</td>
<td>84</td>
<td>31</td>
<td>43</td>
<td>32</td>
<td>52</td>
<td>21</td>
<td>61</td>
</tr>
<tr>
<td>Arthritis, %</td>
<td>39</td>
<td>47</td>
<td>70</td>
<td>33</td>
<td>63</td>
<td>38</td>
<td>27</td>
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<td>Skin rash, %</td>
<td>15</td>
<td>21</td>
<td>40</td>
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<td>14</td>
<td>12</td>
<td>57</td>
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</tbody>
</table>
involvement, and a greater chance of developing amyloidosis. If their prevalence is high in the studied population, the overall clinical expression would be of a more severe disease. If in a given population the frequency of the p.M694V or p.M694I mutations is low, the disease would on average run a milder course.

Thirty years ago it was observed that FMF patients of North African origin in Israel had a much more severe disease than those of Iraqi and Syrian origin (33). Following the isolation of the MEFV gene, a genetic analysis revealed that the patients whose origins were in North Africa mainly carried the p.M694V mutation, explaining why they have a more severe disease, whereas Iraqi Jews carried relatively more of the p.V726A and p.E148Q mutations.

Are there additional factors that may play a role in the disease manifestations and complications? It seems quite obvious that environmental factors may have an influence on the disease. A typical example is the case of amyloidosis. Many years ago, it was shown that in Armenian FMF patients living in Armenia, the prevalence of amyloidosis was higher than in Armenian FMF patients living in the US (34). Recently, similar results were reported in Turkish patients. In FMF patients living in Turkey, the disease score was much higher than that in Turkish FMF patients living in Germany (35). The proposed explanation was the lack of colchicine availability for treating FMF in Turkey and Armenia compared with Germany and the US, respectively. This view is supported by the worldwide study of 2,482 FMF patients, in whom 260 developed amyloidosis (36). It was found that the country of recruitment rather than the MEFV genotype was the key risk for renal amyloidosis. This risk, which paralleled infant mortality rates, indicates a possible environmental origin (availability of health systems) for amyloidosis susceptibility.

In addition to the typical manifestations of FMF, some less frequent presentations should also be mentioned. Protracted febrile myalgia is a rare form of vasculitic disease that affects patients with FMF. Mutation analysis disclosed a high association with M694V homozygosity and more severe disease. This syndrome may last 10–14 days and may require steroids in addition to colchicine treatment (37). A few FMF patients experience severe attacks of FMF during their menstrual period (38). Estrogen can inhibit tubulin assembly using a binding site analogous to colchicine sites. This effect may add to the colchicine action in preventing FMF attacks. In menstruation, estrogen levels are sharply decreased and their protective effect disappears, leading to the acute attack. The central nervous system and the meninges are spared in FMF. However, Mollaret meningitis was reported as part of FMF, although in many cases the causative agent was identified as herpesvirus 6 (39).

**Diagnosis of FMF**

The diagnosis of FMF in countries where the disease is common is principally based on clinical grounds. Typical periodic attacks of fever and serositis lasting 1–4 days in a patient from the appropriate ethnic origin confirm the diagnosis of FMF. Family history of FMF and a good response to colchicine further support this diagnosis.

Blood levels of fibrinogen, SAA, and C-reactive protein are nonspecific and do not contribute to the initial diagnosis of FMF. However, they may be of value in monitoring the course of the disease and the response of the patient to treatment (40,41).

In cases where the patient does not present typical manifestations of FMF and the above components do not exist, a genetic diagnosis is warranted. In countries where FMF is widespread, the genetic test is contributory under 2 conditions: when the patient carries 2 mutations and therefore certainly has FMF, or if the patient does not carry any mutation and thus probably does not have FMF (in almost all cases). However, because in populations with a high prevalence of FMF the carrier rate is high as well, the detection of a single mutation (heterozygosity) does not help in making the diagnosis. In such cases, there is a major role for a therapeutic trial where an FMF patient is expected to respond to colchicine, whereas nonresponders deserve further evaluation. Our practice in patients carrying a single mutation and who respond to colchicine is to discontinue the medication. If the patient develops an FMF attack within a few days following cessation of the drug, this is an additional clue supporting the diagnosis of FMF. This approach for making a diagnosis is also used in patients highly suspected of having FMF but in whom no mutation (among those tested in the particular laboratory) could be detected.

In countries where FMF is rare, the mutations involved in the disease may lead to a milder disease or to an atypical presentation. Furthermore, a family history for the disease would probably be negative. Therefore, a clinical diagnosis of FMF may be too difficult and the role of genetic testing is much more crucial. In these populations, looking for the 5 most common mutations for FMF (in Middle Eastern countries) may not be sufficient and many potential FMF patients may be misdiagnosed.

**Treatment of FMF**

Since the report by Goldfinger in 1972, colchicine remains the treatment of choice for FMF all over the world (3). Colchicine can be given to children with the disease even before the age of 1 year. It was shown that children younger than 5 years of age might need colchicine dosages ranging from 0.03 to 0.07 mg/kg/day (42). Children weighing more than 10 kg can take 1 mg of colchicine daily. In most adults, 1 mg is the optimal dose for controlling the disease and preventing amyloidosis. However, in the more severe disease, the dosage can be increased to 2.5 mg daily provided that the liver and kidney functions of the patient are normal. Interestingly, many adult FMF patients in Japan are asymptomatic even with a single tablet of colchicine (0.5 mg) daily. This may reflect their relatively mild disease. In patients who cannot tolerate colchicine due to its causing diarrhea, it is recommended that the daily dose should be divided and taken 2 or 3 times in the course of a day. In addition, there is the possibility of taking medications such as tincture belladonna or tincture
oppii to counteract the tendency for diarrhea. As a matter of fact, in France there is a formula called Colchimax that contains 1 mg colchicine and 12.5 mg opium powder. Colchicine is a relatively safe medication. It can be given to FMF patients during pregnancy, and in contrast to our previous policy, we no longer recommend amniocentesis (Ben-Chetrit Eli, et al: unpublished observations). We also recommend continuing colchicine while nursing, since the dose to which the newborn or infant is exposed is very low (43). Colchicine does not inhibit a child’s growth. On the contrary, following treatment with colchicine and controlling the FMF attacks the children have a growth spurt (44). In countries where FMF is common, there is a higher incidence of severe disease as well as treatment-resistant disease (45). In cases resistant to colchicine, several therapeutic options have been suggested over the years, including thalidomide, interferon, anti–tumor necrosis factor (anti-TNF) agents, and anakinra (46–48). When thalidomide was tried in FMF patients nonresponsive to colchicine, it showed good efficacy but the side effects were almost intolerable. Studies evaluating the effect of interferon injection in FMF were inconclusive because some studies claimed that it is effective, whereas others did not. The experience with anti-TNF agents and anakinra is very limited and comprises only a few case reports (46–48). All of the treatment modalities other than colchicine have not been tested for their effect in preventing amyloidosis. Nevertheless, some of them showed a beneficial effect in treating already established secondary amyloidosis developed in patients with chronic inflammatory diseases such as rheumatoid arthritis (49,50). In some FMF patients in Japan, treatment with prazosin, reserpine, azelastine, and herbal medicines have also been reported (51).

**Prognosis of FMF**

FMF prognosis primarily depends on the development of amyloidosis. The development of amyloidosis is closely related to the genotype of the patients and their treatment with colchicine. If they have mutations associated with mild disease, they will probably not develop amyloidosis and will respond to colchicine.

However, as already mentioned, there are other genetic modifiers such as sex and SAA polymorphisms and environmental factors that may affect the prognosis (amyloidosis), which should also be taken into account (35). Finally, it should be emphasized that the severity of FMF attacks and their frequency usually decrease as the patient gets older.

**Summary**

The above overview shows that FMF is not restricted to Mediterranean countries, and the lack of diagnosis in other areas of the world is probably due to a lack of awareness of this fascinating disease. Based on the carrier states of MEFV mutations, FMF is expected to be found in many other countries and it may well be that such patients have either mild disease according to the kind of mutations they carry or the environmental factors, or that they were mistakenly diagnosed as having another disease such as BD, systemic lupus erythematosus, palindromic rheumatism, or rheumatic fever, diseases whose clinical features resemble FMF.

We hope that the present review will raise the awareness of physicians regarding this disease so that patients can obtain the correct diagnosis and receive the appropriate treatment.

**AUTHOR CONTRIBUTIONS**

All authors were involved in contributions to study conception and design, acquisition of data, or analysis and interpretation of data, and drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ben-Chetrit had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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