

Familial Mediterranean fever: different faces around the world

E. Ben-Chetrit¹, H. Yazici²

¹Rheumatology Unit,
Hadassah-Hebrew University
Medical Center, Jerusalem, Israel;
²Academic Hospital, Istanbul Turkey.

Eldad Ben-Chetrit, MD
Hasan Yazici, MD

Please address correspondence to:
Dr Eldad Ben-Chetrit,
Rheumatology Unit,
Hadassah-Hebrew University
Medical Centre, POB 12000,
91120 Jerusalem, Israel.
E-mail: eldad@hadassah.org.il

Dr Hasan Yazici,
Academic Hospital Uskudar,
Istanbul 34668, Turkey.
E-mail: hasan@yazici.net

Received on March 6, 2019; accepted in
revised form on May 6, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 121):
S18-S22.

© Copyright CLINICAL AND
EXPERIMENTAL RHEUMATOLOGY 2019.

Key words: familial Mediterranean
fever, *MEFV* gene

Competing interests: E. Ben-Chetrit has
received speaker fee (less than \$5000)
from Novartis. H. Yazici has declared
no competing interests.

Familial Mediterranean fever (FMF) is a well-defined autoinflammatory disease, associated with mutations in the *MEFV* gene (1). Typical presentation of the disease is characterised by recurrent attacks of fever, serositis (peritonitis, pleuritis, pericarditis, etc.) and erysipelas-like erythema (ELE).

Over the years we have encountered patients from around the world whom we have diagnosed as having: FMF, atypical FMF and FMF-like disease, due to atypical presentations and different modes of inheritance. The question raised is whether we really have such diverse entities and whether we can fix the puzzle of these various medical conditions.

The first official description of FMF was reported in the USA by Siegal in 1945 (2). In his monograph the clinical features of the disease included: “Recurrent attacks of fever sometimes with chills, severe abdominal pains (peritonitis), and chest pain due to pleuritis. In some cases patients had nausea and vomiting while diarrhoea was usually absent”. Siegal claimed that he did not see skin eruption during the attacks “though occasionally one could experience urticarial rash”. The onset of FMF was during the second or third decades of life and the course of the disease described as benign.

Reimann, who reported on additional FMF cases from Lebanon, added the following features: pain in the arm, leg, hands and feet during attacks (which means joint involvement). The attacks frequency was regular every 17–22 days (3). The duration of the attacks ranged from 5 to 7 days and between the acute episodes the patient did not experience any symptoms. In most attacks “one could not find the cause but emotional stress (such as death of husband) resulted in higher frequency of attacks”. During the acute event erythrocyte sedimentation rate (ESR) was elevated. In

occasional cases Reimann noticed leukopenia.

It should be pointed out that both physicians Siegal and Reimann saw Middle Eastern FMF patients and yet their description of the disease is very different. This discrepancy raises a question as to whether all the patients they described did have FMF or other autoinflammatory diseases. For example, regular attacks are typical in the syndrome of periodic fever, oral aphthosis, pharyngitis and cervical adenitis (PFAPA) rather than FMF and attack duration of 5–7 days is typical in mevalonate kinase deficiency (MKD) or PFAPA rather than in FMF (4, 5).

Familial Mediterranean fever in the Middle East

Based upon several series from the Middle East, a typical case of FMF includes the following features: recurrent attacks of fever accompanied by serositis (peritonitis, pleuritis, pericarditis, synovitis) in one or more sites in a single attack. The typical skin manifestation of FMF is erysipelas-like erythema (no urticaria or maculopapular rash, as reported by Siegal). Disease onset is usually in early childhood, therefore 90% of patients present before the age of 20 (6). The attack frequency is not regular (in contrast to the Reimann report) and in the Middle East it lasts between 24 to 72 hours, and not 5 to 7 days. Since FMF is a prototype inflammatory disease, it is characterised by elevated acute phase reactants (C-reactive protein [CRP], ESR) and leucocytosis rather than leukopenia. Additional features of “typical” Middle Eastern FMF are as follows: about 60% of the patients carry 2 *MEFV* mutations, 30% carry a single mutation (heterozygotes) and in about 10% there is no detectable mutation. Most common mutations in these populations are: M694V, V726A, M680I, E148Q (1, 7–8). Over 70% of the pa-

tients carry exon 10 mutations and most cases are familial rather than sporadic. Most patients require a relatively high colchicine dose to control the disease. The risk for amyloidosis is relatively high in Middle Eastern FMF patients if not treated. Table I compares 4 Middle Eastern groups of FMF patients (7-10). It seems that the 4 populations have similar FMF features with a higher frequency of pleuritis among Armenians and higher frequency of arthritis and ELE among Non-Ashkenazi Jews in Israel. A possible explanation for this difference is the observation from Turkey (7) that FMF patients carrying M694V tended to have more ELE and arthritis. It may well be that among the non-Ashkenazi Jews, M694V is more common since most of these patients are from North Africa where the main mutations carried are M694V and E148Q.

In Europe and America, FMF patients who have Middle-Eastern ancestry generally display similar genetics and phenotype as those living in the Middle East, though their disease severity may be milder.

Familial Mediterranean fever in Japan

Up to now, more than 600 FMF Japanese patients have been described. What are the clinical manifestations of FMF in Japan?

Two large studies from this country disclose the following observations (11, 12). The frequency of fever and peritonitis is relatively low. On the other hand, the presence of headache is quite common. Table II compares some features of FMF between Turkish (as a representative of the Middle Eastern type) and Japanese patients. It is shown that among the Japanese the attack duration is longer (4–7 days) and the disease responds to a relatively low dose of colchicine. Fifty percent of Japanese FMF patients are on less than 0.5 mg and 84% on less than 1.0 mg colchicine daily.

Familial Mediterranean fever in Europe (with no Middle-Eastern origin)

The clinical manifestations of FMF patients with European origin include the following: their mean age at disease

Table I. Clinical manifestations of FMF in 4 different Middle-Eastern communities.

	Armenians	Turks	Israelis	Arabs
Ref.	(8)	(7)	(9)	(10)
No. of patients	100	2838	470	192
Fever %	100	92	100	100
Peritonitis %	96	93	95	82
Pleuritis %	78	31	66	43
Arthritis %	37	45	77	37
Headache %	—	—	—	—
(Erysipelas like erythema) %	8	21	47	3

Table II. Comparing FMF clinical features between Middle Eastern and Japanese patients.

	Middle-East-Turkey	Japan	
Ref.	(7)	(11)	(12)
Age of onset/y	9.6 ± 8.5	19.6 ± 15.3	23 ± 13
Male/female	1.2	0.84	0.78
Attack frequency/y	15	12	
Attack duration/D	1-3	4.7 ± 7.7	
Average Colch/D	0.5-3.0	0.84 ± 0.45	0.8 mg/day
Mutation Carrier	90%	86%	
Response to Colchicine	85-90%	60-92%	

onset is 16.6 ± 11.2 years, with attack duration of about 5 days (13). Many patients complain of oral aphthosis, erythematous pharyngitis, arthralgia, vomiting, abdominal pain, diarrhoea, conjunctivitis, headache and enlarged cervical lymph nodes. Laboratory test results show increased levels of WBC, ESR, and CRP. The patients usually experience recurrent fever >38°C, but sometimes they present with rash, and in rare cases they do not display elevated acute phase reactants (APR). Furthermore, in some cases the patient does not respond to colchicine.

In a three-generation Spanish kindred, five affected members presented a severe periodic inflammatory disorder segregating with the rare p.H478Y *MEFV* variant located in exon 5 (14). These patients had longer attack duration, resistance to colchicine and dominant inheritance in contrast to the Middle Eastern type of FMF. In a family of British descent with a colchicine-responsive periodic fever syndrome, whole exome sequencing (WES) revealed a c.1730C>A missense mutation in exon 8 resulting in the p.T577N substitution (15). Their disorder was similar to FMF (fever, systemic inflammation, response to colchicine or IL-1 blockade) but somewhat distinct from it (dominant inheritance, week dura-

tion of attacks, evanescent urticaria-like skin rash). Dominant inheritance of genetic variants leading to p.T577N was also recently observed in a Japanese family with pyrin associated autoinflammatory disease (PAAD) (16). Table III compares three populations of FMF patients emphasising the relative resemblance between European and Japanese patients, with a significant difference with the Turkish population presenting Middle Eastern type of FMF. The main differences are related to the age at onset, attack duration, response to colchicine and the presence or absence of headache or skin rash.

Proposed explanation for the different presentations

In order to explain the differences between Japanese and Europeans FMF patients and the Middle Eastern cases, we should look back to see the differences in *MEFV* mutations (genotype) spread among these various populations. Genetic analyses of Japanese patients disclose that only 26% carry exon 10 mutations (11). The main mutation in this exon is M694I and none carry the M694V variant. Other exon 10 mutations such as M680I or V726A, which are most common in the Middle East, are hardly seen among Japanese patients. Seventy-four percent of Japa-

nese patients carry mutations in exons 1 to 4 such as E148Q, P369S-R408Q (in Cis), L110P-E148Q (in Cis) and E84K. Some of them are considered as polymorphisms rather than real disease causing mutations. However, among those with *MEFV* mutations, 60% carry two or more mutations (compound heterozygotes) and their mode of inheritance is recessive.

When the clinical manifestations of Japanese patients carrying exon 10 mutations were compared with those who carry 1-4 exon mutations, an interesting observation was made. In those carrying M694I, the attack duration was shorter (3 days), they had more peritonitis, pleuritis and arthritis, and they had a better response to colchicine (12). Moreover, family history for FMF was significantly higher among carriers of exon 10 mutations compared with those carrying other mutations.

The patients with exon 1-4 mutations have late disease onset, longer attack duration (7 days) and less favourable response to colchicine. Moreover, fifty percent of those with L110P-E148Q did not display fever during the acute attack and some did not have elevated CRP (11-12). It seems that there is no question regarding the correlations between the genotype and the phenotype in Japan. Patients carrying exon-10 mutations resemble more the features of the Middle-Eastern type of FMF, while those with other mutations raise a question as to their exact diagnosis. Similar findings were observed in Europe where patients carrying exon-10 mutations exhibit clinical features of the Middle Eastern pattern. Those carrying non-exon 10 mutations display “atypical” manifestations and sometimes a different mode of inheritance and therefore gained the names “FMF-like” or “atypical FMF”. In some of these “atypical FMF” patients who present with erythematous pharyngitis, headache, skin rash and attack duration of 5 days, there may well be a misdiagnosis of mevalonate kinase deficiency (MVD) or other auto-inflammatory diseases.

Based upon the above observations, we may postulate that the genotype (Exon-10 mutations) is responsible for the Middle Eastern “typical” FMF pattern,

Table III. Comparison of the clinical features of FMF among Middle Eastern, European and Japanese patients.

(Ref)	Middle-Eastern (7)	European (13)	Japan (11-12)
No patients	3600	12	248
Fever %	98	100	89
Peritonitis %	91	92	62
Pleuritis %	57	40	40
Arthritis %	49	42	36
Skin rash (ELE)	20	8	7
Headache %	-	25	12
Age of onset (D)	9.6±8.5	16.6± 11.2	9.6 ± 15.3
Attack duration	1-3	3.0±1.9	4.7 ± 7.7
Colchicine response	good	partial	partial

whereas those with variant FMF presentations carry non exon-10 mutations.

Additional factors affecting the different faces of FMF in the world

Role of country of residence

In a study by Ozen *et al.* it was shown that the offspring of Eastern Mediterranean (Turkish) FMF patients who migrated to Europe (Germany) display a milder disease (17). This may reflect the effect of environment on the expression of a classical genetic disease such as FMF. However, Giese *et al.* did not find such a difference (18).

In Armenian FMF patients living in Armenia, the prevalence of amyloidosis is much higher than that of Armenian FMF patients living in the USA (8). In a large study conducted by Touitou *et al.* it was found that the most significant factor dictating the development of amyloidosis in FMF patients was the country of residence (19). This observation raises a question as to the meaning of country of residence; is it related to health care quality, diet, colchicine availability etc.?

Role of epigenetic and microbiota in the presentation of FMF

Does epigenetics have a role in FMF phenotype? Theoretically, epigenetic mechanisms such as histone modification, methylation, and microRNAs may play a role in the pathogenesis of FMF thereby affecting its phenotype. As a matter of fact, Kirecetepe *et al.* demonstrated a slightly higher methylation level of exon 2 of *MEFV* in FMF patients when compared to healthy controls (20). However, in an additional study, methylation pattern at

the promoter region was not found to be different from controls (21). Thus we do not yet have any clear proof for the role of epigenetics in FMF.

Microorganisms may affect FMF phenotype. It has been shown that pyrin is a pathogen recognition receptor (PRR) which may detect virulent pathogenic activity (22). Therefore, it is conceivable that the cross-talk between the innate immune system and commensal gut bacteria (microbiota) may also affect (or may be affected by) the inflammatory status of the patient, as well. Khachatryan *et al.* showed that the composition and divergence of microbiota were different during attack and attack-free periods as well as between FMF patients and healthy controls (23). However, more studies are needed in order to better evaluate the role of microbiota in FMF phenotype.

What are the implications of the different faces of FMF in the world?

The different faces of FMF around the world have implications on the taxonomy (naming) of this disease, its diagnosis, prognosis and treatment.

Regarding the implication on taxonomy, it seems that we cannot use the name FMF for all entities related to *MEFV* mutations (24). The reason for that is that in some cases the disease is not familial, or not Mediterranean and even seldom with fever. We propose that the name familial Mediterranean fever should be restricted to the “typical” clinical manifestation of the disease, as manifested in the Middle East. This classical expression is dictated mainly by the carriage of mutations in exon-10 of the *MEFV* gene. For the

other non-classical or typical presentation we can use a general term (“roof” name) of pyrin-associated autoinflammatory disease (PAAD). The subtypes of this general term may also include exon-10 mutation associated disease (“typical” “classical” FMF). Patients with atypical FMF features who carry non-exon 10 mutations should remain with the name pyrin-associated autoinflammatory diseases (PAAD) instead of “FMF-like”. Those with specific clinical features will keep their names with suffix “-like”. For example, *MEFV* mutations presenting as chronic recurrent multifocal osteomyelitis should be named CRMO-like disease, whereas when *MEFV* mutations cause totally different features a new name should be used as the case with pyrin-associated autoinflammatory disease with neutrophilic dermatosis (PAAND) (25, 26). Regarding the implication on diagnosis, in a study by Migita *et al.* of 116 Japanese FMF patients, 25 did not meet the Tel Hashomer criteria and would not have an FMF diagnosis (11). This means that Japanese patients need different criteria for FMF diagnosis, since the Tel Hashomer criteria are not applicable in many. Moreover, in Japan and Europe, physicians have to rely more on genetic testing for diagnosis, whereas in the Middle East, in the vast majority of cases, the diagnosis can be made on clinical basis only. In European countries where the disease is relatively rare, there may be a delay in the time from disease onset to diagnosis and treatment (Germany) (18). Delay in diagnosis has also been observed in Japan (11, 12). Regarding the implication on treatment, it is found that in the Middle East, colchicine remained the main effective treatment for most cases of FMF (over 90%). However, in Japan, the response is better when the patients carry exon-10 mutations. Colchicine was effective in 91.8% of these patients at a relatively low dose (mean dose 0.89 ± 0.45 mg/d) (10). In patients with exons 1-4 mutations, colchicine is less effective and some Japanese FMF-like patients were treated with: prazocin, reserpine, azelastine, herbal medicines and interferon (27). In rare cases an earlier decision for anti-IL-1 treatment may be required.

Conclusions

Clinical manifestations of FMF differ between populations (Middle-Eastern vs. Europeans and Japanese). These differences may be related mainly to the different genetic load; typical Middle Eastern FMF pattern is associated with exon-10 mutations. Atypical features of FMF are associated with non-exon-10 mutation. Still, there are differences between FMF patients from the same ethnic populations with the same genotype while living in different countries. These differences are related mainly to the severity of the disease rather than to their clinical presentation. These changes allude to the possible role of epigenetic variants, microbiome influence and additional environmental factors. Based upon the above data we propose that the name FMF remains only for the specific entity commonly found in the Middle East and associated mainly with exon 10 mutations. In Japan and Europe those who carry non-exon-10 mutations may present differently and should be named pyrin-associated autoinflammatory disease (PAAD) or FMF-like syndrome. The *MEFV* gene may cause or be associated with totally different diseases such as: FMF, CRMO-like, pyrin-associated autoinflammatory disease with neutrophilic dermatosis (PAAND), and more (26, 27, 28). In Middle-Eastern patients the diagnosis of FMF may be based on clinical ground only whereas in countries where FMF is rare one should rely on genetic testing for diagnosis. Response to colchicine is best in typical FMF. In the other presentations, IL-1 agents should be considered earlier in the course of the disease. These different clinical entities may lead to a delay in diagnosis and may affect their prognosis. In 1997 the *MEFV* (Mediterranean Fever) gene was isolated. The concept then was that of “one gene, one disease (FMF) and vice versa”. In 2019 *MEFV* is not the correct name for the gene since it is associated with many other syndromes that are totally different from FMF, especially in countries far from the Mediterranean basin. Moreover, we should remember that recently it was reported that mutations in the

MVK gene may display typical features of “classical” FMF, suggesting that *MEFV* is probably not the only gene associated with the clinical presentation of FMF (29). Therefore, we can no longer say that *MEFV* and FMF represent “one gene for one disease and vice versa”.

References

1. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351: 659-64.
2. SIEGAL S: Benign paroxysmal peritonitis. *Ann Intern Med* 1945; 23: 234-4.
3. REIMANN HA: Periodic disease; a probable syndrome including periodic fever, benign paroxysmal peritonitis, cyclic neutropenia and intermittent arthralgia. *J Am Med Assoc* 1948; 136: 239-44.
4. MARSHALL GS, EDWARDS KM, BUTLER J *et al.*: Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *J Pediatr* 1987; 110: 43-6.
5. FRENKEL J, HOUTEN SM, WATERHAM HR *et al.*: Mevalonate kinase deficiency and Dutch type periodic fever. *Clin Exp Rheumatol* 2000; 18: 525-32.
6. SARI I, BIRLIK M, KASIFOĞLU T: Familial Mediterranean fever: An updated review. *Eur J Rheumatol* 2014; 1: 21-33.
7. TUNCA M, AKAR S, ONEN F *et al.*: Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine* (Baltimore) 2005; 84: 1-11.
8. SCHWABE AD, PETERS RS: Familial Mediterranean fever in Armenians. Analysis of 100 cases. *Medicine* (Baltimore) 1974; 53: 453-62.
9. SOHAR E, GAFNI J, PRAS M, HELLER H: Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967; 43: 227-53.
10. EL-SHANTI H, MAJEED HA, EL-KHATEEB M: Familial Mediterranean fever in Arabs. *Lancet* 2006; 367: 1016-24.
11. MIGITA K, UEHARA R, NAKAMURA Y *et al.*: Familial Mediterranean fever in Japan. *Medicine* (Baltimore) 2012; 91: 337-43.
12. KISHIDA D, NAKAMURA A, YAZAKI M *et al.*: Genotype-phenotype correlation in Japanese patients with familial Mediterranean fever: differences in genotype and clinical features between Japanese and Mediterranean populations. *Arthritis Res Ther* 2014; 16: 439-49.
13. GATTORNO M, SORMANI MP, D'OSUALDO A *et al.*: A diagnostic score for molecular analysis of hereditary autoinflammatory syndromes with periodic fever in children. *Arthritis Rheum* 2008; 58: 1823-32.
14. ALDEA A, CAMPISTOL JM, AROSTEGUI JI *et al.*: A severe autosomal-dominant periodic inflammatory disorder with renal AA amyloidosis and colchicine resistance associated to the *MEFV* H478Y variant in a Spanish kindred: an unusual familial Mediterranean fever phenotype or another *MEFV*-associated periodic inflammatory disorder? *Am J Med Genet* 2004; 124: 67-73.
15. STOFFELS M, SZPERL A, SIMON A *et al.*: *MEFV* mutations affecting pyrin amino acid

- 577 cause autosomal dominant autoinflammatory disease. *Ann Rheum Dis* 2013; 73: 455-61.
16. NAKASEKO H, IWATA N, IZAWA K *et al.*: Expanding clinical spectrum of autosomal dominant pyrin-associated autoinflammatory disorder caused by the heterozygous MEFV p.Thr577Asn variant. *Rheumatology* (Oxford) 2019; 58: 182-4.
17. OZEN S, DEMIRKAYA E, AMARYAN G *et al.*: Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. *Ann Rheum Dis* 2014; 73: 662-7.
18. GIESE A, KURUCAY M, KILIC L *et al.*: Quality of life in adult patients with Familial Mediterranean fever living in Germany or Turkey compared to healthy subjects: a study evaluating the effect of disease severity and country of residence. *Rheumatol Int* 2013; 33: 1713-9.
19. TOUITOU I, SARKISIAN T, MEDLEJ-HASHIM M *et al.*: Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. *Arthritis Rheum* 2007; 56: 1706-12.
20. KIRECTEPE AK, KASAPCOPUR O, ARISOY N *et al.*: Analysis of MEFV exon methylation and expression patterns in familial Mediterranean fever. *BMC Med Genet* 2011; 12: 105.
21. AKKAYA-ULUM YZ, BALCI-PEYNIRCIOGLU B, KARADAG O *et al.*: Alteration of the microRNA expression profile in familial Mediterranean fever patients. *Clin Exp Rheumatol* 2017; 35 (Suppl. 108): S90-4.
22. XU H, YANG J, GAO W *et al.*: Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. *Nature* 2014; 513: 237-41.
23. KHACHATRYAN ZA, KTSOYAN ZA, MANUKYAN GP *et al.*: Predominant role of host genetics in controlling the composition of gut microbiota. *PLoS One* 2008; 3: e3064.
24. BEN-CHETRIT E, GATTORNO M, GUL A *et al.*: Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study. *Ann Rheum Dis* 2018; 77: 1558-65.
25. SHIMIZU M, TONE Y, TOGA A *et al.*: Colchicine-responsive chronic recurrent multifocal osteomyelitis with MEFV mutations: a variant of familial Mediterranean fever? *Rheumatology* 2010; 49: 2221-3.
26. MASTERS SL, LAGOU V, JÉRU I *et al.*: Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation. *Sci Transl Med* 2016; 8: 332ra45.
27. NAKAMURA A, YAZAKI M, TOKUDA T, HATTORI T, IKEDA S: A Japanese patient with familial Mediterranean fever associated with compound heterozygosity for pyrin variant E148Q/M694I. *Intern Med* 2005; 44: 177-8.
28. BEN-CHETRIT E, PELEG H, AAMAR S, HEYMAN S: The spectrum of MEFV clinical presentations – Is it FMF only? *Rheumatology* 2009; 48: 1455-9.
29. KARACAN I, UĞURLU S, TOLUN A, TAHIR TURANLI E, OZDOGAN H: Other autoinflammatory disease genes in an FMF-prevalent population: a homozygous MVK mutation and a novel heterozygous TNFRSF1A mutation in two different Turkish families with clinical FMF. *Clin Exp Rheumatol* 2017; 35 (Suppl. 108): S75-81.