Patient management and the association of less common familial Mediterranean fever symptoms with other disorders

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Purpose: In this study, we present clinical data from 16,000 familial Mediterranean fever patients. We also discuss the clinical manifestation of a subset of these patients and their potential symptom associations with other disorders.

Methods: Familial Mediterranean fever patients were confirmed using Tel-Hashomer criteria and were tested for the 12 most common mutations using the familial Mediterranean fever StripAssay. A total of 100 samples were selected, and their *MEFV* gene exons and intron junctions were completely sequenced.

Results: We observed that in children severe phenotypes with polyserositis, erysipelas-like erythema, splenomegaly, and vasculitis are associated with high penetrance of exon 10 mutations, particularly M694V. Several forms of arthritis were associated with familial Mediterranean fever, including acute mono/oligoarthritis in the lower extremities, destructive arthritis, ankylosing spondylitis, sacroiliitis,

arthritis of the hip joint, and juvenile chronic arthritis. Severe life-threatening complications, such as adhesive intestinal obstruction, renal amyloidosis, and uncommon/rare symptoms were sometimes the only form of familial Mediterranean fever manifestation.

Conclusion: We suggest performing familial Mediterranean fever genetic testing for patients presenting with rare/uncommon symptoms also common in other disorders, to prevent misdiagnosis or delayed diagnosis. In our experience, the most effective patient management for familial Mediterranean fever was its rapid diagnosis through genetic testing, initiation of colchicine therapy, and promotion of attack prevention through counseling.

Genet Med advance online publication 1 August 2013

Key Words: diagnosis, FMF, genetic testing, inflammation, mutation, prevention, symptoms

INTRODUCTION

The gene responsible for causing familial Mediterranean fever (FMF), i.e., *MEFV*, was discovered in 1997; subsequently, several mutations in the *MEFV* gene were identified as causing FMF with different symptoms and severities.^{1,2} Recently, Shohat and Halpern³ presented the FMF symptoms in two major categories—common and rare manifestations. The common manifestations included abdominal attacks, arthritis, arthralgia, pleural attacks, preattack symptoms, and amyloidosis; the rare manifestations were described as protracted febrile myalgia, erysipelas-like erythema, vasculitides, and chronic ascites. On the basis of our experience, we have seen additional symptoms in FMF patients, but their cause has not been established (data not shown); therefore, they could be due to the presence of other disorders. These symptoms were adenopathy, splenomegaly, hepatomegaly, nephral syndrome, constipation or diarrhea, aphthae, and orchitis (the last two were quite rare). FMF symptoms are often shared with other disorders, including fibromyalgia syndrome,⁴ livedoid vasculopathy with ulcers, urticaria,⁵ juvenile idiopathic arthritis,⁶ Behcet disease,^{7,8} inflammatory bowel disease, and ulcerative colitis.⁹ Patients can also present only the rare symptoms, potentially delaying the diagnosis. Nonetheless, treatment with colchicine

has been shown to improve these conditions and assist in patient management.³ These studies also indicate that different *MEFV* mutations could have different phenotypic presentations either with or without common FMF symptoms; therefore, the consequences/symptoms of *MEFV* mutations differ from person to person, and the disorder could manifest itself in a personalized manner.

As the above studies show, these disorders have been associated or accompanied by mutations in the *MEFV* gene, yet the exact roles of the *MEFV* mutations in disorders other than FMF, with the exception of their common link to inflammation, are not fully understood. Studies with large data sets are required to gain new insights into association of FMF with other disorders or discover whether FMF may contribute to their onset or pathogenicity. A first step could be the use of a large patient database to extract a subset of clinically confirmed FMF cases who are also diagnosed with other known conditions. Such studies are particularly important because they can provide statistically significant data sets and assist in focusing on the most informative condition(s) by sifting through and narrowing down the association data for future studies. The Center of Medical Genetics in Yerevan, Armenia, is the primary-care center for patients with FMF and is the leading

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Submitted 25 December 2012; accepted 24 June 2013; advance online publication 1 August 2013. doi:[10.1038/gim.2013.112](https://doi.org/10.1038/gim.2013.112)

agency conducting genetic testing for FMF. Since 1999, ~25,000 patients have been referred to this center and more than 16,000 of them have been confirmed to have FMF, using the gold standard of Tel-Hashomer criteria¹⁰ and corroborated by genetic testing. All phenotypic, genotypic, and relevant information for each one of these patients has been stored in a large database at the Center of Medical Genetics prospectively and during subsequent visits. This vast database has allowed us to conduct original research, collaborate with international research groups, and publish dozens of peer-reviewed articles, all contributing to the understanding and better management of FMF patients. Therefore, we intend to present general phenotype and genotype information, as well as atypical cases and symptoms in FMF patients, and introduce their presumptive association with other disorders from thousands of Armenian patients. Furthermore, we suggest different ways to conduct patient management and emphasize the significance of genetic testing, treatment, and prevention of FMF.

MATERIALS AND METHODS

Clinical diagnosis of FMF was conducted using the international Tel-Hashomer clinical criteria.¹⁰ Of course, response to colchicine, which is part of the Tel-Hashomer criteria, is a major factor in clinical diagnosis of FMF. Patient samples were then tested for the 12 most common mutations within the Armenian population. The FMF StripAssay (Vienna Lab Diagnostics, Vienna, Austria),^{11,12} which is based on the reverse-hybridization principle, was used to identify the following 12 *MEFV* mutations: E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H. These 12 mutations cover more than 98.7% of clinically confirmed FMF cases, even in heterozygous patients with mild clinical FMF, which currently represent ~7.6% of the total population.¹³ A total of 100 samples, 30 homozygous or compound heterozygous, 45 heterozygous, and 25 asymptomatic wild-type controls, were selected, and their *MEFV* gene exons and intron junctions were completely sequenced independently in the United States using dideoxy termination methodology on an ABI 3730 capillary electrophoresis instrument (Applied Biosystems, Carlsbad,

CA). The sequencing facility and the designed primers for all exons were provided by Morava (Glendale, CA). All clinically diagnosed patients were adventerly put on colchicine therapy, and almost all had positive response.

RESULTS

Data from 16,000 FMF patients

We have estimated that the frequency of *MEFV* carrier mutations in the Armenian population is ~20% (one in five), with FMF prevalence of up to 3%.¹⁴ Table 1 shows the frequency of common *MEFV* mutations in 15,424 patients and 450 healthy donors. With the exception of M694I, all common mutations were present in healthy individuals with different frequencies, yet only the frequency of the P369S mutation was higher in healthy individuals (i.e., 4.9%) as compared with 0.49% in compound-heterozygous FMF patients. The frequency of the E148Q mutation was similar in both healthy and affected individuals, suggesting that these two mutations have lower penetrance as compared with the others but could still contribute to the overall FMF symptoms in compound-heterozygous patients.¹³

Phenotype-genotype correlation using data from 3,286 homozygous, 9,254 compound heterozygous, and 2,884 heterozygous patients with symptoms ranging from mild to severe FMF indicated that amyloidosis was associated with M694V, M680I, and V726A homozygous patients. Yet the dominant mutation associated with amyloidosis was M694V, with 256 cases as compared with 108 and 99 cases for V726A and M680I homozygotes, respectively ($P = 0.059$). The M694V allele also appeared in all compound heterozygous and heterozygous (tested for 12 common mutations) patients with amyloidosis. The other symptoms were present in all common genotypes, with slight variations observed for arthritis, skin rashes, and hepatomegaly. Arthritis was almost absent in M680I heterozygous patients and relatively less common in compound heterozygotes with one V726A allele. Skin rashes and hepatomegaly were less frequent in V726A homozygous patients, yet surprisingly higher in affected heterozygous patients, whereas splenomegaly was rare in heterozygous M680I patients (Figure 1). Such variation in symptoms points to a personalized manifestation of FMF symptoms in different genotypes, perhaps due to factors such as other associated conditions, environment, and lifestyle. We initiate colchicine therapy for all confirmed FMF patients immediately and have seen overwhelming positive response. In some cases when the diagnosis is delayed or the therapy has not been initiated on time, the effects of colchicine can be less optimal; we have seen colchicine resistance in 0.006% of the cases.

Data on 1,000 children

We observed that severe phenotype with polyserositis (96.5%) is associated with the high penetrance of exon 10 mutations, including M694V (58.1%), V726A (20.4%), and M680I (15.7%), where the most significant association was with M694V mutations ($P = 0.049$). By contrast, mild or atypical FMF phenotypes

Table 1 Frequency of common FMF mutations from 16,000 patients and healthy individuals

Exon	Mutation	Healthy carriers	Affected FMF patients
Exon 10	M694V	4.70%	40.93%
	V726A	4.60%	27.98%
	M680I	1.80%	18.81%
	R761H	0.20%	3.46%
	M694I	—	0.38%
Exon 5	F479L	0.40%	2.43%
Exon 3	P369S	4.9%	0.49%
Exon 2	E148Q	3.4%	5.09%

FMF, familial Mediterranean fever.

Figure 1 Phenotype data for all genotypes with the three most common FMF-causing mutations. FMF, familial Mediterranean fever.

without polyserositis were found in heterozygotes with *MEFV* mutations of exons 2 (E148Q) and 3 (P369S). Armenian children with FMF can develop pleurisy (81.7%), myalgia (37.5%), pericarditis (13.8%), and rare skin lesions (13.4%), mostly as erysipelas-like erythema (10.8%), symptoms that are not reported frequently in other child populations. The development of serositis, erysipelas-like erythema, splenomegaly, and vasculitis (Henoch–Shönlein purpura and protracted febrile myalgia) is associated with M694V homozygous and compound-heterozygous genotypes ($P = 0.092$). These symptoms were present in 111 M694V homozygous and 462 M694V compound-heterozygous genotypes as compared with 150 other homozygous and 81 other compound-heterozygous genotypes. The most common mutation in heterozygous carriers who clinically manifested FMF was also M694V (8.8%), followed by

V726A, M680I, and E148Q (2.7, 1.3, and 0.9%, respectively). Carriers of *MEFV* mutations were associated with abortive and mild FMF features, with arthritis being more frequent in M694V heterozygotes. We also observed that FMF-associated vasculitis (Henoch–Shönlein purpura and protracted febrile myalgia) in children was accompanied by higher than expected frequencies for juvenile idiopathic arthritis (4.7%) and non-amyloid renal involvement (1.1%). The life-threatening complication, adhesive intestinal obstruction, was present in 3.2% of FMF patients, in some cases as the first and only symptom associated with FMF, especially in the M694V carriers.

Analysis of *MEFV* and *SAA1* mutations in FMF patients with renal amyloidosis

Renal amyloidosis was present in 848 (5.49%) patients, 580 (3.76%) with proteinuria and nephrotic syndrome, and 268 (1.73%) with chronic renal insufficiency with available *SAA1* genotype data. Almost all patients homozygous for M694V who developed renal amyloidosis were also homozygous for *SAA1* a/a as compared with just <40% of other genotypes. On the other hand, ~35% of homozygous M694V patients who had other *SAA1* genotypes developed renal amyloidosis, suggesting that standard colchicine therapy and/or dosage adjustments should be initiated for all FMF patients regardless of their *SAA1* genotype. In family studies when one of the affected siblings with the same genotype develops amyloidosis, we may recommend *SAA1* genotyping for family planning purposes.

Arthritis study in 576 FMF patients

A detailed analysis of 576 FMF patients (326 males and 250 females) revealed that more than 68% (392 patients) suffered from arthritis. No gender or *MEFV* allelic dominance was observed. Fifty-four percent of patients had acute mono/oligo-arthritis in the lower extremities, and 39% presented with protracted arthritis. Moreover, destructive arthritis was observed in 33 patients with and 18 patients without renal amyloidosis, suggesting other severe phenotypes besides renal amyloidosis in FMF patients. We also observed ankylosing spondylitis–like symptoms in 27 FMF patients with arthritis. Sacroiliitis and arthritis of the hip joint were also present in many FMF patients, warranting genetic testing for *MEFV* mutations of probable ankylosing spondylitis or juvenile chronic arthritis patients of target ethnic groups because during follow-up visits, almost all patients reported that colchicine therapy alleviated their arthritis pain.

Individuals with three *MEFV* mutations

The genotypes presented in Table 2 for symptomatic FMF patients with three different mutations have been observed in our patient population. As is indicated in Table 2, the majority of these patients expressed common symptoms and could clinically be categorized as having mild-to-moderate disease. Although one would expect that having more than two mutations could potentially increase the severity of FMF symptoms, in reality, we observed less severe symptoms. Because the *cis* or

Table 2 Genotypes of individuals with three mutations for symptomatic and nonsymptomatic individuals

FMF patients' genotypes	Features and symptoms								Healthy (no symptoms) individuals' genotypes
	Fever	Age of onset (years)	Abdominal pain	Thoracic pain	Arthritis	Proteinuria	Hepatomegaly	Erythema	
M694V/F479L/R761H	+	5	+	+	+	–	–	–	P369S/M694V/M680I P369S/M694V/V726A
M694V/V726A/M680I	+	22	+	–	–	+	+	+	P369S/M694V/V726A
M694V/M680I/F479L	+	1.5	+	+	–	–	–	+	P369S/M694V/V726A
M694I/M680I/E148Q	+	5	+	–	–	–	–	–	P369S/V726A/V726A
M694I/M680I/V726A	+	5	+	–	–	–	–	–	P369S/E148Q/M680I
M680I/E148Q/R761H	+	13	+	+	–	–	–	–	P369S/M694V/E148Q
V726A/R761H/E148Q	+	14	+	+	–	–	–	–	P369S/M694V/F479L
M694V/R761H/E148Q	+	20	+	–	–	–	+	–	P369S/M694V/M694V
V726A/V726A/F479L	+	10	+	+	–	–	–	–	P369S/M694I/R408Q

trans positioning of these mutations has not been designated, we refrain from further analysis and comments on the symptom severity of these genotypes.

An interesting feature was seen in healthy individuals with three mutations consisting of one P369S mutation along with two disease-causing mutations. These healthy individuals were all adults and were yet to show any symptoms; so far none of them has returned to the Center of Medical Genetics with FMF symptoms. Although these healthy individuals could potentially show FMF symptoms in the future, we have not yet seen any of these healthy individuals' genotypes in the affected FMF patients so far. A logical, yet less likely, explanation would put all three mutations in *cis* configuration; however, at least one patient was homozygous for M694V and heterozygous for P369S, refuting such an explanation. Alternatively, one may suggest that the presence of a P369S mutation along with an exon 10 mutation in *cis* could result in a functional allele alleviating the effects of the other mutated allele. Future empirical studies are required to test this hypothesis.

Links between FMF and other disorders?

We have observed unrelated diseases in confirmed FMF patients, such as epilepsy, bronchial asthma, and multiple sclerosis in a patient with renal amyloidosis. However, in our experience, neither do all FMF cases contain common symptoms nor do all the same genotypes express similar phenotypes. Sequencing of the *MEFV* gene in a 56-year-old female patient already diagnosed with fibromyalgia syndrome and expressing severe myalgia with occasional skin rashes (rare/uncommon symptoms) resulted in identification of three mutations. She was homozygous for R202Q and heterozygous for V726A, yet was a confirmed fibromyalgia case with perhaps unknown FMF. Moreover, sequencing of the *MEFV* gene in a father and two children (family study) resulted in identification of one M680I mutation in all three and a few known synonymous mutations (polymorphisms) in exons 5 and 2. Only the 7-year-old son had moderate FMF symptoms, including fever, abdominal pain, skin rashes, and occasional

muscle pain. Apparently, the onset of attacks coincided with a severe reaction to vaccination at 15 months of age. The family's 9-year-old daughter and 40-year-old father did not show any FMF symptoms. The above cases are additional evidence to argue that FMF could not and should not be considered a disease with universal symptoms. As we will present in the Discussion section, many studies point to the association of *MEFV* mutations with disorders that share one or several symptom(s) with FMF, suggesting that FMF, or, in other words, mutations in the *MEFV* gene, could potentially contribute to complex phenotypic manifestations of other disorders in different individuals.

DISCUSSION

FMF symptoms in other disorders

FMF has several symptoms that could be manifested in a variety of combinations and could significantly vary among different individuals, making its diagnosis and particularly its management challenging. A significant number of patients presenting with rare/uncommon symptoms may have to endure pain for a long time before being properly diagnosed or treated by colchicine. A major cause for such complexity could be the presence of less common FMF symptoms in other more prevalent inflammatory disorders such as fibromyalgia syndrome,⁴ or autoimmune disorders such as multiple sclerosis.^{15,16} Furthermore, we have observed that the initial onset of FMF could be with rare/uncommon symptoms. In fact, in some cases, even a life-threatening complication, such as adhesive intestinal obstruction, was the first and only symptom that could be associated with FMF, especially in patients with M694V mutation. Although abdominal adhesions are present in FMF patients, they are almost inevitable in most abdominal surgeries, especially in adults. Therefore, a distinction should be made between adhesions due to abdominal surgery and adhesions due to FMF. Ben-Chetrit *et al.*¹⁷ presented cases with distinct clinical presentations uncommon in FMF, but on further investigation, *MEFV* mutations were detected and colchicine treatment was initiated. They reported patients with muscle pain, red rashes, and livedoid vasculopathy

with ulcers in one Armenian and two Israeli Jewish patients who were being treated with topical steroids, nonsteroidal anti-inflammatory drugs, and antibiotics with no real response. Colchicine therapy caused their pain to subside and reversed the rashes and disfigurement on completion of a 1-year treatment period. We also observed patients with sacroiliitis, arthritis of the hip joint, ankylosing spondylitis, and juvenile chronic arthritis with *MEFV* mutations and confirmed FMF cases with positive response to colchicine therapy. The presence of FMF symptoms in other disorders could be due to the significant function of the *MEFV* gene's protein product, pyrin, in inflammation control.^{18,19} Because FMF symptoms could be due to persistent inflammation and lack of pyrin function because of *MEFV* mutations, then recurrent presence of these symptoms in other disorders could exacerbate these conditions and may very well warrant the investigation of possible *MEFV* mutations in affected populations.

Patient management

FMF patient management may seem straightforward due to the general response to colchicine therapy, yet many issues, including, but not limited to, misdiagnosis, delayed diagnosis, and renal amyloidosis could potentially complicate patient management. We have observed a limited response to colchicine at the nephrotic stage of renal amyloidosis in FMF patients homozygous for the M694V mutation presenting with severe phenotype. Almost all such patients were of *SAAI* a/a genotype, suggesting that homozygous M694V patients should unconditionally be on colchicine therapy with regular follow-up visits, dosage adjustment, monitoring of serum amyloid protein, and clinical management of renal amyloidosis. Prophylactic treatment for asymptomatic or mild patients heterozygous for M694V still remains an open question.¹³ By contrast, FMF patients with other genotypes still had a good chance to ameliorate the nephrotic syndrome and to maintain renal function. Misdiagnosis of FMF usually occurred in the absence of common symptoms and presence of rare/uncommon severe symptoms or presence of only one symptom. Recent studies^{15–17} have indicated that presence of one FMF symptom, usually common in other disorders, has been a major factor for misdiagnosis and delay in colchicine treatment, further emphasizing that mutations in the *MEFV* gene could result in various forms and combinations of symptoms in different individuals. Furthermore, diagnosis of a patient (heterozygous for M680I) with FMF in childhood while his father and sister had the same genotype and no symptoms also points to a personalized development and progression of the disease. Therefore, each case should be discussed in detail, using genotype and symptom correlation, and treated accordingly.

We would also like to mention that in our experience, avoidance of triggers of the attacks has been a useful tool in patient management. Yenokyan and Armenian²⁰ recently suggested that multiple stressful events could trigger FMF attacks as early as 2 days. Our patients have reported that abrupt and extreme changes in weather patterns, strenuous activity or exercise, anxiety and stress, and even diet

have triggered FMF attacks. The supposition here could be that these conditions either cause additional inflammation or lower/distort the effectiveness of pyrin in patients with affected genotypes. Therefore, we offer our patients a spreadsheet to record their daily activities up to a week before the attacks start and/or a daily journal to keep of their activities and symptoms. We hope that in the future, we could compile a list of conditions that could potentially trigger FMF attacks and use it to prevent them.

Although colchicine therapy remains the dominant treatment for FMF and largely prevents the development of renal amyloidosis, its effect in some cases remains controversial. Recent studies have suggested new options such as anakinra or other interleukin-1 inhibitors.²¹ With the rapid advancement of science and technology and our knowledge of complex FMF symptoms and pyrin function in inflammation control, alternative treatments in the near future remain a real possibility. FMF could result in severe complications, thus any novel treatment, especially for FMF patients with renal syndrome and amyloidosis, could be of high value to them.

In this study, we propose that presence of any FMF symptom in target populations should be considered for genetic testing because in some cases the disease presents itself with rare/uncommon symptoms. We also discuss the personalized nature of FMF symptoms and treatment based on genotype and other genetic or environmental factors and recommend genetic testing for FMF for even one or two symptoms common in other more prevalent disorders. Once the diagnosis is final, the immediate initiation of colchicine therapy could alleviate the symptoms due to FMF or other disorders and prevent renal complications, yet emphasis on identifying environmental and social factors and/or lifestyles that trigger FMF attacks could reduce their frequency and facilitate patient management.

DISCLOSURE

The authors declare no conflict of interest.

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