The spectrum of *MEFV* clinical presentations—is it familial Mediterranean fever only?

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**Objective.** FMF is an autosomal recessive hereditary disease, associated with a single gene named *MEFV*. This gene is considered to be responsible only for FMF. In the present study, we tried to find out whether the *MEFV* gene is associated with or responsible for clinical conditions other than FMF.

**Methods.** We looked for patients who presented with signs and symptoms not typical for FMF but carried *MEFV* mutations. We also searched for reports about similar conditions in the English medical literature, and we surveyed the website ‘Infevers’ for *MEFV* mutations defined as associated with ‘atypical FMF’.

**Results.** We encountered three patients carrying *MEFV* mutations who presented with distinct clinical presentations not typical of FMF. We identified additional reports about *MEFV*-related non-FMF disease entities such as palindromic rheumatism. By screening the ‘Infevers’ website, we further disclosed 13 cases with *MEFV* mutations that were defined as ‘atypical FMF’ and 4 cases categorized as ‘recurrent arthritis’.

**Conclusions.** These findings suggest that the *MEFV* gene is associated with clinical conditions other than FMF. Changing our concept regarding the *MEFV* gene and its link to such clinical phenotypes may call for a higher awareness of the existence of additional auto-inflammatory diseases. Furthermore, a correct diagnosis of these *MEFV* gene mutation-associated syndromes will justify a therapeutic trial with colchicine, thereby relieving suffering of many patients who up to now have been misdiagnosed.


**Introduction**

FMF is considered as an autosomal recessive hereditary disease, associated with a single gene named *MEFV* [1]. However, about one-third of FMF patients bear a single mutation on one allele, suggesting that the disease might be transferred as an autosomal dominant trait with partial penetration. Alternatively, an additional gene—yet to be identified—might be responsible for the disease in these cases with single allele mutation [2, 3]. This possibility raises a question regarding the current concept of a single gene (*MEFV*) responsible for a single disease (FMF).

Recently, we have encountered several patients who carried *MEFV* mutations either as heterozygote, compound heterozygote or as complex alleles that were presented with various clinical manifestations not typical of FMF, again suggesting that the same gene (*MEFV*) may be responsible for more than a single disease or syndrome.

Herein, we would like to describe three such patients with non-homozgous *MEFV* mutations and distinct clinical presentations not typical for FMF. Together with additional reports and defined *MEFV*-related non-FMF disease entities, these cases may call for entertaining a new concept, suggesting that the *MEFV* gene is associated with more than a single disease (FMF). Changing our concept regarding the *MEFV* gene and its link to such clinical phenotypes may lead to a higher awareness for the existence of additional clinical presentations within the family of the autoinflammatory diseases [4, 5]. Furthermore, a correct diagnosis and further characterization of these *MEFV* gene mutation-associated syndromes will justify a therapeutic trial with colchicine, thereby relieving the suffering of many patients who up to now have been misdiagnosed.

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**Methods**

We looked for patients who presented with clinical features different from typical FMF in families with history of FMF. In one case, we looked for *MEFV* mutations in an Armenian woman with no family history for FMF and with atypical skin lesions resistant to every conventional treatment. We search for reports about patients with *MEFV* mutations and clinical syndromes other than FMF. We reviewed the *MEFV* sequence alterations as reported in the Infevers website—an online database for autoinflammatory mutations available at http://fmm.igh.cnrs.fr/ISSAID/infevers. We searched for patients who carry *MEFV* mutations but defined as ‘atypical FMF’.

**Results**

**Descriptions of cases**

**Case 1.** A 9-year-old boy of Sephardic Jewish origin suffers from recurrent episodes of muscle pains mainly on both legs. He does not have fever, neither has he had abdominal pain or pleuritis. The frequency of the attacks is about once in every 3 months. He has a family history of FMF; his uncle (mother’s brother) and his three cousins have FMF by criteria. Genetic analysis disclosed that he carries two *MEFV* mutations, p.E148Q and p.S108A. Genetic analysis of his mother’s DNA disclosed that she also carries the same mutations, suggesting that they harbour the same allele (in cis). The patient was put on colchicine, and since then he is free of attacks. Interestingly, despite his age and weight (30 kg), his attacks are controlled by low-dose colchicine (0.5 mg/day). A trial of cessation of this medication resulted in reappearance of the attacks. Therefore, he is currently on long-term treatment with colchicine.

**Case 2.** A 20-year-old patient of Ashkenazi Jewish origin suffers from recurrent episodes of red rash over both calves and ankles (Fig. 1). The attacks appear at a frequency of once in every 4–6 months. The patient does not recall fever during the attacks, which last 4–6 days each. The patient does not have peritonitis, pleuritis or arthritis. His grandfather had FMF by
criteria treated with colchicine. Genetic analysis revealed that he carries a single MEFV mutation (p.M694V). Despite the low probability for FMF, as the patient is heterozygous and does not have typical FMF features (fever and serositis), a trial with colchicine 1 mg/day was initiated. Following this treatment, the patient responded extremely well and did not experience any attacks for a year. Following cessation of the medication, the skin lesions reappeared but subsided upon resumption of a long-term colchicine treatment.

**Case 3.** A 27-year-old patient of Armenian origin developed bilateral recurrent livedoid vasculopathy with ulcers at her ankle regions and dorsum of her feet. The lesions evolved into atrophie blanche that caused progressive disfiguration over a year, despite systemic and topical steroids, NSAIDs and antibiotics.

The patient has been working in an office and has otherwise been healthy with a totally unremarkable family history. She has absolutely none of the clinical features encountered in FMF. There is no thrombophilia, and she underwent an uneventful pregnancy 5 years earlier. She is a non-smoker and does not consume alcohol, illicit drugs or medications.

Her physical examination was unremarkable, with the exception of livedoid vasculopathy and atrophie blanche at the ankle region and dorsum of feet, bilaterally (Fig. 2A). Laboratory evaluation, including blood count and extended biochemistry, was unexceptional. Tests for RF, ANAs and aPL antibodies were negative, and complement levels were within normal limits. Vascular evaluation excluded venous insufficiency. Skin biopsy disclosed heavy collagen deposits within dermal septa, but features compatible with active inflammation, vasculitis and panniculitis were absent. It is noteworthy, however, that tissue samples were limited, since deep sub-dermal specimens could not be obtained at the involved regions. DNA analysis revealed that the patient carries three MEFV mutations, p.E148Q, p.P369S and p.R408Q on the same allele (in cis). (Her daughter did not bear any MEFV mutation).

The patient was treated with colchicine 0.5 mg/day with a prompt elimination of new active lesions and gradual healing of existing lesions over 1 month. Burnt-out lesions took the typical scar form of atrophie blanche (Fig. 2B). Maintenance treatment with colchicine was terminated a year later, resulting in emergence of new active lesions within 2 weeks, reaching the extent and severity noted in the pre-colchicine treatment over a month. Low-dose colchicine therapy was resumed, again with a gradual disappearance of all active lesions within the subsequent month.

**Additional MEFV gene-related clinical entities**

**Palindromic rheumatism.** Cañete et al. [6] searched for MEFV mutations in a cohort of 65 Spanish patients with palindromic rheumatism (PR). None of the patients experienced typical manifestations of FMF. The authors found that eight (12.5%) of the patients carried MEFV mutation, a rate which is far beyond that expected in this ethnic population. When they analysed the frequency of MEFV mutations in PR patients negative for anti-citrullinated antibodies and compared them with those positive for these antibodies, it was found that the incidence of MEFV mutations was 22.5 and 5.5% in the two groups, respectively. The findings in this study support the hypothesis that the MEFV gene might serve as a susceptibility gene for PR. Alternatively, it may participate in the pathogenesis of PR, suggesting another clinical presentation associated with the MEFV gene.

**FMF phenotype II.** Very few patients with ‘genetic diagnosis’ of FMF (homozygous for MEFV mutations) present with proteinuria and renal amyloidosis. These patients do not have any history of typical acute FMF attacks. However, the diagnosis of FMF is raised in these patients, because they have close relatives with typical FMF, and genetic evaluation reveals the homozygosity for the p.M694V mutation in most cases. This presentation, termed as FMF phenotype 2, first published in 1962 [7], is clearly different from typical clinical FMF, but is genetically similar to FMF. This illustrates two associated diverse clinical syndromes that share identical homozygous MEFV gene mutation, again supporting the concept of a single gene with multiple phenotypes.

**Web site Infevers.** We have reviewed the whole list of 186 sequence alterations reported in Infevers—an online database
for autoinflammatory mutations available at http://fmf.igh.cnrs.fr/ISSAID/infevers [8]. We found 13 cases where the clinical presentation was described as ‘FMF atypical’. There were also four cases that were described as ‘recurrent arthritis’. None of the cases was defined as a specific new clinical entity different from FMF regarding its presentation, course, therapeutic response or prognosis. However, it should be stressed that Infevers data relate to a single episode or attack of the reported case, so it may well be that in subsequent attacks the patient may present typical clinical manifestations of FMF. Nevertheless, it is still conceivable that many of them do have clinical features different from typical FMF, supporting the concept of various syndromes or diseases associated with the MEFV gene.

Discussion

The above reported cases and complementary data suggest that mutations of the MEFV gene may present with varied distinct clinical presentations, other than FMF. As illustrated in Table 1, we can categorize such patients according to their main clinical presentation or organ involvement: when they meet FMF criteria they will be diagnosed as having the disease. Otherwise, they seemingly need other clinical names or definitions different from typical FMF.

The evolving field of autoinflammatory diseases already provides three examples of distinct phenotypes related to different mutations in a single protein [4, 5]. Mutations in CIAS1, the gene encoding cryopyrin, are associated with Muckle–Wells syndrome (MWS), familial cold urticaria (FCU) and chronic infantile neurological, cutaneous and arthritic disease/neonatal onset multi-organ infantile disease (CINCA/NOMID). The MEFV gene is responsible for hyper IgD syndrome as well as for mevalonic aciduria, and mutations in NOD2 gene are associated with Crohn’s disease, Blau’s syndrome, as well as with familial sarcoidosis. Interestingly, in the case of cryopyrin, the three diseases, MWS, FCU and CINCA/NOMID, were known before the gene (CIAS1) was isolated [9]. When it was identified in patients with MWS, investigators looked for its association with CINCA/NOMID and FCU [10]. Thus, in this case, the concept that a single gene is associated or responsible for at least three different diseases has been anticipated from the start. At the beginning, the first impression was that specific mutations in the CIAS1 gene were related to a specific phenotype (one of the three syndromes). However, quite soon it was realized that the same mutations may lead to different diseases. This observation suggests that in addition to the genotypic background many other genetic or environmental factors may play a role towards the final clinical expression (phenotype) of the disease.

Another example of a single gene mutation responsible for more than a single disease is the hyper IgD syndrome and a severe childhood disease known as mevalonic aciduria [11, 12]. In contrast to the case of cryopyrin-associated diseases, no overlapping mutations were found for the two diseases. Mutations causing mevalonic aciduria do not cause hyper IgD syndrome and vice versa.

In the case of NOD2 it was found that at least three diseases were associated with it, Crohn’s disease, familial sarcoidosis and Blau’s syndrome, although some investigators suggest that the last two diseases are the same [13].

The observations described above illustrate that the MEFV gene, attributed mainly to FMF, may actually be responsible for or associated with additional clinical manifestations that do not meet the criteria of FMF, and sometimes do not have any resemblance to this disease whatsoever.

In the first reported case, the patient had episodes of muscle pains without exercise. These pains do not resemble those of protracted febrile myalgia, since they were milder, of short term, not accompanied by fever and did not require steroids. On the contrary, 0.5 mg of colchicine was sufficient for controlling these attacks. The patient did not have fever, serositis or erysipelas-like erythema typical of FMF.

The second case could be considered as an erysipelas-like erythema of FMF, usually common in childhood. However, in contrast to typical FMF, the said patient did not have fever and the lesion always appeared on both sides concomitantly. Furthermore, this patient too did not experience any episode of peritonitis, pleuritis or arthritis, although he was already 20 years old.

Case 3 described a patient with a rare skin disorder, atrophic blanche [14], referring to star-shaped, or polygonal, ivory-white, depressed atrophic plaques involving the lower leg. It is caused by dermal microangiopathy, often associated with diabetes, venous insufficiency or arteriolosclerosis. It may also result from livedoid vasculopathy, related to anti-phospholipid syndrome, SLE or various forms of thrombophilia. Nevertheless, in many cases, its pathophysiology remains obscure. There is no specific efficient treatment for this disorder. Steroids, anti-inflammatory drugs and measures enhancing regional microcirculation have often been recommended. In the present case, the patient did not have diabetes, venous insufficiency or arteriolosclerosis. Neither did she have SLE, thrombophilia or anti-phospholipid syndrome. On the other hand, she did have three MEFV mutations and responded immediately to colchicine. Furthermore, when this medication was discontinued the lesions recurred. Still one may suggest that the coexistence of the skin disease and the presence of three MEFV mutations is incidental. However, the episodic course with the clear response to colchicine supports the association of this clinical entity with MEFV—yet without being diagnosed as having FMF.

Patients with FMF phenotype 2 could easily be categorized as patients with chronic underlying inflammatory disease with elevated ESR, CRP and SSA, leading directly to renal amyloidosis without the typical attacks of FMF. Yet, their genotype is identical to patients with typical FMF. Furthermore, these two diverse presentations may exist in siblings within the same family. The patients diagnosed as having PR represent another prototype of individuals who bear MEFV mutations, and yet their main complaints derived from joint involvement only.

Thus, the above examples support the possibility that the MEFV gene may be associated with additional syndromes apart from FMF. The identification of the MEFV gene with its corresponding protein pyrin was made through genetic analysis of DNA from FMF patients, who had a definite clinical diagnosis of FMF [15, 16]. Therefore, it is not surprising that the observations led to the conclusion that this is a typical case of single gene (MEFV) associated with a single disease (FMF). Thus, in cases of MEFV mutations identified by chance, such as during family screenings, individuals who bear mutations but do not present with typical manifestations of FMF were previously ignored, whereas others with ‘atypical phenotype’ were evaluated for an alternative disorder. If such cases were related to the MEFV gene, the patients could have benefited from a colchicine therapeutic trial.

### Table 1. Different clinical presentations associated with the MEFV gene

<table>
<thead>
<tr>
<th>Organ involvement/fever</th>
<th>Joints</th>
<th>Skin</th>
<th>Muscles</th>
<th>Kidneys</th>
<th>Fever</th>
</tr>
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<tbody>
<tr>
<td>FMF</td>
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<td>+/-</td>
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<td>Phenotype II</td>
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<td>Recurrent arthritis</td>
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<td>PR</td>
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<td>Recurrent myalgia</td>
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<td>Protracted febrile myalgia</td>
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<tr>
<td>Livedoid vasculopathy/atrophie blanche</td>
<td>+</td>
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What are the lessons we may learn from these observations?

(1) Genes that are associated with autoinflammatory diseases are so important and pivotal during different points and stages of the inflammatory process, because their mutations may lead to or cause totally different clinical presentations. Therefore, we should expect to identify new clinical entities with inflammatory components, which will be found in association with MEFV, CIAS1, MVC, NOD or TNFR1 genes. These genes cannot be considered responsible for a single clinical entity and do not ‘behave’ in a manner of a single gene for a single disease. This point may present another difference between the classical autoimmune diseases and auto-inflammatory diseases. In the former group, many genes cause a single disease (polygenic diseases—SLE and RA); whereas in the latter, a single gene leads to or is associated with many different clinical entities.

(2) In populations where the carrier rate of mutations of the above genes is relatively high, we have to be more aware of the possibility that the so called ‘atypical clinical manifestations’ are actually an independent syndrome associated with these very same genes.

(3) The association of new clinical entities with these genes may justify the adoption of the current treatments we use in the typical disease (FMF, MWS, etc.) in the new clinical presentations as well.

(4) The observation that a low-dose colchicine was effective in the non-typical cases of MEFV-associated diseases is quite interesting. First, it should lead us to reconsider our policy regarding the dose of colchicine used in FMF as well. For example, in Japan, most of the patients with FMF were treated with colchicine 0.5 mg/day with excellent response and no complications [17]. We may try low-dose colchicine in FMF patients with mutations causing or associated with mild disease such as p.E148Q or p.A726V, whereas keeping higher doses for those who bear mutations p.M694V or p.M694I, which are associated with more severe disease and potential amyloidosis [18]. In the present cases of non-FMF MEFV-associated entities, since in most patients the mutations were on exon 2, it is possible that the inflammatory process is milder and therefore a low dose of colchicine is effective. In the patient with atrophic blanche, a single colchicine tablet of 0.5 mg daily led to a complete remission of the active skin lesions too. Yet, an unsolved problem is whether we increase the risk for amyloidosis in these patients with mild disease by using low-dose colchicine.

(5) The fact that mutations in the MEFV or CIAS1 genes may lead to a different clinical manifestation may explain the observations that their concomitant presence in other diseases may contribute to the modification of disease presentations and severity. For example, it was shown that MEFV mutations in patients with RA and IBD were associated with more severe diseases [19, 20]. The presence of MEFV mutations in patients with Behcêt’s disease was associated with more vascular involvement [21]. Furthermore, in Chinese and Indian patients with secondary amyloidosis, due to chronic inflammatory diseases such as RA, the prevalence of p.E148Q mutation was significantly higher than in controls [22]. This suggests that the presence of p.E148Q is a susceptibility factor for the development of secondary amyloidosis in populations where FMF does not exist at all.

(6) In the Infevers web site, we found another patient who carries the complex allele p.[E148Q;P369S;R408Q] (found in Case 3), who developed full-blown FMF by criteria and even amyloidosis. This finding supports the view that there is no absolute correlation between the kind of mutations and the clinical presentation. The same genotype can lead to or may be associated with a totally different phenotype. This observation is shared with the case of CIAS1 gene, where patients with different syndromes bear similar genotype (mutations).

In summary, it seems that we have to reconsider our concept regarding the group of genes associated with the autoinflammatory diseases and especially to pyrin-associated diseases.

There are probably additional clinical presentations to be detected and defined, associated with altered pyrin gene and protein. Furthermore, we might better adopt a general name ‘pyrin-associated disorders’ of which FMF may be one, rather than using the current terminology. By that approach we may identify and effectively treat new pyrin-related disorders, so far overlooked as they do not fully meet FMF criteria.

At this point it may be appropriate to reconsider the name FMF itself. Since Armenia, Iraq, America and Japan are not Mediterranean countries and yet have patients with FMF, the name FMF may not be correct for these geographic areas.

Years ago another periodic fever syndrome, which was described for the first time in Ireland, was named familial Hibernian fever (FHF) based on the ancient name of this island (Hibernia). Since the disease was later found in many other countries and its gene was isolated (TNFR1), the name was changed to ‘TNF receptor-associated periodic fever syndrome’. The name FHF is no longer in use. Since the gene associated with FMF (MEFV) has also been identified, it seems that a more appropriate name for the disease would be ‘pyrin-associated periodic fever syndrome’. For those who prefer a more meaningful clinical name which better characterizes the disease manifestations, ‘hereditary recurrent polyserositis’ may be proposed. This latter name was actually suggested many years ago. It is not limited to any geographical area, and it describes quite accurately the periodic nature of the disease, the fact that it is hereditary and that it affects serious tissues such as the peritoneum, pleura and synovium.

In summary, based upon the above observations, we suggest to reconsider the concept associating MEFV gene with a single disease and whether FMF is still the appropriate name to be used.

Rheumatology key messages
- The MEFV gene may be responsible for diseases other than FMF.
- Like FMF, such entities may respond to colchicine treatment.
- The concomitant presence of MEFV mutations in other diseases may modify their presentation and severity.

Acknowledgement

Funding: This study was supported by the Canadian Friends of the Hebrew University.

Disclosure statement: The authors have declared no conflicts of interest.

References


