

Familial Mediterranean fever phenotype and *MEFV* variations

Sirs,

Several hereditary autoinflammatory disorders, including familial Mediterranean fever (FMF) as being the most common form, usually manifest themselves as periodic fever syndromes. Most of them had historical names, which usually rely on periodic clinical features and ethnicity; and following the elucidation of biologic disease mechanisms by identification of associated genes, those names have been regarded as misnomers and changed with new ones explaining the biologic basis of the disorders.

FMF was originally suggested as an inclusive descriptive name to differentiate it from rarer periodic fever syndromes based on data collected by the detailed analysis of typical patients from Israel (1). After the identification of the *MEFV* gene variants as the underlying biologic mechanism, all components of the disease name, “familial”, “Mediterranean” and “fever” have been questioned because of the patients not fitting to the described picture; and a pathogenesis-driven new name as *pyrin-associated periodic fever syndrome* (PAPS) has recently been proposed to replace it (2).

The requirement for a dynamic evolving taxonomy is obvious for all diseases including autoinflammatory syndromes, to cover all available data about the disease including signs and symptoms as well as molecular mechanisms and mainly aiming to improve diagnosis and management of these conditions (2). Within this context, keeping the historical names may not always be misleading, and they may even serve as an anchor to navigate safely in a complex and overlapping clinical setting.

FMF was first used to describe an inherited condition observed mainly in Eastern Mediterranean populations (1). Its association with secondary amyloidosis and response to colchicine treatment has been established in the same clinical setting (3, 4). Similarly, the gene responsible for FMF was mapped to the short arm of chromosome 16, and certain autosomal recessively inherited *MEFV* gene exon 10 variations were identified in typical consanguineous FMF families (5-7).

As William Harvey said “nor is there any better way to advance the proper practice of medicine than to give our minds to

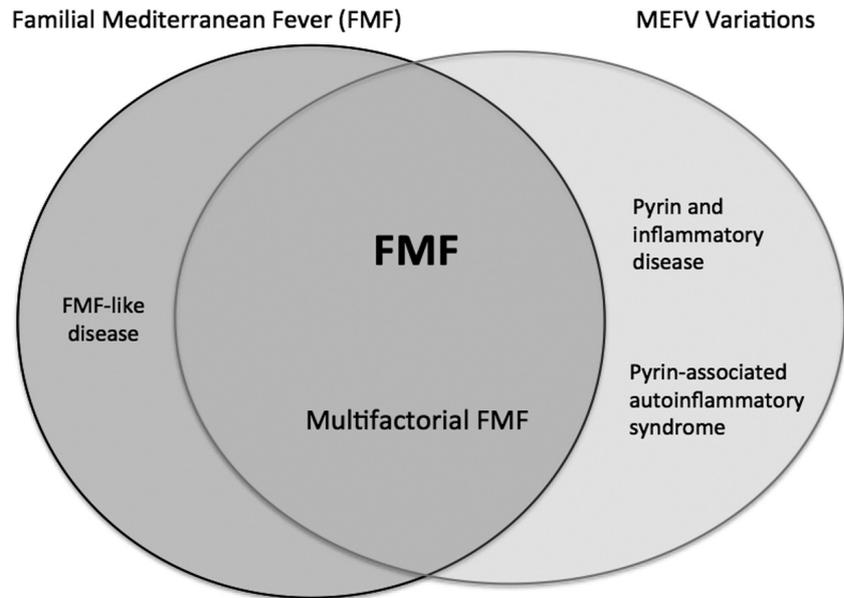


Fig. 1. Relationship between familial Mediterranean fever (FMF) and *MEFV* variations.

the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease”. However, understanding the biology of these rare forms usually leads to a diagnosis of a larger spectrum of patients including much milder and more frequent forms as well as patients with genetic variations not associated with the classical disease, which fit very well to the current challenges we are facing in the management of FMF patients. Increased awareness of FMF has resulted in the diagnosis of more patients fulfilling the suggested diagnostic criteria, but having a milder disease course, later onset, less frequent and less severe inflammatory attacks, and usually no family history. Likewise, genetic analysis of large series revealed that only a single *MEFV* variation could be detected in 20-30% of FMF patients despite the sequencing of whole *MEFV* exons (8, 9). We now know that exon 10 variations are increasing the risk of FMF-phenotype, and a “multifactorial” form of FMF can be observed in heterozygous carriers with the contribution of yet unknown genetic and environmental factors such as severe infections (10-12). This multifactorial form of the disease may have a similar phenotype to the typical autosomal recessive disease, but it may not be necessarily predictive of lifelong illness (9). Also, an “FMF-like” phenotype with a favorable response to colchicine can be observed in a small group of patients with no disease-associated *MEFV* coding region mutations (13).

Therefore, classically defined FMF phenotype (1) is actually a heterogeneous group including typical *autosomal recessively inherited FMF* patients, *multifactorial FMF* patients with a single exon 10 variation, and patients with *FMF-like disease* without *MEFV* mutations (Fig. 1). On the other hand, the *MEFV* gene variations may not necessarily be associated with the FMF-phenotype. Heterozygous state for FMF-associated penetrant *MEFV* variations such as p.Met694Val may contribute to the development of other inflammatory conditions in a context-dependent way, in relation to the background genetic and/or environmental factors, by affecting the inflammasome activity and IL-1 beta processing.

Furthermore, some of the variations such as those occurring in exon 8, exon 5 or other regions of the *MEFV* gene may be associated with atypical autoinflammatory features, which could not be classified as FMF manifestations (14-16), and deserve more to be named as *pyrin-associated autoinflammatory syndrome* (Fig. 1).

We do not know whether patients with *multifactorial FMF* and *FMF-like disease* have the same risk factors for secondary amyloidosis and requiring lifelong colchicine treatment similar to autosomal recessive FMF patients or not. Likewise, we have limited data on the course and treatment requirements of patients with a penetrant *MEFV* variation and other inflammatory conditions or of patients with unusual exon 5 or exon 8 variations.

It would be ideal to collect detailed information prospectively on the description of FMF phenotype and other autoinflammatory features, *MEFV* variations, and colchicine response using an updated taxonomy. I hope that this approach could improve our understanding of laws of nature in a larger context and provide further help in the diagnosis and management of FMF patients.

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Competing interests: none declared.

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