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Editorial

A Call for Action for an Integrated National Registry of Familial Mediterranean Fever (FMF) Patients and MEFV Gene Variants in Iran

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Familial Mediterranean Fever (FMF, OMIM 249100) was the first described hereditary autoinflammatory disorder, and is the most common type one in the world (1). Its prevalence is up to 1 in 200 people, predominantly the Mediterranean and Middle Eastern populations, including Turks, Iranians, Azerbaijanis, Armenians, Arabs, Spaniards, and non-Ashkenazi Jewish groups, especially Sephardic Jews (2).

FMF is a monogenic disorder and Mediterranean Fever (MEFV) gene (OMIM 608107, GenBank NM_000243.2) is responsible for it. MEFV was identified in 1997 on the short arm of chromosome 16 at locus 16p13.3 (3). It has 10 exons and encodes the pyrin protein, also named marenostrin, which is a variable cytosolic pattern recognition receptor that assembles pyrin inflammasome in the innate immune response (4). Pathogenic mutations in the MEFV gene significantly affect this response and lead to inflammatory cascade and reccurent attacks. Patients usually suffer from periodic episodes of fever, aphthous ulcers, and painful serositis, including peritonitis, pleuritis, and synovitis. These episodes typically last 2 to 3 days and occur with variable frequency (5). Patients also usually have poor quality of life (6), and in severe cases or untreated ones, may result in secondary amyloidosis and end-stage renal disease (7).

There are more than 400 reported pathogenic variants. They are mainly inherited in an autosomal recessive pattern, and rare cases of autosomal dominant transmission have also been reported (8, 9). Their distribution varies significantly among different populations. Globally, the most common ones are seeming to be M694V, V726A, M694I, and M680I in exon 10, as well as R202Q and E148Q in exon 2 (9, 10). According to a systematic review study by Alibakhshi et al. (11) on 4,256 patients, M694V, E148Q, V726A, M680I, R761H, and M694I are the most commonly reported mutations in Iran, respectively. However, these results are not representative of all Iranian FMF patients.

The FMF Registration Center in Iran (http://www.fmfiran.ir/) is based in Ardabil, a city in

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northwestern Iran. This city is populated by Azeri Turks, who are known to have higher susceptibility to FMF (12). This registration has added valuable data to the literature through high-quality studies (12-14). However, despite named as a national registry, the system appears to be non-centralized, as most cities and Iranian FMF patients are not registered within this database. Iran is a large and ethnically diverse country, with various ethnic groups, including Persians, Azeri Turks, Kurds, Arabs, Lurs, Gilaks, Mazandaranis, Balochs, Turkmens, Armenians, and others. Clinical and genetic characteristics of Iranian FMF patients among some of these ethnic groups have mainly been reported through various cross-sectional studies. The mentioned registry is also not fully representative of the Iranian Azeri Turks, as two big cities in northwestern Iran, Tabriz and Urmia, both populated by similar population with high number of FMF patients, are not included and they released their data independently. Tehran, as the capital and most populated city of Iran with heterogeneous ethnicity, also not included in the registry (11).

In addition to these ethnic limitations, the registry also appears to be inactive and no studies have been published in the past five years. This limitation is clinically important, because significant advances have been made in the diagnosis and management of the disease in recent years (15). Traditionally, FMF was diagnosed primarily based on clinical manifestations and criteria such as Tel-Hashomer (2), and the registry and most studies reported from Iran have also relied on this criteria. Over time, several diagnostic and classification systems were developed for both pediatric and adult populations. In 2019, the Eurofever/PRINTO classification criteria were released and represented the first system to incorporate both clinical and genetic variables, resulting in a highly sensitive and specific classification tools (16).

These criteria could solve diagnostic challenges of this disease, particularly the overlap of clinical manifestations with some autoinflammatory disorders (17). However, several limitations still exist due to lower specificity results and higher misclassifications (18). The lack of clear genotype-phenotype correlation is the key question for all these diagnostic challenges and limitations. On one hand, clinically diagnosed FMF patients have no identifiable pathogenic variants on genetic testing or carry rare atypical mutations or autosomal dominant inheritance patterns (19), while on the other hand, asymptomatic individuals may carry MEFV variants without developing clinically apparent disease (20).

Diagnostic challenges are not over yet. In recent years, an emerging spectrum of diseases has been introduced with broader spectrum of clinical presentations and different pathogenic variants than FMF, which called pyrinopathies. This new definition complicated the current understanding of autoinflammatory diseases and FMF, and may evolve the current FMF classification criteria (21). Also, MEFV variants have been reported in several well-known inflammatory diseases, with significant association to disease severities (22). **Figure 1** shows some of these diseases, and further studies may reveal more. So, even the combination of clinical findings and positive genetic mutations may not always be sufficient to put a definitive diagnosis. Recent studies have highlighted the role of Next-Generation Sequencing (NGS) in FMF patients with negative or heterozygous MEFV results, as a promising strategy for a deeper understanding of autoinflammatory phenotypes and more efficient individualized diagnostic and therapeutic approaches in clinical practice (23).

Challenges in FMF also extend to treatment, where approximately 5 to 10% of patients do not respond to standard colchicine therapy. These patients are classified as colchicine-resistant and generally suffer from increased disease severity, disturbed quality of life, considerable psychological burden, and increased risks of long-term complications (24). The alternative treatments include anti-interleukin (IL)-1 agents, such as anakinra and canakinumab. There is also ongoing debate about other treatment options such as biological disease-modifying anti-rheumatic drugs (bDMARDs), which require further well-designed studies in different regions to assess their efficacy in clinical practice (25).

Iranian FMF population could serve as a significant national cohort for studies in all aspects of the disease. Iran has the potential to become a leading country in advancing research in this field, due to its large population and ethnic diversity. There are considerable valuable studies

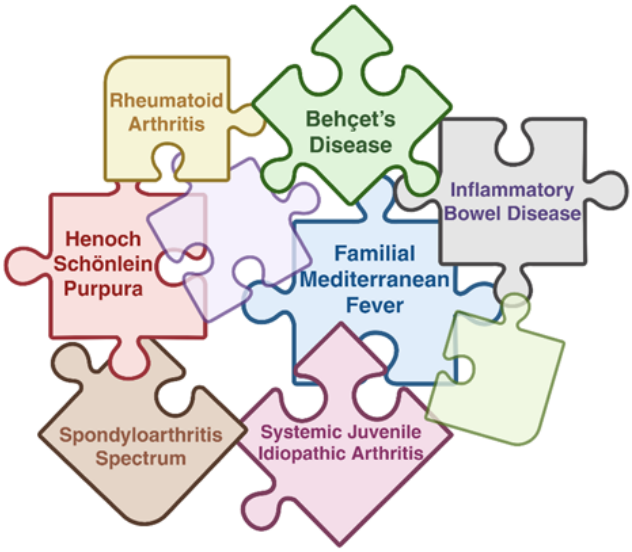

Figure 1. Inflammatory diseases associated with MEFV variants.
The spectrum of inflammatory diseases associated with MEFV variants can be viewed as an incomplete and disorganized puzzle. Some pieces have been identified to date, such as Familial Mediterranean Fever, Behçet's Disease, Inflammatory Bowel Disease, Systemic Juvenile Idiopathic Arthritis, Rheumatoid Arthritis, Spondylarthritis Spectrum, and Henoch-Schönlein Purpura. The blank pieces of this unsolved puzzle in this figure are for potential future additions.

on FMF and MEFV across various cities and ethnics in Iran; however, they are limited and mostly conducted in cross-sectional design. A nationwide study becomes increasingly necessary when paying attention to the opportunity that detailed analyses of epidemiological, clinical, and genetic characteristics, as well as other possible factors, might lead to the development of more refined and efficient diagnostic and classification criteria. Long-term follow-up and the evaluation of treatment responses across different clinical conditions could also be helpful in the development of more effective treatment guidelines in national setting, especially for colchicine-resistant cases. In the era of advanced genetic studies, personalized medicine, and artificial intelligence, these experiences can be translated into various domains of these disciplines.

It is suggested to continue the national FMF patient registry and also to improve by parallel national registry of MEFV gene variants. Because MEFV variants are also observed in other inflammatory diseases, a nationwide, integrated approach could also improve the understanding of autoinflammatory disorders and their broader clinical spectrum.

Conflicts of Interest

The authors declare to have no financial and non-financial conflicts of interests related to this work.

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