

ORIGINAL PAPER

doi: 10.5455/medarch.2019.73.55-57

MED ARCH. 2019 FEB; 73(1): 55-57

RECEIVED: DEC 30, 2018 | ACCEPTED: FEB 15, 2019

Familial Mediterranean Fever Gene Mutations and Gout as an Auto-Inflammatory Arthropathy

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ABSTRACT

Introduction: The auto-inflammatory diseases (AID) are a heterogeneous group of multi-system disorders of innate immunity dysregulation. MEFV gene has major role in AID. **Aim:** The aim of this study is to investigate the frequency of MEFV variant alleles in gout patients as an AID and their genotype-phenotype relationship. **Methods:** Total amount of 224 of the healthy people as a control group (113 male and 111 female) and 24 gouty arthritis patients (20 male and 4 female) entered this study. Blood samples screened for the 12 common pathogenic mutations according to manufacturer`s instructions. **Results:** The mean age of patients was 54 years. MTP joint was the most involved joint (91.66%). Mutations were shown in 5 patients (20.83%) that were not different from healthy population (25%). Five patients carry one mutated MEFV allele, E148Q in 4 patients and V726A in 1 patient. Control group showed 25% mutations as E148Q (18.3%), P369S (3.1%), V726A (2.2%), A744S (1.3%) respectively. The most common mutation detected in patients was E148Q (16.66%) and all of them were males. No significant and meaningful associations were detected between the MEFV gene mutations and gouty arthritis patients. **Conclusion:** There was not any correlation between MEFV gene mutations carriage with age, sex, the number of joint involvement and the course of disease in gouty arthritis. MEFV gene mutations were more frequent in men than women, but this is not statistically significant.

Keywords: Gout, Auto-inflammatory disease, MEFV gene, FMF.

1. INTRODUCTION

The auto-inflammatory disease, also known as periodic fever syndromes, are a heterogeneous group of multi-systemic disorders of innate immunity characterized by fluctuating, self-limiting or irregularly recurring episodes of fever and systemic inflammation (1, 2). FMF is the best-known auto-inflammatory disease, nowadays novel findings provided information that leading to include gout into the spectrum auto-inflammatory diseases (3).

The MEFV gene is located on the short (p) arm of chromosome 16 at position 13.3(16p 13.3) (4). MEFV gene was predominantly expressed in granulocytes and monocytes (5), Both of which play major roles in the pathophysiology of inflammatory disease at the acute phase (6). MEFV gene encodes a protein called pyrin (or marenostirin) (7). Pyrin is involved in inflammations through altered apoptosis, caspase-1 activation, secretion of interleukin (IL)-1 β and activation of the NF- κ B pathway in innate immune system (8).

Several reports revealed that MEFV mutations were associated with vasculitis-related disorders as such Behcet disease, Henoch schonlein purpura (HSP), and polyarteritis nodosa (9, 10, 11), and associated with more severe course of some inflammatory diseases such as ankylosing spondylitis (AS), inflammatory bowel diseases (IBD), rheumatoid arthritis (RA) (12), suggesting that MEFV gene mutations contribute to the development of a broader spectrum of inflammation. Furthermore, it has been reported that MEFV mutations might increase the baseline of inflammation, induced the development of rheumatic diseases, and affect the clinical course of inflammatory disorders (13).

Gout is a clinical syndrome that occurs as an inflammatory response to increased concentration of uric acid and accumulation of monosodium urate crystals (MSU) within the joint (14).

It is one of the most common inflammatory arthritis in the world that has been reported as 1–2 % in

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men over the age of 30 and women over the age of 50 years depending on ethnic variations. The incidence of gouty arthritis increases with the increasing age, and its prevalence is between 6 and 9 % after the age of 80 (15, 16). In recent years, the role of the inflammasome complex in the pathogenesis of the disease has been shown. Neutrophils are prominent mediators of the inflammatory response in gout disease and IL-1 is an important factor that plays a major role in pathogenesis of gout. As for other pathogen crystals, the main mechanism of their inflammatory reaction is the activation of the intracellular caspase-1-activating NLRP3 inflammasome. In recent studies, it was shown that NALP3 inflammasome complex has a significant role in acute inflammation induced by MSU crystals (3, 17, 18).

Gouty arthritis and familial Mediterranean fever share some clinical and pathological features such as being classified as auto-inflammatory disease, associations with inflammasome, short-lived intermittent arthritis, and good response to colchicines and anti-interleukin-1 treatment.

2. AIM

The aim article is to investigate the frequency of MEFV variant alleles in gout patients as an AID and their genotype-phenotype relationship.

3. METHODS

Patients

This is a retrospective study that include 24 gout patients who were diagnosed by the revised American College of Rheumatology (ACR) classification criteria (19). All patients were questioned for presence of FMF (Tel-Hashomer criteria) and positive family history for FMF (20). Patients with suspicious anamnesis and/or positive family history for FMF were excluded. Sex, age, number of gout attacks, history of nephrolithiasis and presence of tophus were also collected. All data were analyzed by simple analytical test.

The study was approved by the local Ethics Committee of faculty of medicine and informed consent was obtained from all the participants.

Control Group

On the basis of FMF frequency (0.1%) in Northwest of Iran, near to eastern Mediterranean area, we performed an investigation simultaneously to evaluate of MEFV gene mutations in normal and healthy population of this area. This study included 224 healthy people as a control group (113 male and 111 female). All of them were over 50 years old, with negative history of FMF symptoms, in themselves and their first degree family.

MEFV gene mutation analysis

Blood samples were screened for the 12 common pathogenic variants (E148Q, P369S, F479L, I692del, M680I(G/C), M680I(G/A), M694V, M694I, K695R, V726A, A 744S, R 761H) by RDB assay (FMF Strip Assay, Vienna lab, Vienna, Austria) according to manufacturer's instructions.

Gouty arthritis patients N=24	Wide type	Mutations
	19	V726A (n=1)
		E148Q (n=4)

Table 1. Distribution of the MEFV gene mutations in the gouty arthritis patients

4. RESULTS

There were 224 of the healthy control group (113 male and 111 female) and 24 gouty arthritis patients (20 male and 4 female). The mean age of the patients was 54 years. The youngest patient was 31 years old and the oldest one was 80 years old. The median number of gouty attacks of the patients were 3 (1-10), 8.33% had renal stone history. Duration of symptom in most of the patients was 10 years. In the clinical evaluations of patients with gouty arthritis; first MTP joint involvement was observed in 22 (91.66%), ankle arthritis in 3 (12.5%), knee arthritis in 3(12.5%), elbow arthritis in 2 (8.33%) and heel arthritis in 1 (4.1%) patients.

Five patients (20.83%) carry one mutated MEFV allele, E148Q in 4 patients (16.66%) and V726A in 1 patient (Table 1). Control group showed 25% mutations, the most common variants were E148Q (18.3%), P369S (3.1%), V726A (2.2%), A744S (1.3%), respectively.

No correlation was found between MEFV gene mutations carriage with age, sex, the number of joint involvement and clinical signs of disease. MEFV gene mutations were more frequent in men (4 patients) than women, but this is not statistically significant.

5. DISCUSSION

Sari et al have investigated MEFV gene mutations frequency in patients with gouty arthritis and they found E148Q as the most common mutation in patients (22.7%), and the control group (24%) respectively. The presence of mutated variants did not show any association with clinical features of gouty arthritis, and MEFV gene mutations role in its pathogenesis (21).

Similar study was published in the literature recently. Balkarli et al investigated the effects of MEFV variant alleles on the manifestations of gout in seventy-one patients diagnosed with gout. MEFV variant alleles were found in 24 (33.8 %) of the gout patients and in 13 (26 %) of the control subjects; the difference was not statistically significant. R202Q and K965R were the most common mutations among the both group. Although they found association between MEFV variant allele and severity of some clinical features, higher incidence of tophus and the higher number of attacks per year, they could not show a pathogenic role of these mutations in patients (22).

Karaarslan et al showed high carriage rate of MEFV gene mutations, in 93 gouty Patients which R202Q in 19.3% compared with 102 healthy control group with E148Q in 10.7% and concluded that MEFV gene mutations may play an important role in the pathogenesis of the disease and predisposing to the disease (23).

MEFV mutations, E148Q as the most common variants in patients with gouty arthritis in our study did not show meaningful difference from frequency of MEFV

mutations in healthy population, 16.6% and 18.3% respectively.

Not only MEFV gene variants did not show any association with clinical features of gouty arthritis, but also the severity of gout did not show any difference between the patients with and without MEFV mutations.

To the best of our knowledge there is no other report regarding the association of MEFV mutations and gout in the literature.

The most common mutation detected in patients with gouty arthritis was heterozygous E148Q (16.66%). However, controversy exists regarding the role of the E148Q alleles in development of clinical feature of FMF, some reports emphasized the over-representation of E148Q in several inflammatory disorders (24). On the other hand the high prevalence of this mutation in normal population (18.3%) suggests that; this finding should be interpreted with caution.

6. CONCLUSION

This study has some limitations such as small sample size of 24 cases, however, despite of these limitations, unlike Karaarslan et al study, the results of this study do not provide a support for a major role of MEFV mutation in gouty arthritis patients.

- **Author's contribution:** F.S, Y.M, A.E, and M.M, gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Financial support and sponsorship:** Nil.
- **Conflicts of interest:** There are no conflicts of interest.

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