Journal of Rheumatology Research
JRR, 1(1): 1-4
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Mini Review: Open Access

Familial Mediterranean Fever Gene Mutations and Inflammatory Arthritis

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Received August 31, 2018; Accepted September 06, 2018; Published January 11, 2019

ABSTRACT

Familial Mediterrranean Fever, i.e., FMF, is an acquired hereditary disease that causes repetitive scenes of fever with serosal, cutaneous and fiery joint inflammation that are commonly joined by agony in the stomach area, chest or joints. It regularly happens in people of Mediterranean and Center Eastern plummet and the principal scenes ordinarily start in adolescence. The unrest has been given diverse names, including familial paroxysmal polyserositis, discontinuous peritonitis, tedious polyserositis, liberal paroxysmal peritonitis, incidental contamination or periodic fever, Reimann irregular infection or Reimann issue, Siegal-Cattan-Mamou illness and Wolff discontinuous disease.

INTRODUCTION

Familial Mediterranean Fever (FMF) is an inherited disease characterized with recurrent episodes of fever with serosal, cutaneous and inflammatory arthritis [1]. One important genetic factor that has been proposed as a candidate gene for the FMF is Mediterranean Fever (MEFV) gene mutation [2,3]. MEFV gene is located on chromosome 16p13 and comprises 10 exons and 781 codons and produces a protein named pyrin or Marenostrin [2,3]. The protein expressed mainly in neutrophils and macrophages and has inhibitory effects on inflammation through leucocyte cytoskeletal organization on polymorphonuclear cells and monocytes and modulates the production of the potent pro-inflammatory cytokine interleukin-1β through regulation of nuclear factor-κB and caspase-1 [4,5]. There are two apparent mutational hot spots: one in exon 2 and the other in exon 10 [3]. Four of five common mutations M694V, V726A, M680I and M694I have been located in exon 10 and one E148Q is identified in exon 2 [3]. According to the literature review MEFV mutations were linked to inflammatory arthritis and also they may have roles in the disease severity [6-9]. Most of these literatures conducted in areas with high prevalence of FMF and they investigated the mutation rate of MEFV genes in patients with ankylosing spondylitis (AS). All of them showed the increased overall mutation rate of MEFV gene in patients with AS [6,10-17]. However, the influence to the prognosis is less likely [10,16]. The M694V mutation was the most common mutation supposed to be associated with sacroiliitis as a predominant feature of AS [11-15,17]. **Table 1** presents the studies conducted on patients with AS.

According to the studies mentioned in **Table 1**, there is an association between MEFV gene mutations and sacroiliitis as a dominant feature of AS. But another question still remains that is there any possible relation between these mutations and other inflammatory arthritis?

There are other studies which carried on patients with rheumatoid arthritis (RA). Most of them assessed the most common mutations of MEFV gene, but, none of them reported an association between MEFV gene mutations and rheumatoid arthritis [11,18-21]. The study which performed in 2005, showed increased mutation rate of exon 2 of MEFV gene (E148Q) in patients with RA, but, the influence to the prognosis was less likely [22,23]. We also performed genetic study on exon 2 and 10 of MEFV gene on thirty four patients with refractory rheumatoid arthritis and healthy control subjects. The results of our study was the same, there was no significant relationship between MEFV gene mutations and patients with refractory rheumatoid arthritis [24,25]. The **Table 2** presents the studies conducted on patients with rheumatoid arthritis (RA).

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Citation: Mirzaei A. (2019) Familial Mediterranean Fever Gene Mutations and Inflammatory Arthritis. J Rheumatol Res, 1(1): 1-4.

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Table 1. MEFV gene mutation in AS patients.

Authors	Topic	Sample size	Overall mutation rate	Specific mutation increase	Influence to the prognosis
Cherqaoui et al. [17]	Boundaries between familial Mediterranean fever and juvenile spondyloarthritis: Analysis of three French retrospective cohorts	16	Increased	M694V	Yes
Zhong et al. [13]	MEFV M694V mutation has a role in susceptibility to ankylosing spondylitis: A meta-analysis	869	Increased	M694V	-
Akar et al. [12]	High prevalence of spondyloarthritis and ankylosing spondylitis among familial Mediterranean fever patients and their first-degree relatives: further evidence for the connection	157	Increased	M694V	Yes
Yigit et al. [6]	Common Mediterranean fever (MEFV) gene mutations associated with ankylosing spondylitis in Turkish population	103	Increased	-	Yes
Koca et al. [22]	Association of familial Mediterranean fever–related *MEFV* variations with ankylosing spondylitis	193	Increased	M694V	Yes
Akkoc et al. [11]	Increased prevalence of M694V in patients with ankylosing spondylitis: additional evidence for a link with familial Mediterranean fever	62	Increased	M694V	N/A
Kaşifoğlu et al. [14]	The frequency of sacroiliitis in familial Mediterranean fever and the role of HLA-B27 and MEFV mutations in the development of sacroiliitis	18	Increased	M694V	Yes
Cinar et al. [10]	The rate and significance of Mediterranean fever gene mutations in patients with ankylosing spondylitis: a three-month, longitudinal clinical study	95	Increased	-	No

Table 2. MEFV gene mutation in RA patients.

Authors	Topic	Sample size	Overall mutation rate
Khabbazi et al. [23]	Molecular Analysis of MEFV Gene Polymorphisms and Mutations in Iranian Azeri Patients with Rheumatoid Arthritis	50	E148Q increased
Inanir et al. [20]	Association of MEFV gene mutations with rheumatoid factor levels in patients with rheumatoid arthritis	110	Not increased
Koca et al. [21]	Prevalence and significance of MEFV gene mutations in a cohort of patients with rheumatoid arthritis	103	Not increased
Akkoc et al. [11]	Increased prevalence of M694V in patients with ankylosing spondylitis: additional evidence for a link with familial Mediterranean fever	42	Not increased
Migita et al. [18]	MEFV mutations in Japanese rheumatoid arthritis patients	126	Not increased
Rabinovich et al. [22]	Severe disease in patients with rheumatoid arthritis carrying a mutation in the Mediterranean fever gene	98	E148Q increased

CONCLUSION

The results of our present study, along with above mentioned published literature, indicate that the prevalence of MEFV gene mutations in patients with ankylosing spondylitis is significant. There is positive relation between common MEFV gene mutations and sacroiliitis. Nevertheless, the influence to the prognosis is less likely. The prevalence of MEFV gene mutations in RA patients is possibly low and not significant. According to the literature review, further studies are needed to investigate the existence of MEFV gene mutations among AS patients and their impact on the disease course in addition to assessment of AS prevalence in patients with FMF.

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