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**Letter to the Editor**

# Molecular Analysis of MEFV Gene Polymorphisms and Mutations in Iranian Azeri Patients with Rheumatoid Arthritis

***Alireza KHABBAZI*** [1], ***Farideh ZOLRAHIM*** [1], ***Mehrdad ASGHARI ESTIAR*** [2], ****Ebrahim SAKHINIA*** [1], ****Sousan KOLAHI*** [1]

1. *Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
2. *Dept. of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:** Email: susan.kolahi@yahoo.com

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## Dear Editor-in-Chief

Some genes have an unproven role in the pathogenesis of Rheumatoid arthritis (RA). One of these suspected genes is the Mediterranean fever (MEFV) gene. MEFV is responsible for familial Mediterranean fever (FMF). Currently, more than 100 FMF-associated mutations of the MEFV gene have been identified. With most located on exon 10, five of these: E148Q, M680I, M694V, M694I, and V726A account for most of the cases of FMF worldwide (1). A result of a study showed that the E148Q, V726A, M680I and M694I mutations are the most common mutations in the Azeri population of Iran with FMF (2). The MEFV mutation carrier rate in the area which shows a high frequency of FMF is also high. The E148Q was the most common mutation followed by V726A. The other common aforementioned mutations were not found in this study. The MEFV gene mutations cause an up-regulation of the inflammatory response, which most likely favors inflammation in general.

To the best of our knowledge, no study has been performed on the prevalence of MEFV gene mutations in RA in the Azeri population of Iran. In this study, we investigated the MEFV mutations on exon 2 and 10 in 50 patients with RA by PCR and direct sequencing and then compared disease activity between mutation carriers and non-carriers in the Azeri population of Iran. None of the participants had clinical manifestations or a family history of FMF. The RA patients were assigned to two groups of MEFV mutation and polymorphism carriers and non-carriers. Disease activity was measured using the DAS28 score to compare the two groups.

The demographical characteristics of the patients are summarized in Table 1. We identified 33 heterozygous patients. None of our study patients had any clinical manifestations or a family history of FMF. We found 3 polymorphisms and 2 mutations in Exon 2 and 4 mutations in Exon 10 of RA patients.

**Table 1:** Demographic and clinical features of study patients

| Characteristics | RA patients (N=50) |
|---|---|
| Age in years (mean±SD) | 38.04±6.62 |
| Males (%) | 10 (20%) |
| Females (%) | 40 (80%) |
| Familial history of RA* | - |
| Disease duration in years (mean±SD) | 4.8±3.54 |
| DAS 28 (mean±SD) | 2.16±1.02 |

*RA: Rheumatoid arthritis

Table 2 shows the distributions of the allele and genotype frequencies for the common MEFV mutations and polymorphisms in our study participants. No significant difference was seen in the disease activity between carriers and non-carriers.

**Table 2:** Common MEFV mutations and polymorphisms in study patients

| | DAS 28 Mean±SD | Results | Number (%) | Location | *P* value |
|---|---|---|---|---|---|
| **Mutation or polymorphism** | 2.22±1.8 | Negative | 29 (58) | Exon 2 | NS |
| D102D polymorphism | 2.05±1 | Positive | | | |
| | 2.27±1.1 | Negative | 19 (38) | | NS |
| G138G polymorphism | 1.90±0.8 | Positive | | | |
| | 2.35±1.1 | Negative | 19 (38) | | NS |
| A165A polymorphism | 1.71±0.7 | Positive | | | |
| | 2.25±1 | Negative | 9 (18) | | NS |
| E148Q mutation | 1.46±0.5 | Positive | | | |
| | 2.17±1 | Negative | 15 (30) | | NS |
| R202Q mutation | 2.13±1.2 | Positive | | | |
| | - | - | 1 (2) | Exon 10 | - |
| A744A mutation | - | - | 1 (2) | | - |
| M694V mutation | - | - | 1 (2) | | - |
| R761H mutation | - | - | 1 (2) | | - |
| V726A mutation | | | | | |

NS: non-significant
MEFV Mediterranean fever

This study is the first assessment of MEFV polymorphisms and mutations in the Azeri population of Iran with RA. Thirty three out of 50 RA patients were found to carry MEFV polymorphisms and mutations. The most common were the D102D, G138G, and A165A polymorphisms. In comparison with the normal Azeri population the carrier state of MEFV mutations in our study patients was higher. Bonyadi et al. in a study on five common MEFV gene mutations showed that 11.5% of normal Azeri people are carriers of E148Q followed by V726A (1.75%) (3). No carriers were found for M694V. We detected E148Q, V726A and M694V mutations in 18%, 2%, and 2% of RA patients, irrespectively. Difference in disease activity in the carrier and non-carrier patients was not significant.

Some studies in other populations also showed the higher frequency of MEFV mutations in RA patients (4). Migita et al. showed the higher frequency of MEFV mutations in patients with RA compared with healthy controls in Japan (5). Similar to this study, the most common mutation in RA patients was E148Q. Another study in Turkey showed 30.7% and 23.6% of RA and healthy control groups are carriers of the MEFV polymorphisms and mutations, respectively (6). Disease severity in MEFV mutation carriers was more than non-carriers.

This study reveals evidence suggesting that MEFV polymorphisms and mutations are associated with RA in the Azeri population of Iran. However our study has a low statistical power due to its small sample size. Further studies with larger populations will be required to confirm these findings MEFV mutations may act as a genetic susceptibility factor for RA. However, it has no major effect on the activity of disease in the Azeri population of Iran.

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The authors declare that there is no conflict of interest.

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