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**Original Research Article**

# The relationship between ABO blood groups and gene mutations frequently observed in Familial Mediterranean Fever

**Hatice Terzi[1]*, Ali Şahin[2], Can Hüzmeli[3], Ahmet Kerim Türesin[4], Gökhan Bağci[5], Mehmet Şencan[1]**

[1]Department of of Hematology-Internal Medicine, Cumhuriyet University Medical Faculty, Sivas, Turkey
[2]Department of Rheumatology- Internal Medicine, Cumhuriyet University Medical Faculty, Sivas, Turkey
[3]Department of Nephrology, Cumhuriyet University Medical Faculty, Sivas, Turkey
[4]Department of Internal Medicine, Cumhuriyet University Medical Faculty, Sivas, Turkey
[5]Department of Biology, Cumhuriyet University Medical Faculty, Sivas, Turkey

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***Correspondence:**
Dr. Hatice Terzi,
E-mail: dr.terzi@hotmail.com



## ABSTRACT

**Background:** The purpose of this study was to investigate the relationship between the genetic mutations, which are frequently detected and known to cause familial Mediterranean fever (FMF) disease, with ABO blood groups.
**Methods:** There were 271 patients with FMF diagnosis and 271 healthy control subject enrolled in the study. The medical files of each case were screened retrospectively and demographic characteristics, genetic mutations, and ABO blood groups were recorded.
**Results:** No statistically significant difference was detected between the two groups with respect to their gender and age (p>0/05). When patient and healthy control groups were compared based on ABO blood groups, the study groups were observed to differ significantly with respect to B blood group (p=0.008). In the patient group, a considerable relationship could not have been found when the gene mutations were compared based on blood groups, either for E148Q (n=64) and M694V (n=142) genes (p>0.05). However, a considerable difference was observed for V726A (n=58) gene; B blood group was more frequently observed among those who were detected to have V726A mutation (p=0.022).
**Conclusions:** In present study cohort, blood type B was more frequent among FMF patients. We observed that there could be a significant association between V726A mutation and ABO blood groups.

**Keywords:** Blood groups, Familial Mediterranean fever, Genetic mutation

## INTRODUCTION

Familial Mediterranean fever (FMF) is a familial autosomal recessive autoinflammatory disease. FMF is characterized by recurrent and self-limiting attacks of fever and polyserositis such as pleuritis, peritonitis, arthritis or erysipelas-like skin eruptions with a marked elevation of acute phase reactants.[1-4]

FMF is the most prevalent genetic monogenic autoinflammatory disease, primarily affecting ethnic groups living along the eastern Mediterranean coast: Armenians, Arabs, Sephardic Jews and Turks.[4,5] FMF in adults appears to be more frequent in males with a male/female ratio of 1.5-2:1. The worldwide prevalence is forecasted to be 100 000-150 000.[6]

After the discovery of an association between stomach cancer and blood type A in, there have been many studies on possible relationship of ABO blood types to certain diseases.[7] If the risk of several diseases is known for different blood groups, it could serve as an epidemiological marker or a main screening aid to specify high-risk populations.[8]

Therefore, distribution of ABO blood groups among patients, as well as presence of a possible association between ABO blood groups and FMF gene mutations was investigated in this study. By doing so, the aim was to demonstrate whether or not having certain blood type could cause a predisposition to FMF.

## METHODS

This is an unmatched case-control study. Between the years 2009 and 2014, a total of 271 FMF patients fulfilling Tel Hashomer criteria 9 (159 female, 112 male) and 271 healthy subjects (159 female, 112 male) were included in this study, retrospectively. The study protocol was confirmed by the local ethics committee and was in accordance with the Declaration of Helsinki 2008. Patients with other inflammatory, malignancies (solid or non-solid organs), autoimmune, diabetes mellitus and acute or chronic infectious diseases and diabetes mellitus were excluded from study. Normal healthy willings without chronic systemic disease, malignancies and with normal physical examination and laboratory findings were chosen as the control group

### *Statistical analysis*

The data collected in this study were entered into the SPSS version 14.0 software. Chi-squared test for multiple comparisons, Monte Carlo method and Fischer's exact test were used in the analysis. A value of $p<0.05$ was considered as statistically significant.

## RESULTS

A total of 271 FMF patients, consisting of 159 females (58.67%) and 112 males (41.32%), and 271 healthy subjects, consisting of 159 females (58.67%) and 112 males (41.32%), were included in the study. The mean age of the participants in the patient group was 35.07±12.85 (17-76) years and 36.74±12.22 (17-76) years in the control group. When the patient and the control groups were compared according to the distribution to A, B, and O blood groups, a statistically significant difference was observed with respect to blood type B (p=0.008) (Table 1), (Figure 1).

**Table 1: Comparison of the patient and control groups by ABO blood group.**

| | FMF, n (%) | Control, n (%) | p |
|---|---|---|---|
| O | 59 (21.8) | 76 (28) | >0.05 |
| A | 116 (42.8) | 123 (45.4) | >0.05 |
| B | 78 (28.8) | 48 (17.7) | 0.008* |
| AB | 18 (6.6) | 24 (8.9) | >0.05 |
| Total | 271 | 271 | |

*Statistically significant.

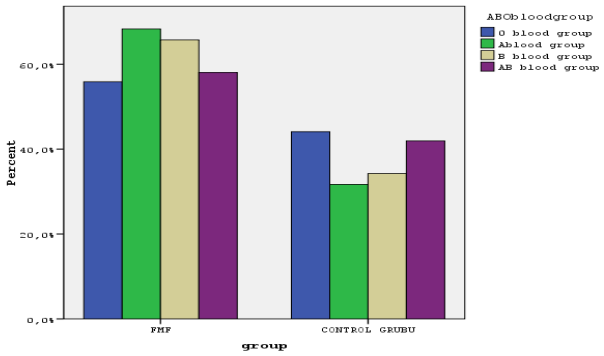


**Figure 1: The distribution of A, B, AB and O blood groups according to FMF and control groups.**

**TABLE 2: V726A mutation comparison based on ABO blood group.**

| | | | V726A mutation | | Total | P-value |
|---|---|---|---|---|---|---|
| | | | Negative | Positive | | |
| ABO blood group | 0 group | n | 46 | 15 | 61 | >0.05 |
| | | % | 75.4 | 24.6 | 100.0 | |
| | A group | n | 108 | 21 | 129 | >0.05 |
| | | % | 83.7 | 26.3 | 100.0 | |
| | B group | n | 37 | 21 | 58 | 0.022* |
| | | % | 63.8 | 36.2 | 100.0 | |
| | AB group | n | 16 | 1 | 17 | >0.05 |
| | | % | 94.1 | 5.9 | 100.0 | |
| **TOTAL** | | n | 207 | 58 | 265 | |
| | | % | 78,1 | 21.9 | 100.0 | |

* statistically significant

When the mutations frequently observed among FMF patients were compared according to A, B, and O blood groups, among patients who had E148Q positive (n=64) and M694V (n=142) genes were not observed to have a statistically significant association with ABO blood types (p>0.05).

A significant difference was observed in comparison of the patients with V726A positive (n=58) gene by blood groups. B blood group was the most common blood group among those who were positive for V726A mutation compared to other blood group types (p=0.022) (Table 2).

## DISCUSSION

FMF is a familial autosomal recessive autoinflammatory disease, characterized by recurrent and self-limiting attacks of fever and serositis. The disease is characterized by irregular, short inflammatory episodes of serositis, accompanied by fever.[5] FMF is caused by mutations of FMF gene (MEFV, Mediterranean fever) composed of 10 exons on chromosome 16p13.3.[10] MEFV gene is expressed especially in myeloid cells and upregulated during myeloid differentiation. Its expression is induced by some inflammatory mediators [i.e. TNF (tumor necrosis factor) and interleukin-1]. Pyrin is a protein encoded by the MEFV gene that prominently expressed in the cytoplasm of mature monocytes and neutrophils and also in dendritic cells and synovial fibroblasts.[11] Pyrin seems to play a principal role in the regulation of both inflammation and apoptosis and mutated pyrin lead to full-blown inflammation characterized by excessive IL-1 β secretion in FMF.

Most of the mutations arisein exon 10, including the four identified in the majority of FMF patients: M694V, M680I, V726A and M694I. They appear to be related to clinical presentation and disease severity using the Tel Hashomer severity score.[12-14]

The diagnosis of FMF is based on clinical symptoms, and supported by family history and ethnic origin. Since the discovery of MEFV gene, molecular genetic testing is used as a diagnostic helper, particularly in atypical cases. Amyloidosis, the most considerable complication of FMF, is the main cause of mortality and may be prevented by prophylactic colchicine treatment, recommended for all patients diagnosed with FMF.[12] The main aim of therapy in FMF is the prevention of recurrent attacks and amyloidosis.

The first genetic marker defined for humans is the ABO blood group antigens.[13,14] Many studies have been published inconsistent results on the distribution of blood types in different diseases.[15,16] Some researchers have shown that structure of certain tumor antigens is similar to that of ABO system antigens. For instance, Forssmann antigen is synthesized predominantly in colon and stomach tumors, and structurally it is almost identical to the A antigen determinant.[17] However, recent studies have reported associations between ABO blood groups and circulating levels of tumor necrosis factor-alpha, soluble ICAM-1, E-selectin and P-selectin suggesting that blood group antigens may influence the systemic inflammatory response.[18-21]

In another study, the association between primary osteoarthritis of the hip and ABO blood groups were investigated and an association was observed for O blood group.[22] In a prior study of seropositive rheumatoid arthritis, ABO and Rh blood group distributions were evaluated. While no statistically significant difference was observed across ABO blood groups, there was a significant difference in terms of Rh blood types.[23] In a study that investigated the association of Behcet's Disease with ABO and Rh blood groups, no significant association was found.[24] We also could not detect any significant relationship between FMF patients and healthy subjects' groups with respect to Rh blood type (p>0.05).

This study was performed to find any association of ABO blood groups in FMF patients. The results of the present study showed that there is a significant difference between the distributions of ABO blood groups in FMF patients. In the comparison of FMF patient group who were positive for V726A mutation by ABO blood groups detected a statistically significant association with blood type B (Table 2, p=0.022).

## CONCLUSION

Our findings indicate that a significant association exists between V726A mutation and ABO blood groups. These findings increase the possibility of using ABO blood group as an epidemiologic marker in societies where V726A mutations are observed more frequently.

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