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Investigation of the effect of vascular endothelial growth factor gene 936 C/T polymorphism in familial Mediterranean fever patients

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ABSTRACT

Objectives: This study aims to investigate the effect of vascular endothelial growth factor (VEGF) gene 936C/T polymorphism (rs3025039) on the appearance of phenotypic characteristics of familial Mediterranean fever (FMF) patients that differ with respect to MEditerranean FeVer (*MEFV*) gene mutations. Here, we investigated a single functional polymorphism in the VEGF gene.

Methods: The study group consisted of 223 FMF patients with definite diagnosis according to Tel-Hashomer criteria who carried *MEFV* gene mutations, while 208 FMF patients with definite diagnosis of FMF but without any mutations, making up the control group, were included in the study. The VEGF gene 936C/T polymorphism was genotyped using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique.

Results: Genotype and allele frequencies of the VEGF rs3025039 polymorphism between the two groups were significantly different ($p = 0.03$ and $p = 0.011$, respectively). The TT genotype was found to be more frequent in the study group than in controls (4.9% vs. 3.3%, respectively).

Conclusions: Our results seem to indicate that the VEGF 936C/T polymorphism affects the appearance of the phenotypic characteristics of FMF. It is possible that other variants of this gene may also have similar effects.

Keywords: Genotyping, hereditary, inflammation, *MEFV* gene, VEGF gene

Autoinflammatory diseases are diseases in which systemic symptoms such as recurrent fever, high acute phase reactants are observed and also accompanied by pathologies such as rash, serositis and arthritis affecting various organs. [1]. Familial Mediterranean fever (FMF) is the most widespread autosomal recessive, inheritable autoinflammatory disease caused by MEditerranean FeVer (*MEFV*) gene mutations [2].

FMF (OMIM 249100) is characterized by recurrent self-limiting attacks of fever, peritonitis, pleuritis, arthritis and erysipelas-like skin lesions [3, 4]. It is estimated that around 150,000 people in the world have this disease, although its prevalence is uneven among ethnic groups [5]. FMF is most frequently observed in individuals of Turkish, Arab, non-Ashkenazi Jewish and Armenian origin [6-9].

The pathogenesis of FMF is not completely understood although the gene responsible for FMF has been identified [10]. *MEFV* gene located on the short arm of chromosome 16, comprising 10 exons and respon-

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sible for FMF was cloned by two independent groups [11, 12]. The *MEFV* gene encodes a protein called pyrin or marenostrin with 781 amino acids. It is expressed in polymorphonuclear leucocytes and cytokine-activated monocytes and acts as an anti-inflammatory protein. More than 70 FMF-related *MEFV* gene mutations have been reported [13, 14].

Vascular endothelial growth factor (VEGF) polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP) technique or VEGF, produced by different cell types, has an important role in both physiological and pathological angiogenesis. [15]. The regulation of angiogenic processes is complex and requires a fine balance between pro-angiogenic and antiangiogenic mediators. One of the most important pro-angiogenic factors is the VEGF [16]. VEGF plays a central role in human rheumatoid arthritis (RA) and animal models of arthritis [17, 18]. VEGF is one of the main regulators of angiogenesis, stimulating the formation of new vessels and increasing the permeability of existing blood vessels. This, in turn, causes the increased and continuity of inflammatory conditions. Due to this, the contribution of VEGF in the pathogenesis of various immunological and inflammatory diseases has been demonstrated. [19].

Single nucleotide polymorphisms (SNPs) of the *VEGF* gene are associated with the production of *VEGF* protein and are reported to be involved in susceptibility to several disorders in which angiogenesis may be critical with regard to pathogenesis [20-23]. *VEGF* gene polymorphisms have been shown to be associated with susceptibility to diseases and angiogenesis is an important process in the pathogenesis of chronic inflammatory disorders such as rheumatoid arthritis [20, 22, 24].

VEGF gene is located on chromosome 6p21.3 and contains 8 exons. The coding region spans approximately 14 kb [25, 26]. Functional polymorphisms of the *VEGF* gene have been associated with low or high *VEGF* protein synthesis. Regarding the V*VEGF* gene 3'- untranslated region C/T polymorphism at 936. position, low plasma levels of VEGF have been reported in carriers of T allele when compared with non-carriers [27].

Neutrophils are the main cell types that play important role in the acute inflammation of FMF. It is also known that VEGF plays a significant role in these cells. Therefore, in this study, our aim is to investigate the possibility of functional *VEGF* gene 936C/T polymorphism being is effective in the emergence of phenotypic characteristics of the FMF disease.

METHODS

Study Populations

Patients who were referred from various clinics to Ondokuz Mayıs University Faculty of Medicine, Department of Medical Biology, Molecular Genetics Laboratory for *MEFV* gene mutation analysis were included in the study. Ethical Board approval was taken for the study from Faculty of Medicine, Ondokuz Mayıs University. In addition, informed consents were taken from patients and each FMF patient filled in an FMF information survey before giving a blood sample. After signing the form, the patients were examined according to Tel-Hashomer criteria and the patients and the controls with definitive diagnosis were evaluated for *VEGF* gene 936C/T polymorphism (rs3025039).

The study group included 223 unrelated FMF patients (SG) with a definitive diagnosis according to the Tel-Hashomer criteria. These patients have two of the twelve most commonly occurring *MEFV* gene mutations (E148Q, P369S, F479L, M680IG/C, M680IG/A, I692del, M694V, M694I, K695R, V726A, A744S, and

Table 1. The demographical characteristics of the FMF patient and control groups

Demographical characteristics	Study group (n = 223)	Control group (n = 208)
Age (years), median (minimum-maximum)	25 (2 - 69)	15 (2 - 88)
Gender (male/female), n (%),	120/103 (53.8/46.2)	91/117 (43.8/56.2)

The study group (FMF patients) = 223 FMF patients with definitive diagnosis according to Tel-Hashomer criteria and carrying two of the 12 mutations commonly seen in MEFV gene, Control group = 208 symptomatic FMF patients who had definitive diagnosis according to the same criteria but did not carry any of the 12 mutations tested.

R761H). The control group (CG) consisted of 208 symptomatic FMF patients who had a definitive diagnosis according to the same criteria but who did not carry any of the twelve most commonly occurring *MEFV* gene mutations indicated above.

Genotyping

Genomic DNA was extracted from peripheral blood cells according to kit directive using Vivantis GF-1 Nucleic Acid Extraction Kit (Qiagen, Istanbul, Turkey). *VEGF* gene 936C/T polymorphism was genotyped using the previously described polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP) technique with minor modifications [28]. The PCR was performed in a total volume of 25 µL using 100 ng of genomic DNA, 5 µL of 10× reaction buffer, 2 mM magnesium chloride (Fermentas), 10 pmol of each primers, 0.5 mM of each dNTP and 2 U of Taq DNA polymerase (Fermentas). The PCR conditions were: 1 cycle at 95°C for 12 minutes; 35 cycles, each consisting of denaturation at 95°C for 30 seconds, annealing at 57°C for 40 seconds, and synthesis at 72°C for 30 seconds; and a final cycle at 72°C for 10 minutes. The PCR products were digested with restriction endonuclease NIaIII (Fermentas), in a 37°C incubator 24 hours. With this enzyme, the C allele remained uncut (198bp), while the T allele was cut into 2 fragments of 114bp and 84bp. The fragments were loaded onto 3% agarose gel, electrophoresed and observed over an UV-transilluminator.

Statistical Analysis

Analyses of data were performed using the Statistical Package Program (SPSS, version 23.0, Chicago, IL, USA). Continuous data were given as mean ± standard deviation and median (min-max). Allele and genotype frequencies of patients and controls were compared with chi square (χ^2) test. All p values were 2-tailed and *p* values less than 0.05 were considered significant. The Hardy-Weinberg equilibrium (HWE) was evaluated by χ^2 test

RESULTS

DNA samples of 223 FMF patients (SG) and 208 con-

Table 2. Clinical characteristics of the FMF patient groups and control group

Clinical characteristics	Study group (n = 223)	Control group (n = 208)
Fever, n (%)		
pozitif	213 (95.5)[a]	202 (97.1)[a]
negatif	10 (4.5)	6 (2.9)
Abdominal pain, n (%)		
pozitif	214 (96.0)[a]	198 (95.2)[a]
negatif	9 (4.0)	10 (4.8)
Amyloidosis, n (%)		
pozitif	20 (9)[a]	23 (11.1)[a]
negatif	203 (91)	185 (88.9)
Arthritis/arthralgia, n (%)		
pozitif	169 (75.8)[a]	149 (71.6)[a]
negatif	54 (24.2)	59 (28.4)
Erysipelas-like erythema, n (%)		
pozitif	59 (26.5)[a]	63 (30.3)[a]
negatif	164 (73.5)	145 (69.7)

[a,b,c]There is no difference between groups with the same letter.

The study group (FMF patients) = 223 FMF patients with definitive diagnosis according to Tel-Hashomer criteria and carrying two of the 12 mutations commonly seen in *MEFV* gene, Control group = 208 symptomatic FMF patients who had definitive diagnosis according to the same criteria but did not carry any of the 12 mutations tested.

trols (CG) were genotyped with regard to VEGF 936C/T polymorphism. In the study group, there were 120 (53.8%) males and 103 (46.2%) females. There were 91 (43.8%) males and 117 (56.2%) females in the control group. Demographic data of the patients are shown in Table 1. The clinical features of FMF patients who had a definitive diagnosis according to Tel-Hashomer criteria were shown in Table 2. In terms of clinical findings (fever, abdominal pain, amyloidosis, arthralgia and erysipelas-like erythema), there was no difference between study groups. The genotype distribution shown in patients who carry mutation in *MEFV* gene (homozygote, heterozygote, and compound heterozygote) in the Table 3.

When the study and the control groups were assessed in terms of genotype and allele frequencies, the difference was found to be statistically significant (Table 4). Based on the findings of the study: of the study group, 152 (68.2%) had CC genotype, 60 (26.9%) had CT genotype and 11 (4.9%) had TT genotype; while, of the control group, 165 (79.3%) had CC genotype, 36 (17.3%) had CT genotype and 7 (3.4%) had TT genotype. When the genotype frequencies of *VEGF* gene 936C/T polymorphism in the study group were compared with those of the control group, the difference between the results of the two groups was found to be statistically significant (χ^2=7.06; p = 0.03).

The study group had a lower frequency of CC genotype when compared with the control group (p = 0.022). CT heterozygous genotype frequency of VEGF gene was observed at a rate of 26.9% in the study group and 17.3% in the control group and was found to be statistically significantly higher (p = 0.015). TT genotype frequency was found to be higher in the control group (3.4%) when compared with the study group (4.9%); however, this difference was not statistically significant (p = 0.41) (Table 4).

When the study group was compared with controls, we observed significant difference between the C and T allele frequencies, with the allele C present in 81.61% of the study group and 88% of the controls and allele T present in 18.38% of the study group and 12% of the controls. T allele was found to be statistically higher in the study group as compared with the control group (χ^2= 6.39; p = 0.011).

Table 3. The distribution of MEFV mutations

	Frequency	%
Mutation non detected	208	48.3
Mutation detected	223	51.7
M694V, M694V	77	34.5
M680I(G/C), M694V	48	21.5
M680I(G/C), M680I(G/C)	20	9.0
M694V, E148Q	16	7.2
M680I(G/C), V726A	16	7.2
M694V, V726A	16	7.2
E148Q, P369S	4	1.8
M694V, R761H	4	1.8
E148Q, M680I(G/C)	3	1.3
E148Q, V726A	2	0.9
F479L, V726A	2	0.9
E148Q, M694I	2	0.9
M680I(G/C), R761H	2	0.9
M680I(G/C), M680I(G/A)	2	0.9
E148Q, E148Q	2	0.9
M694V, A744S	1	0.4
E148Q, R761H	1	0.4
M694V, E148Q, P369S	1	0.4
M694I, M694I	1	0.4
F479L, F479L	1	0.4
M694V, P369S	1	0.4
M680I(G/A), M694V	1	0.4

DISCUSSION

The VEGF plays a significant role in affecting the endothelial cells. The proliferation of endothelial non-proliferative cells on culture deprived of oxygen and food shows that it causes network formation and stimulates ramification. Neovascularization that occurs as a result of the angiogenesis following the abundant production of VEGF is significant in the development of chronic inflammation [24]. Studies have shown that some SNPs in the *VEGF* gene are predisposing factors in rheumatic diseases such as ankylosing spondylitis and rheumatoid arthritis [20, 22]. There are studies which report that *VEGF* gene polymorphisms are associated with VEGF production [24]. However, there is only one study that examines the relationship between *VEGF* gene polymorphism and FMF. This study

Table 4. The comparison of genotype and allele frequencies of VEGF 936C/T polymorphism between FMF patients and the control group

VEGF gene 936 C/T	Study group (n = 223)	Control group (n = 208)	χ^2	*p* value
Genotype, n (%)			7.06	**0.03**
CC	152 (68.2)	165 (79.3)		**0.022**
CT	60 (26.9)	36 (17.3)		**0.015**
TT	11 (4.9)	7 (3.4)		0.41
Allele, n (%)			6.39	**0.011**
C	364 (81.61)	366 (88)		
T	82 (18.38)	50 (12)		

The study group (FMF patients) = 223 FMF patients with definitive diagnosis according to Tel-Hashomer criteria and carrying two of the 12 mutations commonly seen in MEFV gene, Control group = 208 symptomatic FMF patients who had definitive diagnosis according to the same criteria but did not carry any of the 12 mutations tested.

examines whether there is a difference between the study and the control groups of FMF patients regarding VEGF 936C/T polymorphism.

One study showed that the C→T transition at position 936 which is one of the 3 polymorphisms located at 3'UTR is significantly associated with VEGF plasma level. The same study reported that 936C/T polymorphism was associated with significantly lower VEGF plasma levels in healthy men and thus this polymorphism could be a significant genetic indicator for diseases associated with angiogenesis [27].

The purpose of this study was to examine whether *VEGF* gene 936C/T functional polymorphism was associated with the basic phenotypic characteristics of FMF disease. A statistically significant difference was found between the study and control groups in terms of genotype and allele frequencies ($p = 0.03$ and $p = 0.011$, respectively). Our study showed that the study group had lower rates of CC genotype when compared with the control group, while they had higher rates of CT genotype. Although *VEGF* gene 936TT genotype was found to be higher in the study group when compared with the control group, the difference was not statistically significant. In terms of allele frequencies, C allele was found to be lower in the study group when compared with the controls while T allele was found to be higher ($p = 0.011$).

In their study with FMF patients and healthy control groups in 2007, Gunesacar *et al*. [19] did not find a significant difference between the genotype and allele frequencies of *VEGF* gene 936C/T polymorphism. In addition, they reported that 936TT genotype of this gene was found to be higher in FMF patients when compared with the healthy controls; however, this difference was not statistically significant [19]. This result is in parallel with the results of our study.

In a study on patients with rheumatoid arthritis (RA) by Han *et al*. [20] in 2004, the 936T allele was found to be associated with lower production of VEGF in controls; while, compared with controls, the same allele was found to be in significantly higher frequency in patients with RA (22.7 and 13.4%, $p = 0.002$). The results of this study asserted that *VEGF* gene can play a role in RA development. The researchers also examined the two SNPs (at - 2578 and -1154 positions) located in the promoter region and one SNP (at -634 position) in 5'-untranslated region and suggested that these polymorphisms were not associated with RA [20].

In another study conducted with Chinese RA patients in 2013, 3 SNPs (-2578C/A, - 634G/C and 936C/T) were examined and these polymorphisms were not found to be associated with the risk of RA [29].

In a meta-analytic study of the relationship between disease activity and VEGF levels in rheumatoid arthritis in 2018, circulating VEGF levels were found to be significantly higher in RA patients. However, there is no association between VEGF-2578A/C, -634C/G, +936T/C, and -1154A/G polymorphisms and RA development [30].

In another study conducted in 2016, the relation-

ship between serum VEGF protein levels and *VEGF* gene polymorphisms was examined in patients with RA. Studies have shown that VEGF -1154A/G and -2578A/C genetic variants may be genetic susceptibility factors for RA, and increased serum levels of VEGF in RA patients with high disease activity [31]. Similar results in a similar study of the relationship between ankylosing spondylitis and *VEGF* gene polymorphism in the Chinese population and serum VEGF levels in the same year showed that VEGF levels are significantly associated with AS in the inflammatory process [32].

In a study of female RA patients in 2017, an increase in the frequency of VEGF 936CT and a decrease in the 936CC genotype were observed in seronegative patients as compared to healthy controls. Investigators have stated that the presence of certain *VEGF* gene variants in the regulatory region may reflect the nature of immunopathological mechanisms in RA [33].

Many studies have investigated the frequency of *MEFV* gene mutations in Turkey and other countries. A study reported that M694V, M694I, M680I, V726A and E148Q gene mutations were the most frequently observed mutations [8]. In the studies of Federici *et al*. [34], it was shown that five mutations constitute 85% of all *MEFV* gene mutations. It has been reported that M694V, V726A, M680I, E148Q, R761H and P369S are the most frequently observed mutations in Turkey [35]. It is understood that these mutations are much more common in FMF patients than other mutations. The results reported above support that the 12 *MEFV* gene mutations we screened in our study constitute the majority (at least 95%) of *MEFV* gene mutations that can be seen in a population. Therefore, it brings to mind the possibility that patients who do not have any of the 12 *MEFV* gene mutations screened but show FMF phenotype according to Tel-Hashomer criteria may show a phenotype similar to the FMF phenotype due to different factors. We aimed to test the influence of *VEGF* gene 936C/T polymorphism on the occurrence of the FMF symptoms definitely diagnosed but genotypically different (whether or not carrying the 12 most commonly occurring *MEFV* gene mutations) FMF patient groups.

Limitations

Our study assessed the study and control groups based on Tel-Hashomer criteria and the patients who had a definitive diagnosis were included in the study. Thus, the clinical features of the both groups were similar. Hence, no intergroup comparison was done.

CONCLUSION

VEGF gene 936C/T polymorphism might affect the occurrence of phenotypic features of FMF. There is a possibility that the VEGF stimulation of the leucocyte chemotaxis might be the cause of this effect. This may, in turn, cause an increase in the occurrence of the FMF symptoms in the control group that does not carry any of the 12 most commonly occurring *MEFV* gene mutations.

Recommendations

Here, we investigated a single functional polymorphism in the VEGF gene. It is possible that other variants of this gene may also have similar effects. For this reason, other variants can work in FMF patients.

Authors' Contribution

Study Conception: MY, HB; Study Design: MY, HB; Supervision: MY, HB; Funding: MY, HB; Materials: MY; Data Collection and/or Processing: MY; Statistical Analysis and/or Data Interpretation: MY; Literature Review: MY; Manuscript Preparation: MY and Critical Review: MY, HB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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