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I Carry the R202Q Variant Only, Can I Have the Classical Clinical Features of Familial Mediterranean Fever?

Sadece R202Q Varyantını Taşıyorsam, Ailesel Akdeniz Ateşinin Klasik Klinik Özelliklerine Sahip Olabilir miyim?

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by self-limited fever and polyserositis. The disease is associated with mutations in the Mediterranean fever *(MEFV)* gene, of which more than 700 variants have been reported. This study aimed to evaluate the clinical features of children with FMF carrying the R202Q variant by comparing them with other common MEFV variants.

Methods: This retrospective study included 318 patients who were previously diagnosed with FMF according to the Tel-Hashomer criteria. Demographic and clinical data of patients with either heterozygous or homozygous FMF for R202Q variants (group 1) and patients with homozygous or compound heterozygous variants (M694V, M694I, M680I, V726A, E148Q etc.) (group 2) were compared

Results: The R202Q group had a lower frequency of family history of FMF, recurrent fever, abdominal pain, chest pain, erysipelas-like erythema, and growth retardation (p=0.007, p=0.01, p=0.002, p=0.007, p=0.002 and p=0.05 respectively), and higher incidences of arthralgia, myalgia, oral ulcer, and headache (p=0.01, p=≤0.001, p=0.003, p=0.01 respectively). Group 2 had a higher rate of moderate projected retained ability score (PRAS) < scores, whereas group 1 had milder PRAS scores (p=≤0.001). The mean serum amyloid A value of the R202Q group was lower than that of group 2 (p=0.03).

Conclusion: Although prospective studies on larger populations are needed to investigate the relationship between the clinical reflection of FMF and the R202Q variant, we suggest that R202Q alterations may be symptomatic in some patients.

Keywords: FMF, R202Q, variant, heterozygous, homozygous

ÖZ

Amaç: Ailesel Akdeniz ateşi (FMF), kendini sınırlayan ateş ve poliserozit atakları ile karakterize kalıtsal otoenflamatuvar bir hastalıktır. Hastalık Akdeniz ateşi (*MEFV*) genindeki mutasyonlarla ilişkilidir ve 700'den fazla MEFV varyantı bildirilmiştir. Bu çalışmanın amacı R202Q varyantı taşıyan FMF'li çocukların klinik özelliklerini diğer yaygın MEFV mutasyonları ile karşılaştırarak değerlendirmektir.

Yöntem: Bu retrospektif çalışmaya daha önce Tel-Hashomer kriterlerine göre FMF tanısı konmuş 318 hasta dahil edilmiştir. R202Q varyantları için heterozigot veya homozigot olan FMF hastalarının (grup 1) ve homozigot veya bileşik heterozigot varyantları (M694V, M694I, M680I, V726A, E148Q vb.) olan hastaların (grup 2) demografik ve klinik verileri toplandı ve karşılaştırıldı.

Bulgular: R202Q grubunda ailede FMF öyküsü, tekrarlayan ateş, karın ağrısı, göğüs ağrısı, erizipel benzeri eritem ve büyüme geriliği sıklığı daha düşüktü (p=0,007, p=0,01, p=0,002, p=0,007, p=0,002 ve p=0,05) ve daha yüksek artralji, miyalji, oral ülser ve baş ağrısı insidansı (sırasıyla p=0,01, p=≤0,001, p=0,003, p=0,01). Grup 2'deki hastalarda daha yüksek oranda orta derecede gebelik ile ilişkili anksiyete ölçeği (PRAS) skoru görülürken, grup 1'deki hastalarda daha hafif PRAS skoru görülmüştür (p=≤0,001). R202Q grubunun ortalama Serum Amiloid A değeri grup 2'den daha düşüktü (p=0,03).

Sonuç: FMF'in klinik yansıması ile R202Q varyantı arasındaki ilişkiyi araştırmak için daha geniş popülasyonlarda prospektif çalışmalara ihtiyaç duyulmasına rağmen, R202Q değişikliğinin bazı hastalarda semptomatik olabileceğini düşünüyoruz.

Anahtar Kelimeler: FMF, R202Q, varyasyon, heterozigot, homozigot

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INTRODUCTION

Familial Mediterranean fever (FMF) is a genetic disorder characterized by recurrent fever along with serositis, which presents as inflammation of the chest, abdomen, or joints.[1] The condition mainly affects Turkish, Armenian, Jewish, and Arab populations in the Eastern Mediterranean region.[2] Diagnosis is primarily dependent on the clinical features, with family history, ethnic origin, and genetic testing serving as supportive evidence.[3]

Mutations in the *MEFV* gene are the underlying cause of FMF, and they affect the production of pyrin, a protein that plays a critical role in inflammatory responses.[4-7] To date, >700 MEFV variants have been documented. Of particular significance is the observation that five variants (M694V, M694I, M680I, V726A and E148Q) account for >70% of FMF cases observed across different populations.[8] The pathogenic roles of well-known *MEFV* gene variants have been extensively documented in the literature. However, the pathogenicity of the R202Q variant is still debated. While some studies hypothesized that this variant may be pathogenic in some patients with FMF, others suggested that it is not.[9,10] This study aimed to assess and differentiate the clinical presentation and severity of FMF associated with the R202Q variant in children from those with known pathogenic mutations.

METHODS

Study Population

The study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital (approval number: KAEK/2016.3.9, date: 01.11.2016).

Patients aged below 18 years who were diagnosed according to the Tel-Hashomer criteria with FMF in the pediatric rheumatology department between May 2010 and October 2018 were included in the study and evaluated retrospectively. The participants were subdivided into two categories based on their specific MEFV variants they exhibited. Group 1 comprised patients who were heterozygous or homozygous for the R202Q variant. Patients in group 2 were homozygous or compound heterozygous for pathogenic MEFV mutations (Table 1). All patients had received colchicine or anti-IL1 therapy for at least 6 months. In accordance with the established guidelines[11], the recommended colchicine dose is 1.2 mg/m²/day. Under the age of five, the dose was set at 0.5 mg/day; between five and ten years old, the dose was set between 0.5 and 1 mg/day, and above ten years old, the recommended dose was 1.5 mg/day.

For each patient, the following data were recorded at the time of diagnosis: age, time of symptom onset, age at diagnosis, frequency, and features of the attacks. The acute-phase reactants, such as white blood cell, erythrocyte sedimentation rate, C-reactive protein, serum amyloid A (SAA), and platelets, were measured during the attack period. A patient was considered to be "non-responsive to colchicine" if more than one attack at typical sites occurred within a 3-month period while taking the highest appropriate dose of colchicine.[12] Disease severity was evaluated according to the severity scoring system developed by Pras et al.[13] (modified for children with FMF, and the differences between the two groups were compared).

Table 1. Distribution of *MEFV* gene mutations in homozygous and compound heterozygous individuals

Genotype	Group 2, n=243
Homozygous mutations (n=125)	
M694V/M694V, n (%)	69 (55.2)
M680I/M680I, n (%)	36 (28.8)
E148Q/E148Q, n (%)	13 (10.4)
V726A/V726A, n (%)	4 (3.2)
M694I/ M694I, n (%)	3 (2.4)
Compound heterozygous mutations (n=118)	
M694V/726A, n (%)	25 (21.1)
M694V/M680I, n (%)	20 (16.6)
M680I/V726A, n (%)	15 (12.5)
M680I/E148Q, n (%)	9 (7.4)
M694V/E148Q, n (%)	9 (7.4)
M694V/A744S, n (%)	5 (4.1)
M694V/R761H, n (%)	4 (3.7)
M680I/R761H, n (%)	4 (3.7)
V726A/E148Q, n (%)	4 (3.7)
M694V/M694I, n (%)	4 (3.7)
E148Q/R151S, n (%)	4 (3.7)
E148Q/V726A, n (%)	4 (3.7)
E148Q/L110P, n (%)	3 (2.4)
E148Q/R761H, n (%)	3 (2.4)
E148Q/F479L, n (%)	3 (2.4)
V726A/R761H, n (%)	2 (1.5)
MEFV: Mediterranean fever	

Detection of *MEFV* Gene Mutations

Blood samples were processed for deoxyribonucleic acid (DNA) extraction using an ethylenediaminetetraacetic acid-based method and a DNA isolation kit (Sigma-Aldrich, USA). Subsequently, the exon 2 region was amplified (Metabion, Germany). The resulting polymerase chain reaction (PCR) segments were subjected to electrophoresis in 1% agarose gels and visualized under ultraviolet light (Spectroline, USA). They (658 bp) were subjected to PvuII digestion to determine the R202Q mutation. The PvuII-treated PCR segments were subjected to electrophoresis on a 3% agarose gel, and their banding profiles were analyzed. As a result of enzyme-mediated cleavage, homozygous normal samples (G/G) yielded two fragments (582 and 196 bp), heterozygous samples (G/A) yielded four fragments (582, 386, 196, and 75 bp), and homozygous mutant samples (A/A) yielded three fragments (386, 196, and 75 bp).

Upon admission to the hospital, the parents or guardians provided a general consent form authorizing the use of anonymized data. The study was approved by the relevant institutional review board.

Statistical Analysis

The data analysis was conducted using SPSS 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Statistical analyses were performed to assess data distribution and compare variables using standard techniques, such as the Kolmogorov-Smirnov and Student's t-test. Non-parametric variables were evaluated using the chi-square and Mann-Whitney U tests. The numerical variables are expressed as the mean±standard deviation, whereas the categorical variables are expressed as percentages. A p value 0.05 was considered significant.

RESULTS

The study included a total of 318 patients diagnosed with FMF, of whom 150 were female and 168 were male. Group 1 consisted of 75 (23.5%) patients, of whom 58 (77.3%) were heterozygous and 17 (22.7%) were homozygous R202Q variants without any other mutations. Group 2 consisted of 243 patients (76.5%), of whom 125 (51.4%) exhibited homozygous mutations and 118 (48.6%) exhibited compound heterozygous mutations. Table 1 summarizes the frequency distribution of MEFV genotypes.

There were no significant differences between the two groups in terms of sex, age at onset of symptoms, age at diagnosis, arthritis, leg pain after exercise, colchicine dose required (in milligrams per day), or use of a biologic agent.

Group 1 exhibited a lower frequency of family history of FMF, recurrent fever, chest pain, abdominal pain, and erysipelas-like erythema than group 2 (p=0.007, p=0.01, p=0.007, p=0.002 and p=0.002 respectively).

Group 1 exhibited a higher prevalence of myalgia, arthralgia, oral ulceration, and headache (p=≤0.001, p=0.01, p=0.003, p=0.01 respectively). Patients in group 2 had higher moderate PRAS scores, whereas those in group 1 had milder PRAS scores (p<0.001). The post-hoc analysis revealed no significant difference in the occurrence of severe PRAS scores. There were no statistically significant differences between the nephrotic and non-nephrotic proteinuria groups. No patient in the cohort had amyloidosis.

The mean SAA value of group 1 [median 30 (minimum 0.2-maximum 685)] was found to be lower than that of group 2 [median 6 (0.8-1850) (p=0.03)]. A comparison of the groups according to their clinical and laboratory features is presented in Tables 2 and 3.

DISCUSSION

This study revealed that patients carrying the R202Q variant had milder FMF than those carrying homozygous or compound heterozygous pathogenic MEFV mutations. The R202Q alteration was initially described by Bernot et al.[14] As a common variant. Subsequent studies in diverse populations have suggested a potential correlation between the R202Q variant and FMF. In a study conducted by Ritis et al.[15] on Greek patients, four out of 26 individuals with FMF were identified as homozygous for R202Q, compared with none of the 60 healthy controls. The authors proposed the hypothesis that the R202Q homozygous mutation of MEFV may represent a phenomenon that extends beyond the boundaries of mere polymorphism.

The genetic basis of FMF has been the subject of considerable investigation, with studies examining the prevalence and functional consequences of specific gene mutations and the potential clinical implications of R202Q alteration in patients with FMF. Furthermore, independent studies have reported the clinical importance of the R202Q mutation in patients with FMF of Turkish origin. In a study by Tekgoz et al.,[16] the presence of the R202Q variant was theorized to influence disease expression, with the variant associated with milder clinical findings, milder disease severity, and increased response rates to colchicine when found in combination with M694V. The frequency of biological therapy required by patients in group 2 was greater than that required by patients in group 1, although this difference was not statistically significant. However, the disease course in group 1 was milder in our cohort.

The relevance of the heterozygous R202Q mutation to the development of the disease has been the subject of considerable debate. The study by Yigit et al.[17] revealed no significant divergence in R202Q heterozygote frequencies

Table 2. Comparison of groups according to demographicthe demographic and clinical characteristicsfeatures			
	Group 1 (R202Q) n=75	**Group 2 (homozygous and compound heterozygous) n=243**	**p value**
Male/female (n)	37/38	131/112	0.28
Age at onset (years); mean±SD	6.82±3.83	5.18±3.95	0.78
Age at diagnosis (years); mean±SD	8.70±3.61	7.95±4.22	0.17
Family history of FMF, n (%)	19 (25.3)	101 (41.6)	**0.007**
Recurrent fever, n (%)	53 (70.7)	204 (84)	**0.01**
Abdominal pain, n (%)	54 (72)	213 (87.7)	**0.002**
Chest pain, n (%)	12 (16)	75 (30.9)	**0.007**
Arthritis, n (%)	23 (30.7)	99 (40.7)	0.08
Arthralgia, n (%)	48 (64)	118 (48.6)	**0.01**
Erysipelas-like erythema, n (%)	5 (6.7)	52 (21.4)	**0.002**
Leg pain after exercise, n (%)	17 (22.7)	61 (25.1)	0.4
Myalgia, n (%)	39 (52)	50 (20.6)	**<0.001**
Oral ulcer, n (%)	15 (20)	18 (7.4)	**0.003**
Headache, n (%)	9 (12)	9 (3.7)	**0.01**
Proteinuria - Non-nephrotic, n (%) - Nephrotics status, n (%)	 4 (5.3) 0 (0)	 19 (7.8) 1 (0.4)	0.65
The pras severity - Mild, n (%) - Moderate n (%) - Severe n (%)	 35 (46.7) 19 (25.3) 21 (28)	 40 (16.5) 161 (66.3) 42 (17.2)	**<0.001**
Colchicine dose, mg/day (mean±SD)	1.1±0.37	1.2±0.38	0.13
Biologic agent used for treatment, n (%)	3 (4)	19 (12.8)	0.3

Variables with normal distribution are presented as mean±SD, and variables with non-normal distribution are presented as median (min-max) values.
SD: Standard deviation, FMF: Familial Mediterranean fever, min-max: Minimum-maximum

Table 3. Comparison of groups according to laboratorythe laboratory findings			
	Group 1 (R202Q) n=75	**Group 2 (homozygous and compound heterozygous) n=243**	**p value**
WBC (10^6/L); (median; min-max)	11,500 (3300-34,000)	10,500 (3600-26,900)	0.15
Platelet (mL); (median; min-max)	323,000 (143,000-719,000)	307,000 (144,000-710,000)	0.2
CRP (mg/L); (median; min-max)	19 (0-416)	10 (0-346)	0.23
ESR (mm/h); (median; min-max)	20 (1-106)	21 (1-125)	0.91
SAA (mg/L); (median; min-max)	30 (0.2-685)	6 (0.8-1850)	**0.03**

WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SAA: Serum amyloid A, min-max: Minimum-maximum

between patients with FMF and healthy controls. In contrast, the prevalence of R202Q homozygotes was markedly elevated in the FMF patient cohort. The authors proposed that the R202Q variant can only be associated with disease in its homozygous form. However, Comak et al.[18] demonstrated that in addition to 23.3% of patients with homozygous R202Q alterations, 3.6% of patients with heterozygous R202Q alterations exhibited hallmark symptoms of FMF. The authors proposed that R202Q is associated with an inflammatory situation and clinically relevant to FMF. Similarly, in their study of 374 pediatric patients, Celep et al.[19] demonstrated that all individuals with homozygous or heterozygous R202Q variants manifested at least one phenotypic FMF feature with a family history.

Similarly, in our cohort, all homozygous or heterozygous patients with R202Q exhibited at least one clinical feature of FMF. Further genotype-phenotype correlation studies are required to gain a comprehensive understanding of the effects of the R202Q variant on FMF.

The clinical manifestations of FMF vary widely among patients, often complicating the diagnosis and treatment processes. The most frequently observed clinical manifestations among patients diagnosed with FMF were abdominal pain and fever.[20] In the study by Comak et al.,[18] recurrent fever, abdominal pain, and myalgia or arthralgia were observed in homozygous R202Q individuals (23.3%, 53.3%, and 20% respectively. In patients in the heterozygous state, the corresponding rates were 20%, 72.7%, and 40%. Furthermore, patients were categorized according to heterozygous mutation types, which included homozygous or heterozygous R202Q mutations and other MEFV mutations. In the same study, the frequencies of symptoms in patients with R202Q compound heterozygous mutations were 47.8%, 75%, and 28.5%, respectively. A further report from Turkey indicated that 52% of patients with heterozygous R202Q had recurrent fever and 16% had myalgia.[21] A distinct study, conducted by Milenković et al.,[22] revealed that 80% of patients with homozygous R202Q exhibited recurrent febrile episodes, 60% reported abdominal pain, and 30% experienced myalgia. In the *R202Q* group, the frequencies of these symptoms were 70.7%, 72%, and 52%, respectively, with musculoskeletal features being more prevalent than previously reported. In a retrospective study, Arpacı et al.[23] identified the R202Q mutation as the most frequently observed (19.55%) in 2639 patients. The clinical findings observed in patients with the R202Q variant were similar to those observed in patients with the M694V mutation. Additionally, it was noted that unnecessary surgical interventions (e.g., appendectomy) and renal failure were more common in patients with homozygous and heterozygous R202Q variants. It is noteworthy that none of the patients in our cohort had a previous history of appendectomy.

Comparative studies of different mutations provide insights into disease severity and clinical outcomes in FMF. In a study by Kandur et al.[24] comparing the M694V/ and M694V/R202Q mutations, they found that the frequency of arthritis and disease scores were higher in the presence of R202Q. This suggests that this mutation may affect a patient's phenotype under certain genetic and epigenetic conditions that have yet to be defined. Similarly, Sgouropoulou et al.[25] emphasized that the R202Q variant is linked to the inflammatory phenotype of FMF and that its presence is associated with disease expression. They proposed that because not all contemporary methods include this mutation in the panel, genotyping alone may not confirm the clinical diagnosis in some patients. The application of next-generation sequencing may provide insights into the genetic profile of patients, which could inform their treatment.

In a recently published series of 1,570 patients, the most common genotypic condition was R202Q, present in 960 patients (43.5%). The R202Q genotype was frequently present, which is consistent with the known characteristics of the FMF profile. They recommended that these patients be included in routine molecular screening. In addition, functional studies on the R202Q variant of pyrin are needed to gain further insight into FMF. This will clarify whether the R202Q genotype is a mutation or a polymorphism and its validation in the infevers database.[26]

The potential for severe complications, such as amyloidosis, in patients with FMF underscores the need for close monitoring. In a previous study, In a previous study, Nursal et al.[27] proposed that the R202Q variant should be considered a potential risk element in the pathogenesis of amyloidosis. In a different study, 3.7% of patients with the R202Q alteration were found to have amyloidosis.[17] However, Comak et al.[18] reported that none of the patients in their R202Q group developed amyloidosis. Similarly, no cases of amyloidosis were observed in patients belonging to groups 1 and 2. These findings indicate that FMF patients with R202Q alterations tend to experience a milder clinical course although the potential for amyloidosis remains unaddressed. Patients in group 1 exhibited lower SAA levels than those in group 2.

Study Limitations

This research was limited by the lack of a healthy control group and the retrospective, single-center design. The Eurofever criteria have only recently been adopted; therefore, they cannot be used for diagnosing patients.[3] The insufficient number of R202Q homozygous variants precluded subgroup comparisons.

CONCLUSION

In conclusion, the relationship between specific genetic mutations and clinical manifestations in FMF remains a crucial area of research. There is a need for genotype-phenotype evaluation studies to delineate their correlation. Our results suggest that carrying the R202Q variant may cause symptoms in some cases, even in the heterozygous state; thus, its relevance to FMF remains to be clarified.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences

Türkiye, Kanuni Sultan Süleyman Training and Research Hospital (approval number: KAEK/2016.3.9, date: 01.11.2016)

Informed Consent: Upon admission to the hospital, the parents or guardians provided a general consent form authorizing the use of anonymized data.

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Footnotes

Authorship Contributions

Concept: M.T., N.A.A., Design: M.T., Ş.G.K., N.A.A., Data Collection or Processing: M.T., Analysis or Interpretation: Ş.G.K., N.A.A., Literature Search: M.T., Writing: M.T., N.A.A.

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