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Significant Association of Mediterranean Fever Gene Mutations with Acute Rheumatic Fever

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Abstract

Objectives: Acute rheumatic fever (ARF) is a multisystem inflammatory disorder resulting from group A β-hemolytic streptococcal pharyngitis. Previously, role of Mediterranean Fever (MEFV) gene mutations were demonstrated in a number of autoimmune and inflammatory diseases. Thus, we aimed to characterise influence of MEFV gene mutations for a possible susceptibility factor in acquiring clinical implications associated with pathogenesis of ARF, or whether this locus acts as a risk factor.

Subjects and Methods: The study included 66 Turkish patients with ARF clinical diagnosis and 250 origin-matched healthy controls. DNA Sequencing analysis was used for genotyping of MEFV gene mutations.

Results: There was significant difference in mutated allele frequency for the MEFV gene between the ARF group and healthy controls (15.9% vs. 8%, χ^2: 7.491, p= 0.006). Risk assessment showed that possessing a mutated MEFV allele was associated with a 2.1-fold increased risk for developing ARF compared to healthy controls (OR: 2.176, 95% CI: 1.234 to 3.837). Moreover, carrier rates of MEFV gene mutations were 21/66 (31.8%) and 40/500 (16%) in the ARF and healthy controls groups, respectively (χ^2: 8.387, p= 0.004, OR: 2.45, 95% CI: 1.32 to 4.548).

Conclusion: Our findings support the hypothesis that MEFV gene may play important roles in the susceptibility and pathogenesis of ARF, and screening of MEFV gene mutations in ARF patients may exhibit significant further data about early diagnosis, prognosis, follow-up, and treatment.

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Introduction

Acute rheumatic fever (ARF) is an immune-mediated disorder resulting from group A β-hemolytic streptococcal pharyngitis. Clinical characteristics consist of arthritis (affecting approximately 90% of individuals), carditis (affecting 30–50% of RF patients) with chronic and progressive valvular lesions [1]. The most serious complication of ARF is the development of chronic rheumatic heart disease (RHD). The clinical manifestation of the response and its severity in an individual is determined by host genetic susceptibility, the virulence of the infecting organism and a conducive environment [2-4]. The immune damage is believed to be caused by "antigen mimicry" between protein epitopes of group A streptococci and of host tissues (joint, skin, central nervous system, and heart), which leads to tissue damage in susceptible individuals [5]. Ongoing studies to identify why only 0.3–3% of individuals with acute streptococcal pharyngitis go on to develop rheumatic fever and the reason why RHD develops in some but not all patients with ARF are still not fully associated with primary causative gene locus of host susceptibility [3,4].

The gene responsible for FMF, MEFV, was identified by positional cloning, and the protein product pyrin is a 781 amino acid protein which is expressed in neutrophils, eosinophils, monocytes, dendritic cells, and synovial fibroblasts [6,7]. Pyrin functions either as an inducer or a supressor of the inflammatory response within cell depending on the experimental conditions as mutations in MEFV gene result in dysregulation of the inflammatory response. Role of pyrin (PyD) and/or caspase recruitment domain (CARD) containing regulator and adaptor proteins in inflammation, apoptosis, and innate immunity has been previously outlined [8,9].

In a number of inflammatory and autoimmune diseases, role of MEFV gene was identified. Experimental and clinical studies referred to an increased carrier rate of MEFV gene mutations in the pathogenesis and prognosis of certain rheumatic diseases including rheumatic diseases of childhood [10], rheumatoid arthritis [11], palindromic rheumatism [12], Behcet's disease [13], seronegative spondyloarhtropatheis [14], Henoch Schönlein purpura (HSP) , rheumatic heart disease [15,16], polyarteritis nodosa and some forms of juvenile idiopathic arthritis [14].

Since ARF is characterized by inflammation rich in PMNL leukocytes, and activation of certain cytokine network of the inflammatory cascade, Pyrin is considered as potential critical determinant. Pyrin is essential for inflammatory events. To be more prone to the late complications of streptococcal infections like exaggerated antibody response after streptococcal pharyngeal infections in patients who developed ARF may be associated with defects in wild type pyrin function which is responsible for normal regulation of control of inflammatory response. Thus, we aimed to characterise influence of MEFV gene mutations for a possible susceptibility factor in acquiring clinical implications associated with pathogenesis of ARF, or whether this locus acts as a risk factor. To further elucidate these issues, we evaluated the contribution of genotypes at functionally important MEFV locus to disease susceptibility in patients with ARF.

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Subjects and Methods

The study included 66 Turkish patients with ARF clinical diagnosis according to Jones Criteria, 1982 [17](32 female and 34 male; ages 11.16±2.88) and 250 origin-matched healthy controls. Clinical and laboratory characteristics of the studied ARF patients were depicted in Table 1. The most frequent clinical symptoms were arthritis (34.8%) and carditis (30.3%). Serum CRP and ASO titers were determined during admission to the clinic with a rheumatic fever prediagnosis. Serum ASO, CRP, ESR, and WBC counts were increased and in range typical of patients with ARF. Patients did not have any other systemic disease. No medical or family history of any systemic or autoimmune disease has been reported in the control groups. All patients were asked to fast for at least 12 h and to avoid smoking and heavy physical activities for at least 2 h before examination. Blood was collected with minimal stasis during admission to the clinic with ARF pre-diagnosis. Antistreptolysin O (ASO) and C-reactive protein (CRP) were measured colorimetrically on an Olympus AU 2700 chemical analyser. Erythrocyte sedimentation rate (ESR) was measured by the Westergren method. White blood cells count (WBC) was performed with a Coulter counter.

The procedures were in accordance with the ethical standard for human experimentations established by the Declaration of Helsinki of 1975, revised 1983. The study was approved by the Ethic Committee of Ege University, and detailed consent forms were signed by themselves or the parents of all patients.

	n (%)
Female	34
Male	32
Arthritis	23 (34.8)
Carditis	20 (30.3)
Chorea	18 (27.2)
Arthritis+carditis	2 (3)
Carditis+chorea	3 (4.5)
ASO	1.499±2.04 (min 200-max 15,000)
CRP	11.44±10.10 (min 0.86-max 70.4)
ESR	94.97±115.07 (min 12-max 960)
WBC	15.764±5,597 (min 4,800-max 34,000)

Table 1: Clinical and laboratory characteristics of the studied ARF patients.
M:male, F: female, ASO:

Molecular Analysis

Genomic DNA isolation

We obtained blood samples from FMF patients and healthy individuals when the disease was in remission, and the patients had not had an attack of FMF for weeks and sometimes months. Genomic DNA, which was collected into ethylenediaminetetraacetic acid (EDTA)-anticoagulated tubes by the standard venipuncture method, was isolated from peripheral blood leukocytes using a QIAamp DNA Blood Isolation kit (Qiagen GmbH, Hilden, Germany). A Thermo Scientific NanoDrop spectrophotometer (Wilmington, USA) was used to determine the extracted DNA concentration. The quality assessment of the extracted DNA was determined by 2% agarose gel electrophoresis.

PCR (Polymerase Chain Reaction) and Bidirectional DNA Sequencing Analysis of MEFV Gene

Specific primers were designated for MEFV gene and the regions were amplified from total genomic DNA by means of the polymerase chain reaction (PCR). The sequences of the oligonucleotide primer pairs were derived from the published GenBank sequence data. The 4 hot-spot regions (MEFV; NM_000243.2, NP_000234.1, exons 10, 5, 3 and 2) examined for MEFV mutations and were analyzed by PCR amplification followed by automated DNA sequencing analysis. Alternatively, patients who lacked mutations in exons 2, 3, 5, and 10, as well as in 5' untranslated region (UTR) were further screened in exons 1, 6, 7, 8 and 9 of the MEFV gene. Amplification buffer contained; 100 ng genomic DNA, 20 mM Tris (pH 8.3); 50 mM KCl; 1.5 mM MgCl2; 0.2 mM each of dATP, 2'-deoxycytidine 5'-triphosphate, dGTP, and 2'-deoxythymidine 5'-triphosphate; 10 pmol each of reverse and forward primers provided by Invitrogen; and 1.0 U of PlatiniumTaq DNA Polymerase (Invitrogen, Carlsbad, CA) in a total volume of 25 µl. The cycling conditions included a hot-start denaturation step at 95°C for 10 min, followed by 35 amplification cycles of denaturation at 95°C for 30 s, annealing at 61°C for exon 10, 58°C for exons 2 and 3, or 57°C for exon 5 for 40 s; and elongation at 72°C for 45 s; a final extension was performed at 72°C for 7 min (the oligonucleotide sequences are available upon request). Amplified PCR products were purified by ExoSAP-IT PCR Product Clean-Up kit (Amersham Life Science, UK), and bidirectionally sequenced employing the big dye terminator chemistry (PE Biosystems). Cycle sequencing of PCR products followed purification with the BigDye Terminator v3.1 Cycle Sequencing Kit (ABI PRISM, San Diego, California, USA), and sequences were all analysed with an automated ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) using the fluorescent dideoxynucleotide technology and was read at SeqScape 2.0 sequence analysis software (ABI PRISM, San Diego, California, USA).

Statistical Analysis

All statistical analyses were performed with the SPSS 13.0 statistical program. Comparison of the genotypic and allelic frequencies between the groups was performed using the Fisher exact test or Chi-square test when appropriate. Logistic regression analysis was used to identify an odds ratios (OR) and 95% confidence intervals (CI) to determine whether association exists between genotypes and the risk of developing ARF in patients as compared to the control samples. A two tailed p value <0.05 was considered as statistically significant.

Results

Present patients group with the M694V/M694V genotype had an earlier age of disease onset and higher frequency of arthritis compared with M694V heterozygous and compound heterozygous groups ($p<0.001$ and $p<0.001$, respectively). No other significant differences were observed between patients with and those without mutations. Neither the subjects in the control group nor the patients in ARF group that were found to carry MEFV gene mutations fulfilled the criteria for the diagnosis of FMF [18]. There were no age and sex differences between patients with or without mutations. Age and sex distributions were found to be similar between both groups (p-value for age: 0.8 and p-value for sex: 0.7).

During mutation screening, SNPs of the MEFV gene obtained from DNA sequencing analysis were ruled out (exon 2- D102D, D103D,

P124P, G138G, A165A, P180P, R202Q, and G219G; exon 3- R314R and S363S; exon 5- E474E, Q476Q, R501R, I506I, and D510D; exon 9- P588P; and exon 10- S683S, A701A and P706P).

DNA sequencing analysis of the MEFV gene revealed that, 21 patients (31.8%) carried at least one mutated MEFV allele in the ARF group (Table 2). A total of 6 different genotypes were obtained. Mutations in both alleles were identified in 5 patients (7.5%) with missense mutations who were compound heterozygous for various combinations of mutations including E148Q/P369S, E148Q/M694V, and V726A/M694V. Additionally, of the 21 patients, 16 were found to be heterozygous for a single mutation. Genotype frequencies for E148Q/Wt, V726A/Wt, M694V/Wt, E148Q/P369S, E148Q/M694V, and V726A/M694V were 18.1, 3.03, 3.03, 3.03, 1.5, and 3.03%, respectively. V726A/Wt, M694V/Wt, E148Q/P369S, and V726A/M694V were distributed equally among the patients group. Among the healthy controls, mutation analysis showed that 40 (16%) of the subjects were carrying at least one mutated heterozygous MEFV allele (Table 3). A total of 6 different genotypes were obtained. Genotype frequencies for E148Q/Wt, V726A/Wt, M694V/Wt, and A744S/Wt were 7.6, 2.4, 2, 1.6, respectively. M680IG-C/Wt and M694I/Wt were distributed equally (1.2%) among the subjects group. E148Q/Wt was identified as the most common genotype in both of the groups. In the ARF group, V726A/Wt, M694V/Wt, M680IG-C/Wt, M694I/Wt and A744S/Wt mutation rates were insignificantly elevated compared to healthy controls (p>0.05). However, risk assessment showed that patients possessing E148Q mutation were associated with a 2.7-fold increased risk for ARF compared to healthy controls (χ^2: 6.608, p= 0.01, OR: 2.702, 95% CI: 1.237 to 5.9).

Mutation	Mutation state	n	Genotype frequency (%)
E148Q/Wt	Heterozygous	12	18.1
V726A/Wt	Heterozygous	2	3.03
M694V/Wt	Heterozygous	2	3.03
E148Q/P369S	Compound heterozygous	2	3.03
V726A/M694V	Compound heterozygous	2	3.03
E148Q/M694V	Compound heterozygous	1	1.5
Patients with mutations		21	31.8
Patients without mutations		45	68.2
Total number of patients		66	100
Mutation (allele) frequency			21/132 15.9%
Carrier rate			21/66 31.8%

Table 2: MEFV mutations observed in the ARF patients group (n=66).

Mutated MEFV allele frequency was 15.9% (21 of 132), and 8% (40 of the 500) in the chromosomes of ARF patients, and healthy controls, respectively. The most common mutation among ARF patients was E148Q (allelic frequency 9.09%), followed by M694V (1.5%), V726A (1.5%), E148Q/P369S (1.5%), V726A/M694V (1.5%), and E148Q/M694V (0.75%). Similarly, among the Turkish general population, the most frequent healthy heterozygous carrier mutation was E148Q (4.5%), and the carrier rate was 16%, with a mutation frequency

Mutation	Mutation state	n	Genotype frequency (%)
E148Q/Wt	Heterozygous	19	7.6
V726A/Wt	Heterozygous	6	2.4
M694V/Wt	Heterozygous	5	2
A744S/Wt	Heterozygous	4	1.6
M680I/G-C/Wt	Heterozygous	3	1.2
M694I/Wt	Heterozygous	3	1.2
Healthy controls with mutations		40	16
Healthy controls without mutations		210	84
Total number of control group		250	100
Mutation (allele) frequency			40/500 8% (0.06-0.11)
Carrier rate			40/250 16% (0.13-0.25)

Table 3. Frequencies of detected MEFV mutations in 500 chromosomes from 250 healthy Turkish controls (n=250).

of 8%. Other less common mutations included V726A/Wt (1.5%), M680IG-C/Wt, P369S/Wt, and K695R/Wt (1.2% each), M694V/Wt (0.6%), A744S/Wt, M694I/Wt, and E148Q/P369S (0.3% each). Among the patients and the subjects group, comparison of the frequency of mutated alleles was not different (p>0.05).

There was significant difference in mutated allele frequency for the MEFV gene between the ARF group and healthy controls (15.9% vs. 8%, χ^2: 7.491, p= 0.006). Risk assessment showed that possessing a mutated MEFV allele was associated with a 2.1-fold increased risk for developing ARF compared to healthy controls (OR: 2.176, 95% CI: 1.234 to 3.837). Moreover, carrier rates of MEFV gene mutations were 21/66 (31.8%) and 40/500 (16%) in the ARF and healthy controls groups, respectively (χ^2: 8.387, p= 0.004, OR: 2.45, 95% CI: 1.32 to 4.548).

Discussion

As an autoimmune disease, the responsible gene locus and precise pathogenetic mechanism of ARF have not been well defined. So far, as potential risk factors in the pathogenesis of the disease considering streptococcal infection, studies have focused particularly on the human leukocyte antigen (HLA) complex, T cell lymphocytes, tissue-specific antigens and antibodies. Also, particular M types of group A streptococci were reported as potentially rheumatogenic [3,19]. In different populations, association of HLA-DR2, HLADR4, HLA-DQA1, HLA-DRB1, DRB1, and DQA1 genes were shown in the pathogenesis of ARF [20-24]. Moreover, TGF-1β [25]), TNF-α [26-29], IL-1β, IL-1Ra, IL-4, and IL-10 [30], Fcγ and TLRs [31,32], MBL-2 [33] gene polymorphism were also investigated for possible association to disease susceptibility. Among these, FcγRIIA-R/H-131 and TLR-2 gene polymorphisms were reported as important biomarkers in determining predisposition and disease progression to ARF [31,34]. Jin et al [33] investigated no relationship between MBL gene exon 1 site mutations and RHD while Schafranski et al [35,36] showed significantly increased levels of high-producing MBL-2 genotypes in patients with ARF. Schafranski et al [35] investigated no significant association between MASP-2 Asp105Gly mutation and

ARF/RHD. In Taiwan Chinese and Turkish population, ACE gene polymorphism was associated with the pathogenesis of RHD [30,37]. Morsy et al demonstrated a lack of association between eNOS 4b/a gene polymorphism and the development of RHD [38].

Effect of inflammatory genes towards ARF pathogenesis include upregulation of the innate immune system and first inflammatory response. Recently, overlapping of FMF and various inflammatory conditions were reported, and presence of MEFV gene mutations were reported as strong susceptibility factors in the pathogenesis of various inflammatory/rheumatic diseases involving BD [13], juvenile idiopathic arthritis (JIA) [10] and palindromic rheumatism [12]. Moreover, MEFV gene mutations have also been reported as aggravating factors for the severity of some inflammatory diseases including (RA), ankylosing spondylitis [39] inflammatory bowel diseases [40], and multiple sclerosis (MS) [41]. Indeed, increased prevalence of RHD was previously shown in patients with FMF [42-44]. Additionally, FMF patients with/without HSP/PFM were reported to be more prone to the viral infections such as hepatitis A, and late complications of streptococcal infections with high levels of antistreptolysin O (ASO) antibodies and increased frequency of streptococcus-associated diseases such as ARF [43-48]. Moreover, carrying only single heterozygous MEFV mutation was reported to be capable of triggering immune hyperreactivity against streptococcal antigens that leads to predisposition to ARF [15]. Mutations in the MEFV gene was suggested to cause the impaired control of the immune response and trigger inflammation, as, in the inflammasomes, wild type pyrin has been reported to have anti-inflammatory effects and to act on the control of neutrophil mediated inflammation [6,49]. Presence of mutant pyrin may disregulate normal inflammasome function, and activate susceptibility to streptoccocal infections with higher inflammatory response which was also previously demonstrated in ARF patients with certain TLR-2 genotypes [28].

In this study, we obtained a significantly higher prevalance of mutated allele frequency for the MEFV gene in ARF patients compared to healthy individuals. Furthermore, possessing a mutated MEFV allele was associated with a 2.1-fold increased risk for developing ARF compared to healthy controls. According to the mutation frequency results of the present study, 31.8% mutation rate of the patients group was 2-fold higher compared to present control group (16%), and 1.6-fold higher compared to the carrier rate of Turkish population (20%) [50] which were higher than the previously reported prevalances of the MEFV gene in patients with ARF. Tutar et al. [15] found 25.9% (7/27) prevalance of MEFV gene mutations among Turkish RHD patients. Moreover, Simsek at al. [16] identified MEFV mutation frequency in 22% of RHD patients, and 24% of the healthy control group in their study. Also, they found 11% allelic frequency in RHD patients, and 13% in the control group. Thus, our findings support the hypothesis that the MEFV gene may play important roles in the susceptibility and pathogenesis of ARF.

In conclusion, the results of this study suggest that screening of MEFV gene mutations in ARF patients may exhibit significant further data about early diagnosis, prognosis, follow-up, and treatment of the patients particularly in the ancestral populations of FMF.

Competing Interests

The authors declare they have no competing interests.

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