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INVESTIGATION OF THE FREQUENCY OF FC GAMMA RECEPTOR IIIA V/158/F GENE POLYMORPHISM AND COMPARISON OF CLINICAL AND LABORATORY FINDINGS IN RHEUMATOID ARTHRITIS (RA)

ROMATOİD ARTRİT'TE FC GAMA RESEPTÖR IIIA V/158/F GEN POLİMORFİZMİNİN SIKLIĞININ ARAŞTIRILMASI VE HASTA KLİNİK VE LABORATUAR BULGULARIYLA KARŞILAŞTIRILMASI

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ABSTRACT

Objective: Rheumatoid Arthritis (RA) is a chronic multisystem disease with unknown etiology that progressively affects peripheral joints. Receptors, which serve as links between humoral and cellular immune responses, recognize the Fc region of immunoglobulin G (FcR) and have become the focus of many research studies concerning the etiology and pathogenesis of autoimmune diseases. This region displays extensive genetic variation, which has been associated with susceptibility to various chronic inflammatory disorders including RA. This study aimed to investigate the frequency of the FcγRIIIA V158F genetic polymorphism and compare clinical and laboratory findings in RA.

Materials and Methods: Between April 2010 and June 2011, 105 patients, who had been diagnosed with RA according to the American Rheumatology Association (ARA) diagnostic criteria, were admitted to the Cukurova University Department of Rheumatology outpatient clinic and 110 healthy controls were included in this study. Patient groups were divided into stages using the ARA functional classification. The FcγRIIIA V158F gene polymorphism of patients was investigated from blood samples using the real-time Polymerase Chain Reaction (PCR) method.

Results: There was no significant difference in the distribution of the FcγRIIIA polymorphism between patients and controls (p=.106). There were no significant differences between the distribution of age at diagnosis of patients with the gene polymorphism (p=.919) or in the gene polymorphism (p=.552). No association was found between the gene polymorphism and clinical signs of disease such as eye involvement and the presence of rheumatoid nodules. There was also no significant association

ÖZET

Amaç: Romatoid Artrit (RA), nedeni bilinmeyen, esas olarak periferik eklemleri progresif olarak tutan kronik multisistemik bir hastalıktır. Hümoral ve hücresel immün yanıtları arasında bir bağ olan, IgG' nin Fc reseptörleri otoimün hastalıkların etyoloji ve patogenezinde oldukça ilgi çekmektedir. Geniş genetik varyasyon sergileyen bu bölge Romatoid artrit de dahil olmak üzere çeşitli kronik inflamatuvar hastalıklara yatkınlık ile ilişkilidir. Bu çalışmasında Romatoid Artrit' te FcγRIIIA V158F gen polimorfizminin sıklığının araştırılması ve hasta klinik ve laboratuar bulgularıyla karşılastırılması amaçlanmıştır.

Gereç ve Yöntem: Çukurova Üniversitesi Tıp Fakültesi Romatoloji Bilim Dalı polikliniğine Nisan 2010-Haziran 2011 tarihleri arasında başvuran ve Amerikan Romatizma Derneği' nin tanı kriterlerine göre RA tanısı almış 105 RA'lı hasta ve 110 sağlıklı kontrol çalışmaya dahil edildi. Hasta ve kontrollerden öyküsünde diyabet, tiroid fonksiyon bozuklukları, geçirilmiş veya mevcut kalp hastalıkları, malignite, nörolojik hastalıklar ile kronik inflamatvuar hastalıklardan bir ya da daha fazlası olanlar çalışma dışı bırakıldı. RA' lı hastaların hastalıkla ilgili semptomları, sistemik hastalık varlığı, ilaç kullanımı, hastalık süreleri ve aile öyküsü sorgulandı. Tüm olgulara genel fizik muayene ve romatolojik muayeneleri yapıldı ve rutin laboratuvar tetkikleri ile CRP, RF, ESR, ANA, Anti-DNA düzeyleri istendi. Hasta grubu ARA'nın fonksiyonel sınıflandırması kullanılarak evrelere ayrıldı. Alınan kan örneklerinde real time PCR yöntemi ile FcγRIIIA V158F gen polimorfizmleri araştırıldı.

Bulgular: Hasta ve kontrol grubunun Fc γ RIIIA gen polimorfizm dağılımları arasında anlamlı fark saptanmadı (p=0,106). Hastaların tanı aldıkları yaş dağılımları ile gen polimorfizmi arasında

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between the gene polymorphism with rheumatoid factor, anticyclic citrullinated peptide, and antinuclear antibodies (p=.625, p=.136, p=.716, respectively).

Conclusion: In our study, no significant relationship was found between the FcγRIIIA V158F gene polymorphism and the pathogenesis of RA.

Keywords: FcγRIIIA V158F gene polymorphism, rheumatoid arthritis

anlamlı fark saptanmadı (p=0,919). Hastaların cinsiyet dağılımlarına göre de gen polimorfizmi açısından anlamlı fark saptanmadı (p=0,552). Hastalığın klinik bulgularından olan akciğer ve göz tutulumları, romatoid nodül varlığı ile gen polimorfizmi arasında ilişki saptanmadı. RF ve ANA sonuçları ile gen polimorfizmi arasında da anlamlı fark saptanmadı (p=0,625, p=0,716). Hastaların anti-CCP sonuçları ile gen polimorfizmi arasında anlamlı fark saptanmadı (p=0,136).

Sonuç: Çalışmamızda RA patogenezi ile Fc γ RIIIA 158 gen polimorfizmi arasında anlamlı bir ilişki saptanmamıştır.

Anahtar Kelimeler: FcγRIIIA gen polimorfizmi, romatoid artrit

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystemic disease of unknown cause and mainly affecting peripheral joints progressively (1). It is relatively common in all adults in the world with a prevalence of about 0.5-1% (2, 3). RA causes malfunctions of various grades ranging from mild to severe and it can lead to significant social, psychological and economic problems due to its lifetime duration (1). The Fc receptors of IgG (a link between humoral and cellular immunological responses), are highly interested in the etiology and pathogenesis of autoimmune diseases and Fc gamma receptors are encoded in the long arm of chromosome 1 (4, 5). Fc receptors are proteins that contribute to the protective functions of the innate immune system located on the surface of NK, macrophages, neutrophils and mast cells (6). FcγRIIIA is involved in the pathogenesis of autoimmune diseases by acting in the clearing of circulating immune complexes. Fc gamma receptors have functions in phagocytosis, antibody-dependent cellular mediated cytotoxicity, arachidonic acid metabolism, release of histamine and other inflammatory mediators, regulation of lymphocyte production and secretion, and cell proliferation and differentiation. In particular, single nucleotide polymorphisms in FcγRIIA (R131H), FcγRIIB (I123T), FcγRIIIA (V158F) and Fcγ–RIIIB (NA1 / NA2) have been reported in association with Systemic Lupus Erythematosus, Rheumatoid Arthritis and Idiopathic Thrombocytopenic Purpura (7, 8). Studies have shown that the results are the significant effects of Fc γ RIII A functional polymorphisms in RA.

In this study, we aimed to investigate the frequency of Fcγ–RIIIA V158F gene polymorphism and comparison of clinical and laboratory findings in rheumatoid arthritis (RA).

MATERIAL AND METHODS

105 patients who were admitted to the Cukurova University Department of Rheumatology, between April 2010 and June 2011 who had been diagnosed with RA according to American Rheumatism Association diagnostic criteria (9) and 110 healthy controls were included in this study. Patients and controls who had had diabetes, thyroid dysfunction, past or present heart disease, malignancy, neurological disease, and one or more chronic inflammatory diseases were excluded from the study. Patients with RA were checked for disease-related symptoms, systemic disease presence, medication, duration of illness and family history. In all cases, general physical examination and rheumatological examinations were performed and full blood count, biochemical tests, thyroid hormone levels, CRP, RF, anti-CCP, ESR, ANA, and Anti-DNA levels were examined. The patient group was divided into stages using the functional classification of ARA (10). The extraarticular involvement of the patients was recorded. Blood samples were analyzed using RealTime PCR for DNA isolation and FcgRIIIA V158F gene polymorphism. At the beginning of the study, approval was obtained from the Ethics Committee of the Cukurova University for approval of the Ministry of Health.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 15.0 (SPPS Inc., Chicago, IL, USA) package program was used for statistical analysis of the data. Categorical measurements were summarized in terms of number and percentage, mean and standard deviation (continuous median and minimum-maximum where necessary) for continuous measurements. The Chi-square test statistic was used to compare categorical variables. The Mann Whitney U and Kruscal Wallis test were used to compare continuous measurements between groups. The correlation between the variables was tested using the Spearman Correlation test. Logistic regression analysis was performed by taking a dependent variable of patients and healthy groups. The statistical significance level was set as 0.05 across all tests.

RESULTS

Study Patients

Patient characteristics are summarized in table-1. The median age was 51 (20-76) for the patients and 49 (27-79) for the control group. 91 (86.7%) of the patients were female and 14 (13.3%) were male. Of the control group, 96 (87.3%) were female and 14 (12.7%) were male. Of the patients, 86 (81.9%) were non-smokers and 19 (18.1%) were smoking. Median disease duration of RA patients was 6 (1-31) years. According to the functional classification of ARA, 1 (1%) of patients with RA was stage 3, 4

Table 1. Patients characteristics

Characteristics	n (%) (Patients)	n (%) (Controls)
Median age (years old)	51 (20-76)	49 (27-79)
Gender		
Men	14 (13.3)	14 (12.7)
Women	91 (86.7)	96 (87.3)
ARA functional classification		
Stage 1	100 (95.2)	
Stage 2	4 (3.8)	
Stage 3	1 (1)	
Morning stiffness		
No	41 (39.1)	
0-30 minutes	44 (41.9)	
>30 minutes	20 (19)	
RF		
Negative	55 (52.4)	
Positive	50 (47.6)	
ANA		
1 positive	4 (3.8)	
2 positive	14 (13.3)	
3 positive	4 (3.8)	
4 positive	4 (3.8)	
Negative	79 (75.2)	
Anti-CCP		
Negative	22 (20.9)	
Positive	42 (40)	
CRP	Median 6,0 (2,0-62,0)	

RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; ANA: Anti nuclear antibody

(3.8%) stage 2, and 100 (95.2%) stage 1. Thirty-nine per cent of the patients had no morning stiffness. 41.9% of them had less than 30 minutes and 19% had more than 30 minutes of morning stiffness. Pulmonary involvement of RA was present in 9 (8.6%) patients and eye involvement in 4 (3.8%) patients and only 1 patient had rheumatoid nodules. None of the patients had amyloidosis. When evaluated according to DAS28, 8.7% of patients with RA had low activity (n=9), 48.5% had moderate activity (n=50), 17.5% had high activity (n=18) and 25.2% (n=26) were in remission

Table 2. Fcγ R III A gene polymorphism distributions between patients and control groups

			Fcγ R III A			
			VF	FF	VV	p
Group	Control	n	55	40	15	0.106
		%	50%	36.4	13.6	
	Patient	n	63	36	6	
		%	60	34.3	5.7	

VF: Fc gamma receptor IIIA 158 VF heterozygous form; FF: Fc gamma receptor IIIA 158 FF homozygous mutant form; VV: Fc gamma receptor IIIA 158 VV homozygous wild type

Treatment and outcomes

All apart from 2 patients were using more than one medicine. 88 of the patients were using MTX, 17 of them were using leflunomide, 14 were using SSZ and 21 were using corticosteroids. Two patients were using only NSAIDs. Among the patients Fcγ RIII gene polymorphism distributions were found as, 36 (34.3%) homozygous mutant, 63 (60%) heterozygous and 6 (5.7%) homozygous wild type. Forty of the control group (36.4%) were homozygous mutant, 55 (50%) were heterozygous and 15 (13.6%) were homozygous wild type (Table 2).

The relationships between the patients' morning stiffness, functional stages, cigarette smoking, lung involvement, ocular involvement and rheumatoid nodule presence and Fcγ RIII gene polymorphism distributions were investigated. There was no statistically significant relationship between these parameters and the Fcγ RIII gene polymorphism distributions (table-3). There was no statistically significant correlation between the ANA, RF and anti-CCP and Fcγ RIII gene polymorphism distributions of the patients (Table 4).

DISCUSSION

Rheumatoid arthritis is a chronic systemic disease that primarily affects synovial joints, and is characterized by symmetrical, erosive synovitis, severe deformities and it is a disability that can be seen across all racial and ethnic groups (1). The relationship between the etiology and pathogenesis of RA and the association of antibodies, immunocomplexes, complement, and Fc receptors has become a growing focus of attention. Both active and inhibitory Fc receptor mediated signals play a central role in the inflammation associated with the immune complex (11).

Table 3. Polymorphism distributions according to clinical findings of patients

	Fcγ R III A			
Variables	**VV**	**VF**	**FF**	**p**
Gender				
Male	1(16,7)	10 (15.9)	3(8.3)	0.552
Female	5 (83.3)	53 (84.1)	33 (91.7)	
Morning stiffness				
Absent	3 (50)	23 (36.5)	15 (41.7)	0.779
0-30minutes	3 (50)	27 (42.9)	14 (38.9)	
>30 minutes	0 (0)	13 (20.6)	7 (19.4)	
ARA Functional Stage				
1	6 (100)	61 (96.8)	33 (91.7)	0.631
2	0 (0)	2 (3.2)	2 (5.6)	
3	0 (0)	0 (0)	1 (2.8)	
Smoking				
Yes	1 (16.7)	11 (17.5)	7 (19.4)	0.966
No	5 (83.3)	52 (82.5)	29 (80.6)	
Pulmonary involvement				
Yes	0 (0)	3 (4.8)	6 (16.7)	0.09
No	6 (100)	60 (95.2)	30 (83.3)	
Rheumatoid Nodule				
Yes	0 (0)	0 (0)	1 (2.8)	0.38
No	6 (100)	63 (100)	35 (97.2)	
Eye involvement				
Yes	1 (16.7)	2 (3.2)	1 (2.8)	0.237
No	5 (83.3)	61 (96.8)	35 (97.2)	

VF: Fc gamma receptor IIIA 158 VF heterozygous form; FF: Fc gamma receptor IIIA 158 FF homozygous mutant form; VV: Fc gamma receptor IIIA 158 VV homozygous wild type

Table 4. Polymorphism distributions according to laboratory findings of patients

	Fcγ R III A			
Variables	**VV**	**VF**	**FF**	**p**
ANA				
1 positive	0 (0)	4 (6.3)	0 (0)	
2 positive	0 (0)	8 (12.7)	6 (16.7)	
3 positive	0 (0)	2 (3.2)	2 (5.6)	
4 positive	0 (0)	3 (4.8)	1 (2.8)	0.716
RF				
Negative	4 (66.7)	34 (54.0)	17 (47.2)	
Positive	2 (33.3)	19 (52.8)	19 (52.8)	0.625
Anti-CCP				
Negative	2 (100)	13 (33.3)	7 (30.4)	
Positive	0 (0)	27 (66.7)	15 (69.6)	0.136

ANA: Anti nuclear antibody; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; VF: Fc gamma receptor IIIA 158 VF heterozygous form; FF: Fc gamma receptor IIIA 158 FF homozygous mutant form; VV: Fc gamma receptor IIIA 158 VV homozygous wild type

With regard to the FcγRIII surface expression of monocytes and macrophages in circulation and synovium, it was found higher in RA patients than in healthy controls previously (12, 13). In addition, the FcγRIIIA expression in the monocytes of RA patients was found to be higher in synovial fluid than in peripheral blood (14). FcγRIIIA ligation is thought to cause TNF-a production in monocytes (15) and elevated FcγRIIIA in macrophages leads to an increase in the production of TNF-a and matrix metalloproteinase I in the RA synovium (13). Together these results suggest that functional polymorphisms of FcγRIIIA are important in RA.

Kastbom et al. (16) 181 Swedish RA patients were included in the study conducted in 2005 and the association of FcγRIIIA 158V/F polymorphism with disease severity and disease susceptibility in early RA patients was examined. At the end of the study, it was observed that the FcγRIIIA 158 VV genotype in the male population had an increased risk of developing RA and that patients with early-stage RA having 158 V alleles had more severe disease course (16). Ann W. Morgan et al. In 2005, British patients and patients from Kuzhai India and Pakistan were included in the study. In this study, the FcγRIIIA-IIIB 158 V haplotype is the haplotype that has been shown to have the strongest association with RA susceptibility (p=0.03). This relationship was found to be stronger in nodular RA (p=0.01). It has also been found that this haplotype is more common in the North Indian and Pakistani populations (17).

Nieto A. et al. (18) In 2002, 117 RA and 142 healthy controls were included in the study. The Fc γ RIIIA 158 FF genotype was found to be significantly higher in patients than in non-FF patients (p=0.01). The FcγRIIIA 158 VF genotype was found to be elevated in the healthy control group (p=0.021). No association was found between

genotype and clinical findings. Analysis of the FcγRIIIA 158 FF genotype in combination with the common epitope revealed that the presence of both factors increased RA susceptibility (p=0,0009) (18). Morgan AW et al. (11) conducted in 2002 investigated the relationship between FcγRIIIA functional polymorphism and RA in two different ethnic groups. FcγRIIIA 158 V/F polymorphism was associated with RA in both ethnic groups (p=0.028 for the British population, p=0.050 for the North Indian and Pakistani populations, and p=0.003 when combined analysis). Individuals with the FcγRIIIA VF and VV genotypes were found to have an elevated risk of RA in both populations (19).

In a study conducted by Thabet MM and colleagues in 2008, they investigated the distribution of FcγRIIIA 158V/F polymorphism in patients with anti-CCP positive RA. The study included 945 RA patients and 388 healthy controls from the Dutch White race. It has been shown that gene polymorphism is not associated with disease in the whole RA group. However, the FcγRIIIA 158 VV genotype in the anti-CCP positive RA group was found to be more common than in the healthy controls (p=0.05) (20).

We aimed to investigate the frequency of Fc γ RIIIA 158 gene polymorphism in patients with chronic RA under follow-up and treatment, and the relation with the clinical and laboratory findings of the disease. In our study, there was no significant difference between FcγRIIIA gene polymorphism distributions of the patients and the control group (p=0,106). This is the first study in Turkish society investigating the relationship and importance of Fc γ RIIIA 158 gene polymorphism with RA pathogenesis. In our study, no significant relationship was found between RA pathogenesis and FcγRIIIA 158 gene polymorphism. No association was found between lung involvement, ocular involvement, and presence of rheumatoid nodules and gene polymorphism. In the study conducted by Nieto et al. (18), There was no relationship between clinical findings and the FcγRIIIA genotype. There was no statistically significant difference between the RF levels of our patients and FcγRIIIA 158 gene polymorphism (p=0.076). In contrast to the study of Thabet MM and colleagues, no statistically significant relationship was found between anti-CCP levels and FcγRIIIA 158 gene polymorphism in our study (p=0.136).

According to our results, FcγRIIIA 158 gene polymorphism in RA is not associated with disease pathogenesis and clinical and laboratory findings. We believe that further study with larger patient groups is necessary for a better understanding of this relationship.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Çukurova University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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