TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 1819-1825

doi:10.3906/sag-1612-23

TNF-alpha 863C > A promoter and TNFRII 196T > G exonic variations may be risk factors for juvenile idiopathic arthritis

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Received: 07.12.2016 • **Accepted/Published Online:** 06.09.2017 • **Final Version:** 19.12.2017

Background/aim: Juvenile idiopathic arthritis (JIA) is a chronic complex autoimmune disease. Genetic and environmental factors increase the risk of JIA. It is accepted that alterations in immune system pathways play an important role in the pathogenesis of JIA. The aim of the study was to investigate the possible association between immune system regulatory gene polymorphisms and JIA in Turkish patients.

Materials and methods: We analyzed eight polymorphisms, TNF-alpha-863 C > A, TNFRII 196 T > G, IL2-631 G > A, IL13-1112 C > T, CCR2 190 G > A, CCR5delta32, CTLA4-1661 A > G, and PTPN22 1858 C > T, in 76 patients with JIA and in 80 healthy controls, who were of a similar age and same sex. Genotyping was identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: We found significant differences in the genotype frequencies of TNF-alpha-863 C >A variation between the patients and healthy controls (P = 0.007). TNF-alpha-863 C/C wild type genotype was significantly increased risk factor for JIA (OR = 2.56; 95% Cl = 1.30–5.03). Moreover, our results showed that TNFRII 196 T/T genotype frequency was significantly higher in JIA patients compared to controls (P = 0.03; OR = 2.12; 95% Cl = 1.09–4.10). However, we did not find a statistically significant relationship between other polymorphisms and JIA (P > 0.05).

Conclusion: These results indicate that TNF-alpha-863 C > A and TNFRII 196 T > G polymorphisms may be associated with the development of JIA. Further and large cohort studies are needed to elucidate the precise role of these polymorphisms in the pathogenesis of JIA.

Key words: Juvenile idiopathic arthritis, TNF-alpha, TNFRII, variation, RFLP

1. Introduction

Juvenile idiopathic arthritis (JIA) is a group of heterogeneous disorders characterized by chronic inflammation and starts before the age of 16 (1,2). Both genetic and environmental factors affect the risk of JIA (3). As in other autoimmune diseases, it is especially caused by dysregulation of the immune system (1). Several novel putative autoimmune susceptibility loci that have recently been identified are associated with multiple autoimmune diseases.

The tumor necrosis factor-α (TNF-α) gene encodes a multifunctional proinflammatory cytokine (4). A polymorphism located at -863 position (-863 C > A) has been shown to be associated with a decreased transcriptional activity of the gene (5). TNF-α acts through cell surface tumor necrosis factor receptor I (TNFRI) and II (TNFRII). TNFRII is a type I transmembrane protein that plays a role in the stimulation of cell proliferation (6). An SNP at codon 196 (T > G) results in the nonsynonymous amino acid alteration (Met to Arg) in the TNFRII gene.

Interleukin 2 (IL2) has an important role in the proliferation of T and B lymphocytes (7). The most common SNPs of IL2 are -1010 C > T, -962 C > T, -631 G > A, -475 A > T, and -384 T > G. Interleukin 13 (IL13) is a regulatory cytokine produced by activated T cells. Active T cells modulate B-cell responses through activation, proliferation, and differentiation of B-cells (8). The most common SNPs of IL13 gene are -1512 A > C, -1112 C > T, -1055 C > T, 1103 C > T, and 2044 G > A.

Chemokine receptors are primarily expressed on immune and inflammatory cells, such as B- and T-lymphocytes and antigen-presenting cells (9). An SNP with G- to -A at position 190 (codon 64) of the C–C motif of chemokine receptor 2 (CCR2) gene results in an amino

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acid change, valine to isoleucine (CCR2–V64I). A 32-bp deletion in the coding region of CCR5 (CCR5Δ32) induces a premature stop codon in the third extracellular domain of the protein. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) transmits an inhibitory signal to T cells. It has been reported that -1661 A > G promoter polymorphism may affect the CTLA-4 gene expression (10). Protein tyrosine phosphatase, a nonreceptor type 22 (PTPN22) gene, has emerged as an important genetic risk factor for human autoimmunity by multiple mechanisms (11). The PTPN22 1858 C > T polymorphism impairs its binding to the protein tyrosine kinase, resulting in increased T-cell activation (12).

The purpose of the current study was to investigate the relationship between the genetic polymorphisms of immune system regulatory genes, TNF-alpha-863 C > A (rs1800630), TNFRII 196 T > G (rs1061622), IL2-631 G > A (rs2069760), IL13-1112 C > T (rs1800925), CCR2 190 G > A (rs1799864), CCR5delta32 (rs333), CTLA4-1661A > G (rs4553808), and PTPN22 1858 C > T (rs2476601), and susceptibility to JIA in the Turkish population.

2. Materials and methods

2.1. Subjects

JIA patients were diagnosed at the Department of Pediatric Rheumatology of Cerrahpaşa Medical Faculty at İstanbul University. The diagnosis of JIA was made by using the International League of Associations for Rheumatology (ILAR) classification system. The patients (n = 76), who were in remission, comprised 25 (33%) males and 51 (67%) females. Controls (n = 80) were randomly selected from among healthy children during the same time period as the cases were collected. The controls were frequency matched to the cases by age and sex. The healthy control group consisted of 34 (42%) males and 46 (58%) females. Informed consent was obtained from all of the participating individuals and/or their parents. The study was conducted with the approval of the ethical committee from our institution and in keeping with the guidelines of the Declaration of Helsinki.

2.2. Blood samples and DNA isolation

We collected 2 mL of venous blood from JIA patients and controls. Genomic DNA was extracted from blood using a Roche DNA purification kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

2.3. Genotyping

Seven polymorphisms, TNF-alpha-863 C > A, TNFRII 196 T > G, IL2-631 G > A, IL13-1112 C > T, CCR2 190 G > A, CTLA4-1661 A > G, and PTPN22 1858 C > T were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods. CCR5 delta32 was determined using PCR. Table 1 shows the primer sequences, PCR product size, annealing temperature, specific restriction enzymes, and digested fragment size of all analyzed polymorphisms.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of data

Table 1. Primer sequence, annealing temperature, PCR product size, restriction enzyme, and digested fragment size of all analyzed polymorphisms.

Gene - SNP	Primers	Annealing temperature (°C)	PCR product size (bp)	Restriction enzyme	Digested fragment size (bp)
TNF-alpha-863 C/A	F:5′ - GGCTCTGAGGAATGGGTT - 3′ R:5′ - CTACATGGCCCTGTCTTCGTTACG -3′	63	126	Bsa AI	Wild type: 126 Homozygous Variant: 103, 23
TNFRII 196 T/G	F:5′ - ACTCTCCTATCCTGCCTGCT - 3′ R:5′ - TTCTGGAGTTGGCTGCGTGT - 3′	57	242	Nla III	Wild type: 133, 109 Homozygous Variant: 242
IL-2-631 G/A	F:5′ - ATAGACATTAAGAGACTTAAAC - 3′ R:5′ - GTAACTCAGAAAATTTTCTTT -3′	50	332	Rsa I	Wild type: 271, 61 Homozygous Variant: 332
IL-13-1112 C/T	F:5′ - GGAATCCAGCATGCCTTGTGAGG - 3′ R:5′ - GTCGCCTTTTCCTGCTCTTCCCGC - 3′	61	247	Bst UI	Wild type: 224, 23 Homozygous Variant: 247
CCR2 190 G/A	F:5′ - TTGTGGGCAACATGATGG - 3′ R:5′ - CTGTGAATAATTTGCACATTGC - 3′	57	183	Bse JI	Wild type: 183 Homozygous Variant: 165, 18
CCR5delta32	F:5′ - AGGTCTTCATTACACCTGCAGC - 3′ R:5′ - CTTCTCATTTCGACACCGAAGC - 3′	60	169 - 137		Wild type: 169 Homozygous Variant: 137
CTLA4-1661 A/G	F:5′ - CTAAGAGCATCCGCTTGCACCT - 3′ R:5′ -TTGGTGTGATGCACAGAAGCCTTTT - 3′	58	486	Mse I	Wild type: 347, 139 Homozygous Variant: 486
PTPN22 1858 C/T	F:5′ - ACTGATAATGTTGCTTCAACGG - 3′ R:5′ - TCACCAGCTTCCTCAACCAC - 3′	60	218	Rsa I	Wild type: 176, 42 Homozygous Variant: 218

was analyzed by Shapiro–Wilk test and the data were not normally distributed for age. Age was presented as median (25th–75th, interquartile range). Pearson's chi-square and Fisher's exact test were used to compare the sex distribution and test for deviation of genotype distribution from the Hardy–Weinberg equilibrium (HWE). A logistic regression model was used to test the associations between risk factors including SNPs and JIA in the case-control study. The OR and 95% confidence interval (CI) were calculated using logistic regression models adjusted for potential risk factors of JIA for genotype analysis. The post hoc power analysis was performed using PS: Power and Sample Size Calculation Version 3.1.2. P values < 0.05 were considered statistically significant.

3. Results

Table 2 gives the demographic data of the patient and control groups. The groups did not show any statistically difference with respect to age (P = 0.08) or sex (P = 0.28).

Clinical characteristics of JIA patients according to the ILAR classification are given in Table 3.

The distributions of the TNF-α-863, TNFRII 196, IL13-1112, CCR2 190, CCR5delta32, CTLA4-1661, and PTPN22 1858 genotypes were in accordance with the HWE among the controls (P = 0.23, P = 0.76, P = 0.70, P = 0.60, P = 0.60, P = 1.00, P= 0.60, respectively) and the cases (P = 1.00, P = 0.88, P = 0.30, P = 0.50, P = 0.60, P = 1.00, P = 0.60, respectively), but the distribution of the IL2-631 genotype was not in accordance with the HWE among the controls (P < 0.05) and the cases (P < 0.05). There were no significant differences at allele frequencies of all SNPs between JIA subjects and controls. As shown in Table 4, a statistically significant difference was observed in the genotype frequencies of the TNF-α-863 C > A and TNFRII 196 T > G polymorphisms between the patients with JIA and the controls. TNF-α-863 C/C genotype was associated with increased risk for JIA (OR = 2.56; 95% C l = 1.30–5.03). Moreover, TNFRII 196 T/T genotype frequency was significantly higher in JIA patients than in controls (P = 0.03). On the other hand, no association was found between the other polymorphisms and JIA (Table 4). The value of the power was 13% at the 0.05 level of significance, assuming an OR of 1.4 (small sample size).

4. Discussion

Immune system regulatory gene polymorphisms can cause dysregulation of the immune system resulting in a high risk for the development of autoimmune diseases such as JIA, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). In our study, we analyzed eight

Table 2. Demographic data of the patients and controls.

	JIA n (%)	Control n (%)	P
Sex			
Male, n (%)	25 (33)	34 (42)	0.28
Female, n (%)	51 (67)	46 (58)	
Age (years)	(8–12, 4)	(2–11.5, 9.5)	0.08

Age, (25th–75th, interquartile range)

Table 3. Patients' characteristics.

JIA subtypes	Cases	Percentage (%)	Female/Male
Systemic arthritis	12	16	6/6
Oligoarthritis	26	34	18/8
Polyarthritis	32	42	25/7
Long oligoarthritis	1	1	0/1
Juvenile psoriatic arthritis	3	4	1/2
Enthesitis-related arthritis	2	3	1/1
Total	76	100	51/25

Table 4. Logistic regression analysis of the association between TNF-α, TNFRII, IL-2, IL-13, CCR2, CCR5, CTLA4, and PTPN22 gene polymorphisms and JIA risk.

Genotype/allele	Cases, n (%)	Controls, n (%)	OR (95% Cl) [1]	P
TNF-α				
CC	55 (72)	41 (51)	Reference	
CA-AA	21 (28)	39 (49)	2.56 (1.30–5.03)	0.007
C allele frequency	0.85	0.76		
A allele frequency	0.15	0.24	1.79 (0.83–3.89)	0.15
TNFRII				
TT	52 (68)	41 (51)	Reference	
TG-GG	24 (32)	39 (49)	2.12 (1.09–4.10)	0.03
T allele frequency	0.82	0.70		
G allele frequency	0.18	0.30	1.95 (0.96–4.01)	0.06
IL-2				
GG	76 (100)	80 (100)	Reference	
GA-AA	0 (0)	0 (0)		0.99
G allele frequency	1.00	1.00		
A allele frequency	0	0		0.99
IL-13				
CC	38 (50)	46 (58)	Reference	
CT-TT	38 (50)	34 (42)	0.73 (0.38–1.38)	0.38
C allele frequency	0.74	0.74		
T allele frequency	0.26	0.26	1.00 (0.51–1.97)	0.87
CCR2				
wt/wt	57 (75)	61 (76)	Reference	
wt/64I-64I/64I	19 (25)	19 (24)	0.98 (0.47–2.05)	0.96
wt allele frequency	0.88	0.88		
64I allele frequency	0.12	0.12	1.00 (0.39–2.54)	0.83
CCR5				
wt/wt	72 (95)	76 (95)	Reference	
wt/d32-d32/d32	4 (5)	4 (5)	1.00 (0.24–4.20)	1.00
wt allele frequency	0.97	0.98		
d32 allele frequency	0.03	0.02	1.52 (0.25–9.27)	0.50
CTLA4				
AA	59 (78)	62 (78)	Reference	
AG-GG	17 (22)	18 (22)	1.04 (0.48-2.21)	0.93
A allele frequency	0.88	0.88		
G allele frequency	0.12	0.12	1.00 (0.39–2.54)	0.83
PTPN22				
CC	72 (95)	77 (96)	Reference	
CT-TT	4 (5)	3 (4)	0.78 (0.17–3.63)	0.75
C allele frequency	0.97	0.98		
T allele frequency	0.03	0.02	1.52 (0.25–9.27)	0.50

[1]Adjusted for sex and age
OR, Odds ratio
CI, Confidence interval

polymorphisms in JIA patients and healthy controls in a Turkish population. We found a statistically significant association between the risk of JIA and TNF-alpha-863 C > A and TNFRII 196 T > G polymorphisms in this case-control study.

Polymorphisms in the promoter of the TNF-alpha gene may affect the transcription levels and protein production and be associated with specific diseases (13). TNF-alpha-863 C > A is one of the polymorphisms identified in the promoter region of the TNF-alpha gene. Some researchers suggested that a variant allele of -863 C > A polymorphism provides enhanced promoter activity and high TNF-alpha expression (14,15). High TNF-alpha levels can play a role in JIA (16). The current study revealed that TNF-alpha-863 C/C genotype is a risk factor for JIA development. To the best of our knowledge, we showed the association of TNF-alpha-863 C > A polymorphism with JIA for the first time. There are several studies with contradictory results that investigate the association between other TNF-alpha polymorphisms and JIA susceptibility. Maddah et al. observed that the distribution of TNF-alpha-308 G/G and -238 G/G genotypes was significantly increased in JIA patients compared to controls ($P < 0.01$) (17). In another study, Ozen et al. investigated the association of TNF-alpha-238G > A and 308G > A polymorphisms with JIA development. They did not find any significant relationship between these polymorphisms and JIA (18). Schmeling et al. investigated the association between TNF-alpha-163 G > A, -238 G > A, -244 G > A, -308 G > A, and -376 G > A polymorphisms and the risk of developing JIA subtypes, and their results showed an association of TNF-alpha-238 G > A polymorphism with psoriatic arthritis, and of TNF-alpha-308 G > A polymorphism with polyarthritis (19). There are several studies that analyzed the relationship between TNF-alpha gene promoter polymorphisms and another autoimmune disease, rheumatoid arthritis (RA). Date et al. found that -863 A allele of the TNF-alpha gene was associated with systemic juvenile rheumatoid arthritis (15). There is a study in which Rezaieyazdi et al. investigated the association of TNF-alpha-308 G > A polymorphism with RA. They showed no association between the polymorphism and RA (20).

Polymorphisms in the TNFRII gene have been described before. One of them is exon 6 codon 196T > G polymorphism, which results in amino acid change (Met > Arg). In the present study, we found an association of TNFRII 196 T/T genotype with JIA risk. In contrast to our results, Zeggini et al. did not show any significant difference between JIA patients and healthy controls in terms of TNFRII 196 T > G polymorphism (21). There are also several studies that investigated the association between TNFRII 196 T > G polymorphism and other autoimmune diseases, such as RA and SLE. Shibue et al. did not find any association between this polymorphism and RA (22). However, Barton et al. reported an association of TNFRII 196 T > G polymorphism and RA. This study group found that either TNFRII 196 G/G genotype or G allele was a risk factor for RA in a Caucasian population (23). Al-Ansari et al. showed no correlation between the polymorphism and SLE (24).

In our study, we did not find any significant association between JIA and the other polymorphisms, IL2-631 G > A, IL13-1112 C > T, CCR2 190 G > A, CCR5delta32, CTLA4-1661 A > G, and PTPN22 1858 C > T.

There are several studies that investigated the association of IL13-1112 C > T polymorphism with other autoimmune diseases. Heinzman et al. did not find any association between IL13 110 Arg > Gln polymorphism and JIA (25). Possible association of IL13-1112 C > T polymorphism with an autoimmune disease, asthma, was investigated by Wu et al. and it was demonstrated that IL13-1112 T allele carriers were at increased risk for asthma (26).

There are two studies investigating the association between CCR5delta32 polymorphism and JIA. Contradictory results have been observed. Lindner et al. did not show any association (in a Norwegian population) and Scheibel et al. found an association (in a Brazilian population) between this polymorphism and JIA (27,28). When we compared the allele frequencies of our study with these two studies, we recognized that the allele frequencies are different in various populations (in Brazilian, Norwegian, and Turkish populations, delta32 allele frequency in JIA, respectively, is 9.4%, 9.7%, and 3%; in control groups, respectively, is 3.8%, 11.4%, and 2%). This may be a reflection of genetic heterogeneity of JIA susceptibility between different ethnic groups.

In many studies the association was investigated of CTLA4 polymorphisms with JIA. Suppiah et al. investigated whether there was an association between JIA and both CTLA4 + 49 A > G and CTLA4 CT60 polymorphisms. They did not find any marked association between JIA and these polymorphisms (29). In another study, Schubert et al. found an association between JIA and two polymorphisms of the CTLA4 gene, -318 C > T and exon 1 T17A (30).

Contrary to some previously reported results, we did not confirm the association of PTPN22 1858 C > T polymorphism with JIA. Viken et al. (31) and Hinks et al. (32) investigated the association of PTPN22 1858 C > T polymorphism with JIA, and both of them found a significant association between the polymorphism and disease. In accordance with our results, Pazar et al. (33), Seldin et al. (34), and Cinek et al. (35) did not find any association between PTPN22 1858 C > T polymorphism and JIA. The contradictory data reported in these

studies may be due to several factors such as ethnicity, combinations of susceptibility variants, small sample sizes, or variety of environmental factors. The limitation of our study was the small sample size, so that statistical power was reduced.

In conclusion, we revealed that immune system gene polymorphisms, TNF-alpha-863 C/C and TNFRII 196 T/T genotypes, were associated with JIA in a Turkish population. Further and large cohort studies are needed to elucidate the precise role of these polymorphisms in the pathogenesis of JIA.

Acknowledgment
The study was funded by the Research Fund of İstanbul University (Project number: 1444).

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