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The polymorphism rs4696480 in the TLR2 gene is associated with psoriasis patients in the Turkish population

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ABSTRACT

Background: Toll-like receptors (TLRs) have an important role in the host defense. Recent studies demonstrated that TLR polymorphisms might have a role in the pathogenesis of psoriasis vulgaris. The aim of this study was to indicate whether *TLR2* rs11938228 and rs4696480 were associated with susceptibility to psoriasis in the Turkish population.

Methods: This case-control study included 140 psoriasis patients and 250 controls. Genotyping of 2 rs11938228 and rs4696480 SNPs of *TLR2* were determined using LightSNiP Kit (Roche Diagnostic, GmBH, Mannheim, Germany).

Results: Our results demonstrated that the *TLR2*-rs4696480 AA genotype seemed to have a higher risk for psoriasis [crude 95% CI: 1.495–4.514, and $p < 0.001$, adjusted 95% CI: 1.349–4.292, and $p = 0.003$] while as *TLR2*-rs11938228 polymorphism has not shown any significant association with the risk of psoriasis [$p > 0.005$]. There was no statistically significant difference between the mean age, gender, onset age, and PASI level and genotypes for rs11938228 and rs4696480 polymorphisms ($p > 0.05$).

Conclusions: The SNP rs4696480 of *TLR2* may have significant effects on the heritability of psoriasis in the Turkish population.

1. Introduction

Psoriasis is a chronic and immune-mediated inflammatory disease with the polygenic and multifactorial mode of inheritance [1]. Ethnicity, regional and environmental factors are effective in the development of this disease. It affects 0.1%–3% of the adult population worldwide [2]. Psoriasis usually attacks back, scalp, elbows, and knees [3].The pathogenesis of psoriasis is not fairly understood, but it is characterized by attacks and periods of remission and inflammation with epidermal hyperproliferation, local vascular changes, and abnormal keratinocyte differentiation [4]. Several genetic changes associated with the innate immune system are known to play a vital role in the disease [5]. Toll-like receptors (*TLRs*) have a critical role in the host defense to induce the innate immune response to pathogens and in the activation of the adaptive immune response [6].

TLRs are type I transmembrane proteins and are present in different locations within the cell. *TLRs* recognize specific patterns of microbial components. Up to now, 10 *TLR* (*TLR1-10*) family members have been identified in human. The recognition of microbial components by *TLRs* stimulates the expression of different genes and triggers the activation of innate immunity [7]. *TLR2*, which forms a heterodimer with either *TLR1* or *TLR6*, recognizes various bacterial components including the peptidoglycan, lipopeptide, and lipoproteins of gram-positive bacteria and mycoplasma [8]. The previous study showed that *TLR2* and *TLR4* gene expression increased in patients with psoriasis [9]. *TLR2* expression has been reported to increase in skin layers further from the surface [10].

There are several studies of the role of dysregulated *TLR* signaling in the pathogenesis of infectious, autoimmune, allergic, and inflammatory diseases [11,12]. *TLR* polymorphisms can affect the expression of *TLR* genes. The association of *TLR2* in the etiopathogenesis of psoriasis vulgaris in the Turkish population remains unknown. Thus, the aim of this case-control study was to indicate whether *TLR2* rs11938228 and rs4696480 were associated with susceptibility to psoriasis in the Turkish population.

Abbreviations: TLR, toll-like receptor; SNP, single nucleotid polymorphism; PASI, psoriasis area severity index; BSA, body surface area; PAMP, pathogen-associated molecular patterns; PRR, pattern recognition receptors; NF-κB, nuclear factor-kB; APC, antigen-presenting cell

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2. Material and methods

2.1. Study population and characteristics

The study included 140 psoriasis patients who attended our Dermatology outpatient clinic and 250 healthy controls. The study was approved by the local ethics committee (2018 KAEK-189_2018.01.25_05) of Bozok University. An ethical consent was obtained from the patients. This research complied with the principles of the Declaration of Helsinki. Patients with erythrodermic psoriasis, pregnant and breastfeeding women, patients below the age of 18 years were excluded from the study. The demographic data of the patients, along with the duration of disease, Psoriasis Area Severity Index (PASI) and the affected body surface area (BSA), age of onset, family history of psoriasis and treatment were recorded.

2.2. Genotyping

DNA samples were extracted from EDTA-treated peripheral blood, using a commercial kit (High Pure PCR Template Preparation Kit, Roche Diagnostics, Germany). Genotyping of Toll-like receptor 2 single-nucleotide polymorphisms (SNP) rs11938228 and rs4696480 were performed by real-time polymerase chain reaction with LightSNiP reagents (coupled primer and probe) and FastStart DNA Master HybProbe (Roche Diagnostic, GmBH, Mannheim, Germany) in LightCycler 2.0. The cycling conditions for SNPs were: 10 min at 95 °C for activation, followed by 45 cycles of 95 °C for 10 s, 60 °C for 10 s, and 72 °C for 15 s. For the amplicon identification, the following conditions were used: 30 s at 95 °C, 2 min at 40 °C, and 0 s at 75 °C for one cycle. Positive control (heterozygote genotype) and negative control (double distilled water) were used in each experiment.

2.2.1. Statistical analysis

Descriptive statistics for continuous variables were expressed as mean ± SD or median (min-max), where applicable. Number of cases and percentages were used for categorical data. Genotype distribution of polymorphism was calculated for deviation from the Hardy–Weinberg equilibrium (HWE) by using Chi-square (χ^2) tests (one degree of freedom).

While the mean differences in age between groups were compared by Student's t test, otherwise, One-Way ANOVA was applied for comparison among more than two independent groups. Categorical data were analyzed by Pearson's Chi-square or Fisher's exact test, where appropriate.

The effects of genotypes and allele frequency on the existence of psoriasis were evaluated by univariate logistic regression analyses. Whether the associations between genotypes and the existence of disease were keeping on or not were examined by multiple logistic regression analyses after adjustment for both age and gender. Odds ratios and 95% confidence intervals for each genotype and allele type were also calculated.

Data analysis was performed by using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

3. Results

The demographic characteristics data of the study and control participants are summarized in Table 1. The mean age of the case group was statistically lower than the control group ($p < 0.001$). The ratio of women in the case group was statistically lower compared to the control group and the ratio of men was statistically higher ($p < 0.001$).

The genotype frequency distributions for the *rs11938228* and *rs4696480* SNPs investigated were consistent with Hardy–Weinberg equilibrium in the control group respectively ($\chi 2 = 0{,}177$, and $p = 0{,}674$, $\chi 2 = 0{,}326$, and $p = 0{,}568$). The clinical characteristics of the study participants are summarized in Table 2.

Table 1
Demographic characteristics of control and case groups.

	Control (n = 250)	Case (n = 140)	*p*-value
Age (year)	48.6 ± 10.5	43.3 ± 14.0	< 0.001[a]
Gender			< 0.001[b]
Female	166 (66.4%)	60 (42.9%)	
Male	84 (33.6%)	80 (57.1%)	

[a] Student's *t*-test.
[b] Pearson's Chi-square test.

Table 2
Clinical characteristics of psoriasis patients.

	n = 140
Age of onset	
< 40 years	101 (72.1%)
> 40 years	39 (27.9%)
Family history of psoriasis	52 (37.1%)
Duration of psoriasis	10 (1–45)
PASI	5.9 (0.6–44.4)
PASI	
≤6	75 (53.6%)
> 6	65 (46.4%)
BSA	7.0 (1.0–80.0)
Treatment	
Acitretin	17 (12.1%)
Cyclosporine	5 (3.6%)
Methotrexate	13 (9.3%)
TNF alfa inhibitor	13 (9.3%)
Other biological agents	3 (2.1%)
Local treatment	89 (63.6%)

We observed no differences in the genotype or allele frequency of *TLR2*-rs11938228 in the psoriasis group compared to the control group in Table 3.

We observed differences in the genotype frequency of *TLR2*-rs4696480 in the psoriasis group compared to the control group in Table 4.

When the TT genotype was used as the reference group for rs4696480, the TA genotypes [OR = 0.908, 95% CI: 0.557–1.479 ve p = 0.697], appeared to have no risk for psoriasis. However, the AA genotypes have a risk against the development of psoriasis for both crude and adjusted OR results [crude 95% CI: 1.495–4.514, and $p < 0.001$, adjusted 95% CI: 1.349–4.292, and $p = 0.003$]. Compared to the TT genotype, there was a 2.598-fold increased risk of developing psoriasis with the AA genotype. Significant differences were found in allele frequencies as well as in genotypes in the codominant and recessive model, showing that the allele A predisposes to the disease.

The risk of developing psoriasis increased significantly with the allele A of the *TLR2*-rs4696480 polymorphism, showing 1.651-fold increase psoriasis risk with A allele compared to T allele (95% CI: 1.228–2.218 $p < 0.001$).

There was no statistically significant difference between the mean age, gender, onset age, and PASI level and genotypes and alleles for rs11938228 and rs4696480 polymorphisms ($p > 0.05$).

4. Discussion

This study evaluated the association between 2 SNPs of *TLR2* and clinical parameters and genetic risk factors for psoriasis in a Turkish population. The results showed that the *TLR2*-rs4696480 AA genotype seemed to have a higher risk for psoriasis. The risk of developing psoriasis increased significantly with the allele A of the *TLR2*-rs4696480 polymorphism. However, there are no differences in terms of the genotype frequency of *TLR2*- rs11938228 in the psoriasis group compared to the control group. These results can give more insight into

Table 3
Distribution of genotype and allele frequencies (rs11938228) acording to control and case groups.

	Control (n = 250)	Case (n = 140)	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)[1]	*p*-value
GENOTYPE						
AA	42 (16.8%)	23 (16.4%)	1.000 (reference)	–	1.000 (reference)	–
AC	117 (46.8%)	72 (51.4%)	1.124 (0.625–2.021)	0.697	1.044 (0.562–1.937)	0.892
CC	91 (36.4%)	45 (32.1%)	0.903 (0.485–1.681)	0.748	0.833 (0.434–1.601)	0.584
GENOTYPE						
AA	42 (16.8%)	23 (16.4%)	1.000 (reference)	–	1.000 (reference)	–
AC + CC	208 (83.2%)	117 (83.6%)	1.027 (0.589–1.792)	0.925	0.950 (0.529–1.706)	0.865
GENOTYPE						
CC	91 (36.4%)	45 (32.1%)	1.000 (reference)	–	1.000 (reference)	–
AA + AC	159 (63.6%)	95 (67.9%)	1.208 (0.779–1.873)	0.398	1.239 (0.779–1.970)	0.365
Allele						
C	299 (59.8%)	162 (57.9%)	1.000 (reference)	–		
A	201 (40.2%)	118 (42.1%)	1.084 (0.805–1.458)	0.597		

OR: Odds ratio, CI: Confidence interval, [1] After adjustment for age and gender.

the effects of the *TLR2* gene on psoriasis.

The innate immune system includes germ-line-encoded Pattern Recognition Receptors (PRRs), which recognize pathogen threats and activate the response against them. PRRs have roles in recognizing the microbial components, which are called Pathogen-Associated Molecular Patterns (PAMPs) and which have critical roles in microbial pathogenesis, survival and replication. Integral cell membrane and cell wall components, bacterial toxins and DNA, RNA etc. molecules are the best examples for PAMPs. The recognition cascade of PRRs for PAMPs activates the host defense that avoids infection or fights against it and activates the adaptive immune response [13]. The best known group of PRRs is the *TLR*s, which are expressed in the cells of many mammals. Each *TLR* recognizes the specific patterns of microbial components. The recognition of microbial components by *TLR*s stimulates the expression of different genes and triggers the activation of innate immunity. The *TLR*-mediated activation of innate immunity seems compulsory for the development of antigen-specific adaptive immunity [7].

Recent studies have shown that *TLR*s are expressed in psoriatic lesions [14,15]. In addition, it is considered that the activity of *TLR*s is affected by the genetic polymorphisms in the interaction areas between the pathogens and receptors. *TLR2* recognizes various bacterial components that include the peptidoglycan, lipopeptide and lipoproteins of gram positive bacteria and mycoplasma. *TLR2* single-nucleotide-gene polymorphisms has been associated with many diseases like, urinary tract infection, asthma, acute rheumatic fever, and atherosclerosis [16–19].

TLR2-rs4696480 SNP is located in an intronic region of the gene in close proximity to the 3′ region and several transcription factor-binding sites. Therefore TLR2-rs4696480 SNP may have an important role in the TLR2 expression and function [20]. In a study conducted by Veltkamp et al. on sarcoidosis patients, they reported that the prevalence of the *TLR2*-rs4696480 AA genotype increased in patients with chronic diseases when compared to acute/self-remitting sarcoidosis patients. It was also reported that the proinflammatory cytokine secretion like tumor necrosis factor alpha (TNFα), interleukin (IL-6) and (IL-12) increased in *TLR2*-rs4696480 SNP homozygote (AA) genotype with *TLR2* stimulation when compared with the heterozygote or wild-type genotype [21]. The inflammation and keratinocyte hyperproliferation, which occurs with the excessive secretion of these cytokines, exists in the classic pathogenesis seen in psoriasis lesions [22,23]. When a certain *TLR* starts interaction with a microbial ligand, the “outside-in” signal cascade is activated, and the transcription factor nuclear factor-kB (NF-κB) is moved to the nucleus to create an inflammatory response. As well as initiating the inflammatory response, the cytokine pattern that is secreted by the Activated Antigen-Presenting Cells (APCs) might form the adaptive immune response (Th1- vs Th2-dominant responses) during the APC-T-cell interaction. Therefore, when the key role of *TLR*s in innate immune response and their roles in triggering the inflammation are considered, it is reasonable to consider the hypothesis that *TLR*s might play roles in recognizing the exogenous and microbial products during psoriasis, or in recognizing the self-ligands like fibronectin or Heat-Shock Protein (HSP) [24].

In the literature, studies reporting the relation between *TLR2*-rs4696480 SNP and psoriasis are few in number. Unlike our study, Shi et al. conducted a study in the southern Chinese population and did not report any significant relations between psoriasis and *TLR2*-rs4696480 polymorphism [25]. These differences that are observed in the distribution of the *TLR* gene polymorphisms might probably be explained with ethnicity. It was reported that the individuals who carried the *TLR2*-rs4696480 AA genotype had the tendency to different diseases. In another study, the risk of developing oral cancer increased significantly with the minor allele A of the *TLR2*-rs4696480 polymorphism [20]. In

Table 4
Distribution of genotype and allele frequencies (rs4696480) according to control and case groups.

	Control (n = 250)	Case (n = 140)	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)[1]	*p*-value
GENOTYPE						
TT	97 (38.8%)	45 (32.1%)	1.000 (reference)	–	1.000 (reference)	–
TA	114 (45.6%)	48 (34.3%)	0.908 (0.557–1.479)	0.697	0.922 (0.554–1.535)	0.756
AA	39 (15.6%)	47 (33.6%)	2.598 (1.495–4.514)	< 0.001	2.407 (1.349–4.292)	0.003
GENOTYPE						
TT	97 (38.8%)	45 (32.1%)	1.000 (reference)	–	1.000 (reference)	–
TA + AA	153 (61.2%)	95 (67.9%)	1.338 (0.865–2.071)	0.191	1.316 (0.833–2.079)	0.239
GENOTYPE						
AA	39 (15.6%)	47 (33.6%)	1.000 (reference)	–	1.000 (reference)	–
TT + TA	211 (84.4%)	93 (66.4%)	0.366 (0.224–0.597)	< 0.001	0.398 (0.238–0.666)	< 0.001
Allele						
T	308 (61.6%)	138 (49.3%)	1.000 (reference)	–		
A	192 (38.4%)	142 (50.7%)	1.651 (1.228–2.218)	< 0.001		

OR: Odds ratio, CI: Confidence interval, [1] After adjustment for age and gender.

addition, the A allele of the rs4696480 polymorphism was correlated with higher follicular lymphoma risk [26].

Even less is known on rs11938228 SNP in *TLR2*. In this study, *TLR2*-rs4696480, but not *TLR2*- rs11938228 SNP, was associated with psoriasis. In a recent study, *TLR2*-rs11938228 has been shown to be associated with response to anti-TNF treatment in psoriasis patients [27]. This study has shown that genetic variants in genes that regulate cytokines involved in psoriasis are associated with the response when psoriasis is treated with anti-TNF. In addition, another study reported that rs11938228 SNP was associated with Chronic Obstructive Pulmo psoriatic nary Disease [28].

5. Conclusions

To our knowledge, this is the first study about the association of *TLR2*-rs4696480 and *TLR2*- rs11938228 polymorphisms with psoriasis in the Turkish population. The results of the current study made us consider that *TLR2*-rs4696480 polymorphism might play a role in the immunopathologic mechanisms of the psoriasis disease. We believe that the increase in possible inflammatory cytokine levels caused by *TLR2*-rs4696480 polymorphism might be among the mechanisms that prepare the ground for psoriasis. To confirm the data we obtained in our study, and to adopt them to treatment modalities, it is necessary that polymorphisms are investigated in further studies both in Turkish population and in different populations. In this way, the role of *TLR* gene polymorphisms in the pathogenesis of psoriasis may be elucidated and new treatment modalities might be developed.

Author contribution statement

S.SO performed the research, G.G, SSO designed the research study, G.G contributed to data collection, S.S.O analyzed the data, G.G, S.S.O wrote the paper.

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Conflict of interest

The authors have no conflict of interest to declare

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