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Relationship between *Glutathione S-transferase* gene polymorphisms and clinical features of psoriasis: A case-control study in the Turkish population

Glutatyon S-transferaz gen polimorfizmleri ile psoriazisin klinik özellikleri arasındaki ilişki: Türk popülasyonunda olgu kontrol çalışması

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Abstract

Background and Design: In this study, we investigated whether *Glutathione S-transferase Mu 1 (GSTM1)* and *Glutathione S-transferase Pi 1 (GSTP1)* gene polymorphisms are risk factors for psoriasis development and characteristics of psoriasis.
Materials and Methods: Venous blood samples were collected from both the patients and control subjects into 2 mL EDTA tubes. DNA was isolated from 260 psoriasis patients and 200 healthy control subjects, and *GSTM1* and *GSTP1* gene polymorphisms were genotyped by real-time polymerase chain reaction method.
Results: According to the analysis results, although the frequency of the GSTM1 null genotype was 1.33 times higher in patients compared to controls, this difference was statistically insignificant [95% confidence interval (CI): 0.91-1.93, p=0.13]. GSTP1 AG heterozygous genotype and GG homozygous polymorphic genotype frequencies also did not differ between patients and controls [odds ratio (OR): 0.80, 95% CI: 0.55-1.18, p=0.27 for AG genotype; OR: 0.74, 95% CI: 0.35-1.56, p=0.42 for GG genotype]. When both polymorphisms were evaluated based on the onset age and severity of the disease, no significant difference was found between the early onset age group and the late onset age group, nor between the mild group and the severe group.
Conclusion: The results show that *GSTM1* and *GSTP1* polymorphisms do not have a major effect on the etiopathogenesis and clinical characteristics of psoriasis.
Keywords: Psoriasis, GST, gene polymorphisms, cellular detoxification

Öz

Amaç: Bu çalışmada *Glutatyon S-transferaz Mu 1 (GSTM1)* ve *Glutatyon S-Transferaz Pi 1 (GSTP1)* gen polimorfizmlerinin psoriazis gelişimi ve özellikleri açısından risk faktörü olup olmadığını araştırdık.
Gereç ve Yöntem: Hasta ve kontrollerden 2 mL'lik EDTA'lı tüplere kan örnekleri alındı. İki yüz altmış psoriazis hastası ve 200 sağlıklı kontrolden DNA izolasyonu yapıldı ve *GSTM1* ve *GSTP1* gen polimorfizmleri gerçek zamanlı polimeraz zincir reaksiyonu yöntemiyle genotiplendirildi.
Bulgular: Analiz sonuçlarına göre hastalarda GSTM1 null genotip sıklığı kontrollere göre 1,33 kat daha yüksek olmasına rağmen bu fark istatistiksel olarak anlamlı değildi [%95 güven aralığı (GA): 0,91-1,93, p=0,13]. GSTP1 AG heterozigot genotip ve GG homozigot polimorfik genotip frekansları da hastalar ve kontroller arasında farklılık göstermedi (AG genotipi için [olasılık oranı (OO): 0,80, %95 GA: 0,55-1,18, p=0,27; OO: 0,74, %95 GA: 0,35-1,56, GG genotipi için p=0,42]. Her iki polimorfizm hastalığın başlangıç yaşı ve şiddetine göre değerlendirildiğinde erken başlangıçlı yaş grubu ile geç başlangıçlı yaş grubu arasında ve hafif grup ile ağır grup arasında anlamlı fark bulunamadı.
Sonuç: Sonuçlar GSTM1 ve GSTP1 polimorfizmlerinin psoriazisin etiyopatogenezi ve klinik özellikleri üzerinde önemli bir etkisinin olmadığını göstermektedir.
Anahtar Kelimeler: Psoriasis, GST, gen polimorfizmi, hücresel detoksifikasyon

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Introduction

Psoriasis, a chronic inflammatory skin disease with a genetic predisposition, affects people of all ages and genders worldwide[1]. The disease's prevalence varies worldwide between 2 and 3%, depending on ethnic and geographical differences[2]. The most common clinical form of the disease is plaque-type psoriasis, seen in approximately 85-90% of the cases[3].

Although skin and joints are the primary involvements in psoriasis patients, comorbidities such as cardiovascular diseases, metabolic syndrome, chronic kidney disease, and cancer may accompany these involvements[4].

Although our understanding of the disease's pathogenesis is growing daily, we still struggle to fully understand it. It is now known that the mutually inappropriate interactions of immune system cells, especially T-cells, skin cells, and proinflammatory cytokines and chemokines, are responsible for the emergence of the disease[5]. These inappropriate interactions lead to the prominent picture of the disease, which includes hyperproliferation and aberrant differentiation of keratinocytes, capillary dilatation, and infiltration of leukocytes into the dermis[5-7].

Psoriasis, like other multifactorial diseases, has genetic and environmental components. Indeed, there is ample documentation on the triggering role of environmental factors such as trauma, infection, UV radiation, drugs, stress, smoking/alcohol, dietary habits, obesity, and oxidative stress in psoriasis[8-11]. These triggers, together with the genetic component, affect the onset, development, and severity of the disease. The genetic component consists of Psoriasis Susceptibility (PSORS) loci, variations in genes that play a role in most immunity and inflammation, and epigenetic changes[5,7,8,12].

Variations in genes encoding enzymes involved in the cellular protective/detoxifying system have also been associated with many diseases in which environmental factors play a role in their etiology[13-16]. One of these enzyme families is glutathione S-transferases (GSTs). *GSTs* are phase 2 detoxification enzymes that detoxify a large number of endogenous and exogenous components, protect cells from reactive oxygen species (ROS), and contribute to the regulation of inflammation, cellular redox state, and even apoptosis[17-19]. There are several isoenzymes in the GST superfamily, each made by a different gene located at a different locus. These are alpha (GSTA), kappa (GSTK), mu (GSTM), omega (GSTO), pi (GSTP), sigma (GSTS), theta (GSTT), and zeta (GSTZ)[20]. The alpha, mu, and pi classes are the most abundant[21].

In this study, we examined *GSTM1* gene null deletion and *GSTP1* gene 313A>G (rs1695) variants in plaque-type psoriasis patients. Our aim was to determine whether these GST variants play a role in the etiopathogenesis and clinical features of psoriasis vulgaris. Indeed, these GST isoenzymes work in removing ROS and protecting DNA from oxidative damage[21]. Furthermore, *GSTM1* and *GSTP1* play a role in regulating the stress response, apoptosis, and proliferation signaling pathway induced by tumor necrosis factor (TNF), one of the key molecules of psoriasis. In this pathway, *GSTP1* stops *TNF receptor associated factor 2* (*TRAF2*), which bindsfrom binding to the TNF receptor, and *GSTM1* stops apoptosis signal regulating kinase 1 (*ASK1*) kinase, the downstream target of TRAF2[22,23]. It is known that variations in genes encoding these isoenzymes lead to loss or decrease in enzyme activity[24,25]. Therefore, these *GST* variants are likely to play a role in psoriasis etiopathogenesis by causing deficiencies in the removal of oxidative damage and/or impairments in the regulation of the TNF-TNF receptor mediated signal transduction pathway.

Materials and Methods

Study population

The G-Power 3.1.9.7 software calculated a sample size of 460 with a 5% margin of error and 95% power in the χ^2 test. Accordingly, the study population consisted of 460 unrelated individuals (260 psoriasis patients and 200 healthy individuals) who presented to the dermatology clinic between 2012 and 2016. Patients had no history of any other chronic or autoimmune disease, psoriatic arthritis, or cancer. We took care to form the patient population by selecting adult patients who had either never received treatment or had not received treatment in the last 6 months. The control group was selected from adult healthy individuals with no previous history of psoriasis, chronic or autoimmune disease, and/or cancer who presented to the clinic only for cosmetic reasons. Therefore, the number of control subjects was lower than the number of patients. The severity of psoriasis in all patients was evaluated using psoriasis area severity index (PASI) scoring. In order to determine whether *GST* polymorphisms are associated with the clinical features of psoriasis, the patients were first divided into two groups according to their PASI scores as "the mild group" (PASI <12) and "the severe group" (PASI ≥12), then were divided into two groups according to disease onset age as "the early onset group" (<40 years old) and "the late onset group" (≥40 years old) (Table 1). The study was conducted according to the criteria set by the Declaration of Helsinki and was approved by the Selçuk University Faculty of Medicine Ethics Committee (approval number: 2011/205, date: 30.06.2011). We obtained signed informed consent from all patients and control subjects before starting the study.

Genotyping

Venous blood samples were taken from the patients and control subjects into 2 mL EDTA tubes, and the samples were stored at +4 °C until the study started. Genomic DNA was isolated from whole blood with the High Pure PCR Template Preparation Kit (Roche Diagnostics, GmbH, Germany) according to the manufacturer's protocol. A real-time polymerase chain reaction system (Roche LightCycler 480 instrument using hybridization probes in combination with a LightCycler DNA Master Hybridization Probes kit, Roche Diagnostics, GmbH, Germany) was used to detect GST polymorphisms. Sequences of primers and probes used are given in Table 2.

Statistical Analysis

SPSS v18.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. The differences in means of age and gender were analyzed by the Student's t-test. We compared allele distributions using χ^2 and Fisher's exact tests. Logistic regression analysis was performed to test the relationship of GST polymorphisms with psoriasis vulgaris and its clinical features, taking into account different inheritance models. P-values less than 0.05 were considered statistically significant.

Results

The characteristics of the study population are given in Table 1. The age distribution between patients and controls was similar (39.83±24.52 vs. 38.94±18.8 years for patients and controls, respectively, p=0.67). There was no difference between the two groups in terms of gender distribution (118 male/142 female vs. 101 male/99 female for patients and controls, respectively, p=0.30). The age of onset of the disease was before 40 years in 84.62% of the patients. According to the PASI score, 45% of patients had a severe course of disease.

The frequencies of *GSTM1* and *GSTP1* genotypes in patients and controls are shown in Table 3. The *GSTM1* gene was deleted in both alleles in 48.1% of patients and 41% of controls. Although the frequency of null genotype in patients was 1.33 times higher than controls, it was statistically insignificant (p=0.13). The distribution of *GSTP1* genotypes was evaluated separately according to inheritance models such as codominant, dominant, recessive, and overdominant, and no relationship was found between *GSTP1* polymorphism and increased risk of psoriasis in any model.

The results of the analysis performed to determine whether *GST* polymorphisms are a risk factor for the age of onset of psoriasis are presented in Table 4. The frequency of the *GSTM1* null genotype in the early and late age groups was 46.8% and 55%, respectively. No relationship was found between the null genotype and the age of onset of the disease (p=0.34). When considering the distribution of *GSTP1* genotypes, the percentage of mutant genotype (GG) was 6% vs. 7.2%, the percentage of heterozygous genotype (AG) was 36.4% vs. 47.6%, and the percentage of wild genotype (AA) was 57.6% vs. 45.2% for the "early onset group" vs. the "late onset group," respectively. *GSTP1* genotypes showed no association with age of disease onset according to any inheritance model.

The distribution of *GSTM1* and *GSTP1* genotypes and their relationship with disease severity are given in Table 5. The GSTM1 null genotype frequency was 44.4% in the severe group and 51% in the mild group. This polymorphism did not affect the severity of the disease (p=0.34). In *GSTP1* A>G polymorphism, the frequency of variant genotype GG in "severe group" and "mild group" was 6% and 6.3%, respectively. Different inheritance patterns revealed no significant relationship between *GSTP1* genotypes and psoriasis.

Discussion

GSTs are part of the cellular defense system. They play critical roles in protecting cells against oxidative stress, inflammation, mutagenicity, and genotoxicity[17,19,26]. *GSTM1* and *GSTP1* are two of the few members of this enzyme superfamily that are well-known and studied. The genes encoding the *GST* superfamily are highly polymorphic. For this reason, these gene variants have long been the focus of attention in many diseases, especially cancer, where oxidative stress, inflammation, and mutagenesis play a role in the etiopathogenesis.

Table 1. General characteristics of study subjects

	Patients, (n=260)	Controls, (n=200)	p
Age (years)			
Mean ± SD	39.83±24.52	38.94±18.8	0.67
Gender			
Male	118 (45.38%)	101 (50.5%)	0.30
Female	142 (54.62%)	99 (49.5%)	
Family history of psoriasis	No	No	
Cancer history	No	No	
Psoriatic arthritis	No	No	
Autoimmune disease	No	No	
Systemic disease	No	No	
Onset age of psoriasis			
Early onset (<40 age)	220 (84.62%)		
Late onset (≥40 age)	40 (15.38%)		
Severity of psoriasis			
Mild (PASI <12)	117 (45%)		
Severe (PASI ≥12)	143 (55%)		

SD: Standard deviation, PASI: Psoriasis area severity index

Table 2. The primers and hybridization probes used to detect *GSTM1* and *GSTP1* polymorphisms

Gene	PCR primers	Hybridization probes
GSTM1	5'-GAACTCCCTGAAAAGCTAAAGC-3' 5'-GTTGGGCTCAAATATACGGTGG-3'	5'-LCR640-ATGGCCGCTTCCCAGAAACTCTG-3' 5'-TCACTCCTCCTTTACCTTGTTTCCTGCAAA-FL-3'
GSTP1	5'-ACCCCAGGGCTCTATGGGAA-3' 5'-TGAGGGCACAAGAAGCCCCT-3'	5'-LCR640-TGTGAGCATCTGCACCAAGGGTTGGGG-3' 5'-TGCAAATACATCTCCCTCATCTACACAAC-FL-3'

GSTM1: Glutathione S-transferase Mu 1, GSTP1: Glutathione S-transferase Pi 1, PCR: Polymerase chain reaction

We already know that ROS and inflammation play a significant role in the pathogenesis of psoriasis[27]. In addition, there exist few studies conducted in different populations on whether GST variants impose a psoriasis risk factor, with four on *GSTM1* and *GSTT1* variants[28-31] and only a single one on *GSTA1*, *GSTM1*, and *GSTT1* variants[32]. Thus, we investigated in this study the relationship between psoriasis and the *GSTM1* and *GSTP1* gene variants.

The most common variants of *GSTM1* and *GSTT1* are complete deletions[33]. In the current study, we assessed the prevalent polymorphism of *GSTP1*, specifically the 313A>G nucleotide substitution, in conjunction with the common polymorphism of *GSTM1*. This one-nucleotide change in the *GSTP1* gene leads to the codon encoding valine instead of isoleucine (Ile105Val). It is expected that there is no enzyme production in the presence of deletion polymorphism in *GSTM*[34]. Reports indicate that the Ile105Val polymorphism in *GSTP1* modifies the substrate affinity and thermal stability of the enzyme, resulting in a reduction in activity[35]. Upon initiating the study, we hypothesized that the development and/or clinical features of psoriasis could be associated with these two polymorphisms. While making this prediction, we did not only consider the roles of *GSTM1* and *GSTP1* in detoxification, but also the roles of these two isoenzymes in the modulation of inflammation, proliferation, and apoptosis-related

Table 3. Genotype and allele frequencies of *GST* gene polymorphisms in psoriasis vulgaris patients and controls and association of these polymorphisms with psoriasis vulgaris risk

Genotype		Patients, n (%)	Controls, n (%)	OR, (95% CI)	p
GSTM1					
Positive		135 (51.9)	118 (59)	1[a]	
Null		125 (48.1)	82 (41)	1.33 (0.91-1.93)	0.13
GSTP1	**Model**				
AA	Codominant	145 (55.8)	100 (50)	1[a]	
AG		99 (38.1)	85 (42.5)	0.80 (0.55-1.18)	0.27
GG		16 (6.1)	15 (7.5)	0.74 (0.35-1.56)	0.42
AA	Dominant	145 (55.8)	100 (50)	1[a]	
AG + GG		115 (44.2)	100 (50)	0.79 (0.55-1.15)	0.22
AA + AG	Recessive	244 (93.9)	185 (92.5)	1[a]	
GG		16 (6.1)	15 (7.5)	081 (0.39-1.68)	0.57
AA + GG	Overdominant	161 (61.9)	115 (57.5)	1[a]	
AG		99 (38.1)	85 (42.5)	0.83 (0.57-1.21)	0.34
A	**Major allele**	**389 (75)**	**285 (71)**	**1[a]**	
G	**Minor allele**	**131 (25)**	**115 (29)**	**0.83 (0.62-1.12)**	**0.23**

OR: Odds ratio, CI: Confidence interval, [a]: Reference, GST: Glutathione S-transferase, GSTM1: Glutathione S-transferase Mu, GSTP1: Glutathione S-transferase Pi 1

Table 4. Genotype and allele frequencies of *GST* gene polymorphisms in early-onset group and late-onset group and association of these polymorphisms with onset of psoriasis vulgaris

Genotype		Early onset, n (%)	Late onset, n (%)	OR, (95% CI)	p
GSTM1					
Positive		117 (53.2)	18 (45)	1[a]	
Null		103 (46.8)	22 (55)	0.72 (0.34-1.42)	0.34
GSTP1	**Model**				
AA	Codominant	125 (57.6)	19 (45.2)	1[a]	
AG		79 (36.4)	20 (47.6)	0.60 (0.30-1.19)	0.14
GG		13 (6)	3 (7.2)	0.66 (0.17-2.53)	0.42
AA	Dominant	125 (57.6)	19 (45.2)	1[a]	
AG + GG		92 (42.4)	23 (54.8)	0.61 (0.31-1.18)	0.13
AA + AG	Recessive	204 (94)	39 (92.8)	1[a]	
GG		13 (6)	3 (7.2)	0.83 (0.25-3.04)	0.78
AA + GG	Overdominant	138 (63.6)	22 (52.4)	1[a]	
AG		79 (36.4)	20 (47.6)	0.63 (0.32-1.22)	0.17
A	**Major allele**	**329 (76)**	**58 (69)**	**1[a]**	
G	**Minor allele**	**105 (24)**	**26 (31)**	**0.71 (0.43-1.88)**	**0.19**

OR: Odds ratio, CI: Confidence interval, [a]: Reference, GSTM1: Glutathione S-transferase Mu, GSTP1: Glutathione S-transferase Pi 1

signaling pathways. *GSTP1* inhibits *TRAF2* and *GSTM1* inhibits *ASK1* kinase, *TRAF2*'s target. TNF, the key molecule of psoriasis, binds to the *TRAF2* component of TNF receptor-2. *GSTP1* also binds to and inhibits c-Jun N-terminal kinase (JNK). The inhibited JNK cannot translocate to the nucleus and activate c-Jun, thus preventing the expression of target genes (Figure 1a)[22,23]. However, the binding of TNF ligand to the receptor or the presence of oxidative stress separates *GSTM1* and *GSTP1* from these inhibited proteins. *TRAF2* interacts with *ASK1*. Activated *ASK1* also activates downstream proteins in its target. JNK, which survives the inhibition of *GSTP1*, also passes into the nucleus and phosphorylates c-Jun. c-Jun binds to DNA together with FOS, activating the transcription of the relevant genes (Figure 1b)[22,23]. Studies have revealed that the strong binding of *GSTP1* to JNK plays a crucial role in suppressing apoptosis, while the weak binding of polymorphic *GSTP1* acts as an anti-apoptotic[36]. As a result, *GSTM1* polymorphism (absence of *GSTM1* enzyme activity) and *GSTP1* polymorphism (change in

Table 5. The genotype and allele frequencies of *GST* gene polymorphisms in severe (PASI ≥12) group and mild (PASI <12) group and the relationship of these polymorphisms with severity of psoriasis vulgaris

Genotype		Severe, (PASI ≥12), n (%)	Mild, (PASI <12), n (%)	OR, (95% CI)	p
GSTM1					
Positive		65 (55.6)	70 (49)	1[a]	
Null		52 (44.4)	73 (51)	0.72 (0.34-1.42)	0.34
GSTP1	**Model**				
AA	Codominant	62 (53)	83 (58)	1[a]	
AG		48 (41)	51 (35.7)	1.26 (0.75-2.10)	0.37
GG		7 (6)	9 (6.3)	1.04 (0.36-2.95)	0.92
AA	Dominant	62 (53)	83 (58)	1[a]	
AG + GG		55 (47)	60 (42)	1.23 (0.75-2.01)	0.41
AA + AG	Recessive	110 (94)	134 (93.7)	1[a]	
GG		7 (6)	9 (6.3)	0.95 (0.34-2.63)	0.92
AA + GG	Overdominant	69 (59)	92 (64.3)	1[a]	
AG		48 (41)	51 (35.7)	1.25 (0.76-2.07)	0.38
A	**Major allele**	**172 (73.5)**	**217 (75.9)**	**1[a]**	
G	**Minor allele**	**62 (26.5)**	**69 (24.1)**	**1.13 (0.76-1.69)**	**0.54**

OR: Odds ratio, CI: Confidence interval, [a]: Reference, GSTM1: Glutathione S-transferase Mu, GSTP1: Glutathione S-transferase Pi 1, PASI: Psoriasis area severity index

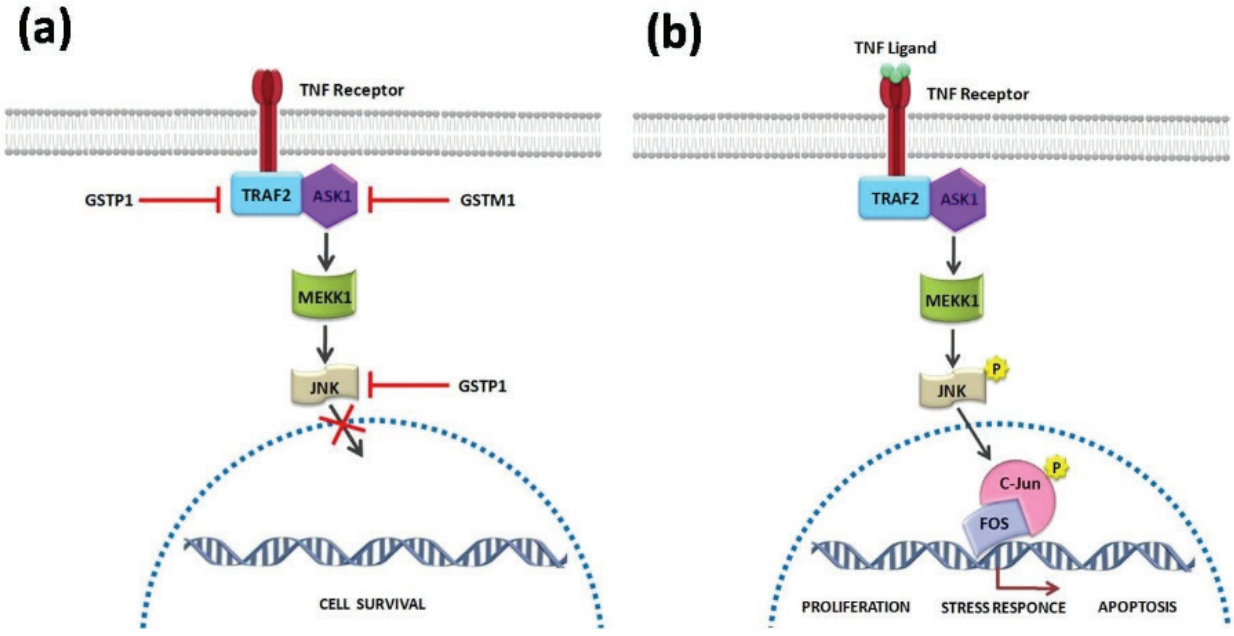

Figure 1. The roles of GSTM1 and GSTP1 in the C-Jun signaling pathway. **(a)** Inhibition of ASK1 by GSTM1 and inhibition of TRAF2 and JNK by GSTP1. **(b)** Activation of TNFR and transcription of target genes
GSTM1: Glutathione S-transferase Mu, GSTP1: Glutathione S-transferase Pi 1, ASK1: apoptosis signal regulating kinase 1, TRAF2: TNF receptor associated factor 2, JNK: c-Jun N-terminal kinase

GSTP1 enzyme activity) eliminate or change the inhibition on ASK1, TRAF2, and JNK, and impair the regulation of the pathway.

However, the data we obtained from our study did not support this hypothesis. According to our results, GSTM1 polymorphism was not a risk factor for the development of psoriasis [odds ratio (OR): 1.33; 95% confidence interval (CI): 0.91-1.93; p=0.13). The situation was also similar for the *GSTP1* polymorphism. There was no difference between patients and controls according to any of the inheritance models (OR: 0.80; 95% CI: 0.55-1.18; p=0.27 for the AG genotype; OR: 0.74; 95% CI: 0.35-1.56; p=0.42 for the GG genotype; OR: 0.79; 95% CI: 0.55-1.15; p=0.22 for the dominant model; OR: 0.81; CI: 0.39-1.68; p=0.57 for the recessive model; OR: 0.83; 95% CI: 0.57-1.21; p=0.34 for the overdominant model) (Table 3).

We evaluated the relationship between GSTM1 and GSTP1 polymorphisms and the psoriasis onset age and found no difference between the "early onset age group" and the "late onset age group." These polymorphisms did not pose a risk for the early onset of psoriasis (Table 4).

In our analysis of the relationship of GSTM1 and GSTP1 polymorphisms with psoriasis severity, we found no difference between the "mild group" with a PASI index of less than 12 and the "severe group" with a PASI index greater than 12. These polymorphisms did not predispose to the severe course of the disease (Table 5).

In a study of 320 psoriasis patients and 235 controls in the German population[28], the *GSTM1* null genotype was found to be associated with the risk of developing psoriasis (OR: 0.70; 95% CI: 0.48-1.00; p=0.055). Likewise, in another study conducted in the Indian population[30], it was revealed that GSTM1 polymorphism has a significant relationship with psoriasis risk (OR: 1.58; 95% CI: 1.02-2.44; p=0.039). Results of two separate studies performed in the Italian population[31] and the Czech population[32] are in agreement with ours. In the first of these studies, *GSTM1* and *GSTT1* polymorphisms were evaluated in psoriasis patients, while *GSTA1*, *GSTM1*, and *GSTT1* polymorphisms were studied in the other study. While *GSTT1* polymorphism was found to be associated with psoriasis in the first study, it was understood that *GSTM1* polymorphism was not associated with psoriasis. In the second study, no relationship was found between psoriasis and studied polymorphisms, including *GSTM1*. In another study from the Turkish population, Solak et al.[29] investigated whether *GSTM1* and *GSTT1* polymorphisms were associated with PSORS and found that neither polymorphism was effective on susceptibility to psoriasis. To the best of our knowledge, there is no other study investigating the relationship between *GSTP1* polymorphism and psoriasis. However, there is a study investigating the relationship of this polymorphism with Behçet's disease, another disease in which oxidative stress and inflammation play a role in its etiopathogenesis. Tursen et al.[13] evaluated the *GSTM1* and *GSTT1* polymorphisms together with the *GSTP1* polymorphism and found the frequency of *GSTM1* polymorphism to be higher in Behçet's disease patients compared to controls, while they found *GSTP1* and *GSTT1* polymorphisms to be not associated with Behçet's disease. The contradiction of the results of the studies with each other is an undeniable result in polymorphism-disease risk relationship studies.

Table 6. Frequency of *GSTP1* and *GSTM1* genotypes in different populations

Population	n	*GSTP1*			*GSTM1*		References
		AA, (%)	AG, (%)	GG, (%)	Positive, (%)	Null, (%)	
UK	952	48.52	37.42	14.06	50.95	49.05	Rollinson et al.[37]
Türkiye	178	48.30	43.80	7.90	75.80	24.20	Tursen et al.[13]
Germany	768	40.00	47.00	13.00	50.00	50.00	Wiesenhütter et al.[38]
Sweden	203	52.70	37.40	9.90	48.80	51.20	Bu et al.[39]
Slovakia	220	57.00	35.00	8.00	52.00	48.00	Matakova et al.[40]
Spain	557	45.06	42.55	12.39	52.06	47.94	García-González et al.[41]
Czechia	218	47.60	45.90	11.50	53.70	46.30	Hezova et al.[42]
Romania	152	65.13	30.92	3.95	43.42	56.58	Bogliș et al.[43]
Russia	270	43.30	47.00	10.70	57.30	42.70	Minina et al.[44]
Poland	221	46.20	43.90	10.00	57.00	43.00	Klusek et al.[45]
Bangladesh	595	53.60	40.30	6.10	59.00	41.00	McCarty et.[46]
Japan	400	71.00	28.30	0.70	43.80	56.20	Yamada et al.[47]
India	564	43.70	48.40	7.90	77.50	22.50	Bhatti et al.[48]
China	384	58.00	35.60	6.40	53.20	46.80	Liu et al.[49]
Jordan	219	55.30	36.50	8.20	32.9	67.1	Al-Eitan et al.[50]
Iran	281	50.80	42.80	6.40	49.10	50.90	Pourkeramati et al.[51]
orocco	210	44.30	45.70	10.00	50.00	50.00	Boujmia et al.[52]
USA	522	43.20	45.70	11.10	52.50	47.50	Agalliu et al.[53]
Brazil	264	39.80	48.90	11.40	51.90	48.10	Honma et al.[54]
Argentina	609	44.00	45.00	11.00	55.00	45.00	Weich et al.[55]
Türkiye	200	50.00	42.50	7.50	59.00	41.00	Present study

*The genotype frequencies in the table belong to the healthy control groups of the studies. The data of the studies with more than 150 subjects are included in the table. GSTM1: Glutathione S-transferase Mu, GSTP1: Glutathione S-transferase Pi 1

This may be due to unintentional biases in the selection of subjects and limited sample sizes, as well as gene-gene/gene-environment interactions and racial/geographic differences.

The frequencies of the *GSTM1* null genotype and *GSTP1* Ile105Val polymorphisms in different geographic and racial populations are shown in Table 6. The frequencies of polymorphisms belong to healthy control individuals in case-control studies. While the highest *GSTM1* null genotype frequency was observed in Romanian[43] and Japanese populations[47] (56.58% and 56.20%, respectively), the lowest *GSTM1* null genotype frequency was detected in the Turkish population (24.2%)[13]. However, in the control subjects of our study, this frequency was 41%. The difference in *GSTM1* null genotype frequency within the same population is probably due to the criteria for case selection. For *GSTP1*, the highest GG polymorphic genotype frequency was found in the UK population[37] as 14.06%, with the lowest GG polymorphic genotype frequency found in the Japanese population[47] as 0.70%. In our study, the GG genotype frequency was 7.50%. As it can be seen in Table 6, the 41% *GSTM1* null genotype frequency we found in our study is the same as that of the Bangladesh[46] population, while the *GSTP1* GG genotype frequency of 7.90% is similar to the GG genotype frequency in Indian (7.90%)[48] and Slovak populations (8%)[40].

Study Limitations

Case-control studies performed in certain populations like ours are small parts of the bigger picture. In order to see the big picture, more such studies should be carried out, and many polymorphisms in other genes that function in oxidative stress and signal pathways in which GST enzymes play a role should be evaluated in more comprehensive population-based studies, and the results should be supported with functional analyzes of these genes.

Conclusion

This study is important to determine whether there is an association in the Turkish population between psoriasis and the polymorphisms in genes encoding enzymes involved in detoxification metabolism. According to our results, these gene polymorphisms do not have a major effect on the occurrence of psoriasis and clinical features of the disease. The present study is the second study evaluating the relationship between psoriasis and *GST* gene polymorphisms in the Turkish population, and the results are consistent with the former one[29]. In the present study, the prevalence of these polymorphisms in the population was determined, and it was observed that the polymorphisms did not cause predisposition to psoriasis. Although these polymorphisms seem to be unrelated to psoriasis clinic, the negative effects of the related enzymes whose activity is reduced or eliminated may be compensated by another isoenzyme or another enzyme family. This may explain the seeming lack of effect of polymorphisms on the clinical manifestation of psoriasis. However, studies should be supported by functional analyses (at the mRNA and protein levels) in order to reveal more clearly the effect of these polymorphisms.

Ethics

Ethics Committee Approval: The study was conducted according to the criteria set by the Declaration of Helsinki and was approved by the Selçuk University Faculty of Medicine Ethics Committee (approval number: 2011/205, date: 30.06.2011).

Informed Consent: We obtained signed informed consent from all patients and control subjects before starting the study.

Authorship Contributions

Concept: H.G.D., Design: H.G.D., R.D., Data Collection or Processing: R.D., M.S.Y., Analysis or Interpretation: H.G.D., İ.Ç.A., A.G.Z., M.S.Y., Literature Search: H.G.D., A.G.Z., Writing: H.G.D., İ.Ç.A.

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