

## The Relationship between Glutathione-S-Transferases Polymorphisms and Lichen Planus Susceptibility

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### ABSTRACT

**Aim:** The glutathione-S-transferases (GSTs) refers to a group of detoxification enzymes that are pivotal components of the cellular defense against oxidative stress and the expressions of GST isoforms have been shown in human skin. This study was planned to determine the effects of GST polymorphisms on the molecular etiology of the lichen planus (LP).

**Materials and Methods:** The study group consisted of 55 patients with LP and 98 age- and sex-matched healthy unrelated controls. GSTM1 and GSTT1 genotypes were determined by multiplex PCR, GSTP1 polymorphisms by using PCR-RFLP technique.

**Results:** GSTM1, GSTT1 and GSTP1 polymorphisms showed significant differences between the patients and controls. We also found that the GSTT1 deletions were more predominant in the patients who had been treated with combined treatments.

**Conclusion:** GSTM1 and GSTT1 null genotypes and from A to G transition in the 105th position of GSTP1 may play an important role in the physiopathology of LP. Moreover, the relation between the GSTT1 polymorphism and the response of the patients to the treatment protocols should be evaluated in detail in the use of new approaches including antioxidant mechanisms in the unresponsive cases to the standard protocols.

**Keywords:** Lichen planus; polymorphism; GSTM1; GSTT1; GSTP1

### INTRODUCTION

Lichen planus (LP) is a rather common, inflammatory and chronic immune-mediated disease of the skin and mucous membranes that affects mainly middle-aged adults in both sexes. The worldwide prevalence of the disease ranges from 0.22% to 5%. Lichen planus may affect the oral cavity (oral lichen planus), skin (cutaneous lichen planus), nails, esophagus, genitalia (penile or vulvar lichen planus) or scalp (lichen planopilaris). Cutaneous LP is characterized by itchy, purple polygonal papules, which are often localized in the flexor regions of the limbs, and the lesions frequently tend to be bilateral and relatively symmetric. The oral LP lesions may be isolated or accompanied by the cutaneous or

other mucosal findings including eyes, gastrointestinal tract and genital area [1-3].

The exact etiology of LP is unknown. Since T-cell activation has the main function in the pathogenesis of the LP, it is considered a T-cell mediated autoimmune disease. The cytotoxic T and T helper lymphocytes, natural killer and dendritic cells are inflammatory cells involved in the LP progression. Cytotoxic T-cell infiltration into the deeper layers of epidermis and at the dermal-epidermal junctions causes the activation of complex MHC antigens by keratinocytes. Following antigen recognition, activated cytotoxic T cells increase keratinocyte apoptosis and cause attraction of additional T helper cells by releasing of chemokines that are

pivotal regulators of cell migration. Previous studies showed the increased expressions of CXCL10, CXCL9 and CXCL11 chemokines at the lymphocyte infiltrated deeper layers of epidermis and dermal-epidermal junctions. Activated T helper cells can also induce additional activations of cytotoxic T cells and apoptosis of keratinocytes. Activated T lymphocytes and the inflammatory cells increased after the release of cytokines are characterized by band-like pattern in the dermal-epidermal junctions and by the basal vacuolar degeneration [4, 5]. The role of genetic factors in LP has yet to be elucidated. Although the possibility of genetic predisposition in familial LP cases and LP in monozygotic twins has been reported previously [6, 7], further studies in different families are necessary to clear familial predisposition of LP and underlying mechanisms in the pathogenesis of LP. On the other hand, the oxidative stress and antioxidant defense mechanisms have been implicated in the pathogenesis of various inflammatory skin diseases, including atopic dermatitis, psoriasis, vitiligo, acne rosacea, and polymorphic light eruption disease [8-11]. The participation of increased reactive oxygen species (ROS) in the pathogenesis of LP, especially in oral LP has been investigated in many respects previously. Since releasing of cytokines by the activated T-cells leads to inflammatory cells attraction and increased keratinocytes apoptosis by the cell-mediated cytotoxicity, excessive ROS production may be the end result of cellular damages of various cells including keratinocytes, inflammatory cells, and fibroblasts through the antioxidant defense mechanisms [12-15].

Although the role of ROS in the pathogenesis of LP has been studied extensively [12, 16-18], the knowledge about the detoxification enzymes genotypes in LP susceptibility is unknown. Wu et al. investigated SNPs associated with myeloperoxidase (MPO) and cyclooxygenase (COX) genes of the cases with oral LP and they reported significant association between MPO polymorphism and oral LP risk in different sexes [19]. Glutathione-S-transferases (GSTs) refers to a group of detoxification enzymes that are pivotal components of the cellular defense against oxidative stress. The cytosolic GST enzymes are divided into at least seven classes, that are encoded by different gene families termed mu (GSTM), pi (GSTP), theta (GSTT), alpha (GSTA), sigma (GSTS), omega (GSTO), and zeta (GSTZ). The expressions of these GST

isoenzymes are tissue-specific and the expression levels of them vary according to the GST isoenzyme genotypes. GST isoforms have been shown to be polymorphic and usually resulting in interindividual differences in related enzyme activities. The expressions of GST isoforms have been shown in human skin [20-23]. However, the association between the GST isoform genotypes and LP susceptibility has not been reported yet. In the present study, we aimed to investigate the relationship between GSTM1, GSST1 and GSTP1 antioxidant genes polymorphisms and LP susceptibility.

## MATERIALS AND METHODS

The study protocol and procedure were approved by the Institutional Ethics Review Committee, and all the procedures pertaining to the study were conducted in accordance with the Declaration of Helsinki, local laws and regulations. After explaining the aim of the study, written informed consent was obtained from each patient.

### Subjects (Patients and Controls)

This study included 55 Turkish patients (17 males 30.9%, 38 females 69.1%). Their age ranged from 22 to 70 years, and the mean age was  $49.55 \pm 13.19$  years (**Table1**). The localizations of the disease were in mucosa (13 cases), skin (28 cases), and scalp (2 cases). The remaining 12 cases had combined lesions in both mucosa and skin. The patients with a history of i) familial LP pedigree, ii) other inflammatory and chronic immune-mediated diseases, iii) pregnancy, iv) medications, and/or operative treatment were excluded. In addition, an age- and sex- matched control group consisted of 98 individuals (30 males; 30.6% and 68 females; 69.4%) with a mean age of  $49.53 \pm 12.9$  years. The inclusion criteria for the control group were i) no evidence of personal or family history of any inflammatory and chronic immune-mediated disease ii) no pregnancy, iii) no history of medications and/or surgery, iv) the same ethnical origin with the LP patients, v) having non-consanguineous parents. All patients and controls were collected from the Dermatology Department of the Eskisehir Osmangazi University Hospital, Turkey. Of the 55 LP patients, 17 had only topical treatments, whereas 30 had combined topical and systemic treatments, and 6 had combined topical, systemic, and phototherapy treatments. Of the remaining 2 patients, 1 had systemic and phototherapy, and the other had topical and phototherapy treatments.

**Table1.** Biological and clinical characteristics of the patients with LP

Characteristics	LP patients (N=55)	Controls (N=98)
Female/Male Ratio, n	2.24	2.26
Age mean, SD (years)	49.55±13.19 (22-70 y)	49.53±12.9 (22-70y)
<b>LP Localizations</b>		
Mucosa	13	
Skin	28	
Scalp	2	
Mucosa+Skin	12	
Duration of treatment (months) (mean±SD)(range)	29.89±18.16 (1-144 m)	
<b>Treatment type</b>		
Topical	17	
Systemic	-	
Phototherapy	-	
Combined topical+systemic	30	
Combined systemic+phototherapy	1	
Combined topical+phototherapy	1	
Combined topical+systemic+phototherapy	6	

### Genotyping

Genomic DNA was isolated from peripheral blood samples with a Vivantis DNA Blood Extraction Kit (Vivantis technology, USA), according to the manufacture's recommendations and DNA was stored at -20 °C. The average genomic DNA concentration was measured with NanoDrop 2000 (Thermo Scientific, Wilmington, DE, USA). The presence or absence of GSTT1 and GSTM1 genes in genomic DNA samples of the patients and controls were analyzed simultaneously in the same tube by the multiplex PCR method. The GSTP1 polymorphism was determined with a polymerase chain reaction-restriction fragment length polymorphism assay [PCR-RFLP].

### GSTT1 and GSTM1 genes

The analysis of the GSTT1 and GSTM1 genes was conducted using a multiplex PCR method with the ubiquitous  $\beta$ -globin gene as an internal control. Briefly, PCR was carried out in a final volume of 25  $\mu$ L containing 10  $\mu$ L genomic DNA template, 5  $\mu$ L of 10X PCR buffer A (Vivantis technology, USA), 2  $\mu$ L of 50 mM MgCl<sub>2</sub> (Vivantis technology, USA), 10 nM of each primer, 0.5  $\mu$ L of 10 $\mu$ M dNTPs (Vivantis technology, USA), and 0.5  $\mu$ L of 5 U Taq polymerase enzyme (Vivantis technology, USA). The primer sequences for the GSTT1 forward and reverse primers were 5'-TTC CTT ACT GGT CCT CAC ATC TC-3' and 5'-TCA CCG GAT CAT GGC CAG CA-3', respectively. The primers of GSTM1 were 5'-GAA CTC CCT GAA AAG CTA AAG C-3'

and 5'- GTT GGG CTC AAA TAT ACG GTG G-3'.

The DNA was initially denatured at 94 °C for 2 min prior to amplification. PCR amplification was accomplished using 35 cycles, consisting of 30 sec denaturation at 94 °C, 30 sec of annealing at 55 °C and 1 min of extension at 72 °C and the final extension cycle at 72 °C for 7 min. The PCR fragments of GSTT1 and GSTM1 were separated by 3% agarose gel electrophoresis stained with ethidium bromide (250ng/ml). The presence or absence of the GSTT1 (480-bp) and GSTM1 (215-bp) amplicons was determined in the presence of the control  $\beta$ -globin gene (268 bp) primers (forward 5'- CAA CTT CAT CCA CGT TCA CC-3' and reverse 5'-GAA GAG CCA AGG ACA GGT AC-3') [11].

### GSTP1 gene

In the GSTP1 gene, an A to G polymorphism at the nucleotide 313 in exon 5 leads to an amino acid substitution (*Ile105Val*) at 105 amino acid position. This residue lied in the substrate-binding site of the enzyme and the polymorphism has been shown to affect enzyme activity. The modified PCR-RFLP method was used to determine the allele distribution for GSTP1 gene in the patients and controls. The primer sequences for the GSTP1 forward and reverse primers were 5'-GGT GGA CAT GGT GAA TGA C-3' and 5'-GAT GCT CAC ATA GTT GGT GGT AG-3', respectively. The PCR product was digested with the restriction endonuclease HpyCH4IV enzyme (BiolabsInc NEB, New England) and then incubated at 37

°C for 16 h. The digested PCR products were separated by 4% agarose gel electrophoresis stained with ethidium bromide and visualized on an UV transilluminator with 50 base pair DNA ladder to assess the size of the PCR-RFLP products. The GSTP1 products after HpyCH4IV digestion were separated into two fragments: at 176bp indicates the wild type (*Ile/Ile*), the presence of two fragments at 66bp and 91bp indicates homozygous mutant type (*Val/Val*) and the presence of two fragments at 91bp and 176bp indicates the heterozygous mutant type (*Ile/Val*)

### Statistical Analysis

The statistical analyses were performed by using IBM SPSS 21 package programme. The Shapiro Wilk test was applied to determine normality of continuous variables distribution. Descriptive statistics of continuous variables were given as mean $\pm$ SD. For the summary representation that did not meet the normal distribution of the quantitative variables, the median (Q1-Q3) were given. Because the normal distribution

assumption could not be met, the Mann Whitney U test was used in the comparison of two independent groups and Kruskal Wallis H test in the comparison among three or more groups. In this study, the qualitative variables were given as frequency and percentage. Fisher Exact test and Pearson Chi-Square test were used to analyze the relationship between qualitative variables that have two categories and more than two categories, respectively. Odds ratio (OR) and confidence intervals (CI) were used to analyze the frequency of occurrence of GST genotypes in patients with LP comparing with the control group. A p-value less than 0.05 was considered as statistically significant.

### RESULTS

In this study, we examined deletion polymorphisms of the GSTM1/GSTT1 genes and p.Ile105Val polymorphism of the GSTP1 gene. The allelic and genotypic distributions of these three polymorphisms in LP patients and controls are given in **Table 2**.

**Table2.** The distribution of glutathione S-transferase genotype polymorphisms in the patient and control groups.

Genotype	LP (N=55) N(%)	Control (N=98) N(%)	OR	95% CI	P
GSTP1					
Ile/Ile	2 (3.64)	15 (15.31)	1	-	<0.05
Val/Val	7(12.72)	0 (0)	-	-	<0.001
Ile/Val	46(83.64)	83(84.69)	4.157	(0.910-18.981)	
GSTM1					
Present	50(90.9)	98(100)	-	-	<0.01
Null	5 (9.1)	0(0.0)	-	-	
GSTT1					
Present	42 (76.4)	98(100)	-	-	<0.001
Null	13(23.6)	0 (0.0)	-	-	

The GSTT1 gene genotyping and association analysis were performed in 153 individuals. The GSTT1 gene deletion was only seen in the patients with LP. No gene deletion was revealed in the control group. The overall frequency of GSTT1 gene deletion in all participants (N=153) was 8.5% and it was 23% in the patients group. The difference was statistically significant ( $p<0.001$ ).

When the frequencies of GSTM1 gene deletions in the patient and control groups were compared, the gene deletion could not be determined in control individuals, it was only seen in five patients with LP (8.93%). The overall frequency of GSTM1 gene deletion in 153 participants was 3.27%. The difference between patients and controls was statistically significant ( $p<0.01$ ).

The GSTP1 genotyping and association studies was performed in 153 participants. The genotyping classification in both controls and patients was as follows: wild type *Ile/Ile*, homozygous mutant *Val/Val* and heterozygous mutant *Ile/Val*. The GSTP1 wild type *Ile/Ile* genotype was revealed in 15 individuals (15.3%) in the control group whereas the wild type genotype frequency in the patients with LP was 3.6% ( $<0.05$ ). The GSTP1 gene *Val/Val* homozygous mutant genotype could not be seen in the control group but seven patients (12.5%) with LP ( $<0.001$ ). The heterozygous *Ile/Val* genotype frequency in the control group was 84.7% and it was 83.6% in the patients group.

When we used AA (*Ile/Ile*) wild type genotype as the reference and compared the patient and control groups in respect to GSTP1 allele



distributions, the GG (Val/Val) genotype was associated with a higher risk of LP ( $p < 0.001$ ). The combination of the genotypes with mutant G allele (AG + GG) was higher in the patient group than the control group ( $p < 0.05$ , OR

$= 4.88$ , 95%CI = 1.07-22.19 ). Contrary to the G allele, the frequency of A allele was higher in the control group compared to the patient group ( $p < 0.05$ ) (Table 3).

**Table3.** GSTP1 allele distributions in the patient and control groups.

Variable			OR	P	95 % CI
	Patients (N=55) N (%)	Controls (N=98) N (%)			
GSTP1				$< 0.001^{***}$	
AA (reference genotype)	2 (11.8)	15 (88.2)	1		
GG	7 (100)	0 (0)	-		
AG	46 (35.7)	83 (64.3)	4.157		0.910-18.981
TOTAL	55 (35.9)	98 (64.1%)			
AG+GG	53	83	4.88	$< 0.05$	1.07-22.19
AA+AG	48	98		$< 0.05$	

We could not find a significant association between the GST genotypes (P1, M1 and T1), and sex ( $P = 0.28$ ,  $0.53$  and  $0.74$ , respectively), and duration of treatment ( $P = 0.12$ ,  $0.39$  and  $0.439$ , respectively). We also compared the treatment types of the patients with their GST genotypes to determine whether specific GST polymorphisms play important roles in responses of the patients to specific treatments. There was no significant relation in the patients with GSTM1 ( $P = 0.797$ ) and GSTP1 ( $P = 0.436$ ) polymorphisms, but statistically significant ( $P = 0.030$ ) association was detected in the patients with GSTT1 deletions. Of 13 patients with GSTT1 null genotypes, 5 received combined topical+systemic+phototherapy and 8 combined topical+systemic treatments.

## DISCUSSION

It is well known that skin is a major target of oxidative stress due to overproduction of ROS, and recent studies have reported an increased oxidative stress and lipid peroxidation in patients with LP [24]. The production of ROS is not only a normal product of cellular metabolism, but also various environmental stresses lead to overproduction of ROS that are involved in progressive oxidative damage and cell death. Whether oxidative damage of ROS to the tissues depends on the activities of nonenzymatic and enzymatic antioxidant defence mechanisms that are present in the tissues for scavenging excessive ROS. GST supergene family is a group of phase II xenobiotic bio-transforming enzymes that have essential components for the purpose of detoxification. They are pivotal components of the cellular defense against oxidative stress. Therefore, the lack of functional GST enzymes

could increase ROS-mediated oxidative stress. Since the participation of increased oxidative stress in the pathogenesis of LP have been reported previously, the lack of functional GST enzymes may be a risk factor for LP development [25]. Aly & Shahin [12] has recently pointed out the importance of increasing oxidative stress and an imbalance in the antioxidant defense mechanisms in the pathogenesis of LP. Therefore we investigated the relation of three different functional antioxidant genes polymorphisms (GSTM1, GSTT1 and GSTP1) with LP. To the best of our knowledge, this is the first trial to show this relationship.

Of the GSTs, GSTM1 and GSTP1 metabolize large hydrophobic electrophiles, whereas GSTT1 is involved in the metabolism of smaller compounds. The GSTM1 and GSTT1 null genotypes result in enzyme inactivation. Moreover, the A/G single nucleotide polymorphism (SNP) for GSTP1 results in an isoleucine to valine amino acid change at codon 105 (Ile105Val). The valine allele is associated with a lower conjugating activity than the isoleucine allele [26]. Therefore, valine amino acid change has been suggested to cause diminished enzyme activities [27].

The evidences indicate that the imbalance between antioxidation of skin and oxidative stress may be a pathogenic factor of skin diseases [28, 29]. Besides, Mc Carty et al. have showed that GSTT1 homozygous wildtype and GSTP1 GG genotypes were significantly associated with increased risk of skin lesions [30]. Yazici et al. have also demonstrated a significant association between the GSTT1 and/or GSTM1 null genotypes and rosacea [31].

Recently, in the meta-analysis by Lu et al. [32], they have suggested a potential association between the GSTM1 null and GSTM1/T1 null/present polymorphisms and increased vitiligo risk.

In this study, the results showed that GG (Val/Val) genotype was associated with a higher risk of LP ( $p < 0.001$ ) for GSTP1 gene. The frequency of the genotype with G (AG + GG) was higher in the patient group than the control group ( $p < 0.05$ , OR = 4.88). Because GSTP1 SNP in the gene (*p.Ile105Val*) leads to a partial or complete loss of enzyme activity, diminished enzyme activity may be associated with LP susceptibility. In this study G allele frequency was higher in the patient group ( $p < 0.05$ ), but reference A allele was predominantly seen in the control group.

Similarly we detected significant differences in the deletions of GSTM1 and GSTT1 genes between the patient and control groups ( $P < 0.01$ ,  $P < 0.001$ ), respectively. Loss of activity for these enzymes may also lead to diminished antioxidant defense mechanism and increased the LP susceptibility.

We found that the GSTT1 deletions were more predominant—in the patients who had been treated with combined treatments. It is well-known that management of LP depends on the location and severity of the disease. If this significant difference may not be due to chance, the detection of GSTT1 null-genotypes in the patients where the course of the disease is severe may be an important marker for the clinicians. Recently, the advantageous use of antioxidant therapy has been reported in the patients with oral LP and they suggested that antioxidants may be alternative approaches when the patients are resistant to the standard treatment protocols [33-35]. The limitation of our study is the small sample size. The investigations performed in larger patient populations would be eligible for meaningful results, especially in the subgroups of patients with mutated GST genotypes. To the best of our knowledge, our study is the first study investigating the role of GSTs polymorphisms in LP. Therefore, we could not compare the results with those from other published studies, and from other ethnic groups.

In conclusion, this study showed that GSTM1 and GSTT1 null genotypes and from A to G transition in the 105th position of GSTP1 may play an important role in the physiopathology of LP. Further studies in larger series and from

different ethnic groups may further enlighten the pathogenesis of LP. Moreover, the relation between the GSTT1 polymorphism and the response of the patients to the treatment protocols should be evaluated in detail in the use of new approaches including antioxidant mechanisms in the unresponsive cases to the standard protocols.

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All the authors have full control of all primary data and agree to allow International Journal of Research Studies in Medical and Health Sciences to review their data upon request

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