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Glutathione S-Transferase M1 and T1 Gene Polymorphisms in Patients with Chronic Plaque-Type Psoriasis: A Case-Control Study

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Key Words
Gene polymorphisms · Glutathione S-transferase · Psoriasis

Abstract
Objective: To determine the role of glutathione S-transferase (GST) isoenzyme polymorphisms as susceptibility factors in patients with psoriasis in a Turkish cohort. ***Subjects and Methods:*** In this case-control study, 105 patients with plaque-type psoriasis and 102 healthy controls were recruited from the dermatology outpatient clinics of two university hospitals. Genomic DNA was extracted from whole blood using a DZ DNA isolation kit. Multiplex PCR was used to determine *GSTM1* and *GSTT1* polymorphisms in the isolated DNAs. ***Results:*** Of the 150 patients with psoriasis, 83 (79%) were identified with the GSTT1 genotype and 22 (21%) with the *null* genotype. Of the 102 patients in the control group, 69 (67.6%) subjects were identified with the GSTT1 genotype and 33 (32.4%) with the *null* genotype. There was no significant difference between the patient and control groups (p = 0.063). Regarding the *GSTM1* polymorphism, 54 (51.4%) patients were identified with this genotype and 51 (48.6%) with the *null* genotype; in the control group, 50 (49%) were identified with this genotype and 52 (51%) with the *null* genotype. Again there was no statistically significant difference between the groups (p = 0.957). ***Conclusion:*** In this Turkish cohort of patients with psoriasis, neither *GSTT1* nor *GSTM1* polymorphisms were associated with disease susceptibility. Larger studies with a wider range of GST isoenzyme are needed.

Introduction

Psoriasis is a chronic inflammatory and proliferative skin disease with an incompletely understood etiology [1]. The pathogenic role of increased oxidative stress and resulting inflammation has been emphasized in psoriasis, and increased oxidative stress has also been ascribed a role as a major contributor to the heightened cardiovascular disease burden in psoriasis [2]. Glutathione S-transferases (GST) are a multigene family of enzymes. These enzymes are involved in the protection against inflammation, mutagenicity and genotoxicity as a result of oxidative stress [3]. GST enzymes are involved in the synthesis of inflammatory mediators, leukotrienes and prostaglandins, and also act in cell signaling as potential regulators

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of apoptosis [4]. Cytosolic human GST exhibits genetic polymorphisms, and this variation can increase susceptibility to carcinogenesis and inflammatory diseases [4, 5]. Polymorphisms of specific subtypes of this enzyme family may lead to an imbalance in pro- and antioxidant systems with ensuing increased production of reactive oxygen species [6]. GST isoenzymes, including but not limited to *GSTM1* and *GSTT1*, were shown to be polymorphically distributed in the population [5]. Presence of *null* genotypes of these enzymes was associated with increased susceptibility to a number of disorders, including colorectal cancer, Behçet disease and some autoimmune diseases such as type 1 diabetes and vitiligo [4, 6–8].

None of the few studies on GST polymorphisms in patients with psoriasis [9, 10] investigated GST polymorphisms as a susceptibility factor for psoriasis using a case-control study design. Thus, the aim of the present study was to investigate *GSTT1* and *GSTM1* polymorphisms in patients with chronic plaque psoriasis as a susceptibility factor for disease development.

Subjects and Methods

Study Design and Participants

This case-control study included 105 patients with psoriasis followed in the departments of dermatology of the university hospitals of Sakarya and Düzce from December 2012 to May 2014. All the patients had been diagnosed with chronic plaque psoriasis clinically and/or histopathologically. Of the 105 psoriasis patients (65 females and 40 males) enrolled in this study; 24 had a first-degree relative with psoriasis and 31 patients were smokers. Weight and height of all the participants were measured and body mass index (BMI) was calculated as weight (kg) divided by height (m^2) for all subjects. Exclusion criteria were diseases which may influence the frequency of GST gene polymorphisms such as diabetes mellitus, cancer or active infection. Patients with a dermatologic disease other than psoriasis were also excluded from the study. Systemically and dermatologically healthy individuals (62 females and 40 males) with no personal or familial history of psoriasis served as the control group. All of the patients and controls were ethnically of Turkish origin. The study protocol was approved by the Institutional Ethics Committee of Düzce University. All subjects gave written informed consent before enrolling in the study. The study was conducted according to the principles of the Declaration of Helsinki.

Extraction of DNA and MBL2 Genotyping

Venous blood samples were drawn from the patients and controls into EDTA tubes. Genomic DNA was extracted from whole blood using a DZ DNA isolation kit (Dr. Zeydanlı Life Sciences Ltd., Ankara, Turkey) according to the manufacturer's instructions, and samples were stored at –20°C until PCR analysis.

Multiplex PCR was used to determine *GSTM1* and *GSTT1* polymorphisms in the isolated DNAs. The following primers were used – *GSTT1* polymorphism forward 5′-TTCCTTACTGGTCCTCACATCTC-3′ and reverse 5′-TCACCGGATCATGGCCAGCA-3′, and *GSTM1* polymorphism forward 5′-GAACTCCCTGAAAAGCTAAAGC-3′ and reverse 5′-GTTGGGCTCAAATATACGGTGG-3′, and albumin forward 5′-GCCCTCTGCTAACAAGTCCTAC-3′ and reverse 5′-GCCCTAAAAAGAAAATCCCCAATC-3 as an internal control; albumin (350 bp), GSTM1 (219 bp) and GSTT1(459 bp) PCR products were formed. PCR was performed as follows: first denaturation for 5 min at 94°C, then 35 cycles for 1 min at 94°C (denaturation), 1 min at 58°C (annealing), 1 min at 72°C (elongation) and finally 10 min at 72°C (final elongation). Genotypes were determined by migration of the products in agarose gel supplemented with 2% ethidium bromide.

Table 1. GSTT1 and GSTM1 genotype distribution among psoriasis patients and controls

	Patient group (n = 105)	Control group (n = 102)	p value
GSTT1 gene polymorphism			
T1 present genotype	83 (79.00%)	69 (67.60%)	0.063
T1 null genotype	22 (21.00%)	33 (32.40%)	
GSTM1 gene polymorphism			
M1 present genotype	54 (51.40%)	50 (49%)	0.729
M1 null genotype	51 (48.60%)	52 (51%)	

Statistical Analysis

Independent-sample t test and Pearson's χ^2 test were performed for comparisons between the groups. Statistical analysis was done using SPSS v. 20; the level of significance was set at $\alpha = 0.05$.

Results

The mean age (mean ± SD) of the patients with psoriasis was 44.5 ±13.2 years (range 20–77), and that of the controls was 45.0 ± 8.8 years (range 24–74; p = 0.733). The mean BMI of psoriasis patients was 26.3 ± 4.2 (range: 15.8–37.3).

Regarding the *GSTT1* polymorphism, 83 (79%) of the 105 patients with psoriasis were identified with this genotype and 22 (21%) with the *null* genotype. Among the 102 subjects in the control group, 69 (67.6%) were identified with the *present* genotype and 33 (32.4%) with the *null* genotype. Statistical analyses of genotypes showed no significant difference (p = 0.063; table 1).

Regarding the *GSTM1* polymorphism in the study, 54 (51.4%) of the 105 psoriasis patients were identified with the *present* genotype, whereas 51 (48.6%) had the *null*

genotype. Among the 102 subjects in the control group, 50 (49%) were identified with the *present* genotype and 52 (51%) with the *null* genotype. Statistical analyses of genotypes showed no significant difference ($p = 0.957$).

Discussion

Our results showed no association between *GSTM1* and *GSTT1 null* genotypes regarding the development of psoriasis in patients with Turkish ethnicity. This result seems counterintuitive considering the putative role of increased oxidative stress in the pathophysiology of psoriasis [2]. However, some factors could be responsible for this lack of association. First, much larger sample sizes may be needed to detect subtle differences between patients and healthy controls of the same ethnic origin. Second, distinct ethnic groups may have different prevalence rates of isoenzymes compared with other ethnicities [9]. Moreover, since GST is a multigene family, one or two single polymorphisms and null genotype expression may not be sufficient to alter the overall enzymatic and antioxidant capacity per se. Thus, studies investigating more isoenzymes in the same cohort could be more valuable to determine disease susceptibility due to GST gene polymorphisms.

Normally, skin has some defense mechanisms against reactive oxygen species which are produced following exposure to UV radiation and other environmental stresses [11]. The antioxidant system of the skin is comprised of a network of enzymatic and nonenzymatic components; glutathione peroxidase, catalase, superoxide dismutase and GST are among the enzymatic antioxidants [11]. The GST isoenzymes *GSTM1*, *GSTM3*, *GSTT1*, *GSTP1* and *GSTZ1* have been shown to be polymorphically distributed [5]. Prevalences of up to 20 and 50% were reported for *GSTT1* and *GSTM1* gene deletions, respectively, in the Caucasian population [9]. Our results were in agreement with the latter findings.

Polymorphisms of GST isoenzymes were studied in various disease states, and *null* gene expression was implicated as a susceptibility factor for particular diseases [7, 12, 13]. However, GST isoenzyme polymorphisms were also studied in a number of dermatologic diseases to be able to account for increased disease susceptibility with regard to null enzyme expression [6, 8, 14, 15].

A number of studies found that increased oxidative stress might play a role in the pathophysiology of psoriasis [2, 16, 17]. It is thought that the majority of the GST activity in psoriatic skin is due to a pi-class isoenzyme, and pi-class GST may represent an index for hyperproliferation [18]. In a study by Gambichler et al. [19], GSTT1 geno- and phenotyping was investigated in psoriasis patients treated with fumaric acid esters, and results were compared with a control group. They showed that GSTT1 geno- and phenotypes were significantly correlated in psoriasis patients but did not substantially differ from healthy controls. The authors concluded that fumaric acid esters may enhance GSTT1 enzyme activity in high and low conjugators [19]. In a mixed cohort of patients of whom some were psoriasis patients, Ibbotson et al. [10] reported that in a psoriatic subset of patients, *GSTM1* genotype was not associated with outcome of psoralen-ultraviolet A photochemotherapy, whereas minimal phototoxic doses and *GSTM1 null* and *GSTP1b* genotypes were associated with clearance of psoriasis. Similarly, Smith et al. [9] showed that the *GSTM1* genotype, but not the *GSTT1* or *MC1R* genotype, influences erythemal sensitivity to phototherapy in adult Caucasian patients with psoriasis. We did not specifically look at the effects of the studied genotypes on the efficacy of the treatment modalities in psoriatic patients.

Only in the study by Yang et al. [20] in a Chinese population, microsomal GST2 gene polymorphism was evaluated by means of single nucleotide polymorphisms. They found that genetic analysis of microsomal GST2 gene common variants did not show any supporting evidence for this polymorphism to be a susceptibility gene for the development of psoriasis in this Chinese sample.

Conclusion

Our results showed that prevalence rates of *GSTT1* and *GSTM1* polymorphisms in patients with chronic plaque-type psoriasis were not different from healthy control subjects in this Turkish cohort. Future studies with larger sample sizes and a wider range of GST gene polymorphisms are needed to determine disease susceptibility factors in psoriasis.

Disclosure Statement

No conflict of interest.

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