Original Article

Polymorphism of glutathione S-transferase M1 and T1 genes and susceptibility to psoriasis disease: A study from North India

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Abstract

Background: Increased oxidative stress and resulting inflammation has been emphasized as a factor in the pathogenesis of many diseases including psoriasis. Glutathione S-transferases (GSTs) protect against oxidative stress, inflammation, and genotoxicity. Polymorphisms in the GST genes may lead to an imbalance in pro- and antioxidant systems resulting in the increased production of reactive oxygen species that could influence the pathogenesis of psoriasis.

Aim: The aim of this study was to investigate the association between GSTs (*GSTM1* and *GSTT1*) gene polymorphism in patients with chronic plaque psoriasis as a factor in the susceptibility and development of psoriasis.

Materials and Methods: We assessed 128 patients with psoriasis and 250 age- and sex-matched healthy controls. Genomic DNA was extracted from peripheral blood by the phenol chloroform method. The null *GSTT1* and *GSTM1* genotypes were identified by multiplex polymerase chain reaction (PCR) method.

Results: The null genotype of *GSTM1* and *GSTT1* was seen in 45.3% and 40.6% in psoriasis patients whereas in the controls it was 34.4% and 20.0%, respectively. A significant association was seen between the null alleles of the *GSTT1* (OR = 2.74) and *GSTM1* (OR = 1.58) alone or in combination with tobacco use ($P < 0.001$) and psoriasis risk. The presence of both null genotypes of *GSTM1* and *GSTT1* further increased the risk of psoriasis (OR = 3.52) when compared with the positive genotypes of *GSTM1* and *GSTT1*.

Limitations: A major limitation of this study was the small sample size. A large epidemiological study is necessary to confirm these findings.

Conclusions: The null genotype of *GSTT1* is a strong predisposing factor for psoriasis in North India.

Key words: Gene-environmental interaction, glutathione S-transferases, polymorphism, psoriasis

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Introduction

Psoriasis is a chronic, inflammatory, hyper-proliferative cutaneous disorder affecting 2–3% of the world population.[1] Although the exact pathogenesis of psoriasis is still unclear, there is evidence that oxidative stress, genetic predisposition, infections, physical trauma, medications, and environmental factors may influence psoriasis either individually or in concert.[2-8] Environmental toxins such as polycyclic aromatic hydrocarbons (PAHs) and hydroxylated metabolites of benzo (a) pyrene (xenobiotics) may influence the development of psoriasis. These chemicals can generate reactive oxygen species leading to oxidative damage of skin cells.[4,5,8-10] Between 20–90% of the variability in disposition of xenobiotics has been attributed to genetic factors.[3,7] The genotype-specific form of drug metabolizing enzymes play an important role in the biotransformation of endogenous or exogenous compounds and might be associated in psoriasis.[4,5,8,9,11,12]

Published data suggest that increased activity of antioxidant enzymes have synergistic effects in the reduction of oxidative damage and have role in cell protection.[13-16] Metabolism of xenobiotics

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involves bioactivation by phase I enzymes (cytochrome p450s) resulting in the production of metabolites that may react with DNA. Phase II enzymes such as glutathione S-transferases (GSTs), are involved in the detoxification process of xenobiotics. GSTs are a family of related isozymes that catalyze the conjugation of reduced glutathione to a wide range of electrophilic substrates and protect against oxidative stress, inflammation, mutagenicity and genotoxicity.[17] Polymorphisms of specific subtypes of GST enzymes might lead to an imbalance in the pro- and antioxidant system. The most extensively studied polymorphisms are the *GSTM1* null, *GSTT1* null, and the *GSTP1313* A/G substitution that are linked to decreased conjugation of biologically active xenobiotic metabolites. The functional consequences of the *GSTM1* and the *GSTT1* null genotype frequencies vary according to nationality and ethnicity.[18,19]

Recent studies have shown that the presence of null genotypes of *GSTM1* and *GSTT1* enzymes are associated with increased susceptibility to several diseases including psoriasis and vitiligo.[20-24] Although some studies of *GSTM1* and *GSTT1* gene polymorphism and susceptibility to psoriasis have been reported,[9,22,25,26] there are no reports from India. The current study was undertaken to ascertain whether high-risk alleles of *GSTM1*/*GSTT1* could influence the susceptibility to psoriasis in the North Indian population. We also aimed to assess whether these alleles could affect the grade and duration of psoriasis, and their relationship with tobacco-use.

Materials and Methods

Subjects

Approval for the study was obtained from the institutional review board. The study group consisted of 128 psoriasis patients with a mean age 41.9 years (SE 1.48), and 250 age and sex-matched normal healthy individuals as controls with a mean age of 42.9 years (SE 0.57). The ethnic origin of the cases and controls were similar. Patients were selected based on the basis of a questionnaire administered in the Outpatient Department (OPD) of the Department Of Skin and VD, Pt. B.D. Sharma PGIMS, Rohtak, that included medical records, family history of disease, gender, and history of consumption of tobacco in any form (cigarette/bidi smoking, chewing tobacco in beetle leaf, pan masala/gutka, etc.). Only patients with uncomplicated chronic plaque psoriasis were selected. Psoriasis patients with associated conditions such as diabetes, bronchial asthma, cancer, or any other diseases were excluded from the study. Consent from the participants was obtained after explaining the aims of the study, and age- and sex-matched healthy individuals were selected as controls. The inclusion criteria for controls were the absence of any prior history of psoriasis lesions.

DNA extraction and genotyping

Five ml of blood was collected in EDTA vials from controls and patients. Genomic DNA was extracted from blood lymphocytes using the proteinase K and phenol chloroform extraction procedure.[27] The multiplex PCR method was used to detect the presence or absence of *GSTT1* and *GSTM1* genes in the genomic DNA samples, simultaneously in the same tube, as described previously.[28] Electrophoreses of PCR products were done in 2% agarose gels and visualized by ethidium bromide staining. DNA from samples positive for *GSTM1* and *GSTT1* genotypes yielded bands of 215 bp and 480 bp whereas internal positive control (*CYP1A1*) PCR product corresponded to 312 bp [Figure 1].

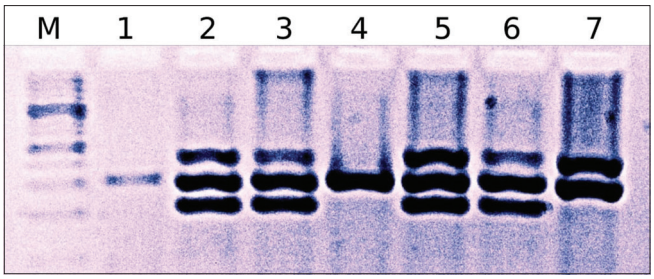

Figure 1: M-100 bp ladder; Lane 1 and 4: Glutathione S-transferase M1 and glutathione S-transferase T1 null; Lane 2, 3, 5, and 6: Glutathione S-transferase M1 and glutathione S-transferase T1 positive, and in Lane 7: Glutathione S-transferase M1 null and glutathione S-transferase T1 positive

Statistical analysis

Statistical analysis was performed using SPSS software version 20.0 (Chicago). Descriptive measures such as mean and standard deviation were applied for normally distributed variables and *t*-test for comparison between groups. Binary logistic regression model (BLRM) assessed differences in genotype prevalence and association between cases and controls. Multivariate analysis, Chi-square test, correlation coefficient, odds ratio (OR), and its 95% confidence interval (CI) were used to describe the strength of association. A *P* value of <0.05 was considered to be statistically significant.

Results

During the course of the study, results of 5% of the samples were checked randomly. Data input and process was double tracked, adopting logic check. Table 1 presents the frequencies of *GSTM1* and *GSTT1* genotypes by case-control status for psoriasis risk. Of the 128 patients with psoriasis, frequency distribution of null genotype of *GSTM1* and *GSTT1* was 45.3% and 40.6%, respectively while in the 250 control samples, the frequency of null genotype of *GSTM1* and *GSTT1* was 34.4% and 20.0%, respectively. We observed a significantly higher risk for psoriasis in patients with the null genotype of *GSTT1* (OR = 2.74; 95% CI = 1.71–4.38) and *GSTM1* (OR = 1.58; 95% CI = 1.02–2.44) as compared to controls [Table 1]. This association was stronger in patients with the null alleles of *GSTT1* ($P < 0.001$) as compared to *GSTM1* null genotypes ($P = 0.039$).

A combination of the two high-risk genotypes (null genotypes of *GSTM1*/*GSTT1*) was also compared to the non-risk genotypes (positive genotypes of *GSTM1*/*GSTT1*) for the risk of psoriasis [Table 2]. The OR for development of psoriasis in the two high-risk genotypes was 3.52-fold higher than the non-risk genotypes ($P < 0.001$).

The association between tobacco use and null genotypes of *GSTT1* and *GSTM1* in patients and controls is summarized in Table 3. Our data indicate that OR for null genotypes of *GSTM1* (OR = 3.14) and *GSTT1* (OR = 4.71) was higher in tobacco users as compared to positive genotypes of nonusers ($P < 0.001$).

The association between gender and changes in null genotypes of *GSTM1* and *GSTT1* in patients and controls is summarized in Table 4. We demonstrated a higher risk in females (3.5-fold) than that in males for *GSTT1* null genotypes for susceptibility to psoriasis (OR = 3.53; $P < 0.001$); however, OR for null genotypes of *GSTM1* was statistically nonsignificant ($P > 0.05$).

Table 1: Distribution of glutathione S-transferases genotypes in controls and psoriasis patients

Genotype	Controls (*n*=250), *n* (%)	Patients (*n*=128), *n* (%)	OR (95% CI)	*P*
GSTM1				
Present	164 (65.6)	70 (54.7)	1.0 (reference)	0.039
Null	86 (34.4)	58 (45.3)	1.58 (1.02-2.44)	
GSTT1				
Present	200 (80.0)	76 (59.4)	1.0 (reference)	<0.001
Null	50 (20.0)	52 (40.6)	2.74 (1.71-4.38)	

P<0.05 was considered significant for the study. *GSTM1*: Glutathione S-transferase M1, *GSTT1*:Glutathione S-transferases T1, CI: Confidence interval, OR: Age-adjusted odds ratio

Table 2: Combined distribution of glutathione S-transferase M1 and glutathione S-transferases T1 genotypes in controls and psoriasis patients

GSTM1 and *GSTT* genotypes	Controls (*n*=250), *n* (%)	Patients (*n*=128), *n* (%)	OR (95% CI)	*P*
Both present	131 (52.4)	47 (36.7)	1.0 (reference)	
GSTM1 null and *GSTT1* present	69 (27.6)	31 (24.2)	1.25 (0.73-2.14)	0.413
GSTM1 present and *GSTT1* null	31 (12.4)	26 (20.3)	2.34 (1.26-4.34)	0.006
Both null	19 (7.6)	24 (18.8)	3.52 (1.77-7.02)	<0.001

P<0.05 was considered significant for the study of gene-gene interaction. OR: Odds ratio, *GSTM1*:Glutathione S-transferase M1, *GSTT1*: Glutathione S-transferases T1, CI: Confidence interval

Table 3: Association between tobacco users and glutathione S-transferase M1, glutathione S-transferases T1 genotypes

Tobacco habit	Gene	Genotype	Controls (*n*=250), *n* (%)	Patients (*n*=128), *n* (%)	OR (95% CI)	*P*
Non-users	*GSTM1*	Present	127 (66.8)	46 (60.5)	1.0 (reference)	
		Null	63 (33.1)	30 (39.5)	1.31 (0.76-2.28)	0.329
Tobacco users		Present	38 (63.3)	27 (51.9)	1.96 (1.08-3.57)	0.025
		Null	22 (36.6)	25 (49.1)	3.14 (1.61-6.09)	<0.001
Non-users	*GSTT1*	Present	155 (81.6)	43 (56.7)	1.0 (reference)	
		Null	35 (18.4)	33 (43.3)	3.39 (1.90-6.09)	<0.001
Tobacco users		Present	47 (81.7)	35 (67.3)	2.68 (1.54-4.67)	<0.001
		Null	13 (21.6)	17 (32.7)	4.71 (2.12-10.46)	<0.001

Data represent frequency distribution among case and control and OR for psoriasis patients. OR: Age adjusted odds ratio, CI: Confidence interval, *GSTM1*: Glutathione S-transferase M1, *GSTT1*: Glutathione S-transferases T1

Table 4: Association between gender and glutathione S-transferase M1, glutathione S-transferases T1 genotypes for psoriasis risk

Gender	Gene	Genotype	Controls (*n*=250), *n*(%)	Patients (*n*=128), *n*(%)	OR (95% CI)	*P*
Male	*GSTM1*	Present	119 (65.4)	59 (55.7)	1.0 (reference)	0.102
		Null	63 (34.6)	47 (44.3)	1.51 (0.92-2.46)	
Female		Present	45 (66.2)	11 (50.0)	1.0 (reference)	0.176
		Null	23 (33.8)	11 (50.6)	1.96 (0.74-5.19)	
Male	*GSTT1*	Present	145 (79.7)	64 (60.4)	1.0 (reference)	<0.001
		Null	37 (20.3)	42 (39.6)	2.57 (1.31-4.37)	
Female		Present	55 (80.9)	12 (54.5)	1.0 (reference)	<0.001
		Null	13 (19.1)	10 (45.5)	3.53 (1.25-9.92)	

OR: Odds ratio, *GSTM1*: Glutathione S-transferase M1, *GSTT1*: Glutathione S-transferases T1, CI: Confidence interval

The body surface area affected by psoriasis (grade of disease) was categorized into three groups: <20%, 21–30%, and >30%. There was no correlation between GSTs genotypes and grade or duration of the disease ($P > 0.05$) with respect to initiation and progression of psoriasis [Charts 1-4].

Discussion

In the present study, we found a 34% frequency of null genotypes of *GSTM1*. This frequency is similar to that reported in African and Southern Asian populations. The 20% frequency observed for null alleles of *GSTT1* among healthy individuals also lies within the range reported in Caucasian, European, and South Asian populations [Table 5].[19,29-31]

Our study indicated that the null allele of *GSTT1* gene is associated with a 2.7-fold higher risk for psoriasis as compared to healthy controls, while the null allele of *GSTM1* gene is associated with a lower risk of 1.58 times. No association was observed between

Table 5: Worldwide comparative frequency of null genotypes of glutathione S-transferase M1 and glutathione S-transferases T1 in different ethnic population

Ethnic origin	Total number of sample for *GSTM1*	*GSTM1* null frequency (range in %)	Total number of sample for *GSTT1*	*GSTT1* null frequency (range in %)	Reference
North Indian	250	0.340 (34.0)	250	0.200 (20.0)	Present study
Indian	5500	0.302 (20-42)	5428	0.178 (12-35)	19,29,31 and present study
Southern Asian	6237	0.329 (20-46)	6195	0.182 (12-38)	29,30
Eastern and South Eastern Asian	10597	0.527 (42-65)	8765	0.463 (25-51)	29,30
European	15126	0.518 (46-58)	11,682	0.183 (10-26)	29,30
Caucasian	2714	0.529 (42-56)	1223	0.197 (12-27)	29,31
African	1291	0.326 (11-55)	1291	0.363 (26-47)	29

GSTM1: Glutathione S-transferase M1, *GSTT1*: Glutathione S-transferases T1

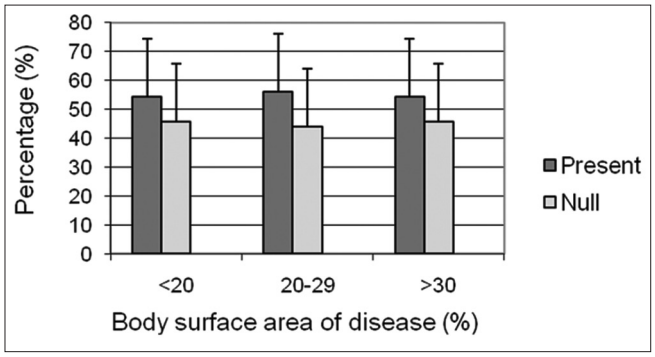

Chart 1: Association of *GSTM1* genotype with body surface area of disease. *P* value in between the strata of <20% and 20–30% = 0.892. *P* value in between the strata of <20% and >30% = 0.982

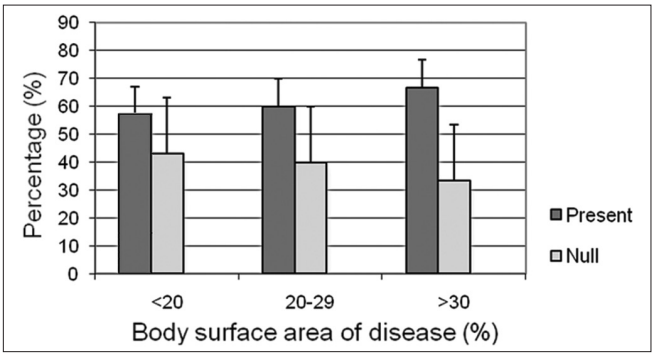

Chart 2: Association of *GSTT1* genotype with body surface area of disease. *P* value in between the strata of <20% and 20–30% = 0.791. *P* value in between the strata of <20% and >30% = 0.402

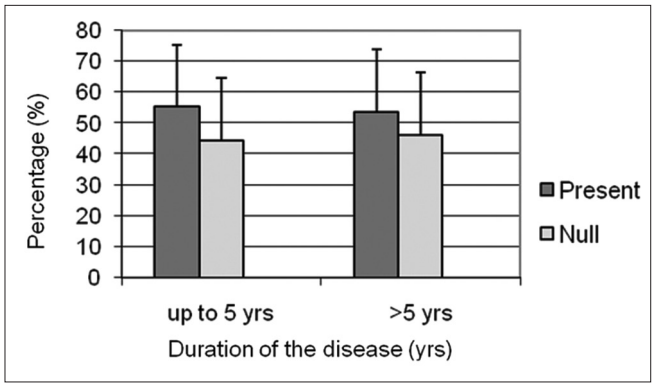

Chart 3: Association of *GSTM1* genotype with duration of the disease. *P* value in between the group = 0.850

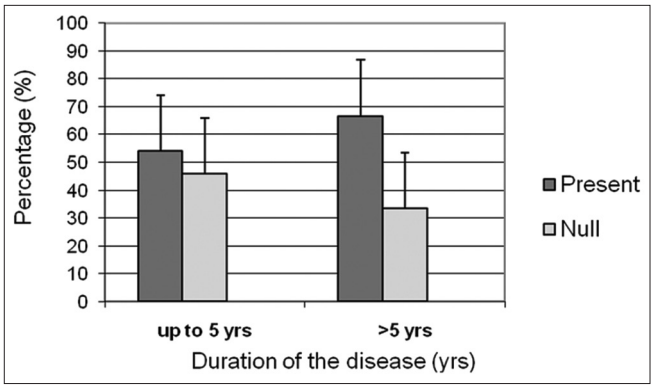

Chart 4: Association of *GSTT1* genotype with disease duration. *P* value in between the group = 0.154

GSTs genotypes and the grade or duration of psoriasis. Our findings are in accordance with published reports of the association of GST genes with a number of dermatologic diseases such as psoriasis,[22] solar keratoses,[23] vitiligo,[24] atopic dermatitis,[32] and Behçet's disease.[33] A pioneer study by Richter-Hintz *et al*. demonstrated that the null alleles of *GSTM1* significantly correlated with psoriasis, but not *GSTT1*.[11] However, a study by Solak *et al*. in a Turkish population showed no association between *GSTM1* and *GSTT1* null genotypes with chronic plaque psoriasis.[26] Smith *et al*. showed that the null genotype of *GSTM1* influences erythemal sensitivity to phototherapy in adult Caucasian patients with psoriasis but not the *GSTT1* genotypes.[22] Another study showed significant correlation with *GSTT1* geno- and phenotypes in psoriasis patients treated with fumaric acid esters but it was not substantially different from healthy controls.[34] Thus, the association of psoriasis risk with null alleles of *GSTM1* or *GSTT1* varies significantly among different populations.

Patients with both high-risk genotypes of *GSTM1* and *GSTT1* gene (*GSTM1* null and *GSTT1* null genotypes) had a 3.5-fold higher risk for psoriasis development compared to positive genotypes of *GSTM1* and *GSTT1* ($P < 0.001$, OR = 3.52). Studies have shown that patients with both null alleles of GSTT1/GSTM1 have a higher risk of diseases the urinary bladder,[21] skin,[35] head and neck cancer,[18] type 1 diabetes,[20] and vitiligo[24] when compared to patients with positive alleles of GSTM1/GSTT1 gene.

We also observed a significant association of psoriasis in tobacco users with null genotypes of *GSTT1* (OR = 4.71, $P < 0.001$)/ *GSTM1* (OR = 3.14, $P > 0.001$) in comparison to tobacco nonusers with positive genotypes. Tobacco smoke contains 10^{15}–10^{17} free radicals and other highly reactive electrophiles such as PAH and hydroxylated metabolites of benzo (a) pyrene and GSTs are instrumental in the elimination of these other toxic metabolites thus protecting cells from oxidative stress.[17] Inter-individual variability in the expression of the PAH and BaP metabolizing enzymes may be explained at least in part by genetic polymorphisms in the human genome. Published data suggest that psoriatic individuals with the null allele of *GSTM1* who smoke have higher PAH or hydroxylated benzo (a) pyrene genotoxicity and mutagenicity.[4,5,8,9,11]

Our data also showed a significant association ($P < 0.001$) of null genotypes of *GSTT1* in both males or females with psoriasis risk; however, no association was observed with gender and *GSTM1* null genotypes ($P > 0.05$). This suggests that females who possess null alleles of GSTT1 have higher risk (OR=3.53) for psoriasis as compared to males (OR=2.57) in north Indian population [Table 4]. This finding is consistent with previous reports in Indian and Chinese populations.[36,37]

GSTs are phase II xenobiotic metabolizing enzymes active in detoxifying a wide variety of potentially toxic electrophiles by conjugating with glutathione and metabolizing them.[2,3,5,8,9] A previous study purified and characterized the expression of glutathione transferase in psoriatic skin.[38] GST enzymes play a crucial role in cell protection against oxidative damage which is probably associated with psoriasis.[12-17] The association with null genotypes of GSTs observed in our study suggests that the inactive form of GSTs enzymes results in reduced detoxification of endogenous/or exogenous toxicants leading to the initiation and progression of psoriasis.

This is the first genetic study in the Indian population exploring the interaction between *GSTM1*/*GSTT1* genotype alone or in combination with tobacco use and susceptibility to psoriasis. To evaluate the interaction between genetic and environmental factors, adequately large sample size is needed. We have examined only two detoxifying genes and further study may be warranted to explore the involvement of other antioxidants and detoxification pathway genes that may be associated alone or in combined analysis in large epidemiological studies.

Conclusion

Our findings indicate that the null allele of *GSTM1*/*GSTT1* genotype alone or in combination with tobacco use are significantly associated with psoriasis risk; however, no association was observed between *GSTM1*/*GSTT1* genotypes and grade/or duration of the disease. Moreover, the presence of both high risk alleles of GST genotypes further augments the risk of psoriasis in the North Indian population.

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Dr. Daya Shankar Lal Srivastava and Professor V.K Jain conceived, designed, and conducted the study; they also wrote, and edited the manuscript. Dr. J.P. Yadav and Dr. P. Verma helped in performing the experiment. The authors are highly thankful to Vice Chancellor, Pt. B. D. Sharma U.H.S. Rohtak for scientific encouragement and financial support.

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Nil.

Conflicts of Interest

There is no conflicts of interest.

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