Deficiency of Glutathione *S*-Transferases T1 and M1 as Heritable Factors of Increased Cutaneous UV Sensitivity

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Glutathione *S*-transferases (GSTs) play a primary role in cellular defense against electrophilic chemical species and radical oxygen species. Because free radical attack is one mechanism of UV irradiation-caused skin damage, we investigated whether genetic variation at the GST loci *GST T1* and *GST M1* influences individual UVB sensitivity. In a double-blind clinical trial, 50 healthy volunteers were evaluated for minimal erythema dose of UVB irradiation, MED (J/cm^2), skin types were assigned, and internal standard-controlled polymerase chain reaction (PCR) was used to identify their *GST T1* and *GST M1* genotypes. The five homozygous carriers of the *GST T1* deletion (*GST T1*0/0*) presented with the most intensive inflammatory reactions after irradiation; they were significantly overrepresented among the highly UVB-sensitive subgroups ($p = 0.006$). Lack of *GST M1* (*GST M1*0/0*, $n = 27$) tended to be more frequent only in UVB-sensitive subjects, and the proportion of the active *GST M1* allelic variants **A* and **B* was similar in all UVB sensitivity subgroups. Three subjects with deficiencies in GST T1 and GST M1 had the most intense inflammatory responses. No effect of gender or genetic variations at the *MC1R* gene locus was established. Thus, heritable GST T1 deficiency may be a genetic determinant of individual skin sensitivity toward UV irradiation. *Keywords: oxidative stress/detoxifying enzymes/polymorphism/MC1R. J Invest Dermatol 108:229–232, 1997*

Ultraviolet (UV) light-mediated formation of radical oxygen species such as hydroxyl and superoxide radicals, hydrogen peroxide, and singlet oxygen is considered to be responsible for noxious effects of UV irradiation upon skin (Black 1987). Damage to cellular proteins, lipids, and DNA, with consequent inflammation, mutagenicity, and genotoxicity, are results of oxidative stress (Ananthaswamy and Pierceall 1990; Halliwell and Aruoma 1991; Darr and Fridovich 1994). Consequently, the skin is equipped with anti-oxidants and enzymatic detoxification reactions to neutralize reactive photochemical products (Vessey 1993). Glutathione *S*-transferases (GSTs) might contribute to the protection against oxidative stress, either by direct inactivation of peroxidized lipids and DNA (Tan *et al*, 1988; Ketterer and Meyer, 1989; Berhane *et al*, 1994) or by detoxification of xenobiotics, which are known co-factors for radical formation.

GSTs catalyze the conjugation of electrophiles with reduced glutathione; they comprise five classes: Alpha (GST A), Mu (GST M), Pi (GST P), Theta (GST T), and a microsomal GST (Mannervik *et al*, 1992). Hereditary deficiencies in enzyme activity caused by homozygous gene deletion have been elucidated for GST M1 (Seidegård *et al* 1988) and more recently for GST T1 (Pemble *et al* 1994). A large proportion (50.7%) of Caucasians were found not to express GST M1 (*GST M1*0/0*; $n = 400$, 95% confidence limits: 45.8–55.6%; Brockmöller *et al*, 1994) and in the remainder, two active alleles, *GST M1*A* and **B*, encode homo- and heterodimeric enzymes. The population frequencies of the GST T1 deficiency (*GST T1*0/0*) showed major differences in several studies (10 to 64%) attributable to ethnicity even among Caucasians (Pemble *et al*, 1994; Nelson *et al* 1995; Warholm *et al*, 1995; Brockmöller *et al*, 1996).

Carriers of *GST M1*0/0* and *GST T1*0/0* may be particularly susceptible to oxidative or chemical stress, and consequently they should suffer from more intense inflammatory reactions after UV irradiation. To test this hypothesis, we initiated a clinical trial of the association of *GST M1* and *GST T1* genotypes with skin sensitivity characterized by minimal erythema dose of ultraviolet B (UVB) irradiation in healthy volunteers.

The melanocyte-stimulating hormone receptor (MC1R) controls the regulation of pigmentation and was recently shown to be polymorphic (Valverde *et al*, 1995). As this might bias our study, all subjects were screened for the two most common variants of *MC1R* gene.

MATERIALS AND METHODS

Subjects Fifty healthy subjects (27 male, 23 female), who were German Caucasians aged between 21 and 35 y (mean 26.4 y), entered the study during the winter months. The skin types were assigned from tanning and burning histories using Fitzpatrick's Classification (Fitzpatrick *et al*, 1987). To exclude observer bias, genotypes were determined only after skin reactions had been classified.

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Abbreviations: *GST M1*, gene coding for GST M1; GST M1, glutathione *S*-transferase class Mu type 1, enzyme; *GST T1*, gene coding for GST T1; GST T1, glutathione *S*-transferase class Theta type 1, enzyme; GST, glutathione *S*-transferase; MC1R, melanocyte stimulating hormone receptor; *MC1R*, gene coding for MC1R.

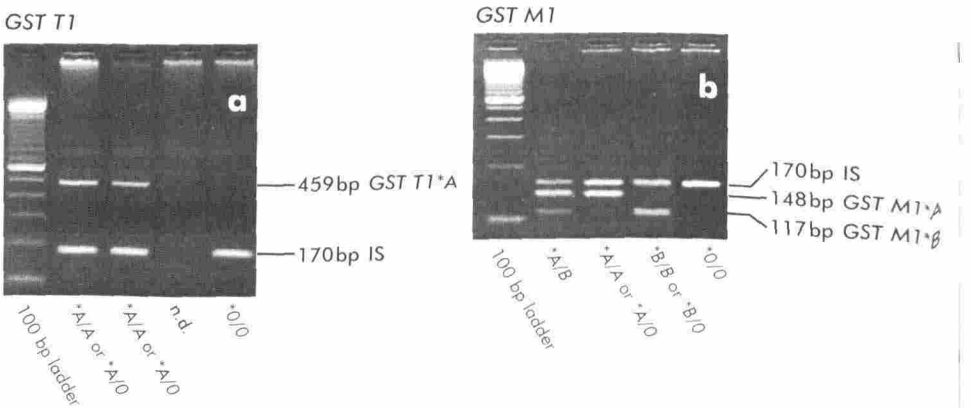

Figure 1. Detection of *GST T1 (a)* and *GST M1 (b)* genotypes by RFLP-PCR. If the 170-bp amplificate of the internal standard (IS) reaction is present, *GST T1* or *GST M1* deletion can be concluded from the absence of the specific 459-bp (GSTT1), 148-bp *(GST M1*A)*, and 133-bp *(GST M1*B)* fragments, respectively. n.d., reaction not detectable.

UVB Irradiation Reactivity to UV light was determined in eight skin fields (1 × 0.6 cm) on the back by increasing UV irradiation in 20% stages (Wucherpfennig, 1931). Before each irradiation, UVB intensity of the radiation source (dermalight 2001™ equipped with an h2 filter, Dr. Höhnle, Munich, Germany) was calibrated to 1.33 mW/cm^2 at 280–315 nm by use of the UVA/B Meter (Dr. Höhnle, Munich, Germany). UVB dose [J/cm^2] was calculated by intensity [mW/cm^2] × time [sec]/1000. Variation of UVB dose was achieved by altering radiation time. UVB doses ranged from 0.07 J/cm^2 to 0.34 J/cm^2. Readings were taken at 20 h after irradiation. The irradiation dose of the first field with perceptible erythema determined the minimal erythema dose (MED). All skin reactions were photographically documented.

Genotyping of GSTs The genotypes of *GST T1* and *GST M1* were detected using internal standard-controlled PCRs by coamplification of the β-interferon gene in the same reaction tube (Brockmöller *et al* 1996). The *GST M1*-specific forward primer (5′-GCT TCA CGT GTT ATG GAG GTT C-3′), located at intron 6 and the reversed primer (5′-ATG AAG TCC TTC AGA TTT GGG AAG GCG TCC AAC CA-3′), located at exon 7, were used to amplify a 148-bp fragment of *GST M1* covering the site of *GST M1*A/*B* polymorphism. At position 3, the reversed primer was modified by a base exchange (C→G) in order to introduce a *Bsr*I restriction site in samples containing the *GST M1*B* allele. Sequences of the *GST T1* primers were 5′-TTC CTT ACT GGT CCT CAC ATC TC-3′ (forward) and 5′-TCA CCG GAT CAT GGC CAG CA-3′ (reversed); (Pemble *et al* 1994).

PCRs were carried out with 100 ng (1 μl) of DNA in 25 μl of 67 mM Tris(hydroxymethyl)aminomethane HCl, pH 8.8, 17 mM $(NH_4)_2SO_4$, 10 mM β-mercaptoethanol, 7 μM ethylenediamine tetraacetic acid, 0.02% (wt/vol) gelatin, 1.0 mM $MgCl_2$ containing 200 μM deoxynucleotide triphosphates, 1 unit of AmpliTaq (Perkin-Elmer, Überlingen, Germany), and 250 nM of each primer. Temperatures for the PCRs were 94°C for 2 min, followed by 30 cycles of 94°C, 64°C (68°C for *GST T1*), and 72°C, each for 30 s. *GST M1* amplificates (25 μl) were digested with 8 units of *Bsr*I (New England Biolabs, Schwalbach, Germany) for 6 h at 65°C. All products were separated by electrophoresis on 3% (wt/vol) agarose gels. Ethidium bromide–stained gels were illuminated at 310 nm and digitally documented **(Fig 1)**.

Genotyping of MC1R A 1081-bp fragment of the MC1R-gene was amplified by PCR according to Valverde *et al* (1995) using the primers 5′-CAG CAC CAT GAA CTA AGC AGG ACA CCT GG-3′ (forward) and 5′-CTC TGC CCA GCA CAC TTA AAG CGC GTG CAC-3′ (reversed). The 50-μl reaction mixture contained 100 ng of genomic DNA, 1.75 units of a *Taq/Pwo* polymerase mixture (Boehringer Mannheim, Mannheim, Germany), 500 mM of Tris(hydroxymethyl)aminomethane-HCl pH 9.2, 160 mM of $(NH_4)_2SO_4$, 17.5 mM of $MgCl_2$, 200 μM of deoxynucleotide triphosphates, and 300 nM of each primer. Samples were amplified for 35 cycles (92°C for 30 s and 68°C for 2 min). The $Asp_{294}His$ substitution, which destroys a restriction site for *Taq*I, and the $Val_{92}Met$ substitution, which inserts an additional restriction site for *Nla*III, were confirmed by RFLP analysis according to the manufacturer's recommendations (New England Biolabs, Schwalbach, Germany).

Statistics The dependency of UVB sensitivity from GST M1 and T1 was tested with Mann-Whitney U-test, and from the three allelic variants of *GST M1* using the Kruskal-Wallis-test. Since two enzymes were tested as markers of light sensitivity, significance level was set to 0.025 (Bonferroni adjustment). The correlation of skin type with MED was tested by Spearman's Rho. Since some genotype frequencies were low, skin types II and III were placed in one category to consider skin type in terms of no protection (type I) and variable protection (type II-III). The correlation with *GST M1*- and *T1*-genotypes were evaluated by Fisher's exact test. Interactions between genotypes and sex on UVB sensitivity was evaluated by two-way factorial analysis of variance.

RESULTS

Skin Types Distribution of skin type is given in **Table I**. As expected, skin types correlated well with inflammatory response 20 h after UVB irradiation ($p = 0.002$). No carrier of the *GST T1* deletion had skin type III, but two individuals with skin type I did lack GST T1, although statistically this could be coincidental.

Inflammatory Response to UVB Irradiation and *GST T1* Genotype **Figure 2** shows that all *GST T1 *0/0* subjects were represented among the highly UVB-sensitive individuals, suggesting that the *GST T1* deletion mutation was associated with increased inflammatory response. These five GST T1 deficients had a mean MED of only 0.12 J/cm^2, significantly lower than 0.18 J/cm^2 in the remaining 45 GST T1-active subjects ($p = 0.006$, **Table II**).

Inflammatory Response to UVB Irradiation and *GST M1* Genotype Mean MED of *GST M1*0/0* individuals ($n = 27$) was 0.16 J/cm^2 and only tended to be lower ($p = 0.1$) than the mean MED of 0.18 J/cm^2 in the 23 GST M1-actives **(Table II)**. The frequency distribution in the lower part of **Fig 2** corroborates this trend, as GST M1 deficients are found more frequently than actives in the subgroups of higher UVB sensitivity. The proportion of the active allelic variants, *GST M1*A* and *GST M1*B*, appeared to be similar in the UVB sensitivity subgroups.

Table I. Skin Types Differentiated by GST T1 and GST M1 Phenotypes

	Skin Type[a]		
GST Enzyme	I	II	III
Phenotype			
GST T1-0	2	3	0
GST T1-1	3	30	12
GST M1-0	4	18	6
GST M1-1	1	15	6
Combined traits			
GST T1-0/GST M1-0	2	1	0
GST T1-0/GST M1-1	0	2	0
GST T1-1/GST M1-0	2	17	6
GST T1-1/GST M1-1	1	13	6
Total	5	33	12
Male/female	4/1	19/14	4/8

[a] According to Fitzpatrick's classification.

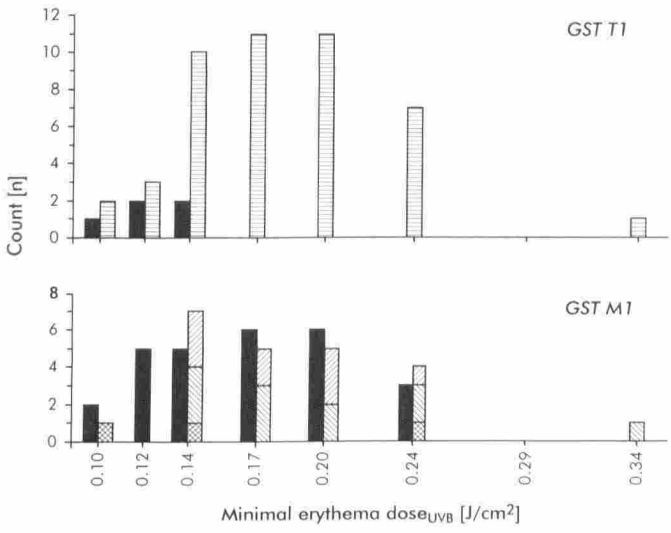

Figure 2. Effect of *GST* genotypes on inflammatory response after UVB irradiation. Frequency distribution of skin sensitivity to UVB is subdivided according to *GST T1* and *GST M1* allelic assignment. *Upper figure*: ■, *GST T1*0/0*; ▤, *GST T1*A/A* or **A/0*. *Lower figure*: ■, *GST M1*0/0*; ▨, *GST M1*A/A* or **A/0*; ▧, *GST M1*B/B* or **B/0*; ▩, *GST M1*A/B*.

Combined Analysis of GST Genotypes The three subjects deficient in both GSTs presented with the highest sensitivity to UV irradiation **(Table II)**. Volunteers active for both GST T1 and GST M1 ($n = 20$) tended to have a higher mean MED (0.19 J/cm^2) than the group with at least one deficient GST ($n = 25$; mean ± SD of MED = 0.17 ± 0.04 J/cm^2). The volunteer who was the most insensitive to UV irradiation in the study was active in both GST enzymes, T1 and M1.

Interaction of Sex Gender had no influence on inflammatory response to UVB irradiation; mean ± SD MED was 0.16 ± 0.04 J/cm^2 and 0.18 ± 0.05 J/cm^2 in men and women, respectively. *GST T1*0/0* had the same effect on UVB sensitivity in both ($p = 0.012$).

***MC1R* Genotype** Only one mutation of the *MC1R* gene was detected. This subject, who had skin type II but an intense inflammatory response (MED = 0.10), was a heterozygous carrier of the His_{294}-substitution and lacked both GSTs.

DISCUSSION

In this study individuals lacking the GST T1 enzyme showed the most intense inflammatory reactions after exposure to UVB light. These homozygous carriers of *GST T1*0/0* express no enzyme and are impaired in detoxification of specific substrates. The influence of the genotype *GST M1*0/0* was less pronounced and failed to reach statistical significance. Individuals deficient in specific GSTs may be less effective in the elimination of oxidatively damaged molecules and therefore more susceptible to the consequences of radical oxygen species attack, such as inflammation or even carcinogenesis (Fahey and Sundquist, 1991).

Clinical Confirmation Our results are corroborated by several studies. Thus, the impact of polymorphic *GST M1* alleles on susceptibility to skin cancer was suggested (Heagerty *et al*, 1994; Lafuente *et al*, 1995). Among other oxidative stress- and inflammation-related diseases, the lack of GST M1 increased the risk for alcoholic cirrhosis (Harada *et al*, 1987), and the course of ulcerative colitis was demonstrated as being worsened by GST M1 (Hertervig *et al* 1994) and GST T1 deficiency (Duncan *et al* 1995). Deficiency of GST M1, but not T1, significantly elevated the risk of urothelial cancer (Brockmöller *et al*, 1994, 1996), whereas an impact on lung cancer remained ambiguous (Brockmöller *et al*, 1993).

Experimental Evidence There is evidence linking GSTs with protection against UV radiation–induced cutaneous damage: (i) Some potentially harmful products of UV-induced radical oxygen species attack on DNA and lipids have been identified as GST substrates (Hayes and Strange, 1995). (ii) An anti-oxidant–responsive element was identified as upregulating the expression of rat GST A in response to radical oxygen species (Rushmore *et al*, 1991) and as being correlated to reduced glutathione levels (Pinkus *et al*, 1995). (iii) reduced glutathione may act as a radical scavenger, and a depletion of reduced glutathione levels in skin was demonstrated by UVA and UVB irradiation (Connor and Wheeler, 1987).

Mechanistical Considerations In our study GST T1 deficiency appears to be much more closely associated with UVB sensitivity than GST M1 deficiency. Differences in substrate specificities, skin distribution, level of expression, or subcellular localization of GST T1 and GST M1 could provide an explanation. Both GSTs were shown to detoxify products of oxidative damage to lipids and proteins. In humans, GST M1 demonstrates activity toward 4-hydroxyalkenals, which are products of lipid peroxidation (Berhane *et al*, 1994), DNA hydroperoxide, and the thymine hydroperoxide 5-hydroperoxymethyl uracil, and nuclear localization has been reported (Tan *et al* 1988). In rats, the activity of GST T1 exceeded

Table II. Skin Sensitivity to UVB Irradiation Dependent on *GST T1* and *GST M1* Genotype

GST Enzyme	Activity	Genotype	Subjects n	Subjects m/f[b]	MED (J/cm^2)[a] Mean	MED (J/cm^2)[a] Range	MED (J/cm^2)[a] SD
Phenotype							
GST T1-0	Deficient	*0/0	5	4/1	0.12[c]	0.10–0.14	0.02
GST T1-1	Active	*A/A or *A/0	45	23/22	0.18	0.10–0.34	0.05
GST M1-0	Deficient	*0/0	27	18/9	0.16	0.10–0.24	0.04
GST M1-1	Active	*A/A or *A/0	11	5/6	0.20	0.14–0.34	0.06
	Active	*B/B or *B/0	9	2/7	0.18	0.14–0.24	0.03
	Active	*A/B	3	2/1	0.16	0.10–0.24	0.07
Total			50	27/23	0.17	0.10–0.34	0.05
Combined traits							
GST T1-0/GST M1-0	Deficient/deficient		3	2/1	0.11	0.10–0.12	0.01
GST T1-0/GST M1-1	Deficient/active		2	2/0	0.14	0.14	0.00
GST T1-1/GST M1-0	Active/deficient		25	17/8	0.17	0.10–0.24	0.04
GST T1-1/GST M1-1	Active/active		20	6/14	0.19	0.10–0.34	0.05

[a] Inflammatory reaction was deteced as minimal erythema dose (MED) at 20 h after irradiation with UVB.
[b] Male/female.
[c] $p = 0.006$, Mann-Whitney U-test.

the activity of GST M1 for linoleic acid hydroperoxide 20 times and for DNA hydroperoxide about 20 to 100 times (Ketterer and Meyer, 1989; Hayes and Strange, 1995). Various GSTs have been detected in the skin (Singhal *et al*, 1993). GST M1 was localized in keratinocytes (Blacker *et al*, 1991), whereas dermal expression of GST T1 is still unexplored.

One might wonder that GST T1 deficiency is much more associated with MED than with skin type, but large ranges of MED values have been already demonstrated within each skin type (Westerhof *et al*, 1990), even though both are, of course, related. Skin type is a subjective classification based on pigmentary and inflammatory response after exposure of the whole body to the sun; any subsequent systemic effects, such as cytokine formation, might modulate skin reaction. In contrast, MED reflects mainly inflammatory processes at the small area of irradiation and may more clearly reveal an impact of GSTs.

Limitations The sample size was fixed prior to initiation of the study, and although the numbers within specific genotypes are limited, the increase of UVB sensitivity in GST T1 deficiency proved to be of high statistical significance. The extent to which GST T1 deficiency affects the inflammatory reaction may well be overestimated and remains to be confirmed in larger studies. This also refers to the pronounced effects observed in the three cases of double deficiencies.The cross-sectional design of our study does not allow us to rule out the possibility that the GST traits are associated with cutaneous light sensitivity via linkage to other genes. The polymorphic *MC1R* gene locus controls tanning response. To explore this possible factor of influence, our study group was retrospectively screened for the two most common *MC1R* variants, without providing an explanation for high UVB sensitivity. Furthermore, *MC1R*, *GST T1*, and *GST M1* are unlikely to be linked, because they are localized on different chromosomes.

Carriers of two active alleles might express higher enzyme activity compared to those with one active and one null allele. Such *GST T1* hemizygotes may tend to have a greater UVB sensitivity than homozygous actives. No methods are presently available, however, to detect precisely a single allelic loss of *GST T1* or *M1*.

Further work is needed to elucidate the mechanisms and magnitude of protection against the hazards of UV radiation by GSTs. We believe, however, that GST T1 and GST M1 phenotypes should be considered in the response of skin to UV radiation.

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