Interaction of Glutathione S-Transferase \( M1 \) and \( T1 \) Genotypes and Malignant Melanoma

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Abstract

The \( \mu \) and \( \theta \) classes of glutathione S-transferases (GST) may affect the development of cutaneous malignant melanoma (CMM) by decreasing cellular oxidative stress in skin. These isozymes are absent in a large proportion of the population because of germ-line homozygous deletions in the genes encoding GSTM1 and GSTT1. To determine the association between GSTM1 and GSTT1 homozygous deletions (GSTM1 null and GSTT1 null, respectively) and CMM, we studied 212 patients with CMM, 150 patients with CMM and dysplastic nevi (DN), 147 patients with DN alone, and 124 healthy persons without CMM or DN. Comparing CMM cases (\( n = 362 \)) to participants without CMM (\( n = 271 \)), we found no association with GSTM1 null [odds ratio (OR), 1.2; 95% confidence interval (CI), 0.86–1.6] or GSTT1 null (OR, 0.82; 95% CI, 0.56–1.2), either independently or in combination (OR, 1.4; 95% CI, 0.81–2.2), after adjusting for age. However, among the subset of participants with red or blond hair, those with CMM were twice as likely to carry GSTM1 null (OR, 2.2; 95% CI, 1.2–4.2) and nearly 10-fold more likely to carry both GSTM1 null and GSTT1 null (OR, 9.5; 95% CI, 1.2–73) compared with those without CMM. These data suggest that among persons with hair colors traditionally associated with increased risk for melanoma, absence of both GSTM1 and GSTT1 may act to further elevate CMM risk.

Introduction

Increased levels of cellular oxidative stress can be harmful to the faithful replication of DNA. Oxidative stress resulting in lipid peroxidation and DNA hydroperoxide formation can be induced in skin by UV radiation (1). Because one function of GST\(^3\) is the reduction of these potential mutagens (2, 3), GST isozymes active in skin, including GSTM1 and GSTT1, may play a role in protection against development of cutaneous neoplasms, including CMM. Polymorphisms in members of the GST family have been shown to influence risk of cancers at several sites, including nonmelanoma skin cancers (4) and multiple cutaneous skin cancers (4–6). Lafuente et al. (7) measured leukocytic GSTM1 levels by enzyme-linked immunoassay and noted that CMM patients were twice as likely to have decreased levels of GSTM1 compared with controls. Two other studies (4, 8) genotyped GSTM1 using PCR and reported no significant difference in the proportion of those homozygous for the GSTM1 deletion (GSTM1 null) between CMM patients and controls. One additional study (9) published in abstract form only reported a significant association between CMM and carriage of the GSTT1 homozygous deletion (GSTT1 null) but not GSTM1 null. DN are atypical moles that are epidemiological risk markers of CMM and nonobligate precursors (10). Their association with GST status has not been reported.

To gain additional insight into the complex etiology of CMM, we designed a case-control study to evaluate the associations among GSTM1 and GSTT1, pigmentation characteristics, DN, and CMM.

Materials and Methods

Setting and Population

Participants in the present study were accrued into a case-control study at the Pigmented Lesion Clinic of the Hospital of the University of Pennsylvania between September 1997 and September 1999. The Institutional Review Board of the University of Pennsylvania that oversees research involving human beings approved this study, and informed consent was obtained from each participant. Any clinic patient with incident CMM, defined as CMM histologically diagnosed within a year of their clinic visit, was eligible to participate. Patients with a first-time clinical diagnosis of DN (within 1 year of their clinic visit) were also eligible to participate. Patients who had an clinical or histological diagnosis of DN 1 year or more before the date of their study participation were excluded from study. We did not select patients based on prior knowledge of family history of melanoma or other melanoma risk factors, and those with more than one primary CMM were not eligible to participate regardless of the date of their first CMM. For each clinic patient enrolled, we asked for the name of a healthy nonblood relative or acquaintance to contact as a potential control subject.

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\(^{3}\) The abbreviations used are: GST, glutathione S-transferase; CI, confidence interval; CMM, cutaneous malignant melanoma; DN, dysplastic nevi; IQR, interquartile range; OR, odds ratio; SULT, sulfotransferase.
Data Collection and Measurement

Information on pigmentation characteristics and sun exposure history was obtained from a brief self-administered questionnaire. We asked about natural hair color as a teenager, natural eye color, initial skin reaction after exposure to the first strong sunlight of summer, skin reaction after long and repeated sun exposure, and freckling on the face and upper back. One research nurse (R.H.) completed a full skin examination, excluding the scalp and genitalia, for all of the study participants, and the following information was recorded: total mole count, total number of large moles (>8 mm), number of DN, and presence or absence of freckling. A buccal sample was self-collected by each study participant using sterile cheek swabs (Cyto-Pak Cytosoft Brush; Medical Packaging Corporation, Camarillo, CA) to collect a germ-line DNA sample.

GSTM1 and GSTT1 Genotyping

Genomic DNA from the buccal swab was extracted using the protocol of Walker et al. (11), and the complete gene deletion at GSTT1 and GSTM1 was determined by using PCR-based assays modified from the protocol of Rebbeck et al. (12). The modified protocol used exon 4 of the sulfotransferase (SULT1E1) gene to serve as a positive internal control for the amplification of GSTM1 rather than the β-globin-positive internal control reported previously. These primers were SULT exon 4 forward, 5' TGG AGT TGC TTA ACC TTT ACT-3' and SULT exon 4 reverse, 5' GAG AAC ACT TGA CTC TGG TTA C 3'. We did not distinguish the homozygous active from the heterozygous active genotype for either GSTM1 or GSTT1.

Data Coding

Case Status. We grouped participants according to the presence or absence of CMM. The CMM case group included patients with CMM alone and those with both CMM and DN. The control group included patients with DN alone and healthy participants without CMM or DN.

GST Genotypes. We dichotomized GST genotypes based on the presence of at least one active allele. “GSTM1 active” indicates the presence of at least one nondeleted GSTM1 allele, whereas “GSTM1 null” indicates the presence of two deleted GSTM1 alleles. Similarly, “GSTT1 active” indicates the presence of at least one nondeleted GSTT1 allele, and “GSTT1 null” indicates the presence of two deleted GSTT1 alleles. A composite GST genotype was created to reflect overall GST activity. “GST active” indicates the presence of at least one nondeleted active allele in either GSTM1 or GSTT1, whereas “GST null” indicates both GSTM1 null and GSTT1 null.

Nevi Outcomes. We categorized the total number of DN and the total number of large nevi as 0, 1, 2–5, 6–9, and 10 or more. All of the classes of nevi, including banal nevi, DN, and congenital nevi, were included in the count of large nevi. Total number of nondysplastic nevi was categorized as 1–24, 25–49, 50–74, and 75 or more and includes counts of large and small (≤8 mm) banal nevi and congenital nevi.

Pigmentation Characteristics. Questionnaire information on hair color was coded as red (including reddish-brown), blond, or dark (including light brown, medium brown, dark brown, gray, and black); on eye color as blue or gray, green or hazel, or dark (including light brown, dark brown, and black); on freckling as many, few, or none; on skin reaction to acute sun as burn and blister, burn without blister, or tan (including mild sunburn followed by a tan, no sunburn and no tan, tan with no sunburn, and no change in skin color); and on skin reaction to chronic sun as no tan, light tan, or medium to dark tan.

### Table 1 Adjusted odds of CMM by pigmentation characteristics

<table>
<thead>
<tr>
<th>Pigmentation characteristic</th>
<th>Without CMM n = 271</th>
<th>CMM n = 362</th>
<th>OR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair color</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red or reddish-brown</td>
<td>8 (3)</td>
<td>43 (12)</td>
<td>4.6 (2.1–10.2)</td>
</tr>
<tr>
<td>Blond</td>
<td>55 (20)</td>
<td>76 (20)</td>
<td>1.3 (0.85–1.9)</td>
</tr>
<tr>
<td>Dark</td>
<td>208 (77)</td>
<td>243 (67)</td>
<td>1.0</td>
</tr>
<tr>
<td>Eye color</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>101 (38)</td>
<td>158 (44)</td>
<td>1.6 (1.1–2.4)</td>
</tr>
<tr>
<td>Green, gray, or hazel</td>
<td>64 (24)</td>
<td>104 (29)</td>
<td>1.8 (1.2–2.7)</td>
</tr>
<tr>
<td>Light or dark brown</td>
<td>104 (39)</td>
<td>96 (27)</td>
<td>1.0</td>
</tr>
<tr>
<td>Skin reaction to acute sun</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burn and blister</td>
<td>26 (10)</td>
<td>49 (14)</td>
<td>1.5 (0.88–2.6)</td>
</tr>
<tr>
<td>Burn without blister</td>
<td>100 (37)</td>
<td>136 (38)</td>
<td>1.2 (0.87–1.8)</td>
</tr>
<tr>
<td>Tan</td>
<td>143 (53)</td>
<td>177 (49)</td>
<td>1.0</td>
</tr>
<tr>
<td>Skin reaction to chronic sun</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No tan</td>
<td>10 (4)</td>
<td>26 (7)</td>
<td>2.6 (1.2–5.6)</td>
</tr>
<tr>
<td>Light tan</td>
<td>58 (22)</td>
<td>121 (34)</td>
<td>2.1 (1.5–3.1)</td>
</tr>
<tr>
<td>Medium or dark tan</td>
<td>198 (74)</td>
<td>209 (59)</td>
<td>1.0</td>
</tr>
<tr>
<td>Freckling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Many</td>
<td>69 (25)</td>
<td>162 (45)</td>
<td>3.7 (2.4–5.8)</td>
</tr>
<tr>
<td>Few</td>
<td>104 (38)</td>
<td>134 (37)</td>
<td>1.9 (1.3–2.9)</td>
</tr>
<tr>
<td>None</td>
<td>98 (36)</td>
<td>66 (18)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Adjusted for age and total number of DN.

Statistical Analysis

Median counts of nevi outcomes were compared nonparametrically using Mann-Whitney U Wilcoxon rank-sum tests. Using unconditional logistic regression models, we calculated age-adjusted ORs and 95% CIs for associations between pigmentation characteristics and CMM, freckling and nevi types and GST genotype, and GST genotype and CMM. For each model, independent variables were entered as (0,1) indicator variables, where 1 specified the presence of the variable and 0 specified the absence of the variable. Independent variables with more than two levels were considered as ordinal variables to test for linear trend. For all of the analyses of pigmentation characteristics and CMM, total number of DN was additionally adjusted for in the logistic model.

To evaluate effect modification, we determined age-adjusted ORs and 95% CIs of CMM within pigmentation categories. Because the stratum-specific number of subjects for some pigmentation characteristics was too small to support subgroup analysis, we combined categories to create dichotomous variables (hair color: red, reddish-brown, blond versus light brown, medium brown, dark brown, gray, and black; eye color: blue, gray, green, hazel versus light brown, dark brown, and black; freckling: any versus none; skin reaction to acute sun: burn without tanning, regardless of blistering versus tanning or no effect, regardless of burning; and skin reaction to chronic sun: no or light tan versus medium or dark tan). We chose to combine the moderate and high risk categories and
keep separate the low risk category in an attempt to highlight subgroups that identify persons at reduced risk of melanoma and persons at some increased risk of melanoma.

**Results**

Our study sample included 362 CMM cases and 271 controls without CMM. All of the participants were Caucasian, and only five (two CMM cases and three controls) reported being of Hispanic origin. The gender distribution was similar among five (two CMM cases and three controls) reported being of Hispanic origin. The mean age of CMM cases (50.6 ± 14.0) was statistically significantly older than that of controls without CMM (45.1 ± 13.4; P = 0.0001). No difference in ever-smoking was noted between the groups (χ² = 0.28; P = 0.60).

**Association of Pigmentation Characteristics and CMM.**

Adjusted ORs for CMM in relation to self-reported pigmentation characteristics are given in Table 1. The strongest predictors of CMM were freckling and skin reaction to chronic sun exposure. CMM cases were nearly four times as likely to report many freckles (OR, 3.7; 95% CI, 2.4–5.8) and nearly two times as likely to report few freckles (OR, 1.9; 95% CI, 1.3–2.9) compared with controls. Compared with controls, CMM cases were over twice as likely to report both an inability to tan (OR, 2.6; 95% CI, 1.2–5.6) and a light tanning ability (OR, 2.1; 95% CI, 1.5–3.1) in response to chronic sun. A statistically significant linear trend was observed for these associations. Patients with CMM were over four times as likely to be redheaded (OR, 4.6; 95% CI, 2.1–10.2) compared with controls without CMM. Blond hair was not predictive of CMM (OR, 1.3; 95% CI, 0.85–1.9).

The total number of DN and total number of large nevi were highly and significantly correlated (Pearson r = 0.76; P = 0.001). Because the total number of large nevi was a composite measure that did not distinguish among large banal nevi, large congenital nevi, and large DN, it was not possible for us to separate the affects of large banal nevi from that of other types of large nevi. Thus, this measure was not considered in subsequent analyses.

### Table 2  Adjusted odds of GSTM1 null, GSTT1 null, and GST null by freckling and nevi type

<table>
<thead>
<tr>
<th>GSTM1</th>
<th>GSTT1</th>
<th>GST null</th>
</tr>
</thead>
<tbody>
<tr>
<td>active</td>
<td>null n = 330</td>
<td>null n = 303</td>
</tr>
<tr>
<td>active</td>
<td>null n = 330</td>
<td>null n = 303</td>
</tr>
</tbody>
</table>

**Association of Cutaneous Markers of CMM Risk and GST Genotype.** Comparing participants who were GST null (n = 78) to those who were GST active (n = 553), there were no statistically significant differences in the median number of total nevi (32.5; IQR, 8–74; and 24; IQR, 8–66, respectively) or median number of DN (1; IQR, 0–6; and 0; IQR, 0–3, respectively). Results were similar comparing median nevus counts across GSTM1 and GSTT1 status (data not shown). Table 2 shows age-adjusted ORs for associations of nondystrophic nevi, DN, and freckling with GST genotype. Persons with 10 or more DN were nearly three times as likely (OR, 95% CI, 1.4–5.6) to be GST null. The linear trend for increasing categories of DN count did not reach significance at the α = 0.05 level. There was no association of reported freckling and GST genotypes.

### Table 3  Adjusted odds of CMM by GST genotype

<table>
<thead>
<tr>
<th>GST genotype</th>
<th>Without CMM</th>
<th>CMM n = 362</th>
<th>ORa</th>
<th>95% CI</th>
</tr>
</thead>
</table>

### Association of CMM and GST Genotype.** We did not find a significant association with GSTM1 null, GSTT1 null, or GST null genotypes and CMM status (Table 3).**

After stratifying the sample on pigmentation characteristics, we found a significant association of GST genotype and CMM in the subgroup of persons with light hair color (red, reddish-brown, or blond; Table 4). Among those with red or blond hair, cases with CMM were nearly 10-times more likely
Table 4
Age-adjusted odds of CMM by GST genotype stratified by pigmentation characteristic

<table>
<thead>
<tr>
<th>Hair color</th>
<th>Eye color</th>
<th>Skin reaction to acute sun</th>
<th>Skin reaction to chronic sun</th>
<th>Freckling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown or black</td>
<td>Light or blue, gray, green, or hazel</td>
<td>Burn then tan or tan</td>
<td>Burn without tanning</td>
<td>Medium or dark tan</td>
</tr>
<tr>
<td>Light or redheaded</td>
<td>Red, reddish-brown, or blond</td>
<td>Burn then tan or tan</td>
<td>Burn without tanning</td>
<td>Medium or dark tan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polymorphisms and Melanoma</th>
<th>Null</th>
<th>Polymorphisms and Melanoma</th>
<th>Active</th>
<th>Null</th>
<th>Polymorphisms and Melanoma</th>
<th>Active</th>
<th>Null</th>
<th>Polymorphisms and Melanoma</th>
<th>Active</th>
<th>Null</th>
<th>Polymorphisms and Melanoma</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTM1</td>
<td>126/105</td>
<td>1.0</td>
<td>57/42</td>
<td>1.0</td>
<td>41/49</td>
<td>1.0</td>
<td>138/96</td>
<td>1.0</td>
<td>87/69</td>
<td>1.0</td>
<td>96/77</td>
<td>1.0</td>
</tr>
<tr>
<td>GSTM1 active</td>
<td>117/103</td>
<td>0.99 (0.68–1.4)</td>
<td>62/21</td>
<td>2.2 (1.2–4.2)</td>
<td>55/55</td>
<td>1.3 (0.72–2.2)</td>
<td>124/69</td>
<td>1.3 (0.85–1.9)</td>
<td>90/74</td>
<td>0.99 (0.63–1.6)</td>
<td>89/49</td>
<td>1.5 (0.94–2.4)</td>
</tr>
<tr>
<td>GSTT1</td>
<td>194/154</td>
<td>1.0</td>
<td>92/51</td>
<td>1.0</td>
<td>75/82</td>
<td>1.0</td>
<td>207/121</td>
<td>1.0</td>
<td>143/112</td>
<td>1.0</td>
<td>143/91</td>
<td>1.0</td>
</tr>
<tr>
<td>GSTT1 active</td>
<td>49/54</td>
<td>0.71 (0.45–1.1)</td>
<td>27/12</td>
<td>1.3 (0.58–2.7)</td>
<td>21/11</td>
<td>1.1 (0.54–2.1)</td>
<td>55/44</td>
<td>0.71 (0.45–1.1)</td>
<td>34/31</td>
<td>0.83 (0.48–1.5)</td>
<td>42/35</td>
<td>0.77 (0.45–1.3)</td>
</tr>
</tbody>
</table>

Adjusted for age.

Discussion
The etiology of CMM is complex and likely involves multiple low penetrance susceptibility genes, interactions among these genes, the influences of environmental exposures such as UV light, and the interaction of genotypes and environments. GSTM1 and GSTT1 represent only two of numerous potential candidate CMM susceptibility genes. Similar to other published reports (4, 8), our data do not support a strong role of GSTM1 or GSTT1 in the development of CMM, either individually or in combination. However, GSTM1 null, predominantly when in combination with GSTT1 null, may exacerbate CMM risk when it occurs in the context of specific phenotypic backgrounds known to increase susceptibility to the development of CMM.

A biological interaction between GST genotype and hair color is quite plausible. Persons with lighter hair color, i.e., red and blond hair, tend to have fairer skin complexion and a corresponding greater proportion of pheomelanin in the epidermis (13). This is in contrast to those with brown or black hair who tend to have darker skin complexion and a greater amount of eumelanin. Pheomelanin is a poorer protector against cellular oxidative stress than is eumelanin because reactive oxygen species may be more likely to form when pheomelanin is exposed to UV radiation (14).

Our data support a moderate yet significant association with GSTM1 null and CMM among persons with light (i.e., red, reddish-brown, and blond) hair color. It is possible that GSTM1 is a more efficient reducer of oxidized DNA and lipids than GSTT1 null in skin. It is clear, however, that the combination of GSTM1 null and GSTT1 null confers the greatest risk of CMM in light-haired individuals. The association between GST null and CMM among persons with light hair color remained statistically significant even after further adjustment for either total number of DN alone or in combination with all of the other pigmentation characteristic variables included in Table 4 (data not shown). Because GSTM1 and GSTT1 have complementary yet somewhat redundant biochemical properties, the absence of an active form of both isozymes may represent a more limited ability to reduce cellular oxidative stress. Kerb et al. (15) noted that the minimal erythematous dose of UVB irradiation was lowest among three healthy subjects who were both GSTM1 null and GSTT1 null.

We acknowledge that our ability to draw strong conclusions based on these data is limited because of the small number of persons who were GST null and the potential for spurious associations resulting from the number of tests of significance performed.

We speculate that the association between GST null and CMM would be even greater among a subgroup consisting of only redheads. We were unable to directly test this in our data. The number of redheads in our study population totaled 51, of whom only 5 were controls and only 3 had DN. None of these redheaded controls were genotyped as GST null. In fact, only one subject without CMM (who was blond) was GST null, which contributed to the imprecision of the parameter estimate.

Of interest was the lack of a clear association between GST genotypes and measures of cutaneous risk markers for CMM, specifically DN. Because some, but not all, CMM arise (OR, 9.5; 95% CI, 1.2–73) to be GST null compared with controls without CMM. The association between GSTM1 null and CMM was also significant in those with light hair color, although to a more modest degree (OR, 2.2; 95% CI, 1.2–4.2).

No other significant interactions with pigmentation characteristics were noted.
from DN precursors, it may be that GSTM1 null and GSTT1 null play a more crucial role in later stage melanocytic carcinogenesis by contributing to the continued deregulation of cellular functions within an already functionally and morphologically abnormal DN.

Seemingly inconsistent was the moderate association between GST null and floridly expressed (10 or more) DN. Because these persons are at greatest risk for development of CMM (10), it is possible that this association is indicative of an undiagnosed CMM rather than increased number of DN per se. To determine whether the lack of association between GST null and DN count was, in part, determined by the presence of CMM, we repeated analyses after stratification on case-control status. The Cochran-Mantel-Haenszel statistic (17.3; \(P = 0.002\)) indicated that the association of GST null and DN was the same in cases and controls. However, we did note an increased likelihood of GST null (OR, 2.0; 95% CI, 0.92–4.5) among CMM cases with a solitary DN, compared with a decreased likelihood of GST null (OR, 0.29; 95% CI, 0.04–2.3) among controls with a solitary DN.

We have extensively evaluated our control group to better understand the potential impact of our sampling design on our reported associations. The majority of controls were partners of clinic patients (87%), 10% were friends, and 3% were in-laws or adoptive relatives. Statistical tests did not reveal any difference between partner controls and friend controls for either pigmentation characteristic or GST genotyping results (data not shown). The prevalence of GSTM1 null in CMM-free controls (46%) was well within the range published for this null polymorphism, whereas the prevalence of GSTT1 null among this group (24%) was slightly higher than that previously reported in Caucasians (reviewed in Ref. 16). Comparing DN controls with referred healthy controls without DN or CMM, there were no statistically significant differences in the proportions with GSTM1 null (\(\chi^2 = 0.84; \ P = 0.36\)), GSTT1 null (\(\chi^2 = 1.9; \ P = 0.17\)), or GST null (\(\chi^2 = 0.01; \ P = 0.92\)).

It is possible that a shared etiology exists between DN and CMM. Under this assumption, bias introduced by including DN into the referent group would likely make it more difficult to detect significant associations. Reassuringly, the associations we found between CMM and pigmentation characteristics were similar to those published previously (reviewed in Ref. 17).

Additional evaluation will be required to further explore the apparent interaction between GST genotypes and hair color phenotype (18) and to relate these results to additional factors determining melanogenesis and melanocytic carcinogenesis, e.g., melanocortin-1 receptor allelic variation (18–20). Phenotypic pigmentation alone is not sufficient to predict CMM risk. The additional information provided by genotyping may contribute significantly to better models of prediction, prevention, and treatment of CMM.

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References

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