Review Article
Association between the polymorphism of glutathione S-transferase genes (GSTM1, GSTT1, and GSTP1) and vitiligo: a meta-analysis

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Abstract: Several evidences indicate that the imbalance between oxidative stress and antioxidation in the epidermal layer of skin may be an important pathogenetic factor of vitiligo. Polymorphisms in the glutathione S-transferase (GST) genes have been identified, which confer risk of vitiligo. There is an impairment of antioxidative system in vitiligo melanocytes with result from free radical mediated damage in melanocyte. The associations between polymorphisms of GSTM1/T1/P1 genes and vitiligo susceptibility have produced diverse results. We conducted a meta-analysis of all relevant study in EMBASE, GOOGLE, KISS, MEDLINE and PubMed before January 2015. In present study, a meta-analysis on the association between the GSTM1/T1 polymorphism and vitiligo was performed for 1,258 patients with vitiligo and 1,573 controls from eligible 5 published studies. The results in our meta-analysis showed that the null type of GSTM1 and null type of GSTT1 genotype was significantly associated with vitiligo (GSTM1, OR=1.494, 95% CI=1.126-1.981, P=0.005; GSTT1, OR=1.318, 95% CI=1.130-1.537, P<0.001). In the subgroup analysis, the null type frequency of the combination of GSTM1-GSTT1 polymorphism in the vitiligo was significantly higher than that of the control group (OR=1.369, 95% CI=1.149-1.633, P<0.001). This result indicated that null type of GSTM1-GSTT1 combination can be a risk factor of vitiligo. However, further larger study considering the gene-gene and gene-environment interactions could be required to provide a very precise evidence for the association of GST polymorphism and the vitiligo susceptibility.

Keywords: Glutathione S-transferase gene, polymorphism, meta-analysis, vitiligo

Introduction
Vitiligo is an acquired, idiopathic, and world-wide common depigmentation disorder affecting people of all ages and both sexes equally. Patients lose their skin color over time, mostly in a patchy and progressive manner [1]. It affects approximately 0.5% to 1% of the population, with an average age of onset at about 24 years, its prevalence appears to be equal between men and women [2-4]. Prevalence rates ranging from 0.06 to 2.28% in the general populations and from 0 to 2.16% in children populations [1]. There is no difference in the rate of occurrence according to skin type or race [2, 5].

It remains unclear what causes damage or death to the melanocytes, there are many potential pathophysiological theories involving autoimmune, genetic, neural, autotoxicotic, biochemical, oxidative stress, melanocytorrhagy, and decreased melanocyte survival hypotheses [2, 6, 7].

Genetic factors appear to play a role 20 to 30 percent of patients may have a family history of the disorder [8, 9]. Many studies suggested that genetic factors, autoimmune dysfunctions and oxidative stress may play an essential role in the development of this disease [10]. Several candidate genes have been proposed for vitiligo susceptibility, including catalase (CAT) gene [11, 12], protein tyrosine phosphatase (PTPN22) [13, 14], angiotensin-converting enzyme (ACE) gene [15], human leucocyte antigen (HLA) [16], catechol-O-methyltransferase (COMT) [17], estrogen receptor 1 [18].
# GST polymorphisms and vitiligo

## Table 1. Characteristic of the case-control studies in this meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Case/Control</th>
<th>Case</th>
<th>Control</th>
<th>GSTM1</th>
<th>GSTT1</th>
<th>GSTP1</th>
<th>GSTM1</th>
<th>GSTT1</th>
<th>GSTP1</th>
<th>GSTM1</th>
<th>GSTT1</th>
<th>GSTP1</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Null</td>
<td>Present</td>
<td>Null</td>
<td>Present</td>
<td>Ile/Ile</td>
<td>Ile/Val</td>
<td>Val/Val</td>
<td>Null</td>
<td>Present</td>
<td>Null</td>
<td>Present</td>
</tr>
<tr>
<td>Uhm et al. (2007)</td>
<td>Korean</td>
<td>310/549</td>
<td>212</td>
<td>98</td>
<td>165</td>
<td>145</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>282</td>
<td>267</td>
<td>289</td>
<td>260</td>
</tr>
<tr>
<td>Bassiouney et al. (2012)</td>
<td>Egypt</td>
<td>101/101</td>
<td>57</td>
<td>44</td>
<td>31</td>
<td>70</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>47</td>
<td>54</td>
<td>23</td>
<td>78</td>
</tr>
<tr>
<td>Guarneri et al. (2011)</td>
<td>Mediterranean</td>
<td>58/150</td>
<td>35</td>
<td>23</td>
<td>22</td>
<td>36</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>82</td>
<td>68</td>
<td>37</td>
<td>113</td>
</tr>
<tr>
<td>Rabou et al. (2011)</td>
<td>Egypt</td>
<td>40/10</td>
<td>21</td>
<td>19</td>
<td>23</td>
<td>17</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>1,258/1,573</td>
<td>751</td>
<td>507</td>
<td>594</td>
<td>664</td>
<td>508</td>
<td>205</td>
<td>36</td>
<td>812</td>
<td>761</td>
<td>647</td>
<td>926</td>
</tr>
</tbody>
</table>

ND, No data; GSTM1, Glutathione S-transferase mu 1; GSTT1, Glutathione S-transferase theta 1; GSTP1, Glutathione S-transferase pi 1.
Table 2. Meta-analysis of GSTM1/T1 polymorphism and the risk of vitiligo

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Effect model</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTM1 null</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>5</td>
<td>Random</td>
<td>1.494</td>
<td>1.126-1.981</td>
<td>0.005</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>Random</td>
<td>1.542</td>
<td>1.097-2.166</td>
<td>0.013</td>
</tr>
<tr>
<td>GSTT1 null</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>5</td>
<td>Fixed</td>
<td>1.318</td>
<td>1.130-1.537</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>Fixed</td>
<td>1.291</td>
<td>1.101-1.512</td>
<td>0.002</td>
</tr>
<tr>
<td>GSTM1/T1 null</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>5</td>
<td>Fixed</td>
<td>1.369</td>
<td>1.149-1.633</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>Fixed</td>
<td>1.331</td>
<td>1.111-1.594</td>
<td>0.002</td>
</tr>
<tr>
<td>Null/present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>5</td>
<td>Fixed</td>
<td>1.154</td>
<td>0.980-1.359</td>
<td>0.087</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>Fixed</td>
<td>1.189</td>
<td>1.004-1.409</td>
<td>0.045</td>
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<tr>
<td>Present/null</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>5</td>
<td>Random</td>
<td>0.981</td>
<td>0.856-1.643</td>
<td>0.943</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>Random</td>
<td>0.964</td>
<td>0.521-1.782</td>
<td>0.906</td>
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<tr>
<td>Present/present</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>5</td>
<td>Fixed</td>
<td>0.598</td>
<td>0.500-0.714</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>Fixed</td>
<td>0.590</td>
<td>0.490-0.709</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, Confidence interval; GSTM1, Glutathione S-transferase mu 1; GSTT1, Glutathione S-transferase theta 1.

Some studies have involved the association between GSTM1/T1/P1 gene polymorphisms and vitiligo susceptibility [26, 32, 38, 39]. However as regard to the relation, there is still a controversy. Therefore, in the present study, we further evaluated the association of GSTM1/T1/P1 gene polymorphisms with vitiligo susceptibility using a meta-analysis.

Materials and methods

Literature search strategy

In order to confirm the association between the risk of vitiligo and GSTM1/T1/P1 polymorphisms were as follows: Case and control studies were searched in database of EMBASE, GOOGLE, KISS, MEDLINE and PubMed, up to January 2015 without language restrictions. Relevant studies were identified using the terms: “glutathione S-transferase”, “GSTM1 or GSTT1 or GSTP1”, AND “polymorphism” or “polymorphisms or variant” AND “Vitiligo”. The study was restricted to human. Additional studies were searched by hand search of original or review articles references. If data or data subsets were published in more than one article,
only the genetic data with the large sample size was included.

Selection criteria for the meta-analysis

Studies were included if they met the following criteria: (1) evaluated the association between the GST polymorphism (GSTM1, GSTT1, and GSTP1) and vitiligo; (2) used a case-control study design; (3) contained sufficient published data for the estimation of an odds ratio (OR) with a 95% confidence interval (CI).

Extraction of the data for the meta-analysis

The two investigators independently extracted data and reached consensus on all of the items. If the two investigators generated different results, they would check the data again and had a discussion to come to an agreement.

Statistical analysis of the study data for the meta-analysis

Meta-analysis was performed using the Comprehensive Meta-analysis software (COrporation, NJ, USA). The pooled P-value, OR and 95% CI were used to investigate association between risk of vitiligo and GSTM1, GSTT1, or GSTP1 polymorphism.

Firstly, we calculated the heterogeneity. A χ²-test-based Q statistic test was performed to test heterogeneity of study and we also performed the effect of heterogeneity by I² test. The random-effects Mantel-Haenszel method was adopted if the result of the Q test was P<0.05 or I² statistic was >50%, which indicated the statistically significant heterogeneity between the studies. Otherwise, the fixed-effects Mantel-Haenszel method was adopted. OR with the corresponding 95% CI was calculated for the dominant model and recessive model, and allele, respectively.

For meta-analysis of GSTM1 and GSTT1 polymorphisms, the pooled ORs, 95% CI, and P-value were calculated using null type versus (vs.) present type, respectively. And combination of GSTM1 and GSTT1 polymorphisms were also analyzed in meta-analysis [40].

The P<0.05 was considered as statistically significant association with vitiligo.

Results

Characteristics of included studies

Five relevant studies investigated the association between GSTM1 and vitiligo or the association between GSTT1, including 1,258 patients and 1,573 controls (Table 1). The association
between GSTP1 and vitiligo, including 749 patients and 763 controls [26, 32, 38, 39, 41]. When we stratified the analyses by ethnic group, 4 Asian and 1 Caucasian populations were included in the meta-analysis of the association between GSTM1/T1/P1 and vitiligo.

**Meta-analysis of GSTM1 polymorphism and vitiligo susceptibility**

Meta-analysis of GSTM1 null polymorphism in 1,258 vitiligo and 1,573 control subjects revealed significantly association between vitiligo and the GSTM1 null genotype (OR=1.494, 95% CI=1.126-1.981, P=0.005, Table 2 and Figure 1A). In subgroup analysis by ethnicity, there was only association between GSTM1 null genotype and vitiligo in Asian population (OR=1.542, 95% CI=1.097-2.166, P=0.013).

**Meta-analysis of GSTT1 polymorphism and vitiligo susceptibility**

Meta-analysis of GSTT1 null polymorphism in 1,258 vitiligo and 1,573 control subjects revealed significantly association between vitiligo and the GSTT1 null genotype (OR=1.318, 95% CI=1.130-1.537, P<0.001, Table 2 and Figure 1B). In subgroup analysis by ethnicity, it indicated association between GSTT1 null genotype and vitiligo in Asian (OR=1.291, 95% CI=1.101-1.512, P=0.002).

**Meta-analysis of GSTP1 polymorphism and vitiligo susceptibility**

There was only one study about GSTP1 polymorphism and vitiligo. So, we did not performed meta-analysis.

**Meta-analysis of combination of glutathione S-transferase genes (GSTM1 and GSTT1) and the risk of vitiligo**

Combination of GSTM1 and GSTT1 polymorphisms were analyzed by meta-analysis (Table 3 and Figure 2). Combination of both null type in GSTM1 and GSTT1 polymorphisms were compared with combination of other types in GSTM1 and GSTT1 polymorphisms between the vitiligo group and the control group. The results revealed significant association between both null type in GSTM1 and GSTT1 polymorphisms and vitiligo susceptibility (OR=1.369, 95% CI=1.149-1.633, P<0.001 in Table 3 and Figure 2A).

**Discussion**

Several studies indicate that the imbalance between oxidative stress and antioxidation in the epidermal layer of skin may be an important pathogenetic factor of vitiligo [23-25]. These findings demonstrate an impairment of antioxidative system in vitiligo melanocytes, and implicate free radical-mediated damage in melanocyte degeneration in vitiligo [26, 28]. GST as a major group of detoxification enzymes are pivotal components of the cellular defense against oxidative stress [23, 42]. GST are correlated with increased susceptibility to diseases associated with oxidative stress, such as cancer, diabetes, asthma, and Parkinson's disease, and may also be associated with rosacea, UV sensitivity, atopic dermatitis, and vitiligo [26, 43-48].

Recently, some research has shown that the risk for the relationship between vitiligo and GSTM1/T1 null polymorphisms. Our results of overall meta-analysis show a significant association of both null type of GSTM1 and null type of GSTT1 and vitiligo susceptibility. Also, this result indicated no association of both null type of GSTM1 and null type of GSTT1 in Caucasian. In the previous study, there was a significant association with null type of GSTM1 genotypes and vitiligo susceptibility but non-significant association with null type of GSTT1 genotypes and vitiligo [26, 38]. These results agreed with Uhm et al. and Bassiouney et al. their study showed a significant association of GSTM1-null genotype with vitiligo patients. On other hand

<table>
<thead>
<tr>
<th>Combination</th>
<th>Population</th>
<th>Model</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTM1 null type/GSTT1 null type vs. other types</td>
<td>All</td>
<td>Fixed</td>
<td>1.369</td>
<td>1.149-1.633</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GSTM1 null type/GSTT1 present type vs. other types</td>
<td>All</td>
<td>Fixed</td>
<td>1.154</td>
<td>0.980-1.359</td>
<td>0.087</td>
</tr>
<tr>
<td>GSTM1 present type/GSTT1 null type vs. other types</td>
<td>All</td>
<td>Random</td>
<td>0.981</td>
<td>0.586-1.643</td>
<td>0.943</td>
</tr>
<tr>
<td>GSTM1 present type/GSTT1 present type vs. other types</td>
<td>All</td>
<td>Fixed</td>
<td>0.598</td>
<td>0.500-0.714</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, Confidence interval; GSTM1, Glutathione S-transferase mu 1; GSTT1, Glutathione S-transferase theta 1.

Table 3. Meta-analysis of combination of glutathione S-transferase genes (GSTM1 and GSTT1) and the risk of vitiligo
GST polymorphisms and vitiligo

Guarneri et al. and Robou et al. showed non-significant associations between null type of GSTM1 and null type of GSTT1 genotype and vitiligo susceptibility [39]. Also studies of Uhm et al. and Bassiouny et al. showed the inverse results that Liu et al. showed a significant association of null type of GSTT1 with vitiligo susceptibility [32]. GSTP1 Ile/Ile polymorphism non-significant association with vitiligo [32].

We analyzed according to null/present type of combination GSTM1/T1 double genotypes. Our results showed significant association the double-null type of combination GSTM1-GSTT1 versus other combination-types. The null/null, null/present, double-present type of combination GSTM1/T1 double genotypes showed significant association vitiligo in Asian but not in Caucasian. These results similar to those of Bassiouny et al. and Guarneri et al. reports. Uhm et al. showed significant association double-null and null/present type of combination GSTM1-GSTT1 genotypes [26, 28]. Rabou et al. showed significant association double-null and present/null of combination GSTM1-GSTT1 genotypes, however it has only 10 numbers in the control, accordingly it limited in the study [41].

We analyzed depending ethnicity as Asian and Caucasian. Our results of overall meta-analysis show a significant association of both null type of GSTM1 and null type of GSTT1 and vitiligo susceptibility in ethnicity.

This data has some limitations, as a result of the stud-

![Figure 2. OR and 95% CI of individual studies and pooled data for the association between the combination GSTM1-GSTT1 polymorphism and susceptibility of vitiligo; A. Null/null type; B. Null/present type; C. Present/null type; D. Present/present type.](image-url)
ies it is restricted to five small study among Asian and Caucasian. There is a need to consolidate through more research than the future in order to reduce the generalization error. Therefore, further larger studies considering the gene-gene and gene-environment interactions could be required to provide a very precise evidence for the association of GST polymorphism and vitiligo susceptibility.

Disclosure of conflict of interest

None.

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References


