Polymorphisms in the glutathione S-transferase theta and mu genes and susceptibility to myeloid leukemia in Brazilian patients

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Abstract

The null genotype for glutathione S-transferase (GST, EC 2.5.1.18) gene polymorphisms is considered a risk factor for leukemia in different populations. In this work we investigated the GSTT1 and GSTM1 polymorphisms using multiplex PCR in 53 patients with chronic myeloid leukemia (CML), 23 with acute promyelocytic leukemia (APL) and 304 apparently healthy controls. In this association study we found that the GSTT1 null genotype was more frequent in our group of APL patients than in the control group [OR = 2.75 (95% CI = 1.10-6.88)], providing evidence that a deletion in the GSTT1 gene could be a risk factor for this type of leukemia.

Key words: acute promyelocytic leukemia, chronic myeloid leukemia, GSTM1, GSTT1, gene polymorphism.

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Leukemias are complex diseases determined by a combination of several factors. It has been shown that DNA damage in hematopoietic precursor cells is directly linked to the risk of acute leukemia in adults (Rollinson et al., 2000) and may result from an interaction between reactive species generated by environmental or endogenous metabolites (Rollinson et al., 2000; Dalo et al., 2004). Human cells possess metabolic systems to eliminate toxic agents and several enzymes are responsible for the degradation of these xenobiotics, one system being the glutathione S-transferase (GST, EC 2.5.1.18) group of enzymes which detoxify environmental carcinogens by conjugation with glutathione (Crump et al., 2000). The GST group is known to be coded for by 16 genes in six GST subfamilies, known as alpha (GSTA), mu (GSTM), omega (GSTO), pi (GSTP), theta (GSTT) and zeta (GSTZ). Two widespread genetic polymorphisms that involve deletions in GSTT1 and GSTM1 have been reported to lead to loss of enzyme activity (Bolufer et al., 2007) and have been investigated in many different populations, including those from Japan (Naoe et al., 2000), Italy (D’alo et al., 2004) and Spain (Bolufer et al., 2007). Furthermore, several studies have proposed that susceptibility to acute and chronic myeloid leukemia (AML and CML respectively) could be related to GSTT1 and/or GSTM1 deletions (Rollinson et al., 2000; Mondal et al., 2005; Ye and Song, 2005.

Brazil is the largest country in South America, with a highly heterogeneous population due to several waves of immigration which have resulted in cultural, socioeconomic and ethnic diversity. In the Northeastern Brazilian state of Bahia, which has a highly mixed population of mainly African descent, the largest city is Salvador (population 2.7 million; RIPS, 2006), 86% of the local population being of African, or European and African, descent. A recent study by Barreto et al. (2006) reported that the Bahian population shows a high prevalence of pediatric acute promyelocytic leukemia (APL), which accounted for 21% of all AML patients (n = 105) evaluated between 1995 and 2004). Ribeiro and Rego (2006) reported that patients with a Latin American background (i.e. some Amerindian genetic input) were much more likely to have APL (18.2%) than were white (7.7%) or black (10.3%) patients without a Latin American background. Based on this, we decided to investigate the frequency of GSTT1 and GSTM1 polymorphisms among patients with APL and CML from the city of Salvador.

We investigated a total of 76 patients with myeloid leukemia, 53 (30 (57%) male, 23 (43%) female; mean age 41 y ± a standard deviation (SD) of 21 y) with CML and 23 (11 (48%) male, 12 (52%) female; mean age 14 y ± 6.8 y) with APL which were selected at diagnosis between 2000
Table 1 - The glutathione-S-transferase (GST) GSTT1 and GSTM1 polymorphism genotype distribution plus the odds ratio (OR) and 95% confidence intervals (CI) for acute promyelocytic leukemia (APL) patients (n = 23) and chronic myeloid leukemia (CML) patients (n = 53) as compared to apparently healthy control individuals (n = 304).

<table>
<thead>
<tr>
<th>GST genotype</th>
<th>APL, n (%)</th>
<th>CML, n (%)</th>
<th>Control, n (%)</th>
<th>APL vs. controls</th>
<th>CML vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
<td>OR (95% CI)</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>GSTM1&lt;sup&gt;normal&lt;/sup&gt;/GSTT1&lt;sup&gt;normal&lt;/sup&gt;</td>
<td>7 (30.4)</td>
<td>28 (52.8)</td>
<td>165 (54.2)</td>
<td>1&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>GSTM1&lt;sup&gt;del&lt;/sup&gt;/GSTT1&lt;sup&gt;normal&lt;/sup&gt;</td>
<td>7 (30.4)</td>
<td>15 (28.3)</td>
<td>100 (33.0)</td>
<td>0.89 (0.32 to 2.40)</td>
<td>0.80&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>GSTM1&lt;sup&gt;normal&lt;/sup&gt;/GSTT1&lt;sup&gt;del&lt;/sup&gt;</td>
<td>5 (21.7)</td>
<td>8 (15.1)</td>
<td>25 (8.2)</td>
<td>2.75 (1.10 to 6.88)</td>
<td>0.04&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>GSTM1&lt;sup&gt;del&lt;/sup&gt;/GSTT1&lt;sup&gt;del&lt;/sup&gt;</td>
<td>4 (17.5)</td>
<td>2 (3.8)</td>
<td>14 (4.6)</td>
<td>3.61 (1.37 to 9.51)</td>
<td>0.02&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Reference group (OR=1.0); †Chi-square test/Yates correction; ‡Fisher’s exact test.
ent pattern of GSTT1 polymorphism frequency among the APL patient group. Since the GSTT1 enzyme is responsible for the detoxification of environmental xenobiotics these results may be associated with high rates of APL in the investigated population. Barragan et al. (2007) recently suggested the influence of GST deletions on treatment follow up after chemotherapy in adult non-promyelocytic patients.

We observed similar frequencies in CML patients and controls but Lourenço et al. (2005) found a lower frequency of the GSTT1 null genotype in CML Brazilian patients who were both in the blast crisis or in the chronic phase, while Mondal et al. (2005) observed an increase in the GSTT1 null genotype in CML patients from India.

Our population was composed of an admixture of Amerindian, African and European-derived subjects, and the GST polymorphisms is known to exhibit different frequencies according to ethnic group (Gattas et al., 2004). Our results were different from those for individuals of European-descent from the Southeastern Brazilian state of São Paulo reported by Gattas et al. (2004), who found frequencies of 22.3 for the GSTT1 null and 55.4% for the tGST1 null genotypes. This difference can be explained by the high percentage of African genes present in Salvador population.

In conclusion, our analyses suggest that the GSTT1 genetic background might be an important marker for APL risk, at least in Salvador.

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