Letter to the Editor

Gaucher disease: frequency of the N370S mutation in the Greek population

To the Editor:

The N370S (c.1226G>A) mutation is exclusively associated with type I Gaucher disease (GD) and has a prevalence of more than 70% in Ashkenazi and up to 63% in non-Ashkenazi patients (1–4). However, studies in the Ashkenazi and Portuguese populations have shown that the estimates of disease and gene frequencies, based on the number of diagnosed cases, are not reliable and present an underestimate of the true situation (5–7).

In Greece, 82 type I GD patients have been diagnosed. In all but one, the N370S mutation has been detected in either homo- or heterozygosity accounting for 97/162 of the studied alleles. In this study, we investigated the true frequency of the mutation by studying the genomic DNA purified from 1933 Guthrie cards, randomly sampled from the Greek National Neonatal Screening Program.

Genomic DNA was isolated by boiling in 5% Chelex 100 resin (8) and the detection of N370S was performed by Beutler et al.’s (9) method.

Eighteen heterozygotes and no homozygotes for the N370S mutation were identified. Thus, according to this finding, the frequency of the N370S allele in the Greek population is 0.0046 with 95% confidence limits between 0.0025 and 0.0068. Applying the Hardy–Weinberg equation, the expected number of homozygotes in our population of $11 \times 10^6$ individuals should be 238, that is 1:50,000 individuals should be a type I GD patient bearing the N370S/N370S genotype. However, in the past 25 years, only 18 such cases have been diagnosed in our laboratory at the Institute of Child Health, which is the reference laboratory for Greece, and homozygosity through parental DNA analysis was confirmed in 5 of 18 patients. It appears, therefore, that there is a considerable underdiagnosis of N370S homozygotes and an underestimation of the frequency of the N370S allele in our population. It was proposed that the homozygosity for N370S is associated with very mild disease that remains undiagnosed. In particular, according to Beutler et al. (5), only one-third of the N370S homozygotes are patients with GD. Should this be the case for our population too, 79 such patients should still have been diagnosed in Greece (one-third of the predicted number).

On the other hand, phenotypic heterogeneity, with a moderate to severe phenotype in a subset of type I GD patients homozygous for the N370S mutation, has been recently reported (10). The main criticism for this report is that it is not clear whether the patients are true homozygotes (11, 12). Nonetheless, phenotypic heterogeneity has been described in homozygous monozygotic twins (13), as well as ‘true’ N370S homozygotes that even showed, for some parameters at least, more severe manifestations than the N370S/55-bp deletion (c.1226G>A/c.1263del55) compound heterozygotes (12). The characteristics of the proven N370S homozygotes diagnosed in our laboratory are shown in Table 1. Phenotypic heterogeneity was observed within this cohort that ranged from the lack of symptoms to onset in early childhood. In particular, although a 19-year-old asymptomatic patient with moderate elevation of plasma chitotriosidase activity was diagnosed following the diagnosis of GD in his mother, early onset of disease with highly increased plasma chitotriosidase activity was observed in a 9-year-old patient. Thus,

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age on enzymic diagnosis (years)</th>
<th>Reason for referral</th>
<th>Chitotriosidase activity (plasma; nmol/ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Splenomegaly</td>
<td>2568</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>Thrombocytopenia</td>
<td>4335</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>Splenomegaly</td>
<td>18,144</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>Splenomegaly</td>
<td>22,595</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>Asymptomatic</td>
<td>1881</td>
</tr>
<tr>
<td>Control range</td>
<td></td>
<td></td>
<td>0–150</td>
</tr>
</tbody>
</table>

*Genotyping of the chitotriosidase gene was possible in patients 2 and 4 and the 24-bp duplication in exon 10 was detected in heterozygosity in patient 2.
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although absent-to-mild disease manifestations can be associated with N370S homozygosity in our population too and possibly account for the under-diagnosis of these cases, more severe phenotypes can also be observed as previously suggested (10). The challenge of understanding the nature of environmental and genetic factors determining this heterogeneity remains to be met.

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