Molecular evidence that fragile X syndrome occurs in the South African black population

Although fragile X syndrome has been described in various populations worldwide, there is limited information on fragile X syndrome in indigenous blacks. The syndrome is proposed to be rare with no case reports apart from one Zulu family originally reported and two black South African families later identified.

In an attempt to determine whether fragile X syndrome occurs in the black population of South Africa, a group of 148 unrelated, institutionalized males (aged 16 to 77 years) was studied. The degree of mental retardation varied from severe (77 cases) to mild (71 cases). They were tested for the presence of the FMR-1 CGG expansion using EcoRI digested DNA which was hybridised with the StB12.3 probe. Nine full mutations (6.1%) were detected, six in 77 (7.8%) of the severely retarded males and three in the 71 (4.2%) mildly handicapped subjects. No premutations were detected in any of the subjects. This figure is comparable to that in worldwide studies, showing a range of 2.2 to 4.2% for frequencies of the syndrome in institutionalised males, depending on the criteria used.

The craniofacial features, typically found in white patients with fragile X syndrome, have been reported to occur less frequently in black patients.

This study presents the first molecular evidence that fragile X syndrome occurs in the South African black population. The previous suggestion of the absence (or low frequency) of this disorder in the black population is certainly the result of ascertainment bias. This finding of a frequency of 6.1% of CGG full mutations in this group of institutionalised blacks indicates that fragile X syndrome has been severely underdiagnosed in the past and is a significant cause of mental handicap in the black population. This is supported by the diagnosis of an additional 19 black families (18%) from the routine DNA diagnostic testing of 103 black families for fragile X syndrome in this department since 1994.

We are grateful to Sr Merlyn Glass and Sr Esther Zware for help in collecting blood from patients, to the staff of the Department of Pathology, Dr J Senaha, superintendent of Tshwane, and Dr J Botha, superintendent of Milaan, for their invaluable help and cooperation, to the Reverend Jean-Louis Mandel for the gift of the probe StB12.3, and to Fahmida Essop who has performed some of the diagnostic work. Financial assistance was received from the Iris Ellen Hodges Cardiovascular Fund, H E Griffin Trust, University of the Witwatersrand, and The South African Institute for Medical Research.

Table 1 Frequency of the C282Y and H63D mutations among healthy Hungarians

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Total No of subjects tested</th>
<th>No of heterozygotes</th>
<th>No of homozygotes</th>
<th>Allele frequency (% 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y</td>
<td>277</td>
<td>31</td>
<td>-</td>
<td>5.6 ± 2.0</td>
</tr>
<tr>
<td>H63D</td>
<td>27</td>
<td>5</td>
<td>-</td>
<td>12.3 ± 2.8</td>
</tr>
</tbody>
</table>

Table 2 Number and ratio (%) of subjects with different point mutations and of compound heterozygotes. CC and HH: normal frequency

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No (%)</th>
<th>HH No (%)</th>
<th>H6D No (%)</th>
<th>DD No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y</td>
<td>13.6%</td>
<td>-</td>
<td>13.6%</td>
<td>-</td>
</tr>
<tr>
<td>H63D</td>
<td>12.3%</td>
<td>-</td>
<td>12.3%</td>
<td>-</td>
</tr>
</tbody>
</table>

High frequency of the haemochromatosis C282Y mutation in Hungary could argue against a Celtic origin of the mutation

Recently, Merryweather-Clarke et al reported mutation frequency data regarding two point mutations of the newly described gene HFE or HLA-H, 13 thinking to play an important role in the pathogenesis of hereditary haemochromatosis (HH). The authors concluded that the distribution pattern of the C282Y point mutation is similar to that of HH and the disease was previously suggested to be of Celtic origin.

In order to obtain comparable data for Hungary, we carried out PCR-RFLP analyses of 277 randomly selected, unrelated, healthy subjects for the presence of the C282Y (G845A) point mutation by using the RAl digestion method, as previously described.

In each case, the results were confirmed by a novel, alternative amplification generated restriction site (AGRS) technique. The DNA samples were amplified using the primers 5’-GGGAAGGCGAGGATAAGGT-3’ and 5’TCTGACCATGCTTCCCAAC−3’ followed by digestion by KpnI. As shown in table 1, we identified 31 heterozygotes, which corresponds to a relatively high C282Y allele frequency (5.6%) in the Hungarian population analysed.

It is the role of the second point mutation of the HFE gene, H63D (C187G), in HH is not yet established. In a number of studies, H63D has been found to be a frequent mutation in normal white populations. For the analysis of this point mutation in the above Hungarian population we used a PCR-RFLP technique using BclI digestion, as previously described.

In our cohort we identified 58 heterozygotes and five homozygotes for the H63D point mutation and an allele frequency of 4.2% (table 1). Interestingly, in the second set of compound heterozygotes in our group, indicating a similar distribution to that previously published.

Our data represent the first frequency data for both point mutations in a large cohort from the central European region. Interestingly, the Hungarian C282Y allele frequency substantially exceeds the European average (3.6 ± 3.8%), while the H63D point mutation is closer to the European average (12.3 ± 13.6%).

A Celtic origin of HH has been proposed by several authors.14 This was supported by studies of white populations with clear Celtic origin, as well as of several African and Asian populations. Merryweather-Clarke et al rejected this as not being the case in their study of non-Celtic populations. However, Hungarians are a sort of population which do have a mixed origin with various ethnic groups. The current study was selected mainly from Budapest which is thought to be a mixed population, representative of the current Hungarian population.

The cohort in the current study was selected mainly from Budapest which is thought to be a mixed population, representative of the current Hungarian population. Although some degree of admixture with people of non-Celtic origin exists among Hungarians, because of the different origin and as a consequence of the profound effects of admixture with people of non-Celtic origin, this study can be viewed as an indicator of the proportion of the population which could be of Celtic origin. However, further studies are needed to establish this conclusion.
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