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

Although fragile X syndrome has been described in many 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, institutionalised 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 FMRI-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 2.4% 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. Similar dysmorphic and behavioural features to those described in white patients were, however, noted in the South African black patients. The phenotype and mutation appears, therefore, to be similar in all racial groups.

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 Dr Merilyn Glass and Dr Esther Zware for help in collecting blood from patients, to the pathologists Drs. T. Ewenson, Dr. J. Semela, superintendent of Tshakane, and Dr J. Botha, superintendent of Milnerton, for their invaluable help and cooperation, to Messrs. Jean-Louis Mandel for the gift of the probe STB12.3, and to Fathima Essop who has performed some of the diagnostic work. Financial assistance was received from the Iris Ellen Hedges Cardiovascular Fund, H E Griffin Trust, University of the Witwatersrand, and The South African Institute for Medical Research.

ANDREA GOLDMAN

TREFOR JENKINS AMANDA KRAUSE
Department of Human Genetics, School of Pathology, The South African Institute for Medical Research and University of the Witwatersrand, PO Box 1038, Johannesburg 2000, South Africa


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, thought 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'-GGGAGACAGAATATAGGT-3' and 5'-CTCAGGCACTCTTCCACG-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.

Table: C282Y and H63D mutations among healthy Hungarians

<table>
<thead>
<tr>
<th>Population</th>
<th>Total No of individuals</th>
<th>Number of heterozygotes</th>
<th>Allele frequency (% ± 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>277</td>
<td>31</td>
<td>5.6 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>277</td>
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</table>

2 C282Y allele frequency (5.6%) in the Hungarian population analysed.

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 5C and five heterozygotes for the H63D point mutation and an allele frequency of 12.3% (table 1). As expected, the frequency of compound heterozygotes in our group, indicating a similar distribution to that previously published.

Our data represent the first frequency data for the H63D point mutations in a large cohort from the central European region. Interestingly, the Hungarian C282Y allele frequency substantially exceeds the European average (5.6 ± 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. 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 reported an average European allele frequency of 3.8% for the C282Y point mutation with a high frequency in Great Britain (6.4%), Norway (6.4%), and Iceland (6.7%), a lower frequency in Germany (3.8%) and Spain (3.7%), and rare occurrence of the mutation in Finnish (0%), Greek (1.4%), and Turkish (0%) populations. In non-European cohorts, the C282Y point mutation was practically undetectable.

Hungarians ("Magyars") settled in the Carpathian basin in the 9th century AD, well after the settlement of Celts, which took place between the 2nd millennium and the 1st century BC. Since the settlement of Hungarians, the original people have mixed with several other populations of different origins, including Slavic, German, Turkish, Gypsy, and Jewish people. Thus, it is currently viewed that Hungarians represent a very mixed population with the closest genetic relationship to Slavic and German people and rare occurrence of the H63D mutation.

The cohort in the current study was selected mainly from Budapest which is thought to be a mixed population, representative of "modern Hungarians". Although some degree of admixture with Celtic people (for example, Germans) exists among Hungarians, because of the different origin and as a consequence of the profound effects of intermarriage with people of non-Celtic origin, the origin of the Hungarians has been viewed as predominantly "Magyar" as for a long time the "Magyar" root seems to have been the dominant one in the Timoros population of Hungary.

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

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(for example, Turks), Hungarians cannot be viewed as a Celtic population. Thus, we show a relatively unexpected high frequency of the C282Y point mutation in Hungarians which, to some extent, argues against a Celtic origin of this mutation.

The help of Éva Bakos and Pavol Ivanýi is gratefully acknowledged. This work was supported by grants from the National Ministry of Social Welfare Health (ETT 211/1996), OMFB (5958), and OTKA (F 17270). AT is a recipient of the “Magyar Zoltán” scholarship.

ATTLA TORDAI
HAJNALKA ANDRIKOVICS
LAJOS KALMÁR
KATALIN RAJCZY
MARIA PÉNZES
BALÁZS SARKADI
National Institute of Haematology and Immunology, and Research Group of the Hungarian Academy of Sciences, Budapest, Hungary

IZABEL KLEIN
ANDRAS VARADI
Institute of Enzymology of the Hungarian Academy of Sciences, Budapest, Hungary


Hypoplastic left heart in cerebrocortical-mandibular syndrome

Cerebrocortical-mandibular syndrome (CCMS) is a rare disorder characterised by severe micrognathia and posterior “rib gap” defects. Since the first report of this condition by Smith et al. in 1966, 50 cases have been reported.1 Severe micrognathia and radiographic evidence of posterior rib gap defects have been constant features. We report a female infant with typical features of CCMS who also had hypoplastic left heart syndrome, which caused her death. A cardiac lesion has been identified in only one before CCMS and an infant with a large ventricular septal defect.1

The female proband was the third child of healthy, unrelated parents. Her father and mother were of French and Mauritian descent, respectively. Neither parent had any clinical or radiographic evidence of mild cardiac malformations even though this finding is uncommon.

EDWIN KIRK LESLEY ADES
Departments of Clinical Genetics, and Paediatrics and Child Health, Royal Alexandra Hospital for Children, Hawthorne Road, Westmead, NSW 2145, Australia


Another dystonia

I read the Syndrome of the Month article on the dystonias by Jarman and Walker with great interest.1 This is a difficult clinical subject to study and the move to a molecular genetic classification is to be applauded. Accordingly I would like to draw attention to another form of dystonia which has been mapped to the short arm of chromosome X (X chromosome region DXS258-310).

The dystonia is manifest mainly in the hands. The onset can be recognised in childhood by an odd positioning for some voluntary movements such as holding a pencil; this has been called “fixing” by the family. More obvious dystonic movements develop in adolescence and these progress slowly over the years. The hands of the oldest affected subject, now aged 68, are severely disabled and he needs to be dressed and fed. This man also has dysarthria.

The other prominent and important feature of this syndrome is mental retardation of mild to moderate degree, more often the latter. The heterozygote carriers do not seem to be affected.

The syndrome is quite well known in medical genetics publications.1,2 It has been given two gene symbols, PRTS1 and MRX515, and is listed in the McKusick catalog (MIM 309510). It was first reported 10 years ago in one family, but so far no other cases have come to light. It is conceivable that it is a private syndrome with the mutation occurring in this family alone, but I believe it more likely that there are other cases with the disorder which have just not been recognised. Part of the reason may be that the neurologists are not familiar with this form of dystonia.

M W PARTINGTON
Hunter Genetics, PO Box 84, Waratah, NSW 2298, Australia