LETTERS TO THE EDITOR

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

Although fragile X syndrome has been described in most 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 reported¹ and two black South African families later identified.²

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 FMR-1 CGG expansion using *EcoRI* digested DNA which was hybridised with the StB12.3 probe.³ 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.⁴ No premutations were detected in any of the subjects. This figure is comparable to that in worldwide studies, showing a range of 2.4% to 4.2% for frequencies of the syndrome in institutionalised males, depending on the criteria used.⁵⁻⁷

The craniofacial features, typically found in white patients with fragile X syndrome, have been reported to occur less frequently in black patients.⁸ 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.

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

Recently, Merryweather-Clarke *et al*¹ reported mutation frequency data regarding two point mutations of the newly described gene HFE or HLA-H,² 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.³

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 *RsaI* digestion method, as previously described.⁴ In each positive case, the results were confirmed by a novel, alternative amplification generated restriction site (AGRS) technique. The DNA samples were amplified using the primers 5'-GGGAAGAGCAGAGATATAGGT-3' and 5'-CTCAGGCACTCCTCTCAACC-3' followed by digestion by *KpnI*. As shown in table 1, we identified 31 heterozygotes, which corresponds to a relatively high

Table 2 Number and ratio (%) of subjects with the different point mutations and of compound heterozygotes. CC and HH: normal genotypes for the respective mutations; CY: C282Y heterozygote; HD: H63D heterozygote; DD: H63D homozygote. Total number of subjects examined = 277

	HH No (%)	HD No (%)	DD No (%)
CC	188 (68)	53 (19)	5 (2)
CY	26 (9)	5 (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.² In a number of studies,¹ H63D has been found to be a frequent mutation in normal white populations.¹ For the analysis of this point mutation in the above Hungarian population we used a PCR-RFLP technique using *BclI* digestion, as previously described.⁵ In our cohort we identified 58 heterozygotes and five homozygotes for the H63D point mutation and an allele frequency of 12.3% (table 1). Table 2 shows the ratio of compound heterozygotes in our group, indicating a similar distribution to that previously published.¹

Our data represent the first frequency figures for the C282Y and 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 v 3.8%) while the H63D point mutation is closer to the European average (12.3 v 13.6%).¹

A Celtic origin of HH has been proposed by several authors.^{1,3,6} This was supported by studies of white populations with clear Celtic origin, as well as of several African⁶ and Asian¹ populations. Merryweather-Clarke *et al*¹ 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 (3.9%) and Spain (3.2%), 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 ethnic groups.⁷

The cohort in the current study was selected mainly from Budapest which is thought to be a mixed population, representative of "modern Hungarians".⁷ 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 admixture with people of non-Celtic origin.

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

Point mutation	Total No of subjects tested	No of heterozygotes	No of homozygotes	Allele frequency (% ± 95% CI)
C282Y	277	31	—	5.6 ± 2.0
H63D	277	58	5	12.3 ± 2.8