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 reported[1] 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 *Eco*RI 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 *Rsa*I 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 *Kpn*I. 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.

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)	—

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 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 *Bcl*I 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 African[6] and Asian[4] 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

(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.

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Hypoplastic left heart in cerebrocostomandibular syndrome

Cerebrocostomandibular 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*[1] in 1966, 50 cases have been reported.[2] 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 only once before in CCMS, in an infant with a large ventricular septal defect.[3]

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

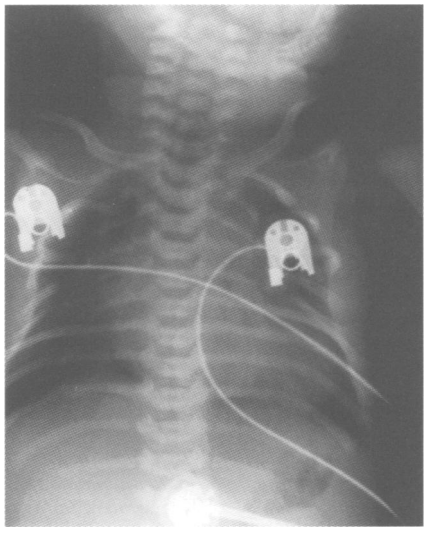

Figure 1 Chest radiograph showing multiple rib gaps.

CCMS. The pregnancy was uncomplicated, with spontaneous vertex delivery at 37 weeks' gestation. Birth weight was 2200 g, length 45 cm, and occipitofrontal circumference 31 cm (all less than the 3rd centile for gestational age). Features noted at birth included severe microretrognathia, glossoptosis, and a midline cleft of the soft palate, all of which contributed to early upper airway obstruction and moderate respiratory distress. Initial examination was otherwise normal.

A chest radiograph (fig 1) showed multiple posterior rib gaps involving the second to sixth ribs on the right and the second to fifth ribs on the left. The gap in the right second rib resembled a pseudarthrosis. There were 11 pairs of ribs. Cranial ultrasound was normal. Karyotype on peripheral blood lymphocyte culture was 46,XX.

On the third day of life a cardiac murmur was noted. Echocardiography showed findings consistent with hypoplastic left heart syndrome. Given the poor prognosis associated with hypoplastic left heart syndrome, active management was withdrawn and she died aged 8 days. Her parents declined necropsy.

This is the second reported case of a cardiac anomaly in CCMS, and the first in which hypoplastic left heart syndrome is described. A potential mechanism to account for the concurrence of hypoplastic left heart and CCMS is unclear. Vascular insufficiency has been postulated in the causation of hypoplastic left heart syndrome, but there is no evidence to support a disturbance in normal rib morphology on this basis. Embryologically, the heart is derived from lateral plate mesoderm and the ribs from paraxial mesoderm. Mandibular deficiency is considered to be the result of a defect in the ventral portion of the first branchial arch secondary to defective neural crest cell migration or proliferation. CCMS and hypoplastic left heart syndrome in our patient may have occurred together as part of a developmental field defect. Alternatively, an underlying basic defect in a developmental transcription control or signalling gene is possible. The CCMS phenotype should be expanded to include cardiac malformations even though this finding is uncommon.

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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 the X chromosome between DX528 and DXS365.[2,3]

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[2]; this has been called "fisting" 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.[4,5] It has been given two gene symbols, PRTS[3] and MRXS1,[4] and is listed in the McKusick catalogue (MIM 309510). It was first reported 10 years ago in one family in Australia 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 others with the same disorder which have just not been recognised. Part of the reason may be that the neurologists are not familiar with this form of dystonia.

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