LETTERS TO THE EDITOR

Huntington's disease in Saudi Arabia

We read with interest the letter by Scrimgeour et al in the November issue of this Journal. Our hospital, King Faisal Specialist Hospital and Research Centre, is the major referral centre for tertiary care in this country and, over a period of six years, four native Saudi families have been diagnosed with Huntington's disease at our hospital. One of these families (family 1) was described by Scrimgeour et al in their letter. The second family lives in Qatif, an old city on the Arabian Gulf. The family live in the mid-northern area of the Arabian peninsula and are of Bedouin (nomad) origin, while the fourth family live in Qassim, the central part of the peninsula.

Huntington's disease is clearly autosomal dominant in all. The disease starts around early adult life with mood and personality changes, clumsiness, and chorea. Brain MRI scan confirmed striking caudate atrophy with increased bicaudate diameter. All metabolic and haematological tests were normal. Apart from a maternal grandfather from family 1 who married into a Moroccan family, there were no known foreign antecedents.

Analysis of the trinucleotide repeat in the Huntington gene IT15 (4p16.3) by means of PCR confirmed the presence of an expanded repeat in members of families 2, 3, and 4. The findings in family 2 were included in the worldwide study of the Huntington's disease mutation organised by Dr Hayden's group. A DNA study in the third and fourth families was done with the help of the Department of Human Genetics at the State University, Leiden, The Netherlands. Expanded repeats were found in all affected patients within a range of 42 to 50.

Similar findings were seen among other Huntington's disease cases from different nations and ethnic groups. As indicated in these reports, CAG expansion is highly specific for Huntington's disease and not seen in other neuropsychiatric disorders with which Huntington's disease can be confused clinically.

While the comment of Scrimgeour et al that the disease gene was transmitted to the Saudi families by Europeans visiting the Red Sea or the Arabian Gulf may be true, we think this is unlikely. Such ethnic intermixing could not be substantiated in our cases; we think this is particularly unlikely in native nomads. Marriage outside the tribe is a very uncommon practice. It is more likely that a fresh mutation accounted for Huntington's disease in these families.

The new mutation rate in Huntington's disease, previously deemed to be exceedingly rare, is now known to be responsible for up to 3% of affected persons. As shown in a study of sporadic cases of Huntington's disease, new mutations arise from parental intermediate alleles which are meiotically unstable and in sporadic cases expand to full mutation associated with the phenotype of Huntington's disease. Patients with sporadic Huntington's disease can transmit their expanded CAG repeat to their offspring, who then will subsequently develop Huntington's disease. So, although the prevalence of Huntington's disease in this country is not known, Saudi Arabia may harbour many more Huntington's patients than previously thought.

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Different muscle specific promoter characteristics in two sibs with Duchenne muscular dystrophy

Molecular analysis of the dystrophin gene in DMD and BMD patients has recently been developed. It has been reported that in DMD mutations in the muscle specific promoter (Pm) region are rare. It has been shown by in vitro CAT assay that only the 149 base pair (bp) upstream sequence of the promoter region is enough for muscle specific transcriptional activation, yet detailed analysis in this region in vivo has not been done. We report DMD sibs in whom the DMD gene is deleted upstream of the Pm region.

We examined two male sibs with typical DMD who showed quite similar clinical features. Both of them were confined to a wheelchair at the age of 11. Their intellectual function was slightly retarded. No cardiac abnormalities were noted in either. Since no gross deletions/duplications in their DMD gene were identified by Southern blots using DMD cDNA probes 1–2a, 2b–3, 4–5a, 5b–6, 7, 8, 9, and 10, we examined the muscle specific promoter region using the polymerase chain reaction (PCR), single strand conformation polymorphism analysis, and heteroduplex analyses. Four sets of primers were used for analysis of the muscle specific promoter gene, that is, Begg's primer (Pm; P4F and E1R), P7F and E0R, P8F and P2R, and BF and BR. BF and BR were located in the brain specific promoter region, and the others were in the muscle specific promoter region (figure).

In the younger sib, PCR products for P4F-E1R, P4F-E0R, or BF-BR were obtained, but not for P7F-E0R, P7F-E1R, or P8F-P2R. In the older sib, PCR products were detected for all the primers (figure). Point mutations were not detected by these analyses for P4F-E1R fragments in either. The size of the HindIII band of the Pm region in the younger sib on Southern blots was different (about 0.1–0.2 kb shorter) from those in the older brother and in their mother. The deleted length in the younger sib was estimated to be within 10 kb according to the physical map of this region (figure).

The muscle specific promoter region includes ATA box, GC box, CARG box, muscle CAT (MCAT), myocyte specific enhancer binding nuclear factor 1-like (mef-1-like), and mef-2 like sequences (figure). Because the promoter region was different in both sibs, we traced the parental origin of the X chromosome using polymeric PCR with p84/ MaelIII, located near the muscle specific promoter region, p87–8Taq, p87–15Xmnl, and 3'CA, and confirmed that the same X chromosome was transmitted to both sibs from their mother. The deletion in the younger sib could have occurred by de novo mutation or germine mosaicism. The pathogenetic significance of this deletion would be (1) the mutation is entirely unrelated to this change, (2) two independent mutational events have occurred on the same haplotype, or (3) one common (unknown) pathogenetic mutation has occurred and has somehow precipitated the second change.

![Schematic representation of the muscle specific promoter region and the location of a mutation in DMD sibs. The younger brother had a micromutation upstream from the P7F-P4F region.](http://jmg.bmj.com/firstpublishedas/10.1136/jmg.32.4.325)