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. Members of this family live in the mid-northern area of the Arabian peninsula and are of Bedouin (nomad) origin, while the fourth family lives in Qassim, the central part of the peninsula.

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 world wide study of the Huntington's disease mutation organise 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 is 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 imprinting at loci 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 (PmA) 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 one of whom the DMD gene is deleted upstream of the PmA 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 sib. 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, Peggs' 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 sib. The size of the HindIII band of the PmA 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 polymorphic PCR with p84/MaelIII, located near the muscle specific promoter region, p87–87′/Taql, p87–15′/Xmnl, 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 germline 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 or more factors (such as hypermethylation) 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 microdeletion upstream from the P7F-P4F region.
Family pedigree.

Autosomal dominant simple microphthalmos: incomplete penetrance and variable expression in a large family

We read with interest the well documented report by Vingolo et al on “Autosomal dominant simple microphthalmos”. The authors describe a large pedigree with 14 persons in four generations affected with bilateral microphthalmos without other ocular or systemic signs. The family data were most compatible with autosomal dominant inheritance with complete penetrance. Based on the findings in this family and a review of published reports the authors concluded that “simple, partial, posterior pure microphthalmos and nanophthalmos are similar clinical entities sharing total axial length and vitreous cavity length reduction”.

During the past few years we have been contacted by several members of a large family (see pedigree in the figure) for genetic counselling after the birth in this family of three children (III-6, III-7, IV-1), two boys and one girl, with “uncomplicated” bilateral anophthalmos. All three are mentally normal at the respective ages of 12, 9, and 8 years.

Further clinical and laboratory examinations, including chromosome studies, were normal but CT scans of the brain showed complete absence of ocular structures but normal optic nerves in all three. Further familial investigation showed normal ophthalmological findings in all family members, except I-1 (paternal great grandfather of IV-1 and maternal grandfather of III-6 and III-7) and I-2 (paternal grandfather of IV-1) and III-4. All three presented a unilateral left sided extreme form of microphthalmos with cloudy corneae and total axial lengths below 8 mm. Clinical and biometric findings of the contralateral eyes were normal.

The ocular anomalies in the affected members of the present family thus varied greatly from bilateral true anophthalmos to unilateral microphthalmos with small anterior segment and cloudy corneae. The findings in this family are most compatible with autosomal dominant inheritance with variable expression and incomplete penetrance and confirm the observations reported by Bateman who described a three generation family with non-colobomatous microphthalmos dominantly inherited with incomplete penetrance and variable expressivity.

Grebe syndrome: a very severely affected case

Grebe syndrome is a very rare form of short limb dwarfism, inherited as an autosomal recessive trait. It is characterised by shortening affecting the lower limbs more than the upper limbs and distal parts more than proximal parts resulting in bulbous fingers and toes, whereas the head, neck, and trunk are essentially normal. The classical clinical and radiological features and other unusual clinical features have been described previously. In the present communication we report an extreme form of Grebe syndrome in which there was a total absence of bones in the lower limbs, features which have not been reported previously.

A male neonate was born at term to a consanguineous couple (uncle-niece) showing characteristic features of Grebe chondrodysplasia (fig 1). There was progressive shortening of the limb bones from the proximal to distal ends. The lower limbs were more severely affected than the upper limbs. The hands and feet were extremely small with bulbous digits. There were four fingers and a thumb on both hands and five toes on both feet. The head, neck, and trunk were essentially normal. His length was 30 cm, upper segment 24 cm, lower segment 6 cm, head circumference 30 cm, chest circumference 27 cm, upper limb length 10-5 cm, lower limb length 8 cm, and weight...
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