LETTERS TO THE EDITOR

Juvenile onset Huntington's disease in an Omani child with asymptomatic, at risk parents

A 6 year old Omani Arab girl presented with one year's history of progressive intellectual deterioration, grimacing, dysarthria, dystonic posturing of the hands, and ataxia with falls, and was now severely retarded and mute. She came from a family affected by Huntington's disease (HD) (fig 1). Her parents, III.19 and III.20, who were cousins aged 36 and 27 years respectively, reported that their mothers, II.2 and II.5, had died from HD. Both parents appeared to be healthy and were asymptomatic, but they suspected that their child had inherited the "familial disease".

Early onset HD was confirmed by CT brain scan, which showed marked atrophy of the caudate nuclei, and DNA studies using PCR techniques, performed in Glasgow, which showed one abnormal band equivalent to 92 CAG repeats in the HD gene (IT14 4p16.3), and a second band equivalent to 18 repeats (indicating one affected parent). Neither parent consented to predictive testing; however, it is suspected that she inherited the mutation (without the massive expansion) from her father. In juvenile cases, the father is the affected parent three to four times more frequently than is the mother and there is a female preponderance.1

Subject III.10, aged 55 years, symptomatic for five years, was also assessed and the diagnosis of HD was supported by CT brain scan which showed marked caudate nuclei atrophy. Subjects III.1 and III.2, reported to be symptomatic, have not yet been assessed.

Since studying the first family, HD has been diagnosed in an unrelated Omani family. The proband was a 23 year old married woman with three children, who presented with 4 years' progressive choreoathetosis and recent onset of early dementia. Her father, who died at 62 years, is presumed to have had HD. The patient's CT brain scan showed marked caudate atrophy, with a 22 mm bicaudate diameter (normal range 12.5-15 mm), and DNA study showed 54 CAG repeats in the HD gene. She has five sibs aged 14 to 28 years, who have not yet been assessed.

HD is known to occur in Arabs in Saudi Arabia,2 Syria,3 Egypt,4 and Lebanon,5 but this is the first report from Oman. Our families appear to be of unmixt Arab ancestry and the gene may have been introduced by mutation.6 However, Oman has had a long history of international trading and contact (for example, the Portuguese ruled Muscat and coastal Oman during the 17th and first half of the 18th centuries), and the gene could have been introduced by foreigners at an earlier time. A HD support service has now been established in Muscat, to provide counselling and to arrange predictive testing according to international guidelines.7

EUAN M SCRMIGEOUR
ROSHAN L KOUIL
PRATAP R CHAND
JOHN K J THARAKAN
Departments of Medicine and Pediatrics, Sultan Qaboos University, PO Box 35, Al-Khod, Muscat, Sultanate of Oman

CATHERINE A FREW
Molecular Genetics Laboratory, Duncan Guttman Institute of Medical Genetics, Netherton, Glasgow, UK


Figure 1  Pedigree of patient's family. III.1 and III.2 are suspected to have HD, but have not been assessed.

Mirror hands and feet

I would like to comment on the article by Hatchwell and Dennis in the April 1996 issue of Journal of Medical Genetics. They described a child with mirror hands and feet or Laurin-Sandrow syndrome. In their discussion of the possible cause of the abnormalities they mention the HOXB-8 gene as a possible candidate gene for this disorder.

I do not agree for a number of reasons. First, mirror image duplications of stylopod (carpals/tarsals and digits) and autopod (forearm/leg) bones have indeed been observed after various HOX mutations in mice.7 However, ectopic expression of HOXB-8 as a consequence of a mutation is not likely. Expression of HOXB-8, like other HOX genes of the Antennapedia class, is likely to be controlled by other genes, the x ray mesodermal patterning. The normal expression pattern of HOXB-8 would certainly suggest this,8 as would the conservation of gene function between Drosophila and vertebrates.9 Second, ectopic expression of HOXB-8 from pre-limb bud stages (at which it first appears in the posterior part of the limb bud) would be expected to result in duplication of the zeugopod (humerus) as well as in loss of function mutations, which were also suggested by the authors as a possible cause, do not result in an ectopic zone of polarising activity in mice.10 Overexpression of HOXB-8 results in transformations of the axial skeleton instead.

I would like to suggest another hypothesis. A number of mouse mutants have a skeletal phenotype similar to Laurin-Sandrow syndrome. One of these, Strong's murine dwarfism,11 has preaxial polydactyly of all limbs as well as reductions of the radius and tibia. The mutant gene is semidominant. Although Hatchwell and Dennis do not define the polydactyly in their patient, the x ray photograph of the right foot that they show suggests a partial preaxial pattern. The extreme varus position of the feet suggests a reduction of the tibia and the supracondylar height of the lower limb radial reduction. These abnormalities are similar to those observed in homo- and heterozygous ltm mice (heterozygous mice have abnormalities of the hind limbs only).

Chan et al12 have recently found evidence for ectopic polarising activity in ltm1 limbs. The skeletal abnormalities are consistent with this finding. HOXB-8 expression in these mice has been found to be normal. These findings of Chan et al12 would remove HOXB-8 from consideration as a candidate gene for Laurin-Sandrow syndrome, provided that the Strong's locus mutation is indeed a homologue. They suggest that the ltm gene product acts either downstream of HOXB-8 or independently of it in specifying the location of the ZPA.

I would like to offer an alternative hypothesis. The "Laurin-Sandrow gene", which could be the ltm gene, could act upstream of HOXB-8 and determine the extent of its expression. Overexpression of HOXB-8 leads to posterior transformations in the upper thoracic vertebrae in mice. An attractive hypothesis would therefore be that HOXB-8 expression determines "posteriority" in the limb bud, specifying posterior cells as ZPA. Posterior identity as a "default state" in the limb is consistent with modern ideas on branching morphogenesis in the limb.13 Absence of the Laurin-Sandrow gene product

J Med Genet 1997;34:701-704

1 10.1136/jmg.34.8.701