# 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 "family 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 4] Syria,[2] Egypt,[2] and Lebanon,[2] but this is the first report from Oman. Our families appear to be of unmixed Arab ancestry and the gene may have arisen by mutation.[5] 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 tests according to international guidelines.[6]

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

CATHERINE A FREW
*Molecular Genetics Laboratory, Duncan Guthrie Institute of Medical Genetics, Yorkhill, Glasgow, UK*

1 Bruyn GW. The Westphal variant in juvenile type of Huntington's chorea. In: Barbeau A, Brunette JR, eds. *Progress in neurogenetics.* Amsterdam: Excerpta Medica, 1967:666-73.
2 Kremer K, Goldberg P, Andrew SE, *et al.* A worldwide study of the Huntington's disease mutation. *N Engl J Med* 1994;**330**:1401-6.
3 Scrimgeour EM, Tahoon SA, Zawawi TH. Huntington's disease in two unrelated Arab kindreds, and in an Afghani family resident in Saudi Arabia. *J Med Genet* 1994;**31**:819-20.
4 Bohlega S, McLean D, Al-Kawi MZ, *et al.* Huntington's disease: report on four Saudi families. *Saudi Med J* 1996;17:456-9.
5 Goldberg YP, Kremer B, Andrew SE, *et al.* Molecular analysis of new mutations for Huntington's disease: intermediate alleles and sex of origin effects. *Nat Genet* 1993;5:174-9.
6 International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *Neurology* 1994;**44**:1533-6.

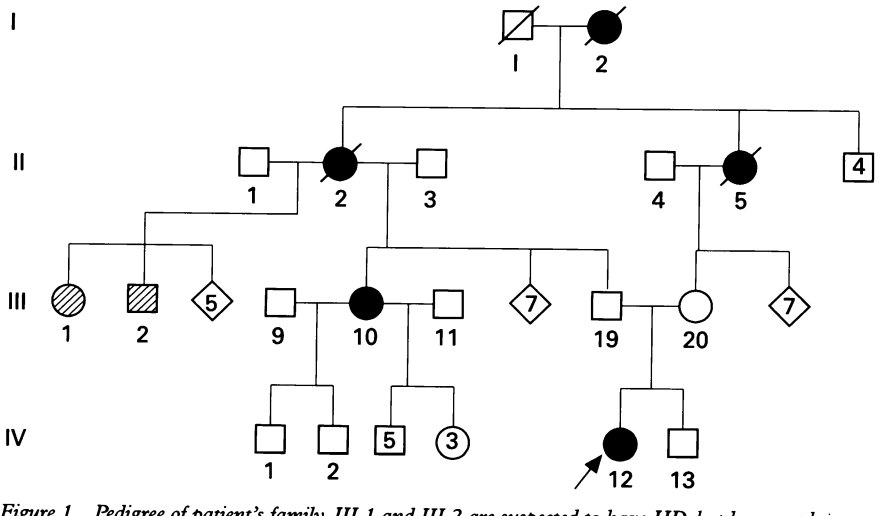


*Figure 1 Pedigree of patient's family. III.1 and III.2 are suspected to have HD, but have not been assessed.*

## 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.*[1] 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 ectopic expression of Hoxb-8 in mice.[2] 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 that control mesodermal patterning. The normal expression pattern of HOXB-8 would certainly suggest this,[3] as would the conservation of gene function between *Drosophila* and vertebrates. 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.[2] Third, gain 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.[3] Overexpression of Hoxb-8 results in transformations of the axial skeleton instead.[3]

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 luxoid* (*lst*) mice, have preaxial polydactyly of all limbs as well as reductions of the radius and tibia.[4] 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 cupped position of the hands radial reduction. These abnormalities are similar to those observed in homo- and heterozygous *lst* mice (heterozygous mice have abnormalities of the hind limbs only).

Chan *et al*[5] have recently found evidence for ectopic polarising activity in *lst/lst* 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 al*[5] would remove HOXB-8 from consideration as a candidate gene for Laurin-Sandrow syndrome, provided that the *Strong's luxoid* mutation is indeed a homologue. They suggest that the *lst* 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 *lst* 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 "posteriorness" 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.[6] Absence of the Laurin-Sandrow gene product

would lead to failure of suppression of HOXB-8 expression in the anterior limb field. Ectopic expression of HOXB-8 would then specify cells in the anterior limb field as ZPA, leading to partial or complete duplication of zeugopod, autopod, and stylopod.

There are no reports of zeugopod (humerus/femur) duplication in Laurin-Sandrow syndrome, which would argue against the above hypothesis. To my knowledge, however, no author has to date thoroughly examined the humeri and femora of Laurin-Sandrow patients for any evidence of abnormal patterning.[7-11] Further delineation of the Laurin-Sandrow phenotype, especially with regard to more proximal skeletal elements, would be most helpful in the search for candidate genes for this intriguing syndrome.

M A M VAN STEENSEL
*Department of Human Genetics, University Hospital Nijmegen, Geert Grooteplein 10, 6500 HB Nijmegen, The Netherlands*

1 Hatchwell E, Dennis N. Mirror hands and feet: a further case of Laurin-Sandrow syndrome. *J Med Genet* 1996;**33**:426-8.
2 Charité J, De Graaff W, Shen S, Deschamps J. Ectopic expression of Hoxb-8 causes duplication of the ZPA in the forelimb and homeotic transformation of axial structures. *Cell* 1994; **78**:589-601.
3 Pollock RA, Sreenath T, Ngo L, Bieberich CJ. Gain of function mutations for paralogous Hox genes: implications for the evolution of Hox gene function. *Proc Natl Acad Sci USA* 1995;**92**:4492-6.
4 Forsthoefel PF. Genetics and manifold effects of Strong's luxoid gene in the mouse, including its interactions with Green's luxoid and Carter's luxate genes. *J Morphol* 1962;**110**:391-420.
5 Chan DC, Laufer E, Tabin C, Leder P. Polydactylous limbs in Strong's luxoid mice result from ectopic polarizing activity. *Development* 1995; **121**:1971-8.
6 Sordino P, Van der Hoeven F, Duboule D. Hox gene expression in teleost fins and the origin of vertebrate digits. *Nature* 1995;**375**:678-81.
7 Kogekar N, Teebi AS, Vockley J. Sandrow syndrome of mirror hands and feet and facial abnormalities. *Am J Med Genet* 1993;**46**:126-8.
8 Laurin CA, Favreau JC, Labelle P. Bilateral absence of the radius and tibia with bilateral reduplication of the ulna and fibula: a case report. *J Bone Joint Surg Am* 1964;**46**:137-42.
9 Martin RA, Jones MC, Jones KL. Mirror hands and feet with a distinct nasal defect, an autosomal dominant condition. *Am J Med Genet* 1993;**46**:129-31.
10 Martinez-Frias ML, Alcaraz M, Espejo P, Gomez MA, Garcia de Leon R, Gonzalez Moro L. Laurin-Sandrow syndrome (mirror hands and feet and nasal defects): description of a new case. *J Med Genet* 1994;**31**:410-12.
11 Sandrow RE, Sullivan PD, Steel HH. Hereditary ulnar and fibular dimelia with peculiar facies: a case report. *J Bone Joint Surg Am* 1970;**52**:367-70.

## A study of brothers with Klinefelter syndrome

Klinefelter *et al*[1] described males with infertility, hypogonadism, and gynaecomastia in 1942. The other clinical features of Klinefelter syndrome are now well delineated but not present in all affected subjects.[2] The live birth prevalence of Klinefelter syndrome is approximately 1 in 1000.[3] The diagnosis is made and confirmed by the cytogenetic finding of 47,XXY. Klinefelter syndrome is considered to be a sporadic disorder resulting from non-disjunction. This is maternal in one half of cases and paternal in the remainder.[4 5] The empirical recurrence risk is negligible as the condition occurs sporadically, with the recurrence risk equal to the birth prevalence, that is, 1 in 1000. Given this, it is not surprising that Klinefelter syndrome is very rarely reported to recur within a family. There are limited reports of sibs with Klinefelter syndrome[6 7] or of twins.[8 9] Therefore we wish to document our clinical, cytogenetic, and molecular findings of a family in which brothers had Klinefelter syndrome.

The older boy was diagnosed as having Klinefelter syndrome at the age of 5 years. He had reduced left elbow supination and radiography showed radioulnar synostosis. Diagnosis was made in the younger sib at the age of 3 years because of undescended testes and a "willowy appearance" similar to his older affected brother. Both had heights approximately on the 50th centile, weights on the 3rd centile, and reduced upper to lower body segment ratios of 0.87 and 0.85. The older sib is at Tanner stage 1 of sexual development at 11 years. Both are otherwise normal on examination, of normal intellectual ability, and neither has any behavioural problems.

Both parents were healthy, normal on examination, and aged 24 years at the time of birth of their first child with Klinefelter syndrome. The couple had no difficulty in conceiving and no recognised pregnancy losses. They are first cousins from the Punjab and are themselves products of first cousin marriages (fig 1). There are no other family members known to have chromosome anomalies, infertility, or frequent miscarriages.

Chromosome analysis of peripheral blood lymphocytes was performed on nuclear family members, 50 cells being examined in each case. The brothers with Klinefelter syndrome were non-mosaic 47,XXY, other family members having normal results. X chromosome haplotype analysis was performed using an Applied Biosystems 373 DNA Sequencer and Genescan 672 software. The microsatellite present in intron 13 of the factor VIIIC gene at Xq28 was informative, but nine microsatellites from the dystrophin gene were uninformative.[10] The results are shown in fig 1; both boys with Klinefelter syndrome had apparently inherited an X chromosome from their father.

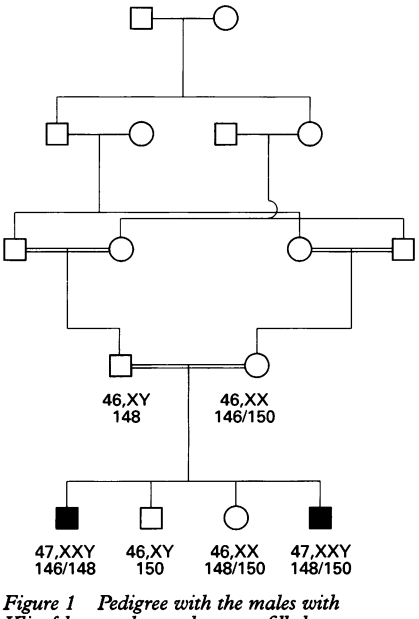


*Figure 1 Pedigree with the males with Klinefelter syndrome shown as filled squares. Cytogenetic analyses and X chromosome genotype results are shown for the nuclear family. The latter were generated using the microsatellite present in intron 13 of the factor VIIIC gene. The results are given as the polymerase chain reaction products measured in base pairs.*

These sibs with Klinefelter syndrome had typical clinical features, non-mosaic 47,XXY, and their additional X chromosome was the result of a paternal meiosis I error. Possible explanations for this situation are chance, that the father is a Klinefelter syndrome mosaic which seems unlikely, or that the father has an autosomal recessive disorder affecting meiosis. We have been unable to investigate the family further by single sperm analysis and because no other relative is known to have had a child with aneuploidy.

C GEOFFREY WOODS
*Yorkshire Regional Genetics Service, Department of Clinical Genetics, Ashley Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK*

JAYNE NOBLE
*Regional DNA Laboratory, Department of Clinical Genetics, Ashley Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK*

ALAISTER R FALCONER
*Department of Paediatrics, Scarborough General Hospital, Woodlands Drive, Scarborough, North Yorkshire YO12 6QL, UK*

1 Klinefelter HF, Reifenstein EC, Albright F, *et al.* Syndrome characterised by gynaecomastia, aspermatogenesis without aleydigism and increased secretion of follicle stimulating hormone. *J Clin Endocrinol Metab* 1942;**2**:615.
2 Jones KJ. *Smith's recognisable patterns of human malformation.* 4th ed. Philadelphia: Saunders, 1988.
3 Nielsen J, Wohlert M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Birth Defects* 1990;**26**:209-23.
4 Jacobs PA, Hassold TJ, Whittington E, *et al.* Klinefelter's syndrome: an analysis of the origin of the additional sex chromosome using molecular probes. *Ann Hum Genet* 1988;**52**:93-109.
5 Lorda-Sanchez I, Binkert F, Maechler M, Robinson WP, Schinzel AA. Reduced recombination and paternal age effect in Klinefelter syndrome. *Hum Genet* 1992;**89**:524-30.
6 Gustavson KH, Gamstorp I, Meurling S. Bilateral teratoma of testis in two brothers with 47,XXY Klinefelter's syndrome. *Clin Genet* 1975;**8**:5-10.
7 Takayasy J, Kinoshita K, Tsuboi T, Kurihara T. Twins with Klinefelter's syndrome. *Lancet* 1967;**ii**:1424.
8 Hatch TR, Moore RJ. Klinefelter syndrome in identical twins. *Urology* 1985;**26**:396-7.
9 Flannery DB, Brown JA, Redwine FO, Winter P, Nance WE. Antenatally detected Klinefelter's syndrome in twins. *Acta Genet Med Gemellol* 1984;**33**:51-6.
10 Laloz MR, McVey JH, Pattison JK, Tuddenham EG. Haemophilia A diagnosis by analysis of hypervariable dinucleotide repeats within the factor VIII gene. *Lancet* 1991;**338**:207-11.

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