

LETTERS TO THE EDITOR

The non-deletion type of α thalassaemia/mental retardation: a recognisable dysmorphic syndrome with X linked inheritance

The association of α thalassaemia and mental retardation (ATR), originally described in 1981,¹ was further analysed in two papers published last year.^{2,3} Of 13 subjects ascertained because of their haematological abnormality, eight had deletions involving the tip of chromosome 16p, where the α globin genes lie ('deletion' cases)²; in the remaining five, the α globin genes appeared intact ('non-deletion' cases).³ Whereas the clinical features of the deletion cases were rather variable, the non-deletion cases showed a strikingly uniform phenotype comprising severe mental handicap, characteristic dysmorphic facies, genital abnormalities, and an unusual, mild form of haemoglobin H (Hb H) disease (a manifestation of α thalassaemia). It was proposed that the non-deletion cases represented a distinct syndrome that probably mapped to the X chromosome³; however, in the absence of pedigrees containing multiple affected cases, the evidence for this was circumstantial. Two recent papers in this Journal^{4,5} lend support to the conclusions of Wilkie *et al*³ and extend the delineation of the non-deletion ATR syndrome.

Harvey *et al*⁴ described a severely retarded 21 year old male with similar haematological and dysmorphic features to the previous cases and a normal α globin genotype. A male sib who was severely retarded and said to have had a similar physical appearance had died some years previously. As pointed out by the authors, this was the first description of two affected males in a sibship and is compatible with X linked inheritance.

Nearly simultaneous with the publication of Wilkie *et al*,³ Porteous and Burn⁵ described a 6 year old boy with an unknown retardation syndrome comprising dysmorphic facies, microcephaly, hypotonia, and small genitalia; his dead maternal uncle had shown similar clinical features, lead-

ing the authors to propose that this syndrome might be X linked. The striking similarity of their case to the non-deletion ATR syndrome prompted further haematological and molecular evaluation of the proband at the age of 7 years 3 months. The results were: haemoglobin (Hb) 10.3 g/dl, red cell count $4.55 \times 10^{12}/l$, mean cell volume 73 fl, mean cell haemoglobin 23 pg, Hb electrophoresis, 2.7% Hb H; 14% of red cells contained Hb H inclusions after incubation with 1% brilliant cresyl blue, and the α globin genotype was $\alpha\alpha/\alpha\alpha$. These results prove that this boy has the non-deletion ATR syndrome; his uncle had been anaemic throughout life and had been treated with iron supplements, so it seems likely that he had the same condition. The boy's parents had normal haematological indices.

Porteous and Burn⁵ suggested that their case resembled two brothers previously thought to have an atypical form of the Coffin-Lowry syndrome and illustrated in *Smith's recognizable patterns of human malformation*.⁶ Haematological evaluation of the surviving brother shows that he too has non-deletion ATR; a male cousin (his mother's sister's son), also mentally retarded, has the same condition. A fuller description of this family will appear in the next issue of the Journal.

This recent work lends weight to the conclusions of Wilkie *et al*³ in two respects. First, the non-deletion ATR syndrome shows a pattern of dysmorphic facial features and associated clinical abnormalities that is sufficiently characteristic to identify potential new cases; the diagnosis is then best confirmed by showing the presence of Hb H inclusions in the red cells. Second, the absence of male-to-male transmission in the three new pedigrees (comprising seven affected cases, all male) greatly strengthens the evidence that the non-deletion ATR syndrome is X linked. Accordingly, we propose that this syndrome³ is henceforth termed 'X linked α thalassaemia/mental retardation' (ATR-X), to distinguish it from the separate syndrome associated with deletion of the α globin complex on chromosome 16 (ATR-16).²

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Leiomyosarcoma in a patient with trisomy 8 mosaicism

We read with interest the short report by Lessick *et al*,¹ in which they describe the development of a gastric leiomyosarcoma in a young boy with constitutional trisomy 8 mosaicism. We agree that gastric leiomyosarcomas are relatively rare tumours, especially at that age, and a relation with the constitutional chromosomal abnormality may be suspected. In this respect it should be mentioned that, in contrast to what the authors state, chromosomal abnormalities involving chromosome 8 have often been reported in benign and malignant smooth muscle tumours: we described several copies of a der(8),t(8;8) in a retroperitoneal leiomyosarcoma² and

Nilbert *et al*³ reported a uterine leiomyosarcoma with a t(8;13). In addition, several uterine leiomyomas with structural or numerical abnormalities of chromosome 8 were reported by Mark *et al*⁴ and Teyssier and Ferre.⁵ Especially interesting in relation to the case under discussion is the latter authors' report of trisomy 8 in another gastrointestinal smooth muscle tumour, an oesophageal leiomyoma.

Thus, the abnormalities in chromosome 8 in smooth muscle tumours described so far involve both numerical and structural abnormalities and concern both benign and malignant tumours. We think that these data give a different perspective to the discussion of the case reported by Lessick *et al*.¹

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Further evidence for the location of the BPES gene at 3q2

We read the paper of Smith *et al*¹ in this journal with interest. They suggested that blepharophimosis plus ovarian failure is a likely candidate for a contiguous gene syndrome, and recommended cytogenetic investigation of all cases of blepharophimosis, ptosis, epicanthus inversus syndrome (BPES). We would like to report a family with autosomal dominant BPES syndrome and a chromosomal abnormality. A father and his 6 month old son were referred for genetic counselling. Both showed the typical

signs of BPES: blepharophimosis, ptosis, telecanthus, and epicanthus inversus. The father had no other dysmorphic features and was of normal intelligence. The son had a small nose with anteverted nostrils and cup shaped ears. His height, length, and head circumference were in the normal range and his mental development was normal. The father had two sons from a previous marriage who had the same eye anomalies. Unfortunately, they were not available for further investigations. Chromosomal examination on cultured lymphocytes of the father and son showed an apparently balanced translocation between the long arms of chromosomes 3 and 11, with respective breakpoints at 3q21 and 11q23. The karyotype was 46,XY,t(3;11)(q21;q23) (figure).

Recently, Fukushima *et al*² reported a newborn infant with BPES and a de novo balanced 3q23;4p15 reciprocal translocation. These findings strongly indicate that the gene for BPES is located in the 3q2 region. Furthermore, blepharophimosis, ptosis, and microphthalmia are consistent features in patients with an interstitial

deletion of band 3q2,³ reinforcing the location of the BPES gene at 3q2.

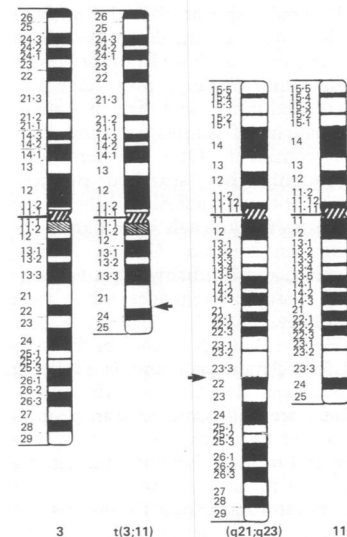
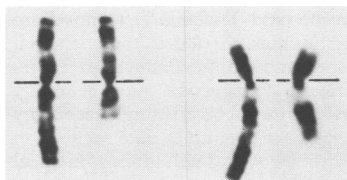
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Karyotype of the proband.

BOOK REVIEWS

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Pathology of the Human Embryo and Previabie Fetus. An Atlas. D K Kalousek, N Fitch, B A Paradise. (Pp 230; DM 248.) Berlin: Springer-Verlag, 1990.

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