Case reports

TABLE Clinical features in 45 reported cases of inv dup (15).

	%
Mental retardation	98
Developmental delay	87
Abnormal tone	58
Seizures	53
Abnormal ears	51
Strabismus	49
Growth retardation	42
Behaviour disturbance	37
Abnormal dermatoglyphs	33
Antimongoloid slant	31
High arched palate	29
Abnormal speech	29
Epicanthus	20
Abnormal EEG	11
Facial asymmetry	7
Anteverted nares	5
Kyphoscoliosis	5

mosaic, and in the remainder parental karyotypes were not performed. In the non-inherited group, parental ages were stated in 20 families: for these the average maternal age at birth was 33.4 years and the average paternal age was 37.4 years. All of these de novo cases have been isolated events. The recurrence risk for parents with normal chromosomes thus appears to be low. To date there have been three reports of recurrence, two owing to parental translocation and one to maternal mosaicism. Those cases where a parental translocation was the cause had additional phenotypic features reflecting the partial trisomy or monosomy of the other chromosome involved in the translocation. In these situations amniocentesis is indicated for future pregnancies.^{2 8}

The origin of the extra chromosome in the non-inherited cases is unknown. Various theories have been postulated.¹¹ A study of the relative significance of birth order to maternal age and paternal age

might help to clarify the likely parental origin in view of the observed increase in mean parental ages.

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Interstitial deletion of the short arm of chromosome 4

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SUMMARY A 17 year old girl investigated for mental retardation and minor anomalies was found to have an interstitial deletion of 4p. Her clinical and cytogenetic findings are compared with previous reported case of interstitial 4p deletion and with terminal 4p— deletions (Wolf-Hirschhorn syndrome).

Before chromosome banding it was not possible to distinguish terminal and interstitial deletions and therefore few interstitial deletions have been reported. We describe a 17 year old girl with an interstitial deletion of segment p12p15 of chromosome 4. Francke *et al*¹ reported a similar patient with a deletion of segment 4p11p15. These patients show some similarity in clinical features suggesting that a recognisable phenotype may be associated with this deletion.

Case report

The patient was born on 3.7.62, the second child of Cree Indian parents. Birth weight was 2721 g. Early medical records are incomplete but she was apparently a very placid child who was healthy, apart from episodes of atelectasis at the age of 2 years and pneumonia at the age of 4 years. Motor and language development were significantly delayed and she walked independently at 6 years and used single words at 3 years. A clinical diagnosis of Down's syndrome was apparently considered. Because of parental neglect and the unavailability of appropriate schooling she was fostered in Winnipeg at 11 years of age and formally investigated for mental retardation. She was found to be functioning at a 3 to 5 year level. A complete physical examination was not carried out but she was noted to be microcephalic and to have a convergent strabismus. A right convex scoliosis was noted at 13 years. Her health was otherwise good except for fractures of the left humerus and left radius sustained in falls. When she was seen for a routine examination at 17 years the diagnosis of Down's syndrome was questioned and she was referred to the department of genetics for evaluation.

Further history revealed that the mother had six other apparently normal children and had been treated for mitral prolapse after the proband's birth. The father had been treated for hypothyroidism. Physical examination revealed a co-operative Indian girl (fig 1) with height and weight on the 40th centile for age, OFC 53.5 cm (25th centile); brachycephaly; a poorly formed right parietal whorl; low anterior hairline; medial eyebrow flaring; straight eyelashes; slightly upward slanting palpebral fissures; prominent epicanthic folds; supraorbital puffiness; normal inner and outer canthal distances (8.8 cm and 3.6 cm respectively); relatively small eyes (palpebral fissures 2.6 cm); strabismus; large nose; normal palate; broad

alveolar ridges; spade shaped incisors with fused left lower incisors; flattened malar area; prominent premaxilla; large mouth (5.7 cm); thick lips; mild facial asymmetry with the left side flatter; ears normal in position and rotation but cupped with prominent antihelices; helices notched bilaterally and thinned in the middle third; neck of normal length with no webbing and circumference 31.7 cm; slight cubitus valgus with some laxity of the elbows; midfinger to total hand ratio of 40.5% (<3rd centile); broad palms (9.2 cm); restricted metacarpophalangeal and proximal interphalangeal joints causing camptodactyly of the 2nd to 5th digits bilaterally; slight skin syndactyly more pronounced between digits 2 and 3; subluxating slightly webbed thumbs; mild distal hypoplasia of the digits with short nails and rounded fingertips (fig 1); simple arches on all digits, except the third fingers bilaterally which have low ridge count ulnar loops; proximal axial triradii bilaterally with a thenar loop and additional distal triradius on the left; normal palmar creases; I³ loop on left, I⁴ loop on right; missing right C triradius; prominent heels; pes planus; hallucal patterns of distal loops; normal chest and abdomen with an accessory nipple on the left; normal female genitalia, Tanner stage III sexual development; a café-au-lait spot on the right breast; some hypo- and hyperpigmented spots on the cheeks; small 'cigarette paper' scars on the left leg and neck; normal muscle development but increased tone; brisk and symmetrical reflexes; flat footed gait. Her developmental level was approximately 11 to 12 years but this was not formally assessed. A venous blood sample was obtained for cytogenetic analysis.

CYTOGENETIC STUDIES

Cytogenetic analysis on peripheral lymphocytes using Q banding revealed a deletion of the short arm of one chromosome 4. The exact position of the deletion, terminal or interstitial, could not be

FIG 1 The patient aged 17 years with camptodactyly of the left hand.

FIG 2 Partial karyotype showing $\text{del}(4)(\text{p}12\text{p}15)$: QFQ banding (left), RBA banding (middle), and diagrammatic representation of chromosome 4 (right). Arrows indicate where breakages occurred.

determined owing to the nature of Q bands in this region (fig 2). R banding analysis of a second blood sample, using BudR-AO, showed an interstitial deletion with breakpoints at p12 and p15 (fig 2). There was no evidence for insertion of the missing piece into another chromosome. No mosaicism was found in 50 cells analysed. The karyotype was thus designated $46,\text{XX},\text{del}(4)(\text{p}12\text{p}15)$. Chromosomal analysis of both parents revealed normal karyotypes. This suggests that the interstitial deletion arose during gametogenesis in one of the parents or immediately after fertilisation.

Discussion

Now that banding of high quality can be achieved, interstitial deletions with accurate breakpoints are being recognised more frequently. We are unaware of other published cases involving an interstitial deletion of the segment $4\text{p}12\text{p}15$ except the girl reported by Francke *et al*¹ whose deletion involved approximately the same segment ($\text{p}11\text{p}15$). We do know of one other potential case with an interstitial deletion of 4p who closely resembles our patient facially (M Preus, 1982, personal communication).

Phenotypically, our patient does not resemble those with Wolf-Hirschhorn syndrome but has findings in common with the patient of Francke *et al*.¹ In particular, both had relatively small eyes, large noses, cubitus valgus, broad hands, a high number of digital arches, and short fingers. Photographs of the two suggest a similar overall facial appearance.

The classic $4\text{p}-$ syndrome has distinct clinical features including growth deficiency, hypertelorism, downward slanting palpebral fissures, colobomata, cleft lip, digital thumbs, seizures, and profound mental retardation. In most cases the abnormal short arm is nearly half the normal length. Lejeune *et al*² and Perez-Castillo and Abrisqueta³ have shown that typical Wolf-Hirschhorn syndrome occurs only if band $4\text{p}16$ is lost. It is also known that duplications or deletions of comparatively small regions of chromosome 21 or 5p are responsible for the phenotypic features of Down's and cri-du-chat syndromes respectively.^{4,5}

We agree with Francke *et al*¹ that a 'proximal $4\text{p}-$ syndrome' exists that involves the segment $4\text{p}11\rightarrow\text{p}15$ and which is distinguishable clinically and cytologically from the 'distal $4\text{p}-$ syndrome' involving deletion of $4\text{p}16$. Advanced banding techniques need to be used to distinguish precisely such structural chromosomal abnormalities. Detailed knowledge of the phenotype and prognosis associated with specific chromosomal anomalies is necessary for proper interpretation of abnormal cytogenetic findings and for genetic counselling, especially in antenatal cytogenetic diagnosis.

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