De novo tandem duplication 17p11→cen

SUMMARY A dicentric chromosome 17 is described in a 5-year-old girl with minor malformations and severe mental retardation. The anomaly is interpreted as a de novo duplication of band 17p11 and centromere 17.

Analysis of prometaphase chromosomes in combination with a variety of banding techniques has greatly improved the cytogenetic diagnostic capacity. Nevertheless, it seems likely that in clinical practice a proportion of duplications/deletions are missed. We exemplify this by a case with a duplication of band 17p11 which might have escaped detection had it not been associated with an extra centromere.

Case report and family history

After a normal pregnancy this girl was delivered normally at term weighing 3·035 kg, length 51 cm, head circumference 34 cm. The cord was wrapped tightly around her neck causing cyanosis but she was resuscitated easily and her Apgar score was 8 at 2 minutes. At 3 months she was admitted to hospital because of feeding difficulties and failure to thrive. She was noted to have odd facies with narrow palpebral fissures, antimongoloid slant to the eyes, large down-turned mouth, high arched palate and micrognathia, somewhat pointed ears, and muscular hypotonicity.

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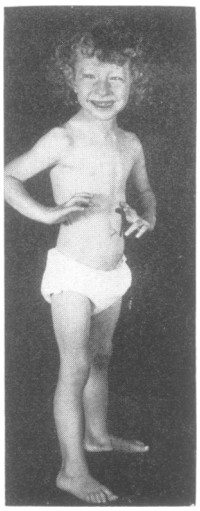

FIG 1 *Patient at 4½ years of age.*

TABLE *Cytogenetic and clinical details of cases with trisomy 17p.*

	Latta and Hoo[1]	*Palutke et al*[2]	*Bartsch-Sandhoff and Hieronimi*[3]	*Shabtai et al*[4]	*Yamamoto et al*[5]	*Present case*
Cytogenetic findings						
Duplicated segment	17pter→q11	17pter→q21	17pter→p11	17pter→cen (in 60% cells)	17pter→q21 (also monosomic for Xpter→q13)	17p11→cen
Clinical features						
Psychomotor retardation	+	+	+	+	+	+
Short stature	+	?	+	+	+	+
Failure to thrive	+	--	+	−	+	+
Microcephaly	+	?	+	+	−	+
Dysplastic low set ears	+	+	+	+	+	−
Hypertelorism	+	Hypotelorism	+	+	−	−
Micrognathia	+	+	+	+	+	+
High arched palate	+	+	+	−	+	+
Antimongoloid slant of the eyes	?	+	+	+	+	+
Narrow palpebral fissures	+	−	+	+	?	+
Muscular hypotonia	+	Hypertonia	+	+	−	+
Flexion contractures of joints	+	+	+	−	−	−
Flexion anomaly of fingers	+	+	+	−	Thumbs only	+
Feet abnormalities	Halluces mallis	Talipes	Hammer toes	−	−	−
Widely spaced nipples	+	?	−	+	−	−
Convulsions	−	+	−	−	− Abnormal EEG	+
Congenital heart disease	+	−	+	−	−	−
Sex	Female	Female	Male	Female	Female	Female
Others	Short neck, ptosis, deformed kidney, slight clitoral hypertrophy	Abnormal wide based gait, deafness, small nose	Kyphoscoliosis, small pupils, small scrotum, testes not palpable	Frontal bossing, mildly protruding mandible	Short neck, corneal opacity, small nose, prominent forehead, streak gonads	Abnormal wide based gait, convergent squint, hyperactive

The patient later developed an intermittent left convergent squint and frequent sideways movement of the head, and at 2½ years she had a prolonged left-sided convulsion associated with a febrile illness. Subsequently her EEG showed high amplitude slow waves, but treatment with sodium valproate has reduced the frequency of her fits to around two per year.

Delayed neurological development was noted at 9 months and subsequent development was retarded in all spheres. She walked at 3½ years, and at 4 years on testing with the Reynell Developmental Language Scales her verbal comprehension level was 1·05 years and her expressive language level was 1·04 years.

The clinical picture was attributed initially to birth

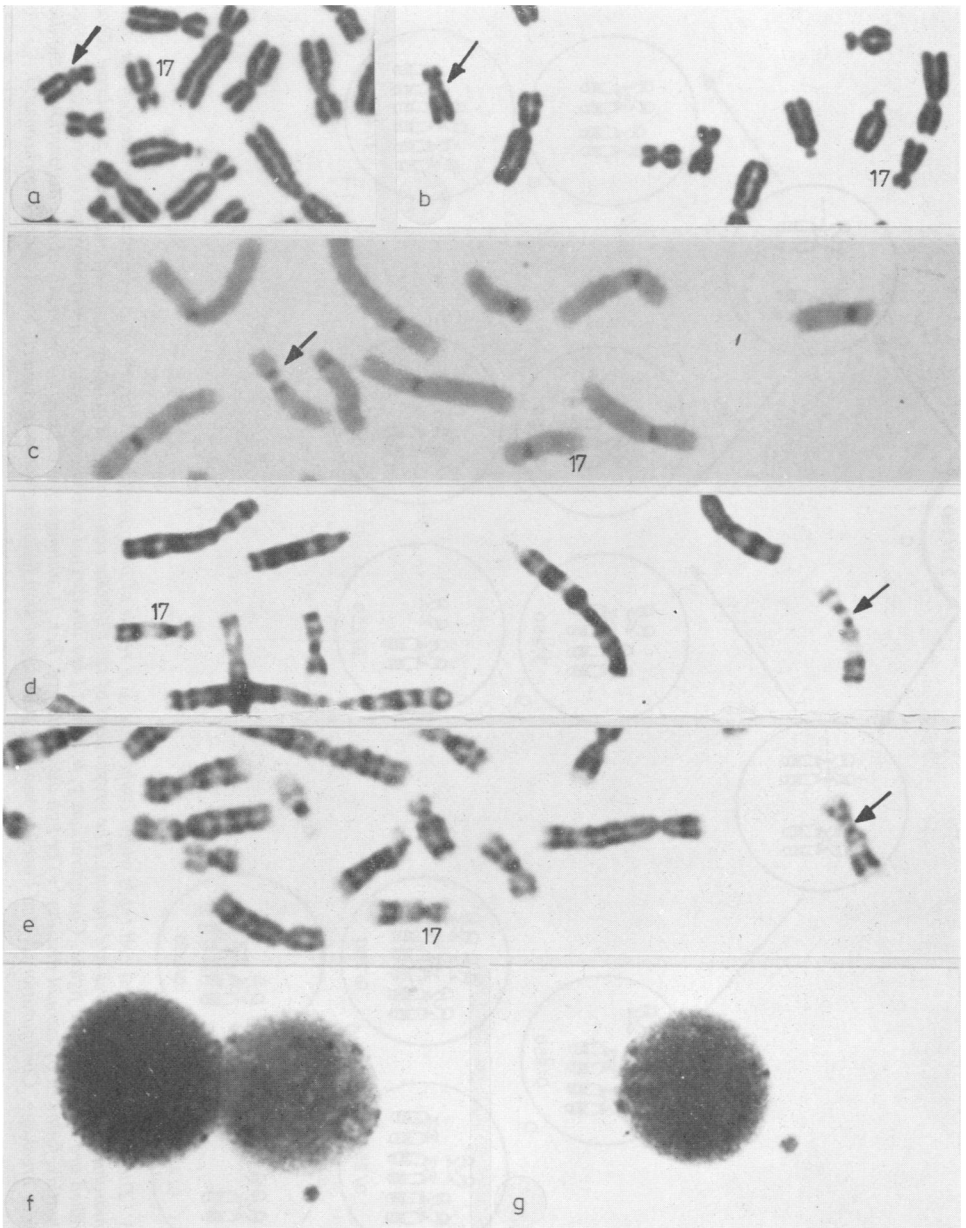

FIG 2 *Abnormal chromosome 17 (arrowed) identified by Giemsa staining (a, b), C banding (c), and G banding (d, e). Micronuclei of similar size from the patient (f, g).*

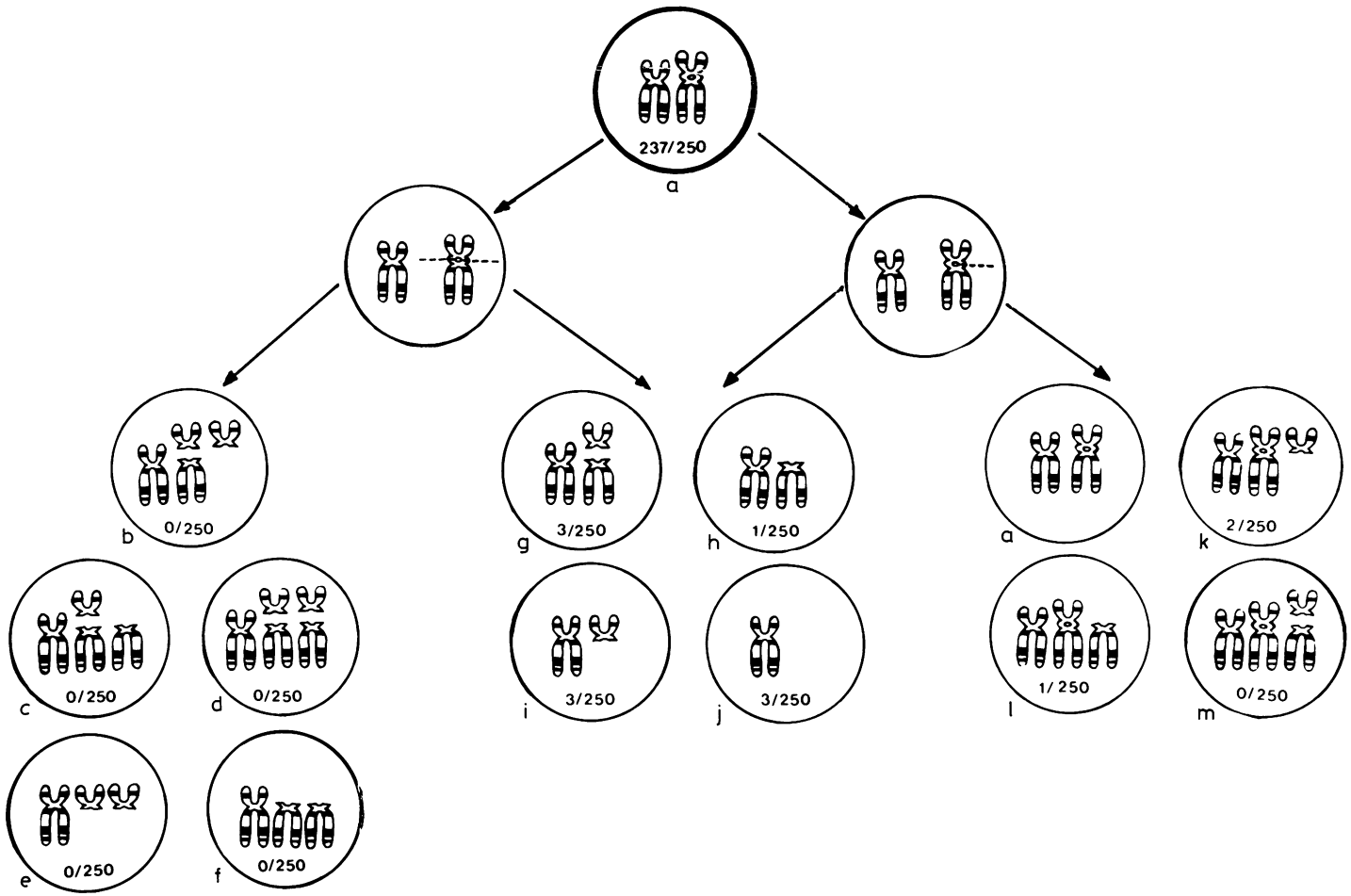

FIG 3 *Diagram of the different cell types which could arise as a result of intercentromeric chromatid/isochromatid breakage of the dicentric 17 (only chromosomes 17 and derivatives are shown). The proportions of the different configurations actually observed out of 250 peripheral blood lymphocytes examined are marked in the figure. Configurations g, h, i, and j are interpreted as being the result of intercentromeric breakage of either one or both chromatids, followed by normal division (g) or non-disjunction (g, h, i, j), although j could also be the result of non-disjunction of the dic(17) without previous breakage. Configurations k and l are the result of non-disjunction following intercentromeric breakage of one chromatid.*

asphyxia but her facies (fig 1) was suggestive of Seckel's bird-headed dwarfism, although her birth weight fell within the normal range. In fact the features accord well with those attributed to partial trisomy 17p (table). When younger, our patient resembled the patients of Latta and Hoo[1] and Bartsch-Sandhoff and Hieronimi.[3]

There are no other known malformations in the family. The parents are normal and are not blood relatives. The mother has had no miscarriages and neither has been exposed to known mutagens or ionising radiation. The patient's only sib is phenotypically normal.

CYTOGENETIC STUDIES

Chromosome analysis on peripheral blood lymphocytes using different banding techniques (GTG, QFQ, RBA, CBG) showed one chromosome 17 to be dicentric with weakly stained C bands (fig 2c) and a light minute G band between them (fig 2d, e). The anomalous chromosome did not silver-stain and did not associate with the acrocentrics. Measurements in 25 cells showed the length of the extra material to be 16·4% of the rest of the chromosome. The dic(17) was also present in 25 skin fibroblasts analysed.

In 69% of cells, two constrictions were clearly present. In 20% only the constriction corresponding to the upper C band positive region was present (fig 2b), while in 11% of cells only the lower heterochromatic region was constricted. Thus in 69% of cells both centromeres appear to be active while in 31% a single constriction indicates that only one of the centromeres is functional.

Out of 250 cells examined, 237 (94·8%) had the dic(17) while the remaining (5·2%) cells showed a variety of anomalies. Three cells lacked the dic(17) and contained fragments 17p and 17q, another three cells had the dicentric plus an extra 17p or 17q, and seven cells lacked either the dic(17) or one of the fragments (fig 3).

The frequency of micronuclei was determined (using criteria by Countryman and Heddle[6]) in 3000 interphase cells each from the patient and her 6½-year-old sister with a normal 46,XX karyotype. The patient had seven and her sister three micronuclei per 1000 cells, a difference which is statistically significant ($p<0·05$). Furthermore, the size of micronuclei in the patient was more homogeneous than in her sister (fig 2f, g).

Both parents are chromosomally normal. Blood grouping and enzyme markers confirm paternity. The father's chromosomes 17 both have a prominent C band, while in the mother the C bands are weaker, one of these being particularly pale and narrow and similar to the two C bands of the anomalous 17 in the patient.

Discussion

The extra chromosome material comprises approximately 0·5% of the total haploid autosomal length. This, however, includes the extra centromeric heterochromatin and is probably an overestimate owing to stretching of the intercentromeric region. We therefore suspect that if the extra euchromatic material had not been located intercentromerically, it might have escaped detection.

The simplest explanation for the configurations in fig 3 (g-l) is that they are the result of intercentromeric chromatid/isochromatid breakage of the dicentric or non-disjunction or both. There was also an increased frequency of micronuclei, the size of which could well correspond to the abnormal chromosome or either fragment, and it seems likely that they represent the result of anaphase lagging. These observations suggest that there are problems in the division of the dicentric in some of the cells, which would be expected since both centromeres appear to have remained active in 69% of cells. The close proximity of the two centromeres probably allows normal behaviour at mitosis in the majority of cells.

Each of the two C bands of the dicentric closely match the C band of one chromosome 17 in the mother and the size and banding of the extra euchromatic segment are similar to those of band 17p11. Thus, the abnormal chromosome is thought to be of maternal origin, and interpreted to have arisen by unequal sister chromatid exchange, producing a direct duplication of band 17p11 and centromere 17; the karyotype of the patient is thus 46,XX,dic(17)(pter→q11·1::p12·00→qter)mat. The clinical picture is compatible with that in five cases of partial trisomy 17p previously published (table), although there is no recorded case trisomic for such a small segment.

The diagnosis of a chromosomal abnormality made it possible to reassure the parents that the recurrence risk is likely to be very low, and, moreover, that antenatal diagnosis would be possible.

We are grateful to Dr M H Winterborn and Professor J H Edwards for referring this case, Mrs Janet A McKeown for providing information on preliminary cytogenetic investigations, Dr M S Grewel for the work on the fibroblasts, and the late Dr Peter Cook for the blood grouping and enzyme investigations.

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References

[1] Latta E, Hoo JJ. Trisomy of the short arm of chromosome 17. *Humangenetik* 1974;**23**:213–7.
[2] Palutke W, Chen H, Woolley P Jr, *et al.* An extra small metacentric chromosome identified as a deleted chromosome no 17. *Clin Genet* 1976;**9**:454–8.
[3] Bartsch-Sandhoff M, Hieronimi G. Partial duplication of 17p. A new chromosomal syndrome. *Hum Genet* 1979; **49**:123–7.
[4] Shabtai F, Shalev A, Chemke J, Halbrecht I, Elian E. Pure trisomy 17 in 60% of cells. *Hum Genet* 1979;**52**: 263–8.
[5] Yamamoto Y, Endo Y, Kuroki Y. A case of partial trisomy 17 resulting from X-autosomal translocation. *J Med Genet* 1979;**16**:395–9.
[6] Countryman PI, Heddle JA. The production of micronuclei from chromosome aberrations in irradiated cultures of human lymphocytes. *Mutat Res* 1976;**41**:321–32.

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Ring chromosome 10 and its clinical features

SUMMARY A 2-year-old boy with mental and growth retardation is presented; he has a 46,XY,r(10)(p15q26) chromosome complement. Five previously reported cases of ring chromosome 10 were reviewed and compared with the present case in an attempt to delineate a clinical syndrome. Since the first description, identified by Giemsa banding by Lansky *et al*,[1] four other r(10) patients have been described.[2–5] Their common features were mental and growth retardation, low birth weight, microcephaly, stubby nose, hypertelorism, strabismus, wide set nipples, single transverse palmar creases, undescended testes, and hypoplastic scrotum. In some of the cases congenital heart disease was present.

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Case report

The proband was born on 5.11.77, the first child of unrelated, healthy parents, after an uneventful term pregnancy and normal delivery. The father was 25 years old and the mother 22 at his birth and there had been no exposure to radiation or drugs. His birth weight was 2540 g (−1·7 SD). At the age of 2 months, he was admitted to hospital because of feeding difficulties and for evaluation of his physical development. He had an episode of febrile convulsions when he was 10 months old, but no abnormalities were found on the electroencephalogram. At the age of 10 months, he was 66·8 cm in height (−3·6 SD), weight was 5·8 kg (−3·9 SD), and head circumference 41 cm (−3·8 SD); he had poor head control.

Clinical features were mental and growth retardation, microcephaly, hypertelorism, internal strabismus, stubby nose, low set ears, long philtrum, bilateral single transverse palmar creases, clinodactyly of the fifth fingers, funnel chest, small penis, undescended testes, and hypoplastic scrotum (fig 1). Dermatoglyphs of the patient showed an increased number of whorls but no other special findings. There was no congenital heart disease.

Routine laboratory examinations of the patient's blood, serum, and urine showed no abnormalities. Slight retardation of bone maturation was found on *x*-ray.

Development quotient was estimated as 40% at the age of 15 months by Thumori-Inage's questionnaire.

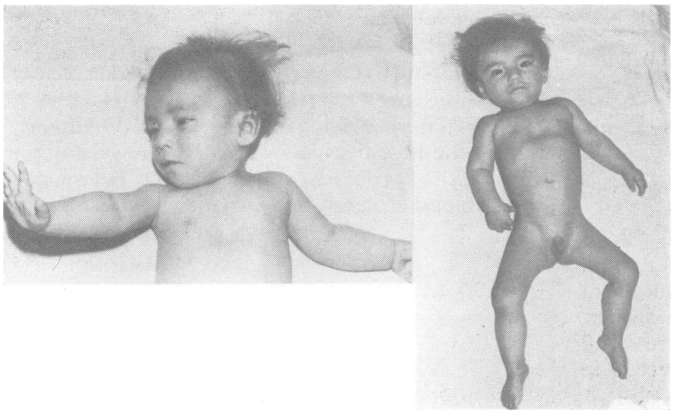

FIG 1 *Front and lateral views of the proband.*