assumed to be the result of the trisomy of the distal long arm, as deletion of the terminal p13 region will have minimal effect. The meiotic mechanism whereby crossing over in an inversion loop leads to unbalanced recombinants has been discussed in a previous case.⁴ In only one family has a pericentric inversion of 13 produced both possible unbalanced recombinants, but one of the two examples of the trisomy p recombinant died at 6 weeks and the second was terminated after diagnosis following amniocentesis.⁵ The family described here has a history of perinatal deaths as well as miscarriage but at least one of the stillbirths was said to have polydactyly, indicating the trisomy q recombinant. A segregation analysis of 60 parents in which one of the parents was a carrier of inv(13) has shown a significant predominance of males among the viable offspring.⁶ This suggests a possible selection against female offspring, but most offspring of this family for three known generations have been female.

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Trisomy 18 phenotype in a patient with an isopseudodicentric 18 chromosome*

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SUMMARY We report a female patient with a typical trisomy 18 phenotype who has a 46,XX,—18,+isopseudodic(18)(p11) karyotype. The lack of features of the 18p— syndrome suggests that a significant amount of short arm material is present and that the Turner-like features associated with 18p— may be determined by monosomy for 18p11. The phenotype-genotype correlations in abnormalities affecting chromosome 18 are reviewed.

A variety of structural abnormalities affecting chromosome 18 has been described including monosomy,¹ trisomy,² and tetrasomy³ for 18p, as

well as partial monosomy⁴ and trisomy⁵ for 18q. We report a patient with a typical trisomy 18 phenotype who had an isopseudodicentric chromosome 18.

Case report

The proband was the 2.4 kg product of a 42 week gestation to a 20 year old G1 mother and her 21 year old husband. Breech presentation prompted a caesarean section delivery. At birth, an omphalocele and multiple dysmorphic features were noted. Examination (fig 1) in the nursery showed the weight and length (42 cm) to be below the 3rd centile for age. Examination of the head showed a circumference of 33 cm (5th centile), a prominent occiput, and low set, poorly formed ears. The face had a short nose, short palpebral fissures (1.75 cm), and micrognathia. Abnormalities of the chest and

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FIG 1 Patient at one month showing characteristic facial features, fisting of hands, and omphalocele scar.

abdomen consisted of a short sternum (4.5 cm), a harsh systolic murmur, and a large omphalocele. Examination of the extremities showed limited hip abduction, hypoplastic second toes, the outer fingers overlapping the middle fingers, a single transverse palmar crease, clinodactyly of the fifth fingers, and six simple arch patterns on the fingertips. In addition to generalised hypertonia, there were poor suck and Moro reflexes.

FIG 2 Chromosome 18 with the isopseudodic(18).

CYTOGENETIC STUDIES

Leucocyte chromosomes from a venous blood sample studied with G and C bands revealed 46,XX,-18,+isopseudodic(18)(p11) (fig 2). G banding of the isopseudodic(18) showed only a single constriction, but with C banding (fig 2) two positive staining regions with a small amount of short arm material between them were seen. Both parental karyotypes were normal.

Discussion

We believe that the phenotypes (table) described with the major structural abnormalities of chromosome 18 are sufficiently distinct to allow phenotype-genotype associations. An example of this association is illustrated by the report of Bass *et al*⁶ of a patient with isochromosome (18q) who had phenotypic features of both trisomy 18 and 18p-. Their patient's karyotype had a single centromere on the iso(18); therefore, he was trisomic for 18q and monosomic for 18p. Our patient, who is trisomic for 18q and 18p11 with monosomy for 18p12→pter, has a phenotype which is typical of trisomy 18. Since no features of the 18p- syndrome were seen, we

TABLE Clinical features of chromosome 18 abnormalities.

	Trisomy 18 or 18q	Monosomy 18q (partial)	Monosomy 18p	Trisomy 18p	Tetrasomy 18p
Birth weight	Low	Low	Low	Normal	Normal to low
Developmental retardation	Severe	Severe	Moderate	Variable	Moderate to severe
Cranium	Prominent occiput, microcephaly	Microcephaly	Microcephaly (mild)	Normal	Prominent occiput, microcephaly
Eyes	Short palebral fissures	Nystagmus, deep set eyes	Epicanthal folds, ptosis	Normal	Not noted
Ears	Low set, poorly formed	Prominent antihelix and antitragus	Large, floppy, low set	Normal	Low set
Nose	Short, upturned	Flat bridge	Flat bridge	Flat bridge	Short, pinched
Palate	Narrow	Narrow	Variable	Normal	High arched
Jaw	Micrognathia	Prominent	Micrognathia	Normal to small	Micrognathia
Neck	Short	Not characteristic	Webbed, short	Normal	Normal
Heart	VSD, PDA	Occasional defects	Rare defects	Normal	Normal
Extremities	Overlapping fingers, dislocated hips, prominent calcaneus	Skin dimples over joints, club foot	Short hands and fingers, lymphoedema	Normal	Long thin limbs, scoliosis
Tone	Hypertonia	Hypotonia	Variable	Normal	Hypotonia
Dermatoglyphs	6 or more arches, distal τ triradius	Increased whorls	Not characteristic	Not characteristic	Not characteristic
Other	GI and renal anomalies, early death	Carp-shaped mouth	Turner-like appearance	Short stature, round face	Carp-shaped mouth

conclude that the Turner-like features associated with 18p— may be determined by monosomy for 18p11.

Abnormalities of the short arm of chromosome 18 show distinctive phenotypes depending on the number of copies of this area present (table). Monosomy 18p has a Turner-like phenotype with moderate mental retardation. Interestingly, trisomy 18p shows little phenotypic effect and mental development has ranged from normal² to mildly delayed.⁷ Tetrasomy 18p has severe phenotypic features including moderate to severe mental retardation, hypotonia, and multiple musculoskeletal anomalies.

Abnormalities of 18q have greater phenotypic effects. Complete monosomy of 18q has not been described, but a fairly consistent phenotype (table), which includes severe mental retardation, has been reported in partial 18q—. Patients who are trisomic for 18q and disomic for 18p have a typical trisomy 18 phenotype, indicating that only trisomy 18q is required for full expression of this phenotype.⁵

Formation of isodicentric chromosomes is poorly understood. If formation occurs during mitotic or first meiotic division, it would result in a derivative chromosome with non-identical arms and centromeres. However, formation during second meiotic division would result in identical arms and centromeres. We are not aware of chromosome 18 polymorphism or polymorphic gene markers that would allow us to choose among these options. The majority of reported dicentric chromosomes have had only one active centromere.⁸ We currently do not understand the centromere inactivation process. Possibly, suppression of one centromere results in a more stable structure that is better able to undergo cell division.

Our report of an isopseudodicentric(18) associated with a trisomy 18 phenotype adds information to the correlation of phenotype and genotype in chromosome 18 abnormalities. Considering the vast phenotypic differences in normal subjects, it is not surprising that phenotypic variation exists in those with similar chromosome abnormalities. It is more remarkable that sufficient similarity exists among these patients to allow phenotype-genotype correlation.

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A genetic combination of silent β -thalassaemia, high Hb A₂ β -thalassaemia, and single α globin gene deletion causing mild thalassaemia intermedia

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SUMMARY This paper reports a Sardinian patient, who was a compound heterozygote for silent β -thalassaemia and high Hb A₂ β °-

thalassaemia with the clinical phenotype of mild thalassaemia intermedia; α globin gene mapping showed a single α globin gene deletion. The reduced α globin chain output resulted in more balanced globin chain synthesis, which in turn accounted for the mild clinical phenotype.

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