

## Case reports

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### Extra small metacentric chromosome identified as i(18p)

**SUMMARY** A case of a supernumerary metacentric small chromosome, diagnosed at birth, is described. The cytogenetic findings support its identification as i(18p). The clinical development from birth to 12 months is reported, with particular attention given to the psychomotor retardation and to the immunological aspect.

Many cases of a supernumerary small metacentric chromosome have been reported in the literature, but their diagnosis has rarely been made during the perinatal period. In this paper we report a case of i(18p) diagnosed at birth, and clinical development up to the present age of 12 months is described.

### Case report

The proposita was a female born at 39 weeks' gestation by caesarian section because of breech presentation after an uneventful pregnancy. The mother, gravida 1, had diabetes B, and both she and the father were 35 years old at the time the child was born. The parents were not related. The proposita, whose birthweight was 2500 g (< 3rd centile), had no perinatal problems: cardiotocography and Apgar score were normal. The physical examination showed low set ears, micrognathia, prominent occiput, epicanthic folds, triangular mouth, and hypertonia of the limbs with opisthotonos (Fig. 1). Because of the neurological findings, instructions for care were given to the mother when the child was discharged. At one month old she was sent to a physiotherapy centre. At three months, she had vomiting and eczema due to cow's milk allergy

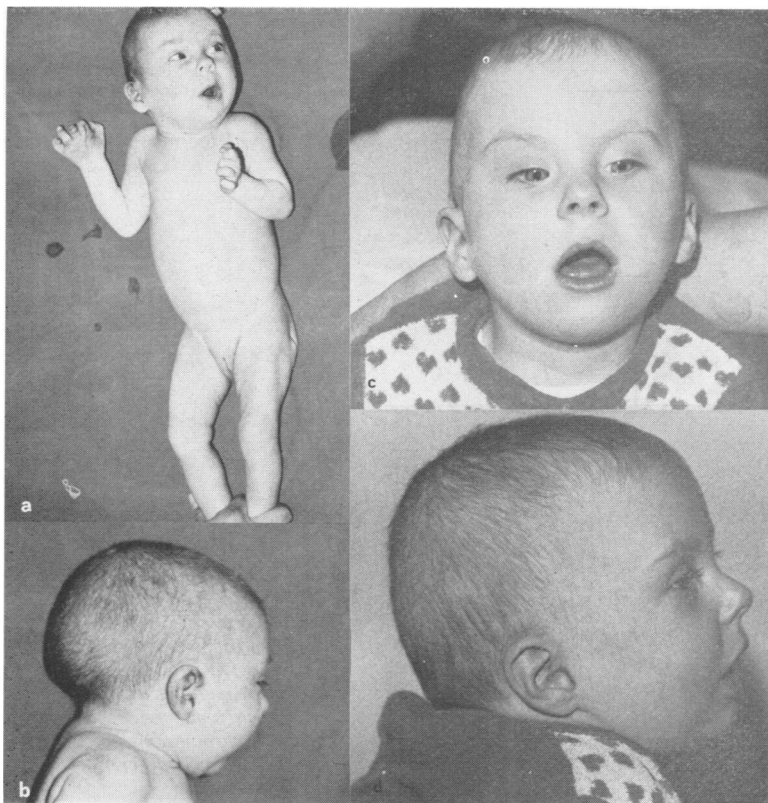


Fig. 1 The proposita (a, b) at birth, (c, d) at 12 months.

associated with IgA deficiency, and therefore dietetic therapy was introduced. In spite of the physiotherapy and stimulation, the psychomotor development, periodically controlled, deteriorated with persistence of hypertonia and spasticity.

Electroencephalogram, examination of the fundus oculi, audiometry, urine and blood aminoacid levels, serum IgM and IgG, urinary mucopolysaccharides, skeleton x-ray, and urography were all normal.

The more significant clinical data are summarised in the Table.

#### CYTOGENETIC FINDINGS

Chromosome investigations were performed in the first week of life on stimulated peripheral lymphocytes, and the metaphases thus obtained were analysed according to our standard method: the

Table Summary of the more significant clinical data

	3 months	6 months	12 months
Weight (centile)	<3rd	3rd	3rd-10th
Length (centile)	<3rd	25th-50th	75th
Head circumference	<3rd	3rd-10th	10th-25th
Hypertonia	+	+	+
Brunet-Lézine	NT	4m 21d	6 m
EEG	N	N	N
IgA (mg%)	10	7	35
E-Rosette forming cells†	NT	50%	63.7%
IgA-producing lymphocytes*	NT	6%	NT

NT, not tested; N, normal

\*normal values, 1-6%

†normal values, 60.12% ± 7.72

same metaphases were stained first with Giemsa and then with quinacrine mustard.

These examinations showed a karyotype of 47,XX,+mar, in which the supernumerary chromosome was represented by a small metacentric chromosome. This finding was present in all of more than a hundred metaphases examined. The marker did not show secondary constriction or satellites and was never involved in acrocentric associations. The partial karyotype (Fig. 2a) shows the morphological aspect. Since Q-banding (Fig. 2b) did not produce decisive evidence either, we used the technique of R-banding by BUdR using acridine orange (RBA) analysing prometaphases particularly. The unwinding, resulting from both the stage of the chromosomes and from the effect of the BUdR made a distinct pattern evident in the extra chromosome (Fig. 2c), supporting its identification as that of i(18p).

In order to discard with certainty the possibility that the marker was an isochromosome for the short arms of acrocentrics, or a remnant of Robertsonian translocation, we used:

- (1) The Ag-As technique (Bloom and Goodpasture, 1976), which is specific for the NOR (Ferraro *et al.*, 1977) (Fig. 3a). Since it is very rare to find all the acrocentrics Ag-stained in the same metaphase, we analysed more than 50 metaphases from 4 different slides to be sure of the conclusions.
- (2) The distamycin A/DAPI technique (Schweizer

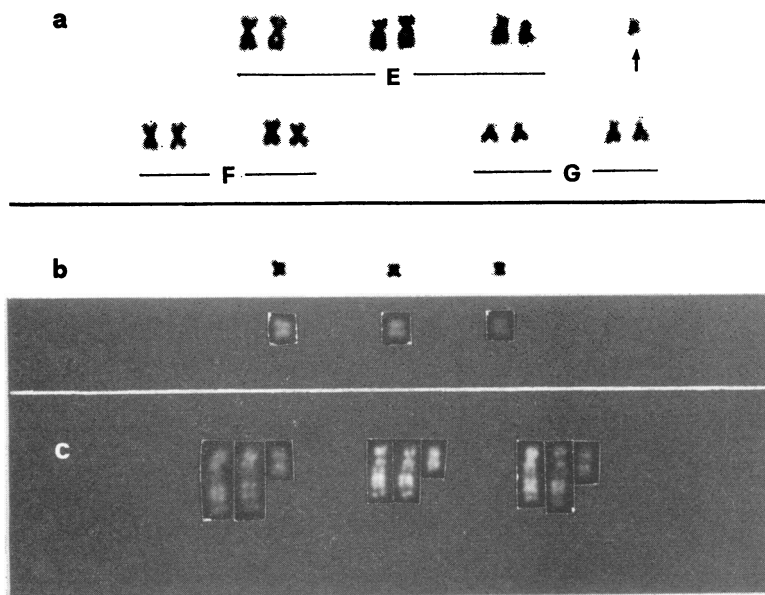


Fig. 2 (a) Proposita's partial karyotype. (b) Single marker chromosome stained first with Giemsa (upper row) and then with QM (bottom row) from 3 different metaphases. (c) Proposita's pair no. 18 and marker chromosomes after RBA banding from 3 different metaphases.

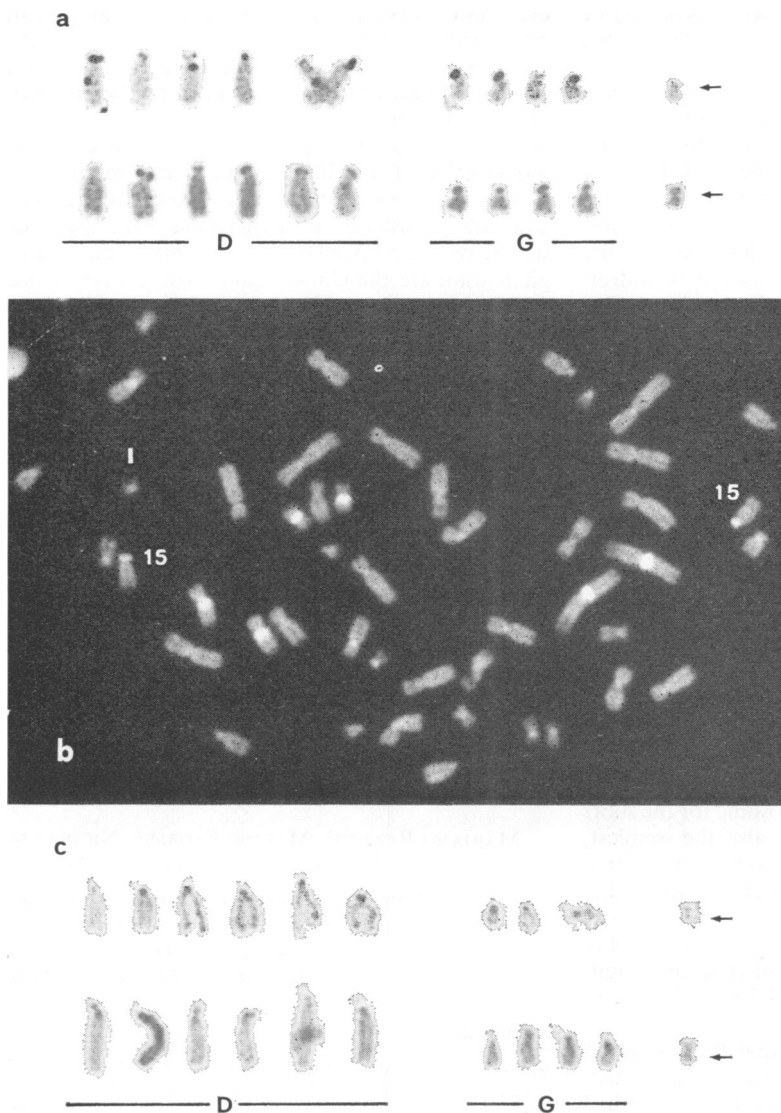


Fig. 3 (a) *Ag-As* technique: D and G group chromosomes plus marker from 2 different metaphases. (b) Metaphase stained with distamycin A plus DAPI technique. The arrow indicates the marker. (c) D and G group chromosomes plus marker from 2 different metaphases, Giemsa-11 stained.

*et al.*, 1978) which stains, in acrocentrics, the short arm of chromosome 15 (Fig. 3b). We used this technique because most additional small metacentric chromosomes are thought by some authors to be isochromosomes for the 15p.

- (3) The Giemsa-11 technique (Bobrow *et al.*, 1972), which stains, besides the 9qh, 'the short arms and sometimes the satellites of all D and G group chromosomes' (Fig. 3c). The marker was not stained by any of these techniques. The karyotype of both parents was normal.

#### DERMATOGLYPHS

All digital patterns were ulnar loops, except for radial loops on both the 2nd digits and a whorl on the left 4th digit. A bilateral simian crease was present and an additional flexion fold in the right 2nd digit was found between the two interphalangeal ones.

#### Discussion

The cases of a supernumerary small metacentric chromosome described before the introduction of

banding techniques show a remarkable variability of phenotypes. Some cases had a normal phenotype, while others had serious anomalies (Dzarlieva *et al.*, 1975). This caused the assumption that there was not a specific syndrome resulting from the small meta-centric chromosome and that the variability of the clinical aspects depended on the origin of the extra chromosome. The cases described after the introduction of banding techniques confirmed this hypothesis. In fact, cases have been described of the extra chromosome being identified as i(18p) (Condrón *et al.*, 1974), 18q— (Fujita and Fujita, 1975), i(17p) (Nielsen *et al.*, 1977), 17q— (Palutke *et al.*, 1976), and isochromosome of the short arm of an acrocentric chromosome or remains of a Robertsonian fusion (Nielsen and Hreidavsson, 1973).

In our case the cytogenetic data can be summarised as follows:

- (1) The extra chromosome is symmetrical and the length of the two arms corresponds to the length of the 18p.
- (2) The fluorescence in Q-bands is also symmetrical and comparable to that of the 18p.
- (3) The RBA bands show a distinct pattern which is also symmetrical and always in accordance with that of the 18p.
- (4) Finally, the marker was not stained by specific techniques for the short arms of acrocentrics.

The most likely hypothesis is, therefore, that the extra chromosome is an isochromosome for the short arm of the 18. This hypothesis is also the simplest, since it only resorts to the misdivision of the centromere of a chromosome 18 in order to explain the origin of the aneuploidy.

The most probable alternative hypothesis, trisomy of 18q—, presupposes a split in 18q and non-disjunction in the first meiotic division, that is, at least two distinct events.

It should also be remembered that the formation of an isochromosome is not a rare occurrence in man, as numerous cases of i(Xq) found in published reports show.

Many of the cases of i(18p) reported so far are in adults who, apart from psychomotor retardation, do not present other serious defects which limit their life span. Besides, as far as we know, no cases of i(18p) in spontaneous abortions have ever been reported (Boué *et al.*, 1976). Such statements suggest that the chromosomal imbalance as a result of i(18p) is not very serious, perhaps because of the small size of the 18p and/or because in this area there are no important genes, and that the functions of the central nervous system are the first to be compromised in the presence of an autosomic derangement.

As regards the clinical data (Table), the little girl

born small-for-dates, has shown normal growth in both head circumference and body length. Weight recovery was delayed because of the cow's milk protein allergy, which was sustained by the presence of anti-milk protein antibodies in the serum. A normal increase in body weight occurred after the introduction of the elimination diet at 5 months.

The presence of serious psychomotor retardation and the persistence of hypertonia with signs of spasticity, accompanied by a normal electroencephalogram are the clinical data most in accordance with the data reported in other reports; these features persisted in spite of immediate treatment (stimulation and physiotherapy).

As regards the immunological data, at 6 months we found low serum IgA and normal serum IgA-producing lymphocytes. This finding pointed towards a temporary immunological deficiency, which was confirmed by complete return to normal at 12 months. The evaluation of the cellular immunity showed a slight defect (50% of E-Rosette-forming cells) at 6 months, which also became normal by 12 months.

Ogata *et al.* (1977) reported low IgA at 6 months in a similar case. In the published reports we found no other references to immunological development in cases of i(18p). Nevertheless, vomiting and nutritional difficulties, not infrequently reported, suggest that initial immunological deficiency is not an unusual finding.

MARIANO ROCCHI<sup>1</sup>, MARINO STORMI<sup>2</sup>, NICOLETTA ARCHIDIACONO<sup>1</sup>, AND GIORGIO FILIPPI<sup>1</sup>  
*Cattedra di Genetica Medica<sup>1</sup> e Cattedra di Puericultura<sup>2</sup>, Università di Trieste-Istituto per l'Infanzia di Trieste, Via dell'Istria 65, 34137 Trieste, Italy*

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## Familial dicentric translocation t(13;18)(p13;p11.2) ascertained by recurrent miscarriages

**SUMMARY** A dicentric translocation is described involving chromosomes 13 and 18 in which the centromere of chromosome 13 was suppressed. The translocation was ascertained by repeated miscarriages and was found in three generations of phenotypically normal carriers.

Familial dicentric translocations have not been reported in man other than in Robertsonian fusions (Daniel and Lam-Po-Tang, 1976). Other dicentric translocations have been described involving at least one non-acrocentric chromosome. The latter,

Requests for reprints to Dr Mariano Rocchi, Istituto per l'Infanzia, Via dell'Istria 65, 34137 Trieste, Italy.

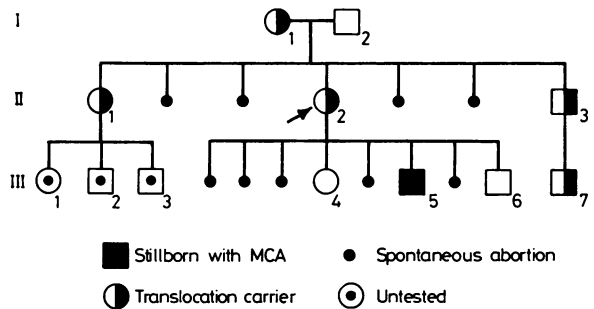


Fig. 1 Pedigree.

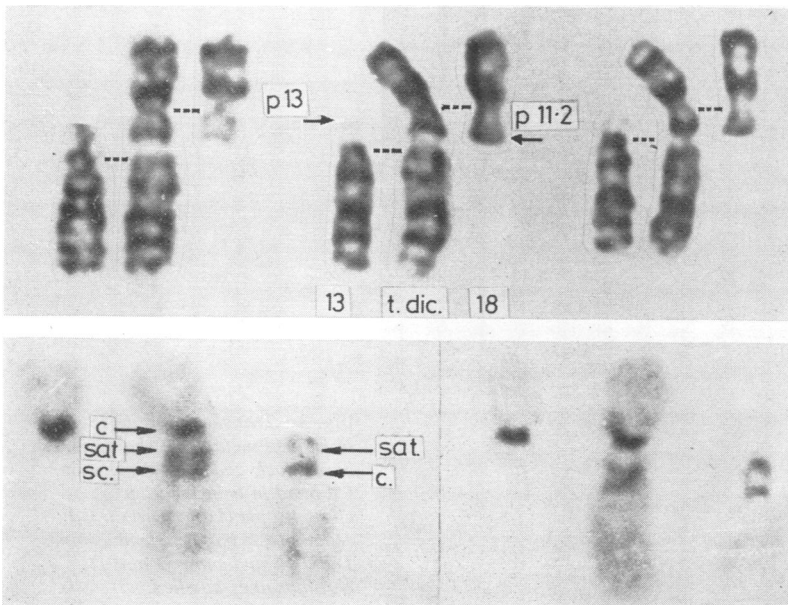


Fig. 2 Translocation dic(13;18).  
 Upper row: G bands of 13,t,18(3 cells); lower row: C bands of 18,t,13(2 cells).  
 c, centromere; sat, satellites; sc, suppressed centromere.