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47,XX,+der(18),t(9;18)(p24;q21) mat: a distinct partial trisomy 18q—syndrome?¹

SUMMARY A moderately retarded girl had a 47,XX,+der(18),t(9;18)(p24;q21)mat abnormality that was inherited from her mother, who had a 46,XX,t(9;18)(p24;q21) karyotype in most cells, and a minor cell line of 47,XX,-t(9;18)(p24;q21). Her dysmorphic features—bilateral epicanthic folds, low-set, abnormal ears, low posterior hairline, clinodactyly of the 5th fingers, and broad great toes—were similar to those of other patients with an additional number 18 chromosome in which all or most of the long arm was missing, thus raising the possibility of a distinct syndrome.

Trisomy for the whole of chromosome 18 is not rare, but duplication of a portion of the number 18 chromosome appears to be uncommon. We have evaluated a moderately retarded, dysmorphic girl whose trypsin-Giemsa banded karyotype was 47,XX,-+der(18),t(9;18)(p24;q21)mat, inherited from her mother who had 2 cell lines: 46,XX,t(9;18)(p24;q21) and 47,XX,+der(18),t(9;18)(p24;q21). In this paper, we describe the patient’s physical features and chromosome abnormalities and compare them with the 4 other reported cases with probable trisomy 18q—. The patient was earlier referred to briefly in a paper by Francke (1972).

Case report

The patient was born to a 26-year-old woman and her 29-year-old husband after a 41-week gestation, during which the mother took a daily thyroid supplement. The parents had been trying to conceive for 6 years, but this was their first and only pregnancy.

Birthweight was 2.84 kg, length 48 cm, and head circumference 32 cm. The infant had the following features: frontal bossing with a narrow bitemporal diameter, bilateral epicanthic folds, downward obliquity to the palpebral fissures, wide nasal bridge, low-set ears with bilateral preauricular skin tags, high arched palate, low posterior hairline, clinodactyly of the 5th fingers, and broad great toes with hypoplastic nails (Fig. 1). The broad great toes initially raised the

¹Supported in part by grants HD-04612 and HD-05615 from the National Institute of Child Health and Human Development.

Fig. 1 Front and lateral view of the patient. See text for description.
question of the Rubenstein-Taybi syndrome. Dermatoglyphs showed: right hand with a t palmar axial triradius and 5 digital ulnar loops; left hand with a t' palmar axial triradius and 5 digital ulnar loops.

At age 5 years her developmental quotient was estimated to be 65 and her weight was 19 kg (50th centile), height 105 cm (25th centile), and head circumference 49 cm (40th centile). Though she had an intermittent right external strabismus, her vision and hearing were normal and her general health good.

An intravenous pyelogram, voiding cystouretrograph, chest x-rays, and x-rays of the long bones and spine were all normal. X-rays of the 5th finger showed only 2 phalanges, while the thumbs and great toes were normal. An electrocardiogram showed right ventricular prominence. Urine amino acid chromatography was normal, as were the following urine screening tests: FeCl₃, glucose, protein, methylmalonic acid, and dinitrophenylhydrazine.

Chromosome analysis

Studies were carried out on peripheral blood and skin fibroblasts of the patient and her mother, and on the peripheral blood of the patient’s father, maternal grandparents, maternal aunt, and maternal uncle. The last 5 all had normal karyotypes.

All of the patient’s skin fibroblasts and lymphocytes contained 47 chromosomes with an additional number 18, in which two-thirds of the long arms (below band q21) were missing (Fig. 2).

Of the mother’s peripheral blood lymphocytes, 107 were examined. Four of these contained 47 chromosomes with an additional number 18q−, while the others had 46 chromosomes with an apparent balanced translocation between the short arms of a number 9 and the long arms of a number 18 chromosome. Her karyotype was: 46,XX,t(9;18)(p24;q21)/47,XX,- +der(18)t(9;18)(p24;q21). All 30 of her skin fibroblasts contained only the major cell line, 46,XX,t(9;18)(p24;q21) (Fig. 3).

Discussion

Only 4 patients with similar karyotypic abnormalities were found in published reports. The first was reported by Lejeune et al. (1970), and again by Marcelli et al. (1974). That patient was a boy, born at term, who weighed only 2.5 kg. In addition to the low birthweight, he showed retardation (developmental quotient 47 at 18 months), microcephaly, plagiocephaly, epicanthic folds, hypertelorism, esotropia, and low-set ears with rolled helices, small tragi, large antitragi, and hypoplastic lobules. It was felt that phenotypically he resembled patients with the 18q− syndrome even though his karyotype was 47,XY,- +der(18)t(18p;20p)mat. This was inherited from his mother and maternal grandfather, who had balanced reciprocal translocations between chromosomes 18 and 20. Thus, the child received 2 normal number 20 and 2 number 18 chromosomes, in addition to a metacentric chromosome containing 18p and 20p.

The second patient was described by Muller et al. (1972) and resembled patients with trisomy 18. She had low birthweight (2.4 kg), prominent occiput,

![Fig. 2 Trpssin-Giemsa banding karyotype of the proband. The arrow points to the +18q− abnormality.](http://jmg.bmj.com/ on June 22, 2017 - Published by group.bmj.com)
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Fig. 3 Trypsin-Giemsa banding karyotype of the mother of the proband. The arrows point to the chromosomes 9 and 18 involved in the translocation resulting in karyotype: 46,XX,t(9;18)(p24;q21).

micronogathia, high arched palate, small eyes, congenital heart disease, overriding fingers, club feet, and hypertonicity. She died of pneumonia at age 4 months and her karyotype (routine and autoradiographic) showed a single number 18 and 2 additional metacentric chromosomes of different sizes. These were thought to represent either 47,XX,+der(18), t(18p+;18q-) or 47,XX,−18,+i(18p),+i(18q). Parental karyotypes were normal.

A third patient, who weighed 2.8 kg at birth, and was also thought to represent the trisomy 18 syndrome phenotypically, was noted in 1974 by Fujita and Fujita to have 47,XX,+(18q−), though the authors were unable to state this with certainty. Parental karyotypes were normal.

The fourth patient, who had more features in common with our patient than any of the 3 described above, was reported by Taylor et al. (1975). This child was a 9-year-old girl with an intelligence quotient of 30, short stature, microcephaly, low posterior hairline, narrow chest, clinodactyly of the 5th fingers, a single palmar crease on the right hand, hypertonicity, and broad thumbs and great toes. She weighed 2.9 kg at birth and was 48 cm long. The patient's karyotype was 47,XX,+i(18p). Her mother's karyotype was 47,XX,del 18(p11),+i(18p). A sister, whose only dysmorphic features were small size and broad thumbs, had 46,XX,del 18(p11).

The Table summarises the clinical features and karyotypes of our patient and the 4 previously reported cases whose karyotypes resemble ours. The Table also includes summaries of patients with 18q+, confirmed by banding studies, and with trisomy 18. There have been no reports of patients with 18p+.

Although additional reports of patients with +18q− have to be awaited, it is suggested in the Table that this particular chromosome defect may result in a distinct constellation of findings, at least in some of the patients. These findings are: relatively low birthweight, mental retardation, microcephaly, low posterior hairline, abnormal ears, high arched palate, clinodactyly, and broad thumbs and great toes.

It is also of interest to speculate as to how the chromosome abnormalities in our patient and her mother came about. The changes in our patient's mother's karyotype are no doubt de novo, as her parents and her 2 sibs all have normal karyotypes. The translocation between 9p and 18q probably occurred first, possibly during meiosis in one of the mother's parents, and was then followed by postzygotic non-disjunction, resulting in a minor cell line containing 47 chromosomes with an additional 18q−.

The daughter inherited her mother's normal number 9 chromosome and one normal 18 chromosome, in addition to the extra 18q−. It is not known if this occurred as a result of meiotic non-disjunction in the mother's 46 chromosome cell line, or from secondary non-disjunction in her minor 47 chromosome cell line.

As for meiotic non-disjunction in the mother's major cell line resulting in her daughter's unbalanced state, this seems to be the more plausible explanation, considering the fact that postzygotic non-disjunction involving 18q− had already occurred while the mother was undergoing embryogenesis herself. It may
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### Table Clinical findings in +18q−, 18q+, and trisomy 18

<table>
<thead>
<tr>
<th>Birthweight</th>
<th>Gestational age</th>
<th>Malformation</th>
<th>Skeletal</th>
<th>Head</th>
<th>Cranial</th>
<th>Cardiac</th>
<th>Respiratory</th>
<th>Skin</th>
<th>Syndactyly</th>
<th>Joint contracture</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>47,XX,+der(13)(p12;q11)</td>
<td>46,XX,13q+pat</td>
<td>Father had 46,XX,y(13q+;18q-)</td>
<td>46,XX,13q+pat</td>
<td>46,XX,4q+pat</td>
<td>Father had 46,XX,y(4q+;18q-)</td>
<td>47,XX,+i(18p)mat</td>
<td>Mother had 47,XX,del(18)(p11),+i(18p)</td>
<td>47,XX,+(18q−). Parental karyotypes normal</td>
<td>47,XX,+i(18q+)mat</td>
<td>47,XX,−(18q−) or 47,XX,−18,+i(18p),+i(18q)</td>
<td>Parental karyotypes normal</td>
</tr>
</tbody>
</table>

### Notes
- For each case, the karyotype and clinical findings are detailed.
- The cases are divided into three groups: +18q−, 18q+, and trisomy 18.
- Clinical findings include malformations, skeletal issues, cardiac and respiratory problems, skin abnormalities, syndactyly, joint contracture, and other features.
- The table is organized to facilitate comparison between the different karyotypes and their associated clinical findings.
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well be that, in this family, 18q— is unable to segregate properly during gametogenesis and early postzygotic mitosis, leading to an unbalanced state and +18q—.

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References


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Trisomy 21 with 47,+18 lymphocyte cell line: double mitotic nondisjunction

SUMMARY

A patient with Down's syndrome was found to have 47,XX,+18/47,XX,+21 mosaicism. Chromosome 18 trisomy was found only in 18% of lymphocytes and not in skin fibroblasts. A likely interpretation is double nondisjunction in a single lymphocyte precursor of a trisomy 21 embryo. A brief review of other cases of mitotic multiple nondisjunction and double aneuploid mosaicism is presented.

Chromosomal mosaicism occurs in a small percentage of patients with Down's syndrome. The vast majority of these mosaics have a normal cell line in addition to the trisomy 21 cell line. This report describes the first reported instance, to our knowledge, of an unusual type of double trisomy mosaicism in lymphocytes involving chromosomes 18 and 21.

Case report

The proposita was referred for chromosome analysis at age 20 years because of numerous signs of trisomy 21. Her facial appearance was typical of Down's syndrome, with a flat nasal bridge, oblique palpebral fissures, and epicanthal folds. There was a high arched palate and a furrowed tongue. The patient was 140 cm tall (less than 3rd centile), obese (weight 50.5 kg), and her head circumference was 50.5 cm (less than 2nd centile). Her hands were broad and short with bilateral simian lines and laterally displaced axial triradii. Her fingers, wrists, and elbows were hyperextensible. There was muscle hypotonia, and her co-ordination was poor. No focal deficits were noted on neurological examination. Her electroencephalogram was interpreted as moderately abnormal because of excessive posterior slowing and had a background alpha rhythm of 8 to 9 Hz moderate voltage activity.

Psychometric examination indicated the patient to be mildly retarded (WAIS: verbal IQ, 64; performance IQ, 63; full scale IQ, 61). Academic skills assessed by PIAT were as follows: mathematics, 1.4 grade equivalent; reading recognition, 3-9 grade equivalent; and general information, 3-2 grade equivalent. In her subjective evaluation she showed a strong tendency towards inappropriate responses and fantasy activities.

The proposita was the 3rd child of unrelated parents. Her mother and father were aged 45 years and 52 years, respectively, at the time of her birth. Her sibs were normal and there was no family history of mental retardation.

CHROMOSOME STUDIES

Of a total of 100 cultured lymphocytes analysed from two blood samples, 82 cells were 47,XX,+21 and 18 were 47,XX,+18. Giemsa banded E and G groups are
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doi: 10.1136/jmg.15.5.391