Double Autosomal Trisomy and Mosaicism for Chromosomes No. 8 and No. 21*

**Summary.** This patient was found to have a previously unreported double trisomy for chromosomes No. 8 and No. 21. She was recognized to have Down's syndrome at birth, and her subsequent development was consistent with that diagnosis. Her general health was good and there were no features suggesting an additional chromosomal abnormality. At this time there is no clearly recognized phenotype associated with trisomy 8. Two non-disjunctive events, occurring in meiosis and/or post-zygotic mitosis, are possible explanations of the chromosomal abnormalities found in this patient.

Double autosomal trisomy is rarely found in viable individuals, in contrast to the more frequently occurring autosomal trisomy with sex chromosomal aneuploidy. Most of the instances of double trisomy or trisomy with sex chromosomal aneuploidy have been observed in Down's syndrome. To our knowledge, double autosomal trisomy for a G chromosome and another autosome (either a D or an E chromosome) has been described in 11 liveborn children (Gagnon et al, 1961; Gustavson et al, 1962; Becker, Burke and Albert, 1963; Hsu et al, 1965; Smith, Tips, and Howard, 1965/1966; Tolksdorf, et al, 1965; Koch, Santamouris, and Ulbrich, 1967; Marks, Wiggins, and Spector, 1967; Zellweger and Abbo, 1967; Glogowska, 1969; Porter, Petersen, and Brown, 1969).

The child described here was found to have double trisomy and mosaicism for chromosomes No. 8 and No. 21, identified by Giemsa-banding patterns. The karyotype was 47,XX,+21/46,XX,+8,+21. At birth the phenotype was readily recognized as Down's syndrome, and there were no unusual features suggesting an additional chromosome abnormality. This is the first reported liveborn child with double autosomal trisomy involving chromosomes No. 8 and No. 21.

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To our knowledge no kindreds have been presented in the literature showing a case of spina bifida cystica in a family with multiple cases of spondylolisthesis. A marked association has been shown between spondylolisthesis and spina bifida occulta, since spina bifida occulta is five to 10 times more common in individuals with spondylolisthesis than in the general population (Pembrey, 1972). In the family presented by Amuso and Mankin (1967) five of the six surviving members of three generations had spondylolisthesis and spina bifida occulta.

The pattern in the family presented here is suggestive of autosomal dominant inheritance with variable expressivity. Given proper environmental conditions the genotype manifests itself phenotypically in spondylolisthesis with spina bifida occulta, the spondylolisthesis occurring during or after childhood with the spina bifida occulta developing embryonically. We suggest that the mother of the proposita carried this abnormal allele, although it was not expressed, and passed it to the proposita. Perhaps this allele, in conjunction with other aspects of the genotype and the intrauterine environment, led to the development of the multiple spinal anomalies of the proposita.

I would like to acknowledge the cooperation of The Children's Orthopedic Hospital and Medical Center in our study of the epidemiology of spina bifida cystica. Some of the data presented in this paper were obtained from consultation reports of the Division of Medical Genetics, Department of Medicine, University of Washington School of Medicine.

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**REFERENCES**


Fig. 1a. Proposita at 2 months. Typical appearance of Down’s syndrome.

Fig. 1b. Proposita at 17 months.

Fig. 2. Karyotype from the proposita demonstrating the cell line of 46,XX,+C,+G. (Conventional staining.)
Case Reports

Following a normal pregnancy and delivery, this female black infant (AH 181071) was born at term to an 18-year-old, gravida 2 mother and a 21-year-old father. The parents were unrelated. Their other child was a normal 2-year-old boy. There was no family history of Down's syndrome, congenital defects, or mental retardation.

Birth weight was 2580 g and the child was immediately recognized to have Down's syndrome (Fig. 1a). She was hypotonic, placid, and hyperextensible at all joints. The following were present: brachycephaly, a flat facial profile, epicanthi, upward-slanting palpebral fissures, a protruding tongue, prominent lips, clinodactyly of the fifth fingers, and a deep cleft between the first and second toes. There were no cardiac murmurs and no Brushfield spots. Palmar creases were normal.

At 3 weeks of age, she was found to have a duodenal stenosis and malrotation and these were corrected by surgery. At 13 months her developmental behaviour was at the 6-month level, and at 20 months was about 9–10 months.

Growth measurements of height and weight were at about the third centile throughout the first year of life, and less than the third centile at 17 and 20 months of age. Head circumference was at about the 10th centile for age during the first 20 months of life.

As the child became older, her tongue protruded less, which resulted in a less striking Down's syndrome phenotype (Fig. 1b). Her only illnesses were occasional respiratory infections.

Dermatoglyphic studies showed ulnar loops on the second fingers, ad angles of 87° (right palm) and 89° (left), and tibial arches on the hallucal area of the soles. According to the Reed dermatogram (Reed et al, 1970), this is within the distribution for Down's syndrome.

Chest radiology showed normal vertebral, ribs, and cardiac silhouette. Radiographs of the pelvis demonstrated normal acetabular angles.

Chromosome Studies

Chromosome analysis from peripheral blood culture showed two cell lines: 47,XX,+G, and 48,XX,+C,+G (Table I). Analysis from fibroblast (skin) culture showed the same mosaicism. The banding patterns, with the use of trypsin Giemsa-staining of Seabright (1971 and 1972) and quinacrine fluorescence staining by the method of Caspersson, Zech, and Johannson (1970) and Caspersson, Lomakka, and Zech (1971), enabled the trisomic chromosomes to be identified as No. 8 and No. 21 (Figs. 2 and 3). The predominant cell line in the blood was 47,XX,+21 (60%) and in the skin, 48,XX,+8,+21 (about 80%).

Cells from the buccal mucosa showed 30% of 300 cells with one Barr body and no cells with two Barr bodies. Autoradiography demonstrated only one late-labelling X chromosome in the 48-cell line (four cells examined).

Chromosome analyses from the parents showed normal results. The karyotype from the mother showed a lengthened short arm of No. 15, which was interpreted as a minor variant (15p+). This variant was also found in the proposita.

Discussion

Trisomy C, often associated with mosaicism, has been reported in a number of instances; however, only recently was it possible to specify the chromosome present in the trisomic state. De Grouchy, Turleau, and Léonard (1971) and Caspersson et al (1972) described five patients with trisomy 8, in which the extra chromosome was identified by quinacrine fluorescence or Giemsa banding patterns. Three of these patients showed mosaicism for trisomy 8 and a normal cell line.

No phenotype specific for trisomy 8 was found in the five patients described by de Grouchy et al (1971) and Caspersson et al (1972). All these patients showed a wide range of clinical findings. All were mentally retarded except for one woman who showed no abnormal physical or mental features and was studied because of two spontaneous abortions. She was found to have trisomy 8 in about 95% of lymphocytes and in about 50% of skin fibroblasts; the other cell line was normal. The other patients were studied because of mental retardation and

TABLE I
CHROMOSOME ANALYSES

<table>
<thead>
<tr>
<th>Tissue</th>
<th>No. of Chromosomes</th>
<th>Total No. of Cells</th>
<th>Results of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood (2 mth)</td>
<td>46 47 48</td>
<td>55</td>
<td>47,XX,+21/48,XX,+8,+21</td>
</tr>
<tr>
<td>Skin (2 mth)</td>
<td>32 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood (20 mth)</td>
<td>4 16</td>
<td>20</td>
<td>47,XX,+21/48,XX,+8,+21</td>
</tr>
<tr>
<td>Mother</td>
<td>Blood</td>
<td>10</td>
<td>46,XX; normal</td>
</tr>
<tr>
<td>Father</td>
<td>Blood</td>
<td>10</td>
<td>46,XY; normal</td>
</tr>
</tbody>
</table>
FIG. 3. Partial karyotype from the proposita demonstrating trisomy 8 and 21 in the 48,XX, +8, +21 cell line. (Trypsin Giemsa-banding.)

### Table II

**Double Autosomal Trisomy**

<table>
<thead>
<tr>
<th>Double Trisomy</th>
<th>Karyotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>G and D chromosomes</td>
<td>48,XX, +D, +G or 48,XX, +D, +Y</td>
<td>Patau's syndrome</td>
</tr>
<tr>
<td>Gustavson et al (1962)</td>
<td>48,XY, +D, +G</td>
<td>Down's syndrome (primarily)</td>
</tr>
<tr>
<td>Becker et al (1963)</td>
<td>48,XY, +D, +G</td>
<td>Not Down's syndrome</td>
</tr>
<tr>
<td>Koch et al (1967)</td>
<td>48,XY, +D, +G</td>
<td>Down's syndrome (primarily)</td>
</tr>
<tr>
<td>Smith et al (1965/1966)</td>
<td>47,XX, +G/48,XX, +D, +G</td>
<td></td>
</tr>
<tr>
<td>G and E chromosomes</td>
<td>48,XX, +E, +G</td>
<td>Edwards' syndrome (primarily)</td>
</tr>
<tr>
<td>Hsu et al (1965)</td>
<td>47,XY, +G/48,XY, +E, +G</td>
<td>Edwards' syndrome</td>
</tr>
<tr>
<td>E. D. Marks et al (1967)</td>
<td>47,XY, +G/47,XY, +E</td>
<td>Down's syndrome</td>
</tr>
<tr>
<td>Zellweger and Abbo (1967)</td>
<td>46,XY/47,XY, +E/47,XY, +G/48,XY, +E, +G</td>
<td>Down's syndrome (primarily)</td>
</tr>
<tr>
<td>G and C chromosomes</td>
<td>47,XX, +21/48,XX, +8, +21</td>
<td>Down's syndrome</td>
</tr>
<tr>
<td>Present case</td>
<td>47,XX, +G, +mar</td>
<td>Down's syndrome</td>
</tr>
<tr>
<td>G chromosomes and unidentified autosome</td>
<td>48,XX, +G, +mar</td>
<td>Down's syndrome</td>
</tr>
<tr>
<td>Dekaban (1965)</td>
<td>46,XX/48,XX, +D, +E</td>
<td>Edwards' syndrome</td>
</tr>
<tr>
<td>Schmidt et al (1967)</td>
<td>47,XY, +D/47,XY, +E</td>
<td>Patau's and Edwards' syndromes</td>
</tr>
<tr>
<td>Zellweger and Abbo (1967)</td>
<td>47,XX, +D/47,XX, +E/48,XX, +D, +E</td>
<td>Edwards' syndrome (primarily)</td>
</tr>
</tbody>
</table>
congenital defects. Abnormal physical findings in several of these patients included strabismus, clinopecty, vertebral and rib abnormalities, and possible abnormalities of the great vessels. Published photographs of several patients showed a long face with large, prominent ears, small chin and protruding lower lip. Growth did not appear to be adversely affected.

We were able to find 11 cases of double autosomal trisomy involving a G chromosome and another autosome, either a D or E chromosome (Table II). One case of Down's syndrome has been reported with 48,XX,+21 and an additional, unidentified small chromosome (Dekaban, 1965). Three additional cases of double trisomy for a D-group and an E-group chromosome (presumably No. 13 and No. 18) have been reported (Schmidt et al, 1967; Zellweger and Abbo, 1967; Garson et al, 1969). In general, it was thought that the phenotype of individuals with double autosomal trisomy corresponded with the more severe condition (Hamerton, 1971). About half of the double trisomies involving a G chromosome and another autosome were associated with the less severe phenotype of Down's syndrome (Table II). Other factors influencing the phenotype may be significant, such as the predominating cell line, particularly in critical periods of fetal life, and the actual distribution of cell lines throughout the body. Clinical familiarity with Down's syndrome may generally bias towards its recognition, rather than that of the more severely affected phenotypes associated with trisomy 13 or 18.

Of double trisomic individuals with trisomy G, the other autosome was a D chromosome in about half of the cases and an E chromosome in the other half. Mosaicism occurred in all but one of the five cases of double trisomy G and E, and in only one of the five instances of double trisomy G and D. In general, mosaicism is more frequent in the single aneuploidy of trisomy E than in trisomy D.

Trisomy for No. 8 chromosome was only recently recognized. Some years ago, it was thought that three autosomal trisomies were all that would be found in man, and that very likely an additional autosomal of the size of the C group would be incompatible with life. At present, it appears that trisomy 8 is clearly compatible with life and may be associated with few congenital defects. To date, mental retardation is a constant feature of the nonmosaic individuals with trisomy 8.

There are a number of mechanisms that would explain the double trisomy-mosaicism of 47,+21 and 48,+8,+21 found in our patient:

1. Post-zygotic non-disjunction occurring after the first division in a trisomic zygote, followed by elimination of the presumably non-viable cell line lacking one autosome.

\[
\begin{align*}
47,+21 & \rightarrow \{47,+21 \rightarrow (46,-8,+21 \text{ (non-viable)} \}
\end{align*}
\]

2. Two non-disjunctive events in a euploid zygote, one non-disjunction occurring at the first post-zygotic division followed by elimination of the monosomal cell lines.

\[
\begin{align*}
46 & \rightarrow \{47,+21 \rightarrow (47,+21 \rightarrow (46,-8,+21 \text{ (non-viable)} \}
\end{align*}
\]

3. Fertilization between two aneuploid gametes, followed by loss of No. 8 in one cell line (e.g., anaphase lag) after at least one division.

\[
(24,+8)+(24,+21) = 48,+8,+21 \rightarrow (47,+21
\]

Mechanism 3 (above) seems the least likely since the simultaneous occurrence of two unusual and independent events resulting in aneuploid gametes is required.

We are grateful for the technical assistance of Dr Joseph A. Towner and Mr Paul Brager.

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**References**


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Turner Phenotype: Mosaic 45,X/47,XY,+18*

**Summary.** A 14-year-old girl with Turner phenotype is described, whose lymphocyte and skin fibroblast cultures both revealed a 45,X/47,XY,+18 chromosomal mosaicism. In blood cultures one third and in fibroblasts 7% of the cells had 47 chromosomes. The identity of the Y and the supernumerary 18 were determined by fluorescence and Giemsa banding patterns. The patient is of normal intelligence and does not exhibit any signs of masculinization or stigmata of trisomy 18.

There are several instances of mosaicism with X-monosomic and 21-trisomic cell lines. Cohen and Davidson (1972) published one case of a mosaic 45,X/47,XX,+21, and Prieur *et al* (1972) one of 45,X/47,XY,+21. Several cases of mosaic 45,X/46,XX/47,XY,+21 (Pfeiffer, 1968) and one case of mosaic 45,X/46,XY/47,XY,+21 (Edgren, de la Chapelpe, and Kåtäriäinen, 1966) have been reported. To our knowledge the present case is the first one involving an extra autosome 18.

**Case Report**

The proposita is the third daughter of healthy unrelated parents; the father was 38 years and the mother 41 years at her birth. All the family is of short stature, the father being 162 cm, the mother 152 cm, the 21-year-old sister 150 cm, and the 18-year-old sister 160 cm. The patient was born by Cesarean section at 36 weeks; birth weight was 2400 g. Swelling of the dorsum of both feet was noted at birth and persisted for more than one year. The patient was said to have been always smaller than her sisters at comparable ages, but otherwise her physical and mental development was normal.

At 12 years of age she was referred to this hospital because of short stature (length 117.7 cm, weight 25.2 kg, both below third centile) and absence of pubertal signs. She presented the following stigmata of Turner’s syndrome: multiple pigmented naevi, prominent auricles, short broad neck with slight pterygium, broad chest with widely spaced hypoplastastic nipples, relatively large clitoris, hyperextensibility of elbow joints, and short fourth fingers. Radiology of both hands revealed short fourth metacarpals, a coarse trabecular pattern of the bone, and a bone age of 9-10 years, giving a predicted adult height of only 139 cm.

Sex chromatin was studied in buccal smears and in hair root preparations (Schmid, 1967a and b). The chromosomes from blood cultures were studied in

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