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SHORT COMMUNICATION

PRENATAL DIAGNOSIS OF PARTIAL TRISOMY 12 AND PARTIAL TRISOMY 21 DUE TO A 3:1 SEGREGATION OF MATERNAL RECIPROCAL TRANSLOCATION t(12;21) (p13.3;q21)

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SUMMARY

We describe the prenatal diagnosis and fetal phenotype of partial trisomy 12 (p13.3-pter) and partial trisomy 21 (pter-q21) due to a 3:1 segregation with tertiary aneuploidy transmitted from a maternal reciprocal translocation 12;21. Genetic amniocentesis of a 39-year-old gravida 2, para 1 woman at 19 weeks' gestation due to advanced maternal age revealed an unusual karyotype of 47,XY,+der(21)t(12;21)(p13.3;q21)mat. The pregnancy was terminated at 24 gestational weeks. The proband postnatally displayed by dysmorphic features of a round flat face with prominent cheeks and high forehead, upward slanting palpebral fissures, epicanthic folds, hypertelorism, a short nose, a broad and depressed nasal bridge, anteverted nares, a deformed philtrum, an open mouth, thin upper vermilion and broad everted lower lip, low-set ears with prominent anthelix and deep concha, broad hands with simian creases, a short neck, and cryptorchidism. The association of the involved chromosomal segments with the phenotype of Down's syndrome and trisomy 12p syndrome is discussed.

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KEY WORDS: partial trisomy 12; partial trisomy 21; tertiary trisomy; Down's syndrome; trisomy 12p syndrome

INTRODUCTION

Uchida and Lin (1973) reported the first case of trisomy 12p due to a malsegregation of a balanced parental chromosomal rearrangement in a 7-month-old boy with some features suggestive of Down's syndrome. Schinzel (1984) also noted the similarity between trisomy 12p syndrome and Down's syndrome in the flat round face, midface hypoplasia, shallow orbits, epicanthic folds, wide nasal bridge and upturned tip of the short nose, and small ears. Since the initial description of trisomy 12p syndrome (Uchida and Lin, 1973), at least 36 additional cases have been reported. Stengel-Rutkowski *et al.* (1981) categorized cases

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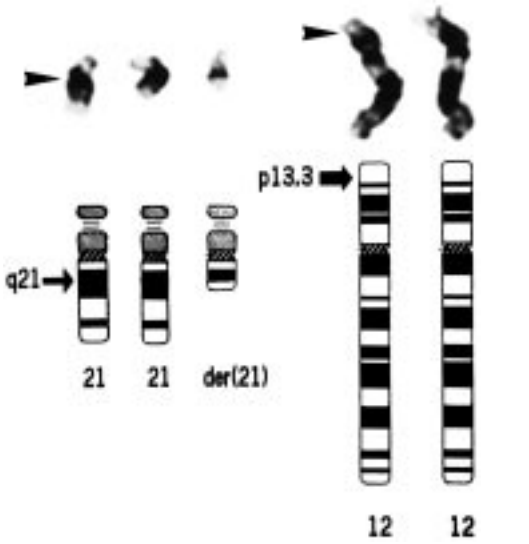

Fig. 1—Partial karyotype of the proband showing the translocation derivative chromosome 21, der(21). Arrows pointing to the diagrams for normal chromosomes 21 and 12 indicate the translocation breakpoints

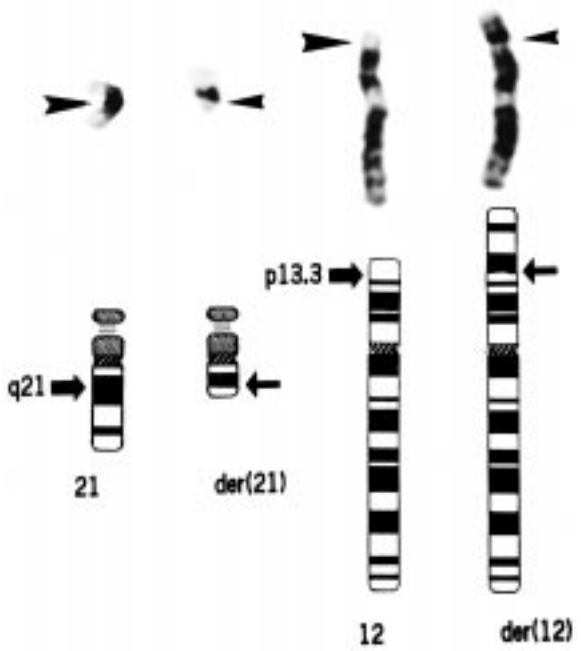

Fig. 2—Partial karyotype of the maternal reciprocal translocation t(12;21)(p13.3;q21) showing translocation derivative chromosomes der(12) and der(21). Large arrows pointing to the diagrams for normal chromosomes 21 and 12 indicate the translocation breakpoints. Small arrows pointing to the derivative chromosomes 21 and 12 indicate the break–rejoin junction

of trisomy 12p into four types based on the extent of the 12p trisomy and the presence of other chromosomal regions besides chromosome 12p: (1) partial trisomy 12p, (2) complete trisomy 12p with an additional trisomy or monosomy of the short arm of an acrocentric chromosome, (3) complete trisomy 12p with an additional trisomy or monosomy of the terminal region of a non-acrocentric chromosome, and (4) complete trisomy of 12p and a proximal 12q segment. In 1996, Allen *et al.* (1996) further expanded the classification of Stengel-Rutkowski *et al.* (1981) by including mosaicism. To the best of our knowledge, the combination of double partial trisomies 12p and 21q has not previously been described. Here we report on the prenatal diagnosis and fetal phenotype of partial trisomy 12 (p13.3-pter) and partial trisomy 21 (pter-q21) due to a 3:1 segregation with tertiary aneuploidy transmitted from a maternal reciprocal translocation 12;21. The contribution of the involved chromosomal segments to the phenotype of Down's syndrome and trisomy 12p syndrome is discussed.

CASE REPORT

Amniocentesis was performed at 19 weeks' gestation in a 39-year-old gravida 2, para 1 woman due to advanced maternal age. Her first pregnancy, 15 years before, had resulted in a second-trimester stillbirth of unknown cause; otherwise, there was no family history of malformations or mental retardation. Prenatal sonography at 19 weeks' gestation showed a biparietal diameter of 4·7 cm (19 weeks) and a femur length of 3·2 cm (19 weeks) without identifiable congenital anomalies. Cytogenetic analysis of the amniotic fluid cells revealed an abnormal extra chromosome 21 (Fig. 1). Genetic counselling was offered immediately and a parental chromosomal study was performed. The proband's mother was found to have a balanced reciprocal translocation between chromosomes 12 and 21, 46,XX,t(12;21)(p13.3;q21) (Fig. 2). Due to a 3:1 non-disjunction segregation with tertiary aneuploidy, the proband contained two normal chromosomes 12, two normal chromosomes 21, and one derivative chromosome 21 resulting in partial trisomy 21 (pter-q21) and partial trisomy 12 (p13.3-pter), 47,XY, + der(21)t(12;21)(p13.3;q21)mat. The mother opted to terminate the pregnancy at 24 gestational weeks. Level II sonography before

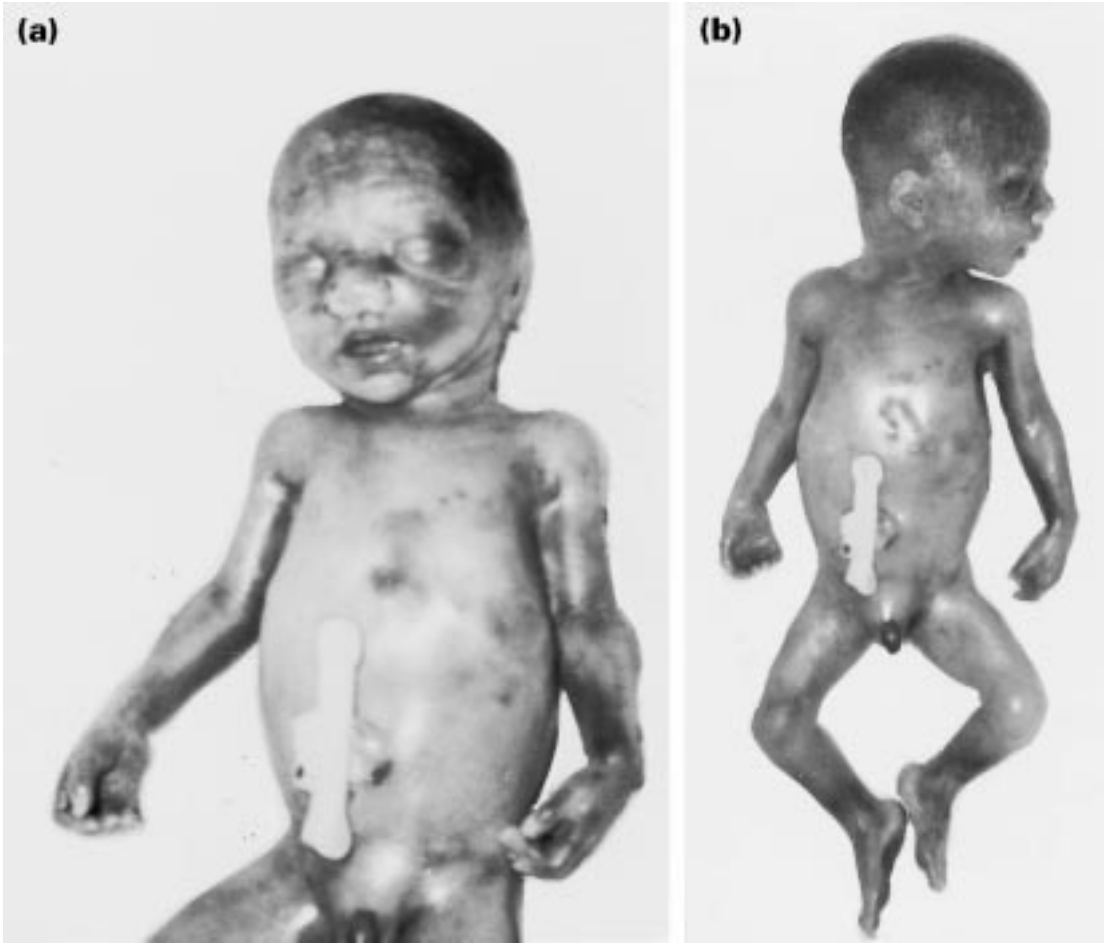

Fig. 3—(a) Facial dysmorphism showing prominent cheeks, high forehead, upward slanting palpebral fissures, epicanthic folds, hypertelorism, a broad depressed nasal bridge, anteverted nares, and an open mouth. (b) Lateral view of the proband

termination revealed no evidence of malformations in the fetal central nervous, cardiovascular, gastrointestinal, and urinary systems. The proband (Fig. 3) postnatally displayed a normal birth weight of 800 g, a normal head circumference of 23·5 cm, a normal body length of 33·5 cm, but dysmorphic features of a round flat face with prominent cheeks and high forehead, upward slanting palpebral fissures, epicanthic folds, hypertelorism, a short nose, a broad and depressed nasal bridge, anteverted nares, a deformed philtrum, an open mouth, thin upper vermilion and broad everted lower lip, low-set ears with prominent anthelix and deep concha, broad hands with simian creases, a short neck, and cryptorchidism. The parents refused the suggestion of necropsy.

DISCUSSION

Table I summarizes the reported clinical findings (Stengel-Rutkowski *et al.*, 1981) for trisomy 12p. Rauch *et al.* (1996) proposed that the smallest duplications of chomosome 12 (p13.2-pter) and chromosome 12 (p13.1–p13.33) produce the trisomy 12p syndrome. They suggested that the critical duplicated segment responsible for the typical appearance of trisomy 12p can be narrowed down to an interval on 12p13.1–p13.33 between D12S178 and FGF6. Our proband carrying a tertiary trisomy resulting from a 3:1 segregation of a maternal t(12;21)(p13.3;q21) demonstrated the gains of 12p13.3-pter and 21pter-q21. Our case implies that the duplication of the involved

Table I—Reported clinical findings in trisomy 12p*

1. Skull
   - Macrocephaly
   - Turricephaly
   - Flat occiput
   - Broad/high/prominent forehead

2. Face
   - Rectangular shaped flat face
   - Prominent cheeks

3. Eyes
   - Slanting eye-axis
   - Abnormal implantation of the eyebrows
   - Hypertelorism
   - Epicanthus
   - Small/almond shaped eye lid aperture
   - Protruding bulbi
   - Abnormalities in the iris

4. Mouth
   - Elongated integumental upper lip
   - Broad, poorly marked philtrum
   - Thin, inverted upper lip
   - Broad/everted lower lip
   - Protruding tongue
   - Downwards slanting corners of the mouth
   - High arched palate
   - Teeth irregularities
   - Small chin

5. Nose
   - Flat/broad nose root
   - Short nose
   - Small/anteverted nostrils

6. Ears
   - Low-set ears
   - Backwards slanting ears
   - Abnormally folded helix
   - Prominent corpus/crus inf. anthelicis
   - Hypo/aplastic crus superius anthelicis
   - Deep conchae

7. Trunk
   - Short neck
   - Abnormally placed nipples
   - Abdominal hernias
   - Cryptorchidism (males)

8. Limbs
   - Abnormal position of the ankles
   - Short/broad hands/feet
   - Short/flexed/abnormal shaped overlapping fingers/toes
   - Clinodactyly, 5th finger
   - Feet deformities
   - Gaps between 1st and 2nd toes
   - Retarded bone age

*Adapted from Stengel-Rutkowski *et al.* (1981).

chromosomal segment of chromosome 12p13.3-pter can also be related to facial dysmorphism of trisomy 12p. The proband did not have accessory nipples, polydactyly, foot deformities, turricephaly, macrocephaly, or a heavy birth weight. Our case also shows that skull deformation, foot deformities or abnormal body weight may not be prominent in an affected second-trimester fetus with partial trisomy 12p. Polydactyly and accessory nipples have been found almost only in cases with complete trisomy 12p, whereas regarding facial anomalies, high birth weight, foot deformities, and lack of gross malformations, no difference has been found between cases with complete trisomy 12p and cases with partial trisomy 12p (Rauch *et al.*, 1996). Cases of trisomy 12p with additional chromosomal imbalances have been reported to be associated with major malformations such as anal atresia (Uchida and Lin, 1973), renal malformation (Rethoré *et al.*, 1975), and congenital heart defects (Qazi *et al.*, 1981). The Pallister-Killian (mosaic tetrasomy 12p) syndrome is expressed with dysmorphisms strongly resembling those of trisomy 12p syndrome; however, it can be associated with other structural malformations, i.e., arrhinencephaly, congenital diaphragmatic hernia, malformation of the intestine, renal dysplasia, and rhizomelic shortened limbs, which are rarely reported in trisomy 12p syndrome (Schinzel, 1991; Los *et al.*, 1995). Cardiac defects such as a hypoplastic heart, renal malformations, anal atresia, and diastasis recti have been described as associated with partial trisomy 12p (Fryns and Kleczkowska, 1990). Inguinal and umbilical hernias, cryptorchidism, and club-feet have been reported as additional findings in individuals with dup(21)(pter→q21 or 22.1) (Schinzel, 1984). Except for cryptorchidism, our case did not show the above associated malformations, although an autopsy should have been done to prove the absence of internal organ abnormalities.

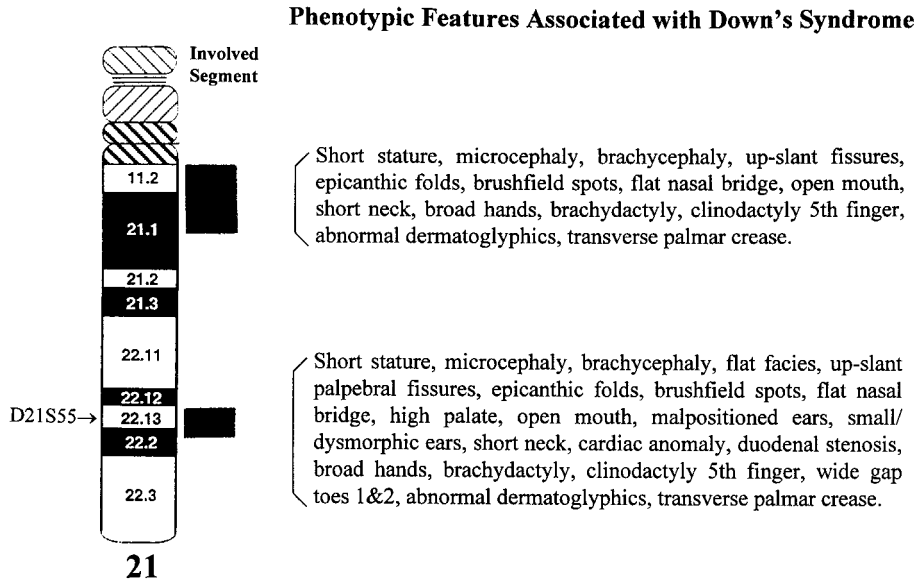

Fig. 4—Phenotypic features of Down's syndrome for the critical region of band 21q22.13 on chromosome 21 and for the involved segment of 21pter-q21.1 in this presentation. Adapted from Korenberg *et al.* (1994)

From the clinical and cytogenetic studies on partial trisomy 21, regions involving 21q22.1 to qter have been suggested by many authors to be essential for the Down's syndrome phenotype (Niebuhr, 1974; Williams *et al.*, 1975; Sinet *et al.*, 1976; Hagemeijer and Smit, 1977; Couturier *et al.*, 1979; Mattei *et al.*, 1981; Habedank and Rodewald, 1982; Miyazaki *et al.*, 1987; Pellissier *et al.*, 1988). However, with the construction of a molecular map of the phenotype associated with Down's syndrome, Korenberg *et al.* (1994) proposed that genes outside the D21S55 region in band 21q22.13 also contribute significantly to the Down's syndrome phenotype and suggested that Down's syndrome is a contiguous gene syndrome. Daumer-Haas *et al.* (1994) also provided evidence that genes contributing to the facial and some of the hand manifestations in Down's syndrome exist in the chromosomal region proximal to D21S55 in band 21q22.1. According to the phenotypic map of features associated with Down's syndrome (Korenberg *et al.*, 1994) (Fig. 4), genes on 21q21.1 contributed some of the dysmorphic features in our case, i.e. epicanthic folds, upwards slanting palpebral fissures, a flat nasal bridge, an open mouth, a short neck, broad hands, and transverse palmar creases. Most of those features can coincidentally occur in trisomy 12p syndrome.

In summary, we have described the prenatal diagnosis of a rare chromosomal imbalance of double partial trisomies 12 and 21 resulting from a maternal reciprocal translocation. Our case demonstrates that intrauterine diagnosis of chromosomal rearrangements by routine prenatal genetic assessments may consequently detect familial chromosomal rearrangements which can provide useful information for genetic counselling in subsequent pregnancies.

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