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Paternal meiotic origin of der(21;21)(q10;q10) mosaicism [46,XX/46,XX,der(21;21)(q10;q10), + 21] in a girl with mild Down syndrome

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Mosaicism for a derivative 21, der(21;21)(q10;q10), is a rare chromosomal abnormality. Since a normal cell line is present, mitotic origin is considered. Chromosome examination of a female with developmental delay and dysmorphic features compatible with mosaic trisomy 21 revealed a normal cell line and a second cell line with a der(21;21)(q10;q10) [46,XX/46,XX,der(21;21)(q10;q10), + 21]. Molecular investigation with a panel of highly polymorphic microsatellites mapping to chromosome 21 demonstrated three different alleles, two of paternal and one of maternal origin. Therefore, either formation of the der(21;21)(q10;q10) during paternal meiosis with subsequent loss of the der(21;21)(q10;q10) and mitotic reduplication of the maternal homologue in the normal cell line, or more likely a zygote with paternally derived trisomy 21 and subsequent mitotic formation of the der(21;21)(q10;q10) have to be considered. This case again shows that mammalian chromosome aberrations may have a more complex mechanism of formation than was previously thought. *European Journal of Human Genetics* (2000) 8, 709–712.

Keywords: isochromosome; mosaicism; translocation; trisomy 21

Introduction

Trisomy 21 is the most common aneuploidy in humans at birth, occurring in about 1:700 live births.¹ Free trisomy 21 constitutes about 95% of all cases with about 68% originating from maternal meiosis I errors, about 20% from maternal meiosis II errors, 6–7% from paternal meiosis errors, and 5–6% from mitotic errors, respectively.¹ Paternal meiosis II errors are twice as frequent as paternal meiosis I errors. Translocation trisomies amount to 5% and within this group almost half have 14/21 translocations. *De novo* derivative chromosomes 21 [(der(21;21)(q10;q10))] are rare, and most of them are isochromosomes.^{1,2} To the best of our knowledge mosaicism with a normal cell line and a der(21;21)(q10;q10) in a second cell line has been described in the literature in 17 cases.^{3–19} Most of them were ascertained by extensive cytogenetic investigations in the parents performed after the birth of a child with trisomy 21 due to der(21;21)(q10;q10) in

all cells. In none of them were origin and formation investigated by molecular methods.

We report on a girl with dysmorphic features and developmental delay compatible with a clinical diagnosis of Down syndrome and a mosaic karyotype 46,XX/46,XX,der(21;21)(q10;q10), + 21.

Subject and methods

Subject

The girl is the first child of healthy unrelated parents, mother 33 years old, father 27 years old at her birth. Two younger sibs are healthy. At birth after 38 weeks of pregnancy, length (43 cm) and weight (2120 g) were below the 10th centile, whereas occipito-frontal head circumference (32.5 cm) was between the 10th and 25th centiles. Feeding difficulties were the major problem in early infancy. Bone age was 3 months at a chronological age of 6 months. At the age of 6 years, height (97 cm) and weight (12.1 kg) were below the 3rd centile, and OFC (48 cm) was around the 3rd centile. Inner canthal distance was 2.2 cm (25th centile). Dysmorphic features resembled Down syndrome. Particularly noticeable were brachycephaly, exophthalmos, divergent strabismus, upslanting palpebral fissures, small nose, flat philtrum, open

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mouth with protruding tongue, prominent lateral alveolar ridges, and long fingers and toes with hypoplastic nails. Psychomotor development was grossly retarded. Moderate conductive deafness and muscular hypotonia were diagnosed.

Methods

Chromosome analysis was performed from GTG-banded karyotypes from a lymphocyte cell culture on a level of about 550 bands according to standard procedures. Fluorescence *in situ* hybridisation was done according to the manufacturer's instructions (Vysis,[®] Downers Grove, IL, USA) using a whole chromosome 21 library.

For molecular investigations, genomic DNA was isolated from whole blood by salt extraction. For PCR-analysis, highly polymorphic and commercially available microsatellites mapping to chromosome 21 and several other chromosomes (Research Genetics[®], Huntsville, AL, USA) were amplified, run on a 6% polyacrylamide gel, and visualised by silver staining.

Results

Cytogenetic investigations revealed mosaicism with 5 metaphases showing a normal female karyotype and 23 der(21;21)(q10;q10) metaphases. FISH with a whole chromosome library 21 documented chromosome 21 origin of the additional segment. Therefore, the karyotype may be written as 46,XX[5]/46,XX,der(21;21)(q10q10), + 21[23]. The karyotypes of both parents were normal in each 10 metaphases.

Results of molecular investigations are listed in Table 1. Whereas the two different paternal alleles of markers D21S263 and D21S1890 clearly indicate the paternal meiotic origin of the aneuploidy, the results of the markers D21S267 and D21S1255 are compatible with paternal as well as

46,XX/46,XX,der(21;21)(q10;q10),+21

Figure 1 Whereas the two different paternal alleles of marker 21S1890 clearly indicate the paternal meiotic origin of the aneuploidy, the results of the marker D21S1255 are also compatible with paternal as well as maternal origin.

maternal origin (Figure 1). The marker D21S1899 mapping to 21q near the centromere revealed reduction to homozygosity of paternal heterozygosity (Table 1). Therefore, non-disjunction at paternal meiosis II is most likely. One recombination was found at 21q21 between markers D21S265 and D21S263. Investigation of several markers mapping to various other chromosomes in no instance showed more than two alleles and was compatible with correct paternity. These results made non-paternity or chimerism highly unlikely.

Discussion

We demonstrated paternal meiotic origin of a der(21;21)(q10;q10) chromosome, which was found in one cell line, the other being normal 46,XX, in a patient with findings of mild Down syndrome.

Mosaicism with one normal cell line and a second presenting a structural chromosome aberration is generally assumed to have occurred postzygotically. Therefore, the finding of three alleles at three loci on chromosome 21 was unexpected. To the best of our knowledge, molecular investigations have been reported from only two patients with mosaicism between a normal cell line and another with an unbalanced structural aberration: one with a direct duplication within chromosome 21q [46,XY,dir dup(21)(q11.2;q22.3)/46,XY],²⁰ the other with a partial trisomy due to an unbalanced translocation [46,XY,der(1)t(1;16)(p36.3;p13.1)/46,XY].²¹ In both instances, the duplicated segment was derived from one maternal homologue.

Three different mechanisms could theoretically result in the molecular findings obtained in the present case.

Table 1 Results of molecular marker analysis

Markers	Alleles (mother/patient/father)	Location
D21S215	a/a/a	q11.1
D21S258	ab/ac/ac	q11
D21S1899	b/bc/ac	q11
D21S11	bc/bd/ad	q21
D21S1437	bc/bd/ad	q21
D21S1905	ab/ab/ab	q21
D21S1409	bd/ad/ac	q21
D21S1257	ab/ab/ab	q21
D21S272	a/a/a	q21
D21S1253	b/b/ab	q21
D21S265	ab/ac/bc	q21-q22.1
D21S263	ac/ <u>abd</u> /bd	q21
D21S267	bc/ <u>abc</u> /ac	q22.1-q22.3
D21S270	bc/ac/a	q22.2-qter
D21S259	a/ab/ab	q22.2-qter
D21S1255	bc/ <u>abc</u> /ab	q22.1
D21S1890	bd/ <u>acd</u> /ac	q22.3-qter

Informative alleles underlined italics.

- (1) Chimerism of a conceptus with one normal cell line and another with a der(21;21)(q10;q10). In the case reported here, chimerism is highly unlikely since microsatellite marker analysis of multiple loci on other chromosomes never showed more than two alleles.
- (2) The der(21;21)(q10;q10) might have been the result of misdivision at the centromere or of a U-type exchange during paternal meiosis. In this case, the zygote should have revealed the abnormal cell line, and the normal cell line should have been formed by two subsequent mitotic errors (Figure 2): non-disjunction of the normal homologue and loss of the der(21;21)(q10;q10) or vice versa. This mechanism implies crossing over during paternal meiosis I with subsequent formation of the der(21;21)(q10;q10) and maternal uniparental isodisomy 21 in the normal cell line. The individuals so far reported in whom maternal uniparental disomy was demonstrated had no abnormal phenotype, and thus maternal uniparental disomy *per se* does not seem to affect the phenotype.^{22,23}
- (3) Initial meiosis II nondisjunction leading to free trisomy 21 in the zygote and subsequent somatic formation of the chromosome rearrangement. In this case, 36 different combinations of the two paternal and one maternal homologue(s) are theoretically possible. Again, in the normal cell line uniparental disomy can be present, as well as a combination of one maternal and one paternal homologue. The der(21;21)(q10;q10) might be formed by a mitotic misdivision at the centromere or by a U-type exchange between sister or non-sister chromatids.

Each of the 3 homologues might be the non der(21;21)(q10;q10) chromosome. Some combinations are excluded by the finding of three alleles.

Considering that chimerism is highly unlikely in our patient, we believe that mechanism (3) is most likely since it requires only one meiotic rearrangement and two subsequent mitotic errors. Moreover, the cascade of meiotic and subsequent postmeiotic errors resembles those leading to an additional isochromosome 9p, 12p, or 18p subsequent to trisomy 9, 12, or 18, respectively, formed at meiosis II^{24–26} and a combination of partial trisomy 16p and maternal UPD 16 in one case.²¹

In conclusion, a minimum of three events is necessary to explain the karyotype in our patient. The first must have happened during paternal meiosis, either nondisjunction or formation of the der(21;21)(q10;q10). Subsequent errors must have occurred postzygotically. The results of molecular marker analysis in the present patient again show that some mosaics have a more complex mode of formation than a single postzygotic structural rearrangement. The findings also lead to modification of the estimation of the recurrence

Figure 2 **A** Diagram showing formation of der(21;21)(q10;q10) at paternal meiosis and of 46,XX/46,XX,der(21;21)(q10;q10), +21 in a subsequent mitosis. **B** Diagram showing meiotic formation of free trisomy 21 and subsequent mitotic formation of one biparentally disomic cell line (left) and another cell line with 21;21 translocation (middle row) or one uniparentally disomic cell line (left) and again another cell line with 21;21 translocation (lower row).

risk, which is higher in the case of a meiotic failure compared with a postzygotic rearrangement.

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