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ARTICLE

Familial Robertsonian translocation 15;21 and rare paracentric inv(21): unexpected re-inversion in a child with translocation trisomy 21

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We present a family with a Robertsonian translocation (RT) 15;21 and an inv(21)(q21.1q22.1) which was ascertained after the birth of a child with Down syndrome. Karyotyping revealed a translocation trisomy 21 in the patient. The mother was a carrier of a paternally inherited RT 15;21. Additionally, she and her mother showed a rare paracentric inversion of chromosome 21 which could not be observed in the Down syndrome patient. Thus, we concluded that the two free chromosomes 21 in the patient were of paternal origin. Remarkably, short tandem repeat (STR) typing revealed that the proband showed one paternal allele but two maternal alleles, indicating a maternal origin of the supernumerary chromosome 21. Due to the fact that chromosome analysis showed structurally normal chromosomes 21, a re-inversion of the free maternally inherited chromosome 21 must have occurred. Re-inversion and meiotic segregation error may have been co-incidental but unrelated events. Alternatively, the inversion or RT could have predisposed to maternal non-disjunction. *European Journal of Human Genetics* (2000) **8**, 815–819.

Keywords: translocation trisomy 21; paracentric inversion 21q; reinversion

Introduction

Robertsonian translocations (RT) are the most common balanced structural rearrangements in humans with a frequency in newborns of about 1:1000.[1] In unbiased studies, RT(13q14q) and RT(14q21q) are the predominant translocations and account for nearly 80% of all RTs, whilst RT(15q21q) is rather uncommon (0.5%). The risk of having a chromosomally unbalanced offspring is approximately 17% in women with RT(13q21q).[1] Inversions are another group of relatively frequent structural rearrangements. In contrast to the more common pericentric inversions (break and reunion between the short and the long arm), paracentric inversions (PAI) consist of breaks and reunions within the same chromosome arm. In general, PAIs are thought to be rare in humans and relatively harmless.[1] Their frequency in the general population is estimated to be in the range 0.1–0.5:1000 and they are seen in nearly all chromosomes, most commonly in chromosomes 1, 3, 5, 6, 7, 11 and 14 and less frequently in chromosomes 4, 16, 17, 18, 19, 20, 21, 22 and Y.[2] So far, only five cases of PAIs of chromosome 21 have been described. Four of them were found in probands with trisomy 21[2–7] (Lindenbaum[3] and Madan *et al*,[4] Niikawa *et al*[6] and Ohta *et al*[7] reported on the same patient respectively). Further testing on additional family members revealed that these inversions were familial and not associated with any symptoms in the healthy carrier. Interestingly, Niikawa's patient with Down Syndrome carried a paracentric inversion in two of his three chromosomes 21[47,XY,–21, +inv(21)(q11.2q22.13)mat, +inv(21)(q11.2q22.13)mat].[6] A fifth case of PAI of chromosome 21 was detected in amniocentesis; the same PAI was found in the mother.[8]

Here we describe the familial occurrence of both a RT(15q21q) and a PAI of chromosome 21 in a healthy woman, whose child carried a translocation trisomy 21 and showed two structurally normal chromosomes 21.

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Case report

The male patient FJ was the second child of healthy Russian parents (mother 25 years, father 28 years, at the child's birth).

The first child was a healthy girl. No history of miscarriages and no family history of Down syndrome is known. The pregnancy was uneventful and FJ was born after 37 weeks of gestation (birth weight 2340 g, length 46 cm, OFC 31 cm). The APGAR score was 8/9/10. The typical features of Down syndrome included (Figure 1): upslanted palpebral fissures, Brushfield's spots, epicanthal folds, small nose with low nasal bridge, simian crease of the right hand, small genitals, cryptorchism, large gaps between the first and second toes and a bell-shaped thorax. Marked muscular hypotonia, even for a child with Down syndrome, was noted. Due to muscular hypotonia breathing was difficult and for some days a palate device helped to keep the tongue in place. There were no feeding problems and weight gain was satisfactory. Echocardiography revealed an atrial septal defect (septum secundum) and cardiomegaly, but surgical correction was not then warranted. FJ's developmental progress revealed an overall delay, as he was not able to sit or roll over at one year of age. He is currently receiving physiotherapy and early developmental support.

The family history revealed the following: the mother of FJ has two healthy brothers. The maternal grandparents of FJ had several healthy sisters and brothers, who had healthy children and grandchildren themselves. In both families no previous history of miscarriages or family members with mental or physical retardation was known.

Materials and methods

Cytogenetic studies

Lymphocytes of our proband, his parents and the maternal grandparents were cultured according to standard methods. Chromosome analysis was done by GTG banding. At least 15 metaphase spreads each were analysed at approximately the 400–500 band level.

Molecular genetic studies

Genomic DNA from peripheral lymphocytes was isolated by a simple salting out procedure.[9] Delineation of the parental origin of the trisomy 21 was performed by STR typing. The used STRs on chromosome 21 are listed in Table 1. Primer and PCR conditions can be obtained from the Genome Database. PCR products were visualised after denaturing gel electrophoresis by silver staining or autoradiograph.

In order to exclude possible mix-up of parental DNA, the samples were tested by PCR for X- and Y-specific fragments as described by Ellis *et al*.[10]

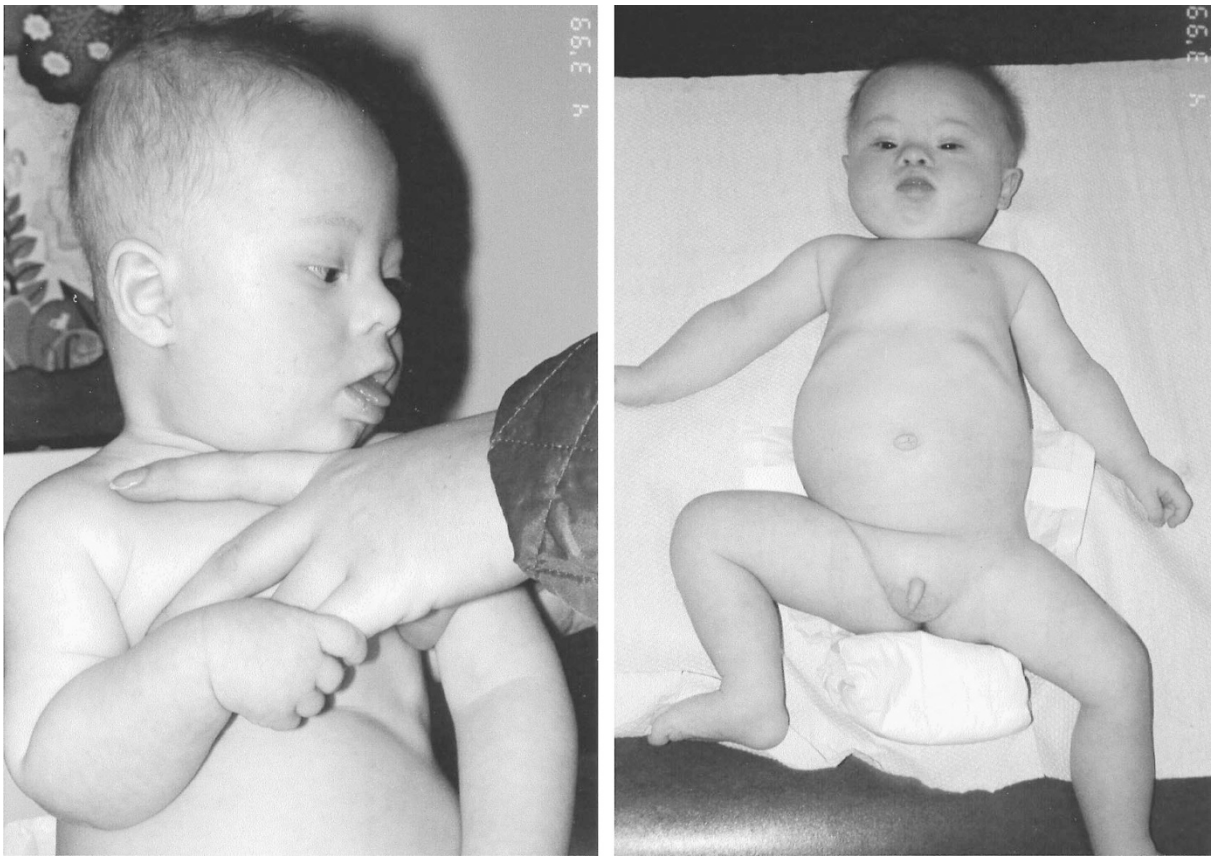

Figure 1 Phenotypic features of our proband at the age of 9 months. **a** Lateral view showing microcephaly, small nose and protruding tongue. **b** Frontal view showing dysmorphic stigmata.

Table 1 Results of chromosome 21 STR typing in the Rob15/21 family. The order of the markers corresponds to the genetic order on chromosome 21 published by Généthon[20]

STR	*Het.*[a]	*cM*[a]	*Maternal grandfather*	*Maternal grandmother*	*Mother*	*Father*	*Patient*	*Informativity*
Cen								
D21S1904	0.52	0.0	2–2	1–2	2–2	2–2	2–2	–
D21S1911	0.69	2.3	1–1	1–1	1–1	1–1	1–1	–
D21S1256	0.65	2.3	2–2	1–1	1–2	3–3	2–2–3	Maternal, R
D21S265	0.84	12	1–2	2–4	2–2	3–3	2–2–3	Maternal
D21S1257	0.80	13	1–3	2–5	2–3	4–5	3–3–5	Maternal, R
D21S272	0.75	13	2–3	1–3	2–3	3–4	2–2–3	R
D21S269	0.72	17	1–2	1–3	1–3	2–2	1–1–2	Maternal, R
D21S1252	0.80	30	–	–	1–1	2–2	1–1–2	Maternal
D21S270	0.85	33	1–2	2–4	1–4	2–3	1–2–4	Maternal, N
D21S267	0.87	33	2–4	1–3	2–3	2–4	2–3–4	N
D21S268	0.85	36	–	–	1	1	1	U
D21S1260	0.74	44	2–4	1–3	1–4	3–3	1–3–4	Maternal, N

N = non-reduction of maternal heterozygosity, R = reduction of maternal heterozygosity, U = uninformative, – = not typed; [a]Heterozygosity and genetic distance in cM were obtained from.[20]

Results

Chromosomal analysis (band level 500) revealed a translocation trisomy 21 in the proband FJ: 46,XY,der(15;21)(q10;q10), + 21 (Figure 2). Paternal chromosomes were normal, the maternal karyotype was as follows: 45,XX,der(15;21)(q10;q10),inv(21)(q21.1q22.1). The Robertsonian translocation was inherited from the maternal grandfather (45,XY,der(15;21)(q10;q10)), the grandmother was a carrier of the inv(21q)(46,XX,inv(21)(q21.1q22.1)).

The short tandem repeat (STR) typing results in FJ and his family are listed in Table 1. Typing of 21q markers showed one chromosome 21 to be of paternal and two chromosomes 21 to be of maternal origin (Figure 2). Furthermore, in distal 21q markers (D21S270, D21S267, D21S1260) maternal

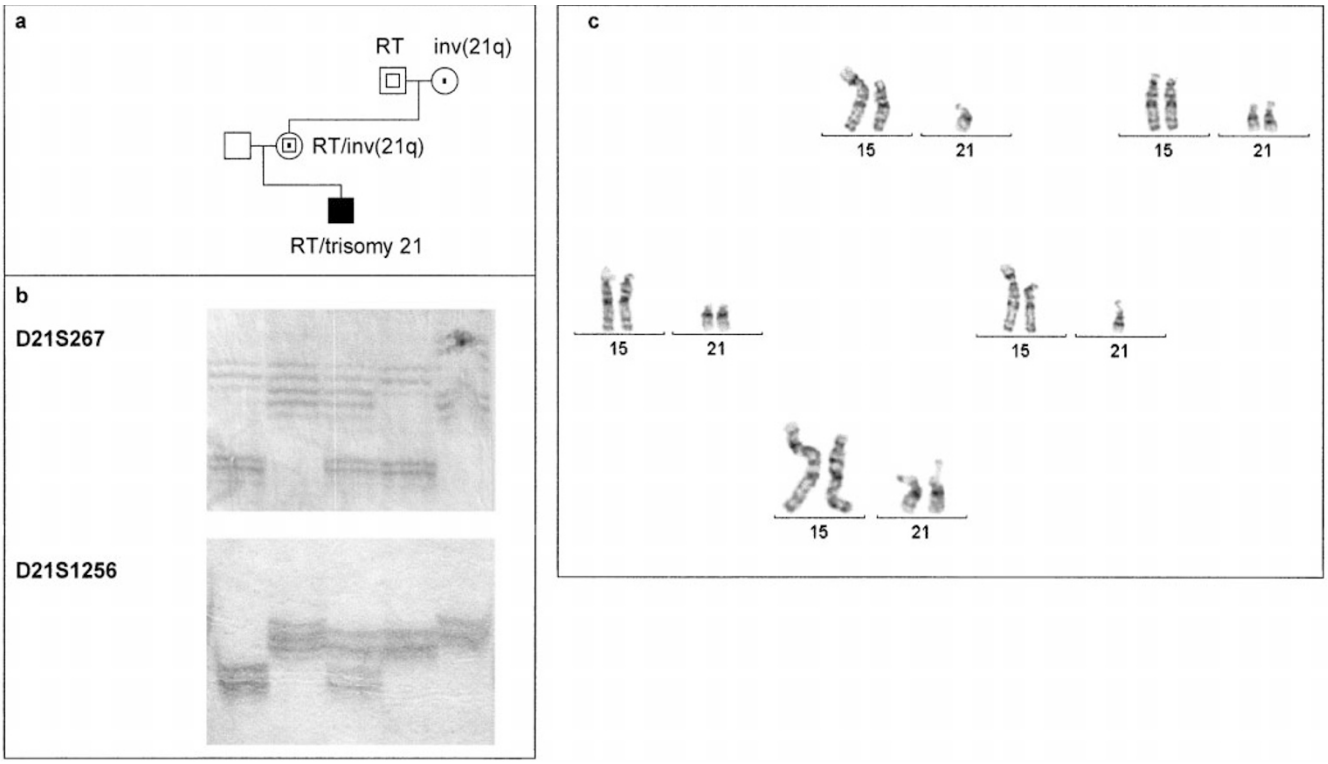

Figure 2 **a** Pedigree of the RT (15q21q) and inv(21q) family. **b** Examples of STR typing showing maternal origin and non-reduction/reduction of maternal heterozygosity in the DS patient. **c** In concordance with the pedigree the partial karyotypes of the family members are presented.

heterozygosity was maintained in the patient. In contrast, typing of STRs (D21S269–D21S1256) localised in the interstitial segment showed reduction of maternal heterozygosity to homozygosity in the proband. The most proximal markers in 21q were not informative.

Discussion

In the RT Down syndrome patient described here, the two free chromosomes 21 as well as the translocation chromosome 21 appeared to be structurally normal. Therefore we expected at first a paternal origin of the two free chromosomes 21 in spite of the fact that the mother as an RT carrier is at increased risk of having unbalanced offspring.[1] Furthermore, trisomy 21 cases caused by paternal meiosis errors are rare.[11] In contrast to our initial expectation, STR typing results indicated that there was paternal contribution of chromosome 21, a maternal contribution of the translocated 15;21, but there was no contribution of the maternally inherited grandmother's PAI21. Instead, the STR pattern indicated that one of the chromosomes 21 was a recombination of the PAI21 and RT21 (Table 1).

Since the free chromosome 21 in the proband's mother showed a rare paracentric inversion, it is possible that a re-inversion must have occurred in maternal meiosis followed by non-disjunction (Figure 3). This is partially confirmed by the results of STR typing (Table 1): distal 21q markers showed non-reduction of maternal heterozygosity in the proband. Thus the two different maternal chromosomes 21 have been inherited, including the one involved in the RT chromosome formation. In maternal meiosis I during homologue pairing, two crossover events may have occurred somewhere in the proximal segment and in the distal segment (proximal to the marker D21S270) outside the inversion, resulting in the structurally normal free chromosome 21 reinversion. The distal recombination was demonstrated in our patient; a proximal crossover was not detectable – unfortunately the respective markers were not informative.

The affected boy FJ had typical signs of Down syndrome showing no unusual symptoms. We suppose that the recombination event between the PAI chromosome and the normal homologue (involved in the RT) led to 'balanced re-inversion' without any hint of an interstitial duplication or deletion.

Cytologically, the corner-stone of meiotic recombination from a PAI is the 'reverse loop' model. In this model, one crossover event in the inversion loop results in the formation of gametes carrying either a dicentric chromatid, an acentric fragment, a normal chromatid, or a chromatid with an inversion. Gametes containing a dicentric or acentric chromosome are generally perceived as being non-viable. Martin[12] did not identify any cytogenetically visible meiotic recombinant chromosomes in a PAI carrier. Pettenati and

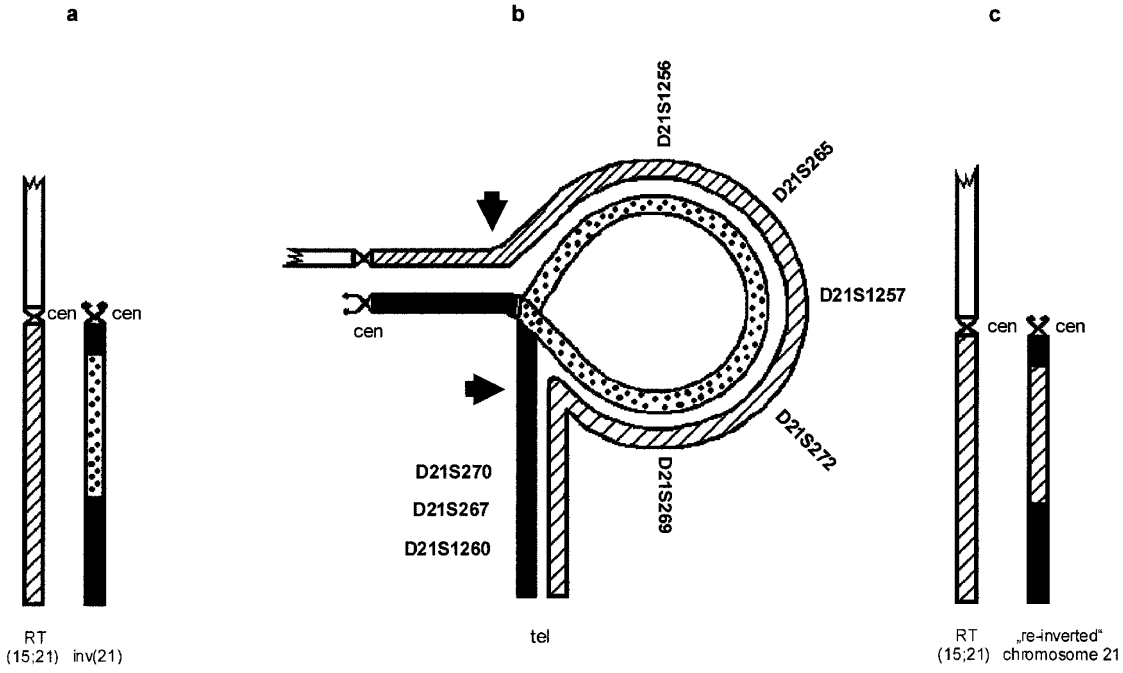

Figure 3 Proposed mechanism of formation of the re-inversion. **a** Long arms of the RT chromosome 21 (hatched parts) and inversion-bearing (blackened/dotted parts) chromosome 21 homologues of the probands mother. **b** Pairing of the homologues shown in a. The inverted region forms a loop to allow alignment of homologue sequences. Arrows indicate the two potential breakpoints resulting in re-inversion. Informative microsatellites at their putative localisation are presented. **c** Products of the exchange inherited by the patient.

co-workers[2] reviewed 15 PAIs with monocentric recombinant chromosomes with duplications and/or deletions. They concluded that the most common viable recombination event from a PAI is either a duplication or a deletion. Nevertheless, the finding of re-inversion resulting in a cytogenetically inconspicuous chromosome 21 in our case demonstrates that this segregation product is also detectable.

Familial PAIs are usually considered to bear a relatively small genetic risk: Daniel *et al*[13] did not detect any unbalanced karyotypes in 30 prenatal diagnoses. Pettenati *et al*[2] estimated the rate of viable offspring with recombinant chromosomes to be 3.8% of the PAI. Nevertheless, Sutherland *et al*[14] pointed out that several of these alleged monocentric recombinants were originally reported to arise from parental insertions (3-break rearrangements) and they should not be included in the analysis, therefore decreasing the risk. According to Madan *et al* carriers of PAIs show no increased incidence of phenotypic abnormalities;[4] additionally he postulated that the risk of producing abnormal gametes is expected to be low and directly proportional to the length of the inverted segment.[15] Gardner and Sutherland[1] commented that virtually all PAI are harmless and that nearly all PAI heterozygotes have been discovered fortuitously and not through an abnormal recombinant attributable to a parental inversion. This corresponds to findings in the family reported here and to the other cases of inv(21)[2–7] which were detected by chance in Down syndrome patients. However, there have been some reports about PAI carriers who had an offspring with unbalanced karyotypes due to meiotic recombination events.[16–18] Therefore Yang *et al*[17] suppose that the risk for meiotic rearrangements in PAI carriers might be higher than previously expected. Our case illustrates that PAIs can lead to monocentric recombinants. We agree with the opinion of Pettenati and Rao[19] that cytogeneticists, if confronted with PAIs, should consider the possibility that alternative mechanisms of pairing and recombination can occur.

A correlation of the coincidental occurrence of the re-inversion of the maternal inv(21) and the trisomy 21 cannot be excluded in the family reported here. The finding of two different chromosomal aberrations in the same carrier as described here is seldom reported. Therefore, it is difficult to estimate the recurrence risk. Prenatal diagnosis in pregnancies of these carriers should be offered.

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