

Partial trisomy for 5q and monosomy for 12p in a liveborn child as a result of a complex five breakpoint chromosome rearrangement in a parent

C J A M Van Der Burgt, G F M Merkx, A H Janssen, J C Mulder, R F Suijkerbuijk, D F C M Smeets

Abstract

A balanced complex chromosome rearrangement (CCR) involving four chromosomes is very rare and may lead to different types of aneuploid germ cells. We report a liveborn child with multiple congenital anomalies and an apparently balanced translocation, t(11;12). High resolution chromosome analysis in the mother showed a CCR involving chromosomes 5, 11, 12, and 16. In situ hybridisation showed that this CCR was the result of a five break rearrangement, and that the derivative chromosome 12 consisted of parts of chromosomes 5, 11, and 12. From this it could be deduced that the karyotype of the child was not balanced, but resulted in partial trisomy for 5q and partial monosomy for 12p. The clinical findings in the child were compatible with partial trisomy for 5q.

(*J Med Genet* 1992;29:739-41)

Balanced reciprocal translocations between two chromosomes are relatively common, occurring in about 1 in 600 newborns.¹ However, balanced complex chromosome rearrangements (CCR) involving four or more breakpoints are very rare. A balanced CCR can lead to various forms of aneuploidy during meiosis in the carrier. Such genetic imbalances will often result in fetal wastage or sometimes even lead to infertility. However, on a few occasions, such an imbalance may give rise to a liveborn child with multiple congenital anomalies.²

We report a child with partial duplication of 5q and deletion of 12p as a result of a very complex rearrangement involving chromosomes 5, 11, 12, and 16 in the mother.

Case report

The male proband was born in 1990, the second child of healthy, non-consanguineous, Dutch parents. The pregnancy was complicated by a haemorrhage in the fourth month and growth retardation. At 36 weeks' gestation he was born spontaneously, with a birth weight of 1610 g (<3rd centile) and head circumference of 28.5 cm (<3rd centile). Multiple congenital anomalies were noted at birth including microcephaly with closure of the coronary and sagittal suture, cleft palate,

hypertelorism, high nasal bridge, long, simple philtrum, thin upper lip, small mouth, low set, dysmorphic ears, small palpebral fissures, hypospadias, small scrotum, oesophageal atresia, a ventricular septal defect, and a large atrial septal defect (fig 1).

On the second day cardiac and respiratory distress occurred and the child died on the fourth day. Necropsy was not permitted. There is no cell line available from the patient.

CYTOGENETICS

Initial routine chromosome analysis on cultured peripheral blood lymphocytes of the proband showed an abnormal male karyotype. In first instance it was interpreted as a balanced translocation between chromosomes 11 and 12: 46,XY,t(11;12)(p15;q12). We were not able to perform high resolution chromosome analysis because of the early death of the infant, so an unbalanced chromosome pattern could not be excluded. Cytogenetic investigation of both parents showed a normal male karyotype in the father, whereas in all cells of

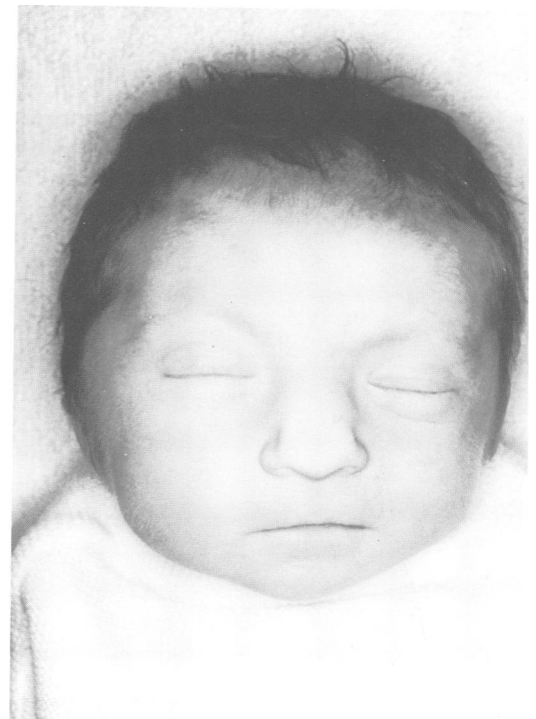


Figure 1 The proband shortly after his death.

Department of Human Genetics, University Hospital Nijmegen, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands.

C J A M Van Der Burgt
G F M Merkx
A H Janssen
R F Suijkerbuijk
D F C M Smeets

Department of Paediatrics, Rijnstate Hospital, Arnhem, The Netherlands.
J C Mulder

Correspondence to Dr Van Der Burgt.

Received 19 December 1991.
Revised version accepted 31 March 1992.



Figure 2 Partial karyotype of the mother carrying a five breakpoint translocation. Top: high resolution trypsin-basic fuchsin banded chromosomes. Below: corresponding ideograms. For specification of the breakpoints see text.

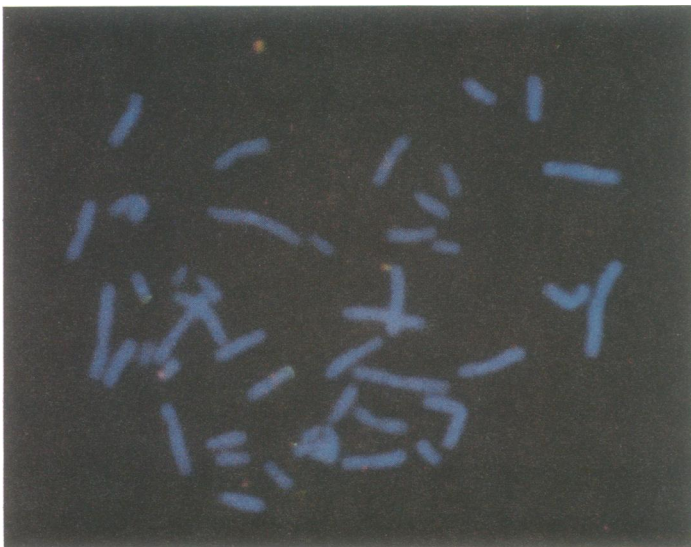


Figure 3 Double in situ hybridisation on lymphocytes of the mother with an alphoid pericentromeric probe from chromosome 12 (red signal on der(12) and 12) and the total DNA from a human*hamster hybrid cell line with an isochromosome 12p as the only human component (green signal on der(16) and 12).

the mother a very complex, balanced rearrangement involving four different chromosomes (5, 11, 12, 16) was encountered. Routine analysis after G banding with trypsin-Giemsa indicated a four breakpoint rearrangement (5q34;11p15;12q12;16p11.2).

High resolution chromosome analysis with the use of a trypsin-basic fuchsin technique³ showed that the distal part of the short arm of the derivative chromosome 12 slightly differed from its normal counterpart. A double in situ hybridisation was performed with an alphoid pericentromeric probe from chromosome 12⁴ combined with the total DNA from a human*hamster hybrid cell line with an isochromosome 12p as the only human component.⁵ This experiment clearly indicated that yet another translocation had occurred. The distal part of the short arm of chromosome 12 had been transferred to the aberrant chromosome 16, while the distal part of 11p must have been translocated to the aberrant chromosome 12 (fig 2). With this additional information the following complex karyotype with a five breakpoint translocation could be constructed for the mother: 46,XX,t(5;11;12;16)(5pter → 5q34::16p11.2 → 16pter;11qter → 11p15.3::12q12 → 12qter; 5qter → 5q34::12q12 → 12p13.1::11p15.3 → 11pter;16qter → 16p11.2::12p13.1 → 12pter) (fig 3). This means that the karyotype of the proband becomes 46,XY,-11,-12,+der(11)t(11;12)(p15.3;q12),+der(12)t(5;11;12)(5qter→5q34::12q12→12p13.1::11p15.3→11pter), resulting in trisomy for the distal part of 5q and monosomy for the distal part of 12p.

Chromosome analysis in the healthy older brother of our patient and both parents of the mother showed normal karyotypes.

Discussion

For delineating complex chromosomal translocations, high resolution chromosome analysis is indispensable but sometimes even insufficient. In these situations in situ hybridisation or chromosome painting can be complementary. In our patient we were able to determine the precise chromosome pattern only after extensive chromosome analysis in combination with in situ hybridisation on peripheral lymphocytes of the mother.

She carried a de novo, balanced, complex chromosome rearrangement involving four chromosomes and including five translocation breakpoints. One of the derivative chromosomes (der(12)) appeared to be constructed of parts of three different chromosomes. The proband inherited the der(12) and der(11) from his mother.

The clinical findings in our patient are compatible with the symptoms found in other patients with partial trisomy for the distal part of 5q, especially the facial dysmorphism (fig 1).

Thirteen cases of trisomy for the distal part of 5q have been published.⁶⁻¹¹ The patient described by Zabel *et al*¹⁰ was trisomic for almost the same part of chromosome 5q as our patient. The facial dysmorphism of this child was also very similar including microcephaly,

hypertelorism, broad nasal bridge, large, simple philtrum, thin upper lip, small mouth, and low set, dysplastic ears. He had a cardiac conduction defect and died at the age of 10 months from acute heart failure.

Partial monosomy of 12p has been described in several patients.¹² Two patients have been reported with a deletion of 12p resembling the deletion in our case.^{13,14} They both had mental retardation, short stature, microcephaly, downward slanting palpebral fissures, receding chin, big and low set ears, and short hands and feet. One of the two had a congenital heart defect. Our patient also had small hands and feet, but the facial dysmorphism was quite different.

The oesophageal atresia, cleft palate, and craniosynostosis appear to be unique in our patient.

Balanced complex chromosome rearrangements involving four or more chromosomes are very rare and all cases were reported as being unique.¹⁵ Most patients with a de novo apparently balanced CCR were mentally retarded or had multiple congenital anomalies. Only a few had no phenotypic effects.^{16,17}

Gorski *et al*¹⁵ determined the empirical reproductive risks for carriers of CCRs involving at least three chromosomes. They found a 53.7% incidence of an abnormal pregnancy outcome, while in 50% of the healthy children a balanced CCR was present.

The mother of our proband had one spontaneous abortion and one healthy child (46,XY) before she gave birth to him. At the moment she is pregnant again and prenatal diagnosis on villi was performed at 10 weeks' gestation. On cytogenetic examination an abnormal female karyotype was found: 45,XX,t(13q;14q). All cells showed a de novo Robertsonian translocation involving chromosomes 13 and 14. There is no explicable relation between this de novo translocation and the CCR in the mother and it may be just coincidental.

- 1 Van Dyke DL, Weiss L, Roberson JR, Babu VR. The frequency and mutation risk of balanced autosomal rearrangements in man estimated from prenatal genetic studies for advanced maternal age. *Am J Hum Genet* 1983;35:301-8.
- 2 Kleczkowska A, Fryns P, Van den Berghe H. Complex chromosome rearrangements (CCR) and their genetic consequences. *J Genet Hum* 1982;30:199-214.
- 3 Scheres JMJC, Merkxx GFM, Hustinx TWJ. Prometaphase banding of human chromosomes with basic fuchsin. *Hum Genet* 1982;61:8-11.
- 4 Looijenga LHJ, Smit VTHBM, Wessels JW, *et al*. Localization and polymorphism of a chromosome 12 specific satellite DNA sequence. *Cytogenet Cell Genet* 1990;53:216-8.
- 5 Zhang J, Marynen P, Devriend K, Frijns JP, Van den Bergh H, Cassiman JJ. Molecular analysis of the isochromosome 12p in the Pallister-Killian syndrome: construction of a mouse-human hybrid cell line containing an i(12p) as the sole human chromosome. *Hum Genet* 1989;83:359-63.
- 6 Curry CJR, Lougham WD, Francke U, *et al*. Partial trisomy for the distal long arm of chromosome 5 (region q34→qter). A new clinically recognizable syndrome. *Clin Genet* 1979;15:454-61.
- 7 Jones LA, Jordan DK, Taysi K, Strauss AW, Toth JK. Partial duplication of the long arm of chromosome 5: a case due to balanced paternal translocation and review of the literature. *Hum Genet* 1979;51:37-42.
- 8 Ostovics M, Kiss P. Familial translocation, t(2;5)(p23;q31). *Clin Genet* 1975;8:112-6.
- 9 Rodewald A, Zankl M, Gley EO, Zang KD. Partial trisomy 5q: three different phenotypes depending on different duplication segments. *Hum Genet* 1980;55:191-8.
- 10 Zabel B, Baumann W, Gehler J, Conrad G. Partial trisomy for short and long arm of chromosome no 5. Two cases of two possible syndromes. *J Med Genet* 1978;15:143-7.
- 11 Bartsch-Sandhoff M, Liersch R. Partial duplication 5q syndrome: phenotypic similarity in two sisters with identical karyotype (partial duplication 5q33→5qter and partial deficiency 8p23→pter). *Ann Genet (Paris)* 1977;4:281-4.
- 12 Schinzel A. *Catalogue of unbalanced chromosome aberrations in man*. Berlin: De Gruyter, 1984.
- 13 Mayeda K, Weiss L, Lindahl R, Dully M. Localization of the human lactate dehydrogenase B gene on the short arm of chromosome 12. *Am J Hum Genet* 1974;26:59-64.
- 14 Magnelli NC, Therman E. Partial 12p deletion: a cause for a mental retardation, multiple congenital abnormality syndrome. *J Med Genet* 1975;12:105-8.
- 15 Gorski JL, Kistenmacher ML, Punnett HH, Zackai EH, Emanuel BS. Reproductive risks for carriers of complex chromosome rearrangements: analysis of 25 families. *Am J Med Genet* 1988;29:247-61.
- 16 Till M, Devillard F, Crost P, Bachy M, Prieur F, Bertheas MF. Balanced complex chromosomal rearrangement with more than four breakpoints: report of a new case. *Am J Med Genet* 1991;40:370-3.
- 17 Del Porto G, Grammatico P, De Sactis S, Esposito M, Di Rosa C, Romano C. A balanced complex chromosomal rearrangement (CCR) with phenotypic effect. *Clin Genet* 1991;40:57-61.