Identification of an unbalanced cryptic translocation t(9;17)(q34.3;p13.3) in a child with dysmorphic features

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Abstract

We report a case of an unbalanced cryptic telomeric translocation 46,XY,der(17),t(9;17)(q34.3;p13.3) in a boy with dysmorphic features and developmental delay. The proband had intrauterine growth retardation, postnatal short stature, and mild microcephaly. Magnetic resonance imaging showed incomplete myelination, but no evidence of lissencephaly. Cytogenetic analysis of the proband's peripheral blood showed an abnormal 17p. Fluorescence in situ hybridisation (FISH) with a Miller-Dieker cosmid probe did not detect a deletion for that area. Further analysis with a 17p telomere specific probe identified an unbalanced telomeric translocation. The same probe was used to determine the presence of an apparent balanced translocation t(9;17)(q34.3;p13.3) in the mother of the proband. The balanced translocation was confirmed with two cosmids that map distally on 9q34.3. Two phenotypically normal half sibs, a maternal aunt, a maternal uncle, and the maternal grandmother were found to be balanced translocation carriers as well. A subtle translocation is one mechanism that can produce an abnormal phenotype in a patient who had a normal karyotype at lower band resolution levels.

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The incidence of cryptic translocations is not known, but they may represent a major contributor to human pathology. Recently several cases of cryptic translocations associated with abnormal phenotypes have been published.¹⁻⁶ The detection of subtle aberrations represents a major challenge in clinical cytogenetics and requires analysis of banded prometaphase (high resolution) chromosomes to identify the abnormal chromosome followed by molecular or molecular cytogenetic confirmation.

Deletions of chromosome 17 band p13 are associated with the Miller-Dieker sequence which is characterised by lissencephaly, severe mental retardation, and characteristic facial features. Isolated lissencephaly has also been described in patients with deletions of 17p13.⁷ Smaller deletions of 17p, not encompassing the Miller-Dieker region, but associated with an abnormal phenotype have not been described.

A well characterised abnormal phenotype is a feature of partial duplication of 9q. The

main characteristics include joint contractures, dolichocephaly, beaked nose, retrognathia, deep set eyes, slender limbs, arachnodactyly, and mental retardation. Heart defects have also been reported.⁸

In this communication we describe a cryptic translocation, t(9;17)(q34.3;p13.3), detected in a chromosomally unbalanced child with dysmorphic features and developmental delay. The clinical features do not include lissencephaly or other features of the Miller-Dieker sequence, and are presumably the result of partial monosomy of 17p and partial trisomy of 9q.

Materials and methods

Blood chromosome analysis was performed on the proband, his mother, two half sibs, a maternal aunt, a maternal uncle, and the maternal grandmother. Routine cytogenetic techniques including high resolution chromosomes prepared using ethidium bromide⁹ and GTG banding were used. Fluorescence in situ hybridisation (FISH) analysis was performed using a Miller-Dieker specific cosmid probe (D17S379) (Oncor); a 17p telomere specific probe which is the most distal locus mapped on 17p13.3 (D17S34)¹⁰ (Oncor); a chromosome 17 library, pBS17 (gift of Dr D Pinkel, University of California, San Francisco); one 9q34.2 cosmid, 5B11; and two 9q34.3 cosmids, 3AE11 and Tan1. The 9q cosmids were a gift from Dr D Kwiatkowski, Harvard Medical School, Boston. The 5B11 cosmid contains the single copy marker D9S113 and maps to 9q34.2 (D Kwiatkowski, personal communication). The Tan1 cosmid¹¹ contains the TAN1 gene (human homologue of the *Drosophila* notch gene) which maps very distal on 9q34.3. The 3AE11 cosmid¹² contains the anonymous marker D9S67 and maps more proximally, but still within band 9q34.3. The non-commercial probes were labelled with biotin using a nick translation kit from Gibco BRL. Single colour hybridisations were performed for each of the probes used.¹³ Confirmation of the chromosome identity was accomplished by destaining the slides after the FISH analysis and subsequent GTG or QTTQ banding.¹⁴

Case report

The proband was the product of a pregnancy complicated by a hepatitis B infection in a 21 year old gravida 2 mother. Sonograms during pregnancy showed progressive intrauterine

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Figure 1 Proband at 2½ years of age. The patient had microcephaly with a flat occiput, mild hypertelorism, epicanthic folds, and anteverted nose, and a smooth philtrum with a down turned, thin upper lip.

growth retardation. He was delivered at 38 weeks by caesarean section for breech presentation. His birth weight was 1786 g (<10th centile) and head circumference was 31.5 cm (<10th centile). In the newborn period, he had persistent pulmonary hypertension, decreased pigment in the ocular fundus, and abnormal BAER (brainstem auditory evoked response). Other phenotypic features included microcephaly with a flat occiput, mild hypertelorism and epicanthic folds, an anteverted nose, and a smooth philtrum with a down turned, thin upper lip. He had a high, narrow palate and low set, posteriorly rotated ears. Bilateral clinodactyly of the fifth finger was also present. He had cryptorchidism and an inguinal hernia. Dermatoglyphics were unusual with distal palmar axial triradii bilaterally and a total of eight low arches and two ulnar loops. An MRI scan

Figure 2 Pedigree of the family in which the $t(9;17)$ is segregating.

of the brain showed incomplete myelination but no lissencephaly. At the age of 4 years, he was proportionately small (below the 5th centile for height, weight, and head circumference). He showed moderate developmental delay with more severe delay in expressive language (fig 1).

Fig 2 displays the pedigree of this family. The maternal grandmother had eight spontaneous abortions and two apparently normal children in addition to the proband's mother. The proband's mother reported two spontaneous abortions, at 13 and 18 weeks of gestation. The proband had two phenotypically normal half sibs. The three children were from different fathers, none of whom was available for testing. The maternal aunt had a pregnancy termination at 23 weeks of gestation because of a congenital heart defect detected on ultrasound. At necropsy, the fetus was an appropriate size for gestational age with congenital heart disease and hypospadias.

Results

Chromosome analysis of GTG banded preparations of PHA stimulated lymphocyte cultures of the proband showed an abnormal 17p at the 850 band level. Although the exact nature of the abnormality could not be identified, it was thought to be a de novo terminal deletion of 17p. Chromosome studies of the mother at the 725 band level of resolution were inconclusive. FISH analysis with a whole chromosome 17 library (pBS17) did not show a structural rearrangement of 17p involving another chromosome in either the mother or the proband. Further analysis with a Miller-Dieker cosmid probe (D17S379) specific for 17p13.3 showed positive signals on both chromosomes 17p in both the mother and child, ruling out a translocation or deletion of the Miller-Dieker region.

Following two subsequent miscarriages, the mother became pregnant again. Karyotyping of amniocytes indicated that the fetus also had the abnormal 17p. At birth, the child appeared phenotypically normal. The FISH analysis was repeated on the infant using a probe for the D17S34 locus. This locus is distal to the Miller-Dieker region. The results showed positive signals on the telomere of the short arm of one chromosome 17 and a second set of signals on the distal q arm of an unidentified C group chromosome. Destaining and subsequent Q and G banding indicated that the C group chromosome was a 9, suggesting the presence of a reciprocal translocation between 17p13.3 and 9q. The presence of the reciprocal translocation was confirmed using two 9q34.3 specific cosmid probes, Tan1 and 3AE11, on both the mother and the two half sibs. Hybridisation of these two cosmids on metaphase spreads of the proband showed three signals: two on 9q34.3 and one on 17p13.3 (fig 3). Cosmid 5B11 (9q34.2) hybridised on 9q in the mother and the proband establishing the translocation breakpoint between 5B11 and 3AE11. The abnormal proband is therefore the result of an adjacent 1 segregation of the maternal

Figure 3 Metaphase spreads from the proband hybridised with two cosmids (Tan1 and 3AE11) specific for 9q34.3. Three sets of signals are seen in each cell.

translocation with a karyotype: 46,XY,-17,+der(17),t(9;17)(q34.3;p13.3)mat. This karyotype results in monosomy 17p13.3→ter and trisomy 9q34.3→ter.

Further family studies indicated that the maternal aunt, uncle, and grandmother are also carriers of the familial translocation t(9;17)(q34.3;p13.3) (fig 4). Analysis of fetal cord blood of the maternal aunt's pregnancy termination showed that the male fetus also had the same unbalanced translocation that was originally detected in the proband.

Discussion

The extent of the segmental aneusomy for chromosome 17 (fig 4) may be estimated to be approximately 2 Mb or less. This is based on

calculations that the Miller-Dieker locus, which is not deleted, is located approximately 2 Mb from the telomere.¹⁵ An association between monosomy for this region of chromosome 17 and an abnormal phenotype has not been described in published reports. However, a deletion of the D17S34 locus has been described in 50% of paediatric medulloblastomas, 66% of highly anaplastic astrocytomas, and 21% of pilocytic astrocytoma.¹⁶ In a series of 20 medulloblastomas, it was found that the p53 tumour suppressor gene was mutated infrequently. All of the children with a deletion of the D17S34 locus fared very poorly, as compared to those without a deletion. These results suggest the presence of a new tumour suppressor gene distal to the p53 locus. The possible implication of the deletion of the D17S34 locus in our patient is unknown.

The partial duplication of chromosome 9q leading to a partial trisomy is a relatively uncommon event. Although limited in number, these cases have been well documented.⁸ Most reports of partial duplication 9q are of much larger duplications than the one described in this study, and the most common breakpoints are q21→qter and q32→qter. The length of the segmental aneusomy with breakpoints at 9q21 or 9q32 range from four to eight fold that of our patient (fig 4). Moreover, all of the published cases were unbalanced products of parental translocations involving a variety of segmental monosomies with the exception of a family reported by Allderdice *et al.*¹⁷ An insertion of chromosome 9 resulted in seven recombinant family members with duplication of band 9q34.

Figure 4 Ideograms of chromosomes 9 and 17 with the translocation breakpoints of 9q34.3 and 17p13.3 shown (left). Chromosomes of the proband's half sib showing the balanced translocation t(9;17)(q34.3;p13.3). Arrowheads point to the translocation breakpoints of the normal 9 and normal 17 (right).

Review of published reports of partial trisomy 9q31→qter

	References														This report
	18	19	20	21	22	22	22	17	17	17	17	17	17	17	
Low birth weight	—	—	+	+	—	0	+	+	+	+	+	+	+	+	+
Dolichocephaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—
Severe physical and mental retardation	+	+	+	+	+	+	+	b	b	b	b	b	b	b	a
Stereotypic movement of extremities	+	0	+	0	+	+	+	—	—	—	—	—	—	—	—
Low set, malformed ears	+	0	0	+	+	+	+	—	—	—	—	—	—	—	+
Deep set eyes	+	+	+	+	+	+	+	0	0	+	0	0	0	0	—
Prominent, beaked nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—
Retrognathia	+	+	+	0	+	+	+	+	+	+	0	0	0	0	—
Short neck with redundant skin	—	+	+	0	+	0	+	0	0	0	0	0	0	0	—
Long fingers and toes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—
Flexion deformities of fingers	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—
Limited joint movements	—	+	+	0	+	+	+	+	+	+	+	+	+	+	—
Congenital heart disease	—	+	—	0	+	—	—	—	—	—	—	—	—	—	—
Translocation parent	m	p	m	p	m	m	m	—	—	—	—	—	—	—	m
Trisomic segment→qter	31	32	32	32	32	32	32	34	34	34	34	34	34	34	34:3

+ = present; — = absent; 0 = not observed; m = maternal; p = paternal; a = moderate; b = slight psychomotor retardation, limited vocabulary

The general clinical features of partial trisomy 9q include low birth weight, dolichocephaly, severe physical and mental retardation, stereotypic movement of the extremities, low set, malformed ears, deep set eyes, prominent, beaked nose, small, down turned mouth, microretrognathia, and long tapering fingers.^{8,18–22} Congenital heart disease has also been documented in some cases.^{19,22} A review of published patients with partial duplications of 9q equal to or smaller than 9q31→qter is presented in the table. Our index patient shared some of those features such as low birth weight, failure to thrive and continued small stature, down turned mouth, small jaw, low set, malformed ears, and clinodactyly. Because he lacked several of the more specific features such as dolichocephaly, deep set eyes, long tapering digits, and flexion contractures, his condition was not immediately recognisable as 9q duplication. Also, our patient's mental retardation and delayed development is less severe than other patients with partial duplication of 9q.

This patient, together with those previously reported with duplication of 9q34, provides evidence in support that the size of the duplication appears to influence the severity of the phenotype in partial duplication of 9q.

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1 Overhauser J, Bengtsson U, McMahon J, et al. Prenatal diagnosis and carrier detection of a cryptic translocation by using DNA markers from the short arm of chromosome 5. *Am J Hum Genet* 1989;45:296–303.

2 Altherr MR, Bengtsson U, Elder FFB, et al. Molecular confirmation of Wolf-Hirschhorn syndrome with a subtle translocation of chromosome 4. *Am J Hum Genet* 1991;49:1235–42.

3 Kuwano A, Ledbetter SA, Dobyns WB, Emanuel BS, Ledbetter DH. Detection of deletions and cryptic translocations in Miller-Dieker syndrome by in situ hybridization. *Am J Hum Genet* 1991;49:707–14.

4 Mewar R, Kline AD, Jackson L, Overhauser J. Confirmation of a cryptic unbalanced translocation using whole chromosome fluorescence in situ hybridization. *Am J Med Genet* 1992;44:477–81.

5 Alvarado M, Bass HN, Caldwell S, et al. Miller-Dieker syndrome. Detection of a cryptic chromosome translocation using in situ hybridization in a family with multiple affected offspring. *Am J Dis Child* 1993;147:1291–4.

6 Köhler A, Hain J, Müller U. Familial half cryptic translocation t(9;17). *J Med Genet* 1994;31:712–14.

7 Ledbetter SA, Kuwano A, Dobyns WB, Ledbetter DH. Microdeletions of chromosome 17p13 as a cause of isolated lissencephaly. *Am J Hum Genet* 1992;50:182–9.

8 Wilson GN, Raj A, Baker D. The phenotypic and cytogenetic spectrum of partial trisomy 9. *Am J Med Genet* 1985;20:277–82.

9 Ikeuchi T. Inhibitory effect of ethidium bromide on mitotic chromosome condensation and its application to high resolution chromosome banding. *Cytogenet Cell Genet* 1984;38:56–61.

10 Nakamura Y, Lathrop M, O'Connell P, et al. A mapped set of DNA markers for human chromosome 17. *Genomics* 1988;2:302–9.

11 Ellisen LW, Bird J, West DC, et al. TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. *Cell* 1991;66:649–61.

12 Kwiatkowski DJ, Weimer K, Ozellus L, Gusella JF, Haines JL. A GT polymorphism map of 9q. *Cytogenet Cell Genet* 1991;58:1941.

13 Pinkel D, Gay JW. Cytogenetic analysis by in situ hybridization with fluorescently labelled nucleic acid probes: Cold Spring Harbor Symposium. *Quant Biol* 1986;51:151–7.

14 Zhu HM, Lee ML, Finkernagel SW, Sciorra LJ. Sequential G-banding and non-radioactive in situ hybridization. *Appl Cytogenet* 1993;19:33–5.

15 Ledbetter SA, Wallace MR, Collins FS, Ledbetter DH. Human chromosome 17 NotI linking clones and their use in long-range restriction mapping of the Miller-Dieker chromosome regional (MDCR) in 17p13.3. *Genomics* 1990;7:264–9.

16 Cogen PH, Daneshvar L, Metzger AK, et al. Involvement of multiple chromosome 17p loci in medulloblastoma tumorigenesis. *Am J Hum Genet* 1992;50:584–9.

17 Allderdice PW, Eales B, Onyett H, et al. Duplication 9q34 syndrome. *Am J Hum Genet* 1983;35:1005–19.

18 Turleau K, de Grouchy J, Chavin-Colin F, et al. Partial trisomy 9q: a new syndrome. *Humangenetik* 1975;29:233–41.

19 Subrt I, Janovsky M, Jodl J. Partial trisomy 9q—chromosomal syndrome. *Hum Genet* 1976;34:151–4.

20 Aftimos SF, Hoo JJ, Parslow MI. Partial trisomy 9q due to maternal 9/17 translocation. *Am J Dis Child* 1980;134:848–50.

21 Soltan HC, Jung JH, Pyatt Z, Singh RP. Partial trisomy 9q resulting from a familial translocation t(9;16)(q32;q24). *Clin Genet* 1984;25:449–54.

22 Ten SK, Chin YM, Tan SK, Hassan K. Three cases of partial trisomy 9q in one generation due to maternal reciprocal t(6;8;9) translocation. *Clin Genet* 1987;31:359–65.