Familial half cryptic translocation t(9;17)

Angelika Köhler, Juliane Hain, Ulrich Müller

Abstract

A half cryptic translocation t(9;17) (p24.2; p13.3) was detected in a large family by fluorescence in situ hybridisation. Unbalanced karyotypes resulted either in lissencephaly and early death or in mental retardation, microcephaly, high arched palate, and deformities of the vertebrae. Some of the features observed in affected persons are characteristic of known syndromes involving either 17p or 9p.

(J Med Genet 1994;31:712-714)

Deletions of the short arms of both chromosomes 9 and 17 are associated with well defined syndromes. The 9p- syndrome is characterised by mental deficiency, craniofacial anomalies such as craniosynostosis, hypoplastic supraorbital ridges, depressed nasal bridge, anteverted nares, and micrognathia. Skeletal anomalies are short distal phalanges and scoliosis.¹² Deletion of the distal short arm of chromosome 17 results in the Miller-Dieker syndrome.³⁴ Hallmarks of this syndrome are lissencephaly, severe mental retardation, and seizures. Craniofacial anomalies include microcephaly, hypoplastic midface, and anteverted nares.⁵⁶

Trisomies of the short arms of chromosomes 9 and 17 also occur. The trisomy 9p syndrome is characterised by growth retardation and severe mental deficiency, macrocephaly, hypertelorism, kyphoscoliosis, and distal phalangeal hypoplasia.¹ A trisomy 17p syndrome is less well characterised, mainly owing to its rare occurrence and aneuploidy of ad-

ditional chromosomal segments. Out of five cases reported by 1990, four had unbalanced translocations involving 17p and other chromosomes. A "pure" trisomy 17p has only been described in one case. Findings included microcephaly, developmental delay, high arched palate, and micrognathia.⁷⁸

Here we describe the detection of a half cryptic familial translocation t(9;17)(p24.2; p13.3) by fluorescence in situ hybridisation. The clinical findings in family members with chromosomal imbalances of distal 9p and 17p are described.

Case reports

The pedigree of the family is given in fig 1. Subjects III.4, III.7, and III.8 were physically examined at various ages. Subjects III.1, III.2, III.3, and III.5 died on day 2, week 4, year 2, and month 7, respectively, and were not seen. A necropsy, however, was performed on III.5 and Miller-Dieker syndrome was diagnosed with typical facial stigmata not further specified and lissencephaly, specifically agyria of both frontal regions and microgyria of the temporal and posterior parts of the brain. While alive, the patient is reported to have suffered from seizures. The parents of III.1 to III.8 were not related and healthy. Subject IV.3 was the product of the fifth pregnancy of III.4 and died at the age of 3 years.

III.4

She is the healthy sister of the affected subjects III.7 and III.8. She has two healthy daughters and an affected son who died at the age of 3 years (IV.3). In addition, she had two early miscarriages.

III.7

He was first seen at the age of 3 years. There was no history of an abnormal pregnancy or birth. At 3 years he had microcephaly (<2.5th centile) and psychomotor retardation. The nasal bridge was flat, he had a haemangioma above the glabella, downward slanting palpebral fissures, and a high arched palate. Additional findings included gait ataxia, muscular hypotonia, and hyperextensible joints. Hypochromic anaemia was diagnosed. At 14 years he was severely mentally retarded, had prominent supraorbital ridges, pronounced prognathia, and convergent strabismus. He had both scoliosis and lordosis and short fingers and toes. His testes were within the normal size range. He was last seen at the age of 20 years (fig 2, left). At this time his condition had not changed apart from a deterioration of both the scoliosis and lordosis.

Institut für
Humangenetik, Justus-
Liebig-Universität
Giessen,
Schlangenzahl 14,
D35392, Giessen,
Germany

A Köhler
J Hain
U Müller

Correspondence to
Dr Köhler.

Received 24 February 1994
Revised version accepted for
publication 28 April 1994

Figure 1 Pedigree of the family with translocation t(9;17). II.1, III.4, III.6, III.7, III.8, and IV.3 were investigated cytogenetically. In III.4, III.7, and III.8 FISH was performed. For further details see case reports.

Figure 2 Patient III.7 at 20 years (left) and patient III.8 at 17 years (right).

III.8

He was first seen at the age of 2 months. Hypoxia occurred at birth owing to strangulation by the umbilical cord. On examination he had microcephaly (<2.5th centile), psychomotor retardation, a haemangioma above the glabella, and a flat nasal bridge. He had hypochromic anaemia. At the age of 5 years he was mentally retarded. He was hyperkinetic and displayed repetitive movements of the trunk and extremities. Ocular findings included convergent strabismus, downward slanting palpebral fissures, and prominent supraorbital ridges. CT scan was performed but did not show any anomalies. He was seen again at the age of 11 years. In addition to previous findings, a high arched palate, lordosis and scoliosis, short fingers and toes, and pronounced hirsutism of the trunk and extremities were observed. At 17 years (fig 2, right) he was severely mentally retarded and the vertebral malformations had deteriorated.

IV.3

He had severe mental and motor retardation. Seizures occurred and typical signs of Miller-Dieker syndrome including midface hypoplasia and anteverted nares were observed. He died at the age of 3 years.

Material and methods

CHROMOSOME ANALYSIS

Chromosomes were prepared from peripheral blood lymphocytes (III.7, III.8) and from a lymphoblastoid cell line (III.4) according to standard protocols; 10 µg/ml of ethidium bromide and 10 µg/ml colcemid were added two hours before harvesting. All chromosome preparations were GTG banded. Fluorescence in situ hybridisation (FISH) was performed after destaining of GTG banded metaphases. All biotin or digoxigenin labelled hybridisation probes were obtained from Oncor/Gaithersburg, MD, USA. The Miller-Dieker cosmid/chromosome 17 α satellite (17Z1) probe consists of pooled cosmids including the Miller-Dieker region in chromosome 17p13.3 and a 17 α satellite probe for the identification of chromosomes 17.⁹ The chromosome 17 specific painting probe and the chromosome 9 specific painting probe were applied for veri-

fication of the size of the translocated segments. All probes were applied to FISH according to the manufacturer's recommendations. The metaphases were photographed using a Kodak Ektachrome 400 film.

Results

Initial karyotypes of II.1, III.4, III.6, and III.8 appeared normal. Chromosome analysis of IV.3 showed an extra band at the tip of the short arm of one chromosome 17. No additional chromosomal abnormalities were identified. The finding of a derivative chromosome 17 in this patient indicated a translocation involving chromosome 17 in this family. FISH analysis was performed in III.4, III.7, and III.8 using chromosome 17 specific probes. Fig 3a shows the findings obtained in III.4. While the Miller-Dieker cosmids clearly labelled the distal short arm of one chromosome 17, no signal was detected on the homologous chromosome. Instead, labelling was observed on distal 9p. Given that the proband is unaffected, the translocation is obviously balanced. This was confirmed by chromosome painting with chromosome 9 and 17 specific libraries. A small portion of chromosome 9 is translocated to

Figure 3 (a) The half cryptic translocation in the carrier III.4 using the biotinylated Miller-Dieker cosmid/chromosome 17 α satellite probe. The arrowheads indicate the signals for the Miller-Dieker cosmid on the derivative chromosome 9 and the normal chromosome 17. The arrow shows the derivative chromosome 17. (b) The three chromosomal segments containing the Miller-Dieker region in patient III.7. Note the translocated segment on chromosome 9.

chromosome 17 and the reverse result was obtained with the chromosome 17 specific library (not shown). The proband's karyotype is 46,XX,t(9;17)(p24.2;p13.3).

Patients III.7 and III.8 were also studied by FISH. Fig 3b gives the results obtained in III.7 using the Miller-Dieker cosmids. Both homologues of chromosome 17 are labelled, in addition to a chromosome 17 specific signal at the tip of chromosome 9. Thus, trisomy of 17(p13.3-pter) is present in this patient. The identical result was obtained in the patient's brother, III.8 (not shown). Their karyotypes were thus 46,XY,-9,+der(9)t(9;17)(p24.2;p13.3).

Discussion

Patient IV.3 had lissencephaly and an extra band was observed on the tip of one of his chromosomes 17. The FISH findings in the patient's mother suggest that the extra band observed after GTG banding was derived from chromosome 9. Both chromosomes 9 must have been normal. The karyotype of the patient probably was 46,XY,-17,+der(17)t(9;17)(p24.2;p13.3). The presence of a locus in 17p13.3 involved in lissencephaly is well established. Patients with deletions of this chromosomal region have either Miller-Dieker syndrome or isolated lissencephaly sequence. A gene, *Lis 1*, identified in distal 17p, has been found to be a likely candidate for lissencephaly.^{10,11}

Lissencephaly was the predominant feature in IV.3. Symptoms specific for trisomy 9p such as macrocephaly, hypertelorism, downward slanting palpebral fissures, deep set eyes, and short fingers have not been reported in this patient. Interestingly, lissencephaly was also found in an aunt (III.5) of this patient at necropsy. This subject probably had the same karyotype as IV.3. The early death of family members III.1, III.2, and III.3 may also be ascribed to lissencephaly and a deletion of 17p.

Unlike the patients with deletions of 17p and lissencephaly, two persons (III.7 and III.8) with trisomy 17p and monosomy 9p are alive. They do not have lissencephaly but are severely mentally retarded. Several clinical findings in these patients can be ascribed to the trisomy 17p including mental retardation without lissencephaly, microcephaly, downward slanting palpebral fissures, and a high arched palate.

Many other features described in trisomy 17p, however, are not present. These include growth delay, hydrocephalus, long philtrum, hypogenitalism, and flexion contractures of the joints. In agreement with monosomy of 9(p24.2-pter) the patients have deformities of the vertebrae, downward slanting eyes, and a flat nasal bridge. Additional symptoms described in the 9p- syndrome, such as micrognathia, trigonocephaly, or prominent forehead, are not present.

The findings indicate the importance of FISH in the identification of cryptic chromosome translocations in patients with dysmorphic stigmata when probes are available. This has also been shown by Kuwano *et al*¹² who found a half cryptic translocation t(3;17) and a full cryptic translocation t(8;17) among their Miller-Dieker syndrome families. In the present family prenatal diagnosis can now be offered to translocation carriers.

This paper is dedicated to Professor Walter Fuhrmann on the occasion of his 70th birthday.

- 1 Jones KL. *Smith's recognizable patterns of human malformation*. 4th ed. Philadelphia: WB Saunders, 1988.
- 2 Huret JL, Leonard C, Forestier B, Rethoré MO, Lejeune J. Eleven new cases of del(9p) and features from 80 cases. *J Med Genet* 1988;25:741-9.
- 3 Van Tuinen B, Dobyns WC, Rich DM, *et al*. Molecular detection of microscopic and submicroscopic deletions associated with Miller-Dieker syndrome. *Am J Hum Genet* 1988;43:587-96.
- 4 Schwartz CP, Johnson JB, Holycross M, *et al*. Detection of submicroscopic deletions in band 17p13 in patients with Miller-Dieker syndrome. *Am J Hum Genet* 1988;43:597-604.
- 5 Dobyns WB, Curry CJR, Hoyme HE, Turlington L, Ledbetter DH. Clinical and molecular diagnosis of Miller-Dieker syndrome. *Am J Hum Genet* 1991;48:584-94.
- 6 Dobyns WB, Stratton RF, Greenberg F. Syndromes with lissencephaly I: Miller-Dieker and Norman-Roberts syndromes and isolated lissencephaly. *Am J Med Genet* 1984;18:509-26.
- 7 Schrander-Stumpel C, Schrander J, Fryns JP, Hamers G. Trisomy 17p due to a t(8;17)(p23;p11.2)pat translocation. Case report and review of the literature. *Clin Genet* 1990;37:148-52.
- 8 Palmer CG, Hubbard TW, Henry GW, Weaver DD. Failure of X inactivation in the autosomal segment of an X/A translocation. *Am J Hum Genet* 1980;32:179-87.
- 9 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.
- 10 Reinder O, Carrozzo R, Shen Y, *et al*. Isolation of a Miller-Dieker lissencephaly gene containing G protein β -subunit-like repeats. *Nature* 1993;364:717-21.
- 11 Dobyns WB, Reiner O, Carrozzo R, Ledbetter DH. Lissencephaly - a human brain malformation associated with deletion of the *LIS1* gene located at chromosome 17p13. *JAMA* 1993;270:2838-42.
- 12 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.