Miller-Dieker syndrome resulting from rearrangement of a familial chromosome 17 inversion detected by fluorescence in situ hybridisation

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Abstract

We report a case of Miller-Dieker syndrome (MDS) owing to an unbalanced rearrangement of a familial pericentric inversion of chromosome 17 (inv(17)(p13.3q25.1)). In addition to lissencephaly and the facial features of MDS, the affected child had other congenital malformations consistent with distal 17q duplication. Initial cytogenetic analysis failed to show any abnormality and fluorescence in situ hybridisation (FISH) studies confirmed the 17p deletion in the proband and identified the chromosome 17 inversion in his mother. FISH studies were performed in other relatives and enabled first trimester prenatal diagnosis by chorionic villus sampling in a subsequent pregnancy of the proband's mother. These findings underline the value of FISH in the investigation of MDS families.

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Key words: Miller-Dieker syndrome; fluorescence in situ hybridisation; chromosome 17 inversion.

Lissencephaly is a severe brain malformation characterised by a smooth cerebral surface (agyria-pachygyria) and abnormal neuronal migration resulting in profound mental retardation, seizures, and other neurological abnormalities.¹ Classical type I lissencephaly may occur as an isolated abnormality or in association with dysmorphic features in Miller-Dieker syndrome (MDS).^{2,3} The characteristic craniofacial appearance in MDS consists of bitemporal hollowing, prominent forehead and furrowed brow, short nose with anteverted nares, prominent upper lip, and small jaw.^{4,5} Cardiac defects and other malformations may also be present.

Deletions of chromosome 17p13.3 can be shown in the majority of MDS patients. About 50% of cases have a visible deletion detected by high resolution cytogenetic analysis.⁵ The remainder can be detected by molecular methods such as RFLP analysis or somatic cell hybrid analysis⁵⁻⁸ and more recently by fluorescence in situ hybridisation (FISH).^{9,10} A gene containing G protein β subunit-like repeats designated lissencephaly-1 (LIS-1) has been identified in this region, and non-overlapping deletions affecting either the 5' or 3' end of the gene found in two patients with

MDS identify LIS-1 as a candidate for the disease gene.¹¹ Deletions including LIS-1 have been reported in 92% of Miller-Dieker probands and 38% of classical ILS cases.¹² Homology between the sequence of the 45K subunit of platelet activating factor (PAF) acetylhydrolase present in bovine cerebral cortex and the protein encoded by the LIS-1 gene has been reported.¹³

Many cases of MDS are sporadic, but familial cases are well documented, including the families originally described by Miller² and Dieker *et al.*³ Recurrence within families is always because of a balanced parental chromosome rearrangement.¹⁴ We report a case of Miller-Dieker syndrome owing to a familial inversion of chromosome 17 detected by FISH analysis which enabled investigation of relatives and prenatal diagnosis in a subsequent high risk pregnancy.

Case report (fig 1)

The proband IV.2 was born at term following a pregnancy complicated by intrauterine growth retardation and polyhydramnios from 20 weeks' gestation. Prenatal ultrasonography indicated short limbs and a cystic mass in the right hypochondrium, thought to be a dilated gall bladder. Chromosome analysis of cultured amniocytes showed an apparently normal male karyotype.

At delivery the birth weight was 2300 g and multiple congenital anomalies were detected consisting of rhizomelic shortening of the limbs, short digits, proximally placed thumbs, partial 2-3 syndactyly of the toes bilaterally, cleft of the soft palate, glandular hypospadias, bilateral undescended testes, and sacral tail. Dysmorphic craniofacial features included prominent forehead, large anterior fontanelle, three hair whorls on the crown, a short neck with a low posterior hairline and redundant skin, short and unusually shaped palpebral fissures, small ears, and small jaw (fig 2). Postnatally the proband developed laryngeal stridor and growth parameters for length, weight, and OFC followed the 3rd, 3rd, and 10th centiles respectively. Convulsions started at the age of 6 months, at which time the EEG showed clusters of raised voltage high frequency rhythms, raising the possibility of lissencephaly. Very high amplitude activity increasing in frequency from theta through alpha to beta activity has been described in lissencephaly.¹⁵ CT brain scan

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Figure 1 Pedigree of the family indicating several cases of fetal death in utero (FDIU), stillbirth (SB), and neonatal death (NND). For further details see family report.

Figure 2 The proband aged 4 months.

showed type I lissencephaly, absent corpus callosum, and dilated ventricles (fig 3). A clinical diagnosis of Miller-Dieker syndrome was made. Subsequent developmental progress was extremely limited, and after recurrent episodes of aspiration pneumonia and status epilepticus the proband died at the age of 2 years 7 months. No necropsy was performed.

Family history

There were several cases of intrauterine death, stillbirth, or neonatal death in the extended family. The first pregnancy of the proband's mother (III-1) had resulted in a fetal death in utero at 22 weeks' gestation. No obvious external abnormalities were documented in the macerated male fetus. The proband's grandmother (II-1) had an unexplained male stillbirth and a fetal death in utero in late pregnancy. Two other maternal relatives had

Figure 3 CT brain scan of the proband showing type I lissencephaly with dilated ventricles.

respectively an infant death owing to hydrocephalus and a neonatal death of unknown cause. No further information was available for these four latter cases.

Cytogenetic studies

Banded chromosome analysis in the proband and his mother failed to show any abnormality of chromosome 17. FISH studies were performed on peripheral blood lymphocytes with a chromosome 17 centromeric alpha satellite probe (D17Z1) and a set of three overlapping cosmids (c197-2, c197-4, and c197-9) from the MDS critical region of 17p13.3.¹⁰ A 17p deletion was detected in the proband and a pericentric inversion of chromosome 17 in the mother (fig 4). Subsequent G banded chromosome analysis confirmed a 46,XX,inv(17)(p13.3q25.1) karyotype in the mother. The proband's karyotype can thus be designated 46,XY,rec(17), dup q,inv(17)(p13.3q25.1)mat. FISH studies performed in six other relatives identified the presence of the pericentric inversion only in the proband's grandmother. It is possible that II-2 also carried the mutation and III-5 who declined testing remains at risk.

First trimester chorionic villus sampling was performed during the third pregnancy of the proband's mother. Chromosome analysis showed an apparently normal 46,XX karyotype, but FISH analysis on both direct and cultured villus preparations identified the presence of a balanced pericentric inversion of chromosome 17. Second trimester ultrasonography showed no fetal abnormalities and a healthy female infant has subsequently been born. Presence of the balanced pericentric inversion was confirmed postnatally by FISH analysis.

Figure 4 (Top) FISH analysis of metaphase chromosomes from the proband. The normal chromosome 17 displays both centromeric alpha satellite (arrowed) and MDS cosmid probe signals. The abnormal chromosome 17 displays only a centromeric probe signal (arrowed) indicating a deletion at 17p13.3. (Bottom) FISH analysis of metaphase chromosomes from the proband's mother. Both chromosomes 17 display signals with the centromeric alpha satellite probe (arrowed). The normal chromosome 17 displays a signal on 17p with the MDS cosmid probe. The abnormal chromosome 17 displays a hybridisation signal on the distal long arm with the MDS cosmid probe resulting from a pericentric inversion: 46,XX, inv (17)(p13.3q25.1).

Discussion

Structural chromosome abnormalities resulting in Miller-Dieker syndrome include sporadic terminal deletions and ring chromosome 17,^{14,16-18} as well as a variety of unbalanced products of reciprocal translocations.^{14,19} Variation in phenotype in the latter group may be attributed to the presence of different duplicated segments in addition to the 17p monosomy. One other family with Miller-Dieker syndrome owing to rearrangement of a pericentric inversion of chromosome 17 has been reported,²⁰ although this involved a larger unbalanced segment that could be identified by chromosome banding analysis. Additional features representing distal 17q duplication^{21,22} were present in the affected offspring. In our case additional features consisted of frontal bossing, broad midface, narrow palpebral fis-

tures, cleft palate, multiple abnormal hair whorls, short neck, short proximal limbs, short digits, 2-3 syndactyly of the toes, sacral tail, hypospadias, and bilateral undescended testes. There was no polydactyly, congenital heart disease, or evidence of renal anomalies. The rudimentary tail present in our case and those of Greenberg *et al*²⁰ has also been observed in another MDS patient,²³ but not in cases with duplication of 17q. Caine *et al*²⁴ described calcified gallstones as a previously unreported feature of 17q duplication and it is interesting that our case had a cystic mass in the right hypochondrium detected by prenatal ultrasonography thought to represent a dilated gall bladder.

FISH analysis is a valuable tool in the clarification of subtle reciprocal rearrangements^{25,26} and has been used to identify cryptic and half cryptic translocations in several cases of Miller-Dieker syndrome.^{9,27-29} The study of Kuwano *et al*⁹ included a half cryptic 3q;17p and a full cryptic 8q;17p translocation. The case of Alvarado *et al*²⁷ represented a full cryptic 17p;19q translocation, while those of Kohler *et al*²⁸ and Brecevic *et al*²⁹ both represented half cryptic 9p;17p translocations. In our case initial conventional cytogenetic analysis did not identify any chromosome 17 abnormality in the proband or his mother, even though the family history was highly suggestive of a familial chromosome rearrangement and the presence of an abnormality was suspected. Definitive diagnosis of Miller-Dieker syndrome was made by FISH analysis which showed a 17p deletion in the proband. A pericentric inversion of chromosome 17 was detected in the proband's mother and grandmother. FISH analysis was offered to other relatives at risk, and enabled first trimester prenatal diagnosis in a subsequent pregnancy of the proband's mother. A fetus with the balanced pericentric inversion was detected, and a healthy infant has subsequently been born.

It is clearly important to distinguish between sporadic 17p deletions and those resulting from cryptic familial rearrangements which have a high recurrence risk in order to provide accurate genetic counselling. In our case the availability of a definitive first trimester prenatal diagnosis was an important factor in the couple's decision to embark upon a further pregnancy. The value of FISH for diagnosis, investigation of relatives, and prenatal diagnosis in this family supports the recommendation of Kuwano *et al*⁹ that FISH analysis should be performed in all parents of children with MDS resulting from submicroscopic deletions to detect subtle rearrangements associated with a high recurrence risk.

A permanent cell line of one of the balanced inversion carriers is available at St Mary's Hospital, Manchester via Dr H Kingston.

- 1 Dobyns WB. The neurogenetics of lissencephaly. *Neurol Clin* 1989;7:89-105.
- 2 Miller JQ. Lissencephaly in two siblings. *Neurology* 1963;13:841-50.
- 3 Dieker H, Edwards RH, Zurhein G, Chou SM, Hartman HA, Opitz JM. The lissencephaly syndrome. *Birth Defects* 1969;2:53-64.
- 4 Jones KL, Gilbert EF, Kaveggia EG, Opitz JM. The Miller-Dieker syndrome. *Pediatrics* 1980;66:277-81.

- 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 Schwartz CE, Johnson JP, Holycross B, *et al.* Detection of submicroscopic deletions in band 17p13 in patients with the Miller-Dieker syndrome. *Am J Hum Genet* 1988;43:597-604.
- 7 vanTuinen P, Dobyns WB, Rich DC, *et al.* Molecular detection of microscopic and submicroscopic deletions associated with Miller-Dieker syndrome. *Am J Hum Genet* 1988;43:587-96.
- 8 Ledbetter DH, Ledbetter SA, vanTuinen P, *et al.* Molecular dissection of a contiguous gene syndrome: frequent submicroscopic deletions, evolutionarily conserved sequences, and a hypomethylated "island" in the Miller-Dieker chromosome region. *Proc Natl Acad Sci USA* 1989;86:5136-40.
- 9 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.
- 10 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.
- 11 Reiner 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.
- 12 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.
- 13 Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K. Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor. *Nature* 1994;370:216-8.
- 14 Stratton RF, Dobyns WB, Airhart SD, Ledbetter DH. New chromosomal syndrome: Miller-Dieker syndrome and monosomy 17p13. *Hum Genet* 1984;67:193-200.
- 15 Gastaut H, Pinsard N, Raybaud C, Aicardi J, Zifkin B. Lissencephaly (agyria-pachygyria): clinical findings and serial EEG studies. *Dev Med Child Neurol* 1987;29:167-80.
- 16 Dobyns WB, Stratton RF, Parke JT, Greenberg F, Nussbaum RL, Ledbetter DH. Miller-Dieker syndrome: lissencephaly and monosomy 17p. *J Pediatr* 1983;102:552-8.
- 17 Carpenter NJ, Leichtman LG, Stamper S, Say B. An infant with ring 17 chromosome and unusual dermatoglyphs: a new syndrome? *J Med Genet* 1981;18:234-6.
- 18 Sharief N, Craze J, Summers D, Butler L, Wood CBS. Miller-Dieker syndrome with ring chromosome 17. *Arch Dis Child* 1991;66:710-2.
- 19 Berry R, Wilson H, Robinson J, *et al.* Apparent Smith-Lemli-Opitz syndrome and Miller-Dieker syndrome in a family with segregating translocation t(7,17)(q34;p13.1). *Am J Med Genet* 1989;34:358-65.
- 20 Greenberg F, Stratton RF, Lockhart LH, Elder FFB, Dobyns WB, Ledbetter DH. Familial Miller-Dieker syndrome associated with pericentric inversion of chromosome 17. *Am J Med Genet* 1986;23:853-9.
- 21 Serotkin A, Stamberg J, Waber L. Duplication 17q mosaicism: an infant with features of Ellis-van Creveld syndrome. *J Med Genet* 1988;25:258-69.
- 22 Bridge J, Sanger W, Mosher G, *et al.* Partial duplication of distal 17q. *Am J Med Genet* 1985;22:229-35.
- 23 Daube JR, Chou SM. Lissencephaly: two cases. *Neurology* 1966;16:179-91.
- 24 Caine A, Knapton DM, Mueller RF, Congdon PJ, Haigh D. Duplication of distal 17q from a maternal translocation: an additional case with some unique features. *J Med Genet* 1989;26:577-89.
- 25 Ledbetter DH. Minireview: cryptic translocation and telomere integrity. *Am J Hum Genet* 1992;51:451-6.
- 26 Sullivan BA, Leana-Cox J, Schwartz S. Clarification of subtle reciprocal rearrangements using fluorescence in situ hybridisation. *Am J Med Genet* 1993;47:223-30.
- 27 Alvarado M, Bass HN, Caldwell S, Jamehdor M, Miller AA, Jacob P. Miller-Dieker syndrome. Detection of a cryptic chromosome translocation using in situ hybridisation in a family with multiple affected offspring. *Am J Dis Child* 1993;147:1291-4.
- 28 Kohler A, Hain J, Muller U. Familial half cryptic translocation t(9;17). *J Med Genet* 1994;31:712-4.
- 29 Brecevic L, Binkert F, Boltshauser E, Schinzel A. Fluorescent in situ hybridisation detection of a balanced t(9;17) translocation in the father of a child with lissencephaly and additional abnormalities. *Dev Brain Dysfunct* 1994;7:147-54.