LETTERS TO THE EDITOR

Detection of a familial cryptic translocation by fluorescent in situ hybridisation

We read with great interest the report by Kohler *et al*[1] on a family with a half cryptic translocation involving chromosomes 9 and 17. In that report, three females in two generations had seemingly balanced translocations, and one male infant who died had exhibited features typical of Miller-Dieker syndrome. Additionally, two living male sibs, aged 20 and 17, had multiple congenital malformations as well as mental retardation. Chromosome analysis had shown the subtle translocation, which was further defined by FISH analysis using chromosome 17 specific probes.

Recently, we evaluated a family in which we eventually discovered a similar translocation involving chromosomes 17 and 22. The translocation was not detectable cytogenetically, even at a 850 band level. Because of a subtle clinical clue, however, it was discovered fortuitously by FISH analysis using chromosome 17 specific probes.

The proband was a 6 month old white male infant, born to healthy, non-consanguineous parents. The father was 35 years of age, and the mother was 33. The couple had two other healthy children, aged 4 and 3. The mother reported three early spontaneous miscarriages and one ectopic pregnancy. The only other significant family history was mild mental retardation in the mother's paternal uncle,

aged 49. The pregnancy was uneventful, until about 39 weeks of gestation, when the mother developed severe pre-eclampsia. Labour was induced one week later, with clinical signs suggesting that partial abruption of the placenta occurred immediately before delivery. The infant weighed 3355 g and the Apgar scores were 3 and 5 at one minute and five minutes, respectively. The infant was hypotonic, with a weak respiratory effort, and had to be intubated and transferred to a neonatal intensive care unit.

Our initial examination findings a few hours after birth included midfacial hypoplasia with a prominent nose, micrognathia, low set, incompletely rotated ears, and a small mouth with a high arched palate and wide alveolar ridges. Also, excess soft tissue was noted around the neck, which showed creasing bilaterally. Other findings included premature closure of the metopic suture, syndactyly between the third and fourth fingers on the left, bilateral simian creases, adducted thumbs, laterally displaced nipples, penile attachment high on the scrotum, rocker bottom feet, second toe overriding the third, and hypoplastic toenails. He had generalised muscular hypotonia and hyperactive deep tendon reflexes. Cardiac evaluation revealed tricuspid insufficiency, and an unusual aortic arch in which the transverse aortic section connected with the ascending and descending aortic sections at acute right angles. He had severe anaemia, for which idiopathic haemosiderosis was considered as a diagnostic possibility but could not be proven. Our clinical impression was that this patient probably had a triploidy/diploidy mosaicism; however, routine chromosome analysis showed a 46,XY karyotype.

An MRI study of the brain at 3 months of age showed agenesis of the corpus callosum, unusual Sylvian fissures, and probable polymicrogyria. As a result of these findings, the possibility of Miller-Dieker syndrome was

considered. High resolution chromosome analysis at the 850 band level was again normal. Then, FISH analysis was carried out using the probe D17S379 for Miller-Dieker syndrome at 17p13.3 (ONCOR). Clear signals were seen on both chromosomes 17p as well as at the control locus, RARA, and an additional signal for D17S379 was seen on the q terminus of a G group chromosome (figure). This chromosome was identified as a 22 by GTL banding, and a 22q deletion was confirmed by FISH using a D22S39 probe at 22q13.3 (ONCOR). FISH analysis was also carried out on both parents using the same probes, and a balanced translocation between 17p13.3 and 22q13.3 was found in the mother. This rearrangement was not detectable by high resolution chromosome analysis. The karyotype of the proband, therefore, is 46,XY,-22,+der(22),t(17;22)(p13.3; q13.3) mat. No cell line is available.

Unfortunately, the infant continued to have problems with anaemia and pneumonia, and died at 6 months of age. However, we are now able to provide genetic counselling to this family, and offer prenatal diagnosis using FISH analysis in the mother's future pregnancies, and test her two apparently normal children and other family members for carrier status.

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

Chromosome fragments with alphoid sequences derived from a pseudoisodicentric Y chromosome

Isodicentric Y chromosomes constitute a relatively common form of normal length, non-fluorescent Y chromosomes. They probably originate from an isochromatid breakage in the Yq euchromatin followed by rejoining of the broken chromatids in the male germline. Their symmetrical appearance would result from centromere division in meiosis.[1] Habitually, but not always, one of the resulting centromeres is inactivated, thereby allowing normal segregation. They commonly occur in mosaicism with a 45,X cell line, and the associated phenotypic anomalies can be heterogeneous depending on the frequency of the 45,X cell line and the localisation of breakpoints. Thus, they can be diagnosed in patients with Turner's syndrome, ambiguous genitalia, apparently normal males, azoospermic males, or autistic children.[1-4]

Accurate identification was not easy in the past, and G11 banding offered the best results. Nowadays, fluorescence in situ hybridisation (FISH), usually with specific centromeric Y alphoid sequences, allows these chromosome aberrations to be identified precisely.[4-6] Demonstration of Y specific sequences may be relevant to therapeutics since gonadal dysgenesis patients with Y chromosome material have a 15–20% risk of developing gonadal neoplasia, gonadectomy usually being recommended.[7]

FISH analysis using ONCOR probe for Miller-Dieker syndrome (D17S379) showing additional signal on the derivative chromosome 22 (right centre arrow).