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LETTERS TO THE EDITOR

Recurrent miscarriage in a carrier of a balanced cytogenetically undetectable subtelomeric rearrangement: how many are we missing?

Although 10–15% of clinically recognized pregnancies are lost spontaneously (Regan *et al*., 1989), recurrent miscarriage, or loss of two or more pregnancies, is less frequent, affecting 1% of all women (Stirrat, 1990). Recurrent miscarriage has heterogeneous etiologies including coagulation-related, immunological, endocrine-related, anatomical and genetic/chromosomal disorders (Bick *et al*., 1998). Chromosomal aberrations account for a significant proportion of miscarriages but are mostly numerical, and only about 7% of couples with recurrent miscarriage carry a balanced chromosomal rearrangement with a resulting unbalanced rearrangement in the abortuses (Boue *et al*., 1985). Although small compared to other etiological groups, the latter group is clinically significant. A carrier of a balanced chromosomal rearrangement has a significant risk of having a chromosomally unbalanced offspring with the potential for developmental disabilities and multiple congenital anomalies. Identifying the carrier status thus enables the otherwise unwary couple to be informed of such risk and of the various reproductive options available to them.

Although there is no consensus on the approach to couples with recurrent miscarriage, a karyotype is usually performed as part of the workup. This is particularly true when there is family history of congenital anomalies, mental retardation, infertility, spontaneous abortion, perinatal death or recurrent miscarriage. In spite of the awareness of clinicians of chromosomal aberrations as a cause of recurrent miscarriage, it is not uncommon for a couple to first learn about their carrier status after a child is born with an unbalanced chromosomal rearrangement. Our case below illustrates how this unfortunate scenario can take place despite previous normal karyotype results on the parents.

The propositus is a 36-year-old female of Greek descent with a history of three first-trimester miscarriages. Her workup for recurrent miscarriage included a conventional G-banded karyotype that was reportedly normal. Her recent pregnancy and delivery were uneventful. Her newborn was initially resuscitated for poor respiratory effort and admitted to the NICU. His birth weight was 5 lb 15 oz and his length was 17 inches. He had a cleft palate and multiple dysmorphic features. His cardiac evaluation was notable for a VSD and a hemodynamically significant PDA, which necessitated transfer to our institution for surgical management. Our examination showed symmetrical IUGR, hypertelorism, underdeveloped supraorbital ridges, flat nasal bridge, cleft palate, and micrognathia (Figure 1). His hands showed brachydactyly and single palmar creases. The scrotum was underdeveloped with undescended testicles. Although his initial karyotype was normal, his clinical appearance, which was highly suggestive of a chromosomal aberration, prompted us to order further testing with a subtelomeric FISH panel (Figure 2). He was found to have a cryptic unbalanced rearrangement resulting in monosomy for the subtelomeric region of 10q26.3 and trisomy for the subtelomeric region of 17q25, his karyotype therefore was 46,XY.ish der(10)t(10;17)(qtel;qtel)(D10S2490−,D17S928+). In light of these results, subtelomeric FISH (STFISH) was performed on both parents and the mother was found to carry a balanced subtelomeric rearrangement between 10q26.3 and 17q25 (Figure 3). Therefore, her karyotype was reinterpreted as follows: 46,XX.ish t(10;17)(qtel;qtel)(D10S2490−,D17S928+; D10S2490+,D17S928−). Given the otherwise negative extensive workup the proband had, her recurrent miscarriage is most likely related to her cryptic chromosomal rearrangement although chance association cannot be excluded.

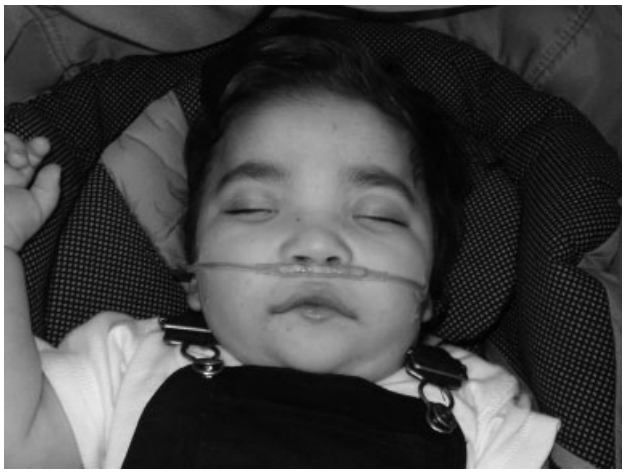

Figure 1—Front view of the infant at 8 months of age depicting the features mentioned in the text

De Vries *et al*. (2003) concluded that 10q26.1-qter deletion patients seem to have a consistent phenotype that includes mental disability, growth retardation (pre- and/or postnatal), with microcephaly, triangular face, hypertelorism, strabismus, prominent nasal bridge, low-set ears, micrognathia, short neck, cryptorchidism, ano/genital defects, and cardiac and renal anomalies. Our patient's phenotype, therefore, overlaps significantly with that of 10q26.1-qter deletion. On the other hand, the very few patients reported with 17q25-qter trisomy

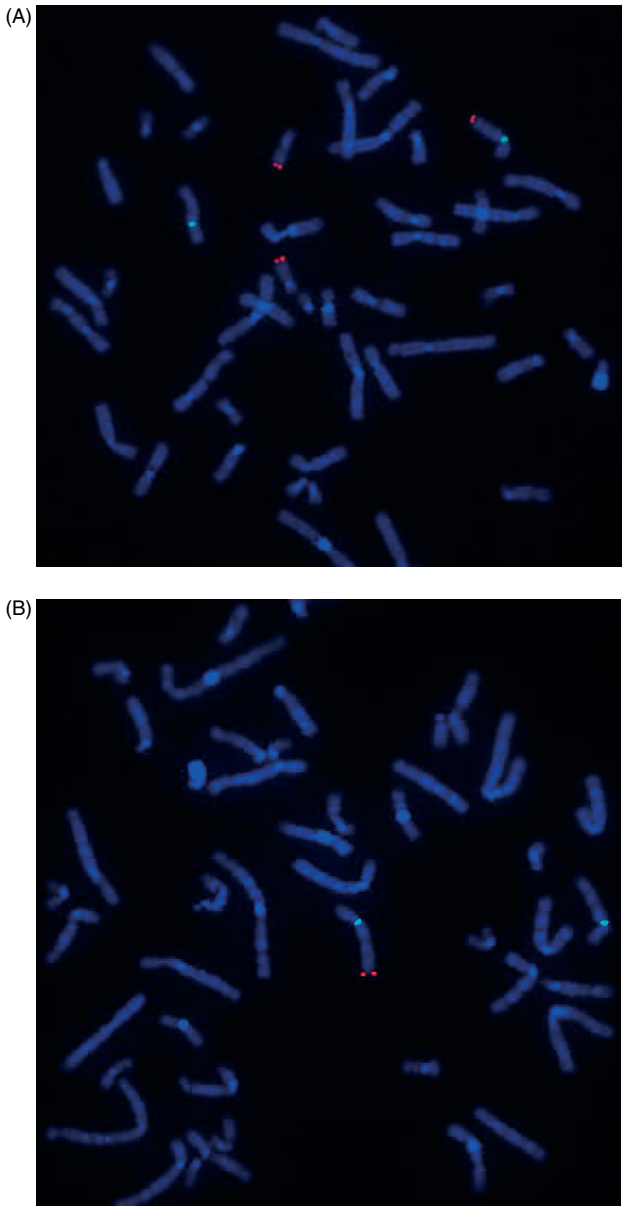

Figure 2——FISH images on the proband's child showing (A) 17q subtelomere probe (D17S928) in red shows three signals on the two 17 homologs and on the abnormal chromosome 10, and a 10 centromere control probe (D10Z1) in green. (B) 10q subtelomere probe (D10S2490) shows only one signal from the 10q

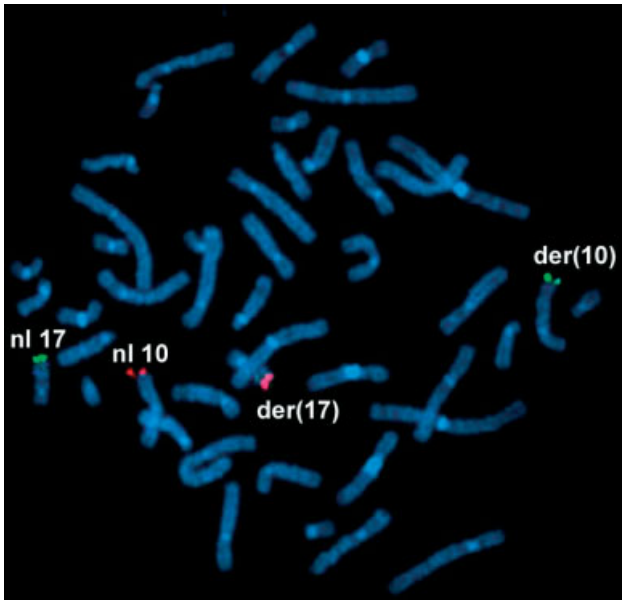

Figure 3—FISH image on proband using 17q subtelomere probe (D17S928) in green and 10q subtelomere probe (D10S2490) in red. Each probe hybridizes to both the normal corresponding chromosome as well as the nonhomologous chromosome involved in the translocation

do not demonstrate much similarity to our patient (see Bridge *et al*., 1985; Ohdo *et al*., 1989).

STFISH panels have been in use for clinical diagnostics for the past few years and, despite their associated cost and labor, have the advantage of revealing chromosomal aberrations not otherwise diagnosed by conventional G-banding (Flint *et al*., 1995). Interestingly, these subtelomeric aberrations represent the unbalanced products of their balanced counterparts in parental gametes in approximately 50% of the cases (Knight *et al*., 1999; Adeyinka *et al*., 2005). Brackley *et al*. reported on the identification of a balanced subtelomeric rearrangement seen only by STFISH in a male who fathered multiple miscarriages (Brackley *et al*., 1999). In that report, there was also compelling evidence for a submicroscopic chromosomal rearrangement given the history of two offspring with severe multiple congenital anomalies.

So when should STFISH be considered in the setting of recurrent miscarriage? A number of studies have been conducted to investigate the frequency of cryptic subtelomeric rearrangement in couples with recurrent miscarriage. The frequencies, and subsequent conclusions, were different in those studies, partly because of the different ascertainment criteria and the size of the study samples. For example, Cockwell *et al*. (2003) studied 50 couples (100 patients) with three or more miscarriages and a normal karyotype and found one case with a subtelomeric rearrangement. Benzacken *et al*. (2002) studied a comparable population and found none. Fan and Zhang (2002) did not find any subtelomeric rearrangements in 80 patients with a history of more than three fetal losses, and concluded that a history of recurrent miscarriage alone without a live-born abnormal child is not a clinical indication for STFISH. Similarly, Jalal *et al*. (2003) did not identify any subtelomeric translocations in their cohort of 44 patients with 'multiple' miscarriages. Finally, Yakut *et al*. (2002) identified two patients with subtelomeric rearrangement in five couples (ten patients) with five or more miscarriages.

With the exception of Yakut's report, most of these studies cast doubt on the utility of STFISH in the setting of recurrent miscarriage. One could argue that the disproportionately high prevalence of subtelomeric rearrangements identified by Yakut *et al*. (2002) was secondary to their ascertainment of couples with five or more miscarriages, the most selective cohort of all aforementioned reports. There is good support for aggressively pursuing a chromosomal etiology for

recurrent miscarriage when a malformed child is born, and STFISH is certainly a powerful addition to the clinician's armamentarium in this regard. However, as previous studies indicated, evidence is not in favor of recurrent miscarriage as a stand-alone indication for STFISH with the possible exception of five or more fetal losses.

In conclusion, clinicians taking care of patients with recurrent miscarriage should be aware that a normal karyotype does not eliminate the possibility of a balanced chromosomal rearrangement. In the setting of a family history of stillbirths, perinatal deaths, mental retardation or congenital malformations, there is a potential for subtelomeric FISH to provide valuable information with significant impact on the reproductive choices of couples seeking medical attention for recurrent miscarriage.

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Prenatal cranial ultrasound features of duplication chromosome 3q(21–24)

The clinical features of partial duplication of the long arm of chromosome 3 have been well described. However, the prenatal cranial ultrasound features of this chromosomal abnormality have not been reported in the literature. In this report, we present the central nervous system ultrasound findings in a fetus with a duplication in the long arm of chromosome 3 involving the region q21 to q24.

A 37-year-old black African woman presented in her sixth pregnancy for prenatal care. She had three healthy babies and two first-trimester miscarriages previously. There was no history of consanguinity and both parents were healthy. The nuchal translucency scan at 13 weeks gave her a low risk for trisomies. Her routine anomaly scan at 22 weeks revealed an enlarged cisterna magna, mild ventriculomegaly and a deficient cerebellar vermis (Figure 1a). The cisterna magna measured 12.8 mm, which is well above the 95th centile. Other fetal biometry was in the normal range. A viral infection screen was negative and a fetal MRI was organised. This confirmed hypoplasia of the cerebellar vermis and also demonstrated the absence of the *corpus callosum* (Figure 1b). Invasive testing for fetal karyotype was offered, but was declined by the parents. Follow-up scans at 33 and 35 weeks showed a small-for-gestational-age fetus with the abdominal circumference below the 5th centile. Fetal arterial Dopplers remained normal.

At 36 weeks, she developed pre-eclampsia and the CTG became abnormal. An emergency caesarean section was performed and a female infant weighing 1754 g was delivered (less than 2nd centile). At birth, there was no respiratory effort and the baby was intubated. Physical examination revealed head circumference on the 50th centile, widely spaced sutures, hypertelorism,