Letter to the Editor

Reported Tandem Duplication/Deletion of 9q Is Actually an Inverted Duplication

To the Editor:

In the August 14, 2000 issue of this journal, we published an article describing an apparent tandem duplication/deletion in a supernumerary chromosome 9 [Wyandt et al., 2000]. Recently, Britt Ravnan, who saw the figure in our article, raised the possibility that the chromosome in question could be a pseudo-dicentric chromosome 9 with an inverted duplication, rather than the tandem duplication/deletion we had suggested. The banding patterns of these two alternatives would be indistinguishable at the G-band resolution we published. Nevertheless, we tested this possibility with subtelomeric probes that were not available to us when we first studied this case in 1998. We also hybridized the material with an alpha satellite probe (D9Z; Vysis, Downers Grove, IL) for the chromosome 9 centromeric region, which we had not done previously. The probe (D9Z1; Oncor, Gaithersburg, MD) we originally used was a mixture of alpha and classic satellite sequences that did not allow distinction of the alpha satellite region from the rest of the 9qh region. In fact, the chromosome in question has 9p subtelomeric sequences on both ends of the chromosome (Fig. 1a) and alpha satellite signals at the centromere and at a non-constricted site in the long arm (Fig. 1b), consistent with the interpretation that it is a pseudo-dicentric inverted duplication [der(9)dup(9)(pter→q21.2)del(9)(qter→21.2)] (Fig. 1c). This new interpretation is also consistent with the polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) results we previously reported. However, our original interpretation was that the fetus was trisomic for 9pter→9q12, tetrasomic for 9q12→9q33 and disomic for 9q33→9q34.3. We now determine it to be tetrasomic for 9pter→9q21.2 and disomic for 9q21.2→qter.

With this new interpretation, our previously proposed mechanism for the de novo origin of the der(9) in this case is no longer applicable. The proposed mechanism fits perfectly with a case of duplication/deletion in Xp that we studied at the same time, which was confirmed by more extensive FISH studies [Milunsky et al., 1999]. In the present case with +der(9), we initially applied quantitative PCR to determine parental origin, with the surprising finding that distal 9q polymorphic markers were deleted. We applied a subtelomeric painting probe for 9q (AL Technologies, Arlington, VA) and confirmed that distal 9q was deleted. The probe D9Z1 (Oncor) showed two copies of classic satellite sequences in the 9qh region, suggesting a tandem duplication. The findings of a duplication/deletion in both Xp and 9q suggested to us a similar mechanism of origin for both cases.

Tetrasomy 9p due to dicentric inverted duplications with breakpoints in distal 9q and with one active centromere (pseudo-dicentric) is much less common than cases with more proximal breakpoints in or close to the 9qh region that may or may not be dicentric. A search of the literature for 9q duplications shows both tandem and inverted duplications [Stalker et al., 1993; Teebi et al., 1993; Lindgren et al., 1994]. One report [Lindgren et al., 1994] describes an inserted inverted duplication of 9q that includes the 9qh region, but the possibility that it is pseudo-dicentric is not discussed. Only one earlier report, from Worsham et al. [1989], describes a large recombinant dicentric 9, with mosaicism for one or two active centromeres by Cd staining. In our case we were looking for duplication of 9q, but we were not looking for tetrasomy 9p.

As a final note regarding phenotype, our fetus, originally thought to have a mixture of partial 9q tetrasomy and 9p trisomy, now must be compared with cases having tetrasomy for 9p and proximal 9q. Grass et al. [1993] reviewed 20 cases of tetrasomy 9p due to inverted duplications, which they classified into three types: (a) i(9p) with a break in the centromere, (b) idic(9)(q12-13), and (c) idic(9)(q21-22). The present case falls into the third category. Two abnormalities seen in this fetus that were not previously reported in chromosome 9 imbalances are horseshoe kidney and bicornate uterus. Other findings are consistent with those seen in 9p tetrasomy. Phenotype-genotype correlation in chromosome 9 is still complex and often contradictory. Some of this complexity may be because pseudo-dicentrics or other mechanisms have not been recognized. Detailed study of such cases by molecular or molecular cytogenetic techniques is now necessary for...
phenotype comparison. PCR quantification of highly polymorphic regions, applied initially in our study, is a very useful approach to detecting and characterizing cryptic chromosomal gain or loss.

REFERENCES


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Fig. 1. a: Hybridization of metaphase with +der(9) with subtelomeric sequences (pcp9p and D9S325; Vysis) showing brighter pcp9p sequences on both ends (arrows). Two normal 9 chromosomes show a bright pcp9p sequence on the short arm and a dull D9S325 sequence on the long arm. b: Hybridization of der(9) with alpha satellite sequence (D9Z; Vysis) showing signals at two loci, one at the primary constriction (small arrow) and a pair of signals at a non-constricted site (large arrow), suggesting that the chromosome is pseudo-dicentric with one active and one inactive centromere. A normal 9 with a single signal is at the extreme left. c: Ideogram of normal 9 (left) and proposed inversion duplication (9) (right).