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Editorial: Uniparental Disomy: A Rare Consequence of the High Rate of Aneuploidy in Human Gametes

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The paper by Spence et al. (this issue) demonstrates for the first time a new way in which the effects of aneuploidy can lead to human genetic disease. A girl with an apparently normal diploid chromosome complement was shown by molecular-biological techniques to have uniparental disomy for chromosome 7, i.e., both members of the chromosome pair came from the mother. The elegance and the power of current methods for genetic analysis are particularly striking when one realizes that the investigators had to accomplish the tour de force of demonstrating this mechanism in spite of the fact that the mother was dead and her genome could not be studied.

In 1980 Eric Engel suggested that uniparental disomy was not only possible but quite likely, given the high proportion of human gametes that have nullisomy and disomy. A personal confession is in order here: for several years his paper sat on my desk, because he had sent it to me for comment, suggesting that I look into this possibility in spontaneous abortions. I neither replied nor followed up the lead, but every once in a while I would reach the point in the pile where the reprint lay and have guilty regrets. Well, Eric, you were right.

While technically this phenomenon could have been recognized by using chromosome heteromorphisms, a random search for such a situation among normal diploid individuals would not really have been a productive task. The present case was studied because of the expression of a recessively inherited mutation in a child who also had growth failure. Initial studies of linked markers around the CF gene indicated lack of paternal alleles. The next step in the process was to rule out nonpaternity, a much more likely cause of this result than uniparental disomy.

One can make a crude estimate of the frequency of uniparental disomy that might be present at human conception owing to "gamete complementation," i.e., the union of a nullisomic and a disomic gamete. The available data on sperm chromosome complements (Brandriff et al. 1985; Martin et al. 1987) and the much less reliable estimates of numerical abnormalities in oocytes (Wramsby et al. 1987) indicate a frequency of ~1% for each of nullisomy and disomy in sperm and of 12% for each in oocytes. Using the data for trisomy 21, one can estimate that approximately one-eighth of disomic oocytes and one-half of disomic sperm result from second-division nondisjunction and thus will be partially homozygous. If one assumes an equal probability of each autosome being involved (which is approximately true for sperm, but probably not for oocytes), one can estimate that ~1/30,000 conceptions might have isodisomy by this mechanism.

Of course, this estimate does not take into account cases that arise as a result of a "correction" of an initial trisomic or monosomic conception through loss or gain of a chromosome. The latter is a likely mechanism in the case described by Spence et al., given the large degree of homozygosity of the two maternal chromosomes 7. Uniparental disomy has also been demonstrated by cytogenetic techniques in cases of trisomy/normal mosaicism. The frequency of other possible mechanisms leading to mosaicism for homozygosity, such as somatic crossing-over and gene conversion, are completely unknown, although their occurrence in tumor tissue has been clearly demonstrated. The picture is further complicated because there are also reasons for believing that isodisomy might often result in a nonviable conception. Homozygosity could lead to expression of embryonically lethal recessive genes, and the necessity during embryonic development for maternally and paternally

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derived copies of at least some chromosomes has been demonstrated in mice (Cattanach and Kirk 1985).

If x is the frequency of isodisomy, and $x/22$ is the frequency of isodisomy for a particular autosome, then the proportion of cases in which isodisomy will lead to homozygosity for a particular mutant gene with frequency q will be $qx/22$, whereas the proportion of cases due to normal Mendelian segregation is q^2. Thus the proportion of all affected individuals due to isodisomy will be $\sim x/22q$ and will decrease with increasing gene frequency. The estimate made above of 1/30,000 for the frequency of isodisomy at conception probably at least provides the right order of magnitude, unless mitotic recombination is much more common than expected. It can then be seen that for relatively common mutant genes such as cystic fibrosis the proportion of cases due to isodisomy must be very small: with $q = .02$ it is only 1/10,000. Even for very rare recessive genes it will never be large; for a condition that occurs with a frequency of 1/100,000 births, it would be ~1/2,000.

It seems unlikely, then, that uniparental isodisomy will turn out to be anything but an interesting rarity. However, the demonstration of its existence is an extraordinary piece of human genetic sleuthing, which provokes the same admiration for the detectives and satisfaction in a carefully reasoned conclusion as does a good mystery novel.

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