vinciali (1993) APP717 and Alzheimer's disease in Italy. Nat Genet 4:10

Spurr NK, Kelsell DP, Black DM, Murday VA, Turner G, Crockford GP, Solomon E, et al (1993) Linkage analysis of early-onset breast and ovarian cancer families, with markers on the long arm of chromosome 17. Am J Hum Genet 52: 777–785

Teare MD, Santibanez-Koref MF, Wallace SA, White GRM, Evans DGR, Burnell LD, Harris M, et al (1993) A linkage study in seven breast cancer families. Am J Hum Genet 52: 786–788

Tonin P, Serova O, Simard J, Lenoir G, Feunteun J, Morgan K, Lynch H, et al (1994) The gene for hereditary breast-ovarian cancer, BRCA1, maps distal to EDH17B2 in chromosome region 17q12-q21. Hum Mol Genet 3:1679–1682

van der Mey AGL, Maaswinkel-Mooy PD, Cornelisse CJ, Schmidt PH, van deKamp JJP (1989) Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. Lancet 2:1291–1294

van Duijn CM, Hendriks L, Farrer LA, Backhovens H, Cruts M, Wehnert A, Hofman A, et al (1994) A population-based study of familial Alzheimer disease: linkage to chromosome 14, 19, and 21. Am J Hum Genet 55:714–727

Vaxillaire M, Boccio V, Philippi A, Vigouroux C, Terwilliger J, Passa P, Beckmann JS, et al (1995) A gene for maturity onset diabetes of the young (MODY) maps to chromosome 12q. Nat Genet 9:418–423

Zuppan P, Hall JM, Lee MK, Ponglikitmongkol M, King M-C (1991) Possible linkage of the estrogen receptor gene to breast cancer in a family with late-onset disease. Am J Hum Genet 48:1065–1068

Address for correspondence and reprints: Dr. Arturas Petronis, Neurogenetics Section, Clarke Institute of Psychiatry, 250 College Street, Toronto, Ontario M5T 1R8, Canada. E-mail: petronisa@cs.clarke-inst.on.ca

0002-9297/96/5901-0038$02.00

Am. J. Hum. Genet. 59:268–269, 1996

When Does Maternal Age–Dependent Trisomy 21 Arise Relative to Meiosis?

To the Editor:

Polymorphic DNA markers have recently been used to estimate the fraction of trisomy 21 (Down syndrome) cases that may be attributable to postzygotic nondisjunction—indicative of a loss in the fidelity of the first few cell divisions after fertilization (Antonarakis et al. 1993; Sherman et al. 1994). In these studies, a postzygotic nondisjunction is defined as a case in which two chromosomes of the trisomic set are homozygous for all informative markers (i.e., for those markers that were heterozygous in their parent of origin). These studies estimate that the postzygotic mutation mechanism accounts for 4.5% (11/238) and 3.5% (9/255) of their cases, respectively, but their estimates may actually be conservative, since all noninformative haplotypes (frequency not reported) are arbitrarily attributed to meiosis II–type nondisjunction. Nevertheless, even the conservative estimates would, if confirmed, constitute a new and nonnegligible source of chromosomal segregation errors leading to trisomy. These studies' conclusions are supported by the observation that the 20 reported "postzygotic" cases (5 paternal and 15 maternal) appear to be less dependent on maternal age (mean maternal age 28.4 years) than maternal meiosis I–type failures (mean maternal age 31.2 years). However, given the limited sample size involved, one should be cautious in positing the absence of a maternal age effect.

In the absence of evidence for somatic mosaicism (Antonarakis et al. 1993; Sherman et al. 1994), it seems prudent to use linkage analysis to test for the proposed postzygotic origin of the extra chromosomes, because a truly postzygotic origin for homozygous segregants should result in their being recombined in approximately half of the cases. For the sake of simplicity, we assume (fig. 1) that only a single crossover has occurred between the relevant pair of chromosomes in each germ cell, yielding two recombined chromatids and two nonrecombined ones. If the nondisjunction were postzygotic in origin, the probability that a recombined chromatid would be transmitted to the zygote should be the same (50%) as the probability that a nonrecombined one would be transmitted from the same meiosis. Subsequently, both recombined and nonrecombined chromosomes should be subject to postzygotic nondisjunction to the same extent. If the observed proportion of recombined chromosomes were close to 50%, the postzygotic-nondisjunction hypothesis would be upheld. If, on the other hand, the observed proportion were to differ significantly from the expectation (i.e., if the majority of cases showed duplication of a nonrecombinant chromosome), then alternative mechanisms should be considered more plausible.

Specifically, it may be the case that nondisjunction occurred before meiosis in the parental germ lines, rather than postmeiotically (Vig 1984; Zheng and Byers 1992; Sensi and Ricci 1993). Chromosomes that had suffered nondisjunction prior to meiosis would proceed into meiosis in the manner typical of trisomies, forming either a trivalent or a bivalent-plus-univalent configuration during meiotic prophase. In either case, two identical chromosomes that had arisen within the premeiotic cellular lineage and had then undergone recombination with one another in meiosis would remain identical in their marker configurations. They would then falsely appear to represent the products of meiosis II–type nondisjunction with no recombination ("postzygotic-type nondisjunction"; see fig. 1). On the other hand, if either duplicated chromosome had exchanged marker alleles with

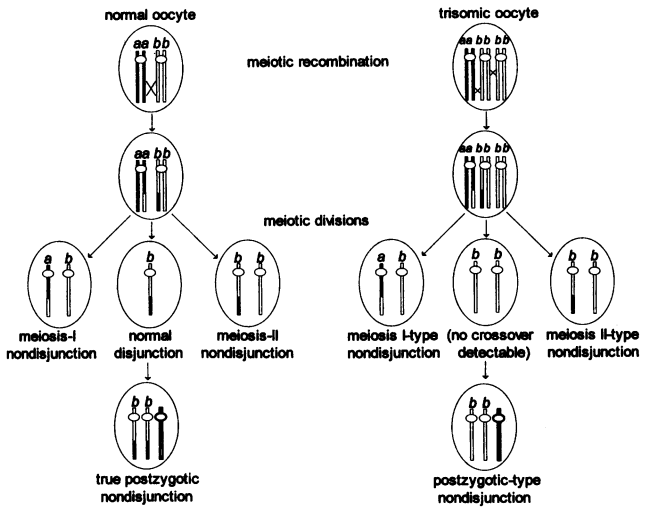

Figure 1 *Left,* Diagram indicating how nondisjunction in meiosis I leads to heterozygosity (*a/b*) for a centromere marker and meiosis II nondisjunction results in homozygosity (*b/b*) for the marker, whereas true postzygotic nondisjunction would create homozygosity for all markers on the extra chromosome. Complete reduction to homozygosity for well-spaced markers should not arise by true meiosis II nondisjunction (Antonarakis et al. 1993; Sherman et al. 1994). True postzygotic nondisjunction should often result in the duplication of a recombined chromosome. The proposed linkage analysis would identify the expected recombination events and distinguish postzygotic nondisjunction from the premeiotic errors that are diagrammed in the right-hand panel. *Right,* Results if nondisjunction had occurred before meiosis. The type of segregation designated "postzygotic-type nondisjunction" and characterized by homozygosity for maternal markers should appear among the trisomic offspring. Diagnostically, these wholly homozygous segregations should display an unrecombined parental haplotype, as opposed to the recombined haplotype expected in approximately half of the cases if true postzygotic nondisjunction were occurring.

the third homologue (present singly), then the likely outcome is that all three chromosomes would bear distinct sets of markers. This is seen as a meiosis II–type nondisjunction with recombination (i.e., the "meiosis II errors" defined by Antonarakis et al. [1993] and Sherman et al. [1994]). Therefore, trisomic progeny who are homozygous for markers on both chromosomes of maternal origin could represent either a maternal haplotype or a recombination of the two maternal haplotypes. Duplication of a maternal haplotype could have its origin in premeiotic nondisjunction, whereas the complete duplication of a recombined haplotype should be diagnostic for a duplication that arose postmeiotically. Similarly, paternal premeiotic nondisjunction leading to trisomy would often be signaled by duplication of a paternal haplotype.

The proposed genetic-linkage study would require inclusion of additional siblings or other close relatives from each affected family, to monitor recombination between polymorphic DNA markers spanning the length of the affected chromosomes. One hopes that the authors of the studies that we have cited will perform this analysis, which should be capable of unequivocally determining whether homozygous segregations could have their origin in postzygotic nondisjunction.

CHANG-JIANG ZHENG[1] AND BRECK BYERS[2]
[1]*Epidemiology, Statistics and Data Systems Branch, National Institute on Deafness and Other Communication Disorders, Bethesda; and*
[2]*Department of Genetics, University of Washington, Seattle*

Acknowledgments

The authors thank Stanley Gartler and Suresh Moolgavkar for discussions and suggestions. B.B. is supported by NIH grant GM18541.

References

Antonarakis SE, Avramopoulos D, Blouin JL, Talbot CC Jr, Schinzel AA (1993) Mitotic errors in somatic cells cause trisomy 21 in about 4.5% of cases and are not associated with advanced maternal age. Nat Genet 3:146–150

Sensi A, Ricci N (1993) Mitotic errors in trisomy 21. Nat Genet 5:215

Sherman SL, Petersen MB, Freeman SB, Hersey J, Pettay D, Taft L, Frantzen M, et al (1994) Non-disjunction of chromosome 21 in maternal meiosis I—evidence for a maternal age-dependent mechanism involving reduced recombination. Hum Mol Genet 3:1529–1535

Vig BK (1984) Sequence of centromere separation: another mechanism for the origin of nondisjunction. Hum Genet 66: 239–243

Zheng CJ, Byers B (1992) Oocyte selection: a new model for the maternal-age dependence of Down syndrome. Hum Genet 90:1–6

Address for correspondence and reprints: Dr. Chang-Jiang Zheng, Epidemiology, Statistics and Data Systems Branch, NIDCD/NIH, EPS Building 432, 6120 Executive Boulevard, Bethesda, MD 20892-7180.

0002-9297/96/5901-0039$02.00

Am. J. Hum. Genet. 59:269–271, 1996

A Rational Approach to Cystic Fibrosis Mutation Analysis in Hispanics: Reply to Arzimanoglou et al.

To the Editor:

This is in response to a letter by Arzimanoglou et al. (1995), who challenge our use of "Hispanic" for individuals in the cystic fibrosis (CF) mutation analysis by Grebe et al. (1994). These authors contend that the term