deletion of only sY158, sY166, and sY167 (subinterval F) (fig. 2, *a–b*). In both subjects, sY254 and sY255, mapping within the DAZ gene, and MK5, mapping within the RBM1 gene, were maintained (fig. 3).

In general, a Y-chromosome deletion that is associated with male infertility occurs as a de novo deletion (Reijo et al. 1995; Stuppia et al. 1996). In this study, both the proband and his father showed a del(Y)(q11), but the deletion in the proband was actually larger compared with that in his father, since the proband's deletion also involved STSs sY243 and sY269, which are located within the more proximal subinterval E of interval 6 (fig. 3, *right*). This result provides a biological support to the infertility found in the proband. This observation also confirms the critical role of interval 6 in the spermatogenetic process, which suggests that deletion of subinterval F, per se, is not associated with infertility. An additional point of interest is that both the proband and his father retained RBM1 and STSs sY254 and sY255, which are mapped within DAZ, in subinterval D. The segment deleted in the proband only, which likely is related to infertility, lies within subinterval E, which is outside the DAZ region. This implies that, in oligozoospermic patients at least, other genes in the region distal to DAZ and RBM1 may be involved in the spermatogenetic process. A matter of speculation is the role of the paternal deletion in the germ-cell mutation, which leads to the infertility in the proband. Deletions related to the spermatogenesis failure are regarded as de novo mutations. On the basis of the infertility rate among men and the percentage of infertile patients showing deletions of the Y chromosome, Reijo et al. (1995) have suggested that these mutations should occur in ~ 1 in 10^4 male newborns and that this high figure could arise by a mechanism involving repeated sequences flanking the gene. The present observation argues that some deletions should not lead necessarily to infertility, but these deletions make the Y chromosome more liable to a second mutation resulting in the spermatogenesis failure, as a consequence of DNA instability.

LIBORIO STUPPIA,[1] GIUSEPPE CALABRESE,[2] PAOLO GUANCIALI FRANCHI,[2] RITA MINGARELLI,[2] VALENTINA GATTA,[2] GIANDOMENICO PALKA,[2] AND BRUNO DALLAPICCOLA[3]

[1]*Istituto di Citomorfologia Umana Normale e Patologica, CNR, and* [2]*Istituto di Biologia e Genetica, Università "G. D'Annunzio," Chieti, Italy; and* [3]*Istituto di Genetica, Università Tor Vergata Roma and Ospedale CCS, S. Giovanni Rotondo, Italy*

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Address for correspondence and reprints: Dr. Giandomenico Palka, Via B. Buozzi 93, 65100 Pescara, Italy.

0002-9297/96/5906-0027$02.00

Am. J. Hum. Genet. 59:1395–1397, 1996

Premeiotic Trisomy 21 in Oocytes and Down Syndrome: A Reply to Zheng and Byers's Hypothesis

To the Editor:

The parental and meiotic or mitotic origin of supernumerary chromosome 21 (HC21) in trisomy 21 has been extensively studied in recent years by use of DNA polymorphisms. According to the segregation of these DNA markers in nuclear families with trisomy 21 (father, mother, and trisomy 21 offspring), the origin of supernumerary HC21 has been assigned to maternal or paternal meiosis I or meiosis II errors or to postzygotic mitotic

errors (Antonarakis et al. 1993; Sherman et al. 1994). There is probably a slight misassignment of the origin of the supernumerary HC21 because of the lack of a true centromeric marker; however, this error is not likely to be substantial, since the DNA polymorphisms used to "mark" the centromere were not >~2 Mb distal to the centromeric locus D21Z1.

Zheng and Byers (1992) had published a hypothesis in which the supernumerary HC21 in trisomy 21 is the result of a preexisting, mostly maternal, germ-cell trisomy 21 (mitotic premeiotic error). They had attributed the advanced maternal age to a weak selection against the preexisting aneuploid oocytes. According to their hypothesis, all the observed results that were obtained by use of DNA polymorphic markers can be explained on the basis of meiotic segregation from a trisomy 21 oocyte. Particularly, the previously assigned postzygotic errors could be owing to fertilization of an oocyte that contained two identical chromatids. The same investigators now propose that the study of recombination that uses additional family members may differentiate between postmeiotic and premeiotic mitotic errors (Zheng and Byers 1996). I agree with Zheng and Byers that the study of crossovers in appropriate families will support one or the other hypothesis. This will only be informative if phase-known meioses are studied.

The data, however, obtained from the analysis of DNA polymorphisms are not compatible with the Zheng-Byers hypothesis. The figure in Zheng and Byers's 1996 letter to the editor predicts that if all maternal errors were premeiotic the frequency of "meiosis I–type nondisjunction," "meiosis II–type nondisjunction," and "postzygotic–type nondisjunction" (Zheng and Byers's [1996] nomenclature) would have been equal (~33% each). There are, however, more theoretical products from a normal meiosis of trisomy 21 oocytes. Those are shown in figure 1. For the schematic recombination between chromosomes 1 and 2 (fig. 1, *top*), the expected ratio of meiosis I–type nondisjunction, meiosis II–type nondisjunction, and postzygotic-type nondisjunction is 8:2:2. The same is expected after an exchange between chromosomes 1 and 3 (fig. 1, *middle*). A recombination between chromosomes 2 and 3 will result in an expected ratio of 8:0:4 (fig. 1, *bottom*). The yield from all theoretical possibilities will be 66.7%, 11.1%, and 22.2% for meiosis I–type nondisjunction, meiosis–II type nondisjunction, and postzygotic-type nondisjunction, respectively. A recent compilation of data from our laboratory (Antonarakis et al. 1993; author's unpublished data) and that of Sherman et al. (1994) reveals that, in 465 families in which the supernumerary HC21 was maternal in origin, the observed frequencies were 74.6%, 21.7%, and 3.6%. The frequencies of meiosis II–type and mitotic-type errors were very different from those expected.

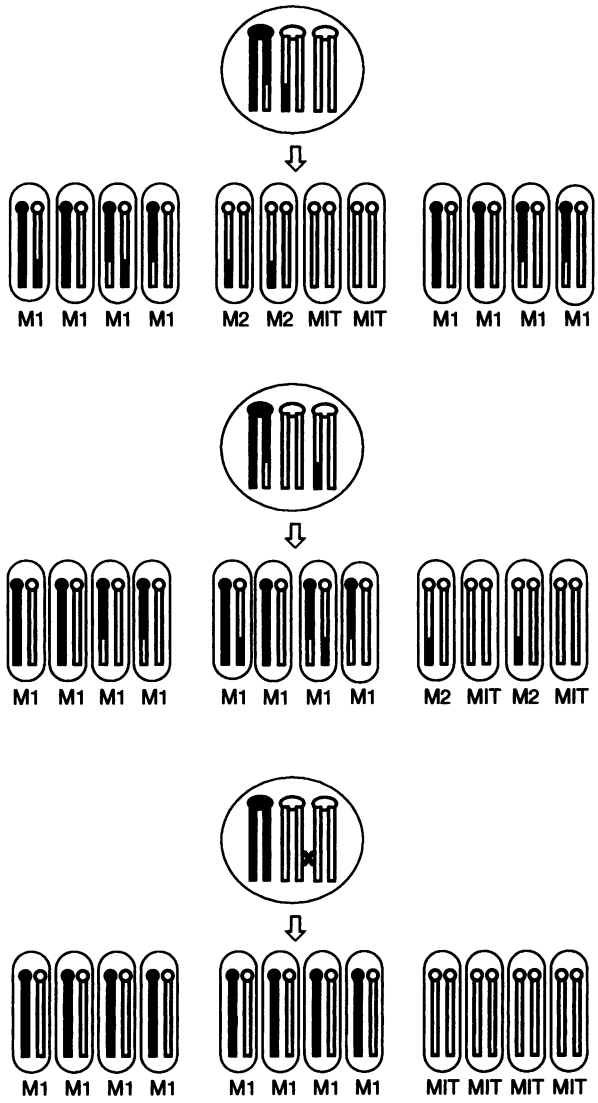

Figure 1 Schematic representation of meiotic products of a trisomic oocyte after one crossover event had occurred. All potential outcomes are shown given only one crossover. In the top panel, the crossover occurred between chromosomes 1 and 2, in the middle panel between chromosomes 1 and 3, and in the bottom panel between chromosomes 2 and 3. M1, M2, and MIT are the meiosis I–type nondisjunction, meiosis II–type nondisjunction, and postzygotic mitotic–type nondisjunction, respectively, as defined by Zheng and Byers (1996).

In addition, the Zheng-Byers hypothesis predicts that all maternally derived errors should occur at advanced maternal age. It is true that meiosis I–type and meiosis II–type nondisjunction are associated with advanced maternal age, as expected from their hypothesis (Antonarakis 1993). However, the mean maternal age in meiotic-type nondisjunction is ~28 years, which is not different from the mean maternal age in Western societies.

Furthermore, our knowledge of crossovers and meiotic segregation of aneuploid oocytes is primitive, and

the meiotic events schematically represented both in the figure of this letter and in that of Zheng and Byers's 1996 letter are oversimplifications and probably represent only some of many possible alternative meiotic events. It is clear that the mystery of advanced maternal age has not yet been solved, and hypotheses similar to that of Zheng and Byers (1992) are extremely useful in both the reevaluation of existing data and the planning of additional experiments.

STYLIANOS E. ANTONARAKIS
Division of Medical Genetics
Department of Genetics and Microbiology
University of Geneva Medical School and University Hospital
Geneva

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Address for correspondence and reprints: Dr. Stylianos E. Antonarakis, Division de Génétique Médicale, Centre Médical Universitaire, 1, rue Michel-Servet, CH-1211 Genève 4, Switzerland. E-mail: sea@medsun.unige.ch

0002-9297/96/5906-0028$02.00

Am. J. Hum. Genet. 59:1397–1398, 1996

Implications of the Oocyte-Selection Hypothesis: A Response to the Interpretation by Antonarakis

To the Editor:

Antonarakis (1996 [in this issue]) agrees with us that a linkage study should establish unequivocally the origin of the apparent postzygotic nondisjunction events reported by Antonarakis et al. (1993) and Sherman et al. (1994). The possibility that such errors actually might have arisen from parental germ-line mosaicism was previously noted by Antonarakis et al. (1993) and by Sensi and Ricci (1993). Our recent letter (Zheng and Byers 1996) was intended principally to point out how these two alternative explanations (postzygotic vs. premeiotic nondisjunction) could be distinguished by obtaining linkage data. The legitimacy of the proposed approach does not depend on whether the hypothetical ovarian aging mechanism that we had described previously is correct (Zheng and Byers 1992), but findings of the linkage study could help to test the hypothesis.

The oocyte-selection hypothesis (Zheng and Byers 1992) was proposed to explain the maternal age dependence in Down syndrome (Penrose and Smith 1966). Predictions of this hypothesis include the following: (1) that unilateral oophorectomy in adult women should increase the risk of producing Down syndrome offspring; (2) that earlier menopause should be seen in women with affected offspring; (3) that the recurrence risk of trisomy 21 to siblings should be elevated, particularly in young mothers (Zheng 1995); (4) that the mean maternal age should be elevated in both MMI-type and MMII-type nondisjunction, possibly being more significant in MMII-type cases (Zheng and Byers 1992); and (5) that the proportion of trisomic oocytes in the resting pool should increase with advancing maternal age. Systematic examination of these and other predictions is needed for verification or rejection of the hypothesis.

Antonarakis's (1996) criticisms of the oocyte-selection hypothesis contain assumptions that we consider to be implausible. The following points should be considered in a complete evaluation of the model and these criticisms:

1. The mean maternal age of 28.4 years that we and Antonarakis have quoted for postzygotic nondisjunction is derived from only 20 cases (5 paternal and 15 maternal). Six more postzygotic-type cases with a mean maternal age of 31.5 years (parental origin not separated) have been reported recently (Yoon et al. 1996). Thus the 26 postzygotic-type cases now available have a mean maternal age of 29.1 years. Comparison with the mean maternal age in a Western society may now yield a significant *P*-value. However, we must reemphasize that mean values of this sort, which are sampled from a skewed underlying maternal age distribution, are statistically sensitive to extreme values and should be viewed with caution (Zheng and Byers 1996).

2. The relative proportion of cases falling into each of the three nondisjunction categories (MMI type, MMII type, and postzygotic type) necessarily will reflect a variety of unknown variables, including (*a*) possible differences in the survival of the germ cells and embryos generated from either pattern of segregation (Flannery 1988) and (*b*) possible additional contributions from errors in meiosis or in postzygotic cell divisions. Furthermore, it