Trisomy: Chromosome Competition or Maternal Strategy?

Increase of Trisomy Incidence with Increasing Maternal Age Does Not Result from Competition Between Chromosomes

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Axelrod and Hamilton (*Science* 211:1390, 1981) suggested that trisomies may result from an end-game strategy between chromosomes competing to get on the gamete as the mother approaches menopause. We tested this hypothesis by reviewing studies of the parental origin of the extra chromosome in trisomy 21 births. These data show that there is no significant rise in trisomy 21 conceptions as the mother ages. The increase in trisomies with maternal age results not from an increase in nondisjunctions, but from a decrease in rejection of trisomy zygotes, which may be adaptive for the mother towards the end of her reproductive life. This decreasing rate of rejection may result from the changing inclusive benefits of two maternal strategies as menopause approaches.

KEY WORDS: Chromosome abnormalities; Competition; Down Syndrome; Female; Game theory; Genetic; Human; Maternal age; Meiosis; Nondisjunction; Prisoner's Dilemma; Sociobiology, Trisomy.

In a seminal article on the evolution of cooperation, Axelrod and Hamilton (1981) suggested a possible explanation for trisomy 21 and other nondisjunctions that increase with maternal age. "It seems possible that . . . the situation in oogenesis is a Prisoner's Dilemma: a chromosome which can be 'first to defect' can get itself into the egg nucleus rather than the polar body . . . and when both members of a homologous pair try it at once, an extra chromosome in the offspring could be the occasional result." They admit (p. 221) "that this would occur is pure speculation" but note that "our model would explain the much greater incidence of abnormal chromosome increase in eggs (and not sperm) with parental age."

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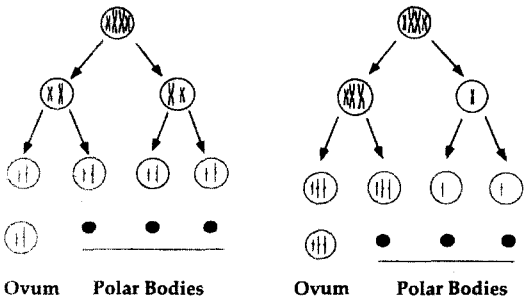

FIGURE 1. Comparison of chromosomal migration in normal meiosis and in trisomy nondisjunction.

In a Prisoner's Dilemma, the two contestants maximize their long-term mutual gain by cooperating, but on any one move each can gain more by defecting. Thus, if the next move is known to be the last, the best strategy is to defect. Menopause may be viewed as the end of a Prisoner's Dilemma game between chromosomes. In the competition to get on the ovum, one chromosome succeeds, the other must yield and is lost. If neither yields, the result is a trisomy zygote.

Meiosis creates gametes with half the number of chromosomes characteristic of the somatic cells of the species. The gamete precursor cell divides twice, but since there is only a single chromosome duplication, the result is four haploid cells. In humans, these haploid cells have 23 chromosomes. Thus, when a sperm and an ovum combine, they form a diploid zygote with the full complement of 46 chromosomes. In oogenesis, only one haploid cell (23 chromosomes) becomes the ovum, the remaining three are discarded as polar bodies (see Figure 1). In spermatogenesis, the four haploid cells become four sperm.

Errors during meiosis can result in absence of a chromosome (anaploidy) or an extra chromosome (trisomy) in the resultant gamete. If the disjunction of the chromosomes is not complete, the result is one gamete that is missing a particular chromosome, and another gamete with two homologous chromosomes. If the sex cell with the extra chromosome combines with a normal haploid cell in fertilization, the resultant cell has 47 chromosomes and is called a trisomy. Trisomy can result from nondisjunction during either the first or second meiotic division.

Down Syndrome results from an extra 21st chromosome. It occurs in about 1/1000 infants, making it the most common human trisomy. The rate of trisomy 21 births increase with increasing maternal age. Between ages 20 to 30, the frequency increases slowly from a low of 0.04%, but after age 35 there is an exponential increase from 0.16% to 3.33% at 45 years (Hook and Lindsjo 1978; Schreinemachers et al. 1982). Several statistical models have been proposed to explain this marked rise (Hassold et al. 1989). The inci-

dence of trisomy 21 does not increase with paternal age (Hassold and Jacobs 1984).

The parental origin of the extra chromosome in a trisomy can now be determined. Previously this was only possible if there was a structural abnormality in the chromosome, but since 1970, visual identification of Q-band polymorphism—where chemically "banded" chromosomes are used as a "fingerprint" to match with paternal or maternal chromosomes—has allowed determination of the origin of the trisomy in most cases. If the Axelrod and Hamilton hypothesis is correct, then the rate of trisomy 21 zygotes of maternal origin should increase rapidly as menopause approaches.

We reviewed human data studies of the sources of trisomy 21. Though some authors (Gould et al. 1981) have claimed that higher primates also undergo climacteric, humans are the only species that regularly cease ovulating well within their normal life span. Recent studies of trisomy 21 have been able to identify different types of trisomies as well as the parental origin of the trisomic chromosome. We examined these studies to identify three variables: the age of mother at conception, rate of trisomy births, and parental origin of trisomy.

Competition between chromosomes to be on the ovum may only be one cause of trisomy. Trisomy 21 was found to be of paternal origin in only 20% of cases studied by Juberg and Mawrey (1983), and the ratio of nondisjunctions during first vs second meiotic division was 60:40; in the 80% of cases of maternal origin the ratio was 80:20. Thus, the majority of errors occur during first meiotic division of the ovum, and only a few occur during the second meiotic division and during spermatogenesis.

Stein et al. (1986) reviewed 258 cases of trisomy 21 births in which parental age and parental origin of triploidy was reported. They determined the ratio of maternal to paternal origin (M/P ratio) of the trisomies across maternal ages. Trisomy shows no significant increases with paternal age (Ferguson-Smith and Yates 1984; Hook and Cross 1982; Hook et al. 1981; Hook and Regal 1984; Roecker and Huether 1983; Roth et al. 1983). If there is an association of maternal age to trisomy 21 at fertilization then the M/P ratio should increase with maternal age.

Table 1 shows no change in the M/P ratio with increasing maternal age. Therefore, the incidence of trisomy births in older mothers must result from something other than an increase in nondisjunctions. The hypothesis that trisomies result from an increase in errors of the first meiotic division is not supported by this data. Stein et al. (1986) also examined the idea that the rate of increased trisomy 21 births is a result of lowered miscarriages in older mothers. Their data from karotypes from miscarriages show that the proportion of trisomies 21 in miscarriages is 54% in women under 30 years to 67% in women older than 30 years. These data exclude the possibility of attrition mechanisms before fertilization and after implantation/recognition (Stein 1986, p. 945), "the remaining possibility is a mechanism in the pre-recognition phase that becomes less sensitive with advanced age." This

Table 1. Down Syndrome: Ratio of Maternal to Paternal Origin (M/P) by Maternal Age at Birth

Maternal Age	M:P Ratio, Rounded	n
<20	7	8
20–24	3	48
25–29	3	65
30–34	3	65
35–39	6	35
40–44	3	39
45 up	∞	5
Total		258

From [Stein et al. 1986].

means that the rate of increase in trisomy 21 births with maternal age is probably due to decrease in rejection of the defective embryo—not because of an increase in trisomy 21 conceptions.

DISCUSSION

Although the rise in rate of trisomy 21 births with maternal age does not result from competition between the chromosomes, it may, nonetheless, be explained as an end-game strategy. The uterine implantation rate is much reduced for zygotes with chromosomal and other abnormalities (Hook 1978, 1983). The mechanism that detects abnormalities is little understood, as is the regulation of implantation. It does appear, however, that the sensitivity of this mechanism decreases as maternal age increases. Thus, as age increases, the implantation rate for defective zygotes increases. This explains the increase of trisomy 21 births with maternal age.

As the mother nears the end of her reproductive life, the risk of rejecting a viable zygote may increase, relative to the risk of delivering a defective child. By contrast, a younger mother would be better served by spontaneously aborting a possibly defective fetus and conserving resources for a normal child later.

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