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Recombination and Maternal Age–Dependent Nondisjunction: Molecular Studies of Trisomy 16

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Summary

Trisomy 16 is the most common human trisomy, occurring in ≥1% of all clinically recognized pregnancies. It is thought to be completely dependent on maternal age and thus provides a useful model for studying the association of increasing maternal age and nondisjunction. We have been conducting a study to determine the parent and meiotic stage of origin of trisomy 16 and the possible association of nondisjunction and aberrant recombination. In the present report, we summarize our observations on 62 spontaneous abortions with trisomy 16. All trisomies were maternally derived, and in virtually all the error occurred at meiosis I. In studies of genetic recombination, we observed a highly significant reduction in recombination in the trisomy-generating meioses by comparison with normal female meioses. However, most cases of trisomy 16 had at least one detectable crossover between the nondisjoined chromosomes, indicating that it is reduced—and not absent—recombination that is the important predisposing factor. Additionally, our data indicate an altered distribution of crossing-over in trisomy 16, as we rarely observed crossovers in the proximal long and short arms. Thus, it may be that, at least for trisomy 16, the association between maternal age and trisomy is due to diminished recombination, particularly in the proximal regions of the chromosome.

Introduction

Increasing maternal age remains the only factor incontrovertibly linked to human trisomy. The relationship between maternal age and Down syndrome was described by Penrose (1933) >25 years before the chromosomal basis of the disorder was recognized. Subsequently, studies of spontaneous abortions have shown that most, if not all, human trisomies are similarly affected by increasing maternal age (Hassold and Jacobs 1984). Furthermore, these studies suggest that, by age 40–45 years, a majority of all ovulated oocytes may be aneuploid.

Despite the obvious clinical importance of the maternal age effect on trisomy, we still know very little about its basis. Several models have been proposed to explain the effect and, conceptually, these can be divided into five types, on the basis of the time at which the effect is hypothesized to originate: (1) in the fetal premeiotic stage of germ-cell development, during which time rapid mitotic divisions occur (Zheng and Byers 1992); (2) in fetal meiosis I, during which time pairing of homologues and genetic recombination occur (see, e.g., Henderson and Edwards 1968); (3) in the prolonged dictyotene stage of meiosis, during which time the oocyte is meiotically "arrested" (see, e.g., Hawley et al. 1994); (4) in the periovulatory stage, at which time meiosis I is resumed and completed (see, e.g., Crowley et al. 1979; Eichenlaub-Ritter and Boll 1989; Warburton 1989); or (5) in the second meiotic division (see, e.g., German 1968). Recently, Sherman et al. (1994) provided evidence of an association between reduced genetic recombination and maternal age–dependent trisomy 21. If true, this implies that the age effect originates at either the second or the fourth of the above time points; i.e., at the time at which recombination occurs or at the time when recombinational events are resolved.

However, this interpretation must be viewed with caution, for several reasons. First, the normal female genetic map of chromosome 21 is only 70–80 cM (Matise et al. 1994), so that chromosomes 21 without detectable crossovers are not unexpected; thus, there is a limited ability to detect differences in the level or location of crossovers between normal and trisomy-generating meioses. Second, determinations of the meiotic stage of origin of trisomy 21 are hampered by the lack of useful chromosome 21 centromeric polymorphisms; thus, some cases may be misclassified, possibly compromising inferences regarding aberrant recombination and meiosis I trisomy. Finally, trisomy 21 has both maternal age–independent and age–dependent components (Penrose and Smith 1966; Risch et al. 1986), thus complicating inferences regarding the maternal age effect.

To circumvent these difficulties, we have been inter-

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ested in examining the relationship between aberrant recombination and trisomy 16. This is the most common trisomy in our species (Hassold and Jacobs 1984) and, in analyses of recombination and nondisjunction, has several advantages over studies of trisomy 21. For example, chromosome 16 has a normal female genetic map of ~180 cM (Shen et al. 1994), over twice that of chromosome 21; thus, on average 3–4 crossovers are anticipated during female meiosis. Further, a chromosome 16 centromeric polymorphism is available, thus making it possible to distinguish between meiosis I and meiosis II nondisjunctions. Finally, studies of spontaneous abortions indicate that trisomy 16 is completely dependent on maternal age, with no age-independent component (Risch et al. 1986; Morton et al. 1988). Thus, trisomy 16 may well serve as a prototype for understanding the basis of the association of advancing maternal age and human nondisjunction.

In the present report, we summarize our studies of the parent and meiotic stage of origin of trisomy and the association with genetic recombination, in 62 cases of trisomy 16. All informative cases were maternally derived, almost always because of an error at meiosis I. We also observed a significant reduction in recombination in the trisomy-generating meioses. The effect was restricted to the pericentromeric region of the chromosome, suggesting that altered, and not absent, recombination is the important correlate of chromosome 16 nondisjunction.

Material and Methods

Study Population

The present study population consists of 62 trisomy 16 spontaneous abortions, ascertained during cytogenetic studies of spontaneous abortions at the University of Hawaii, Honolulu, and Emory University, Atlanta. Details of the collection, culturing, and cytogenetic processing of the tissue samples have been provided elsewhere (Hassold et al. 1980).

Of the 62 cases, 58 were single, nonmosaic trisomies, while 4 had other abnormalities in addition to trisomy 16 (table 1). Preliminary data on 26 of these cases have been presented elsewhere (Hassold et al. 1991).

DNA Marker Analysis

DNA was extracted from fetal tissue samples and parental blood samples, and chromosome 16 polymorphisms were analyzed by Southern blotting or PCR as described elsewhere (Sherman et al. 1994). A total of 31 markers were used in the study, consisting of 14 from 16p, 16 from 16q, and 1 from the centromeric region (table 2). The markers were grouped into 15 "marker groups," which we defined as a group of markers known to be tightly linked in normal individuals and among which no recombination was observed in our trisomic data set. By doing this, we were able to maximize the linkage information for each interval.

In our analyses, we first determined the parent of origin of trisomy, typically on the basis of at least two markers. Next, we determined the meiotic stage of origin by using the pSE16-2 (D16Z2) locus, which detects a complex set of polymorphic fragments in the alpha satellite sequences of the centromere of chromosome 16. Nondisjunction was scored as being of meiosis I origin if all fragments in the parent of origin of trisomy were present in the trisomic fetus. Alternatively, nondisjunction was scored as being of meiosis II or mitotic origin if only a subset of the fragments were present in the trisomic fetus. We then distinguished between meiosis II and mitotic errors by studying other, noncentromeric markers. If, at any marker, parental heterozygosity was maintained in the trisomic fetus, we concluded a meiosis II error; if parental heterozygosity was reduced to homozygosity at all informative loci, we concluded a mitotic error.

Genetic Linkage Studies

Centromere-gene mapping techniques were used to evaluate recombination between the two nondisjoined chromosomes. The use of this mapping approach has been described in detail elsewhere (Chakravarti et al. 1989). In brief, our method involved identifying loci at which the parent of origin of trisomy was heterozygous and studying those loci in the trisomic offspring to determine whether heterozygosity was maintained ("nonreduction" = N) or was reduced to homozygosity ("reduction" = R). All pairs of markers were then analyzed to determine whether both markers were nonreduced ($N > N$), both were reduced ($R > R$), or one was nonreduced and the other reduced ($N > R$ or $R > N$). The first two categories are consistent with no recombination between the markers, while the third indicates that recombination occurred between the markers. Recombination fractions and lod scores were then derived from the estimated probability of nonreduction, assuming at most two chiasmata within any interval (Morton and MacLean 1984), using the program TETRAD. To increase the amount of information for each map interval, loci that were tightly linked were grouped and analyzed as a single locus.

For comparison to the trisomic meioses, we analyzed normal female meiotic events. We estimated two-point recombination fractions and lod scores by using CRI-MAP (Lander and Green 1987), on the basis of CEPH family genotypes kindly provided by Drs. Grant Sutherland and Aravinda Chakravarti.

The normal female and trisomy 16–derived genetic maps were then compared using a procedure outlined elsewhere (Sherman et al. 1994). On the basis of the

Table 1

Summary of Cytogenetic and Molecular Studies of Trisomy 16

Identification No.	Chromosome Constitution	Paternal Age (years)	Maternal Age (years)	Parent and Meiotic Stage of Origin	No. of Detectable Crossovers	
					16p	16q
K3021	45,X/46,X,+16	34	34	Mat I or II	0	0
K3029	47,XX,+16	42	30	Mat I	1	1
K3056	47,XX,+16	37	34	Mat I	3	1
K3074	47,XY,+16	34	28	Mat I	1	0
K3086	47,XX,+16	32	30	Mat I	0	1
K3164	47,XX,+16	35	33	Mat I	1	0
K3259	47,XY,+16	33	29	Mat I	0	1
K3361	47,XY,+16	34	32	Mat I	1	1
K3375	47,XY,+16	28	29	Mat I	1	1
K3407	47,XX,+16	23	21	Mat I	1	1
K3409	47,XX,+16	35	32	Mat I	0	0
K3425	47,XY,+16	37	35	Mat I	0	1
S0003	47,XY,+16	28	39	Mat I	0	2
S0009	47,XX,+16/48,XX,+2,+16	35	33	Mat I	0	1
S0016	47,XY,+16	33	33	Mat I	0	1
S0037	47,XX,+16	30	30	Mat I	1	1
S0055	47,XX,+16	32	34	Mat I	0	2
S0134	47,XY,+16	30	29	Mat I	0	0
S0138	47,XY,+16	30	30	Mat I	0	1
S0145	47,XY,+16	29	32	Mat I	1	0
S0244	47,XY,+16	30	28	Mat I	1	1
S0245	47,XX,+16	29	28	Mat I	0	1
S0343	47,XY,+16	32	30	Mat I	0	1
S0356	47,XY,+16	35	31	Mat I	1	1
S0374	47,XY,+16	38	37	Mat I	0	0
S0382	47,XX,+16	31	36	Mat I	0	0
S0407	47,XX,+16	45	39	Mat I	1	0
S0418	47,XY,+16	22	23	Mat I	0	0
S0454	47,XY,+16	29	27	Mat I	1	0
S0455	48,XY,+2,+16	41	34	Mat I	0	2
S0462	47,XY,+16,t(6;11)	32	35	Mat I	0	0
S0469	47,XX,+16	43	40	Mat I	1	0
S0473	47,XX,+16	33	31	Mat I	1	1
S0496	47,XX,+16	28	27	Mat I	1	1
S0511	47,XX,+16	34	33	Mat I	0	1
S0515	47,XY,+16	35	35	Mat I	1	1
S0525	47,XX,+16	33	28	Mat I	0	0
S0553	47,XY,+16	26	26	Mat I	1	1
S0588	47,XY,+16	31	29	Mat I or II	0	1
S0621	47,XX,+16	35	36	Mat I	0	2
S0636	48,XY,+15,+16	34	36	Mat I	1	0
S0682	47,XX,+16	43	33	Mat I	1	0
S0683	47,XY,+16	29	29	Mat I	1	0
S0698	47,XY,+16	28	30	Mat I	0	2
S0753	47,XX,+16	29	28	Mat I	0	0
s0760	47,XY,+16	29	30	Mat I	1	0
S0761	47,XX,+16	33	29	Mat I	0	0
S0782	47,XX,+16	31	29	Mat I	1	0
S0838	47,XX,+16	31	25	Mat I	1	0
S0973	47,XX,+16	Unknown	28	Mat I	1	1
S1007	47,XY,+16	29	27	Mat I	0	0
S1052	47,XY,+16	30	31	Mat I	0	0
S1094	47,XX,+16	32	32	Mat I or II	1	0
S1100	47,XX,+16	32	33	Mat I	0	1
S1114	47,XY,+16	41	40	Mat I or II	0	1
S1131	47,XY,+16	32	34	Mat I	1	0
S1137	47,XX,+16	31	28	Mat I or II	1	1
S1140	47,XX,+16	31	31	Mat I	1	0
S1144	47,XX,+16	26	32	Mat I	1	0
S1189	47,XX,+16	38	34	Mat I or II	1	0
S1281	47,XX,+16	28	28	Mat I	0	1
S1310	47,XX,+16	41	35	Mat I	0	0

Table 2

Comparison of Observed and Expected Number of Crossovers in 56 Cases of Maternal Meiosis I Trisomy 16, Assuming a Normal Female Map of 175 cM

	No. of Detectable Crossovers				
	0	1	2	3+	
Observed (n = 56)	12	26	17	1	
Expected:[a]					
Low variance	5.3	5.3	24.5	21.0	(χ_3^2 = 110.6; P < .001)
High variance	6.9	6.9	21.4	20.6	(χ_3^2 = 76.2; P < .001)

[a] From Robinson et al. (1993).

order of markers presented in figure 1, we used the program MAP (Morton and Andrews 1989) to estimate the interval distances between markers from the pairwise recombination fractions weighted by their lod scores. For these determinations, interference was set at P = .35 (Rao et al. 1977). In our initial analyses, we compared the overall genetic length of the two maps assuming a constant-interval distance ratio (k) between the two maps; in the absence of an association between recombination and nondisjunction, k should equal 1.0. To test this, the likelihood of the two maps estimated assuming $k = 1$ ($L_{k=1}$) was compared with the likelihood obtained when k was estimated (L_k). Significance was tested as $\chi_1^2 = 2\ln L_{k=1} - 2\ln L_k$.

In subsequent analyses, we estimated each map interval separately to determine whether the distribution of crossing-over differed between the normal and nondisjoined chromosomes (i.e., whether k was constant over the length of the chromosome). The likelihood obtained was compared with the likelihood of the two maps by assuming a constant ratio k (L_k) as described above. Significance was tested as before, with $n - 1$ df, where n is the number of intervals estimated.

In addition, we compared the distribution of the number of crossovers in the meiosis I trisomy 16 cases with that expected for chromosome 16 in normal female meiotic events. For this analysis, we used the calculated values of Robinson et al. (1993), assuming a normal female map length of 175 cM for chromosome 16.

Results

Parent and Meiotic Stage of Origin of Trisomy

Table 1 provides the chromosome constitutions and the results of studies of the origin of trisomy for the 62 cases in the study population. We were able to determine the parental origin in all cases, with each having an extra maternally derived chromosome 16. Additionally, in the 56 cases in which we were able to specify the meiotic stage of origin, nondisjunction occurred at meiosis I. In the remaining six cases, the centromeric polymorphism was uninformative or was not tested; however, in each of these, nonreduction was observed at one or more of the noncentromeric markers, indicating that trisomy originated at either meiosis I or II and not postzygotically.

Genetic-Mapping Studies

In initial linkage studies, we constructed a genetic map of chromosome 16 on the basis of genotyping data from the CEPH database and compared it to a map generated from the 56 meiosis I trisomies. The total genetic lengths of the two maps were highly significantly different. That is, when the interval distance ratio between the maps was estimated, there was a 50% reduction in recombination in the trisomy-based map (i.e., k = .51; χ_1^2 = 49.93; P < .001).

In subsequent analyses, we tested two alternative explanations for the reduction in recombination: (1) failure of recombination in a proportion of the trisomy-generating meioses or (2) alteration in the distribution of recombinational events in these meioses. If the former were true, we would expect that the interval distance ratio of the two maps (k) would remain constant over the length of the chromosome, while if the latter were correct the ratio should be variable. In fact, the ratio varied significantly among intervals (χ_{13}^2 = 96.52; P < .001), indicating that it is altered, not absent, recombination that is the important correlate of trisomy 16 (fig. 2).

This interpretation was confirmed by a separate analysis, in which the number of detectable exchanges in the trisomy-generating meioses were compared to the expected number of exchanges, assuming a normal female chromosome 16 map of 175 cM. For this analysis, we used the expected values calculated by Robinson et al. (1993) for 175-cM maps with either of two different chiasma distributions, one with a high and one with a low level of variance in chiasma number (i.e., strong and weak interference, respectively). We assumed that

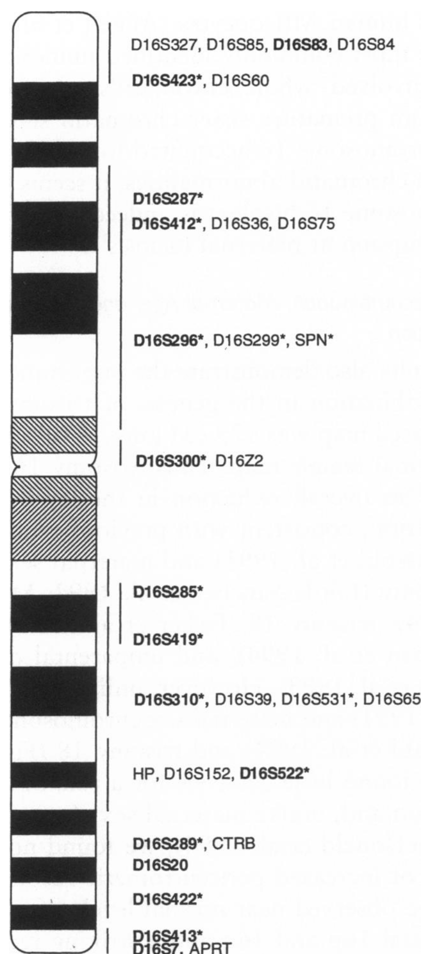

Figure 1 Chromosome 16 markers used in the study. The figure shows the approximate physical location of each of the 15 marker groups studied and the individual loci comprising each marker group. An asterisk (*) indicates a PCR-formatted polymorphism; others are Southern-based polymorphisms. For each of the marker groups, one locus is shown in bold type; in the text, this marker is used to represent the marker group.

our DNA markers provided complete coverage of chromosome 16; this minimizes the expected number of 0-exchange events and, thus, provides a conservative test of the relative effects of reduced versus absent recombination. The results of this analysis are given in table 2. The observed distribution of exchanges was significantly different from expectation under either assumption of interference, and in each situation there was an increase in the observed number of 0-exchange events. However, most of the trisomy-generating meioses exhibited at least one exchange, and the largest differences between the observed and expected values involved the increase in 1-exchange events and the decrease in the 3+ exchange category. Thus, these results confirm the importance of reduced, but not absent, recombination in the genesis of trisomy 16.

If this is true, is it important to determine which regions of chromosome 16 were affected in the trisomy-causing meioses. From figure 2, it is clear that the effect was largely limited to the proximal long and short arms. That is, from the D16S83 marker group to the D16S412 marker group (encompassing the region from 16pter to p13.11-12.1), the estimated genetic distance in the trisomic meioses was 69.2 cM, actually increased over the 42.5-cM value for normal female meioses. Similarly, on the distal long arm, the estimated distances from D16S310 to D16S7 (encompassing the region from 16q12.1-13 to qter) were 44.1 and 43.7 cM in the trisomic and normal meioses, respectively. However, between D16S412 and D16S310 (encompassing proximal 16p and proximal 16q), the difference between the two maps was remarkable. The estimated distance in trisomic meioses was only 4.4 cM, a reduction of nearly 20-fold from the 77.3-cM value estimated for normal

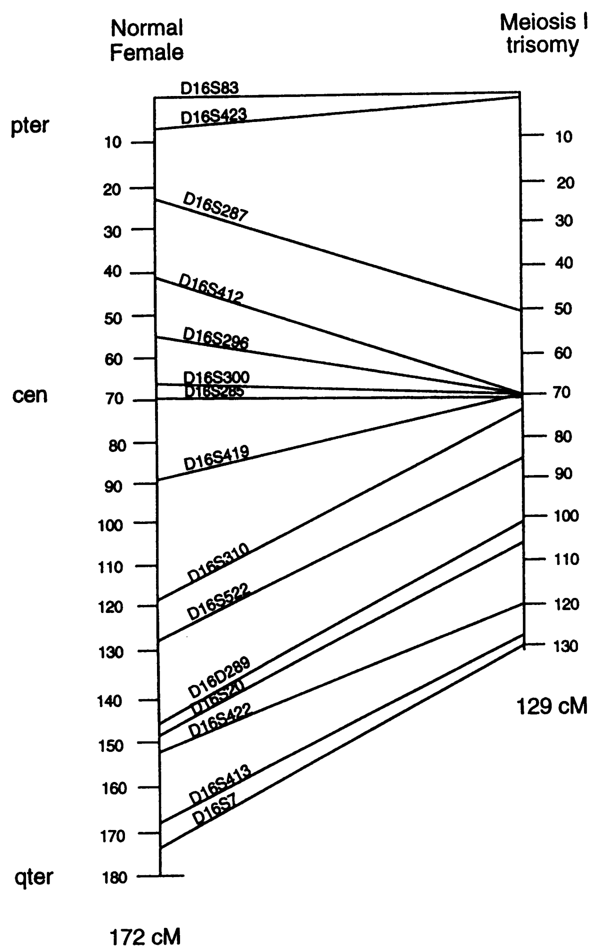

Figure 2 Comparison of genetic maps of normal female meioses (based on genotypes from CEPH database) and trisomy 16-generating meioses (based on 56 cases of meiosis I trisomy). Note that, while the centromere is not included in the genetic maps, it has been localized to the interval between D16S300 and D16S285 (Shen et al. 1994).

meioses. The effect was observed on both the short and long arms, since between D16S412 and D16S300 (on 16p) the trisomic and normal values were 0.7 cM and 25.0 cM, respectively, and between D16S285 and D16S310 (on 16q) the values were 2.8 and 50.7 cM, respectively.

Discussion

The Parent and Meiotic Stage of Origin of Trisomy 16

In 1986, Risch et al. suggested that all cases of trisomy 16 might originate from the same maternal age–dependent nondisjunctional event. Our studies of the parent and meiotic stage of origin of trisomy 16 support this interpretation. In each of the 62 cases studied, the additional chromosome arose as a result of a maternal meiotic error, and, in each, the results were consistent with an MI origin. This indicates that most, if not all, cases of trisomy 16 arise from a mechanism of nondisjunction that operates at maternal meiosis I. Further, it suggests that trisomy 16 is unique among human trisomies, since, in other trisomies studied to date, paternally derived cases or cases of maternal meiosis II origin are commonly identified. For example, ~50% of cases of 47,XXY are paternal in origin (MacDonald et al. 1994), most cases of trisomy 18 arise from an error at maternal meiosis II (Fisher et al. 1995), and, among acrocentric trisomies, ~10% are paternally-derived and an estimated 10%–25% arise from maternal meiosis II nondisjunction (Zaragoza et al. 1994).

The basis for the difference between trisomy 16 and the other trisomies is not known, but conceptually it could be explained in one of three ways: first, paternal or maternal meiosis II nondisjunction for chromosome 16 could be rare, or nonexistent; second, paternally derived trisomy 16 could be at a selective disadvantage by comparison with maternally derived trisomy 16; or, third, maternal meiosis I errors involving chromosome 16 could be extraordinarily common, thus reducing the apparent frequency of the other categories of nondisjunction. There is relatively little available information to discriminate among these possibilities. However, studies of sperm chromosome constitutions using either human-hamster fusions (Martin et al. 1993) or FISH (Williams et al. 1993) suggest that disomy 16 occurs as frequently as other autosomal disomies, thus reducing the likelihood that the first explanation is correct. Reports of paternal and maternal uniparental disomy 16 (e.g., Ngo et al. 1993; Sutcliffe et al. 1993) provide little evidence that developmentally important imprinted loci reside on chromosome 16, suggesting that differential selection is also not responsible for the observations. Thus, we favor the third alternative, namely, that chromosome 16 is particularly susceptible to mal-segregation at maternal meiosis I. This view is consistent with recent studies of human MII oocytes (Angell et al. 1994), in which the most commonly identified numerical abnormalities involved whole chromatids, presumably resulting from premature sister chromatid separation at MI. As chromosome 16 accounted for nearly one-third of all such chromatid abnormalities, it seems likely that the chromosome 16 bivalent is, indeed, particularly liable to disruption at maternal meiosis I.

Aberrant Recombination, Maternal Age, and Chromosome 16 Nondisjunction

Our results also demonstrate the importance of aberrant recombination in the genesis of trisomy 16. Our trisomy-based map was 129 cM long, ~70% the length of the normal female map. Thus, trisomy 16 is associated with an overall reduction in the level of genetic recombination, consistent with previous reports of paternal (Hassold et al. 1991) and maternal sex chromosome trisomy (Lorda-Sanchez et al. 1992; MacDonald et al. 1994), trisomy 18 (Fisher et al. 1995), trisomy 21 (Sherman et al. 1994), and uniparental disomy 15 (Robinson et al. 1993). However, unlike paternal (Hassold et al. 1991) and maternal sex chromosome trisomy (MacDonald et al. 1994) and trisomy 18 (Fisher et al. 1995), we found little evidence for a role of absent recombination and, unlike maternal sex chromosome trisomy (MacDonald et al. 1994), we found no evidence for a role of increased pericentromeric recombination. Instead, we observed near-normal levels of recombination on distal 16p and 16q and a striking reduction in recombination in the proximal regions of the chromosome. The simplest explanation for these observations is that the mere presence of a chiasma does not ensure normal segregation and that, at least for chromosome 16, the presence of a proximal exchange helps to stabilize the bivalent at meiosis I. Since similar observations have been reported for trisomy 21 (Sherman et al. 1994), it may be that this situation applies to other chromosomes as well.

Consistent with recent reports of trisomy 21 (Sherman et al. 1994) and sex chromosome trisomy (MacDonald et al. 1994), our results also implicate aberrant recombination in the generation of the maternal age effect on trisomy. However, as the present data set is the first involving a trisomy thought to be entirely maternal age dependent (Risch et al. 1986; Morton et al. 1988), it provides the strongest evidence to date linking aberrant recombination and maternal age–related trisomy. Further, the present data indicate that, at least for chromosome 16, there is an association between aberrant location of recombinational events and maternal age–dependent trisomy. The basis for this association is not yet clear. One possibility, similar to a recent model proposed by Hawley et al. (1994), is that the aging ovary is less able to process certain meiotic configurations.

Specifically, we suggest that, in the "young" ovary, the presence of a single chiasma is usually sufficient to ensure normal segregation. However, with advancing age, normal segregation becomes increasingly dependent on the presence of a proximal, "anchoring" chiasma. In its absence, there might be an increased likelihood that one or both of the homologues will establish its own bipolar spindle; this could result from an age-related defect in a plus-end-directed motor protein, which normally helps to hold the homologous centromeres in close register. As a result, the sister chromatids of one or both homologues separate at meiosis I (i.e., they undergo an equational meiosis I). At meiosis II, the single chromatid segregates randomly, resulting in disomy 16 one-half of the time. Genetically, this disomic oocyte would be indistinguishable from one resulting from "true" meiosis I nondisjunction (i.e., an MI error in which both homologues travel to the same pole).

This model assumes that aberrant recombination is correlated with, but is not the proximal cause of, trisomy 16. Rather, we propose that, with increasing maternal age, specific meiotic configurations are less likely to be properly processed. Thus, our model differs from proposals that suggest that the maternal age effect is established prenatally (e.g., the *production-line* model of Henderson and Edwards 1968) and instead assumes that—at least for trisomy 16—the effect results from factors acting at the time of reinitiation of meiosis I.

Our model also makes certain testable predictions. For example, to explain the high frequency of trisomy 16 relative to other human trisomies, we might expect the chromosome 16 bivalent to have a higher level of pairing abnormalities than other bivalents, particularly in the proximal region. This can be assayed by evaluating chromosome-specific pairing configurations in human fetal pachytene preparations, using the FISH methodology recently described by Cheng and Gartler (1994). Second, we would expect that, in cytogenetic studies of human MII oocytes, whole chromatid abnormalities would preferentially involve chromosome 16 and that these would increase in frequency with increasing age of the woman. Recent studies by Angell and her colleagues (e.g., Angell 1994; Angell et al. 1994) provide preliminary evidence consistent with this prediction. Third, in studies of recombination in trisomy 16 fetuses, we would expect recombination levels to be normal for chromosomes other than chromosome 16; this distinguishes our model from the *production-line* hypothesis (Henderson and Edwards 1968), which predicts an overall reduction in recombination in trisomy-generating meioses. This can be tested by using a conventional linkage approach to study recombination on all chromosomes in trisomy 16 fetuses and their sibs. Finally, we would expect to see age-related changes in the normal female genetic map of chromosome 16. That is, if advancing maternal age increases the likelihood that a specific type of chromosome 16 bivalent (i.e., one deficient in recombination in proximal 16p, 16q, or both) falls into the nondisjunctional pool, there should be a relative increase in proximal recombination in the normal meioses. This effect may be below present detection levels, since available linkage resources such as the CEPH database only allow analysis of a few hundred meioses. Nevertheless, trisomy 16 is estimated to occur in 4% of clinically recognized pregnancies involving women ⩾40 years of age; thus, the predicted effect on older women might be substantial.

Summary

The results of our analyses of 62 trisomy 16 fetuses indicate that most, if not all, cases of trisomy 16 arise from nondisjunction at maternal meiosis I. Further, our studies of genetic recombination provide evidence of an important predisposing factor, namely, diminished recombination in the proximal regions of chromosome 16. On the basis of these findings, we propose a model of age-dependent chromosome 16 nondisjunction and suggest some predictions that it should fulfill. Our results provide strong evidence that the effect of maternal age on trisomy 16 is linked to the frequency and location of recombinational events. Further studies of recombination in this and other trisomies may lead to an eventual understanding of some of the causes of age-dependent human nondisjunction.

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