Association between Maternal Age and Meiotic Recombination for Trisomy 21

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Altered genetic recombination has been identified as the first molecular correlate of chromosome nondisjunction in both humans and model organisms. Little evidence has emerged to link maternal age—long recognized as the primary risk factor for nondisjunction—with altered recombination, although some studies have provided hints of such a relationship. To determine whether an association does exist, chromosome 21 recombination patterns were examined in 400 trisomy 21 cases of maternal meiosis I origin, grouped by maternal age. These recombination patterns were used to predict the chromosome 21 exchange patterns established during meiosis I. There was no statistically significant association between age and overall rate of exchange. The placement of meiotic exchange, however, differed significantly among the age groups. Susceptible patterns (pericentromeric and telomeric exchanges) accounted for 34% of all exchanges among the youngest class of women but only 10% of those among the oldest class. The pattern of exchanges among the oldest age group mimicked the pattern observed among normally disjoining chromosomes 21. These results suggest that the greatest risk factor for nondisjunction among younger women is the presence of a susceptible exchange pattern. We hypothesize that environmental and age-related insults accumulate in the ovary as a woman ages, leading to malsegregation of oocytes with stable exchange patterns. It is this risk, due to recombination-independent factors, that would be most influenced by increasing age, leading to the observed maternal age effect.

Introduction

Common themes concerning the origin and etiology of chromosomal aneuploidy are at last beginning to emerge, aided by studies comparing the different chromosomal conditions (reviewed by Hassold and Hunt [2001]). Meiotic errors of the oocytes predominate, especially errors originating at the first meiotic stage. In addition, most, if not all, human trisomies are affected by increasing maternal age, although the magnitude of the effect varies between different classes of trisomy (Risch et al. 1986; Morton et al. 1988). In general, the percentage of trisomies among all clinically recognized pregnancies climbs from 2% for women <25 years of age to 35% for women >40 years of age (Hassold and Chiu 1985).

Altered genetic recombination has been identified as a risk factor as well. In model organisms, absent or reduced levels of recombination, along with suboptimally placed recombinant events, increase the likelihood of malsegregation (Rasooly et al. 1991; Moore et al. 1994; Sears et al. 1995; Zetka and Rose 1995; Koehler et al. 1996; Ross et al. 1996; Krawchuk and Wahls 1999). Exchanges too close to the centromere or too close to the telomere seem most susceptible to error. The association between altered meiotic recombination and trisomy has been confirmed in human nondisjunction, and significant reduction in recombination has been found for all meiosis I (MI)–derived trisomies studied to date, including trisomies 15, 16, 18, 21, and X of maternal origin and trisomy 21 and Klinefelter syndrome (47 XXY) of paternal origin (Hassold et al. 1991, 1995; Lamb et al. 1996, 1997*a*; Bugge et al. 1998; Robinson et al. 1998; Savage et al. 1998; Thomas et al. 2001).

Previous studies of maternal MI-derived trisomy 21 estimated that 40% of the cases were derived from oocytes in which no meiotic exchange had occurred along chromosome 21 (Lamb et al. 1996, 1997*a*). Of those maternally derived MI cases that did undergo single exchange, the majority of the exchanges were located in the distal 6.5 Mb of the chromosome. In addition, so-called meiosis II (MII)–derived cases were highly associated with pericentromeric exchanges, or those that occurred within the most centromeric 3.5 Mb of chromosome 21. This association led to the hypothesis that many of the cases classified as MII were actually the result of errors initiated in MI. Thus, similar to what is observed in experimental organisms, telomeric or

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pericentromeric exchanges increase the susceptibility of nondisjunction for human chromosome 21.

A key unanswered question concerns the potential association between maternal age and altered recombination patterns. Previous studies of trisomy 21 failed to identify any such association; however, the sample size was relatively small with respect to the amount of variation in recombination along this short chromosome (Lamb et al. 1996). Intriguingly, studies of other chromosomes have raised the possibility of a connection between maternal age and recombination. In examining chromosome 15 nondisjunction, Robinson et al. (1998) found that the age of the mother was significantly higher among maternal MI-derived errors with multiple recombinants versus those with zero or only one detectable recombinant. This finding suggested that cases with multiple recombinants might be more resistant to nondisjunction because of an increase in bivalent stability. Similarly, an analysis of maternal nondisjunction of the X chromosome showed that the mean maternal age of cases with recombination was significantly older than that of cases with no recombination (Thomas et al. 2001). This same pattern was observed for trisomy 18, although the difference was not statistically significant (Bugge et al. 1998). However, there was no association between maternal age and the position of exchanges along the nondisjoined chromosome, for either trisomy 18 or trisomy of the maternal sex chromosome.

An association between maternal age and recombination has also been identified among the normally disjoining population (Kong et al. 2004). On the basis of genomewide microsatellite data compiled from >23,000 individuals, a positive correlation was identified between maternal age and the level of maternal recombination, determined from live-birth offspring. Kong et al. (2004) suggest not that the recombination rate of eggs increases with maternal age but rather that the apparent increase is the consequence of selection—that is, high recombination counts decrease the likelihood of nondisjunction and thereby increase the chance of a gamete becoming a live birth. It is important to note that this maternal age effect is very slight, estimated at two additional recombinants across the entire genome over a 25-year period.

The number of maternal MI-derived trisomy 21 cases available for analysis has tripled since the last analyses of exchange and age (Lamb et al. 1996, 1997*a*). Additionally, the physical map of chromosome 21 has been completed (Hattori et al. 2000), allowing meiotic exchange intervals to be determined with a greater degree of accuracy. As a result, the current trisomy 21 population can be subdivided by maternal age at the time of conception, and the exchange analyses can be determined for each age group.

Subjects and Methods

Trisomic Sample

Families with an infant with free trisomy 21 were ascertained through a multisite study of risk factors associated with nondisjunction (Lamb et al. 1996, 1997*a*). This multisite study has been approved by all of the necessary institutional review boards, and informed consent was obtained from all participating families. Only those families with biological samples from both of the parents and the infant were included in this study. Each family was genotyped for a battery of chromosome 21–specific STR markers that span 21q. A core set of markers was used to establish parental origin, and conclusions were based on at least two informative loci. Subsequently, the type of nondisjunction error was determined on the basis of the genotype of the most pericentromeric informative marker from our panel (centromere-*D21S369-D21S215-D21S258-D21S120-D21S1911-D21S16-D21S192*). Specifically, if parental heterozygosity was retained in the trisomic offspring ("nonreduction"), an MI error was inferred.

To characterize recombination, chromosome 21 was divided into six roughly equal physical intervals (fig. 1). The recombination profile was determined by typing a subset of markers from a master set of 46 polymorphic markers spanning chromosome 21q. Generally, between

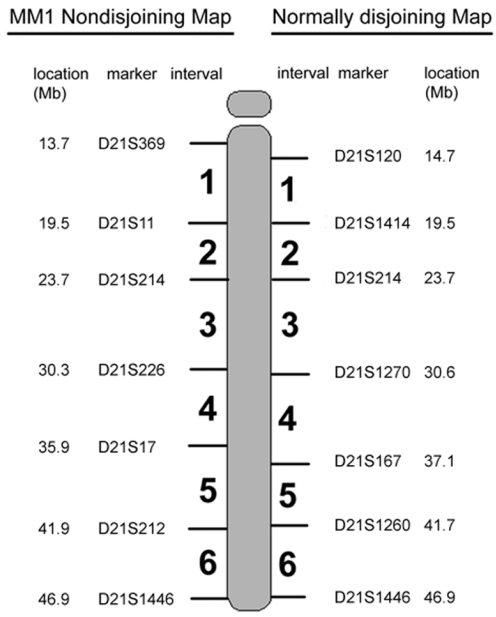

Figure 1 Comparison of 21q interval boundaries between trisomic and normally disjoining samples. Interval distances for chromosome 21 markers are taken from the Ensembl Genome Browser (see Ensembl Web site), in which the "0 bp" position is at the telomere of the p arm and the most centromeric contig for the q arm begins at 13.3 Mb.

Table 1

Observed Frequency of Chromosome 21q Recombination Patterns

Sample Group	No. (%) of Subjects with		
	0 Observed Recombinants	1 Observed Recombinant	⩾2 Observed Recombinants
Trisomic, with maternal age (in years) of:			
<29 (n = 126)	91 (72)	24 (19)	11 (9)
29–34 (n = 138)	84 (61)	44 (32)	10 (7)
>34 (n = 136)	93 (68)	32 (24)	11 (8)
Normally disjoining (n = 92)	48 (52)	38 (41)	6 (7)

10 and 30 markers were typed for each family. A recombinant was defined as a transition from nonreduction to reduction of homozygosity (or vice versa) among the ordered set of markers along 21q. We included only families who had at least one informative marker in every interval. The resulting 400 cases of maternal MI-derived trisomy 21 were then subdivided into three groups on the basis of the age of the mother at the time of conception: mothers <29 years of age (n = 126), mothers 29–34 years of age (n = 138), and mothers >34 years of age (n = 136).

Normally Disjoining Sample

For comparison, 92 normally disjoining female meiotic events were obtained from eight CEPH families (1331, 1332, 1347, 1362, 1413, 1416, 884, and 102), by use of the Marshfield genotype database (see Marshfield Web site). All individuals were white. Although the maternal ages for these events were not available to us, studies published elsewhere have found no association between the amount of recombination and maternal age in these families (Broman et al. 1998).

As a result of differences in marker panels, the interval definitions between the trisomic and normally disjoining samples differed slightly. We attempted to minimize differences by choosing markers in the normal sample that were closely linked to and had the same heterozygosity level as those used in the trisomic sample (fig. 1). However, the Marshfield data set lacks markers near the centromere. As a result, a 1-Mb pericentromeric region extending to marker *D21S120* could not be measured among normally disjoined chromosomes. In addition, the boundary between intervals 4 and 5 was fairly different for the two data sets, with interval 5 covering 4.6 Mb for the normally disjoining sample, versus 5.9 Mb for the trisomic sample.

Genetic Maps

For the normally disjoining sample, a genetic map was created directly on the Marshfield Web site by use of female map distances and the Kosambi map function. For the trisomic age groups, we estimated maps by multipoint methods implemented in the program NDJMap (Feingold et al. 2000) and then applied the Kosambi map function to convert the recombination fractions into map distances.

Calculation of Exchange Distributions

The spatial distribution of observed recombination was used to infer the spatial distribution of exchanges occurring at the four-strand stage of meiosis, by use of the methods initially described by Lamb et al. (1997*b*) and extended by Yu and Feingold (2001, 2002). We used a version of the analysis (described by Yu and Feingold [2002]) that handles ambiguous recombination patterns by use of an estimation-maximization algorithm.

For the normally disjoining events, we used the CHROMPIC option of CRIMAP software to identify the locations of recombination events. For the trisomic events, locations of recombination events were identified by inspection of the genotyped marker data.

Statistical tests to determine whether there were differences in exchange patterns between age groups and between trisomic and normal disjoining samples were performed using likelihood-ratio tests as described by Yu and Feingold (2002). Because of the boundary conditions in the estimation, P values for the tests were estimated using bootstrap methods explained by Yu and Feingold (2002).

Results

Recombination-Based Maps of Chromosome 21

We took several approaches to determine whether the recombination differences among nondisjoined chromosomes 21 were related to maternal age. To begin, genetic maps were created for each age group as well as for the normally disjoining sample. Consistent with previous reports (Warren et al. 1987; Lamb et al. 1996), the genetic maps of maternal MI-derived trisomy 21 were all shorter than the standard chromosome 21 map, indicating less recombination among the trisomic cases (fig. 2*a*). Although the map distances vary somewhat, there were no significant differences in the overall amount of recombination across the age groups (P = .38). However, by standardizing the maps to show the

Table 2

Overall Exchange Distribution of Inferred Meiotic Exchange for Trisomic and Normally Disjoining Samples

Sample Group	Frequency in Sample for		
	0 Overall Exchanges	1 Overall Exchange	⩾2 Overall Exchanges
Trisomic, with maternal age (in years) of:			
<29	.52	.32	.16
29–34	.29	.57	.14
>34	.45	.39	.16
Normally disjoining	.16	.58	.26

relative size of each chromosome interval, a clear difference in the placement of recombination was observed (fig. 2*b*). On the basis of previous studies, we identified the telomeric region (interval 6) as most likely to predispose for nondisjunction (Lamb et al. 1996, 1997*a*). The youngest trisomic group exhibited the highest proportion of susceptible telomeric recombination (37%), compared with the middle (28%) and oldest (24%) age groups. All proportions were larger than that observed for the normally disjoined map (4%). Similarly, the proportion of susceptible pericentromeric recombination, also identified as predisposing for nondisjunction, decreased with increasing age (fig. 2).

Recombination maps do not, however, allow for a distinction to be made between single- and multiple-exchange events. This makes it difficult, for example, to discern whether the increase in pericentromeric exchange is due to an increased proportion of pericentromeric single or double exchanges. To identify specific patterns of meiotic exchange, we turned to tetrad analysis.

Estimates of Meiotic Exchange for Chromosome 21

To obtain a more detailed examination of the patterns of recombination, the number and placement of exchanges at the four-strand stage of meiosis was inferred from the observed transition data for all groups (tables 1 and 2). This yields an estimate of the sample frequency of every possible exchange pattern—for example, exchange in interval 1 only or exchange in intervals 2 and 5. We use these estimates to study exchange patterns. Several hypotheses were tested using these patterns; the *P* values for each comparison are given in table 3.

With respect to the overall number of exchanges, the frequency distributions of all three trisomic groups were significantly different from that of the normally disjoining sample (first row of table 3). The frequency distributions of the trisomic groups were not significantly different from each other. The largest proportion of achiasmate bivalents (52%) was observed in the youngest age group. The proportion of achiasmate bivalents decreased in the middle age group (29%) and then increased in the oldest age group (45%), although these differences were not significant. It is worth noting that, among the normally disjoining sample, 16% of the meiotic tetrads were inferred to be achiasmate (table 2). This value is within the error bounds of other published studies examining exchange (Yu and Feingold 2002). Although it has been generally accepted that achiasmate tetrads are a risk factor for nondisjunction, it is not absolutely clear whether these tetrads are present at some level among the normally disjoining population.

As observed among the genetic maps, the location of the exchanges varied significantly with age. The spatial distribution of all exchanges for the normally disjoining sample was significantly different from that of each of the trisomic age groups (second row of table 3). The spatial distribution was significantly different between the youngest trisomic group and both the middle and oldest trisomic groups but was not significantly different between the middle and oldest trisomic groups. With increasing age, the overall distributions began to approximate that found among the normally disjoining sample. For example, consider the spatial distribution of single exchanges shown in figure 3. Among the youngest age group, nearly 80% of the single exchanges occurred in the most telomeric interval. Among the other age groups, the distribution shifts toward the center of the chromosome, away from the most susceptible region. Of single exchanges among the middle and oldest age groups, 33% and 14% occur in the most telomeric region, respectively. For all three trisomic groups, the distribution of single exchanges is significantly different from that for the normally disjoining sample; however, the degree of significance declines with increasing age (third row of table 3).

The location of the most centromeric exchange (i.e., the location of a single exchange or of the most proximal exchange for a two-exchange bivalent) provides another way to examine spatial distribution (fig. 4). This approach allows an examination of single exchanges at the telomere together with single or double exchanges that involve the pericentromeric region. Susceptible exchange patterns (either single exchange at the telomere or any exchange at the pericentromere) occurred 78% of the time for the youngest trisomic group, compared with

Table 3

***P* Values of Hypothesis Tests Involving Exchange Frequency and Placement**

	P Value for Groups					
Test	Normal vs. Youngest Trisomic	Normal vs. Middle Trisomic	Normal vs. Oldest Trisomic	Youngest Trisomic vs. Middle Trisomic	Youngest Trisomic vs. Oldest Trisomic	Middle Trisomic vs. Oldest Trisomic
Frequency distribution of all exchanges	.01	.03	.05	.08	.77	.28
Spatial distribution of all exchanges	.0005	.0005	.0005	.001	.0005	.11
Spatial distribution of single exchanges	.01	.02	.04	.006	.0005	.34
Spatial distribution of most-centromeric exchanges	.0005	.0005	.05	.001	.001	.34

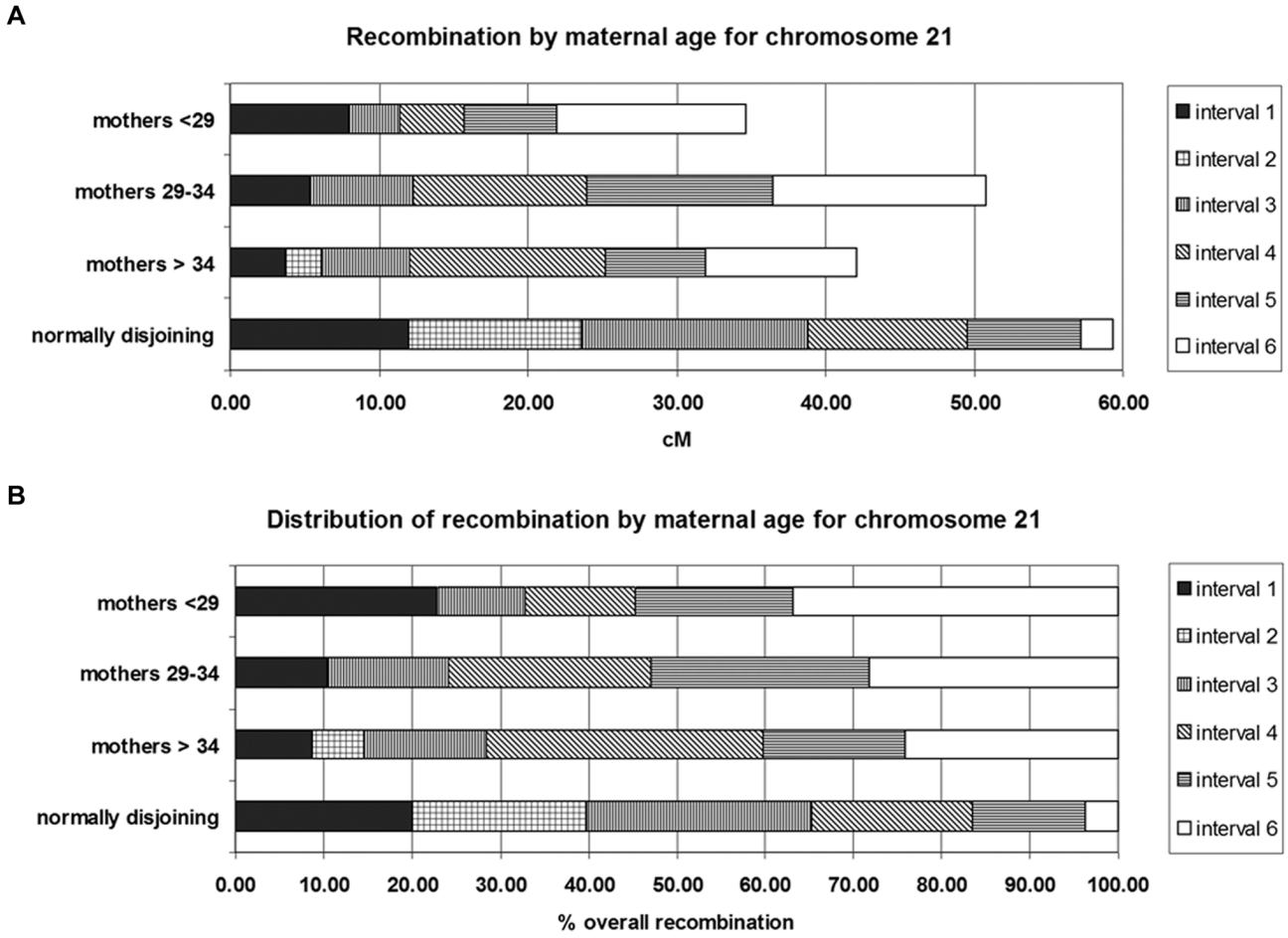

Figure 2 Recombination-based genetic maps of 21q for trisomic and normally disjoining samples. Genetic maps were created either directly on the Marshfield Web site (normally disjoining sample) or by use of the program NDJMap followed by application of the Kosambi map function to convert recombination fractions into map distances (trisomic sample). *a,* Overall map lengths divided into the six chromosome 21 intervals. *b,* Relative contribution of each interval to the entire map length.

34% for the middle age group and 19% for the oldest group. For all three trisomic age groups, the distribution was significantly different from that for the normally disjoining sample. However, as described for the single-exchange distribution, the level of significance declined with increasing age (bottom row of table 3).

Discussion

This study identifies the first association between advancing maternal age and location of genetic recombination, the two most important risk factors for chromosome 21 nondisjunction that have been identified. Altered patterns of recombination appear to exert their greatest effects on nondisjunction at a younger age. As women age, the proportion of trisomic cases exhibiting susceptible exchange configurations decreases and, among the oldest group, the distribution of exchange placement moves strikingly in the direction of that observed among a normally disjoining sample.

We postulate that multiple risk factors, some age dependent and others age independent, lead to nondisjunction. In a young woman, meiotic machinery (spindles, sister-chromatid adhesive proteins, microtubule motor proteins, etc.) functions optimally and correctly segregates all but the most susceptible exchange configurations (achiasmate bivalents and exchanges close to either the centromere or the telomere). For young women, then, the greatest risk factor for nondisjunction is the presence of a susceptible exchange pattern in the oocyte.

As a woman ages, her meiotic machinery accumulates the effects of years of environmental and age-related insults, becoming less efficient and/or more error prone. Suboptimal exchange bivalents are still susceptible to nondisjunction, but even correctly placed bivalents are

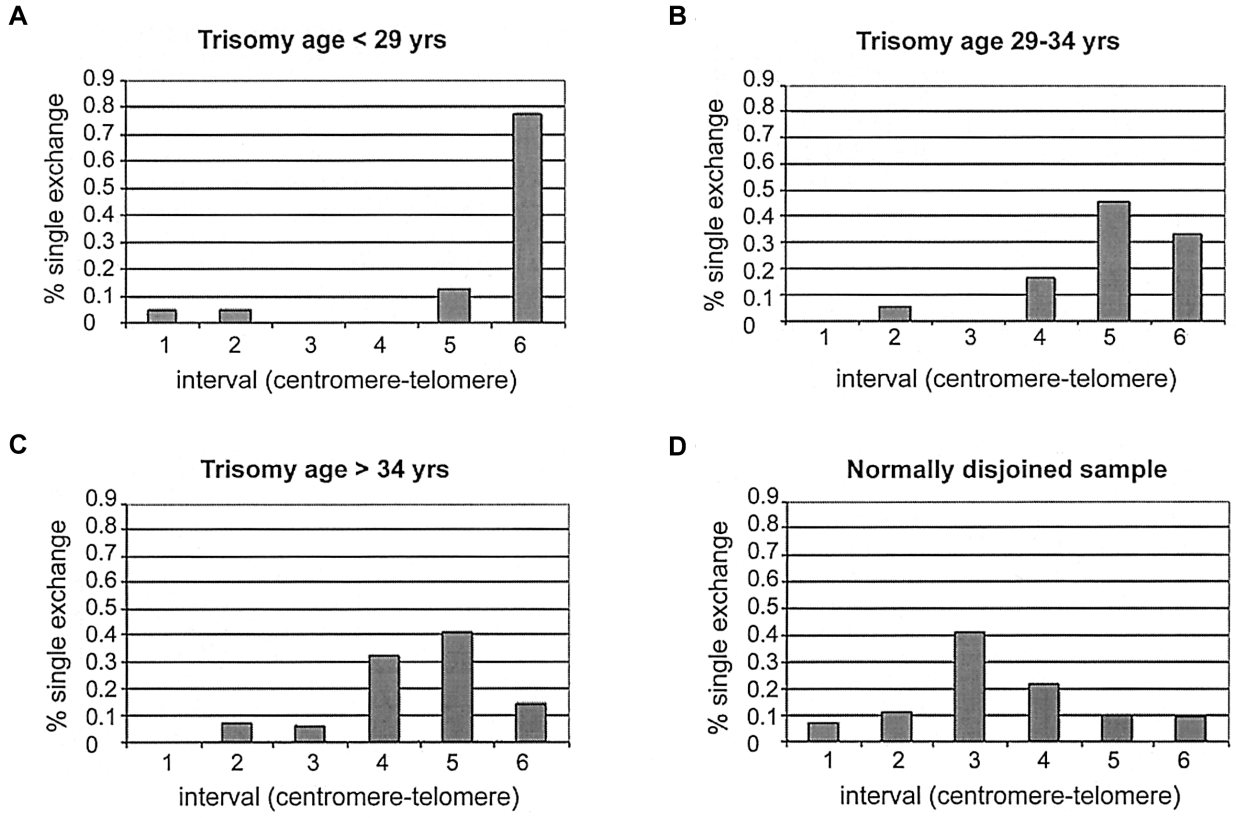

Figure 3 Comparison of single-exchange events along chromosome 21q. The percentage of single exchanges in each chromosome interval is based on predictions from recombination data. The panels show the results of maternally inherited chromosomes that have undergone MI nondisjunction in women aged <29 years (*A*), 29–34 years (*B*), and >34 years (*C*) and chromosomes that segregated normally (*D*).

now at risk. The proportion of nondisjunctions occurring among oocytes with normal exchange configurations increases over time as age-dependent risk factors exert their influence. As a result, the most prevalent exchange profile of nondisjoined oocytes shifts from susceptible to nonsusceptible patterns.

How should these results be viewed against the backdrop of previous studies of maternal age and trisomy? For maternal trisomies 15 and 18 and the maternal sex-chromosome trisomies, maternal age was higher among the cases in which recombination was present compared with the cases in which no recombination was observed (Bugge et al. 1998; Robinson et al. 1998; Thomas et al. 2001). There exists no such age difference among the trisomy 21 population. Rather, the placement of recombination appears to differ with maternal age. As has been noted elsewhere (Hassold and Hunt 2001), whereas altered recombination appears to be a common risk factor for nondisjunction, the magnitude and direction of the alteration seems to vary with the chromosome involved.

These data should also be considered in light of the recent report suggesting the possible presence of stem cells within the mammalian ovary (Johnson et al. 2004). If these stem cells are present, it would suggest that some oocytes are relative newcomers to the ovary, escaping many of the insults that have accumulated over time. The strength of the maternal age effect, however, indicates that a large proportion of oocytes in the aged ovary are undergoing nondisjunction. It is possible that the number of newly created oocytes comprises only a small fraction of the ovary. Alternately, these oocytes may themselves be damaged or susceptible to the aged ovarian environment.

Although maternal MI–derived nondisjunction is a predominant feature of most trisomy, MII–type errors also play an important role, comprising 30% of maternal trisomy 21. Previous studies of these errors also show an association with altered recombination (Lamb et al. 1996), leading to the suggestion that these errors may have actually originated in MI. Although the overall number of MII cases is too small for conclusive findings, preliminary studies have been initiated in the search for an association with maternal age. Interestingly, trisomy 21 resulting from MII-type errors shows an increase in the amount of meiotic exchange with increasing maternal age. The numbers are too small to

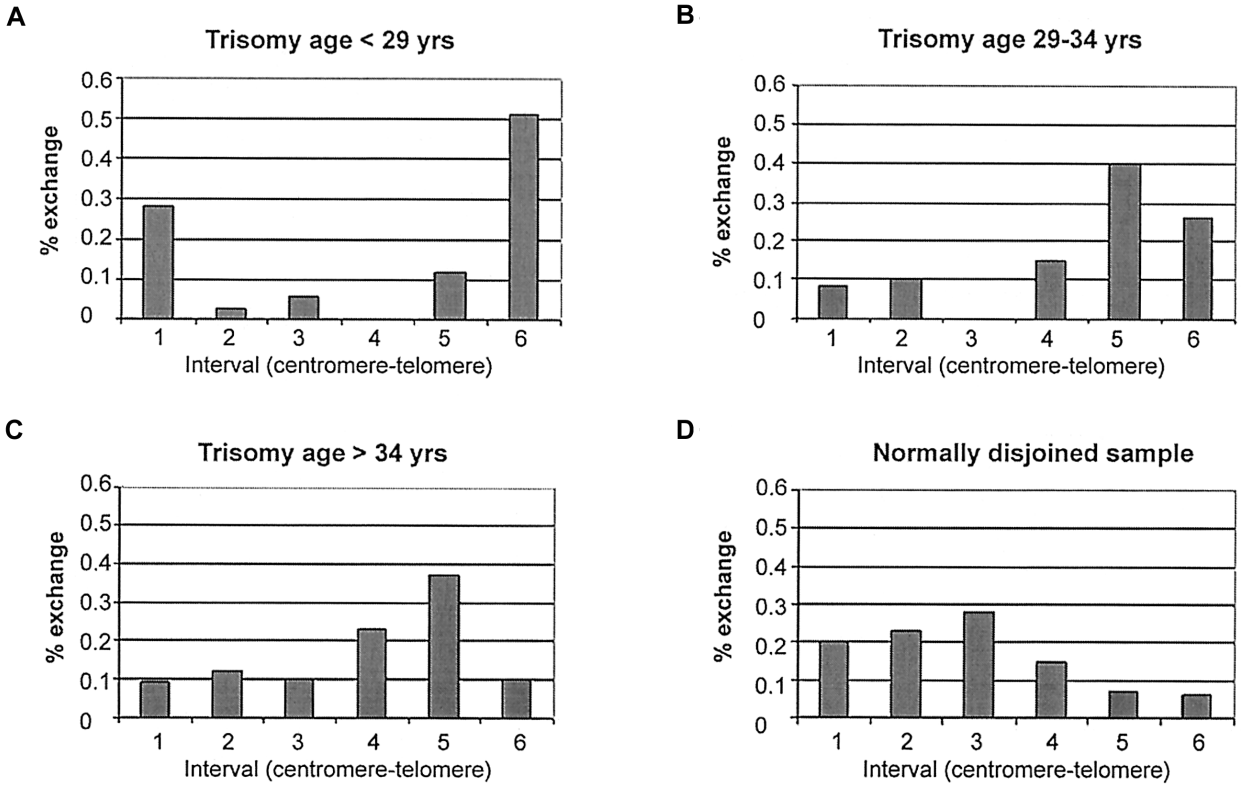

Figure 4 Examination of the location of the most-proximal meiotic exchange events along chromosome 21q. The location of the most proximal exchange was determined for each population, to examine the distance between the centromere and the closest meiotic exchange. The panels show the distribution for maternally inherited chromosomes that have undergone MI nondisjunction in women aged <29 years (*A*), 29–34 years (*B*), and >34 years (*C*) and for chromosomes that segregated normally (*D*).

describe overall spatial distribution with age. Whether these results are robust remains to be seen, but, at the moment, it appears that maternal age may be associated with MII-type trisomy as well.

A limitation of our analysis concerns the inability to subdivide the normally disjoining sample on the basis of maternal age. However, the maternal age effect on genomewide recombination is likely several orders of magnitude lower than the effect on trisomic cases—in fact, its detection required the use of nearly 15,000 meiotic events and only translated into two additional recombinants genomewide across the maternal reproductive lifespan (Kong et al. 2004).

The finding of an association between maternal age and meiotic exchange placement has important implications in the search for additional risk factors of nondisjunction. Our data suggest that the lack of recombination or the altered placement of recombination is a major risk factor, especially among younger women. This observation, together with the altered frequency of recombination noted among trisomies of chromosomes 15, 18, and X, provides a unifying hypothesis: the presence of recombination located medially along the chromosome protects the tetrad against the effects of the aging ovarian environment. The identification of mechanisms that determine recombination frequency and location is the next key step in understanding the process of chromosome nondisjunction.

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Electronic-Database Information

The URLs for data presented herein are as follows:

Ensembl, http://www.ensembl.org/ (for marker distances)
Marshfield, http://research.marshfieldclinic.org/genetics/ (for genotype database)

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