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Report

Obligate Short-Arm Exchange in De Novo Robertsonian Translocation Formation Influences Placement of Crossovers in Chromosome 21 Nondisjunction

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Robertsonian translocations (ROBs) involving chromosome 21 are found in ~5% of patients with Down syndrome (DS). The most common nonhomologous ROB in DS is rob(14q21q). Aberrant recombination is associated with nondisjunction (NDJ) leading to trisomy 21. Haplotype analysis of 23 patients with DS and de novo rob(14q21q) showed that all translocations and all nondisjoined chromosomes 21 were maternally derived. Meiosis II NDJ occurred in 21 of 23 families. For these, a ROB DS chromosome 21 genetic map was constructed and compared to a normal female map and a published trisomy 21 map derived from meiosis II NDJ. The location of exchanges differed significantly from both maps, with a significant shift to a more distal interval in the ROB DS map. The shift may perturb segregation, leading to the meiosis II NDJ in this study, and is further evidence for crossover interference. More importantly, because the event in the short arms that forms the de novo ROB influences the placement of chiasmata in the long arm, it is most likely that the translocation formation occurs through a recombination pathway in meiosis. Additionally, we have demonstrated that events that occur in meiosis I can influence events, such as chromatid segregation in meiosis II, many decades later.

Robertsonian translocations (ROBs) in humans are whole-arm rearrangements between the acrocentric chromosomes 13, 14, 15, 21, and 22. Unbalanced karyotypes involving ROBs cause ~5% of Down syndrome (DS) (Giraud and Mattei 1975), with rob(14q21q) as the most common nonhomologous rearrangement in this population. When ascertained in a newborn or through prenatal testing for reasons other than a familial translocation, ~69% of the cases are new mutations (Shaffer et al. 1992).

The breakpoints of rob(14q21q)s occur in the short arms of the participating chromosomes, leading to dicentric rearrangements (Han et al. 1994; Page et al. 1996; Bandyopadhyay et al. 2002). Because of the location of the rRNA genes on all acrocentric short arms, nonhomologous acrocentric chromosomes are brought into close proximity during the early stages of meiosis I to form the nucleolus and remain in this association throughout meiosis I. Rob(14q21q)s likely form during oogenesis (Page and Shaffer 1997; Bandyopadhyay et al. 2002), and this close association during meiosis may facilitate the exchange in the short arm responsible for ROB formation. We speculate that this obligate short-arm event leading to the formation of the ROB may influence the segregation of the homologues or sister chromatids. One such mechanism could be the alteration of the recombination pattern along the long arm of chromosome 21, which may increase the risk for malsegregation of the ROB from the free-lying homologous chromosomes or sister chromatids, leading to nondisjunction (NDJ).

One important role of recombination is to ensure proper segregation of chromosomes during meiosis. The frequency and location of recombination has been shown to be aberrant in most human trisomies (Warren et al. 1987; Sherman et al. 1991, 1994; Koehler et al. 1996; Lamb et al. 1996, 1997; Hassold and Sherman 2000).

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For example, trisomy 21 originating in maternal meiosis I is associated with a decrease in recombination, especially in the proximal regions near the centromere, resulting in an overall shorter map length as compared with the normal chromosome 21 map (Sherman et al. 1994; Koehler et al. 1996; Lamb et al. 1996). Alternatively, trisomy 21 of maternal meiosis II origin is associated with an increase in proximal recombination, resulting in an overall longer chromosome 21 map length (Koehler et al. 1996; Lamb et al. 1996). We investigated whether the obligate short-arm event involved in de novo ROB formation influenced the chromosome 21 map length and/or the location of the exchanges of the nondisjoined chromosomes 21.

The study population included 23 individuals with three copies of chromosome 21 (Down syndrome) associated with a de novo rob(14q21q) (46,XX,rob(14;21)(q10;q10),+21 or 46,XY,rob(14;21)(q10;q10),+21) and their chromosomally normal parents. For three families, the father was not available (table 1). Informed consent was obtained from each of the families using a Baylor College of Medicine Institutional Review Board–approved protocol.

The parental origins of the nondisjoined chromosomes 21 were determined by comparing fully informative, microsatellite polymorphisms in total genomic DNA of the parents to the total genomic DNA of the child, as described elsewhere (Shaffer et al. 1993). The parental origins of the de novo rob(14q2q) translocations were determined using somatic cell hybrid analysis as described elsewhere (Page and Shaffer 1997) (fig. 1). Previous studies have shown that most de novo ROBs are of maternal origin, probably forming prior to or during meiosis I in oogenesis (Petersen et al. 1991; Shaffer et al. 1992; Page and Shaffer 1997; Bandyopadhyay et al. 2002). In the current study, all chromosomes comprising the translocations were of maternal origin and, thus, originated from a single parent. The likelihood that these ROBs occurred during meiosis is high because a postzygotic model would predict a random assortment of possible translocations with 50% of ROBs comprising a maternal and a paternal chromosome, 25% comprising two maternal chromosomes, and 25% comprising two paternal chromosomes (Page and Shaffer 1997; Bandyopadhyay et al. 2002). This postzygotic model can be rejected in the current study in favor of a meiotic model for ROB formation ($\chi^2_2 = 69$; $P < .0001$). These findings support the previous data suggesting that rob(14q21q) formation occurs primarily during oogenesis (Page and Shaffer 1997; Bandyopadhyay et al. 2002). The nondisjoined chromosomes 21 were also of maternal origin in each

Table 1

Haplotypes in Patients with rob(14q21q),+21 in Which the Father's DNA Was Unavailable

			Haplotypes in Family					
			21		22		23	
Marker	Location	Heterozygosity	Mother	Child	Mother	Child	Mother	Child
D21S369	21q11.1	.70	1 2	1 1 1	2 2	1 2 2	1 1	1 1 2
D21S215	21q11.1	.68	1 2	2 2 2	1 1	1 1 1	1 2	1 1 2
D21S258	21q11	.87	1 2	1 2	1 3	1 1 2	**1** 2	**1** 1 3
D21S120	21q11.2	.75	1 1	1 1 1	1 1	1 1 1	1 1	1 1 1
D21S16	21q11	.69	1 2	2 2 2	2 2	1 2 2	1 1	1 1 1
D21S13E	21q11.2	.69	1 1	1 2	1 1	1 1 2	2 3	1 2 2
D21S192	21q11	.54	1 1	1 1 1	1 1	1 1 2	1 2	2 2 2
D21S11	21q21	.90	1 2	1 2 2	1 2	2 2 3	2 2	1 2 2
D21S214	21q21	.82	1 1	1 1 1	1 2	1 2	1 2	1 2 2
D21S232	21q21	.68	1 1	1 1 2	1 1	1 1 2	**1** 2	**1** 2 3
D21S210	21q21	.86	1 2	1 2 2	1 3	1 2 3	1 1	1 1 2
D21S213	21q21	.74	1 2	1 2 2	**2** 3	1 **2** 3	1 2	1 2 2
D21S223	21q22.1	.80	1 1	1 2	2 2	1 2 2	1 1	1 1 1
D21S224	21q22.1	.74	1 2	1 2 2	1 2	1 2 3	1 1	1 1 1
IFNAR	21q22.1	.83	1 1	1 1 2	1 2	1 2 2	1 2	1 1 2
D21S167	21q22.2	.82	1 2	1 2 2	**2** 3	1 **2** 3	1 2	1 1 2
D21S156	21q22.3	.84	1 3	1 1 2	2 3	1 2 3	1 3	1 2 3
D21S168	21q22.3	.76	**1** 3	**1** 1 2	1 1	1 2	1 2	1 1 1
HMG14	21q22.3	.74	1 2	2 2 2	1 3	1 2 3	1 2	1 2
D21S212	21q22.3	.86	2 **3**	1 **3** 3	1 2	1 2	1 2	1 1 1
D21S1446	21qter	.79	1 2	1 2 2	1 1	1 2	1 2	1 2

Note.—A paternal DNA sample was not available for three of the families. However, the haplotypes in these cases, constructed from a large number of markers and analysis of some markers in somatic cell hybrids containing the ROB, are consistent with two chromosomes 21 originating from the mothers. Underlined, boldface alleles are known by somatic cell hybrid analysis to be inherited on the chromosome 21 in the rob(14q21q).

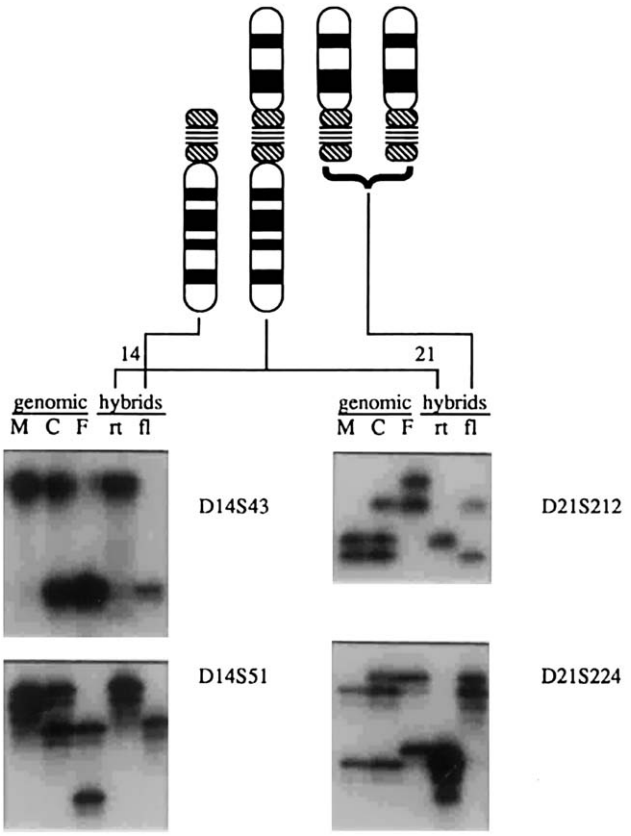

Figure 1 Somatic cell hybrid analysis. Parental origins of the chromosomes comprising the ROB were determined by comparing informative microsatellite marker genotypes in the parents (M, F) and the genomic DNA of the child (C) to the haplotypes of the somatic cell hybrids isolating the ROB (rt) from its free-lying homologues (fl). Each chromosome of the translation was analyzed with two markers. In this figure, a somatic cell hybrid was constructed that contained both free-lying chromosomes 21. The results show that one chromosome 21 is of maternal origin and one is of paternal origin. The chromosomes in the ROB (both chromosomes 14 and 21) were found to be of maternal origin. The free-lying chromosome 14 was of paternal origin.

of the 23 individuals studied. This may indicate that the events of de novo ROB formation and NDJ are somehow interrelated.

The stage of NDJ was inferred by analyzing pericentromeric (proximal), microsatellite markers for chromosome 21 (marker groups A or B; see table 2) involved in the de novo ROB and the chromosome 21 contributed by the same parent. Markers that are heterozygous in the parent of origin can be used to identify the stage of NDJ. The retention of heterozygosity (nonreduction) in the nondisjoined chromosomes infers a meiosis I error, compatible with failure of the homologous chromosomes to separate. Reduction of parental heterozygosity to homozygosity (reduction) in the individual with de novo rob(14q21q) DS suggests a meiosis II NDJ (failure of sister chromatids to separate). The vast majority of NDJ of chromosome 21 resulting in free-lying trisomy 21 is maternal, with most resulting from meiosis I errors (reviewed in Koehler et al. 1996). In contrast to free-lying trisomy 21, the stage of NDJ was consistent with meiosis I in only 2 of the 23 individuals studied and was consistent with meiosis II in the remaining 21 individuals.

Previous studies of free-lying trisomy 21 have shown that there is aberrant recombination associated with NDJ of chromosome 21 (Sherman et al. 1994; Koehler et al. 1996; Lamb et al. 1996, 1997; Hassold and Sherman 2000). The differences in recombination observed in the previous studies were both in frequency and in location (Sherman et al. 1994; Koehler et al. 1996; Lamb et al. 1996). To examine the frequency and location of recombination in our study subjects, we generated a ROB-associated DS chromosome 21 genetic map. Using

Table 2

PCR-Based Microsatellite Markers for Chromosome 21 Genetic Studies, Grouped into Megaloci

Megalocus and Locus	Physical Location	Grouped Intervals
A:		
D21S369	21q11.1	1
D21S215	21q11.1	1
B:		
D21S258	21q11	1
D21S120	21q11	1
C:		
D21S16	21q11	1
D21S13E	21q11	1
D21S192	21q11	1
D:		
D21S11	21q11	2
E:		
D21S214	21q11	2
D21S232	21q11	2
F:		
D21S210	21q11	2
G:		
D21S213	21q11	3
H:		
D21S223	21q22.1	3
D21S224	21q22.1	3
IFNAR	21q22.1	3
I:		
D21S167	21q22.2	3
J:		
D21S156	21q22.3	4
D21S168	21q22.3	4
HMG14	21q22.3	4
K:		
D21S212	21q22.2-qter	4
L:		
D21S1446	21qter	4

NOTE.—Megaloci are those markers with almost no observed recombination.

21 polymorphic microsatellite markers (table 2), chromosome 21 was divided into 12 regions (megaloci), each defined as a group of markers known to be tightly linked in normal individuals. Recombination was assessed in each of the individuals with translocation DS, as described elsewhere (Sherman et al. 1994). Genotype intercrosses, such as ab × ab, may result in ambiguous outcomes; however, with the appropriate hybrids (i.e., a hybrid isolating the ROB and a hybrid isolating the maternal free-lying homologous chromosome 21 from the ROB), many of these intercrosses were informative.

A centromere-gene mapping approach was used to estimate genetic distances and LOD scores between all possible pairs of markers representing the different regions of chromosome 21. Maximum-likelihood estimates (MLE) of the probability of nonreduction between all pairs of markers were obtained. The MLE was determined from the total number of informative nondisjoined chromosomes 21 associated with a de novo rob(14q21q). Recombination fractions and LOD scores were calculated from the estimated probability of nonreduction, assuming interference with, at most, two chiasmata within any interval (Morton and MacLean 1984), using the computer program TETRAD. The interval distances between adjacent markers were estimated from the recombination fractions, and the significance of the recombination fractions was tested by their LOD scores for all pairwise combinations of markers using the program MAP (Morton and Andrews 1989) (table 3).

The fact that the frequency of meiosis II NDJ among the trisomy 21 cases associated with de novo ROB formation is strikingly different than that seen in free-lying trisomy 21, in which most cases originated in maternal meiosis I, suggests that ROB formation is influencing sister chromatid segregation. We reasoned that if the meiosis II NDJ was occurring independent of ROB formation, the frequency and location of recombination events in these cases would be similar to that found in meiosis II NDJ, resulting in free-lying trisomy 21, and that alterations from this expectation may indicate the effect of ROB formation on recombination and malsegregation. Thus, de novo ROB formation through an obligate exchange in the short arms of the acrocentric chromosomes may be analogous to proximally (centromeric) placed recombination that predisposes to meiosis II NDJ. To examine this possibility, recombination along the length of chromosome 21 was assessed for ROB-associated DS. In 17 of the 21 meiosis II cases, one exchange was observed. Three showed two exchanges, and one had no exchanges (case 21). The father was not available for the study subject who showed no exchanges, and many of the genetic markers were uninformative (table 1).

To determine if the amount of recombination differed between chromosomes 21 involved in normal segregation and ROB-associated NDJ, the overall genetic length of the maps was compared assuming a constant interval-distance ratio, k, between the two maps, as described elsewhere (Sherman et al. 1994). Comparisons were made between the normal chromosome 21 map generated from the CEPH families, the ROB-associated nondisjoined chromosome 21 map generated in this study, and the nondisjoined chromosome 21 meiosis II trisomy map based on data from Lamb et al. (1996). The "normal" genetic linkage map for chromosome 21 based on CEPH linkage data (derived using CRI-MAP) has been published elsewhere (Lynn et al. 2000) and used for this type of comparison (Lamb et al. 1996). If there is no association between recombination and NDJ, the interval-distance ratio should equal 1.0. Comparisons were made between the overall genetic map lengths of normal disjoined chromosomes 21, nondisjoined chromosomes 21 during meiosis II, and nondisjoined chromosomes 21 associated with de novo ROB formation. To determine if there were differences in the distribution of exchanges, the distances for each map interval were examined, and the ratios were compared between maps. The ratio for each interval should be constant if there are no significant changes in the distribution. To perform this analysis, maps were generated with each map interval estimated independently, as described elsewhere (Sherman et al. 1994). Although the ROB DS map is somewhat longer than the normal female chromosome 21 genetic map, no significant difference in the total length was identified ($k = 1.07 \pm 1.11$; $\chi^2_1 = 0.43$; $P > .10$). However, the distribution of exchanges was significantly different between these two maps ($\chi^2_{10} = 27.40$; $P < .005$), with an increased number of exchanges occurring in the middle of the long arm on the ROB DS map (fig. 2). The comparison between the meiosis II trisomy 21 map and the ROB DS map showed that the meiosis II trisomy

Table 3

Genetic Distances between Megaloci

	Genetic Distances between Megaloci (cM)		
Megaloci	Normal Female	Meiosis II	ROB-associated
A and B	3.4	10.1	.001
B and C	3.8	9.5	.001
C and D	11.1	27.0	6.8
D and E	7.8	18.4	5.2
E and F	4.6	7.3	4.0
F and G	11.8	11.0	23.4
G and H	2.5	.001	7.5
H and I	7.1	13.4	10.1
I and J	3.3	5.6	10.4
J and K	11.9	17.2	25.4
K and L	3.7	6.2	.001

Note.—Megaloci are those markers with almost no observed recombination. Distances were estimated between megaloci assuming a unique interval-distance ratio.

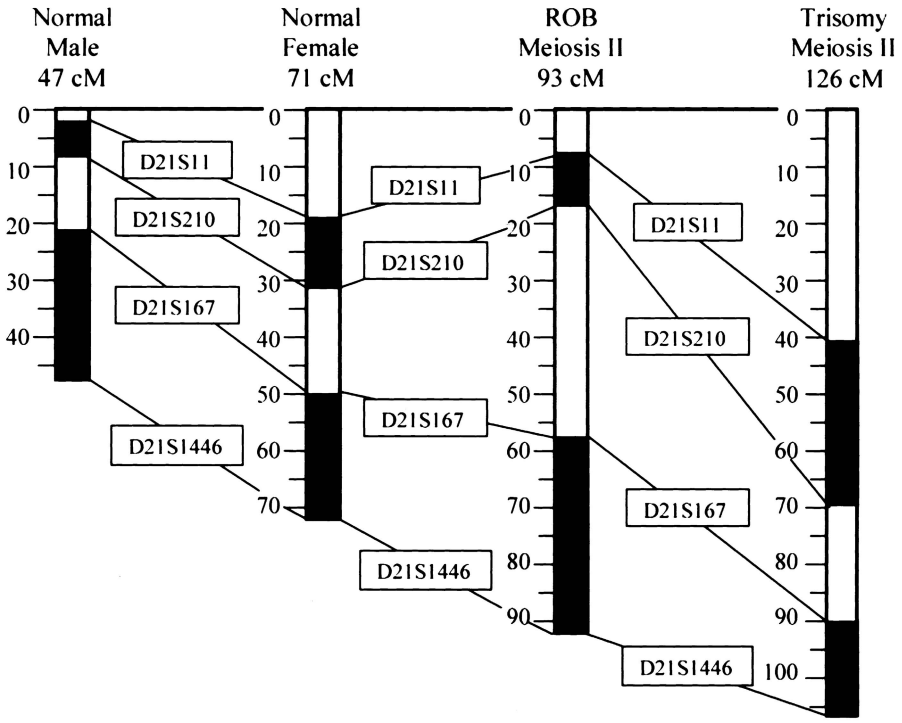

Figure 2 Comparison of the ROB DS map to other chromosome 21 maps. The following chromosome 21 maps are compared: normal male map, normal female map, ROB meiosis II map, and the trisomy 21 meiosis II map. Total map lengths of each are shown at the top (cM). The four separate regions represent the distance between the following markers from the centromere to the end of the long arm of chromosome 21: D21S369–D21S11, D21S11–D21S210, D21S210–D21S167, and D21S167–D21S1446. The distances were measured in cM and were estimated using a unique interval-distance ratio between each megalocus.

map was significantly longer ($k = 1.70 \pm 0.20$; $\chi^2_1 = 19.18$; $P < .001$) and had a different distribution of exchanges ($\chi^2_{10} = 48.33$; $P < .001$), with the exchanges shifted to a more distal interval on the ROB DS map than on the meiosis II trisomy map (fig. 2). Thus, the ROB-associated DS map is unique in that it differs from each of the other maps, either in the total length of the map or in the distribution of exchanges or in both (fig. 2). Because the total length did not differ from that of the normal female map, we postulate that the amount of recombination is probably not the crucial factor leading to NDJ associated with de novo ROBs, but rather, the location of exchanges may be important.

Our results suggest that ROB formation most likely occurs during meiosis I of oogenesis. The mechanism by which the short arms become translocated is largely unknown. Given the repetitive nature of the DNA located in the acrocentric short arms and the extent of DNA sequence sharing between nonhomologous acrocentric short arms (Bandyopadhyay et al. 2001), a recombination-based mechanism is hypothesized. It is unknown if the short-arm "exchange" that results in ROB formation occurs simultaneously with normal recombination or if it occurs prior to or after the normal crossover events. Regardless, it is likely that these events affect one another. We propose that the translocation event occurs during the time between premeiotic replication and the completion of meiosis I (segregation of the homologues) (fig. 3). This timing is necessarily so because if translocation formation occurred prior to premeiotic replication, and then NDJ occurred, meiosis I NDJ would lead to nonreduced chromosomes 21, and meiosis II NDJ would lead to a double trisomy, with two copies of the translocation. To observe the findings in our study, and as proposed elsewhere (Petersen et al. 1991), translocation formation would have to occur between single sister chromatids of replicated chromosomes (fig. 3).

Two hypotheses have been proposed to explain the finding of increased proximal recombination in meiosis II NDJ trisomy 21, "chromosome entanglement" and "premature sister chromatid separation" (Lamb et al. 1996; Hassold et al. 2000). Both hypotheses implicate events in meiosis I as contributing to apparent meiosis II NDJ events. In a somewhat different way, in our study, events in meiosis I—the formation of the translocation—probably influence meiosis II events as well. The finding of significantly more meiosis II NDJ events in our study ($\chi^2_1 = 15.69$; $P < .0001$) provides a compel-

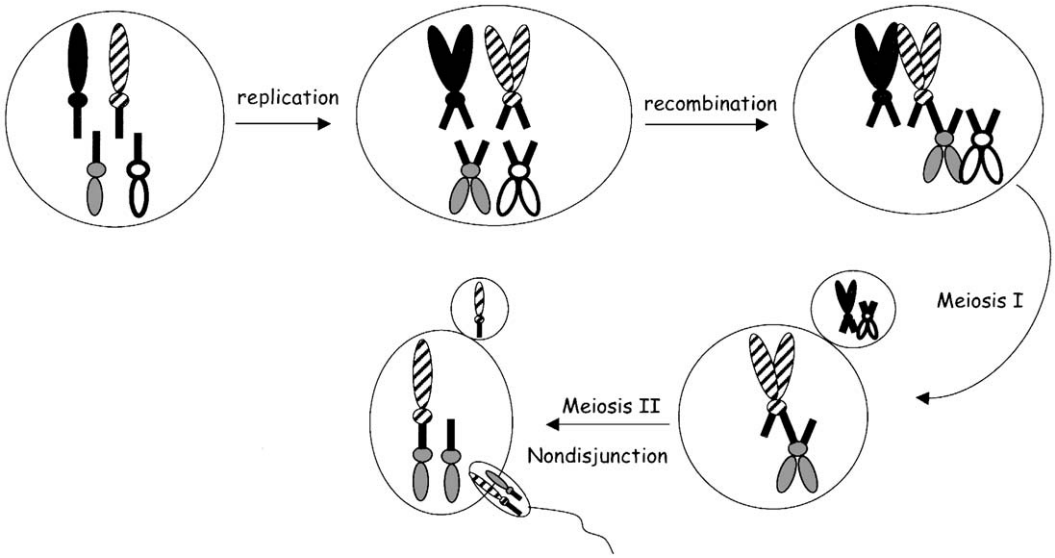

Figure 3 Proposed model for de novo ROB formation and nondisjunction of chromosome 21 in oogenesis. Chromosomes 14 (*solid black* or *hatched*) and 21 (*gray* or *white*) are shown. Replication duplicates the chromosome into two sister chromatids. During recombination of the homologous chromosomes, single chromatids from chromosomes 14 and 21 become translocated at the short arms, producing a dicentric ROB. Reciprocal acentric short-arm product is not shown. At meiosis I, homologous chromosomes separate into the secondary oocyte and one polar body. Nondisjunction at meiosis II results in a mature ovum containing the ROB and an extra chromosome 21. The extra chromosome 21 is the same chromosome as that translocated within the ROB. Shown is the second polar body containing only a chromosome 14 and nullisomy for chromosome 21. Fertilization results in a zygote that is disomic for chromosome 14 but trisomic for chromosome 21.

ling argument that events in meiosis I can influence segregation of sister chromatids in meiosis II resulting in aneuploidy associated with de novo ROBs.

Crossover interference is defined as the nonrandom placement of chiasmata on individual chromatids (Broman and Weber 2000). Interference is probably an important process that ensures an even distribution of chiasmata across a chromosome in a system that has limitations to the number of chiasmata per genome in meiosis (Broman and Weber 2000). At least one chiasma per homologous pair, even for the smallest of chromosomes, is believed to be necessary for proper segregation of the homologues (Laurie and Hultén 1985). Mather (1938) proposed that the centromere provides a barrier to interference. In this model, chiasmata in one chromosome arm would not influence the placement (location) of chiasmata in the other chromosome arm. Thus, the location of chiasmata in the two arms of the chromosome would be independent.

However, recent studies have provided evidence that crossover interference probably occurs across the centromere (Laurie and Hultén 1985; Colombo and Jones 1997; Broman and Weber 2000) and therefore, the location of chiasmata in one chromosome arm influences the placement of chiasmata in the other arm. For example, cytogenetic studies in spermatogenesis showed that the number of chiasmata on each arm was not independent (Laurie and Hultén 1985). Recent molecular studies using pooled data for all human chromosomes that showed at least one exchange on each arm demonstrated that the locations of chiasmata on each chromosome arm are not independent; thus, interference does act across the centromere (Broman and Weber 2000). Thus, when a crossover occurred near the centromere in one arm, the nearest crossover in the other arm tended to be farther away from the centromere (Broman and Weber 2000). However, because recombination could not be assessed in the short arms of the acrocentric chromosomes, these chromosomes were not included in the analyses of Broman and Weber (2000).

ROBs provide a unique marker for tracking particular chromosomes, because the chromosomes are permanently translocated. Additionally, if we presume that there is at least one obligatory exchange event in the short arms in de novo ROB formation, by examining the locations of recombination on the long arms, we can assess whether the translocation event in the short arms influenced the placement of recombination in the long arm (i.e., crossover interference). Our studies demonstrate crossover interference across the centromere in meiosis II NDJ associated with de novo rob(14q21q) formation because there is a shift in recombination to a more distal location in the long arm. Because recombination cannot be measured in the acrocentric short arms, the de novo ROBs studied here provide a model for studying crossover interference across the centromere in a human acrocentric chromo-

some, which has not been accomplished previously. More importantly, because crossover interference occurs, the "event" in the short arms of chromosomes 14 and 21 that form the de novo rob(14q21q) must be a recombination-based mechanism, probably occurring through the normal recombination pathway during meiosis I in oogenesis.

Insight into recombination during meiosis in the acrocentric short arms may aid in the elucidation of the role of short-arm recombination in NDJ of chromosome 21. For meiosis II NDJ events leading to free-lying trisomy 21, the data suggest that susceptibility to NDJ is associated with the distance between the centromere and the nearest exchange (Hassold and Sherman 2000). This conclusion is supported by our findings of altered recombination in meiosis II NDJ associated with de novo ROB formation. Recombination in the long arm may be influenced by the translocation event in the short arm, supported by our findings of crossover interference in the de novo ROB DS cases.

Understanding the mechanisms of de novo ROB formation and associated NDJ are complicated by the fact that, on the basis of our observations and hypotheses, ROB formation occurs in pachytene I of meiosis I, but the chromosome 21 NDJ occurs at meiosis II. Thus, because of the timing of events of meiosis in females, the ROB would form when the mother was a fetus, by 7–9 mo of gestation, but the meiosis II NDJ event would not occur until fertilization of that particular ovum, several decades later (fig. 3). Thus, environmental or intrinsic factors that may influence either of these events occur at very different times during gametogenesis in human females.

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References

Bandyopadhyay R, Heller A, Knox-Du Bois C, McCaskill C, Berend SA, Page SL, Shaffer LG (2002) Parental origin and timing of de novo Robertsonian translocation formation. Am J Hum Genet 71:1456–1462

Bandyopadhyay R, McQuillan C, Page SL, Choo KHA, Shaffer LG (2001) Identification and characterization of satellite III subfamilies to the acrocentric chromosomes. Chromosome Res 9:223–233

Broman KW, Weber JL (2000) Characterization of human crossover interference. Am J Hum Genet 66:1911–1926

Colombo PC, Jones GH (1997) Chiasma interference is blind to centromeres. Heredity 79:214–227

Giraud F, Mattei JF (1975) Aspects epidemiologiques de la trisomie 21. J Genet Hum 23:1–30

Han J-Y, Andy Choo KHA, Shaffer LG (1994) Molecular cytogenetic characterization of 17 rob(13q14q) Robertsonian translocations by FISH, narrowing the region containing the breakpoints. Am J Hum Genet 55:960–967

Hassold T, Sherman S (2000) Down syndrome: genetic recombination and the origin of the extra chromosome 21. Clin Genet 57:95–100

Hassold T, Sherman S, Hunt P (2000) Counting cross-overs: characterizing meiotic recombination in mammals. Hum Mol Genet 9:2409–2419

Koehler KE, Hawley RS, Sherman S, Hassold T (1996) Recombination and nondisjunction in humans and flies. Hum Mol Genet 5:1495–1504

Lamb NE, Feingold E, Savage A, Avramopoulos D, Freeman S, Gu Y, Hallberg A, Hersey J, Karadima G, Pettay D, Saker D, Shen J, Taft L, Mikkelsen M, Petersen MB, Hassold TJ, Sherman SL (1997) Characterization of susceptible chiasma configurations that increase the risk for maternal nondisjunction of chromosome 21. Hum Mol Genet 6: 1391–1399

Lamb NE, Freeman SB, Savage-Austin A, Pettay D, Taft L, Hersey J, Gu Y, Shen J, Saker D, May KM, Avramopoulos D, Petersen MB, Hallberg A, Mikkelsen M, Hassold TJ, Sherman SL (1996) Susceptible chiasmate configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II. Nat Genet 14:400–405

Laurie DA, Hultén MA (1985) Further studies on chiasma distribution and interference in the human male. Ann Hum Genet 49:203–214

Lynn A, Kashuk C, Petersen MB, Bailey JA, Cox DR, Antonarakis SE, Chakravarti A (2000) Patterns of meiotic recombination on the long arm of human chromosome 21. Genome Research 10:1319–1332

Mather K (1938) Crossing-over. Biol Rev 13:252–292

Morton NE, Andrews V (1989) MAP, an expert system for multiple pairwise linkage analysis. Ann Hum Genet 53: 263–269

Morton NE, MacLean CJ (1984) Multilocus recombination frequencies. Genet Res 44:99–107

Page SL, Shaffer LG (1997) Nonhomologous Robertsonian translocations form predominantly during female meiosis. Nat Genet 15:231–232

Page SL, Shin J-C, Han J-Y, Choo KHA, Shaffer LG (1996) Breakpoint diversity illustrates distinct mechanisms for Robertsonian translocation formation. Hum Mol Genet 5:1279–1288

Petersen MB, Adelsberger PA, Schinzel AA, Binkert F, Hinkel GK, Antonarakis SE (1991) Down syndrome due to de novo Robertsonian translocation t(14q;21q): DNA polymorphism analysis suggests that the origin of the extra 21q is maternal. Am J Hum Genet 49:529–536

Shaffer LG, Jackson-Cook CK, Stasiowski BA, Spence JE, Brown JA (1992) Parental origin determination in thirty de novo Robertsonian translocations. Am J Med Genet 43: 957–963

Shaffer LG, Overhauser, J Jackson L, Ledbetter DH (1993) Genetic syndromes and uniparental disomy: a study of 16

cases of Brachmann-de Lange Syndrome. Am J Med Genet 47:383–386

Sherman SL, Petersen MB, Freeman SB, Hersey J, Pettay D, Taft L, Frantzen M, Mikkelsen M, Hassold TJ (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

Sherman SL, Takaesu N, Freeman SB, Grantham M, Phillips C, Blackston RD, Jacobs PA, Cockwell AE, Freeman E, Uchida I, Mikkelsen M, Kurnit DM, Buraczynska M, Keats BJ, Hassold TJ (1991) Trisomy 21: association between reduced recombination and nondisjunction. Am J Hum Genet 49: 608–620

Warren AC, Chakravarti A, Wong C, Slaugenhaupt SA, Halloran SL, Watkins PC, Metaxotou C, Antonarakis SE (1987) Evidence for reduced recombination on the nondisjoined chromosomes 21 in Down syndrome. Science 237:652–654