Molecular Analysis of Nondisjunction in Mice Heterozygous for a Robertsonian Translocation

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ABSTRACT

A Robertsonian translocation results in a metacentric chromosome produced by the fusion of two acrocentric chromosomes. *Rb* heterozygous mice frequently generate aneuploid gametes and embryos, providing a good model for studying meiotic nondisjunction. We intercrossed mice heterozygous for a (7.18) Robertsonian translocation and performed molecular genotyping of 1812 embryos from 364 litters with known parental origin, strain, and age. Nondisjunction events were scored and factors influencing the frequency of nondisjunction involving chromosomes 7 and 18 were examined. We concluded the following:

1. The frequency of nondisjunction among 1784 embryos (3568 meioses) was 15.9%.
2. Nondisjunction events were distributed nonrandomly among progeny. This was inferred from the distribution of the frequency of trisomics and uniparental disomics (UPDs) among all litters.
3. There was no evidence to show an effect of maternal or paternal age on the frequency of nondisjunction.
4. Strain background did not play an appreciable role in nondisjunction frequency.
5. The frequency of nondisjunction for chromosome 18 was significantly higher than that for chromosome 7 in males.
6. The frequency of nondisjunction for chromosome 7 was significantly higher in females than in males.

These results show that molecular genotyping provides a valuable tool for understanding factors influencing meiotic nondisjunction in mammals.

ANEUPLOIDY results from nondisjunction of chromosomes in meiosis and, in humans, occurs in ~5% of clinically recognized pregnancies (Warburton 1997) and 0.3% of newborns (Hassold 1985). Therefore it is important to elucidate the underlying causes of nondisjunction (Hamerton *et al.* 1975; Nicolaidis and Peterson 1989). Mice heterozygous for Robertsonian translocations undergo an increased rate of nondisjunction compared to karyotypically normal mice (Beechey and Evans 1996). Utilizing genetically defined mice that carry *Rb* translocations to measure the incidence of nondisjunction provides great opportunities to learn more about aneuploidy and its origins.

An association between nondisjunction and advanced maternal age in humans has long been observed, but the mechanism for this observation is not completely understood. Studies of trisomies 16 and 21 in humans have linked the frequency and location of recombinational events in meiosis I with advanced maternal age (Sherman *et al.* 1994; Hassold *et al.* 1995). Age effects in mice have also been reported among karyotypically normal mice as well as in mice with *Rb* translocations (Fabricant and Schneider 1978; Gropp and Winking 1981).

Another factor that is likely to play an important role in the occurrence of nondisjunction is genetic background. Considerable variation in the frequency of aneuploidy between strains of mice has been observed (Fabricant and Schneider 1978; Vekemans 1989). Wild populations of *Rb* translocation mice exist mostly in Western Europe and North Africa (Redi and Capanna 1988). The heterozygotes of these populations show relatively low frequencies of spontaneous nondisjunction as do karyotypically normal laboratory mouse strains (Beechey and Evans 1996). However, as wild *Rb* derivatives were introduced into laboratory mouse genetic backgrounds, significant increases in the frequency of nondisjunction were observed (Wallace *et al.* 1992). Thus the incidence of nondisjunction can be studied between different strains of mice harboring *Rb* chromosomes.

Perhaps the most intriguing of all, however, is the observation of chromosomal and sex differences associated with nondisjunction frequency. Factors that can affect the frequency of nondisjunction among individual chromosomes include centromere position, size and

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position of centromeric repetitive sequences, and the presence of large blocks of nonheterochromatin and nucleolus organizing regions. Specific recombination patterns and individual genes may also contribute to the incidence of nondisjunction (Warburton and Kinney 1996). Male and female nondisjunction rates of several different chromosomes involving *Rb* translocations have been studied and in the majority of cases females show an elevated frequency of nondisjunction over males (Gropp and Winking 1981; Redi and Capanna 1988).

In this study, we have used molecular markers to study the segregation of chromosomes in *Rb* (7.18) heterozygotes. This technique is a valuable way to accurately score multiple nondisjunction events in large numbers of mouse crosses. Our study surveys 1812 embryos of known strain parentage from 364 litters of mice. Meiotic nondisjunction leads to the formation of progeny that are trisomic or monosomic for the chromosomes of the *Rb* translocation at an equal frequency; however, monosomics die early in gestation, prior to 8.5 days postcoitum (dpc; Gropp and Winking 1981). Uniparental disomies (UPDs) occur at a lower frequency but are viable and detectable at 8.5 dpc. The aneuploid embryos detected in the progeny from this cross include trisomies and UPDs of chromosomes 7 and 18. A trisomy represents the product of one nondisjunction event (a normal gamete fusing with a disomic gamete) and a UPD represents the product of two nondisjunction events (a nullisomic gamete fusing with a disomic gamete). Documented birth dates of males and females allowed maternal and paternal age effects on the incidence of nondisjunction to be assessed. Additionally, with the parentage of each offspring documented, effects of strain difference on nondisjunction were also investigated. Finally, chromosomal and sex-specific differences in the frequency of nondisjunction were evaluated.

MATERIALS AND METHODS

Mice: All mouse strains were obtained from The Jackson Laboratory. *Rb(2.8)2Lub(7.18)9Lub* (RbWt) and C57BL/6JEi-*Rb(7.18)9Lub* (B6Rb) strains were obtained from the Robertsonian Resource at The Jackson Laboratory. Four out of five of the parental strains were inbred laboratory mice (a combination of *Mus musculus musculus* × *M. musculus domesticus*) and one strain was a more genetically distant subspecies, *M. musculus castaneus* (Beck *et al.* 2000). The Rb wild-type strain has been maintained on its own inbred background, a combination of ~50% wild-derived *M. musculus domesticus* and 50% laboratory mouse strain backgrounds (Davisson and Akeson 1993). The B6Rb mice were derived by repeated backcrossing to mice with a C57BL/6J-Ei background. Rb wild-type mice were crossed to DBA/2J and B6Rb mice were crossed to C3H/HeJ or *M. musculus castaneus* to generate progeny carrying one copy of the (7.18) Robertsonian chromosome.

F_1 mice with a single copy of the (7.18) Robertsonian chromosome (*i.e.*, *Rb* heterozygotes) were intercrossed and produced 1812 F_2 progeny that were harvested at 8.5 dpc in 364 timed matings. This is the latest timepoint at which phenotypically normal embryos with UPD of 7 or 18 can be isolated (Oakey *et al.* 1995). The parental ages at the time of mating and mating types (maternal × paternal strain), as well as litter size and composition (viable embryos and resorptions) at 8.5 dpc, are summarized in Table 1. Embryos were dissected, visualized under a dissection microscope, and scored phenotypically as normal or abnormal. A normal phenotype was recorded when an embryo appeared to be the correct size for the gestational age with normal developmental physical features such as having 8–12 pairs of somites. An abnormal phenotype was scored when an embryo appeared underdeveloped for the age of harvest or had an obvious developmental defect by comparison with normal embryos (Kaufman 1992). The number of resorptions was counted in each uterus. A tissue sample was procured from each embryo and frozen for DNA preparations. DNA was isolated as in Oakey *et al.* (1995).

TABLE 1

Characteristics of the study mice and litters

Characteristic	Median	Range
A. Median values and ranges for continuous variables		
Maternal age (wk)	15.0	4.0–48.0
Paternal age (wk)[a]	21.0	7.0–71.0
Litter size	8	1–14
Viable embryos	5	1–11
Resorptions	3	0–9
Characteristic	**No.**	**Frequency (%)**
B. Numbers and frequencies for discrete variables		
Maternal age		
≤26 wk	218	86.5
>26 wk	34	13.5
Paternal age[a]		
≤26 wk	142	70.6
>26 wk	59	29.4
Mating cross (female × male)		
BX3 × DXR	100	27.6
BXC × DXR	65	17.9
DXR × BX3	142	39.1
DXR × BXC	56	15.4

Cross abbreviations: R, *Rb(2.8)2Lub(7.18)9Lub*; B, C57BL/6JEi-*Rb(7.18)9Lub*; D, DBA/2J; 3, C3H/HeJ; and C, *M. musculus castaneus*.

[a] Males may have been used for more than one cross.

Primers and PCR: Simple sequence repeat polymorphism primers (Map Pairs) were purchased from Research Genetics (Huntsville, AL). The primary chromosome 7 marker used was D7Mit25, with D7Mit222 as the secondary marker for confirmation of UPD and trisomy genotypes. D18Mit14 was used for chromosome 18 genotyping with D18Mit87 as the marker of choice for confirmation of aneuploid genotypes. Genotyping was performed as in Oakey *et al.* (1995). The genotypes were scored independently by two individuals and the embryos were considered to be chromosomally normal, trisomic, or uniparental disomic for chromosomes 7 and 18. The number of maternal and paternal nondisjunction events involving chromosome 7 and 18 per litter was scored.

Statistical analysis: The distribution of genotypes observed among the embryos was compared to the expected distribution using chi-square analysis. In theory, *Rb* heterozygous mice can produce six types of gametes, in equal proportions, and

matings between *Rb* heterozygous mice will give rise to embryos with 36 (6×6) equally likely, distinct genotypes, when maternal and paternal chromosomes are differentiated (see Oakey *et al.* 1995). However, 18 of the expected genotypes are monosomic, nullisomic, or tetrasomic and are not observed in 8.5-dpc embryos. The remaining 18 genotypes include balanced arrangements, trisomy 7, trisomy 18, UPD 7, UPD 18, and double trisomy and are observed at 8.5 dpc. Assuming no gametic or postfertilization selection, the ratio of these genotypes in 8.5-dpc embryos is expected to be 2:2:2:1:1:1, respectively. Hence, the expected number of embryos in each category was determined by the product of the number of embryos scored for both chromosome 7 and 18 ($N = 1784$) and the expected, relative frequency of a particular genotype [*e.g.*, expected number of trisomy 7 = $N(2/9) = 396$; expected number of UPD 7 = $N(1/9) = 198$].

The likelihood-ratio test was used to determine whether the nondisjunction events were randomly distributed across embryos or clustered within litters. The distribution of this statistic approximately follows a chi-square distribution, with degrees of freedom equal to the difference in the number of parameters estimated by the two models. Specifically, two logistic regression models—one with and one without a random effect for litter—were compared. The likelihood-ratio chi-square comparing these two models provides a test of the significance of the random effects parameter. These analyses were performed separately for data on maternal and paternal nondisjunction events.

These data provided strong evidence that maternal and paternal nondisjunction events are correlated or clustered within litters. The impact of parental age and strain on the risk of nondisjunction, as well as chromosomal and sex-specific estimates of the frequency of nondisjunction, were therefore assessed using regression models fit with generalized estimating equations (GEEs). GEEs provide a practical method, with reasonable statistical efficiency, for the analysis of correlated data such as embryos within litters. GEE-based models for the impact of parental age and strain used a logit link and binomial error structure, as in logistic regression. The significance of parental age and strain were determined by the Wald chi-square statistic. GEE-based models to estimate differences in frequencies used an identity link and a Gaussian error structure, as in linear regression. Chromosomal and sex-specific nondisjunction frequencies were based on the GEE parameter and empirical standard error estimates. Chromosomal and sex-specific differences in the frequency of nondisjunction events were assessed using the 95% confidence interval, adjusting for clustering within litters, for the difference between the estimates of interest.

RESULTS

Maternal and paternal chromosomes 7 and 18 were completely scored in 1784 embryos from 355 litters. As expected, no monosomic, nullisomic, or tetrasomic embryos were detected at 8.5 dpc. A total of 568 nondisjunction events were observed, for a frequency of 15.9%. The observed frequency of chromosomally balanced, trisomic, and UPD embryos was significantly different ($P < 0.001$) from what would be expected if there were neither gametic nor postzygotic selection against such embryos (Table 2). Specifically, the observed number of chromosomally abnormal embryos, of all types (*e.g.*, trisomy 7, UPD 18), was markedly less than expected.

The distribution of nondisjunction events across the 355 litters is summarized in Table 3. The null hypothesis of the absence of a random effect for litters (*i.e.*, random effects parameter = 0) was rejected for maternal nondisjunctions ($\chi^2_1 = 18.6$, $P < 0.001$), suggesting that these events tend to cluster within litters. There was also evidence, albeit weaker, for the nonrandom distribution of paternal nondisjunctions ($\chi^2_1 = 3.70$, $P = 0.054$). All subsequent analyses take account of the clustered nature of these data.

TABLE 2

Observed and expected numbers of viable embryos with trisomy or UPD involving chromosomes 7 and 18

Karyotype	Observed no.	Expected no.
Chromosomally balanced	1328	396
Trisomy 7[a]	144	396
Trisomy 18[a]	200	396
Double trisomy[b]	12	198
UPD 7[b]	46	198
UPD 18[b]	54	198

[a] Trisomic embryos are the result of a single nondisjunction.
[b] Double trisomic and uniparental disomic embryos are the result of two nondisjunctions.

Parental age: Maternal age was not significantly related to nondisjunction of chromosomes 7 ($\chi^2_1 = 0.01$, $P = 0.93$), 18 ($\chi^2_1 = 0.00$, $P = 0.96$), or 7 and 18 combined ($\chi^2_1 = 0.02$, $P = 0.90$). Similarly, paternal age was not significantly related to nondisjunction of chromosomes 7 ($\chi^2_1 = 0.76$, $P = 0.38$), 18 ($\chi^2_1 = 0.09$, $P = 0.76$), or 7 and 18 combined ($\chi^2_1 = 0.08$, $P = 0.77$).

Nondisjunction and strain background: Maternal strain was not significantly related to nondisjunction of chromosomes 7 ($\chi^2_2 = 0.92$, $P = 0.63$), 18 ($\chi^2_2 = 3.94$, $P = 0.14$), or 7 and 18 combined ($\chi^2_2 = 3.17$, $P = 0.20$). Paternal strain was also not significantly related to nondisjunction of chromosomes 7 ($\chi^2_2 = 2.08$, $P = 0.35$), 18 ($\chi^2_2 = 0.87$, $P = 0.63$), or 7 and 18 combined ($\chi^2_2 = 0.80$, $P = 0.67$).

Chromosomal and sex-specific differences in the frequency of nondisjunction: As neither parental age nor parental strain was significantly associated with nondisjunction, chromosomal and sex-specific estimates of nondisjunction were made accounting only for the tendency of events to cluster within litters. Nondisjunction

TABLE 3

Distribution of maternal and paternal nondisjunction events among litters

	No. of nondisjunction events (% of litters)				
	0	1	2	3	>3
Maternal	171 (48.2)	108 (30.4)	51 (14.4)	17 (4.8)	8 (2.2)
Paternal	174 (49.0)	113 (31.8)	49 (13.8)	15 (4.2)	4 (1.1)

TABLE 4

Chromosomal and sex-specific frequencies of nondisjunction

Sex	Chromosome	No. of informative meioses	No. of nondisjunctions	% nondisjunction (95% C.I.)[a]
Male	7	1806	103	5.7 (4.6–6.8)
	18	1787	171	9.5 (8.0–10.9)
	7 or 18	1784	273	15.2 (13.4–17.0)
Female	7	1806	149	8.3 (6.9–9.6)
	18	1787	149	8.4 (7.0–9.8)
	7 or 18	1784	295	16.6 (14.6–18.6)

[a] Estimates are from GEE models, and therefore confidence intervals are adjusted for clustering of mice within litters.

of maternal chromosomes 7 or 18 occurred in 16.6% of embryos (Table 4), whereas nondisjunction of paternal chromosomes 7 or 18 occurred in 15.2% of embryos. The difference between these two frequencies was not significant (95% C.I. for difference: −1.3 to 4.0).

In females, the frequency of nondisjunction was 8.3% for chromosome 7 and 8.4% for chromosome 18. The difference in the frequency of nondisjunction of chromosome 7 and 18 in females was not statistically significant (95% C.I. for difference: −1.9 to 2.1%). In males, the frequency of nondisjunction was 5.7% for chromosome 7 and 9.5% for chromosome 18. The difference in the frequency of nondisjunction of chromosomes 7 and 18 in males was statistically significant (95% C.I. for difference: 2.0–5.7%).

The difference in frequency of maternal and paternal nondisjunction of chromosome 7 was also statistically significant (95% C.I. for difference: 0.8–4.3%), whereas the difference in frequency of maternal and paternal nondisjunction of chromosome 18 was not significant (95% C.I. for difference: −0.9 to 3.17%).

DISCUSSION

Nondisjunction and parental age: A variety of studies in the mouse show that nondisjunction frequencies increase with advancing maternal age. One study reported hyperhaploidy to be significantly higher in the embryos and oocytes of aged mice (24–28 weeks old) *vs.* those of young adult mice (10–12 weeks old; Catala *et al.* 1988). Several other studies involving first cleavage and early- to midgestation embryos have been utilized to investigate the phenomenon of advanced maternal age and nondisjunction. Results vary from study to study with reported aneuploidy frequencies of 0–21% involving mice aged 1–16 months (Bond and Chandley 1983). However, the spontaneous aneuploidy frequency among mice still does not approach the consistency of that of the human population. Few reports on Robertsonian mice are available but one study recorded an age effect in *Rb*(1.3)1*Bnr*/+ female heterozygotes. No appreciable age effect was detected in the males of the same group (Gropp and Winking 1981).

In our study, the overall nondisjunction frequency was not associated with advanced maternal or paternal age. Perhaps if greater numbers of older females (>26 weeks) were used, an age effect may have been detected. The nature of the specific chromosomes involved in the translocation also may have played a role in masking the effects of parental age. We suspect, however, that the failure to detect any effects of parental age on nondisjunction may be due to the increased nondisjunction frequency that results from the Robertsonian chromosome itself (from <1 to 16%) masking any measurable subtle effects due to parental age.

Nondisjunction and genetic background: The effect of genetic background on the incidence of and tolerance to nondisjunction is poorly understood in mammals. Studies involving trisomy 19 in crosses between male Robertsonian translocation mice and females of several different non-Robertsonian strains have revealed a striking difference in the incidence of trisomy 19. The frequency of trisomy 19 at 15 dpc varied greatly (7.2–21.6%) between the different strains of mice and this range fits a bimodal distribution suggesting that specific loci are responsible for these strain differences (Vekemans 1989).

Although a direct test of genetic background effects is difficult, we did measure the frequency of nondisjunction with respect to the parental strains used in this breeding program. Our study detected little or no effect of strain background on the incidence of nondisjunction. It is possible that our method of measurement is insensitive to background effects because of the overwhelming increase in nondisjunction frequency, due to the presence of the Robertsonian chromosome. However, it could be due to the very subtle nature of the background differences in these strains.

Chromosomal and sex-specific differences in the frequency of nondisjunction: When a *Rb* chromosome

forms in house mice, segments of satellite DNA are lost and each chromosome contributes equally to the newly formed metacentric (Garagna *et al.* 2001). It is possible, given these structural changes, that while no detrimental effects are seen phenotypically, gametic segregation of homologs is affected in the *Rb* heterozygote and to what degree may vary depending on which chromosomes are involved in the rearrangement (Ruvinskii *et al.* 1986). Abnormal spindle assembly has been identified as a possible mechanism of malsegregation of chromosomes in meiosis (Woods *et al.* 1999). Mice deficient in MLH1 (a mismatch repair protein) not only fail to show a reduction in recombination crossovers, but also fail to establish stable spindle attachments to opposite poles of the germ cell (Woods *et al.* 1999). Consequently, germ cells of males and females are arrested at metaphase I. Since MLH1 serves as a marker for chiasmata in spermatocytes and oocytes at the pachytene stage, the number and location of crossover regions can be identified (Baker *et al.* 1996). In spermatocytes there is a variation in the number of foci among chromosomes and they are distributed in a nonrandom fashion (Anderson *et al.* 1999). Furthermore, the smaller chromosomes tend to have fewer chiasmata than the larger chromosomes. In our *Rb* (7.18) cross, embryos with paternally derived chromosome 7 nondisjunctions occurred at a lower frequency than embryos with paternally derived chromosome 18 nondisjunctions. It is plausible that due to the larger size of chromosome 7, which consequently has a greater number of foci than chromosome 18, that the chromosome was more stable during recombination and therefore produced fewer nondisjunction events. It would be of interest to determine the stability of spindle attachments in spermatocytes and oocytes of *Rb* heterozygotes and to examine their implications on male and female fertility as well as to determine the number and distribution of functional chiasmata. In our study, it may be that sperm with chromosome 7 nondisjunctions are less successful than sperm with chromosome 18 nondisjunctions. We did not, however, compare a range of chromosomes to observe size trends and infer other mechanisms. Studies involving MLH1 foci in humans showed that females have almost twice as many foci as males. Given this sex difference, the chance for premature sister chromatid separation may be greater in females and thus there is a more common occurrence of meiotic nondisjunction (Broman *et al.* 1998).

Other genes associated with recombination involve proteins such as SCP1, SCP2, and SCP3. These proteins associate with a structure called the synaptonemal complex and have been identified to be important components of the meiotic process (Moens *et al.* 1998). While female mice deficient for the SCP3 gene retain a level of fertility, although less so than wild-type females, the males are sterile (Yuan *et al.* 2000). The authors proposed that activation of a meiotic checkpoint may lead to the demise of the male germ cells (Yuan *et al.* 2000). Interestingly, SCP2 and SCP3 proteins are detectable in males until anaphase II, but disappear prior to the first meiotic division in female mice (Dobson *et al.* 1994; Hodges *et al.* 2001). This finding suggests a possible mechanism for the increased nondisjunction often seen in female gametes. The results of our study include a sex-specific difference in which females contributed to more nondisjunction events with respect to chromosome 7. Reasons for differences in nondisjunction frequency between males and females carrying the same chromosomal abnormality are not well understood but in addition to gamete impairment may include complex gene interactions (Redi and Capanna 1988).

In summary, we have intercrossed Robertsonian heterozygous mice to determine that the frequency of meiotic nondisjunction was 15.9% and was nonrandomly distributed among litters. The age or strain of mouse did not influence the frequency of nondisjunction appreciably. The frequency of nondisjunction is greater for paternally derived chromosome 18s than for chromosome 7s. The nondisjunction frequency for chromosome 7 was significantly higher in females than in males. Thus, it is clear that the use of Robertsonian mouse strains is a valuable tool for measuring nondisjunction by molecular methods and for accumulating information on parameters that contribute to our understanding of the mechanisms underlying nondisjunction.

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