Sex-of-Offspring-Specific Transmission Ratio Distortion on Mouse Chromosome X

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ABSTRACT

During our study of the DDK syndrome, we observed sex ratio distortion in favor of males among the offspring of F1 backcrosses between the C57BL/6 and DDK strains. We also observed significant and reproducible transmission ratio distortion in favor of the inheritance of DDK alleles at loci on chromosome X among female offspring but not among male offspring in (C57BL/6 × DDK)F1 × C57BL/6 and (C57BL/6 × pgk1−/− × DDK)F1 × C57BL/6 backcrosses. The observed transmission ratio distortion is maximum at DXMit210 in the central region of chromosome X and decreases progressively at proximal and distal loci, in a manner consistent with the predictions of a single distorted locus model. DXM mit210 is closely linked to two distortion-controlling loci (Dcsx1 and Dcsx2) described previously in interspecific backcrosses. Our analysis suggests that the female-offspring-specific transmission ratio distortion we observe is likely to be the result of the death of embryos of particular genotypic combinations. In addition, we confirm the previous suggestion that the transmission ratio distortion observed on chromosome X in interspecific backcrosses is also the result of loss of embryos.

During the course of these experiments we noted a modest, but significant, overall male bias in the sex ratio of offspring obtained from these crosses. Although the cause of the observed sex ratio bias was not obvious, we began examining the segregation of alleles at chromosome X loci among the offspring of F1 females. We adopted this strategy for two reasons: (1) because the location of the maternal and paternal components of the Om genetic incompatibility system had not yet been established; and (2) because Biddle (1987) noted a correlation between sex ratio distortion and sex-of-offspring-specific transmission ratio distortion (TRD; Pardo-Manuel de Villena et al. 2000a) at loci on chromosome X in an interspecific backcross. Although sex ratio distortion has not been reported to be a consistent feature of interspecific F1 backcrosses, TRD at chromosome X loci among these crosses has been confirmed by several laboratories (European Mouse Backcross Collaborative Group 1994; Johnson et al. 1994; Rowe et al. 1994; Montagutelli et al. 1996).

We observed TRD in favor of DDK alleles at chromosome X loci among female offspring from the backcross of (B6 × DDK)F1 females × B6 males. This result has been duplicated in two independent backcrosses. The TRD is compatible with the presence of a single locus responsible for distortion in the vicinity of DXM it210, in the same region of chromosome X to which one or more distortion-controlling loci have been mapped in interspecific backcrosses (Montagutelli et al. 1996).

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Our analysis suggests that the female-offspring-specific TRD we observe is the result of loss of embryos. In addition, our analysis of interspecific backcross data indicates that chromosome X TRD, though not sex-offspring specific, is also the result of loss of embryos, as proposed by Montagutelli et al. (1996).

MATERIALS AND METHODS

Mouse crosses: All F1 backcrosses used in this study have been described previously (Sapienza et al. 1992; Pardo-Manuel de Villena and Sapienza 1996; Pardo-Manuel de Villena et al. 1996, 1997, 2000a), with the exception of the C57BL/6 × (DDK × C57BL/6)F1 backcross. However, all of the genotypic information at loci on chromosome X given in this report represents new data. In all crosses described in the text, the dam is listed first and the sire second. The C57BL/6-6-Pgk1 congenic strain (designated "PG" in the remainder of the text) contains the central region of chromosome X derived from Danish wild mice. All animals described in this report were treated according to the recommendations of the Canadian Council on Animal Care or the IACUC of Temple University School of Medicine.

Genotype determination: DNA extractions from tail biopsies, gel electrophoresis, and autoradiography were performed as described previously (Maniatis et al. 1982; Hogan et al. 1986). Oligonucleotide primers for all "DXM"it genetic markers (Dietrich et al. 1994) were purchased from Research Genetics (Huntsville, AL), and PCR reactions were performed as suggested by the manufacturer. DXPas29 was synthesized as described (Simmler et al. 1993). DXMit124, DXMit166, DXMit210, DXPas29, DXMit117, and DXMit28 were scored in all of the (C57BL/6-6-Pgk1 × DDK)F1 × C57BL/6 offspring. The genotypes of all (C57BL/6 × DDK)F1 × C57BL/6 F1 offspring were determined at DXMit124, DXMit166, DXMit210, DXMit117, and DXMit28. Additional markers were scored when recombination was observed between consecutive loci.

Sex determination: The sex of each offspring was determined by visual inspection at birth or at weaning. In addition, genotypic confirmation of the sex of all offspring was obtained by determining their genotypes at X-linked markers. Because it was possible that individuals that were homozygous at all X-linked loci examined could be either males or females, such individuals were tested additionally for the presence of a chromosome Y by PCR amplification of the Tdy gene (Gubbay et al. 1990) using the following primers: TDY-F, 5'-CCCATGAA TGCAATTATGGTGTTG-3'; and TDY-R, 5'-TTAGCCCTCCG ATGAGGCTG-3'.

Statistical analyses: The test for number and location of distortion-controlling loci was performed as described previously (Montagutelli et al. 1996; Pardo-Manuel de Villena et al. 2000a). The test for origin of maternal TRD was performed as described in the accompanying article (Pardo-Manuel de Villena et al. 2000a).

RESULTS

Sex ratio and chromosome X inheritance among the offspring of F1 females: Among the original eight F1 backcrosses involving the DDK and B6 inbred strains performed in our laboratory (see materials and methods), we observed modest but significant overall sex ratio distortion in favor of males \( H_0 \), equal numbers of males and females, \( \chi^2 = 13.08, 1 \text{ d.f.}, P < 0.001; H_0, 51.2\% \) males, which is the observed sex ratio in the B6 strain (Jackson Laboratory 1997), \( \chi^2 = 8.16, 1 \text{ d.f.}, P < 0.005 \); Table 1). This bias in favor of males is significant in backcrosses involving F1 females but not in crosses involving F1 males, after correction for performing three tests \( H_0 \), equal numbers of males and females; crosses involving F1 females, \( \chi^2 = 9.42, 1 \text{ d.f.}, P < 0.01 \); crosses involving F1 males, \( \chi^2 = 3.86, 1 \text{ d.f.}, \) not significant). Note that we do not conclude from these data that there is a significant difference in the sex ratio of offspring of F1 females vs. F1 males as fewer offspring of F1 males were obtained. However, these data do provide evidence that the sex ratio of offspring of F1 females is not 1:1.

Because Biddle (1987) had noted that sex ratio distortion among the offspring of interspecific F1 females was accompanied by TRD at loci on chromosome X, we began to examine allelic segregation at chromosome X loci among the offspring of F1 females. The genotype of these offspring was determined at five loci that span most of the length of chromosome X: DXMit124 (position 2.8 cm from the centromere), DXMit166 (37.0 cm), DXMit117 (50.8 cm), and DXMit28 (65.6 cm) (Mouse Genome Database (MGD) 3.1, 1998; Table 2). We observed substantial sex-of-offspring-specific biases in the inheritance of alleles at several loci. In addition, these allelic biases were in the direction expected to explain a sex ratio bias in favor of males. The biases were most apparent in two of the four backcrosses: (DDK × B6)F1 × DDK and (B6 × DDK)F1 × B6 (numbers in bold in Table 2; n.b., we have not attempted to ascribe any degree of statistical significance to these differences but have used them to motivate additional experiments).

In the (DDK × B6)F1 × DDK backcross (Table 2), male offspring that inherit the DDK allele at DXMit124

<table>
<thead>
<tr>
<th>Backcross</th>
<th>n</th>
<th>Females</th>
<th>Males</th>
<th>% Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>(B6 × DDK)F1 × DDK</td>
<td>214</td>
<td>97</td>
<td>117</td>
<td>54.7</td>
</tr>
<tr>
<td>(DDK × B6)F1 × DDK</td>
<td>163</td>
<td>68</td>
<td>95</td>
<td>58.3</td>
</tr>
<tr>
<td>(B6 × DDK)F1 × B6</td>
<td>100</td>
<td>43</td>
<td>57</td>
<td>57.0</td>
</tr>
<tr>
<td>(DDK × B6)F1 × B6</td>
<td>120</td>
<td>53</td>
<td>67</td>
<td>55.8</td>
</tr>
<tr>
<td>Subtotal</td>
<td>597</td>
<td>261</td>
<td>336</td>
<td>56.3</td>
</tr>
<tr>
<td>DDK × (B6 × DDK)F1</td>
<td>102</td>
<td>48</td>
<td>54</td>
<td>52.9</td>
</tr>
<tr>
<td>DDK × (DDK × B6)F1</td>
<td>105</td>
<td>40</td>
<td>65</td>
<td>61.9</td>
</tr>
<tr>
<td>B6 × (B6 × DDK)F1</td>
<td>101</td>
<td>46</td>
<td>55</td>
<td>54.5</td>
</tr>
<tr>
<td>B6 × (DDK × B6)F1</td>
<td>106</td>
<td>53</td>
<td>53</td>
<td>50.0</td>
</tr>
<tr>
<td>Subtotal</td>
<td>414</td>
<td>187</td>
<td>227</td>
<td>54.8</td>
</tr>
<tr>
<td>Total</td>
<td>1011</td>
<td>448</td>
<td>563</td>
<td>55.7</td>
</tr>
</tbody>
</table>

An average of 22 litters (17-28) were analyzed from each backcross.
appear to be overrepresented (55 individuals) when compared to the number of males that inherited B6 alleles (33 individuals) and the number of females that inherited either B6 or DDK maternal alleles at the same locus (32 females in each category). This result is unlikely to be caused by the death of the substantial fraction of embryos from the three classes that would be required to explain these observations because the (DDK × B6)F₁ × DDK backcross has been characterized as "viable" (Wakasugi 1974; Pardo-Manuel de Villena et al. 1999). We have not pursued this result further in this report due, in part, to the difficulty in obtaining the number of (DDK × B6)F₁ hybrids required to test the reproducibility of this result [recall that 95% of such embryos fail to complete development (Tomita et al. 1960; Wakasugi 1973, 1974)]. However, we note that this backcross and the reciprocal backcross of DDK females × (DDK × B6)F₁ males both exhibit sex ratio distortion and the levels of distortion are the highest observed among the eight backcrosses (Table 1).

In the (B6 × DDK)F₁ × B6 backcross (Table 2), female offspring inheriting B6 alleles at both DXM it124 and DXM it16 appear underrepresented (43 individuals) when compared to the number of females that inherit the DDK allele (62 individuals) and the number of males that inherit either B6 or DDK alleles (68 and 67 individually, respectively). This result suggests that the relative deficiency of females in this cross might be related to the inheritance of B6 alleles in the central region of chromosome X. We note, also, that the apparent TRD in this region of chromosome X occurs only among the female offspring of (B6 × DDK)F₁ females when they have been sired by B6 males. Female offspring of these same F₁ females inherit similar numbers of B6 and DDK alleles when sired by DDK males (Table 2).

**TRD at chromosome X loci among female offspring:** We used the preliminary results shown in Table 2 to motivate two independent backcrosses to test whether the sex-of-offspring-specific distortion observed in the backcross of (B6 × DDK)F₁ females with B6 males was reproducible. We used two different types of F₁ females in these experiments: (B6 × DDK)F₁ females, as in the preliminary experiment, while in the second experiment we substituted the C57BL/ 6-Pgk1⁺ (PG) congenic strain for the B6 strain.

We first examined whether TRD in the central region of chromosome X was reproducible by scoring the offspring of both backcrosses at DXM it210 (position 29.5 cM; Mouse Genome Database (MGD) 3.1, 1998), a genetic marker that is informative in both crosses. DXM it210 is located between DXM it46 and DXM it16, neither of which is informative in the (PG × DDK)F₁ × B6 backcross. Apparent bias in favor of the inheritance of DDK alleles at DXM it210 was observed among female offspring in both backcrosses. Therefore, we determined the genotype of all offspring from the preliminary (B6 × DDK)F₁ × B6 backcross at this locus, and the combined results are shown in Table 3. We observe TRD in the female offspring of both backcrosses but not in the male offspring.

To localize the region of maximum distortion, we examined additional loci on chromosome X in both backcrosses (Table 3). The maximum TRD observed among female offspring from both types of F₁ females occurs in the vicinity of DXM it210 and decreases at proximal and distal loci.

Because the (B6 × DDK)F₁ × B6 and (PG × DDK)F₁ × B6 backcrosses are not heterogeneous for the inheritance of alleles at loci on chromosome X (χ² = 1.01, 8 d.f., not significant), the segregation data have been combined (representing 423 females and 453 males) and are represented in Figure 1a as percentage of offspring that inherit DDK alleles at each locus. Overall, 247 female offspring inherit DDK alleles at DXM it210, while 176 female offspring inherit non-DDK alleles (H₀, equal transmission, χ² = 11.92, 1 d.f., P < 0.005, corre-
TABLE 3
Maternally inherited alleles among male and female offspring at loci on chromosome X in the (B6 × DDK)F1 × B6 and (PG × DDK)F1 × B6 backcrosses

<table>
<thead>
<tr>
<th>Locus</th>
<th>Position</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DDK</td>
<td>B6</td>
</tr>
<tr>
<td>DXMit210</td>
<td>(29.5)</td>
<td>122</td>
<td>89</td>
</tr>
<tr>
<td>DXMit124</td>
<td>(2.8)</td>
<td>102</td>
<td>109</td>
</tr>
<tr>
<td>DXMit166</td>
<td>(15.5)</td>
<td>113</td>
<td>98</td>
</tr>
<tr>
<td>DXMit144</td>
<td>(20.0)</td>
<td>118</td>
<td>93</td>
</tr>
<tr>
<td>DXMit46</td>
<td>(24.5)</td>
<td>118</td>
<td>93</td>
</tr>
<tr>
<td>DXMit211</td>
<td>(33.0)</td>
<td>122</td>
<td>89</td>
</tr>
<tr>
<td>DXMit16</td>
<td>(37.0)</td>
<td>118</td>
<td>93</td>
</tr>
<tr>
<td>DXMit169</td>
<td>(40.4)</td>
<td>118</td>
<td>93</td>
</tr>
<tr>
<td>DXPas29</td>
<td>(42.15)</td>
<td>116</td>
<td>95</td>
</tr>
<tr>
<td>DXMit117</td>
<td>(50.8)</td>
<td>116</td>
<td>95</td>
</tr>
<tr>
<td>DXMit28</td>
<td>(65.6)</td>
<td>103</td>
<td>105</td>
</tr>
</tbody>
</table>

The numbers of animals that inherit DDK vs. B6 or PG alleles at each locus are listed for each sex in each cross (PG alleles designate the alleles that are neither DDK nor B6 and arise from the portion of chromosome X derived from Danish wild mice). Numbers in parentheses represent the map position (in centimorgans from the centromere) of each locus (Mouse Genome Database (MGD) 3.1, 1998). The observed recombination fractions (percentages) between markers typed for both crosses are as follows: DXMit124-22.8-DXMit166-7.4-DXMit144-4.2-DXMit210-4.5-DXMit121-5.0-DXMit169-1.6-DXPas29-7.0-DXMit17-19.9-DXMit28. Note that DXMit46 and DXMit16 were not scored in the (PG × DDK)F1 × B6 offspring because they are not informative in this backcross. In the (B6 × DDK)F1 × B6 cross, the observed recombination fractions between these markers are DXMit46-3.0-DXMit210-3.9-DXMit211-3.9-DXMit16.

TRD is the result of a single locus on chromosome X. We have used the method of Montagutelli et al. (1996) to compare the degree of TRD observed at each locus with that predicted by the presence of a single distorted locus closely linked to DXMit210. The line joining the filled circles in Figure 1b represents the combined observations on female offspring from both backcrosses. The line joining the open circles indicates the percentage of DDK alleles predicted if only a single locus resulting in distortion is present on chromosome X and placed at DXMit210 at a distortion level of 57.3%, at which we observe the best fit to the data (goodness-of-fit = 2.50, 9 d.f., not significant, see materials and methods). The observed values are in close agreement with the expectations of a single locus being responsible for distortion.

Origin of sex-of-offspring-specific TRD on chromosome X: The data we have presented for chromosome X TRD in this study fulfill the requirements for the use of the test of the origin of maternal TRD, presented in a companion article (Pardo-Manuel de Villena et al. 2000a). The TRD is reproducible and is the result of a single locus that is linked to the centromere. We find no evidence for gene conversion or inversions in the region exhibiting distortion.

We have tested for independence of maternal chromosome X haplotype inherited (defined on the basis of genotype at DXMit124 and DXMit210) and TRD level (Table 4). The level of TRD observed among the female offspring cannot be distinguished from that expected if distortion is independent of the chromosome X haplotype inherited ($x^2 = 0.79, 1$ d.f., not significant). These data are consistent with the occurrence of TRD as the result of postmeiotic loss of a fraction of female offspring that do not carry the DDK allele at the distorted locus.

Origin of maternal TRD on chromosome X in interspecific backcrosses: Maternal TRD on chromosome X has also been observed in interspecific (Mus musculus × Mus spretus)F1 × Mus spretus backcrosses by several groups (Biddle 1987; European Mouse Backcross Collaborative Group 1994; Johnson et al. 1994; Rowe et al. 1994; Montagutelli et al. 1996). Neither inversions nor gene conversion has been implicated in the TRD, and the number and location of the distortion-controlling loci involved in those crosses has been addressed in detail (Montagutelli et al. 1996). Although a two-locus model gives a better fit to the experimental data in one of these backcrosses (cross 2 in Table 5), we believe that the null hypothesis of TRD as a result
of postmeiotic selection can be tested even in this cross because no locus proximal to DXMit91 (which is close to the more proximal distortion-controlling locus) is implicated in the TRD (Montagutelli et al. 1996). This locus is clearly linked to the centromere, and we have used it to define the haplotypes in cross 2 (Table 5, see also Montagutelli et al. 1996).

When the test for a postmeiotic origin of maternal TRD (Pardo-Manuel de Villena et al. 2000a) is applied to the results of the two largest interspecific backcrosses (European Mouse Backcross Collaborative Group 1994; Rowe et al. 1994), the results indicate that the level of TRD is independent of the chromosome X haplotype inherited (Table 5); i.e., we do not reject the null hypothesis that TRD is the result of postfertilization loss of embryos ($\chi^2 = 0.70$, 1 d.f., not significant and $\chi^2 = 0.03$, 1 d.f., not significant, in crosses 1 and 2, respectively; Table 5).

**DISCUSSION**

Our preliminary results indicated preferential transmission of the DDK allele in the central region of chromosome X among female offspring of a $\text{(B6} \times \text{DDK)}\text{F}_1 \times \text{B6}$ backcross. We have confirmed the presence of preferential transmission of DDK alleles in the vicinity of DXMit210 among female offspring in two independent experiments: $\text{(B6} \times \text{DDK)}\text{F}_1 \times \text{B6}$ and $\text{(PG} \times \text{DDK)}\text{F}_1 \times \text{B6}$. The observed TRD is reproducible, can be explained by a single locus linked to the centromere, and is not the result of gene conversion (Table 3 and Figure 1). Therefore, female-offspring-specific TRD fulfills the requirements for testing the origin of maternal TRD, as defined by Pardo-Manuel de Villena et al. (2000a). Using this test, we are unable to reject the null hypothesis that the origin of the TRD is postmeiotic loss of a fraction of female offspring that carry the non-DDK allele at the distorted locus.

TRD at loci in the central region of chromosome X has also been observed in interspecific backcrosses (Biddle 1987; European Mouse Backcross Collaborative Group 1994; Johnson et al. 1994; Rowe et al. 1994; Montagutelli et al. 1996). The conditions for testing the origin of maternal TRD (Pardo-Manuel de Villena et al. 2000a) are satisfied by these backcrosses, and we are unable to reject the hypothesis that chromosome X TRD in these instances is also caused by postmeiotic selection.

Failure to reject the null hypothesis that TRD is the consequence of postmeiotic selection could result from the following: (1) simultaneous selection at both the first meiotic division (M1) and the second meiotic division (MII; see Figure 1 in accompanying article (Pardo-Manuel de Villena et al. 2000a)); (2) insufficient power of the dataset; or (3) true postmeiotic selection (Pardo-Manuel de Villena et al. 2000a).

In both the interspecific and the intraspecific back-
TABLE 4
Number of females that inherit each of the four possible maternal haplotypes at DXMit124 and DXMit210

<table>
<thead>
<tr>
<th>Haplotypes</th>
<th>Parental</th>
<th>Nonparental</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDK</td>
<td>B6/ PG</td>
</tr>
<tr>
<td>DXMit124</td>
<td>DDK</td>
<td>B6/ PG</td>
</tr>
<tr>
<td>DXMit210</td>
<td>DDK</td>
<td>B6/ PG</td>
</tr>
<tr>
<td>(B6 × DDK)F₁ × B6 females</td>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>(PG × DDK)F₁ × B6 females</td>
<td>81</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>161</td>
<td>122</td>
</tr>
</tbody>
</table>

TRD¹ is the percentage of TRD observed in each cross. TRD²/ TRD³ are the levels of TRD (percentage) observed in offspring bearing parental and nonparental chromosomes, respectively.

crosses analyzed in this article, we note that TRD is observed when the offspring have been sired by males of one parental strain but not when sired by males of the other (Montagutelli et al. 1996 and Table 2). As fertilization in the mouse takes place after the completion of MI, the genotype of the sire cannot affect MI; therefore, we can reject the origin of TRD as the result of selection at MI and, consequently, may also reject simultaneous selection at both MI and MII.

In the larger interspecific backcross, the analysis of the haplotypes of 415 offspring (cross 2, Table 5) demonstrates that not only is selection at MI rejected [because the effect of paternal genotype and TRD²/ (the level of TRD among parental chromosomes) is not greater than TRD³/ (the level of TRD among nonparental chromosomes; Pardo-Manuel de Villena et al. 2000a)] but these data also have sufficient power to reject the alternative hypothesis of selection at MII. If TRD occurs at MII, the maximum level of TRD that could be observed in cross 2 in Table 5 can be estimated by using the ratio of individuals arising from achiasmate tetrads/single crossover tetrads (Pardo-Manuel de Villena et al. 2000a) [double recombinants represent a very small fraction of the total offspring because the distortion-controlling loci are relatively close to the centromere (Montagutelli et al. 1996)]. Individuals arising from single recombinant tetrads may be estimated as twice the number of nonparental haplotypes observed, while the number of individuals arising from achiasmate tetrads are estimated as the difference between the total and the number of individuals arising from single recombinant tetrads. Therefore, the expected ratio is 275:140 (Table 5). The maximum overall level of TRD expected in the case of 100% selection within the single recombinant class would be 66.9%. This value is lower than the observed level of TRD, 82.2 ± 3.7% (Table 5). Moreover, the hypothesis of an MII origin for TRD can be rejected ($\chi^2 = 25.58, 1$ d.f., $P < 10^{-5}$). The other interspecific backcross represents a limited number of offspring (cross 1, Table 5), and this dataset does not have sufficient power to reject the alternative hypothesis that TRD is the result of selection at MII. However, it is unlikely that strong TRD in favor of M. spretus alleles on chromosome X will have two different origins, even if the source of M. spretus and B6 is slightly different in each case (European Mouse Backcross Collaborative Group 1994; Rowe et al. 1994).

Although the backcrosses performed in our labora-

TABLE 5
TRD in offspring inheriting parental and nonparental maternal haplotypes between the centromere and the distorted locus on chromosome X

<table>
<thead>
<tr>
<th>Cross</th>
<th>Haplotype</th>
<th>p₂</th>
<th>p₁</th>
<th>n₂</th>
<th>n₁</th>
<th>TRD¹</th>
<th>TRD²/ TRD³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (B6 × M. spretus)F₁ × M. spretus</td>
<td>81</td>
<td>55</td>
<td>13</td>
<td>57</td>
<td></td>
<td>82.2</td>
<td>82.3/81.4</td>
</tr>
<tr>
<td>2. (B6 × M. spretus)F₁ × M. spretus</td>
<td>61</td>
<td>284</td>
<td>13</td>
<td>57</td>
<td></td>
<td>86.2</td>
<td>88.1/81.5</td>
</tr>
</tbody>
</table>

In both crosses the dam is listed first and the sire second. Crosses 1 and 2 have been reported previously (European Mouse Backcross Collaborative Group 1994; Rowe et al. 1994; Montagutelli et al. 1996). The most centromeric and distorted loci used in each cross and their map positions are as follows: cross 1, DXMit126 (1.6) and DXMit187 (25.5); and cross 2, DXWas70 (0.5) and DXMit91 (17.5); genotypes at these loci and their map position were obtained from Mouse Genome Database (MGD) 3.1 (1998). p₂ parental B6, n₂ nonparental B6 at the centromere and M. spretus at the distorter. p₁ parental M. spretus, n₁ parental B6. TRD¹, TRD², and TRD³ are as defined in Table 4.
We also note some differences between these crosses: cle (intra- and interspecific backcrosses is unclear because these observations is explored in an accompanying arti-
result of a common biochemical mechanism in both offspring from these crosses. The relationship between
level of TRD p in one cross but less in the other. This In the intraspecific backcrosses, the fact that TRD is
result is qualitatively inconsistent and is not expected present in both the (B6
TRD, we note that the level of TRDn is greater than the backcrosses (data not shown).

We conclude that chromosome X TRD in the interspec-
cific backcrosses we have analyzed is the result of the
loss of embryos that inherit particular combinations of
alleles and that the same mechanism of postmeiotic loss
is also likely to be the cause of chromosome X TRD in
the intraspecific crosses described in this article.

Interestingly, TRD at chromosome-X-linked loci in
interspecific and intraspecific backcrosses displays sev-
eral common features:

1. Postmeiotic origin of maternal TRD.
2. Linkage between the distorted locus characterized
in this study in intraspecific backcrosses and the chro-
omosome X distortion-controlling loci (Dcsx1, Dcsx2)
described in interspecific backcrosses (Montagutelli et al. 1996). These three loci have been placed
using the method described by Montagutelli et al. (1996). Although their positions are not identical,
we note that the candidate intervals overlap exten-
sively. In addition lhp, a locus that contributes to
abnormal placental development (Zechner et al. 1996, 1997), is located in the same region and may
be the same as Dcsx1 (Boy d 1996).
3. Selection against maternal B6 alleles in both inter-
specific and (B6 \times DDK)F1 \times B6 backcrosses; and
4. TRD depends on the genotype of the sire (Montagutelli et al. 1996; this article).

Whether TRD at chromosome X is likely to be the
result of a common biochemical mechanism in both in-
tra- and interspecific backcrosses is unclear because we also note some differences between these crosses:

1. Both male and female offspring of the interspecific
backcrosses show TRD (Montagutelli et al. 1996),
but it is restricted to female offspring in the intra-
specific backcrosses.
2. The offspring of interspecific backcrosses show TRD
when M. spretus is used as the sire but not when
B6 males are used (Montagutelli et al. 1996). In
interspecific backcrosses, TRD does occur when B6
is used as the sire.
3. The level of TRD in interspecific backcrosses (82.2%; 86.2%) is much higher than the TRD we observe in
intraspecific backcrosses (58.4%).
4. Epistasis between chromosomes X and 2 accounts
for most or all of the TRD observed at X-linked loci
in the interspecific backcrosses (Montagutelli et al.
1996), but we do not observe an epistatic interaction
between chromosomes X and 2 in the intraspecific
backcrosses (data not shown).

In the intraspecific backcrosses, the fact that TRD is
present in both the (B6 \times DDK)F1 \times B6 and the (PG
\times DDK)F1 \times B6 backcrosses suggests that the observed
preference for the inheritance of DDK alleles by female
offspring is neither a preference for a DDK allele over
a B6 allele in particular (unless the wild-derived portion
of the PG chromosome X carries the same allele at the
distorted locus as the B6 strain) nor a specific deleteri-
eous effect of maternal B6 alleles in this region of chro-
mosome X. We also note that TRD is observed among
the offspring of (B6 \times DDK)F1 females when they are
mated to B6 males, but TRD is not apparent when the
reciprocal (DDK \times B6)F1 females are mated to B6 males,
which may suggest a parental origin effect on the trans-
mission of alleles at chromosome-X-linked loci, as has
been described in humans (Naumova et al. 1998). In
that case, male offspring inherit more maternal grand-
paternal alleles than maternal grandmaternal alleles at
DXS1068, while female offspring inherit both alleles
equally. The basis of this TRD is unknown but it occurs
in families that were not selected for genetic disease.
The region of the human chromosome X involved
appears to be homologous (Naumova et al. 1998) to the
region of the mouse chromosome X at which TRD is
observed in both inter- and intraspecific backcrosses
(Montagutelli et al. 1996; this article). Whether these
observations are related mechanistically is unclear.

Finally, we note that we observe TRD at loci on two
different chromosomes, X and 11, among offspring
from the same backcrosses (Pardo-Manuel de Villena et al. 2000a; this article). In the case of chromosome
11, TRD in favor of DDK alleles at Om occurs among
both male and female offspring (Pardo-Manuel de Villena et al. 1996, 1997, 2000a), while TRD in favor
of DDK alleles at DXM it210 occurs only among female
offspring from these crosses. The relationship between
these observations is explored in an accompanying arti-

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