Epistatic Control of Non-Mendelian Inheritance in Mouse Interspecific Crosses

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ABSTRACT

Strong deviation of allele frequencies from Mendelian inheritance favoring Mus spretus-derived alleles has been described previously for X-linked loci in four mouse interspecific crosses. We reanalyzed data for three of these crosses focusing on the location of the gene(s) controlling deviation on the X chromosome and the genetic basis for incomplete deviation. At least two loci control deviation on the X chromosome, one near Xist (the candidate gene controlling X inactivation) and the other more centromERICally located. In all three crosses, strong epistasis was found between loci near Xist and marker loci on the central portion of chromosome 2. The mechanism for this deviation from Mendelian expectations is not yet known but it is probably based on lethality of embryos carrying particular combinations of alleles rather than true segregation distortion during oogenesis in F1 hybrid females.

THE few examples of transmission ratio distortion (TRD) are genetically complex and involve chromosome rearrangements that preserve particular combinations of distortion-controlling alleles at closely linked loci (Crow 1991). TRD is defined as a statistically significant departure from Mendelian transmission, regardless of its basis. When due to meiotic drive, as in SD in Drosophila (Sandler and Novitski 1956; Sandler and Golic 1985; Lyttle 1991) and the HSR inverted duplication in wild populations of Mus musculus (Agulnik et al. 1993a; Ruvinsky 1995), it is appropriate to refer to the phenomenon as segregation distortion. By contrast, TRD associated with t haplotypes is not a consequence of meiotic drive but rather of the differential ability of sperm to fertilize eggs (LYON 1984; Silver 1985). In a third situation, deviation from Mendelian inheritance (DMI) probably results from lethality of embryos carrying particular combinations of alleles at unlinked loci (Zechner et al. 1996).

Modest but significant DMI is occasionally found in linkage testing crosses, e.g., chromosome 2 (Siracusa et al. 1989), chromosome 4 (Ceci et al. 1989) and chromosome 10 (Justice et al. 1990). Except for chromosome 2 (Siracusa et al. 1991), these phenomena have not been studied further. It is likely that all three DMI result simply from sampling fluctuations that are expected when relatively small numbers of mice are typed for many loci. This interpretation is supported by the fact that none of these DMI has been replicated in independent crosses.

By contrast, strong DMI (70–90%) favoring M. spretus-derived alleles at chromosome X-linked loci has been found in all four linkage crosses in which (C57BL/6J [or C3H] X M. spretus) F1 hybrid females were backcrossed to M. spretus males (Biddle 1987; European Mouse Backcross Collaborative Group 1994; Johnson et al. 1994; Rowe et al. 1994). Because the magnitude of DMI and the map location of affected loci were similar in all four backcrosses to M. spretus, it was unlikely that this deviation was due to sampling fluctuations alone. Three of these crosses afford an exceptional opportunity to study the genetic basis of the deviation because, as mapping panels available to the community, they have been typed for numerous loci spanning the entire genome (European Mouse Backcross Collaborative Group 1994; Johnson et al. 1994; Rowe et al. 1994). The aim of work presented here was to localize the gene(s) controlling DMI on chromosome X and investigate the genetic basis for incomplete deviation.

MATERIALS AND METHODS

Interspecific crosses: The backcrosses that we analyzed were either the BSS type [(C57BL/6J X M. spretus)F1 X M. spretus] or the BSB type [(C57BL/6J X M. spretus)F1 X C57BL/6J]. The following crosses were analyzed: (1) the Jackson Laboratory (C57BL/6J X M. spretus)F1 X C57BL/6J and (C57BL/6J X M. spretus)F1 X C57BL/6J/(Ei X SPR/En)F1 X SPR/Ei crosses (Rowe et al. 1994), referred to here as "JAX1 BSB" and "JAX1 BSS," respectively; (2) the (C57BL/6J X SPR)F1 X C57BL/6J and (C57BL/6J X SPR)F1 X SPR European Collaborative Interspecific Backcross (EUCIB) crosses (European Mouse Backcross Collaborative Group 1994), referred to here as "EUCIB BSB" and "EUCIB BSS," respectively; and (3) (C57BL/6J X SPR)F1 X SPR/(Ei X SPR)F1 X SPR/Ei crosses (Johnson et al. 1994) made at the Jackson Laboratory and referred to here as "JAX2." The M. spretus strain that was used (SPR) was not fully inbred although the mice are kept in a closed colony (European Mouse Backcross Collaborative Group 1994). Results for a second EUCIB inter-

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specific backcross were not included in the present analysis because of small sample size and partial genotyping.

Source of published genotypes: Genotypes for the JAX1 BSS and BSB crosses were obtained from the WWW Jackson Laboratory server (URL: http://www.jax.org). These data were posted on Feb. 21, 1995. Genotypes for the EUCIB BSS and BSB crosses were obtained from the MBX database as posted on Dec. 19, 1994 (BROWN 1995). On the X chromosome, only anchor loci DXMit8, DXWas70, Grpr, Plp and Xist were considered because they were typed for most animals. Genotypes from the JAX2 cross were provided by K. JOHNSON (personal communication). The analysis was restricted to a subset of loci (Figure 1); some loci were excluded because they did not recombine with others, some because more than six genotypes were missing for a given locus, and some because certain genotypes were unlikely (double recombinants in a short genetic interval). Where possible, we retained loci that were typed in all three panels, thereby facilitating map comparison.

Rules used to infer genotype: To increase the sample size for subsequent analyses, genotypes were inferred for animals that did not have a crossover between anchor loci. The rules for inferring a genotype were as follows: genotypes were not inferred for anchor loci; the map position of the locus for which a genotype was inferred relative to the two flanking loci was firmly established before the inference, i.e., alternative inferences did not affect the gene order; and distances between this locus and each of the flanking loci was <15 cM. Alternative inferences would result in apparent "single locus double crossovers," which are rare in these mapping panels (EUROPEAN MOUSE BACKCROSS COLLABORATIVE GROUP 1994; JOHNSON et al. 1994; ROWE et al. 1994). Loci between adjacent crossovers, i.e., within a crossover bin, show identical strain distribution patterns. For simplicity in data presentation, we present only one locus per bin. The identity of the other loci can be obtained from the primary data sources (see above).

Microsatellite genotype determination: To fill gaps in the published maps and to add marker loci for comparing mapping information from different crosses, additional microsatellite loci were added to the published EUCIB BSS and JAX2 mapping panels. PCR primers for microsatellite loci were described by DIETRICH et al. (1992–1994) and were obtained from Research Genetics (Huntsville, AL). Standard nonradioactive PCR methods were used to amplify microsatellite loci. PCR products were size-fractionated by using electrophoresis on 4% agarose gels and were detected with ethidium bromide (MONTAGUTELLI et al. 1991). For the EUCIB BSS crosses, we typed DXMit57, DXMit60, DXMit91, and DXMit105 for animals with crossovers between DXWas70 and DXMit8 (n = 112), DXMit16 for animals with crossovers between DXMit8 and Xist (n = 30), and DXMit28 for animals with crossovers between Plp and Grpr (n = 69). For the JAX2 cross, we typed DXMit57 (n = 92). New genotypes have been deposited in the MBX database (BROWN 1995) for the EUCIB cross or with K. JOHNSON (Jackson Laboratory) for the JAX2 cross.

Analysis of linkage, segregation and epistasis: All data were analyzed with the program Gene-Link (MONTAGUTELLI 1990), using an enhanced version to be described separately that includes tests for transmission ratio distortion and for epistasis. Unless specified otherwise, P values were calculated from the two-tailed binomial probabilities.

RESULTS

Segregation analysis: We first examined transmission of alternative alleles for each locus in all three crosses, then tested models for monogenic and digenic control of DMI, and finally examined transmission of recombinant chromosomes. For each X-linked locus, deviation from Mendelian inheritance was measured as the proportion of animals having inherited the S allele from their F1 hybrid mother for the BSS crosses and the B allele for the BSB crosses (Table 1 and Figure 1).

In the JAX1 BSS cross, the frequency of S alleles fluctuated ~50% as expected in the absence of deviation. The JAX1 BSS cross, but not the BSB cross, showed significant DMI, which was centered near DXMit87 and affected a ~50-cM segment of chromosome X. The EUCIB BSS cross, but not the BSB cross, also showed DMI, but a distinct DMI peak was not found and deviation was ≥80% over a ~40-cM region decreasing slowly toward the chromosome ends (DXMit91–Pfp, Table 1). JAX2 is derived from different crosses, one using C57BL/6J (designated JAX2/J, n = 95) and the other the substrain C57BL/6J/Ei (designated JAX2/Ei; n = 49) (JOHNSON et al. 1994; K. JOHNSON, personal communication). Progeny derived from C57BL/6J showed a broad, more telomerically located peak somewhat similar to that found in the EUCIB cross. By contrast, progeny derived from C57BL/6J/Ei showed a more centromerically located DMI peak somewhat similar, although not as distinct, as that found in the JAX1 cross. The contrasting results for these two crosses could reflect strain divergence between C57BL/6J and C57BL/6J/Ei, sampling effects, or both. Because of its small sample size, the JAX2/Ei subset was not analyzed further.

In all three crosses, DMI was usually stronger in male than female progeny (Table 1). However, because distortion favored the same alleles at the same loci in both sexes, data for males and females were pooled where appropriate in subsequent analyses.

DMI was occasionally found for autosomal loci (results not shown; cf. EUROPEAN MOUSE BACKCROSS COLLABORATIVE GROUP 1994; JOHNSON et al. 1994; ROWE et al. 1994). But because DMI was usually confined to a single locus and did not affect closely linked loci, or because it was found in only one of the three crosses, we suspect that these examples represent typing errors, incomplete typing, sampling fluctuations, or weak biological effects. Where records were available, we tested whether DMI depended on parity or age of the hybrid female, but neither factor contributed significantly to DMI.

The simplest hypothesis to explain DMI is a single distortion-controlling locus on the X chromosome (DCSX). Because linked loci will also show DMI, with distortion decreasing as recombination distance increases, the expected DMI at any locus can be calculated given the map location and strength of the proposed DCSX (see Figure 2 legend for a formal description of the model). Because the strongest DMI was near DXMit87, we first calculated the test statistic GF (RAO 1978) for the model with DCSX at DXMit87. We then incrementally moved the proposed DCSX centromerically or telomerically from DXMit87 and recal-
FIGURE 1.—Percentage of homozygotes, e.g., SS or BB vs. BS depending on the cross, at each locus on chromosome X in three interspecific crosses between C57BL/6 and inbred strains derived from Mus spretus. For each cross, the loci analyzed are listed on the right. Asterisks denote loci typed in more than one cross; these loci can be used to compare results for different crosses. (a) Jackson Laboratory crosses: □, JAX1 BSS (94 animals in total, all typed for individual loci); percentages of SS homozygotes are taken from Table 1; ■, JAX1 BSB (94 animals in total, 89–94 animals typed for individual loci); percentages of BB homozygotes were calculated from data stored in MGD and available on the World Wide Web (Rowe et al. 1994). (b) EUCIB crosses: □, EUCIB BSS (429 animals in total, 385–425 animals typed for individual loci); percentages of SS homozygotes are taken from Table 1; ■, EUCIB BSB (264 animals in total, 236–261 animals typed for individual loci); percentages of BB homozygotes were calculated from data stored in MBx (Brown 1995). (c) JAX2 crosses: □, (C57BL/6 × SEPRET/Ei)F1 × SEPRET/Ei cross (95 animals in total, 61–94 animals typed for individual loci); percentages of SS homozygotes are taken from Table 1; ○, (C57BL/6 × SEPRET/Ei)F1 × SEPRET/Ei cross (49 animals in total, 31–49 animals typed for individual loci); percentages of SS homozygotes were calculated separately (data not shown).

calculated GF at each point. GF estimates were compared for various proposed DCSX locations and the location that minimized GF was concluded to be the most likely location. A DCSX located 1.3 cM distal to DXMit87 with a predicted DMI (Kp) of 89% gave the best fit to the empirical data (GF = 2.33, 16 d.f., P ≈ 1; Figure 2a). This DCSX is designated Dcsxl. The JAX2 cross was also tested against a single locus model (Figure 2b). The best fit was obtained with a DCSX located ~2.1 cM distal to Hmg17-rs3 with a predicted DMI (Kp) of 75%.
**TABLE 1**

Distribution of SS and BS genotypes at different loci on chromosome X in three interspecific crosses between C57BL/6J and inbred strains derived from *Mus spretus*.

<table>
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<th>Offsets</th>
<th>n'</th>
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<th>BS</th>
<th>DMI</th>
<th>log(P)</th>
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**EUCIB BSS cross**

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**JAX 2/F cross**

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**JAX 2/Ei cross**

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For each locus in each cross, the allele frequency, DMI, and degree of significance are listed for each sex and for the entire data set. Codes A–P for the JAX1 BSS cross, A–K for the EUCIB cross, and A–J for the JAX2 cross enable comparisons between these typing results and graphic representations of transmission ratios (Figure 1). To calculate this proportion for male progeny, which are hemizygous X^Y or X^Y, homozygotes were those inheriting the allele from the F_1 parent that was also shared with the backcross parent, e.g., the S allele would be considered the homozygous allele when it was inherited from the F_1 hybrid crossed to a M. spretus parent, and it would be considered the heterozygous allele when it was inherited in crosses to C57BL/6J.

A letter is given to each locus for further reference in figures.

Offsets represent genetic distance from the centromere. Values in bold were taken from the 1994 Mouse chromosome X Committee Report (HERMAN et al. 1994). Other values were calculated from experimental data. All: males and females combined.

Number of animals typed for this locus.

Percentage of SS genotypes at this locus.

Logarithm of the probability to observe a similar or greater DMI under expected 1:1 Mendelian segregation ratio.
Non-Mendelian Inheritance in Mice

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Observed RF (%) from G (DXMit87)

FIGURE 2.—Comparison of the observed DMI on chromosome X with that expected from a single-locus model. Model: If $K_0$ is the DMI caused by $D_0$, and $d$ the recombination fraction between $D$ and a given locus $L$, then $K_i = d + K_0 (1 - 2d)$ where $K_i$ is the expected DMI at marker locus $L$ (cf. BAILEY 1961, p. 59, with modifications). Significance test: For $N$ loci analyzed, the goodness-of-fit was estimated by $GF = 4 \sum_{i=1}^{N} \left[ \arcsin \left( \sqrt{K_{o,i} - K_{e,i}} \right) \right]^2$ where $n_i$ is the number of animals typed for locus $i$, $K_{o,i}$ the observed DMI at locus $i$ and $K_{e,i}$ the expected DMI. $GF$ follows a chi-square distribution with $N$ degrees of freedom (RAO 1978).

When fitting the models to the data, $GF$ was more sensitive to changes in DMI ($\Delta$) values than in DCSX location. The actual location of the DCSXs identified in this analysis could well be several centimorgans away from the predicted location. In all instances, similar locations and DMI ($K_0$) values were found when sexes were analyzed separately. (a) Percentage of SS homozygotes on chromosome X in the JAX1 BSS cross. The horizontal axis shows observed recombination fraction (in percentage) between each locus and DXMit87 (G); left of 0, loci located proximal to DXMit87; right of 0, loci located distal to DXMit87. The DM1 observed in experimental data; $\blacklozenge$, DMI expected from a model involving a single DCSX located 1.3 cM distal to DXMit87, shown as a vertical bar ~21.3 cM from the centromere, with 89% homozygotes at this locus. (b) Percentage of SS homozygotes on chromosome X in the JAX2/J BSS cross. The horizontal axis shows observed recombination fraction (in percentage) between each locus and HmgJ7-rs3 (E); left of 0, loci located proximal to HmgJ7-rs3; right of 0, loci located distal to HmgJ7-rs3. The DM1 observed in experimental data with error bars showing the 95% confidence interval; $\blacklozenge$, DMI expected from a model involving a single Dcsx located 2.1 cM distal to HmgJ7-rs3, shown as a vertical bar ~36.6 cM from the centromere, with 75% homozygotes at this locus.

(GF = 6.27, 9 d.f., $P \approx 0.71$). This DCSX was designated Dcsx2. According to the X Chromosome Committee Report (HERMAN et al. 1994), Dcsx1 and Dcsx2 are located ~21.3 and ~36.6 cM from the centromere, respectively. Analysis of results for male and female progeny separately led to different values for the predicted DMI ($K_0$) but to similar positions for the DCSX loci.

When the single locus model was tested against the EUCIB BSS data, the “best” fit was obtained with a DCSX located ~1.5 cM proximal to DXMit16 with a predicted DMI ($K_0$) of 88% (Figure 3a). However, the predicted DMI did not give a good fit to the empirical data (GF = 36.1, 11 d.f., $P < 0.0002$). We therefore tested an alternative model involving two linked loci. We again varied the locations of the proposed DCSXs to find those that minimized GF. The best fit was obtained with a DCSX located ~2.5 cM distal to DXMit91 with a predicted DMI ($K_0$) of 85% and another DCSX located ~5.3 cM distal to Xist with a predicted DMI ($K_2$) of 84% (GF = 0.954, 11 d.f., $P \approx 1$; Figure 3b). These loci are designated Dcsx3 and Dcsx4, respectively. According to the X Chromosome Committee Report (HERMAN et al. 1994), these DCSXs are located ~20.5 and ~47.3 cM from the centromere. We note that Dcsx3 has a similar position (20.5 cM vs. 21.3 cM) as Dcsx1 identified in the JAX1 BSS cross, suggesting that these
loci are probably identical. Dcxs2 and Dcxs4 may also be identical, because they are within \(~36.6\) and \(~47.3\) cM, respectively. It is difficult to rule out the possibility of identity given the inherent variability between crosses and the modest number of loci that have been typed in the EUCIB and JAX2/J crosses and that can be used for integrating the results.

Two explanations could account for evidence of a single DCSX in the JAX1 and JAX2/J crosses while two DCSXs are found in the EUCIB cross. First, it could be due to a strain difference, since JAX1 and JAX2/J have been established from the inbred SPRET/Ei M. spretus strain, whereas the EUCIB cross used the outbred SPR stock. Second, it is possible that the distal DCSX is also present in JAX1 and JAX2/J crosses, but its modest effect is masked by the prominent deviation resulting from the proximal DCSX.

**Recombinant chromosome analysis:** The segregation analysis presented above was based on data for each locus in all progeny, and data were combined for
progeny with nonrecombinant and recombinant chromosomes. By examining haplotype data for progeny with recombinant chromosomes, it should be possible to obtain additional evidence for the genetic control of DMI. We divided chromosome X into five intervals and for each interval, compared the number of animals carrying the two reciprocal haplotypes that showed a recombination breakpoint in this interval. Only haplotypes with a single recombination breakpoint were analyzed. If a single locus controls DMI, it should be possible to identify the DCSX-containing interval among progeny with recombinant chromosomes. When comparing reciprocal haplotypes, if the interval considered is proximal to the DCSX, then all the chromosomes that are BS centromeric to the breakpoint-containing interval and SS distal to it are also SS at the DCSX and should therefore be systematically more frequent than their counterpart. The reverse applies to chromosomes that recombine in an interval distal to the DCSX. However, if the DCSX is contained in the interval studied (and approximately in its center), there should be no difference between reciprocal haplotypes since recombination might have occurred within the interval proximally or distally to the DCSX, and chromosomes that are SS toward the centromere will be either SS or BS at the DCSX.

For the JAX1 BSS cross, only the DXBir3-DXMit7 interval showed equal frequency of reciprocal haplotypes (Figure 4a). By contrast, significant deviation was observed for haplotypes with crossovers centromeric to DXBir3 or telomeric to DXMit7. The DXBir3-DXMit7 interval corresponds to the peak DMI in the segregation analysis and to the predicted peak based on modeling. This result provides additional evidence that deviation in this cross can be explained by a single DCSX. The EUCIB BSS cross, by contrast, showed three successive intervals with an equal frequency of reciprocal haplotypes; these intervals, which extend over 40 cM, were delimited by DXMit91 centromerically and Ptp telomerically. This analysis could not be applied to the JAX2 cross because DMI was weak and incomplete typing reduced the sample size of informative mice.

These results are not compatible with the hypothesis of a single DCSX. We propose that at least one DCSX is located in the centromeric interval that showed no deviation (DXMit91-DXMit60), another in the telomeric interval (Xist-Ptp), and that the middle interval does not have a DCSX. This interpretation is similar to that described above for chromosomes with a single DCSX. Chromosomes with a crossover in the DXMit91-DXMit60 interval that are BS toward the centromere could be either BS or SS at the proximal DCSX and SS at the distal DCSX. Depending on the mode of interaction between the two DCSXs, these chromosomes could be transmitted with a similar frequency as the reciprocal chromosomes. Chromosomes with crossovers in the DXMit60-Xist interval show equal frequency of reciprocal haplotypes, either because both DCSXs are required on the same chromosome for DMI or because each independently causes DMI. Regardless of the nature of their interaction, however, at least two DCSXs are required to explain three successive intervals showing normal transmission. Analysis of recombinant chromosomes confirms the number and location of the DCSXs proposed with the segregation and modeling analyses.

**Epistasis:** We next examined alternative explanations for incomplete DMI. We questioned whether DMI was 85% rather than 100% because of incomplete penetrance at the X-linked loci or whether “survival” of mice with the disfavored C57BL/6J derived the X chromosome depended on cosegregation of C57BL/6J-derived allele(s) elsewhere in the genome. Because the three crosses have been typed for large numbers of loci, these alternatives could be evaluated by testing for allelic associations, namely preferential occurrence of BS on the X chromosome and BS at the independently segregating locus, among all possible interlocus pairwise comparisons for the closest marker to each DCSX and autosomal marker loci in the three data sets. Significant associations were sometimes found in one cross but not in the other crosses (Figure 5). We suspect that lack of reproducibility reflects sampling fluctuations or weak strain-specific effects, e.g., chromosome 4 in JAX2/J (Figure 5). Simulation studies emphasize the importance of replication in complex trait analysis (Lander and Kruglyak 1995).

Only on chromosome 2 was strong, reproducible allelic association observed in the JAX1, EUCIB, and JAX2/J BSS crosses (Figure 5). Transmission of C57BL/6J-derived alleles on the X chromosome depended strongly on cosegregation of C57BL/6J-derived alleles on chromosome 2 (Table 2). In the JAX1 cross, transmission of the C57BL/6J-derived X chromosome at DXMit87 was rare in the absence of C57BL/6J-derived chromosome 2 alleles near D2Mit254 (2.4%, 1 of 41), but not when they were present (24.0%; 12 of 50, P < 0.006). Remarkably, the strongest association did not correspond to the locus showing the strongest DMI in the JAX1 cross. When testing all possible interlocus pairwise comparisons for loci on chromosomes X and 2, the most significant allelic association was found with loci near Xist rather than DeoxI, namely DXBir15 and D2Mit254 (P < 0.002). For the EUCIB cross, transmission of the C57BL/6J-derived allele at Xist was 8.3% (15 of 181) or 23.1% (51 of 221) depending on absence or presence, respectively, of C57BL/6J-derived chromosome 2 alleles at D2Mit304 (P < 0.00007). For the JAX2/J cross; transmission of the C57BL/6J-derived allele at Hmgl7-rs3 was 12.2% (5 of 41) or 43.5% (20 of 46) depending on absence or presence, respectively, of C57BL/6J-derived chromosome 2 alleles at Hmgl7-rs7 (P < 0.0018). Hmgl7-rs3 is located near Xist (Herman et al. 1994).

Only one exceptional mouse, which was SS on chromosome 2 and BS on the X chromosome, was found in the
FIGURE 4.—Frequency of recombinant X chromosomes in JAX1 BSS and EUCIB BSS crosses. For each class, animals were sorted according to their genotype for the most centromeric marker, the most telomeric marker, and two markers depicted with vertical bars. For each cross, letters refer to loci (and offsets) listed in Table 1. Open boxes represent regions of chromosome X that are homozygous SS and shaded boxes regions that are heterozygous BS. A cross indicates that a crossing-over occurred between the two markers depicted with vertical bars. P is the two-tail probability (as calculated from the binomial distribution) of observing a similar or greater deviation from the expected 1:1 ratio between the two alternative chromosomes. The graph below the chromosomes illustrates the value of log(P) for each interval. (a) JAX1 BSS cross (94 animals); (b) EUCIB BSS cross (429 animals).

JAX1 cross and only 15 exceptions in the EUCIB cross. Several of these exceptional progeny have recombinant chromosomes with breakpoints in the interval flanking the locus showing the strongest association. For example, the exceptional mouse in the JAX1 BSS cross has a crossover between DXMit87 and DXMit7, suggesting that Dcx1 is near but telomeric to DXMit87. Finally, epistasis between chromosomes 2 and X was asymmetric. Transmission of X-linked M. sat†us-derived alleles did not depend on cosegregation of particular chromosome 2 alleles, i.e., 38 2m vs. 40 2s in Xs for the JAX1 cross and 170 2m vs. 166 2s in Xs for the EUCIB cross (Table 2).

Epistasis between chromosomes 2 and X accounts for most but not all of the disfavored X-linked alleles that were transmitted; the remaining variation may reflect sex effects, reduced penetrance, epistasis with additional loci that have weaker or more variable effects, or sampling fluctuations. Because additional partitioning of the data substantially reduces statistical power, it was difficult to test these effects rigorously. However, it may be noteworthy that the distortion on chromosome 2 in animals that were BS for the X chromosome was statistically significant only among female progeny (female progeny: JAX1, P < 0.004; EUCIB, P < 2.0 × 10⁻⁶; JAX2/J, P < 0.007; male progeny: no significant differences in any of the three crosses). Thus, although DMI is generally stronger in male than female progeny in all three crosses, the association between chromosomes X and 2 occurred primarily among female progeny (Table 2). These results suggest that epistasis may be difficult to detect because of the small number of Xs males, or because presence of 2s does not provide as strong “rescue” of Xs in males as in females.

DISCUSSION

Our analysis has several unique attributes, including replication with similar inbred strains, large numbers
Non-Mendelian Inheritance in Mice

Although DMI is occasionally reported for linkage testing crosses, the evidence is usually based on small to modest sample sizes. As a result, statistical fluctuations are difficult to eliminate as an explanation (Lande and Kauffman, 1995). We were fortunate to have access to large samples sizes. Although DMI is occasionally reported for a single cross, the evidence is usually based on small to modest sample sizes.

**Cross (Chr X locus)**

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**Figure 5.** Epistasis between X-linked and autosomal loci in three interspecific crosses. For each cross, animals were classified according to their genotype at the closest marker to the DCSX identified in the modeling analysis: □, all animals; ■, animals heterozygous at the X-linked locus; ♦, animals homozygous at the X-linked locus. Only chromosomes showing a significant departure from Mendelian segregation in one of the three crosses are shown. For readability, only representative loci are shown. The horizontal axis shows approximate recombination distance from the centromere as taken from the 1994 Chromosome Committee Reports (Silver et al. 1994) where appropriate or estimated from experimental data. The vertical axis is a measure of the deviation from 1:1 Mendelian transmission at the autosomal locus. Its absolute value is the decimal logarithm of the probability of observing deviation by chance. Positive values indicate an excess of homozygotes, negative values an excess of heterozygotes.
results for three large and independent crosses based on closely related strains. Similar results in independent crosses increases the chance that the results are real rather than sampling artifacts.

Two X-linked loci are proposed, one located near DXMit87 at ~20.0 cM and the other located more telomERICally near Xist at ~42.0 cM. For the JAX1 and EUCIB crosses, which involved different substrains of both C57BL/6 and M. spretus, DCSX loci were mapped to ~21.3 and ~20.5 cM (Table 1, Figures 1–3). Analysis of DMI in mice with recombinant chromosomes mapped a DCSX to the same region in both crosses, namely the interval between ~18.0 and ~28.0 cM (Figure 4). The failure to find similar evidence in the JAX2/J cross is perplexing, but may simply result from DMI and statistical fluctuations. The most parsimonious explanation for these results is that a single DCSX near DXMit87 contributes to DMI. No evidence was found in any cross for epistasis involving this DCSX locus (Figure 5).

Recently a locus affecting placental mass (Ihpd) was mapped near DXMit8 in interspecific backcrosses (ZECHNER et al. 1996). In backcrosses to M. spretus, placental mass was significantly decreased among heterozygous BS progeny as compared with their homozygous SS sibs. By contrast, placental hypertrophy was found in reciprocal backcrosses to inbred strains of laboratory mice with placental weight being significantly higher among heterozygous BS segregants than among homozygous BB sibs. Differences in placental mass could lead to biased embryonic lethality and to non-Mendelian inheritance. The similar map locations for the centromeric DCSX and loci controlling placental weight and epistasis must be involved to account for these differences between segregating crosses and the parental strains (ZECHNER et al. 1996), but the chromosomal location and genetic identity of the autosomal locus remain to be determined.

All three crosses provided evidence for a more telomERICally locus DCSX locus within 13 cM of each other and near Xist at ~42.0 cM. Modeling placed a DCSX at 47.3 cM in the EUCIB cross and at ~36.6 in the JAX2/J cross. Analysis of mice with recombinant chromosomes in the EUCIB cross supported this localization with a DCSX in the interval between ~42.0 and ~56.0 cM. Because relatively few X-linked loci have been typed in the JAX2/J cross (JOHNSON et al. 1994; Table 1), insufficient recombinant chromosomes were available for a meaningful analysis. No evidence was found for a telomeric DCSX in the JAX1 cross, perhaps because C57BL/6Ei (JAX1) has a weaker allele at this locus than does C57BL/6J (EUCIB and JAX2/J). In all three crosses, remarkably strong epistasis involved the same X-linked locus: near DXBir5 at ~46.8 cM in the JAX1 cross, near Xist at ~2.0 cM in the EUCIB cross, and near Hmg17-rs3 at ~34.5 cM in the JAX2/J cross.
Heterogeneity between these map localizations, between ~34.5 and ~47.5 cM, is greater than for the centromeric DCSX. But heterogeneity is not surprising given the genetic and statistical variability for results with different crosses. In fact, the consistent map localizations despite heterogeneity is striking. The most parsimonious explanation for these results is therefore that a second DCSX near Xist contributes to DMI and shows strong epistasis with a locus on chromosome 2.

Siracusa et al. (1991) found strong DMI favoring "spretus"-derived alleles and mapping to the central portion of chromosome 2 for female progeny; DMI in male progeny mapped near the telomere. No evidence for epistasis was detected. Although DMI did not occur on chromosome 2 in the BSS crosses, strong epistasis involving genes on the similar portion of the chromosome was detected (Table 2, Figure 5). It is possible that these two effects, namely, DMI in BSS crosses and epistasis in BSS crosses, are different manifestations of the same chromosome 2 gene.

A curious and perhaps informative feature of these crosses is similar litter sizes in the reciprocal backcrosses. If DMI results from lethality of particular embryos, then litter sizes could be smaller in backcrosses to M. spretus than in crosses to C57BL/6J. However, review of the breeding records provided little evidence for a difference in litter size (results not shown; cf. European Mouse Backcross Collaborative Group 1994; Johnson et al. 1994; Rowe et al. 1994). A possible explanation is that DMI occurs early in development before litter size is determined. If gametogenesis is biased, or if more embryos are conceived than implant and loss of some embryos allows others to survive, then DMI without litter size reduction could occur. For t haplotypes, the effects of distortion are revealed at conception and litter sizes are not substantially reduced, despite a transmission ratio of 90% (Chesley and Dunn 1936; Silver 1985). This hypothesis predicts that DMI in interspecific crosses results from biased oogenesis in eggs fertilized by sperm from M. spretus but not from C57BL/6J (cf. Agulnik et al. 1993a; Ruvinsky 1995) or that DMI arises from loss of certain embryos before implantation. Studies addressing this question are underway.

The mechanism responsible for the non-Mendelian inheritance remains unclear. Because DMI is not observed when F1 females are mated with B6 males, the simplest hypothesis is that deviation originates from early death of embryos with specific combinations of alleles. However, an additional hypothesis is required to explain the empirical data. In the EUCIB cross, only 10 (13%) 2o2o males are XoYo, whereas 68 (87%) are XoY. Under the differential embryonic viability model, this deviation from equal frequency is explained by partial lethality of the 2o2o XoYo males. However, F1 males, which are also 2o2o XoYo, should also be affected and a reduced number of males per F1 litter should result. Because lethality of XoXo females is partially avoided by M. spretus-derived alleles on chromosome 2 (Table 2), F1 female embryos should be less affected than males, resulting in strong sex ratio distortion (one male per four females). Such distortion has not been reported in the literature or observed in our experience (data not shown). This model would require either that additional autosomal loci (undetected so far) are involved in the epistatic control of DMI, or that the lethality associated with the XoYo or XoXo genotype depends on the genotype of the mother that transmitted the Xo chromosome (no lethality if Xo transmitted by a C57BL/6J female and partial lethality if Xo transmitted by an F1 female).

An alternative mechanism for DMI is meiotic drive during female gametogenesis. Female meiosis is arrested at metaphase II until fertilization. When the sperm enters the oocyte, meiosis resumes, resulting in the production of the second polar body, before pronuclei merge to constitute the zygote. Agulnik et al. (1993a,b; Ruvinsky 1995) reported meiotic drive in mice that are heterozygous for an inversion on chromosome 1. Progeny from heterozygous females mated with inversion homozygous males show modest deficiency of inversion heterozygotes among their progeny because of increased preweaning lethality. When inversion heterozygous females were mated with wild-type males, wild-type progeny were found in large excess (85%). By comparing the number of resorbing and developing embryos in pregnant females, these authors showed that distortion was due to meiotic drive in females and that it was controlled by the genotype of the sperm fertilizing the oocyte (Agulnik et al. 1993b). The DMI observed in interspecific crosses shows many similarities and could have the same origin. However, the molecular mechanism would be complex being controlled by both chromosome X and chromosome 2-linked genes.

DMI in interspecific crosses may be an example of genetic coadaptation (Dobzhansky 1936; Muller 1939, 1940, 1942; Hurst and Pomianko 1991b; Coyne 1992; Cabot et al. 1994; Wu and Palopolli 1994; Orr 1995) rather than true meiotic drive (or segregation distortion) (Sandler and Novitski 1957; Crow 1991). With genetic divergence, coadaptations arise that cause or reinforce reproductive isolation and speciation. Disrupted coadaptations are usually detected as reduced fitness in interspecific hybrids (Dobzhansky 1936; Muller 1942; Cabot et al. 1994). These coadaptations could also be disrupted among progeny of interspecific crosses. If appropriate loci are typed among progeny of these crosses, these disruptions might be detected as DMI where deficiency of progeny with the maladaptive allelic combination causes biased transmission ratios (Guenet 1985; Coyne 1986). Because coadaptations do not depend on linkage, epistasis would be a characteristic of coadapted genes in segregating interspecific crosses. DMI in these interspecific crosses
may therefore represent an opportunity to study the evolution of coadapted genes that contribute to reproductive isolation and speciation.

Epistasis involving unlinked loci is not a common feature of the classical examples of DMI. SD, t haplotypes, the HSR inversion, and many other examples of DMI involve closely linked loci that act as "selfish DNA," in violation of Mendel's laws (Silver 1993). Particular combinations of alleles at these loci are called haplotypes. Preferential transmission of selfish haplotypes to the detriment of alternative haplotypes results in DMI. Distortion can occur in females, e.g., one chromosome is preferentially included in the egg nucleus rather than the polar body (Agulnik et al. 1993b; Ruvinsky 1995), or in males, e.g., sperm with a particular chromosome are preferentially transmitted (Sandler and Golick 1985; Seltz and Bennett 1985; Lyttle 1991). Chromosome rearrangements such as inversions protect these haplotypes from crossingover and recombination, thereby preserving the selfish alleles (Lyon 1984; Sandler and Golick 1985; Silver 1985; Lyttle 1991; Agulnik et al. 1993a,b; Crow 1991; Ruvinsky 1995). Unlinked loci are rarely involved because independent assortment disrupts the allelic combination required for DMI (Hartl 1975; Thomson and Feldman 1974–1976; Liberman 1976; Eshel 1985; Crow 1991; Haig and Grafen 1991; Hurst and Pomianowski 1991a). Unlinked modifiers of DMI have been described in these systems, but their effects are generally weak (Bennett et al. 1983; Sandler and Golick 1985; Crow 1991).

The effect of the chromosome 2 locus is consistent with theoretical expectations in that the C57BL/6J-derived allele decreases rather than increases DMI. As Crow (1991) showed, selection favors unlinked modifiers that reduce DMI. As shown in Table 2, DMI for X-linked loci in pooled data for the three crosses is 91.3% (221 of 242 progeny) without the C57BL/6J-derived allele and only 73.8% (234 of 317 progeny) with the allele. Of course, DMI in these interspecific crosses would only occur in hybrid zones between natural populations. Presumably the combinations of alleles that occur within each population or species are mutually adapted and it is only in interspecific crosses that allelic incompatibilities are manifested. The effect of the chromosome 2 gene as a modifier of DMI may therefore be a special case because it would have limited opportunities to evolve as a response to X-linked DMI.

Muller (1942) showed that allelic incompatibilities should be asymmetric: if one combination of alleles at two loci is incompatible, the other combination must be compatible. This phenomena has been called "reinforcing" epistasis (Crow and Kimura 1970, pp. 80–81), where a maladaptive effect at one locus depends on the genotype at other loci. The interspecific crosses described here represent an example of this phenomena. The allelic combinations 2ns and Xns in females (and Xn in males) are incompatible, but 2ns and Xns (and Xn in males), 2ns and Xns (and Xn in males but to a lesser extent), and 2ns and Xns (and Xn in males) are compatible. This asymmetry may simply reflect an intermediate stage in the divergence of interacting proteins where one protein must lose its ability to interact first, e.g., a receptor loses its ability to recognize a ligand before the ligand loses its ability to activate the receptor.

Reinforcing epistasis may also explain why DMI does not occur in reciprocal backcrosses, but instead occurs only in backcrosses to M. spreitus and not to C57BL/6J. In backcrosses to C57BL/6J, all progeny have C57BL/6J-derived chromosome 2 alleles that seem to be required for transmission of C57BL/6J-derived the X chromosome alleles (Table 2). But in crosses to M. spreitus, progeny will be at a disadvantage if they inherit the C57BL/6J-derived the X chromosome without also inheriting the C57BL/6J-derived chromosome 2. Reinforcing epistasis may represent a step in the process leading to reproductive isolation. The next step might be loss of the alternative allelic incompatibility, e.g., 2ns and Xns, and speciation.

The parental strains used in these crosses cannot be strictly compared with natural populations for at least two reasons. First, C57BL/6J, like most laboratory inbred strains, is an artificial hybrid whose genome is composed of DNA derived from at least two different subspecies, namely M. musculus domesticus and M. musculus musculus. Second, C57BL/6J and SPRET/Ei are inbred strains where genetic variation is rarely found. However, these interspecific backcrosses provide a simple experimental system to investigate genetic coadaptation because mice with various allelic combinations can be created and characterized. Allelic interactions may not be similar to those acting in wild populations, particularly since M. musculus domesticus and M. spreitus are sympatric in parts of their range but very rarely interbreed or produce hybrids. However, these crosses can be used as a model to study coadapted genes that contribute to reproductive isolation and speciation.

Finally, it is tempting to speculate that an anomaly in X inactivation (or reactivation) (Chapman 1986; Rastan 1994) accounts for DMI. In the EUCIB and JAX2 crosses, an X-linked DCSX gene maps near Xist, the candidate gene for X inactivation (Brockdorff et al. 1991, 1992). In addition, the X-linked locus showing the strongest association with loci on chromosome 2 is near Xist in all three crosses. If the timing or specificity of X inactivation (or reactivation) differed between the species represented in these inbred strains, fertilization or embryogenesis might be compromised (Kay et al. 1993). An autosomal locus is thought to be involved in controlling X inactivation (or reactivation), but its location and identity are unknown (Kay et al. 1994). If it is on chromosome 2 near D2Mit254 and D2Mit304 (Table 2), these interspecific crosses may offer an opportunity to find this gene.
We are grateful to Ken Johnson for sharing DNAs for additional marker typings and pedigrees for mice in his mapping panel, Francck Bourgard for technical assistance, and Aravinda Chakravartii, Wayne Frankel, Ken Johnson, Ken Morgan, Carmen Sapienza, Lee Silver, Ben Taylor and Fernando Paro Manuel de Villena for discussions of this problem and comments on a draft of this manuscript. This work was supported by National Institutes of Health Grant HG-00330.

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