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Note

Variation in Genomic Recombination Rates Among Heterogeneous Stock Mice

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ABSTRACT

We used a large panel of pedigreed, genetically admixed house mice to study patterns of recombination rate variation in a leading mammalian model system. We found considerable inter-individual differences in genomic recombination rates and documented a significant heritable component to this variation. These findings point to clear variation in recombination rate among common laboratory strains, a result that carries important implications for genetic analysis in the house mouse.

THE rate of recombination—the amount of crossing over per unit DNA—is a key parameter governing the fidelity of meiosis. Recombination rates that are too high or too low frequently give rise to aneuploid gametes or prematurely arrest the meiotic cell cycle (Hassold and Hunt 2001). As a consequence, recombination rates should experience strong selective pressures to lie within the range defined by the demands of meiosis (Coop and Przeworski 2007). Nonetheless, classical genetic studies in Drosophila (Chinnici 1971; Kidwell 1972; Brooks and Marks 1986), crickets (Shaw 1972), flour beetles (Dewees 1975), and lima beans (Allard 1963) have shown that considerable inter-individual variation for recombination rate is present within populations. Recent studies examining the transmission of haplotypes in human pedigrees have corroborated these findings (Broman *et al.* 1998; Kong *et al.* 2002; Coop *et al.* 2008).

Here, we use a large panel of heterogeneous stock (HS) mice to study variation in genomic recombination rates in a genetic model system. These mice are genetically admixed, derived from an initial generation of pseudorandom mating among eight common inbred laboratory strains (DBA/2J, C3H/HeJ, AKR/J, A/J, BALB/cJ, CBA/J, C57BL/6J, and LP/J), followed by >50 generations of pseudorandom mating in subsequent hybrid cohorts (Mott *et al.* 2000; Demarest *et al.* 2001). The familial relationships among animals in recent generations were tracked to organize the mice into pedigrees. In total, this HS panel includes ~2300 animals comprising 85 families, 8 of which span multiple generations. The remainder consists of nuclear families (sibships) that range from 1 to 34 sibs, with an average of 9.6 sibs (Valdar *et al.* 2006) (Table 1). Additional details on the derivation and history of these HS mice are provided elsewhere (see Mott *et al.* 2000; Demarest *et al.* 2001; Shifman *et al.* 2006).

With the exception of several founding individuals, most of these HS mice have been genotyped at 13,367 single nucleotide polymorphisms (SNPs) across the genome (available at http://gscan.well.ox.ac.uk/). Although the publicly available HS genotypes have passed data quality filters (Shifman *et al.* 2006), we took several additional measures to ensure the highest possible accuracy of base calls. First, data were cleansed of all non-Mendelian inheritances, and genotypes with quality scores <0.4 were removed. Genotypes that resulted in tight (<10 cM in sex-specific distance) double recombinants were also omitted because strong positive crossover interference in the mouse renders such closely spaced crossovers biologically very unlikely (Broman *et al.* 2002). A total of 10,195 SNPs (including 298 on the X chromosome) passed these additional quality control criteria; the results presented below consider only this subset of highly accurate (>99.98%) and complete (<0.01% missing) genotypes. The cleaned data are publicly available (at http://cgd.jax.org/mousemapconverter/).

We used the *chrompic* program within *CRI-MAP* (Lander and Green 1987; Green *et al.* 1990) to estimate

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TABLE 1

Heterogeneous stock mouse pedigrees

Pedigree	Pedigree class	No. of nonoverlapping sibships in the pedigree	No. of retained sibships	No. of meioses
1	Multigenerational	17	17	464
2	Multigenerational	27	20	728
3	Multigenerational	23	19	602
4	Multigenerational	14	9	254
5	Multigenerational	11	9	242
6	Multigenerational	5	3	68
7	Multigenerational	4	3	100
8	Multigenerational	2	1	16
9	Sibship[a]	2	1	20
32–85	Sibship		51	1146
Total		180	132	3640

[a] This family was composed of two sibships sharing a common mother but with different fathers.

the number of recombination events in parental meioses. The algorithm implemented in *chrompic* first phases parent and offspring genotypes using a maximum-likelihood approach. Next, recombination events occurring in the parental germline are identified by comparing parent and offspring haplotypes across the genome (Green *et al.* 1990). For example, a haplotype that first copies from one maternal chromosome and then switches to copying from the other maternal chromosome signals a recombination event in the maternal germline.

chrompic is very memory intensive and cannot handle the multigenerational pedigrees and the large sibships included in the HS panel. To circumvent these computational limitations, several modifications to the data were implemented. First, the eight multigenerational pedigrees were split into 102 nonoverlapping sibships, retaining grandparental information when available (Table 1). Two of these sibships shared a common father, but had different mothers. Combined with the 77 single-generation families in the HS panel, this data set then comprised a total of 180 sibships (one single-generation family consisted of two sibships with a common mother but different fathers). Second, we eliminated 35 of the 180 sibships for which neither parent was genotyped, and 13 additional families that featured only one genotyped parent and fewer than seven offspring (Table 1). These filters were implemented to avoid overestimating crossover counts (Cox *et al.* 2009). Finally, large sibships were subdivided: sibships with >13 progeny were split into two groups: those with >26 progeny were split into three groups and those with >39 sibs were split into four groups. Partitioning large sibships by units of 10, 11, or 12, rather than 13, had no effect on the estimation of crossover counts, suggesting that the estimates were robust to the unit of subdivision. These subdivided families were used only for haplotype inference; all other analyses treated whole sibships as focal units. In total, we analyzed 132 nonoverlapping sibships, ranging in size from 2 to 48 sibs (mean = 13.9). This data set encompassed 3640 meioses—300–2000% more meioses than previously studied human pedigrees (Broman *et al.* 1998; Kong *et al.* 2002; Coop *et al.* 2008)—providing excellent power to detect recombination rate variation among individuals.

The recombination rate for the maternal (or paternal) parent of a given sibship was estimated as the average number of recombination events in the haploid maternal (or paternal) genomes transmitted to her (or his) offspring. Our analyses treat males and females separately, as previous observations in mice (Murray and Snell 1945; Mallyon 1951; Reeves *et al.* 1990; Dietrich *et al.* 1996; Shifman *et al.* 2006; Paigen *et al.* 2008), along with findings from this study, point to systematically higher recombination rates in female than in male mice (this study: $P < 2.2 \times 10^{-16}$, Mann–Whitney *U*-Test comparing autosomal crossover counts in the 131 HS females to those in the 131 HS males).

There is considerable recombination rate heterogeneity among the 131 mothers and 131 fathers in the HS pedigrees (Figure 1). The female with the highest recombination rate had an average of nearly twice as many crossovers per meiosis compared with the lowest (female range: 9.0–17.3; mean = 13.3; SD = 3.28). Similarly, the least actively recombining male had only 55% the amount of recombination as the male with the highest recombination rate (male range: 7.7–14.7; mean = 11.7; SD = 2.76). These average values are similar to previously reported recombination counts in house mice, determined using both cytological (Dumas and Britton-Davidian 2002; Koehler *et al.* 2002) and genetic (Dietrich *et al.* 1996) approaches. Note that the recombination rates that we report reflect the number of exchange events visible in *genetic* data. Under the assumption of no chromatid interfer-

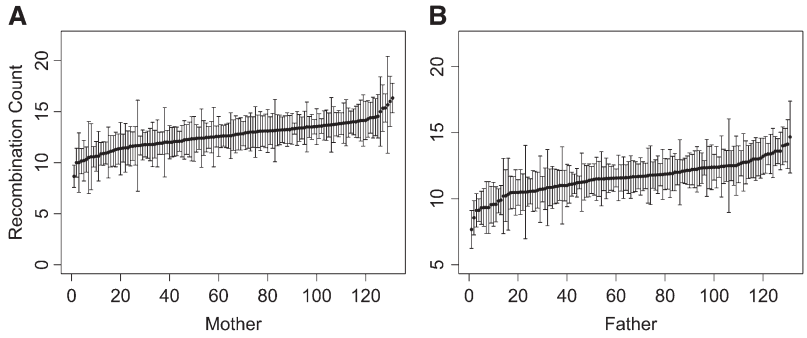

FIGURE 1.—Variation in recombination frequency in HS mice. The mean number of recombination events per transmitted gamete in each mother (A; $n = 131$) and father (B; $n = 131$) was inferred by comparing parent and offspring genotypes at >10,000 autosomal and X-linked markers using the *CRIMAP chrompic* computer program. Error bars span ±2 SEs.

ence, the expected number of crossovers that occur at meiosis is equal to twice these values.

To test for variation in recombination within the HS females and within the HS males, we performed a one-way ANOVA using parental identity as the factor and the recombination count for a single haploid genome transmission on the pedigree as the response variable. Significance of the resultant *F*-statistic was empirically assessed by randomizing parental identity with respect to individual recombination counts, recomputing the *F*-statistic on the permuted data set, and determining the quantile position of the observed *F*-statistic along the distribution of 10^6 *F*-statistics derived from randomization. There is highly significant variation for genomic recombination rate among HS females ($F = 1.7842$, $P < 10^{-6}$; Figure 1A) and males ($F = 2.3103$, $P < 10^{-6}$; Figure 1B).

We next examined patterns of recombination rate inheritance using the eight complex families to test for heritability of this trait. We fit a polygenic model of inheritance using the *polygenic* command within *SOLAR* v.4, accounting for the uneven relatedness among individuals through a matrix of pairwise coefficients of relatedness (ALMASY and BLANGERO 1998). Sex was included as a covariate in the model to account for the well-established differences between male and female recombination rates in mice (MURRAY and SNELL 1945; MALLYON 1951; REEVES *et al.* 1990; DIETRICH *et al.* 1996; SHIFMAN *et al.* 2006; PAIGEN *et al.* 2008). Recombination rates show significant narrow-sense heritability ($h^2 = 0.46$; SE = 0.20; $P = 0.008$), indicating that variation for recombination rate among HS mice is partly attributable to additive genetic variation. This result agrees with previous evidence for genetic effects on recombination rate variation in the house mouse (REEVES *et al.* 1990; SHIROISHI *et al.* 1991; KOEHLER *et al.* 2002).

In summary, we have shown that HS mice differ significantly in their genomic recombination rates and have demonstrated that this variation is heritable. These findings indicate that interstrain variation for genomic average recombination rate exists among at least two of the eight progenitor strains of the HS stock, mirroring observations of significant variation among inbred laboratory strains for many other quantitative characters (GRUBB *et al.* 2009). Indeed, cytological analyses have already revealed significant differences in recombination frequencies between A/J and C57BL/6J males (KOEHLER *et al.* 2002), two of the HS founding strains.

This interstrain variation in genomic recombination rate carries important practical implications for genetic analysis in the house mouse. Most notably, crosses using inbred mouse strains with high recombination rates will provide higher mapping resolution than crosses using strains with reduced recombination rates. However, the strategic use of high-recombination-rate strains will not necessarily expedite the fine mapping of loci. The distribution of recombination events in mice is not uniform across chromosomes and appears to be strain specific (PAIGEN *et al.* 2008; GREY *et al.* 2009; PARVANOV *et al.* 2009).

The history of the classical inbred mouse strains as inferred from pedigrees (BECK *et al.* 2000), sequence comparisons to wild mice (SALCEDO *et al.* 2007), and genomewide phylogenetic analyses (FRAZER *et al.* 2007; YANG *et al.* 2007) suggests that much of the interstrain variation for recombination rate arises from genetic polymorphism among *Mus domesticus* individuals in nature. However, many other factors have likely shaped recombination rate variation among the classical strains, including inbreeding, artificial selection, and hybridization with closely related species (WADE and DALY 2005). These aspects of the laboratory mouse's history challenge comparisons between recombination rate variation in the HS panel and human populations and provide strong motivation for studies of recombination rate variation in natural populations of house mice.

Although we find a strong genetic component to inter-individual variation in recombination rate, a large fraction (~54%) of the phenotypic variation for recombination is not explained by additive genetic variation alone. Sampling error and other forms of genetic variation (*e.g.*, dominance and epistasis) likely combine to account for some of the residual variation. In addition, micro-environmental differences within the laboratory setting (KOREN *et al.* 2002) and life history differences

among families, including parental age (Koehler *et al.* 2002; Kong *et al.* 2004), might contribute to variation in recombination rates among the HS mice.

Identifying the genetic loci that underlie recombination rate differences among the HS mice (and hence in the eight founding inbred strains) presents a logical next step in the research program initiated here. The complicated pedigree structure, relatively small number of animals with recombination rate estimates ($n = 262$), and potentially sex-specific genetic architecture of this trait (Kong *et al.* 2008; Paigen *et al.* 2008) will pose challenges to this analysis. Nonetheless, dissecting the genetic basis of recombination rate variation is a pursuit motivated by its potential to lend key insights into several enduring questions. Why do males and females differ in the rate and distribution of crossover events? What are the evolutionary mechanisms that give rise to intraspecific polymorphism and interspecific divergence for recombination rate? What are the functional consequences of recombination rate variation? Alternative experimental approaches, including those that combine the power of QTL mapping with immunocytological assays for measuring recombination rates *in situ* (Anderson *et al.* 1999), promise to offer additional clues onto the genetic mechanisms that give rise to variation in this important trait.

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