REPORT

Polymorphic Variation in Human Meiotic Recombination

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In this study, our phenotype of interest is meiotic recombination. Using genotypes of ~6,000 SNP markers in members of the Centre d'Étude du Polymorphisme Humain Utah pedigrees, we found extensive individual variation in the number of female and male recombination events. The locations and frequencies of these recombination events vary along the genome. In both female and male meiosis, the regions with the most recombination events are found at the ends of the chromosomes. Our analysis also shows that there are polymorphic differences among individuals in the activity of the recombination "jungles"; these preferred sites of meiotic recombination differ greatly among individuals. These findings have important implications for understanding genetic disorders that result from improper chromosome segregation.

Meiotic recombination is a key mechanism for generating genetic diversity. In meiosis, crossovers result in genetic exchanges that provide daughter cells with new combinations of parental alleles. Because of the fundamental role of meiotic recombination, there is intense interest in identifying and characterizing the sites and the frequencies of crossovers during meiosis. These have been studied using different methods. Recombination sites have been inferred from family-based linkage data that identify DNA segments shared between related individuals.[1–3] In other studies, recombination sites were identified from genotypes in individual or pooled sperm samples.[4–6] Crossovers have also been analyzed directly by cytogenetic analysis with the use of labeled proteins, such as MLH1, that are involved in meiosis[7–9] (for a recent review, see the work of Lynn et al.[10]). More recently, historical recombinations have been inferred by coalescent analysis.[11]

Results from these studies showed that there is extensive natural variation in human meiotic recombination. Across the human genome, there are regions with high and low recombination rates. Sperm-typing studies and cytogenetic analyses have reported interindividual variation in recombination frequency in men and women.[6,8,9,12] However, linkage-based studies found significant variation in recombination only among women.[1,2] In this study, we analyzed meiotic recombination with genotypes from 38 CEPH Utah families.[13] A linkage-based approach allows better resolution and analysis of more individuals for assessment of variability in recombination phenotypes than does a cytogenetic approach, since collection of spermatocytes and oocytes is not necessary. Compared with inference methods that rely on patterns of linkage disequilibrium, the linkage-based approach analyzes female and male recombinations separately, which is important since there are major differences in female and male meioses.

From our analysis, we found extensive interindividual variability in the number of meiotic crossovers in men and women. We also identified genomic regions—recombination "jungles"—with significantly more recombination events than other regions in the genome, and we showed that there are polymorphic differences in the activity of these recombination jungles among individuals.

We collected genotypes for 6,324 SNP markers from all members of 38 CEPH families. Among these markers, 2,205 were from the SNP Consortium,[3] and 4,119 were obtained using the Illumina Linkage III Panel. About 3.2 million genotypes were analyzed. After the genotypes with Mendelian inconsistencies were removed, the average intermarker distance was ~408 kb (median 205 kb). First, we used genotype data to identify the sites of recombination in the mothers and fathers. Data were available for 34 mothers and 33 fathers. The average number of children in these families is 8.1. From the 34 mothers and 33 fathers, there were 283 maternal meioses and 274 paternal meioses. To locate points of recombination, we used genotypes to determine the DNA segments shared identical by descent (IBD) between each grandparent and grandchild. The IBD sharing results between each child and his/her paternal and maternal grandparents were analyzed separately. A paternal recombination event is noted when the IBD sharing "switches" from one paternal grandparent to the other, and similarly for the maternal side (fig. 1). All recombination events were supported by information from more than one marker. From the 38 families, 17,461 recombination events were detected over the 22 autosomes, corresponding to 10,881 maternal recombinations and 6,580 paternal recombinations.

The average number of recombinations is 38.4 (range 27.5–46.4; SD 5.3) in female meiosis and 24.0 (range 16.9–28.9; SD 2.7) in male meiosis. As noted above, there are more recombination events in female meiosis than in male meiosis. The female:male ratio in our data is 1.6, which is

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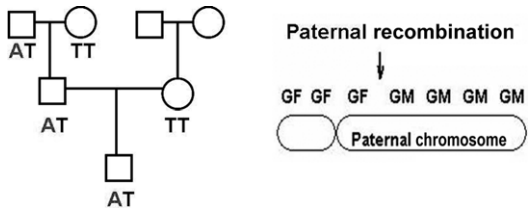

Figure 1. Identification of recombination events. For the genotype of each child, we determined the grandparental origin. Then, we scanned along the paternal and maternal chromosomes separately and assigned a recombination event when there was a switch from one grandparental origin to the next. GF = grandfather; GM = grandmother.

the same as in previous studies of CEPH (1.6) and Icelandic (1.65) families.[1,2] Our findings also correlate with those obtained by cytogenetic analyses with MLH1 foci.[8,9]

Previous linkage-based studies showed significant variation in recombination frequency among women but not among men.[1] However, direct analysis with MLH1-staining and sperm-typing studies reported significant individual variation in recombination among men.[8,12] We used our data to assess variation in the total number of recombination events in men and women. Each individual has multiple offspring, therefore allowing observations of multiple meiotic events. Figure 2 shows the distribution of recombination events for each individual. By analysis of variance, there are extensive interindividual differences in mean recombination frequency between men ($P = 2.9 \times 10^{-11}$) and women ($P = 8.3 \times 10^{-13}$). The variability is less among men than among women; this may explain why the original linkage-based study with eight CEPH families[1] failed to detect this variation, but, with 33 fathers in our study, we are able to detect significant interindividual variation in the number of male recombination events. In the study of Icelandic families,[2] individual variation in recombination events among men was also not significant. Even though the sample size was large (146 families) in that study, the number of meioses per individual (~3–4) was smaller than in our study. The larger number of meioses per subject in our study provides a more accurate estimate (with more degrees of freedom) and therefore may contribute to our ability to detect significant individual variation in recombination events in both men and women.

There have been reports that the number of recombinations per meiosis is correlated with maternal age. However, the findings between studies are inconsistent. One study showed a negative correlation[14] and another showed a positive correlation between maternal recombination counts and maternal age,[15] whereas others showed no significant correlation.[1] We examined our data and did not find correlation between recombination counts and age in men or in women (correlation coefficients 0.07 and −0.01, respectively). The sample sizes differ among studies, which may have contributed to the different findings. Among them, the study of Icelandic families,[15] which analyzed >14,000 maternal meioses, has the largest sample size. It showed that there is a positive correlation between recombination counts and age in women.

The preceding analyses concerned the total number of recombinations and did not consider differences among chromosomal regions. Next, we surveyed recombination across the human genome to identify regions with high and low recombination counts. We divided the genome into 553 bins of 5 Mb each and determined the number of recombinations in each bin separately for female and male meioses. Results are shown in figure 3. We assumed that, if recombinations are randomly distributed across the genome, their distribution over bins would be approximately Poisson, with mean 19.67 (10,881 in 553) in women and 11.90 (6,580 in 553) in men. In our data, the range of recombinations per 5 Mb in women is 0–64, and the mean number is 20.1 recombinations per 5 Mb (me-

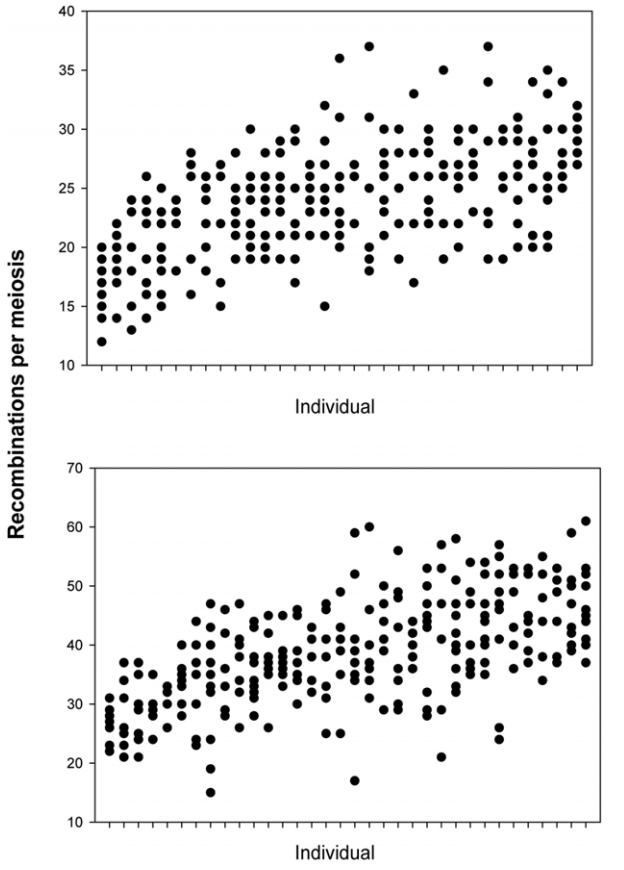

Figure 2. Individual variation in the number of recombination events per meiosis. The graphs show the number of recombination events per meiosis in each individual. The panels show data for men (*top*) and women (*bottom*). The number of recombination events per meiosis is shown as a dot. Individuals are arranged in ascending order of the average number of recombination events per meiosis.

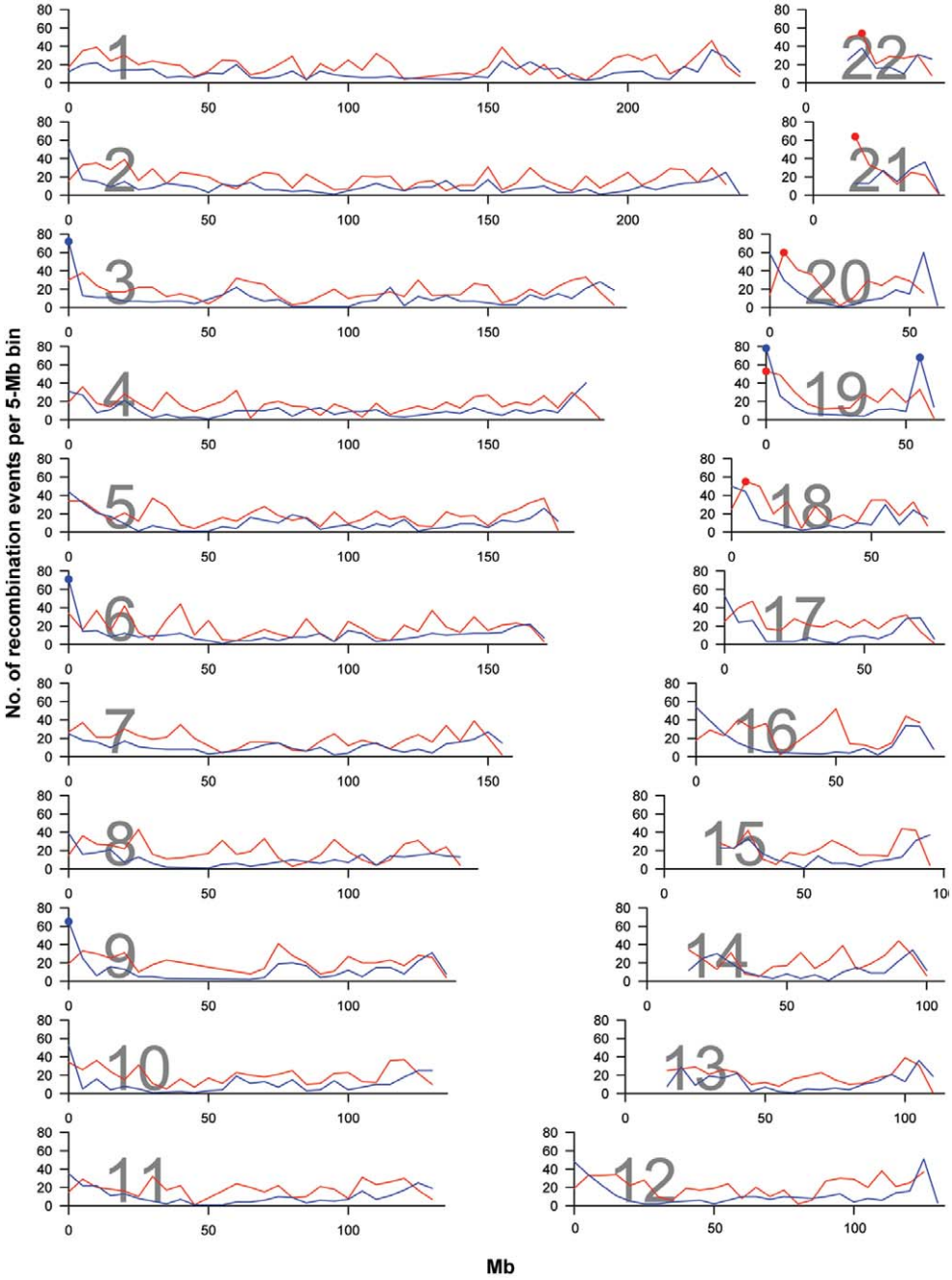

Figure 3. Variation in recombination events across the human genome. The graphs show the number of recombination events per 5-Mb bin on each chromosome. The number of recombination events in each 5-Mb bin is plotted separately for men (*blue*) and for women (*red*). The five bins with the largest number of recombination events are indicated by blue and red dots for men and women, respectively.

dian 19). For men, the range of recombination per 5-Mb bin is 0–78, and the mean is 12.5 (median 9). If recombination events are randomly distributed throughout the genome, the probability of observing, in women or in men, a bin with ⩾50 recombinations per bin by chance is 6×10^{-9} and 4×10^{-16}, respectively. In both sexes, there are genomic regions that contain many more crossovers than expected. Since the bins are 5 Mb in size, we refer to them as recombination "jungles"[16] rather than "hotspots," the latter of which are only hundreds of base pairs in size.[11,17,18] These jungles may contain several hotspots and tend to cluster toward the ends of chromosomes (fig. 3, marked by red and blue dots). We focused on the five bins that contain the most recombinations; in men and women, they are either the most or the second-most telomeric bins on the chromosomes.

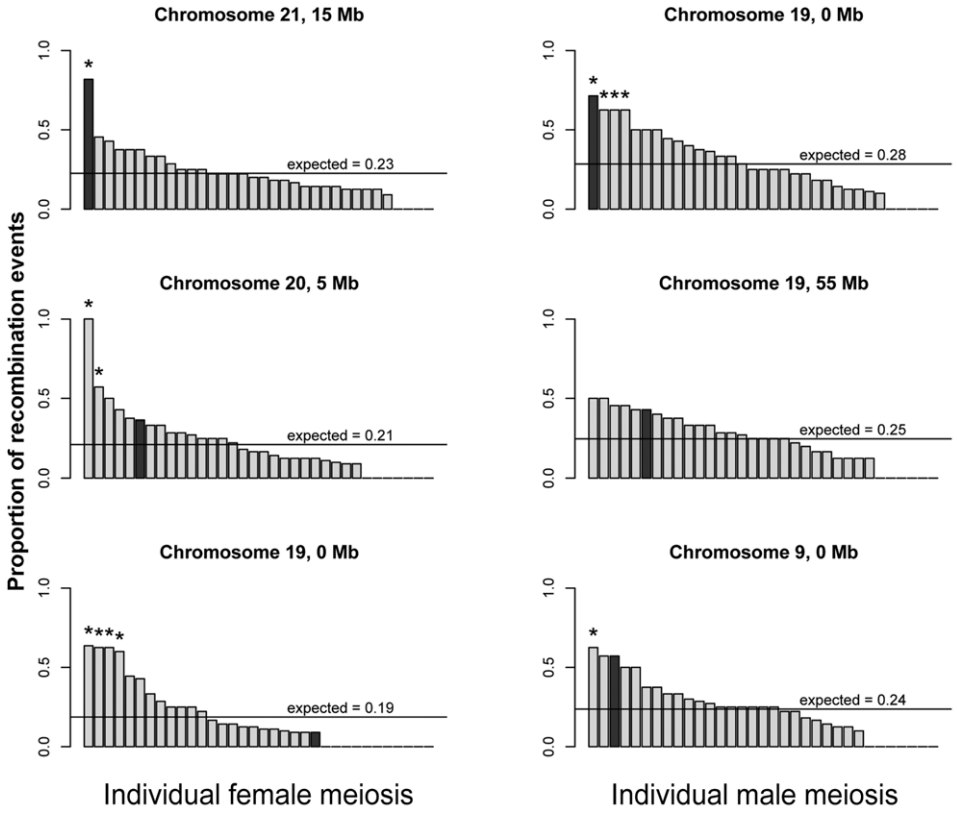

Figure 4. Polymorphic activity in recombination jungles. For three female and three male recombination jungles, the proportions of recombination events observed in each subject are shown. The expected number of recombination events is given to indicate deviation of the observed events from the expected. In each jungle, the individuals who recombined more frequently than expected ($P < .05$) are shown with an asterisk (*). The black columns represent data for the mother of family 1331 and the father of family 1340. Data for all subjects (34 women and 33 men) are shown, including those who did not recombine in the jungles (0 in the right sides of the graphs).

To further explore the recombination jungles, we examined whether individuals contribute equal proportions of crossovers to each jungle or whether some individuals contribute more to some jungles than to others. In other words, are recombination jungles the "preferred sites" where crossovers occur for most people, or are the preferred sites different for different people? For an individual, we calculated, at each recombination jungle, the probability of finding the observed proportion of (or more) recombination events, using a binomial distribution. The expected proportion of recombinations per jungle is calculated as the number of recombinations per jungle divided by the total number of meiotic events. Our data set includes 283 maternal meiotic events, so, for the chromosome 21 jungle (15 Mb from pter) that contains 64 crossovers, if everyone contributes equally to this jungle, we would expect to observe a recombination in ~23% (64 of 283) of the meiotic events. Instead, we found some individuals who did not have any recombinations, while others had more recombination events than expected. For example, for this chromosome 21 jungle, a recombination was observed in 9 (81%) of the 11 meioses of the mother of family 1331 (significantly more than expected [corrected $P = 1 \times 10^{-4}$]), but no recombination events were observed for the mothers of families 1341, 1346, 1358, and 1418 in the same region (fig. 4). When we examined the contribution of the mother of family 1331 to other jungles, we found that she did not contribute more than the expected number of recombinations to those jungles. As shown in figure 4, in the other female and male recombination jungles, we also found that one or a few individuals have more crossovers than expected. The results therefore suggest that there are polymorphic differences in the activity of the recombination jungles. The preferred locations of meiotic crossovers differ among individuals.

In summary, our data show that there is extensive variation in recombination phenotype. Recombination frequency varies among individuals and along different regions in the genome. In addition, there are polymorphic differences in recombination jungle activity. Studies reported elsewhere have shown that recombination hotspot activities differ between mouse strains.[19,20] By analysis of sperm DNA, Jeffreys and colleagues have reported polymorphism in activity in the *NID1,* MSTM1a, and MSTM1b

hotspots on chromosome 1.[21,22] Our data suggest that this polymorphism is not limited to male recombination but appears to be a more general property of human meiotic recombination. This has important clinical implications, since improper segregation of chromosomes due to aberrant recombination can result in aneuploidy, a leading cause of miscarriages. Studies of yeast, flies, and humans have suggested that proper chromosome segregation relies on the placement of meiotic recombination.[23] Recombinations that occur too close or too far from the centromere are more likely to lead to nondisjunction.[24,25] If the preferred sites of recombination differ between individuals, then those with very proximal and those with more-distally placed recombinations would be at higher risk of having gametes with aneuploidy.

Our results show that, similar to many human phenotypes, there is extensive variability in human recombination events. Identification of the determinants of variation in recombination phenotype will lead to a better understanding of the mechanism that regulates this fundamental cellular process. The results will also be important for the study of chromosomal aberrations that underlie many congenital abnormalities.

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