Letter to the Editor

Imprinted Chromosomal Regions of the Human Genome Have Unusually High Recombination Rates

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WHILE considerable attention has been given to the problem of the evolution of recombination rates (for review see Otto and Lenormand 2002), a related problem is relatively little studied: Why is it that in many species the recombination rates in males and females are different (for review see Korol *et al.* 1994)? In humans, for example, the recombination rate is, on the average, higher in females than in males (Broman *et al.* 1998; Kong *et al.* 2002), but it is unknown why this might be. One possible avenue from which to gain understanding of this issue is to ask whether there are particular classes of genes that show a different pattern, *e.g.*, a reversal or an increase of the usual sex bias. Importantly, from analysis of recombinational and physical maps of three regions of imprinted genes in humans, Paldi *et al.* (1995) claimed that the recombination rate in males was significantly higher than that in females for at least two of these clusters (11p15.5 and 15q11–13), the opposite of what is observed more generally. The recombination rate in the remaining location (11p13) was higher in males but not significantly so. On the basis of these observations, Paldi *et al.* suggested that imprinted regions in general show higher male recombination rates and proposed a chromatin-based model for this.

The facts and their interpretation, however, are far from clear. 11p15.5 is subtelomeric, and subtelomeric sequences tend to have male-biased recombination rates regardless of their imprint status (Broman *et al.* 1998; Kong *et al.* 2002). Further, in direct contradiction to the claim regarding the imprinted region in 15q11–13, a detailed analysis failed to show a male bias (Robinson and Lalande 1995), although in the nonimprinted flanking region such a male bias was observed. With the recent publication of the deCODE high-resolution recombination map (Kong *et al.* 2002) and with knowledge of many more clusters of imprinted genes, we here ask whether the pattern observed by Paldi *et al.* is both repeatable and generally true for imprinted regions.

We located 38 imprinted human genes (http://cancer.otago.ac.nz/igc; Morison *et al.* 2001) on the human genome (University of California, Santa Cruz, August 2001 assembly, http://genome.cse.ucsc.edu). These resolved to 16 imprinted regions, each containing between 1 and 10 genes (see supplementary table at http://www.genetics.org/supplemental/ for a list of genes, locations, and recombination rates). Sex-specific recombination rates were calculated on the basis of an analysis of 5136 microsatellite markers over 1257 meiotic events (Kong *et al.* 2002), by linear regression of genetic against physical distances for all markers within 2 Mb of the region boundaries. The recombination rate obtained from this procedure represents a regional average. Due to the existence of recombination hot spots (see, *e.g.*, Jeffreys *et al.* 2001), it would be preferable to obtain much finer measures of recombination rates; however, such measures are currently not available. The limited resolution of recombination rates makes our study conservative: Any significant observation indicates a corresponding (and possibly stronger) pattern on a more local scale.

In Figure 1 we show the distribution of male and female recombination rates for the 16 imprinted regions. In contradiction to the earlier claim (Paldi *et al.* 1995), 13 show higher rates in females than in males (which is significantly different from 50:50, $P = 0.011$, sign test). One of the regions that we find to have higher recombination rate in males is 11p15.5, as previously reported (Paldi *et al.* 1995). However, 11p15.5 is unusual in being subtelomeric. As subtelomeric regions generally have higher male than female rates (Broman *et al.* 1998; Kong *et al.* 2002), it is not clear that a special explanation is needed. Indeed, one of the other two imprinted regions with a greater paternal than maternal rate (1p36.33, containing TP73) is also subtelomeric.

At first sight then, imprinted regions appear simply to have the sex-biased recombination rate that one might expect given where they reside. However, closer exami-

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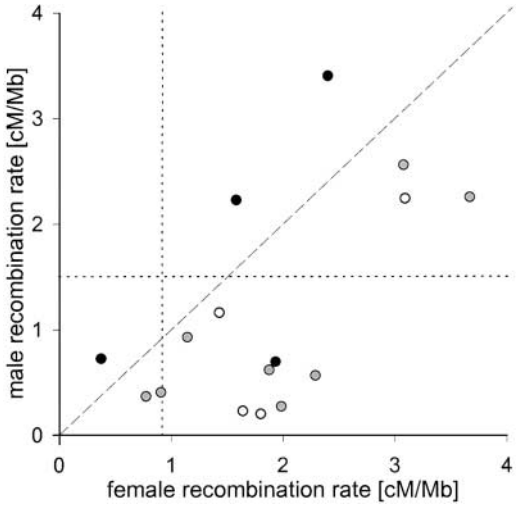

FIGURE 1.—Female and male recombination rates for regions of imprinted genes. Predominant expression pattern: maternal (solid circle), paternal (shaded circle), or mixed/unknown (open circle). For 13 out of 16 regions, recombination rates in females exceed those in males (the dashed line corresponds to equal rates). Female recombination rates of imprinted regions exceed the genomic average (dotted lines indicate average female and male rates, calculated across 1-Mb chromosomal windows).

TABLE 1

Comparison of recombination rates for regions with ($N = 16$) and without ($N = 2067$) imprinted genes

	Imprinted[a]	Nonimprinted[a]	P[b]
Sex averaged			
Raw data	1.7 ± 0.8	1.2 ± 0.8	0.011
Residuals[c]	0.3 ± 0.6	0.0 ± 0.7	0.063
Female			
Raw data	2.1 ± 1.2	1.5 ± 0.8	0.0029
Residuals[c]	0.4 ± 1.1	0.0 ± 0.7	0.020
Male			
Raw data	1.3 ± 0.9	1.0 ± 1.0	0.10
Residuals[c]	0.1 ± 0.8	0.0 ± 0.8	0.28

[a] Values are mean recombination rates ±SD calculated across contiguous 1-Mb bins.

[b] Probability of finding a larger or equal mean recombination rate when randomly drawing 16 bins from the distribution of all autosomal bins (100,000 iterations).

[c] Residuals are from multiple regression of recombination rates on GC, CpG, and poly(A)/poly(T) content.

nation suggests that imprinted regions are unusual. Consider the second cluster that was previously ascribed a significantly higher male rate (PALDI *et al.* 1995), 15q11–13. We find it has a higher female than male rate (3.67 *vs.* 2.25), consistent with the results of ROBINSON and LALANDE (1995). However, more remarkably, the sex-averaged rate is exceptionally high.

To ask more generally whether the regional average and sex-specific recombination rates are higher than expected, we compared our sample of imprinted regions to nonimprinted regions. We divided each autosome into contiguous 1-Mb bins and classified all bins containing at least one imprinted locus as imprinted. For each bin, we averaged over the recombination rates as given by KONG *et al.* (2002). We found a marked increase in recombination rates of the imprinted bins compared to nonimprinted bins (Table 1). While the increase in sex-averaged recombination rates is significant, this is largely owing to the rate of recombination being especially high in females but not in males. The slightly higher male rate of imprinted regions is almost all accounted for by the two subtelomeric regions.

Approximately one-third of the variation in sex-averaged recombination rate can be predicted by multiple regression on three aspects of local nucleotide composition: GC content, CpG content, and poly(A)/poly(T) content (KONG *et al.* 2002). At the same time, we find that imprinted bins have slightly higher GC content (44% compared to 41%, $P = 0.007$ from t-test), higher CpG density (2.5% compared to 2.0%, $P = 0.022$), and lower poly(A)/poly(T) content (7.3% compared to 8.3%, $P = 0.0056$) compared to nonimprinted bins. To account for this bias, we repeated the analysis after correcting for these variables first through multiple regression of the 1-Mb bin averages. Residuals were calculated for sex-averaged, female, and male recombination rates independently. Consistent with the uncorrected results, we find that imprinted regions have higher than expected corrected recombination rates in males and females, but this is significant only for the female rate (Table 1). Thus, imprinted regions are unusual in having higher recombination rates overall, with this mostly owing to much higher rates in females. [Note: It is interesting that while GC, CpG, and poly(A)/poly(T) content predict $r^2 = 27\%$ of the sex-averaged recombination rate variation, the predictive value differs markedly between female recombination rates ($r^2 = 12\%$) and male recombination rates ($r^2 = 29\%$). For 3-Mb bins, as used by KONG *et al.* (2002), the corresponding values are 36, 13, and 43%.]

To further establish the unusually high recombination rates of imprinted regions, it is informative to ask whether these have higher recombination rates than their flanking sequences. Of 16 bins containing an imprint, 3 have a sex-averaged recombination rate lower than the mean of the 3 flanking bins on either side, while 13 have a higher rate ($P = 0.011$, sign test; similar results are obtained for comparisons to the 5 or 10 flanking bins on either side). To examine the magnitude of this difference, we considered the difference in the recombination rate for every autosomal 1-Mb bin and the mean of the 3 flanking bins on either side. We then compared the data for imprinted bins with that of the genome as a whole. The sex-averaged recombina-

tion rate is higher than that predicted from the flanking blocks (Mann-Whitney *U*-test, $P = 0.0074$).

Thus, we report that for 13 of 16 imprinted regions the rate of recombination is higher in female meiosis compared to male meiosis, strongly suggesting that Paldi *et al.*'s prior results are not generally true. Unexpectedly, we find that the sex-averaged recombination rate of imprinted regions is significantly higher than expected. This is true after controlling for local nucleotide composition or flanking effects and appears to be owing to a higher rate during female meiosis.

We can imagine at least two interpretations of our results. Paldi *et al.* (1995) suggested that the pattern they observed might be consistent with a model in which chromatin remodeling was involved in both recombination and imprinting. If open chromatin during meiosis is required for the initiation of chiasmata formation, then a sex bias might be an inevitable consequence of anything that modifies the state of chromatin differentially in the sexes (*e.g.*, transcription). In principle a similar model might yet explain why imprinted regions appear to have high recombination rates.

However, our results are also consistent with a recent population genetics analysis of this issue (Lenormand 2003), which predicts a sex dimorphism in recombination under three conditions: (i) a sex difference in haploid epistasis, (ii) a sex difference in *cis*-epistasis minus *trans*-epistasis in diploids, or (iii) a difference in epistasis between combinations of genes inherited maternally or paternally. The last condition is particularly relevant for imprinted genes, where epistasis must be absent for the silenced gene copies. Three predictions can be derived under the assumptions of this theoretical analysis (T. Lenormand, personal communication): (1) Imprinted regions should differ systematically from other regions in their sex-specific recombination patterns, (2) the sex dimorphism should be higher in imprinted than in nonimprinted regions, and (3) regions containing mostly maternally expressed genes should display higher recombination rate in males and vice versa.

In agreement with the very general prediction (1), we found that the recombination rates of imprinted regions differ systematically from those of the rest of the genome. To test prediction 2, we calculated the absolute sex difference in recombination rate for each of the contiguous 1-Mb bins in the human genome. We find a mean of 0.95 cM/Mb for imprinted regions and 0.90 cM/Mb for nonimprinted regions; however, this difference is not significant ($P = 0.36$ from 10,000 random assignments of bin imprinting status). Finally, the theoretical model also predicts (3) that recombination rate is higher in the sex whose genes' expression will be suppressed in the next generation. This is consistent with our results, although descriptions of the imprinted regions are no doubt incomplete, and any conclusions must be provisional. Nonetheless it is noteworthy that all eight regions with mostly paternally expressed genes have higher female than male recombination rates; in contrast, three out of the four regions with mostly maternal expression show higher rates in males than in females.

While this last observation supports the population genetical model, it may also be consistent with an explanation based on chromatin remodeling. If imprinting status is established in the parent whose copy will be silenced, then the putative link between chromatin remodeling and imprinting will be restricted to that parent's sex. Similarly, if chromatin remodeling also facilitates a higher rate of recombination, then we expect a corresponding increase only for this sex.

Although the greater paternal recombination rate seen in 1p36 and 11p15 might be accounted for by the fact that they are subtelomeric, two facts suggest that a special explanation is still needed. First, a third subtelomeric region containing one maternally and one paternally expressed locus at 14q32 shows higher female than male recombination rate. Thus, a paternal excess in the recombination rate need not be an inevitable consequence of being subtelomeric. Second, the imprint at 13q14 (associated with HTR2A) is associated with maternal expression and has a higher paternal than maternal recombination rate, while not being subtelomeric. This suggests that maternal expression might indeed be related to a paternal excess of recombination. Were this so, one might speculate that the subtelomeric location of two of the maternally expressed regions is no accident. Assuming this pattern to hold, we should add the caveat that the higher recombination rate in female meiosis may not be true for imprinted genes generally, but may be specific to those regions where paternally expressed imprinted genes are especially common.

In sum, our results are broadly consistent with the predictions based on the theoretical model of Lenormand (2003), although not to the exclusion of a model based on chromatin remodeling (Paldi *et al.* 1995). We find that imprinted regions have unusually high female recombination rates. Paternally expressed regions appear to have higher female recombination rates, while maternally expressed regions appear to have lower female rates. This latter pattern must, however, be considered only weakly supported at present. With higher-resolution recombination data it should be possible to resolve this issue.

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