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Connecting recombination, nucleotide diversity, and species divergence in Drosophila

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Abstract

The association between recombination rate and nucleotide diversity provides compelling evidence for the action of natural selection across much of the *Drosophila melanogaster* genome. This conclusion is further supported by the lack of association between recombination rate and nucleotide divergence between species. However, studies of other species, including other Drosophila, have not always yielded the same results. Our recent study measured these parameters within the *D. pseudoobscura* species group using next-generation sequencing and high-throughput genotyping technologies. We documented fine-scale variation in crossover rate within *D. pseudoobscura*, and we observed that crossover variation was strongly associated with nucleotide diversity only when measured at a fine-scale. We also observed associations between crossover rate and sequence differences between *D. pseudoobscura* and its close relatives. These latter associations could have been driven in part by mutagenic effects associated with double-strand break repair, but we cannot exclude the possibility that it results primarily from shared ancestral polymorphisms. Overall, this work strongly underscores the importance of scale in testing for associations of recombination rate with other parameters, and it brings us one small step closer to understanding the role of natural selection and other evolutionary forces in shaping divergence among genomes.

Keywords

crossover; gene conversion; recombination; double-strand break repair; variation; polymorphism; divergence

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A primary thrust of evolutionary research has been determining the importance of natural selection relative to other forces in shaping patterns of variation within species and divergence between species. At the molecular level, many researchers strive to quantify the role of natural selection in shaping patterns of DNA sequence diversity and divergence. Natural selection may shape such patterns directly, such as by favoring one particular sequence variant over another, or indirectly, where the spread (or loss) of selected variants affects patterns of diversity at sites with which they fail to recombine freely.

Rates of recombination are thus intrinsically tied to the effects of selection on DNA sequence diversity across the genome. As such, it's small wonder that the seminal survey of Begun and Aquadro1 has been cited over 400 times. Begun and Aquadro1 assembled restriction site data from 20 loci across *Drosophila melanogaster* and identified a strong positive correlation between nucleotide diversity and local recombination rate. Such a relationship may exist if recombination itself is mutagenic, but in contrast to this interpretation, recombination rate was uncorrelated with nucleotide divergence to *D. simulans* (see also ref 2). Hence, these results are most consistent with indirect effects of natural selection acting ubiquitously across the genome. Nonetheless, studies in other systems have yielded variable results.3–5

My colleagues and I recently investigated similar patterns in the *Drosophila pseudoobscura* species group.6 *D. pseudoobscura* is of particular interest because its average recombination rate is much higher than that of *D. melanogaster*.7 We had at our disposal single published, assembled, annotated genome sequences of *D. pseudoobscura* and *D. persimilis*.8,9 To this backbone, we added a low-coverage 454 sequence of another strain of *D. pseudoobscura* (so diversity could be estimated), a moderately high-resolution linkage map of one chromosome of this species (for estimates of recombination), and some direct sequencing of targeted regions in *D. pseudoobscura* and *D. miranda*.

Similar to the published results in the *D. melanogaster* group, we detected a strongly positive correlation between local recombination rate and nucleotide diversity in noncoding regions.6 Impressively, this strong correlation was apparent when very low-recombination telomeric and centromeric regions were excluded, and even among a set of windows that were all within 150 kilobases of each other. If recombination was measured at a broader scale, the association was nonsignificant. In contrast to published results in the *D. melanogaster* group, however, we also observed a positive correlation between local recombination rate and nucleotide divergence between species in noncoding regions.

We proposed a two-phase model to explain the association of recombination with diversity and divergence.6 We suggested that, in regions with very low crossing over such as near centromeres, natural selection eliminates nucleotide diversity, but divergence still accumulates due to mutational errors associated with double-strand DNA break repair (DSBR). In such regions, crossing over may be effectively eliminated, but DSBR still occurs and resolves preferentially into gene conversions.10 DSBR-related divergence may come from mutagenicity associated with strand invasion in the single stranded phase (akin to results observed in mitochondria, see ref 11). In contrast, in regions of normal-to-high crossing over such as the ones we surveyed, recombination rate and diversity are still correlated (as are recombination and divergence), but here, both of these correlations result from mutational errors associated with DSBR. In high-recombination regions, indirect effects of natural selection will be minimized.

While we can acknowledge that different processes may operate in the different species groups, we strive as evolutionary biologists to identify single overarching explanations for different observations. In our study of the *D. pseudoobscura* group, we focused away from telomeric and centromeric regions where there is severely restricted crossing over but still some gene conversion (and therefore likely some DSBR). If our model is correct, we should detect an association of recombination and divergence between *D. melanogaster* and *D. simulans* if just higher-recombination regions are studied. However, neither diversity nor divergence was significantly correlated with recombination when only high-recombination regions were surveyed in non-overlapping 50 kb windows.6 This nonsignificance likely stems from insufficient and/or imprecise recombination estimates that were available: figure 3 of Begun et al2 (which uses larger but overlapping windows that would be inappropriate for direct statistical analysis) shows an impressive tracking of these measures with crossover rate outside of the telomeric region on the left. Despite the nonsignificance of our test using their data, I am confident that a positive association between recombination rate and at least diversity is present in high recombination regions of *D. simulans*.

Our interpretation of the results has several caveats. The most severe is that “divergence” between species was measured in two very close relatives. *D. pseudoobscura* and *D. persimilis* share extensive allelic variation,12 and although we tried to correct for this, what we label “divergence” may reflect variation in levels of shared ancestral polymorphism. We do still observe an association of recombination rate and divergence with the more distantly related species *D. miranda*,6 even when examined at a genome-wide level (unpublished

data), but this species, too, shares variation with *D. pseudoobscura*.13 Chip Aquadro (personal communication) suggested that the correlation with divergence we observed in high recombination regions may reflect the preferential retention of ancestral polymorphism in such regions. This is a very compelling possibility, as regions of very high recombination should have a higher effective population size and thus be more able to retain variation (see also ref 2). Since publication of our study, I've also found that very-fine scale recombination is uncorrelated (or negatively correlated) with divergence among Saccharomyces species.14 In hindsight, I think we downplayed too much the likelihood that most of the association of divergence with recombination in our study came from shared ancestral polymorphism, and this is an area that we are currently examining more closely through additional empirical and theoretical studies to get at this question.

Nonetheless, our work has several interesting and novel elements. Our results identify fine-scale variation in crossover rate in this species, whereas earlier reviews had suggested Drosophila species lacked such fine-scale variation. We further found that this fine-scale recombination variation is evolutionary meaningful because of the strong positive correlation between it and nucleotide diversity. Indeed, if the association of recombination with diversity within species among such small regions of high recombination stems primarily from natural selection rather than mutational causes, then natural selection must be acting very frequently across much of the *D. pseudoobscura* genome. Finally, and perhaps most fundamentally, our results underscore the importance of measuring recombination at the finest possible scale to examine its evolutionary effects on patterns of DNA sequence diversity within species and divergence between species.15 Previous studies (including one by my laboratory) failed to detect an association between recombination rate and diversity in this species because too coarse a scale was used. I'm personally excited to continue to study these genome-wide patterns and to identify the evolutionary processes causing them.

Abbreviation

DSBR double-strand break repair

References

1. Begun DJ, Aquadro CF. Levels of naturally occurring DNA polymorphism correlate with recombination rates in *D. melanogaster*. Nature. 1992; 356:519–20. [PubMed: 1560824]
2. Begun DJ, Holloway AK, Stevens K, Hillier LW, Poh YP, Hahn MW, et al. Population Genomics: Whole-Genome Analysis of Polymorphism and Divergence in Drosophila simulans. PLoS Biol. 2007; 5:e310. [PubMed: 17988176]
3. Hellmann I, Ebersberger I, Ptak SE, Paabo S, Przeworski M. A neutral explanation for the correlation of diversity with recombination rates in humans. Am J Hum Genet. 2003; 72:1527–35. [PubMed: 12740762]
4. Roselius K, Stephan W, Stadler T. The relationship of nucleotide polymorphism, recombination rate and selection in wild tomato species. Genetics. 2005; 171:753–63. [PubMed: 16085701]
5. Tenaillon MI, U'Ren J, Tenaillon O, Gaut BS. Selection versus demography: a multilocus investigation of the domestication process in maize. Mol Biol Evol. 2004; 21:1214–25. [PubMed: 15014173]
6. Kulathinal RJ, Bennett SM, Fitzpatrick CL, Noor MAF. Fine-scale mapping of recombination rate in Drosophila refines its correlation to diversity and divergence. Proc Natl Acad Sci USA. 2008; 105:10051–6. [PubMed: 18621713]
7. Ortiz-Barrientos D, Chang AS, Noor MAF. A recombinational portrait of the *Drosophila pseudoobscura* genome. Genet Res, Camb. 2006; 87:23–31.
8. Clark AG, Eisen MB, Smith DR, Bergman CM, Oliver B, Markow TA, et al. Evolution of genes and genomes on the Drosophila phylogeny. Nature. 2007; 450:203–18. [PubMed: 17994087]

9. Richards S, Liu Y, Bettencourt BR, Hradecky P, Letovsky S, Nielsen R, et al. Comparative genome sequencing of Drosophila pseudoobscura: Chromosomal, gene, and cis-element evolution. Genome Res. 2005; 15:1–18. [PubMed: 15632085]

10. Blitzblau HG, Bell GW, Rodriguez J, Bell SP, Hochwagen A. Mapping of Meiotic Single-Stranded DNA Reveals Double-Strand-Break Hotspots near Centromeres and Telomeres. Curr Biol. 2007; 17:2003–12. [PubMed: 18060788]

11. Faith JJ, Pollock DD. Likelihood analysis of asymmetrical mutation bias gradients in vertebrate mitochondrial genomes. Genetics. 2003; 165:735–45. [PubMed: 14573484]

12. Machado CA, Haselkorn TS, Noor MAF. Evaluation of the genomic extent of effects of fixed inversion differences on intraspecific variation and interspecific gene flow in *Drosophila pseudoobscura* and *D. persimilis*. Genetics. 2007; 175:1289–1306. [PubMed: 17179068]

13. Charlesworth B, Bartolome C, Noel V. The detection of shared and ancestral polymorphisms. Genet Res. 2005; 86:149–157. [PubMed: 16207392]

14. Noor MAF. Mutagenesis from meiotic recombination is not a primary driver of sequence divergence between Saccharomyces species. Mol Biol Evol. 2008 in press.

15. Spencer CCA, Deloukas P, Hunt S, Mullikin J, Myers S, Silverman B, et al. The influence of recombination on human genetic diversity. PLoS Genet. 2006; 2:e148. [PubMed: 17044736]