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Review

# Variation in Recombination Rate: Adaptive or Not?

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**Rates of meiotic recombination are widely variable both within and among species. However, the functional significance of this variation remains largely unknown. Is the observed within-species variation in recombination rate adaptive? Recent work has revealed new insight into the scale and scope of population-level variation in recombination rate. These data indicate that the magnitude of within-population variation in recombination is similar among taxa. The apparent similarity of the variance in recombination rate among individuals between distantly related species suggests that the relative costs and benefits of recombination that establish the upper and lower bounds may be similar across species. Here we review the current data on intraspecific variation in recombination rate and discuss the molecular and evolutionary costs and benefits of recombination frequency. We place this variation in the context of adaptation and highlight the need for more empirical studies focused on the adaptive value of variation in recombination rate.**

## Trends

Recombination rate varies in all taxa studied to date.

Recombination rate varies along three primary axes: crossover number, crossover distribution, and crossover: non-crossover ratio.

Crossover number and crossover distribution are determined in part by genotype, although the genetic architectures of these traits are largely independent.

Despite huge variation in average genome-wide crossover number between species, the magnitude of variation in crossover number within species is surprisingly similar.

Upper and lower bounds on recombination rate within species are likely to be set by molecular and evolutionary costs and benefits.

Potential for local adaptation in recombination rate exists.

## Genetic Architecture of Natural Variation in Recombination Rate

Variation in **recombination rate** (see Glossary) abounds at all levels: across areas of a genome, among individuals of a species, between the sexes, and between species. Two primary axes on which this variation manifests are variation in the number of **homologous recombination** events per genome and variation in how those recombination events are distributed across the genome. A third, less-discussed axis of variation concerns the relative proportions of **crossovers** and **non-crossovers** – the two potential outcomes of recombination. Resolution of programmed double-stranded breaks during meiosis can yield either crossover events or non-crossover events, with the former generating reciprocal exchange of genetic information between homologous loci and the latter generating unidirectional transfer of information between homologous loci. The relative ratio of crossover to non-crossover outcomes varies among species [1] and the mechanisms driving interspecific variation in this ratio remain unknown.

Variation in crossover distribution has lately been a topic of intense study. In recent years we have gained incredible insight into how crossovers are distributed across mammalian chromosomes and how this distribution differs between sexes, populations, and species [2–9]. Innovation in genotyping and sequencing technologies has made characterizing the fine-scale distribution of crossovers possible in other systems as well, including yeast and *Drosophila* species. These studies show that crossover distribution in these systems is highly heterogeneous across the genome, between populations, and between species [10–15].

Arguably less attention has been paid to variation in genome-wide crossover number, particularly within populations. Population-level variation in crossover number, referred to hereafter as 'recombination rate', is thus the topic of this review. The idea that there is population-level

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variation in recombination rate is not new. Early work in *Drosophila melanogaster* and *Drosophila pseudoobscura* illustrated that recombination rates are variable according to genetic background in both laboratory stocks and natural populations [16–20]. Artificial selection experiments, particularly in *Drosophila* [21–24] and *Bombyx mori* [25,26], have also revealed population-level variation in the **frequency** of crossing over.

What is new, however, is our understanding of the scale and scope of intraspecific variation in recombination rate in populations. Increasing attention to population-level variation has been directly and indirectly influenced by technological advances in genotyping and sequencing. For instance, the comparative ease of large-scale genotyping at present has empowered detection of recombination events using molecular diagnostics [27–29]. High-throughput genotyping and next-generation sequencing have further enabled investigators to explore the genetic architecture of recombination rate variation by coupling phenotypic data on recombination rate with high-density genotype data. These studies may be primarily motivated by fundamental quantitative genetic questions regarding the genotype–phenotype map but simultaneously provide novel insight into the magnitude of phenotypic variation in recombination rate in natural or laboratory populations [30,31]. Finally, in some cases genotype data are used both to infer recombination events and for association mapping to identify loci that mediate phenotypic variation in recombination [32,33].

## Population-Level Variation

With these new data on population-level variation in recombination rate, we can start to ask questions about how that variation is partitioned in populations. One factor that clearly contributes to phenotypic variation in recombination within populations is biological sex. Most extreme, of course, are the cases in which one of the two sexes does not recombine during meiosis for proper chromosomes segregation. This is certainly true in *Drosophila* [34,35] and *Bombyx* [36], where the **heterogametic sex** lacks meiotic recombination entirely. The idea that, when one of the two sexes lacks recombination (achiasmy), it tends to be the heterogametic sex is known as the Haldane–Huxley rule. This rule appears to hold across an impressive diversity of taxa [37].

Heterochiasmate species differ from achiasmate species in that, with heterochiasmy, both sexes recombine during meiosis but do so at different rates. Heterochiasmy is incredibly common in plants and animals (for a review see [38] and for more recent studies, see [2,39–43]). One extreme example of heterochiasmy comes from European tree frogs, where the female autosomal genetic map is >14 times the length of that of males [44]. At the other end of the spectrum is the Japanese flounder, in which the length of the female genetic map is only 0.135 times the length of that of males [45]. One of the most peculiar examples of sex differences in recombination comes from the saltwater crocodile; females consistently show increases in recombination rate relative to their male counterparts [46], but sex determination in this species is temperature dependent rather than under genetic control. Interestingly, species with heterochiasmy generally do not adhere to the Haldane–Huxley rule. Although differences between recombination rates in males and females are very common, which sex has the higher recombination rate does not appear to depend on whether that sex is the heterogametic one. How sexual dimorphism might evolve has been given careful theoretical consideration [47]. One potential reason that males and females differ in recombination rate is that the sexes may have different opportunities for selection at the gametic/haploid stage. In animals, for instance, females lack a haploid phase because meiosis is not completed until fertilization. Males, however, have ample opportunity for selection at the gametic stage, and if haploid selection is strong this could yield differences in recombination rate between males and females. Empirical data from plants are consistent with a role for haploid selection in generating and maintaining sex differences in recombination in natural populations, as heterochiasmy is

## Glossary

**Aneuploid:** containing an atypical number of chromosomes.
**Chiasma:** the point at which two homologous chromatids exchange genetic material during the process of crossing over; plural: chiasmata.
**Crossover:** reciprocal exchange of genetic information between homologous chromosomes.
**Heterogametic sex:** the sex (male or female) that carries two different sex chromosomes (XY or ZW).
**Homogametic sex:** the sex (male or female) that carries two copies of the same sex chromosome (XX or ZZ).
**Homologous recombination:** the exchange of genetic information between homologous chromosomes. Recombination has two possible outcomes: crossovers and non-crossovers.
**Non-crossover:** non-reciprocal exchange of genetic information between homologous chromosomes.
**Nondisjunction:** the failure of homologous chromosomes (meiosis I) or sister chromatids (meiosis II, mitosis) to separate properly during cell division.
**Recombination frequency:** the frequency of crossing over, typically measured in centimorgans (cM). A recombinational distance of 30 cM between two loci indicates that the chromosomal region separating the two loci has a 30% chance of containing a crossover event during meiosis.
**Recombination rate:** recombination frequency (in cM) measured per unit of physical distance.

observed in species with marked differences in opportunities for selection at the haploid stage [38].

Several approaches have been used to estimate variation in crossover frequency among individuals. One can directly assay meiotically active cells and estimate the frequency of crossing over using microscopy. **Chiasma** frequency has been estimated using this approach in both *Arabidopsis thaliana* [48,49] and *Locusta migratoria* [50]; these data show 1.35-fold (estimated as the ratio of the highest-recombination accession to the lowest-recombination accession) variation in crossing-over in Arabidopsis and 1.20-fold variation in *L. migratoria*. Using immunohistochemical approaches to estimate crossover counts in house mice revealed 1.9-fold variation in crossover frequency in both males and females [30]. Estimates of recombination rate variation among strains in *Drosophila* are typically made using genetic markers and crosses. This type of approach has revealed that crossover counts vary ~1.1- to 2-fold, depending on the interval surveyed [31,51]. Estimating recombination using genotype data yields similar ranges of intrapopulation variability in recombination rate. In maize there is 1.6-fold variation in genome-wide recombination rate among inbred lines [29] and in *Eucalyptus globulus* 1.3-fold variation in genomic recombination rate was observed among ten unrelated individuals [28]. Integrating genotype data with pedigree information has revealed an approximately twofold variation in crossover frequency in both male and female humans [27] and 1.7-fold variation in male cattle [32].

Thus, it appears that the magnitude of variation in recombination rate within populations is similar across taxa (Figure 1). If this is the case, it suggests that there must be constraints on recombination rate such that it cannot be too high or too low. What is the nature of these constraints?

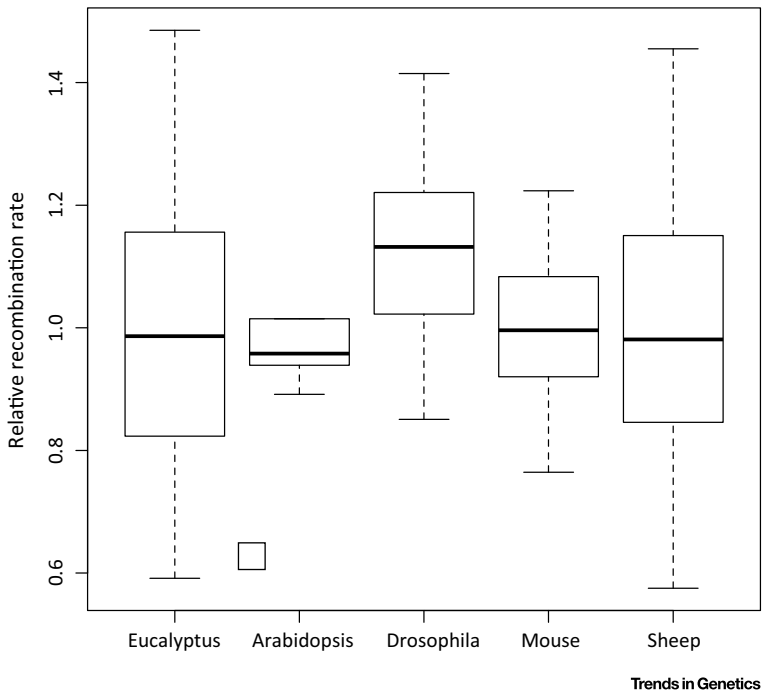


Figure 1. The median is depicted with a black line. The edges of the box are the first and third quartiles. Whiskers extend to 1 times the interquartile range. Data from [28,30,31,33,49]

## Molecular Constraints on Recombination Rate

Recombination is a tightly controlled process for the repair of double-stranded breaks and is vital to the success of meiosis in most eukaryotes [52]. However, the fundamental molecular mechanics of recombination place a variety of constraints on recombination rate.

### Constraints on the Minimum Recombination Rate

The molecular mechanisms of recombination place a number of constraints on the minimum possible rate of recombination. Faithful crossing over during prophase I is heavily dependent on the formation of chiasmata, or the sites of reciprocal meiotic exchange that lock the homologs together. At least one crossover per chromosome pair is considered necessary (the 'obligate crossover'), although in many cases there are two, with one on each arm of the chromosome [53,54]. This puts a lower bound on the amount of recombination that occurs in most organisms, referred to as 'crossover assurance'. While mutations in some genes are known to disrupt crossover assurance in some organisms (e.g., [55–57]), we do not yet have a complete understanding of how crossover assurance is accomplished at the molecular level.

Unless an organism has a specific mechanism to cope with it, the absence of the obligate crossover can be deleterious. For example, failure to properly cross over can result in chromosomal **nondisjunction**, which can in turn yield **aneuploid** gametes. Nearly all human trisomies are thought to be the result of low or absent recombination and consequent nondisjunction in meiosis I, perhaps the most infamous being trisomy 21 [58]. Support for selection against low recombination exists in both men and women. Low recombination in men has been associated with low sperm production, infertility, and sperm aneuploidy [59,60]. In women, low genomic germline recombination is a strong predictor of aneuploidy, and euploid oocytes have ~5.8 more recombination events than aneuploid oocytes. Additionally, oocytes have a ~6.6% greater occurrence of crossovers than polar bodies, suggesting that cells containing chromosomes with lower recombination are shunted to the polar bodies [61,62].

### Constraints on Maximal Recombination Rate

The molecular mechanism of recombination also imposes constraints on the maximum rate of recombination. For example, the occurrence of a crossover at one location discourages the occurrence of another in close proximity, resulting in a pattern where recombination events appear evenly spaced [53]. This phenomenon is known as crossover interference and was first described a century ago by Hermann Muller in *D. melanogaster* [63]. Crossover interference is widespread and has been observed in additional model systems, including humans, budding yeast, *Caenorhabditis elegans*, and *Arabidopsis* [52,64–66]. The limitation of crossover locations has been proposed as a self-regulating mechanism to prevent excessive recombination [64]. As with crossover assurance, the precise mechanisms of crossover interference are not yet fully understood and continue to be studied (for reviews see [57,67,68]).

Indirect evidence for an upper bound to recombination rates comes from the association between genomic instability and high recombination. High levels of crossing over have been observed in a wide variety of disease phenotypes, notably some human cancers [69–73]. Recombination rates are more than 100-fold greater in p53 mutants, a gene renowned for its role in approximately 60% of cancer types and colloquially called the 'guardian of the genome' [74,75]. Wild-type p53 is thought to maintain genomic stability by suppressing excessive recombination through modulation of the cell cycle [74,76]. Further, observations that patients with higher recombination rates have a higher prevalence of cancer potentially implicates recombination in carcinogenesis [77].

## Evolutionary Costs and Benefits of Recombination

### Evolutionary Benefits of Recombination

Recombination has a variety of well-known effects that can facilitate adaptation. Perhaps the most commonly invoked long-term benefit of recombination is the creation of novel combinations of alleles. Specifically, recombination mitigates a phenomenon called 'Hill–Robertson interference', of which there are two forms. First, when advantageous alleles at different loci arise on different backgrounds, competition occurs between them and inhibits adaptation. Recombination allows existing advantageous alleles at different loci to be brought into a common background, preventing this competition and facilitating adaptation [78]. The second form of Hill–Robertson interference occurs when an advantageous allele is linked to a deleterious allele, reducing the efficacy of selection on the advantageous allele. Recombination can mitigate this by breaking apart the associations between advantageous and deleterious alleles. Population-genetic evidence for Hill–Robertson interference has been observed in a host of different taxa (e.g., [79–87]).

Another advantage to recombination is that it facilitates the purging of deleterious mutations from natural populations. With limited recombination deleterious mutations accumulate in natural populations because offspring free of such mutations are not formed, a process termed Muller's ratchet [88,89]. Natural selection is still able to remove a subset of deleterious mutations but this results in a reduction in variation throughout much of the genome [90]. Muller's ratchet has been observed in numerous systems, most often those with limited or no recombination, including organelles [91–93], viruses [94–97], asexually reproducing populations [98,99], and the Y chromosome [100]. Mechanisms to avoid the ratchet have also been documented, including the use of horizontal gene transfer in bacteria [101] and gene conversions to slow the ratchet in bdelloid rotifers [102].

### Evolutionary Benefits of Reduced Recombination

When populations adapt to new environments, beneficial alleles may become associated on the same haplotype and act in concert to increase fitness. In this case recombination can break this association, resulting in lower progeny fitness, particularly if there is positive epistasis between the beneficial alleles ('recombination load'; see the review in [103]). Hence, selection favors modifiers that restrict recombination across sets of coselected loci. The effects of recombination load were first documented in *Drosophila*, where decreased recombination resulted in higher fecundity [104].

One mechanism for reducing recombination to protect adaptive loci is through chromosomal inversions, which are strong suppressors of recombination across a potentially large stretch of chromosome. Suppression of recombination can maintain adaptive gene combinations (for a review see [105]) and adaptive allele combinations may be preserved within inversions when multiple arrangements are maintained within a population [106]. Inversion polymorphisms have been studied extensively in multiple *Drosophila* species. Selection for multiple karyotypes within a population increases average fitness and allow the persistence of *D. pseudoobscura* in heterogeneous environments [107,108]. Recent studies also suggest that inversions in natural populations may assist in adaptation to climate change [109,110]. Locally adaptive inversion polymorphisms have also been identified in systems other than *Drosophila* (e.g., [111–113]), confirming the role of recombination suppression in adaptation.

Sex chromosome evolution provides another well-studied example of selection for reduced recombination to preserve the associations among alleles between loci. One hypothesis for the emergence of sex chromosomes is that recombination is suppressed between a pair of ancestral autosomes containing sex-determining loci that when recombined result in sterility or reversion to hermaphroditism [114,115]. Recombination suppression may spread as these

chromosomes become a genomic safe zone for loci with sex-specific functions, eventually leading to no recombination (as is the case between the *Drosophila* X and Y) or very little recombination (such as between the mammalian X and Y) [116,117]. There is an abundance of support for this model in species such as humans, mice, birds, plants, and *Drosophila* [114,115,118].

## Genetic Basis of Population-Level Variation in Recombination Rate

All of these factors presumably jointly act as bounds on recombination rate in natural populations. Nonetheless, variation in recombination rate persists among individuals in natural populations (Figure 1). Understanding the genetic architecture of that variation may provide insight into its functional significance. In mammals variation in four genes has been associated with population-level variation in genome-wide rates of crossing over. The gene RNF212 is associated with variation in crossover rate in several mammals, including humans, cattle, and Soay sheep [32,33,119,120]. Other loci associated with variation in genomic recombination rate in one or both sexes in mammals include CPLX1, REC8, and PRDM9 [3,32,43]. In addition, in humans, inversion 17q21.31 has been associated with recombination rate variation in European females [121], although it is unknown what genetic variation within that inversion is the contributing factor or whether it is the inversion itself. Although the repeated identification of certain genetic elements indicates that at least some of the genetic architecture of recombination rate variation is conserved across mammals, variation in these loci explains only ~3–11% of the phenotypic variance observed among individuals [3,33]. Thus, much remains to be discovered regarding the causes of population-level variation in recombination rate even in mammalian systems.

Outside mammals even less is known regarding the genetic basis of recombination rate variation within populations. A recent association analysis in *Drosophila* revealed a handful of high-confidence candidate loci [31] that may contribute to population-level variation in recombination rate. Notably, these genes identified in *Drosophila* do not overlap with those identified as driving recombination rate variation in mammals. Indeed, *Drosophila* lacks PRDM9, RNF212, and REC8 entirely. However conserved the genetic basis of recombination rate variation in mammals may be, this conservation does not appear to extend to *Drosophila*.

## Is Recombination Rate Adaptive?

The evolution of sex and recombination has been extensively reviewed from a variety of angles, including speciation [122,123], adaptation [124,125], the advantage of sex in specific systems such as humans [126], and many more [88,103,127–129]. Behind these reviews is a profuse literature empirically demonstrating that sex is adaptive in organisms such as yeast [130,131], rotifers [132,133], *Escherichia coli* [134], and chlorophytes [135], where sexual systems can be compared with asexual analogs. One recent study in budding yeast demonstrated that sexual populations adapt more quickly under selection than asexual populations [130]. This study beautifully illustrates what evolutionary biologists understand well: sex and recombination increase the efficacy of selection and speed of adaptation. Similarly, it has been shown that recombination rate can increase as a correlated response to direct selection on other traits ([103], see Figure 1) [136,137], suggesting that high recombination rates may be favorable under strong selection. Also consistent with this idea, recombination has been observed to increase in domesticated species compared with their wild progenitors [138–140], although not universally (e.g., [141]).

While it is clear that having at least some recombination is adaptive, a level of complexity is added when the variation in non-zero recombination rates is considered. It seems plausible that the recombination rate in natural populations, given molecular constraints, balances evolutionary costs and benefits and is maintained at a level that is optimal for a given population.

Several theoretical studies have shown that optimization of recombination rate can result in higher fitness. This is the case in heterogeneous environments where the environmental fluctuations are periodic [142]. The benefit of increased recombination is related to period length; if the environment changes more rapidly, recombination rate is expected to be higher. Antagonistic coevolution between pathogen and host can also affect the evolution of recombination rate [143]. These results are indicative of an optimal recombination rate for populations under selection, with these rates being defined by numerous features including the strength of the modifier allele and the strength of selection imposed by the pathogen on the host [143]. Recent work exploiting gene gain/loss and genome rearrangement data in prokaryotes forms the basis of a population model for the maintenance of recombination in populations [144]. When recombination is allowed to be a mutable, heritable trait, selection can maintain recombination rate at or near its optimal value [144]; this value is in turn set by the relative rates of gene gain/loss and genome rearrangement.

To empirically determine whether a trait is adaptive, that trait must be: (i) heritable; and (ii) provide a reproductive or survival advantage. Genetic variation for recombination rate has been observed in a variety of taxa including *Drosophila* (e.g., [19,51]), mice (e.g., [58]), maize (e.g., [145]), and humans (e.g., [146]). Recombination can be selected on directly, also demonstrating heritability, with observable changes in as few as ten generations in *Drosophila* [21,24,147].

Empirical data supporting the adaptive value of recombination rate (beyond presence versus absence) are in far shorter supply. Recombination rates are correlated with reproductive output in humans and *Drosophila* [146,148], which is consistent with a reproductive advantage for mothers with particular recombination rates. However, other studies have failed to find a relationship between recombination rate and organismal fitness, even in the same species (e.g., [31]), or have found a relationship between recombination and fitness but only under certain conditions (e.g., [149]). What, then, is the relationship between recombination rate and organismal fitness? How context dependent is this relationship?

## Future Directions

Moving forward, more empirical studies are needed in a diversity of taxa that place recombination rate in the context of organismal fitness (see Outstanding Questions) in natural populations. What aspects of organismal fitness, if any, are correlated with recombination rate? How robust is this correlation to environmental conditions? Are there sex-based differences in the relationship between recombination rate and fitness? While placing recombination rate in the context of fitness is not without challenges, these data are critical for understanding of the extent to which recombination rate is selectively maintained at an optimum in natural populations. In addition, indirect evidence of the adaptive value of recombination would also be valuable in gaining traction on this fundamental question. For instance, data indicating that recombination rates vary clinally would be consistent with population-specific optimal values of recombination rate. Testing for parallel clines in recombination rate – either between different organisms in the same geographic area or between the same organisms in different geographic areas – would help bolster an adaptive argument over a demographic one. Other evidence of parallel evolution would also support the idea that recombination rate is subject to local adaptation. If, for instance, recombination rates are higher in spatially or temporally variable environments than they are in uniform environments in a variety of species, this not only would be consistent with selection on recombination rate, but would also suggest that higher recombination rates are favored in variable environments. Further, support for local adaptation in recombination rates could be gleaned from reciprocal transplant experiments. If there are population-specific optimal values of recombination rate, each population should have higher fitness than any other population in the same site. Common-garden experiments such as these have the additional benefit of being able to distinguish plastic differences from genetic

differences in recombination among individuals. However, such studies on recombination are complicated because, unlike a simple trait such as 'height', the presumed advantage conferred by high or low recombination is not manifested in the survival of or reproductive output of a focal individual but rather in the descendants of that individual. Hence, such explorations require multigenerational assays.

Other lines of future research should include quantitative-genetic studies that partition phenotypic variation in recombination rate to genetic and environmental sources. What kinds of environmental cues trigger variance in recombination rate? What kinds of environments support population-level variation in recombination rate? These types of studies will help disentangle the relative roles of genetic and environmental variation in phenotypic variation of recombination rate. Further exploration of the genetic basis of recombination rate variation within populations and potentially between genetically differentiated, locally adapted populations will enhance our understanding of what genes and alleles contribute to recombination rate variation in nature.

## Outstanding Questions

Do quantitative differences in recombination rate sometimes provide a fitness advantage? Does such an advantage manifest with respect to reproductive output or offspring survival? Is such a fitness advantage realized in different ways in different populations or species?

Is recombination rate under stabilizing selection? Does actual or optimal recombination rate vary among natural populations or across seasons? Do evolutionary or mechanistic constraints on high or low recombination rate vary across species?

Are the different types of recombination (e.g., crossing over versus gene conversion) subject to distinct selection pressures?

## Concluding Remarks

Variation in recombination rate is pervasive in natural populations. While recombination rate is certainly bounded by numerous molecular and evolutionary constraints, less is known about what modulates recombination rate between the upper and lower extremes. While genetic variation certainly contributes, the identity of the particular loci that mediate recombination rate variation in natural systems is poorly understood. Perhaps more importantly, the consequences of this variation for organismal fitness and function and for the adaptive potential of populations are also largely unknown. In the future, understanding the adaptive value of recombination rate will require detailed empirical work in natural populations of a variety of species.

### Acknowledgments

This work was supported in part by funding from NSF DEB1545627 to M.A.F.N. and NSF MCB1412813 to N.D.S.

### References

1. Singh, N.D. (2012) Classical genetics meets next-generation sequencing: uncovering a genome-wide recombination map in *Drosophila melanogaster*. *PLoS Genet.* 8, e1003024
2. Kong, A. *et al.* (2010) Fine-scale recombination rate differences between sexes, populations and individuals. *Nature* 467, 1099–1103
3. Kong, A. *et al.* (2014) Common and low-frequency variants associated with genome-wide recombination rate. *Nat. Genet.* 46, 11–16
4. Winckler, W. *et al.* (2005) Comparison of fine-scale recombination rates in humans and chimpanzees. *Science* 308, 107–111
5. Hinch, A.G. *et al.* (2011) The landscape of recombination in African Americans. *Nature* 476, 170–175
6. Ptak, S.E. *et al.* (2004) Absence of the TAP2 human recombination hotspot in chimpanzees. *PLoS Biol.* 2, e155
7. Ptak, S.E. *et al.* (2005) Fine-scale recombination patterns differ between chimpanzees and humans. *Nat. Genet.* 37, 429–434
8. Wall, J.D. *et al.* (2003) Comparative linkage-disequilibrium analysis of the beta-globin hotspot in primates. *Am. J. Hum. Genet.* 73, 1330–1340
9. Fearnhead, P. and Smith, N.G.C. (2005) A novel method with improved power to detect recombination hotspots from polymorphism data reveals multiple hotspots in human genes. *Am. J. Hum. Genet.* 77, 781–794
10. Cattani, M.V. *et al.* (2012) *Cis*- and *trans*-acting genetic factors contribute to heterogeneity in the rate of crossing over between the *Drosophila simulans* clade species. *J. Evol. Biol.* 25, 2014–2022
11. Heil, C.S.S. *et al.* (2015) Recombining without hotspots: a comprehensive evolutionary portrait of recombination in two closely related species of *Drosophila*. *Genome Biol. Evol.* 7, 2829–2842
12. Chan, A.H. *et al.* (2012) Genome-wide fine-scale recombination rate variation in *Drosophila melanogaster*. *PLoS Genet.* 8, e1003090
13. Cirulli, E.T. *et al.* (2007) Fine-scale crossover rate heterogeneity in *Drosophila pseudoobscura*. *J. Mol. Evol.* 64, 129–135
14. Mancera, E. *et al.* (2008) High-resolution mapping of meiotic crossovers and non-crossovers in yeast. *Nature* 454, 479–485
15. Comeron, J.M. *et al.* (2012) The many landscapes of recombination in *Drosophila*. *PLoS Genet.* 8, e1002905
16. Lawrence, M.J. (1958) Genotypic control of crossing-over on the first chromosome of *Drosophila melanogaster*. *Nature* 182, 889–890
17. Broadhead, R.S. *et al.* (1977) Variation of recombination fraction in *Drosophila melanogaster* females. *J. Hered.* 68, 323–326
18. Broadhead, R.S. and Kidwell, J.F. (1975) A note on the distribution of recombination fraction in *Drosophila melanogaster*. *J. Hered.* 66, 309–310
19. Levine, R.P. and Levine, E.E. (1955) Variable crossing over arising in different strains of *Drosophila pseudoobscura*. *Genetics* 40, 399–405
20. Levine, R.P. and Levine, E.E. (1954) The genotypic control of crossing over in *Drosophila pseudoobscura*. *Genetics* 39, 677–691
21. Charlesworth, B. and Charlesworth, D. (1985) Genetic variation in recombination. I. Responses to selection and preliminary genetic analysis. *Heredity* 54, 71–83

22. Chinnici, J.P. (1971) Modification of recombination frequency in *Drosophila*. I. Selection for increased and decreased crossing over. *Genetics* 69, 71–83
23. Chinnici, J.P. (1971) Modification of recombination frequency in *Drosophila*. II. Polygenic control of crossing over. *Genetics* 69, 85–96
24. Kidwell, M.G. (1972) Genetic change of recombination value in *Drosophila melanogaster*. I. Artificial selection for high and low recombination and some properties of recombination-modifying genes. *Genetics* 70, 419–432
25. Turner, J.R.G. (1979) Genetic-control of recombination in the silkworm. I. Multigenic control of chromosome 2. *Heredity* 43, 273–293
26. Ebinuma, H. and Yoshitake, N. (1981) The genetic system controlling recombination in the silkworm. *Genetics* 99, 231–245
27. Fledel-Alon, A. *et al.* (2011) Variation in human recombination rates and its genetic determinants. *PLoS One* 6, e20321
28. Gion, J.M. *et al.* (2016) Genome-wide variation in recombination rate in *Eucalyptus*. *BMC Genomics* 17, 590
29. Bauer, E. *et al.* (2013) Intraspecific variation of recombination rate in maize. *Genome Biol.* 14, R103
30. Dumont, B.L. *et al.* (2009) Variation in genomic recombination rates among heterogeneous stock mice. *Genetics* 182, 1345–1349
31. Hunter, C.M. *et al.* (2016) The genetic architecture of natural variation in recombination rate in *Drosophila melanogaster*. *PLoS Genet.* 12, e1005951
32. Sandor, C. *et al.* (2012) Genetic variants in *REC8, RNF212*, and *PRDM9* influence male recombination in cattle. *PLoS Genet.* 8, e1002854
33. Johnston, S.E. *et al.* (2016) Conserved genetic architecture underlying individual recombination rate variation in a wild population of Soay sheep (*Ovis aries*). *Genetics* 203, 583–598
34. Morgan, T.H. (1912) Complete linkage in the second chromosome of the male of *Drosophila*. *Science* 36, 719–720
35. Morgan, T.H. (1914) No crossing over in the male of *Drosophila* of genes in the second and third pairs of chromosomes. *Biol. Bull.* 26, 195–204
36. Tanaka, Y. (1914) A study of Mendelian factors in the silkworm, *Bombx mori*. *Mol. Gen. Genet.* 12, 161
37. Bell, G. (1982) *The Masterpiece of Nature: The Evolution and Genetics of Sexuality,* University of California Press
38. Lenormand, T. and Dutheil, J. (2005) Recombination difference between sexes: a role for haploid selection. *PLoS Biol.* 3, e63
39. Smeds, L. *et al.* (2016) High-resolution mapping of crossover and non-crossover recombination events by whole-genome re-sequencing of an avian pedigree. *PLoS Genet.* 12, e1006044
40. Giraut, L. *et al.* (2011) Genome-wide crossover distribution in *Arabidopsis thaliana* meiosis reveals sex-specific patterns along chromosomes. *PLoS Genet.* 7, e1002354
41. Yan, J.J. *et al.* (2013) A genetic linkage map of the sea cucumber (*Apostichopus japonicus*) based on microsatellites and SNPs. *Aquaculture* 404–405, 1–7
42. Wang, S. *et al.* (2009) Construction of a high-resolution genetic linkage map and comparative genome analysis for the reef-building coral *Acropora millepora*. *Genome Biol.* 10, R126
43. Ma, L. *et al.* (2015) Cattle sex-specific recombination and genetic control from a large pedigree analysis. *PLoS Genet.* 11, e1005387
44. Berset-Brandli, L. (2008) Extreme heterochiasmy and nascent sex chromosomes in European tree frogs. *Proc. Biol. Sci.* 275, 1577–1585
45. Coimbra, M.R.M. *et al.* (2003) A genetic linkage map of the Japanese flounder, *Paralichthys olivaceus*. *Aquaculture* 220, 203–218
46. Isberg, S.R. *et al.* (2006) First evidence of higher female recombination in a species with temperature-dependent sex determination: the saltwater crocodile. *J. Hered.* 97, 599–602
47. Lenormand, T. (2003) The evolution of sex dimorphism in recombination. *Genetics* 163, 811–822
48. Sanchez-Moran, E. (2002) Variation in chiasma frequency among eight accessions of *Arabidopsis thaliana*. *Genetics* 162, 1415–1422
49. Lopez, E. *et al.* (2012) Looking for natural variation in chiasma frequency in *Arabidopsis thaliana*. *J. Exp. Bot.* 63, 887–894
50. Quevedo, C. *et al.* (1997) Correlated variation of chiasma frequency and synaptonemal complex length in *Locusta migratoria*. *Heredity* 78, 515–519
51. Brooks, L.D. and Marks, R.W. (1986) The organization of genetic variation for recombination in *Drosophila melanogaster*. *Genetics* 114, 525–547
52. Hillers, K.J. (2004) Crossover interference. *Curr. Biol.* 14, R1036–R1037
53. Wang, S. *et al.* (2015) Meiotic crossover patterns: obligatory crossover, interference and homeostasis in a single process. *Cell Cycle* 14, 305–314
54. Jones, G.H. and Franklin, F.C.H. (2006) Meiotic crossing-over: obligation and interference. *Cell* 126, 246–248
55. Shinohara, M. *et al.* (2008) Crossover assurance and crossover interference are distinctly regulated by the ZMM proteins during yeast meiosis. *Nat. Genet.* 40, 299–309
56. Yu, Z.L. *et al.* (2016) Meiotic recombination and the crossover assurance checkpoint in *Caenorhabditis elegans*. *Semin. Cell Dev. Biol.* 54, 106–116
57. Wang, S.X. *et al.* (2015) Meiotic crossover patterns: obligatory crossover, interference and homeostasis in a single process. *Cell Cycle* 14, 305–314
58. Koehler, K.E. *et al.* (1996) Recombination and nondisjunction in humans and flies. *Hum. Mol. Genet.* 5, 1495–1504
59. Gonsalves, J. *et al.* (2004) Defective recombination in infertile men. *Hum. Mol. Genet.* 13, 2875–2883
60. Ferguson, K.A. *et al.* (2007) Abnormal meiotic recombination in infertile men and its association with sperm aneuploidy. *Hum. Mol. Genet.* 16, 2870–2879
61. Ottolini, C.S. *et al.* (2015) Genome-wide maps of recombination and chromosome segregation in human oocytes and embryos show selection for maternal recombination rates. *Nat. Genet.* 47, 727–735
62. Brieno-Enriquez, M.A. and Cohen, P.E. (2015) Double trouble in human aneuploidy. *Nat. Genet.* 47, 696–698
63. Muller, H.J. (1916) The mechanism of crossing-over. IV. *Am. Nat.* 50, 421–434
64. Libuda, D.E. *et al.* (2013) Meiotic chromosome structures constrain and respond to designation of crossover sites. *Nature* 502, 703–706
65. Berchowitz, L.E. and Copenhaver, G.P. (2008) Fluorescent *Arabidopsis* tetrads: a visual assay for quickly developing large crossover and crossover interference data sets. *Nat. Protoc.* 3, 41–50
66. Zhang, L. *et al.* (2014) Topoisomerase II mediates meiotic crossover interference. *Nature* 511, 551–556
67. Berchowitz, L.E. and Copenhaver, G.P. (2010) Genetic interference: don't stand so close to me. *Curr. Genomics* 11, 91–102
68. Joyce, E.F. and McKim, K.S. (2011) Meiotic checkpoints and the interchromosomal effect on crossing over in *Drosophila* females. *Fly* 5, 134–140
69. Nikolaitchik, O. *et al.* (2015) High recombination potential of subtype A HIV-1. *Virology* 484, 334–340
70. Pal, J. *et al.* (2011) Genomic evolution in Barrett's adenocarcinoma cells: critical roles of elevated hsRAD51, homologous recombination and Alu sequences in the genome. *Oncogene* 30, 3585–3598
71. Mao, Z. *et al.* (2009) DNA repair by homologous recombination, but not by nonhomologous end joining, is elevated in breast cancer cells. *Neoplasia* 11, 683–691
72. Obama, K. *et al.* (2008) Enhanced expression of RAD51 associating protein-1 is involved in the growth of intrahepatic cholangiocarcinoma cells. *Clin. Cancer Res.* 14, 1333–1339
73. Meyn, M.S. (1993) High spontaneous intrachromosomal recombination rates in ataxia–telangiectasia. *Science* 260, 1327–1330

74. Rieckmann, T. *et al.* (2013) p53 modulates homologous recombination at I-SceI-induced double-strand breaks through cell-cycle regulation. *Oncogene* 32, 968–975
75. Mekeel, K.L. *et al.* (1997) Inactivation of p53 results in high rates of homologous recombination. *Oncogene* 14, 1847–1857
76. Sengupta, S. and Harris, C.C. (2005) p53: traffic cop at the crossroads of DNA repair and recombination. *Nat. Rev. Mol. Cell Biol.* 6, 44–55
77. Bishop, D.K. and Zickler, D. (2004) Early decision: meiotic crossover interference prior to stable strand exchange and synapsis. *Cell* 117, 9–15
78. Hill, W.G. and Robertson, A. (1966) The effect of linkage on limits to artificial selection. *Genet. Res.* 8, 269–294
79. Gray, J.C. and Goddard, M.R. (2012) Sex enhances adaptation by unlinking beneficial from detrimental mutations in experimental yeast populations. *BMC Evol. Biol.* 12, 43
80. Henry, L. *et al.* (2012) Deleterious mutation accumulation in asexual Timema stick insects. *Mol. Biol. Evol.* 29, 401–408
81. Kent, C.F. *et al.* (2012) Recombination is associated with the evolution of genome structure and worker behavior in honey bees. *Proc. Natl Acad. Sci. U. S. A.* 109, 18012–18017
82. McGaugh, S.E. *et al.* (2012) Recombination modulates how selection affects linked sites in *Drosophila*. *PLoS Biol.* 10, e1001422
83. Gossmann, T.I. *et al.* (2014) Highly variable recombinational landscape modulates efficacy of natural selection in birds. *Genome Biol. Evol.* 6, 2061–2075
84. Hough, J. *et al.* (2014) Genetic degeneration of old and young Y chromosomes in the flowering plant *Rumex hastatulus*. *Proc. Natl Acad. Sci. U. S. A.* 111, 7713–7718
85. Hussin, J.G. *et al.* (2015) Recombination affects accumulation of damaging and disease-associated mutations in human populations. *Nat. Genet.* 47, 400–4004
86. Castellano, D. *et al.* (2016) Adaptive evolution is substantially impeded by Hill–Robertson interference in *Drosophila*. *Mol. Biol. Evol.* 33, 442–455
87. Martin, S.H. *et al.* (2016) Natural selection and genetic diversity in the butterfly *Heliconius melpomene*. *bioRxiv* 203, 042796
88. Felsenstein, J. (1974) The evolutionary advantage of recombination. *Genetics* 78, 737–756
89. Muller, H.J. (1964) The relation of recombination to mutational advance. *Mutat. Res.* 1, 2–9
90. Charlesworth, B. *et al.* (1993) The effect of deleterious mutations on neutral molecular variation. *Genetics* 134, 1289–1303
91. Llopart, A. *et al.* (2014) Sequential adaptive introgression of the mitochondrial genome in *Drosophila yakuba* and *Drosophila santomea*. *Mol. Ecol.* 23, 1124–1136
92. Rispe, C. and Moran, N. (2000) Accumulation of deleterious mutations in endosymbionts: Muller's ratchet with two levels of selection. *Am. Nat.* 156, 425–441
93. Lynch, M. (1996) Mutation accumulation in transfer RNAs: molecular evidence for Muller's ratchet in mitochondrial genomes. *Mol. Biol. Evol.* 13, 209–220
94. Chao, L. (1990) Fitness of RNA virus decreased by Muller's ratchet. *Nature* 348, 454–455
95. Jaramillo, N.I. *et al.* (2013) Evidence of Muller's ratchet in herpes simplex virus type 1. *J. Gen. Virol.* 94, 366–375
96. Xiao, Y. *et al.* (2016) RNA recombination enhances adaptability and is required for virus spread and virulence. *Cell Host Microbe* 19, 493–503
97. Stern, A. *et al.* (2014) Costs and benefits of mutational robustness in RNA viruses. *Cell Rep.* 8, 1026–1036
98. Andersson, D.I. and Hughes, D. (1996) Muller's ratchet decreases fitness of a DNA-based microbe. *Proc. Natl Acad. Sci. U. S. A.* 93, 906–907
99. Söderberg, R.J. and Berg, O.G. (2011) Kick-starting the ratchet: the fate of mutators in an asexual population. *Genetics* 187, 1129–1137
100. Kaiser, V.B. and Charlesworth, B. (2010) Muller's ratchet and the degeneration of the *Drosophila miranda* neo-Y chromosome. *Genetics* 185, 339–348
101. Takeuchi, N. *et al.* (2014) Horizontal gene transfer can rescue prokaryotes from Muller's ratchet: benefit of DNA from dead cells and population subdivision. *G3 (Bethesda)* 4, 325–339
102. Flot, J.F. *et al.* (2014) Genomic evidence for ameiotic evolution in the bdelloid rotifer *Adineta vaga*. *Nature* 500, 453–457
103. Otto, S.P. and Lenormand, T. (2002) Evolution of sex: resolving the paradox of sex and recombination. *Nat. Rev. Genet.* 3, 252–261
104. Charlesworth, B.Y.B. and Charlesworth, D. (1975) An experiment on recombination load in *Drosophila melanogaster*. *Genet. Res.* 25, 267–274
105. Hoffmann, A.A. and Rieseberg, L.H. (2008) Revisiting the impact of inversions in evolution: from population genetic markers to drivers of adaptive shifts and speciation? *Annu. Rev. Ecol. Evol. Syst.* 39, 21–42
106. Kirkpatrick, M. and Barton, N. (2006) Chromosome inversions, local adaptation and speciation. *Genetics* 173, 419–434
107. Schaeffer, S.W. (2008) Selection in heterogeneous environments maintains the gene arrangement polymorphism of *Drosophila pseudoobscura*. *Evolution* 62, 3082–3099
108. Schaeffer, S.W. *et al.* (2003) Evolutionary genomics of inversions in *Drosophila pseudoobscura*: evidence for epistasis. *Proc. Natl Acad. Sci. U. S. A.* 100, 8319–8324
109. Rane, R.V. *et al.* (2015) Genomic evidence for role of inversion 3RP of *Drosophila melanogaster* in facilitating climate change adaptation. *Mol. Ecol.* 24, 2423–2432
110. Balany, J. *et al.* (2006) Global genetic change tracks global climate warming in *Drosophila subobscura*. *Science* 313, 1773–1775
111. Lowry, D.B. and Willis, J.H. (2010) A widespread chromosomal inversion polymorphism contributes to a major life-history transition, local adaptation, and reproductive isolation. *PLoS Biol.* 8, e1000500
112. Joron, M. *et al.* (2011) Chromosomal rearrangements maintain a polymorphic supergene controlling butterfly mimicry. *Nature* 477, 203–206
113. Jones, F.C. *et al.* (2012) The genomic basis of adaptive evolution in threespine sticklebacks. *Nature* 484, 55–61
114. Bergero, R. and Charlesworth, D. (2009) The evolution of restricted recombination in sex chromosomes. *Trends Ecol. Evol.* 24, 94–102
115. Charlesworth, D. (2005) Steps in the evolution of heteromorphic sex chromosomes. *Heredity (Edinb.)* 95, 118–128
116. Rice, W.R. (1987) The accumulation of sexually antagonistic genes as a selective agent promoting the evolution of reduced recombination between primitive sex chromosomes. *Evolution* 41, 911–914
117. Wright, A.E. *et al.* (2016) How to make a sex chromosome. *Nat. Commun.* 7, 12087
118. Bachtrog, D. (2013) Evolution of sex chromosomes. In *The Princeton Guide to Evolution* (Losos, J.B. *et al.*, eds), pp. 387–396, Princeton University Press
119. Kong, A. *et al.* (2008) Sequence variants in the *RNF212* gene associate with genome-wide recombination rate. *Science* 319, 1398–1401
120. Chowdhury, R. *et al.* (2009) Genetic analysis of variation in human meiotic recombination. *PLoS Genet.* 5, e1000648
121. Stefansson, H. *et al.* (2005) A common inversion under selection in Europeans. *Nat. Genet.* 37, 129–137
122. Butlin, R.K. (2005) Recombination and speciation. *Mol. Ecol.* 14, 2621–2635
123. Ortiz-Barrientos, D. (2016) Recombination rate evolution and the origin of species. *Trends Ecol. Evol.* 31, 226–236
124. Rice, W.R. (2002) Evolution of sex: experimental tests of the adaptive significance of sexual recombination. *Nat. Rev. Genet.* 3, 241–251
125. Otto, S.P. and Michalakis, Y. (1998) The evolution of recombination in changing environments. *Trends Ecol. Evol.* 13, 145–151
126. Coop, G. and Przeworski, M. (2007) An evolutionary view of human recombination. *Nat. Rev. Genet.* 8, 23–34

127. Crow, J.F. (1994) Advantages of sexual reproduction. *Dev. Genet.* 15, 205–213
128. Burt, A. (2000) Perspective: sex, recombinatin, and the efficacy of selection – was Weismann right? *Evolution* 54, 337–351
129. Hadany, L. and Comeron, J.M. (2008) Why are sex and recombination so common? *Ann. N. Y. Acad. Sci.* 1133, 26–43
130. McDonald, M.J. *et al.* (2016) Sex speeds adaptation by altering the dynamics of molecular evolution. *Nature* 531, 233–236
131. Goddard, M.R. *et al.* (2005) Sex increases the efficacy of natural selection in experimental yeast populations. *Nature* 434, 636–640
132. Becks, L. and Agrawal, A.F. (2010) Higher rates of sex evolve in spatially heterogeneous environments. *Nature* 468, 89–92
133. Becks, L. and Agrawal, A.F. (2012) The evolution of sex is favoured during adaptation to new environments. *PLoS Biol.* 10, e1001317
134. Cooper, T.F. (2007) Recombination speeds adaptation by reducing competition between beneficial mutations in populations of *Escherichia coli*. *PLoS Biol.* 5, e225
135. Colegrave, N. (2002) Sex releases the speed limit on evolution. *Nature* 420, 664–666
136. Korol, A.B. and Iliadi, K.G. (1994) Increased recombination frequencies resulting from directional selection for geotaxis in *Drosophila*. *Heredity (Edinb.)* 72, 64–68
137. Flexon, P.B. and Rodell, C.F. (1982) Genetic recombination and directional selection for DDT resistance in *Drosophila melanogaster*. *Nature* 298, 672–674
138. Smukowski, C.S. and Noor, M.A.F. (2011) Recombination rate variation in closely related species. *Heredity (Edinb.)* 107, 496–508
139. Ross-Ibarra, J. (2004) The evolution of recombination under domestication: a test of two hypotheses. *Am. Nat.* 163, 105–112
140. Burt, A. and Bell, G. (1987) Mammalian chiasma frequencies as a test of two theories of recombination. *Nature* 326, 803–805
141. Munoz-Fuentes, V. (2015) Strong artificial selection in domestic mammals did not result in an increased recombination rate. *Mol. Biol. Evol.* 32, 510–523
142. Sasaki, A. and Iwasa, Y. (1987) Optimal recombination rates in fluctuating environments. *Genetics* 115, 377–388
143. Peters, A.D. and Lively, C.M. (2007) Short- and long-term benefits and detriments to recombination under antagonistic coevolution. *J. Evol. Biol.* 20, 1206–1217
144. Lobkovsky, A.E. *et al.* (2016) Evolvability of an optimal recombination rate. *Genome Biol. Evol.* 8, 70–77
145. Williams, C.G. *et al.* (1995) Comparative recombination distances among *Zea mays* L. inbreds, wide crosses and interspecific hybrids. *Genetics* 141, 1573–1581
146. Kong, A. *et al.* (2004) Recombination rate and reproductive success in humans. *Nat. Genet.* 36, 1203–1206
147. Abdullah, N.F. and Charlesworth, B. (1974) Selection for reduced crossing over in *Drosophila melanogaster*. *Genetics* 76, 447–451
148. Cvetkoviá, D. and Tuciá, N. (1986) Female recombination rates and fitness in *Drosophila melanogaster*. *J. Zool. Syst. Evol. Res.* 24, 198–207
149. Jackson, S. *et al.* (2015) Increased exposure to acute thermal stress is associated with a non-linear increase in recombination frequency and an independent linear decrease in fitness in *Drosophila*. *BMC Evol. Biol.* 15 (175),