

Recombination Rates in *Drosophila*

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Recombination occurs during meiosis to produce new allelic combinations in natural populations, making it important for studying evolution. The model system *Drosophila* has been crucial for understanding the mechanics underlying recombination and assessing the association between recombination rate and several evolutionary parameters. *Drosophila* was the first system in which genetic maps were developed using recombination frequencies between genes. Linkage maps have been subsequently developed in many biological systems, including humans. Fungal systems have been helpful in highlighting the mechanics of recombination and identifying particular enzymes that perform various steps in the process; however, similar proteins have been identified in *Drosophila*. Further, *Drosophila* has been used to determine genetic and environmental conditions that cause variation in recombination rate. Finally, *Drosophila* has been instrumental in elucidating associations between local recombination rate and nucleotide diversity, divergence and codon bias, as well as helping determine the causes of these associations.

Population genetics is concerned with the inheritance of traits from generation to generation within populations. Offspring generally resemble their parents, but the inheritance of phenotypic combinations is not always in the same combinations as the parents, which leads to 'recombinant' offspring. There are two distinct genetic mechanisms that lead to recombinant offspring: independent assortment and crossing over. Mendel's second law of independent assortment explains how each parental chromosome is equally likely to be segregated to the gametes, such that new combinations of traits on different chromosomes arise each generation, based simply on the principles of probability. The focus of this article is on the second mechanism of producing recombinant offspring, known as crossing over. Although technically the term 'recombination' could refer to either independent assortment or crossing over, typical usage focuses on the latter, and we use it in that context here. The underlying molecular pathway involves physical exchange between chromosomes and leads to alleles on the same chromosome being shuffled in the offspring. This process occurs in sexual species during meiosis and is hypothesized to serve two main categories of functions: to stabilize chromosomes during meiosis and to

increase adaptability of sexual organisms. The model system *Drosophila* has been crucial in the scientific exploitation of this process to determine the order of genes on chromosomes, but some fungal systems have proven more useful in the discovery of key enzymes in the molecular pathway. Further, surveys of *Drosophila* have been instrumental in the discovery of factors that cause recombination rate variation, as well as how recombination rate variation shapes the genome. **See also:** [Meiosis](#)

Using Recombination Frequencies to Map the Genome

Pairs of genes that assort in a 1:1 ratio as expected due to Mendel's law of independent assortment are said to be in *linkage equilibrium*. However, when they deviate from this expectation, scientists refer to the pair of genes as being in *linkage disequilibrium*. One of the most influential genetic observations in the early 1900s was the deviation of recombination fraction between certain genes from the expected ratio of 1:1. This observation led scientist Alfred Sturtevant to conclude that these genes were *physically linked* on a chromosome (Sturtevant, 1913). By measuring the recombination fraction between series of genes in *Drosophila*, he constructed the first genetic linkage maps, which are maps of the linear order of genes along a chromosome (**Figure 1**). This analysis was possible before the development of molecular tools because of the many different phenotypic mutant markers discovered in the Thomas Hunt Morgan fly lab. **See also:** [Genetic Linkage Mapping](#); [History of Classical Genetics](#); [Linkage and Crossing over](#);

Advanced article

Article Contents

- [Using Recombination Frequencies to Map the Genome](#)
- [Mechanics of Crossing Over](#)
- [Variation in Crossing Over](#)
- [Evolutionary Effects of Recombination on Structure of the Genome](#)

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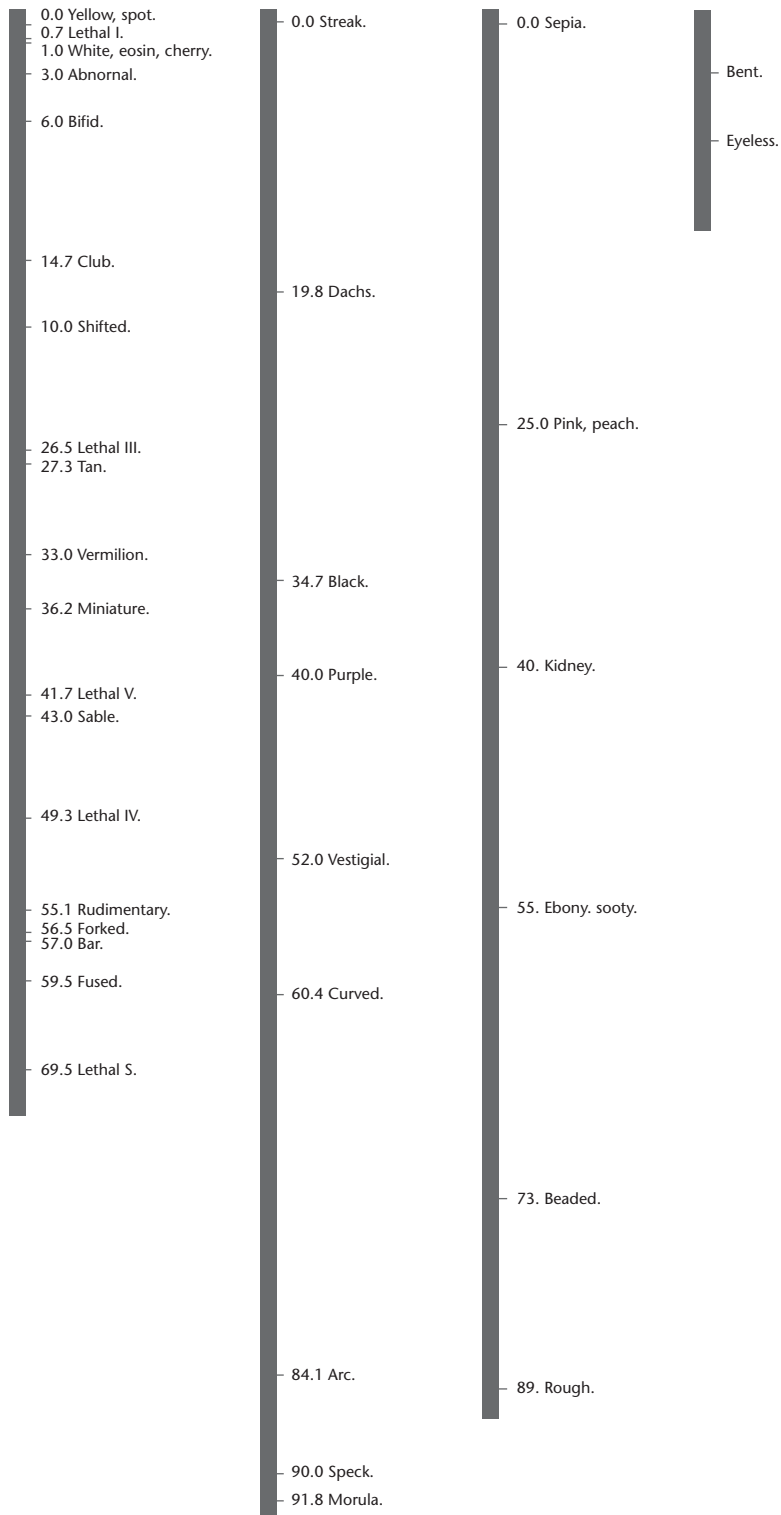


Figure 1 A genetic linkage map of the four chromosomes of *Drosophila*. Reproduced from Morgan TH, Sturtevant AH, Muller HJ and Bridges CB (1915) *The mechanism of Mendelian heredity*. New York: H Holt and Company.

Mendel, Gregor Johann; Morgan, Thomas Hunt; Sturtevant, Alfred Henry

Linkage maps are now generated using a variety of phenotypic or molecular *markers*. By using a combination of markers with known relative genomic locations, scientists can pinpoint where in the genome an unknown mutation resides based simply on the recombination fraction between markers in a genetic cross and the phenotype of interest. For species such as humans, genetic crosses between individuals are more difficult. As a result, scientists either use pedigree information to reconstruct the genotypes of individuals at various markers or, more recently, survey populations for a million or more genetic markers at known locations throughout the genome. This information is then used to infer the order of those genotypes in individuals, referred to as haplotypes, or to map traits of interest. **See also:** [Recombination and Human Genetic Diversity](#)

Although *Drosophila* played a central role in using recombination fractions to construct the first genetic maps, fungal systems have been particularly useful in elucidating the molecular pathway of recombination. One reason for this is the ease of *tetrad analysis* with fungal systems such as

yeast and *Neurospora*. Unlike the egg and sperm products of meiosis in fruit flies and other animals, fungal tetrads constitute four haploid gametic products of a single meiosis that are fused, and deviations from the expected 1:1 ratio can be easily observed by dissecting and analyzing these tetrads directly. **See also:** [Neurospora Genetics](#)

Mechanics of Crossing Over

Figuring out the steps

It has taken scientists decades to decipher the recombination pathway, and new critical enzymes are still being discovered. Organisms that lack crucial enzymes offer insight into these models and suggest additional pathways that can lead to the same outcome. In 1964, Robin Holliday presented a model for recombination that is still influential, at least in a modified form, today (**Figure 2a**) (Stahl, 1994; Haber *et al.*, 2004). This early model described a single-stranded nick in the deoxyribonucleic acid (DNA) backbone; however, we learned through the experiments in 1981 by Orr-Weaver and colleagues that recombination is

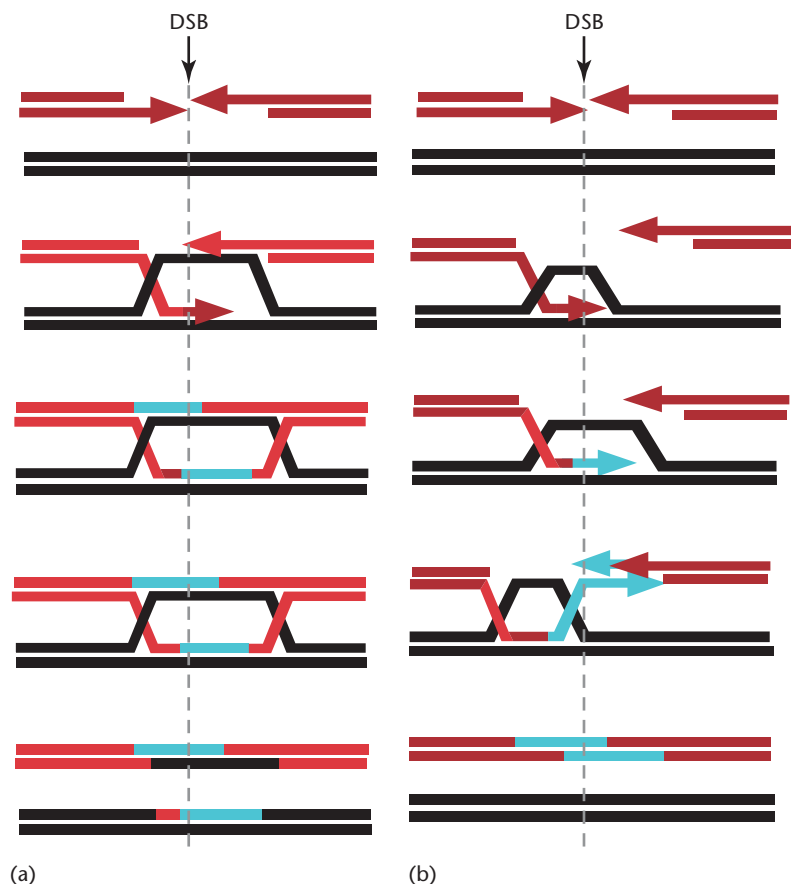


Figure 2 Two major models of genetic recombination (a) Szostak (1983) DSB model (b) Allers and Lichten (2001) SDSA model. Modified from Haber *et al.*, 2004. Repairing a double-strand chromosome break by homologous recombination: revisiting Robin Holliday's model. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences* 359: 79–86. Reproduced with permission from The Royal Society.

initiated by a double-stranded break (DSB) in the DNA (Orr-Weaver *et al.*, 1981; Szostak *et al.*, 1983). In 1997, Scott Keeney and colleagues discovered the cause of this double-stranded break was an endonuclease protein called Spo11 in yeast that breaks DNA and causes a series of subsequent recombination events to occur (Keeney *et al.*, 1997). These experiments were carried out in yeast, but homologous proteins have been found in other systems including *Drosophila*. **See also:** [Eukaryotic Recombination: Initiation by Double-strand Breaks](#); [Homologous Genetic Recombination in Eukaryotes](#)

Early models predicted many of the steps needed for recombination to take place, however, the actual enzymes that perform these steps were discovered much later. For example, scientists knew meiotic exchange between chromosomes required some type of DNA strand invasion, but the double-stranded DNA ends needed to become single-stranded first. Then, scientists discovered the Mre11 exonuclease enzyme complex that is involved in chopping DNA after DSB initiation to create single-stranded DNA (D'Amours and Jackson, 2002). This DNA then invades the nearby homologous chromosome and causes a displacement known as the *D-loop* formation (see **Figure 2**). The scissor-shaped DNA complex that results is known as a *double Holliday Junction (dHJ)* since this type of formation was predicted in 1964 in Dr. Holliday's original model for recombination. It is the cleavage of these Holliday junctions that decides whether the recombination pathway results in crossover or noncrossover products. In a crossover pathway, a horizontal and a vertical cleavage result in rearrangement of the flanking sequence, whereas two horizontal cleavages result in a noncrossover.

Noncrossovers do not result in downstream genetic exchange, but they can allow some very localized genetic exchange through mismatch repair. During recombination, the formation of mismatched DNA resulting from exchange of heterozygous DNA sequence yields *heteroduplexed* DNA, where noncomplementary bases are paired in the double helix. This mismatching targets mismatch repair mechanisms in the cell to fix the strain in the double helix. This can lead either to no exchange or unequal exchange where one chromosome is modified to have the same genetic material as the homologous chromosome and the original information is lost. This process is known as *gene conversion*, and unlike crossovers which can cause exchange over megabases of DNA, gene conversion events are generally under a kilobase. **See also:** [Gene Conversion](#)

Additional modern recombination models – SDSA

The small scale of gene conversion events makes them difficult to detect without very dense genetic mapping; however, crossovers are much easier to detect. Despite this, experimental work shows that the majority of recombination products result in noncrossovers rather than crossovers. This observation has led to modification of the simple Holliday junction resolution models which predicted either

outcome to be equally likely. One such advance is the arrival of synthesis dependent strand annealing (SDSA) models, which rather than predicting a 50% crossover rate, predicts a majority gene conversion rate, fitting empirical results better than previous models. **See also:** [Meiotic Recombination Pathways](#)

As shown in **Figure 2**, SDSA models differ from the classic double-strand break repair (DSBR) models in a few critical ways (1) strand invasion and D-loop formation, (2) location of dHJ relative to DSB and (3) outcome of crossovers versus noncrossovers (Allers and Lichten, 2001; Haber *et al.*, 2004). First, strand invasion is seen as rate-limiting, such that initially only one strand participates until the second strand finally captures the invading loop to result in a D-loop formation. Unlike DSBR models where D-loop formation always occurs, D-loop formation is not always the result of SDSA models. Once D-loop formation has occurred, the resulting dHJ is depicted as on one side of the DSB. In DSBR models, the dHJ is always depicted as flanking the DSB. Finally, this process results in a majority of noncrossover events as discussed earlier, which contrasts the traditional DSBR models. This also means that recombination proceeds in a fashion more reminiscent of transcription rather than replication since the strand where the DSB formation occurs is the only strand that has newly synthesized DNA whereas in DSBR, both strands receive some new genetic material.

Unique features of recombination in *Drosophila*

As discussed earlier, the ability to perform genetic crosses in *Drosophila* make them very useful for determining the genomic location of unknown markers in the reconstruction of genetic maps. The current availability of very dense genetic maps in multiple species with a variety of markers and marker types make it a great model for looking at fine scale recombination events. Further, haplotype reconstruction is often not necessary in fruit flies since the haploid genotypes of individuals are known due to the widespread use of inbred lines which are homozygous at most genetic loci.

When genetic crosses are performed, an extra layer of experimental control is available to fruit fly geneticists due to a unique aspect of male *Drosophila* biology. *Drosophila* males do not undergo crossing over, allowing for greater experimental control over recombination events from generation to generation. The biological phenomenon where the heterogametic sex, the male in *Drosophila*, does not undergo crossing over is referred to as the Haldane–Huxley rule. This is not the case for all species of *Drosophila* as *Drosophila ananassae* males do exhibit some limited crossing over.

Further, many *Drosophila* researchers take advantage of 'balancer' chromosomes that have large chromosomal inversions preventing recombination to maintain a known haplotype within the stock. Such balancers are used for making segments of the genome homozygous or for

maintaining haplotypes that are homozygous sterile or lethal. Although the meiotic products of crossovers within the chromosomal inversion are not viable, the viability of the stock is not reduced as these meiotic products are shunted to the polar bodies during oogenesis. This means that genetic crosses using these stocks do not suffer from reduced numbers of offspring, another useful experimental feature of fruit flies. **See also:** *Drosophila* Oogenesis

Genetic manipulation of fruit flies is also possible to make them even more useful as a model in studying recombination. As discussed earlier, fungal systems are unique in their ability to do tetrad analysis; however, a few systems including *Drosophila* have found ways to artificially create fused gametes. In *Drosophila*, irradiation can generate fused X-chromosomes which are inherited as a single unit in female offspring. These fused chromosomes, or *half tetrads*, can be used for tetrad analysis to determine the location of actual genetic exchange similar to analysis in fungal systems (Hilliker *et al.*, 1994). By using a combination of markers on the X-chromosome, genetic exchange over very small genetic distances can be observed in females. This technique has been useful for determining gene conversion rates in *Drosophila*.

Variation in Crossing Over

Recombination rates can vary dramatically between species, ranging from no recombination in asexual systems to very high levels of allelic exchange across the genomes of some sexual systems. Within any particular genome, meiotic recombination rates are also variable, such that some regions have higher rates of crossing over than others. *Drosophila* have been particularly useful in determining several factors which cause recombination rate variation. For example, early work in the Morgan lab found that there is variation with maternal age, where eggs developing later in life exhibit higher numbers of crossovers than eggs generated earlier in life (Bridges, 1927, 1929). Further attempts to examine plasticity in recombination rates have demonstrated that factors such as temperature (Plough, 1917, 1921), nutrition (Neel, 1941), age of mating (Redfield, 1966) and number of matings (Priest *et al.*, 2007) also affect recombination rates in *Drosophila*. These factors seem to affect recombination rates in other systems as well. The pattern that has emerged from the synthesis of these data is that *stressful* conditions tend to trigger an increase in recombination rates (Parsons, 1988; Hadany and Beker, 2003; Agrawal *et al.*, 2005).

In addition to condition-dependent changes in recombination rates, recombination within the genome can vary based on genotype. For instance, some alleles can induce more double-strand breaks leading to higher rates of recombination in particular regions of the genome (Symington, 2002; de Massy, 2003). Recent interest in fine scale variation in recombination rates has led to the discovery of recombination *hotspots* which are regions of high recombination limited to very small parts of the genome.

These findings are particularly surprising when summed over the whole genome. For example, in humans, hotspots cover only 6% of the sequenced genome, but approximately 60% of recombination in the genome occurs in these locations (Frazer *et al.*, 2007). Such hotspots seem to be associated with particular DNA sequence motifs in some cases (Myers *et al.*, 2008).

Evolutionary Effects of Recombination on Structure of the Genome

Recombination is well-known for its evolutionary advantages of combining advantageous alleles onto single haplotypes and removing deleterious alleles from haplotypes that persist within a species. However, recombination rate variation is also associated with various aspects of the structure of eukaryotic genomes, and the nature of these associations is sometimes less clear. Three associations that have been studied extensively in *Drosophila* species are those of local recombination rate with nucleotide diversity within species, nucleotide divergence between species and *codon usage bias*. **See also:** *Codon Usage in Molecular Evolution*; *Sex: Advantage*

Nucleotide diversity and divergence

The seminal compilation of data from 20 loci by Begun and Aquadro (1992) elegantly demonstrated an overall strong positive association of recombination rate and nucleotide diversity in this species. Subsequent studies have repeatedly confirmed this observation in this and other *Drosophila* species, including whole-genome sequencing efforts of its sister species *Drosophila simulans* (Begun *et al.*, 2007), examinations of fine scale crossover variation and sequence diversity along one chromosome in distantly related species *Drosophila pseudoobscura* (Kulathinal *et al.*, 2008) and studies of a few loci in *D. ananassae* (Baines *et al.*, 2004).

Causes

Such a positive association between recombination rate and nucleotide diversity could be driven by a variety of mechanistic or evolutionary causes. Mechanistically, the simplest explanation would be that the process of crossing over, or its DSB precursor, is mutagenic. Consistent with this possibility, a few studies have found evidence for a mutational effect of recombination in primates (Lercher and Hurst, 2002), and functional studies of yeast recombination support possible mutagenicity of DSBs (Strathern *et al.*, 1995). Mutation rate and recombination rate may also be associated indirectly via common causes, such as base composition or rates of biased gene conversion. For example, areas that are targets for DSBs may incidentally be regions that experience higher mutation rates. Also, heteroduplexed DNA resulting from recombination may be preferentially repaired to keep GC nucleotide bases over AT nucleotides, creating a GC bias in the gene conversion process.

Multiple evolutionary processes can explain such an association of recombination rate and nucleotide diversity as well. In regions of low recombination, the spread of a new, advantageous allele will be associated with a reduction in nucleotide diversity across a large window of the genome, a process called *hitchhiking*. In regions of high recombination; however, the advantageous allele will dissociate from most of its neighbours during its spread. Negative selection against deleterious mutations can also generate a similar pattern through a process called *background selection*. As new detrimental mutations arise within a population, other alleles at loci near these new mutations are destined for eventual loss in regions of very low recombination (because they cannot dissociate from them), whereas new mutations can be eliminated without loss of much nearby variation in regions of high recombination. Other evolutionary processes may also contribute to this pattern, such as *interference* among weakly selected alleles in close proximity to one another.

Distinguishing between different scenarios

Simple mechanistic causes for an association of recombination rate and sequence diversity predict that recombination rate should also be associated with sequence divergence *between* species. However, the opposite has typically been observed: *Drosophila* species often exhibit similar levels of sequence divergence in regions of high and low recombination (e.g. Noor and Kliman, 2003), demonstrating the lack of an association of recombination rate with divergence. Any association between recombination rate and divergence between species is consistently weaker than the association of recombination rate and sequence diversity within species. These observations argue against neutral explanations for the associations in *Drosophila*.

However, complicating factors may obscure the association of recombination rate to sequence divergence between species. For example, recombinational 'hotspots' arise and disappear quickly over generations within some species, and such turnover of recombination rates over time may obscure associations with interspecies divergence (Spencer *et al.*, 2006). Additionally, studies in *Drosophila* have assumed that mutations would be associated with crossovers in particular, but mutations may instead be associated with DSBs more generally, including ones that result in gene conversion without crossing over. In regions of severely reduced recombination, such as adjacent to centromeres, DSBs occur but do not resolve into crossovers. To date, no one has tested directly for an association between interspecies divergence and DSB rate in *Drosophila*, though one study failed to identify such an association among *Saccharomyces* species (Noor, 2008). Hence, overall, although selective forces clearly contribute to the association of recombination rate and sequence diversity within species, it is unclear if there may also be a (lesser) contribution from possible mutagenicity of recombination.

Perhaps an even greater challenge is distinguishing the relative contributions of hitchhiking versus background selection as selective forces driving the association of recombination rate and nucleotide diversity within species. Looking across loci, the process of hitchhiking should produce an excess of abundant new alleles, and this frequency distortion of alleles is not predicted by background selection. This prediction has been developed and applied using test statistics, and strong signatures of hitchhiking have been identified in genome-wide comparisons. However, detecting hitchhiking from the spread of adaptive alleles does not disprove the operation of background selection and its effects on overall patterns of nucleotide diversity. As with mutational contributions, we are left with support for one explanation but an ambiguous picture regarding the relative contribution of others.

Codon bias

Although the genetic code permits multiple synonymous codons to produce the same amino acid, many taxa exhibit strong biases for particular codons across their genome. This 'codon usage bias' is thought to be driven largely by selection favouring efficient translation of codons into proteins, though perhaps the pattern may also be influenced by mutational biases (see later). Because natural selection is more effective in regions of high recombination than low recombination as described earlier, selective explanations for codon usage bias predict that it should be the most apparent in regions of high recombination. This expectation has been validated, particularly in studies of *Drosophila* (e.g. Hey and Kliman, 2002).

Many studies have suggested that codon bias is weak in regions of low recombination because of the so-called Hill-Robertson (1966) effects. Essentially, selection would be less efficient at particular sites in such regions because of interference from selection acting on many other nearby sites. For example, a favoured codon may be near an unfavoured one, and thus its spread is hampered, particularly in regions of low recombination. If such interference is common, then looking across a gene, those codons near the centre should exhibit the most interference (since they have many other codons near them) whereas codons at the ends of genes should exhibit less interference. As a result, one would predict that the centre codons of long amino-acid coding sequences should exhibit less codon bias than the codons near the edges, and this prediction has been supported (Comeron and Kreitman, 2002). With high recombination, interference is reduced because the codons evolve more independently, and the association of codon bias and recombination seems to disappear in *Drosophila melanogaster* when the recombination rate exceeds 1.5 cM/Mb (Hey and Kliman, 2002). **See also:** [Recombination and Human Genetic Diversity](#)

However, a mutational process may also explain some of the association of recombination rate and codon bias. In *Drosophila*, preferred codons typically end in a C or G. As mentioned earlier, in some recombination hotspots, the

repair of mismatches that arise during recombination is biased towards G + C richness, such that gene conversion preferentially results in increased numbers of C or G nucleotides (Marais *et al.*, 2001; Marais, 2003). If such biased gene conversion solely contributes to the relationship of recombination to codon bias, one predicts that recombination should be equally strongly associated with GC content in third codon positions as in nearby noncoding regions. This predicted relationship was not observed in *D. melanogaster* (Hey and Kliman, 2002; Kliman and Hey, 2003), suggesting that natural selection for C- or G-ending codons is a driving force for causing codon bias.

Other patterns

Many other patterns in the genome associate with recombination rate. From an evolutionary perspective, the reduced effectiveness of natural selection (through interference or otherwise) in regions of low recombination should leave multiple other signatures in the genome. Recombination increases the effectiveness of protein adaptation throughout the *D. melanogaster* genome because genes residing in low recombination regions are more often recombinationally linked with detrimental mutations for multiple reasons. First, low recombination makes it more difficult to remove the deleterious alleles and they accumulate in regions of low recombination, and second, beneficial mutations are less likely to spread in regions of low recombination than in regions with higher recombination rates and are thus lost due to random chance more often (Presgraves, 2005).

Additionally, high *transposable element* densities have been identified in low recombination regions of multiple *Drosophila* species, but the exact form of selection causing this pattern is not understood (Bartolome *et al.*, 2002; Dolgin and Charlesworth, 2008). Various DNA sequence motifs also associate with recombination rate in many species (Myers *et al.*, 2008), but whether these motifs are actual causes of recombination rate variation or both parameters covary with another causative factor is not yet known. Clearly, we have only begun to scratch the surface of understanding effects caused by or related to recombination rate variation within and among genomes. **See also:** [Transposons](#)

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