

# The genetic basis and evolution of meiotic recombination rate variation - what have we learned?

Susan E. Johnston.

Institute of Ecology and Evolution, School of Biological Sciences,  
University of Edinburgh, EH9 3FL, United Kingdom.

[Susan.Johnston@ed.ac.uk](mailto:Susan.Johnston@ed.ac.uk)

## Abstract

Meiotic recombination is the exchange of DNA between homologous chromosomes, through chromosomal crossover and gene-conversion events. It is a fundamental feature of sex, and an important driver of diversity in eukaryotic genomes. The toolbox of recombination is remarkably conserved, yet meiotic genes show substantial variation even between closely related species. Furthermore, the rate and distribution of recombination is diverse across eukaryotes, both within and between genomic regions (i.e. “hotspots”), chromosomes, individuals, sexes, populations, and species. In recent decades, major advances have been made in understanding recombination rate variation, in terms of measuring it, identifying its genetic architecture and evolutionary potential, and understanding the complex dynamics of recombination landscapes. In this perspective, written for the 40<sup>th</sup> anniversary of the journal *Molecular Biology and Evolution*, I explore what we have learned and are still learning about the genetic basis and evolution of recombination rates, and present open questions for future research.

## Introduction

Meiotic recombination is the exchange of DNA between homologous chromosomes, through chromosomal crossover and gene-conversion events. It is a fundamental feature of sex, and an important source of genetic diversity (Stapley et al. 2017; Henderson and Bomblies 2021). The crossover process was first discovered more than a century ago, through experiments of the student Alfred Sturtevant on the co-inheritance of mutant phenotypes in *Drosophila melanogaster* in the laboratory of Thomas Hunt Morgan (Sturtevant 1913), with Harriet Creighton and Barbara McClintock showing empirical proof of this concept in cytological experiments in maize (Creighton and McClintock 1931; Hunter 2015). The molecular mechanisms of meiotic recombination were less understood until the late 1980s, where the first genes were identified in the yeast *Saccharomyces cerevisiae* (Zickler and Kleckner 1999). We now know that the toolbox of recombination is remarkably conserved into the deep evolutionary past of animals, plants, and fungi, with homologous loci involved chromosome pairing via the synaptonemal complex, the formation of DNA double strand breaks (DSBs), and their repair via crossovers and gene conversion. Despite this, these genes and proteins show remarkable variation in their sequence and function, even between closely related species (Gerton and Hawley 2005; Kumar et al. 2010; Arter and Keeney 2023). We also know that the rate and distribution of recombination is diverse across eukaryotes, both within and between

genomic regions (i.e. “hotspots”), chromosomes, individuals, sexes, populations, and species (Choi and Henderson 2015; Stapley et al. 2017; Haenel et al. 2018; Peñalba and Wolf 2020).

The diversity of recombination rates presents an interesting conundrum, as it is a trait characterised by both molecular and evolutionary trade-offs. From a molecular perspective, the formation of crossovers is critical to ensure the proper disjunction of chromosomes and avoid aneuploidy (i.e. the wrong number of chromosomes segregating into gametes), with most species having a minimum of one obligate crossover per chromosome pair to ensure that resulting zygotes are viable (Koehler et al. 1996; Hassold and Hunt 2001; Jones and Franklin 2006; Wang et al. 2015). However, recombination also requires the formation of hundreds of DSBs in the genome, and their repair is directly mutagenic, with higher *de novo* mutation rates seen at DSB repair sites compared to the rest of the genome (Halldorsson et al. 2019; Hinch et al. 2023)(but see (Liu et al. 2017)). Therefore, one could argue that molecular trade-offs should constrain the rate of recombination to few DSBs and crossovers as possible, yet widespread variation at the chromosomal level persists (Stapley et al. 2017; Fernandes et al. 2018).

A compelling explanation for the diversity of recombination rates is an evolutionary one (Otto and Lenormand 2002). Recombination provides a mechanism to rapidly purge deleterious mutations from the genome (Muller 1964; Kondrashov 1988) and can bring together beneficial variants at linked loci, increasing the speed and magnitude of responses to selection (Fisher 1930; Muller 1932; Felsenstein 1974). Similarly, recombination can mitigate the effects of selection at one locus interfering with selection at linked loci (i.e. Hill-Robertson interference; (Hill and Robertson 1966)), particularly in finite populations where selection and/or genetic drift are more likely to generate negative associations between loci (Felsenstein 1974; Charlesworth et al. 2009). There are also evolutionary costs to recombination: the same mechanisms can generate “recombination load”, where beneficial variants at linked loci are uncoupled (Charlesworth and Charlesworth 1975; Charlesworth and Barton 1996); and as described above, DSB repair is a major source of new and potentially deleterious mutations. There are many evolutionary processes that can be influenced by recombination, such as the effects of background selection (Booker et al. 2021), adaptive evolution (Gossmann et al. 2014; Castellano et al. 2016; Kosheleva and Desai 2018), adaptive substitution rates (Rousselle et al. 2019), sex chromosome evolution (Charlesworth 2017; Olito and Abbott 2023), nucleotide diversity (Campos et al. 2014), hybridisation and the fate of introgressed alleles (Martin and Jiggins 2017; Schumer et al. 2018; Duranton and Pool 2022), and speciation (Ortiz-Barrientos et al. 2016). All things considered, the optimal level of recombination is likely to vary dynamically depending on (a) the strength of selection or drift at a given time, and (b) the resolution at which it is occurring, e.g. within specific genomic regions, or the level of the chromosome, genome, individual, population, and species. If recombination rate itself has a genetic basis, then it can theoretically evolve towards this optimal level.

Over the last 40 years, major advances have been made in understanding the evolution of recombination rate variation. We can quantify recombination in many species at a high resolution, showing variation in their rate and distribution (Peñalba and Wolf 2020). We know that recombination rates can be plastic, and affected by temperature, population densities, infection status, and oxidative stress (Bomblies et al. 2015; Rybnikov et al. 2023). We know that

specific genomic features influence or correlate with recombination rate (Webster and Hurst 2012; Zelkowski et al. 2019). We know that recombination rates can be underpinned by heritable genetic variation, meaning that they have the potential to evolve (Stapley et al. 2017). Finally, we know that recombination rates can evolve in response to selection, both directly via gamete and zygote viability, and/or indirectly via the fitness of the offspring (Otto and Barton 2001; Ritz et al. 2017; Stapley et al. 2017). In this perspective, written for the 40<sup>th</sup> anniversary of the journal *Molecular Biology and Evolution*, I explore what we have learned about the genetic basis, evolution and evolutionary potential of recombination rates and landscapes, and present open questions for future research.

## Understanding variation in recombination in the genomics era.

New insights into recombination rate evolution have been tightly coupled with advances in technologies and methodologies. Since the 1970s, variation in the number and distribution of crossovers had been noted in model systems such as *Drosophila* and mice (Henderson and Edwards 1968; Lyon 1976), and recombination hot-spots were identified in fungi such as *S. cerevisiae* and *Neurospora* (Lichten 1995). From the late 1990s onwards, the emergence of pedigree-based studies with dense molecular marker data showed that there could be individual, age, and sex-specific variation in crossover counts and crossover interference in humans and mice (Broman et al. 1998; Kong et al. 2004; Campbell et al. 2015). This was rapidly followed by population-based studies investigating linkage patterns in whole-genome sequence data, which showed that recombination also occurred in hot-spots of 1-10kb in many animals and plants (Myers et al. 2005; Hellsten et al. 2013; Choi and Henderson 2015). Today, a variety of technologies and methods exist to measure recombination rates at different resolutions and timescales, ranging from high-resolution imaging and microscopy-based cytogenetic approaches, to genomic approaches quantifying pedigree-, gamete-, and population-level estimates (see Box 1 and (Peñalba and Wolf 2020)). The advent of next-generation sequencing and high-throughput genotyping arrays has been a key development in understanding recombination rate variation in a diverse range of species, giving a better insight into individual and genomic factors and mechanisms associated with this variation.

From an evolutionary perspective, this progress has led to several key developments. First, it has shown that the context in which recombination occurs can have a large impact on rates and landscapes. This can be plastic and associated with individual and environmental factors, such as age, temperatures, population densities, infection status, and levels of oxidative stress (Bomblies et al. 2015; Martin et al. 2015; Rybnikov et al. 2023). Second, the majority of variation can be attributed to the structure of the genome itself, where having more chromosomes and/or shorter chromosomes will increase the per-base rate of recombination, due to obligate crossing over (Stapley et al. 2017). Third, we observe consistently large differences in recombination rates and landscapes between female and male gametes within the same species (known as “heterochiasmy”), including in hermaphroditic animals and plants (Lenormand and Dutheil 2005; Theodosiou et al. 2016). Despite this observation, there remains little understanding of the evolutionary drivers of heterochiasmy (Sardell and Kirkpatrick 2020). Fourth, and most importantly, it has identified individual-level phenotypic and genetic variation in recombination rate, as well as variation in the distribution, or landscape of recombination across the genome.

This development gives clear indications on the evolutionary potential of recombination, which I discuss in the following sections. Finally, these developments have aided studies that require knowledge of recombination, such as identifying and interpreting selective sweeps (Josephs and Wright 2016), inferring phylogenies and demographic histories (Li et al. 2019; Feng et al. 2023; Soni et al. 2024), and predicting responses to selection (Battagin et al. 2016; Epstein et al. 2023).

#### Box 1: Methods to quantify recombination rate variation.

See (Peñalba and Wolf 2020) for a detailed review on these approaches. References are methods and/or empirical examples.

**Cytogenetics:** Directly visualises chromosomes in meiotic cells using immunostaining of meiotic proteins to identify crossovers (COs), often targeting foci of the DNA mismatch repair protein MLH1. Can also identify the number and distribution of DSBs and the length of the meiotic axis/synaptonemal complex through immunostaining (e.g. RAD51, SYCP3). Physical positions can be determined e.g. in  $\mu\text{m}$ . Sample size:  $\geq 1$  individual. (Malinovskaya et al. 2018; Peterson et al. 2019).

**Pedigree-based estimation:** Integrates pedigree and genetic marker information (e.g. SNPs) to identify marker pairs separated by a CO in gametes transmitted from genotyped parents to genotyped offspring. Can be used to estimate recombination rates and distributions in: (a) **individuals**, using information on CO positions to determine CO counts, CO interference, CO positioning, and inter- and intra-chromosomal allelic shuffling; and (b) **populations**, by creating linkage maps measured in centiMorgans (cM), where 1cM is a 1% chance that two loci are separated by a CO event per meiosis. Sample size:  $\geq 100$ -1000s individuals to capture enough COs. (Veller et al. 2019; Brekke, Berg, et al. 2022; McAuley et al. 2023).

**Population-based estimation:** Uses whole genome sequence data to estimate the population-scaled recombination rate ( $\rho$ ), based on patterns of linkage disequilibrium and the coalescent. Estimates are the sex-averaged recombination rates over the previous 100s to 1000s of generations. Demographic history and selection patterns can affect the power to detect hotspots and must be accounted for, although new methods (e.g. using neural networks) may overcome this requirement. Sample size:  $\geq 10$ -30 individuals, including outgroups. (Dapper and Payseur 2018; Adrion et al. 2020; Bascón-Cardozo et al. 2024)

**Gamete sequencing:** Sequencing at the single- or pooled-gamete level can identify CO positions based on the deviation from on consensus allele frequencies (e.g. within the same gamete, or on the same sequencing read). Sample size:  $\geq 1$  individual. (Dréau et al. 2019; Xie et al. 2023).

**Chromatin immunoprecipitation sequencing (ChIP-Seq):** Identifies DNA binding sites for the proteins that initiate meiotic DSB formation (e.g. DMC1), which are then sequenced and used to map DSB positions. Sample size:  $\geq 1$  individual. (Smagulova et al. 2016; Tock et al. 2021; Lian et al. 2022).

## Genetic architecture and evolutionary potential of recombination rate variation.

Recombination rate evolution has been observed in over short experimental timescales (e.g. in *Drosophila*, mice, and mustard; (Otto and Barton 2001)), implying that standing genetic variation for recombination rates exists within populations. Therefore, a key advance in understanding the evolution and evolutionary potential of recombination variation has been to determine its genetic architecture in different systems. Specifically, these studies aim to identify the proportion of variation that is “heritable” (i.e. explained by additive genetic effects), the genes that contribute to heritable variation, their effect sizes, and if they are *trans*-acting (i.e. affecting the genome-wide recombination rate) or *cis*-acting (i.e. affecting the recombination rate within the vicinity of the gene).

One approach has been to use genome-wide association studies (GWAS) to identify genes of moderate to large effect. Vertebrate populations with large genotyped pedigrees have been highly suitable for this, as they not only allow individual rates to be quantified (Box 1), but also for GWAS of recombination rates to be applied to the same data. These studies have generally been limited to model and domestic vertebrates, such as humans, cattle, pigs, sheep, Atlantic salmon and chickens (Kong et al. 2014; Ma et al. 2015; Kadri et al. 2016; Petit et al. 2017; Weng et al. 2019; Johnsson et al. 2021; Brekke, Johnston, et al. 2022; Brekke, Berg, et al. 2022; Brekke et al. 2023), and increasingly in long-term wild pedigrees, such as in Soay sheep, Red deer, and house sparrows (Johnston et al. 2016; Johnston et al. 2018; McAuley et al. 2023).

Recombination rates, most often measured as crossover count, are heritable in all of these systems. In particular, all mammal studies have shown a remarkably consistent pattern of large effect, *trans*-acting loci affecting the genome-wide recombination rate. Nearly all identified loci are associated with meiotic processes, such as double strand break initiation and repair, the synaptonemal complex, and crossover designation (*RNF212*, *RNF212B*, *REC8*, *MEI1*, *MSH4*, *PRDM9*, etc). Furthermore, these loci can often have sex-differential or sex-limited effects on recombination, i.e. loci that have a large effect in one sex, more often females, have little or no discernible effect in the other sex (Kong et al. 2014; Johnston et al. 2016; Kadri et al. 2016; Johnston et al. 2018; Weng et al. 2019; Brekke, Johnston, et al. 2022; Brekke, Berg, et al. 2022; Brekke et al. 2023). I note here that the locus *PRDM9* is a special case, and I discuss its role in individual variation in more detail in the next section.

Recombination rate variation has also been shown to have a genetic basis in non-vertebrate systems. A GWAS in a large hybrid population of domestic and wild barley identified the locus *Rec8* has having a large *trans*-acting effect on crossover number and patterning, and quantitative trait locus mapping in *Arabidopsis* has identified naturally segregating loci associated with meiotic crossover rate (Ziolkowski et al. 2017; Lawrence et al. 2019). In insects, GWAS and family crosses of *Drosophila* species have identified loci were associated with *cis*- and *trans*-variation in crossover rates and heterogeneity (Cattani et al. 2012; Hunter et al. 2016), and a study of fine-scale recombination rates in the honey bee (*Apis mellifera*) also identified *trans*-acting, heritable variation in recombination rates (Kawakami et al. 2019).

Nevertheless, recombination rates are not always driven by large-effect loci. In non-mammal vertebrates, such as house sparrows, chickens and Atlantic salmon, GWAS studies have shown

that crossover rates are heritable but polygenic, i.e. controlled by many loci of relatively small effect (Weng et al. 2019; Brekke et al. 2023; McAuley et al. 2023). In such cases, it is more difficult to interpret if heritable variation is acting in *trans*, through very small effects on e.g. the cell environment, overall chromatin structure, and meiotic processes affecting the global recombination rate, or in *cis*, through heritable aspects of the chromatin accessibility affecting the local recombination rates. A chromosome partitioning approach in house sparrows indicated that whilst most variation appears to have a *trans* effect on crossover rate, the positioning of crossovers is likely driven by loci operating in both *cis* and *trans* (McAuley et al. 2023). In Atlantic salmon and house sparrows, the cross-sex additive genetic correlation is relatively low (~0.11 and ~0.30, respectively), meaning that females and males have largely different genetic architectures of recombination rate, similar to what has been observed in mammals (Brekke et al. 2023; McAuley et al. 2023).

Taken all together, these studies have shown that natural genetic variation in recombination rates is pervasive and that genome-wide recombination rates have the potential to evolve. They also provide biological realism for theoretical models of recombination rate evolution. The focus on genome-wide recombination rates has led to the discovery of many *trans*-acting loci; however, it should be noted that the rarity of crossovers at the regional level can make it difficult to identify *cis*-acting loci unless sample sizes are very large (such as in (Hunter et al. 2016)). The discovery of sex-differences in the genetic architecture of recombination indicates that female and male rates have some potential for independent evolution, and may provide a mechanism for observed differences in heterochiasmy even between closely related species. One factor that remains unexplained is why some large-effect loci consistently maintain genetic variation within populations. An notable example of this is the ring finger protein *RNF212*, which is essential for the crossover designation process (Reynolds et al. 2013), yet consistently has a large effect on recombination rate variation in nearly every mammal study discussed above. Therefore, as the genetic basis of recombination rate variation becomes clearer in more systems, the next step is to understand the association between an individual's genetic merit for recombination and individual fitness, such as reproductive success and offspring viability. However, at present, such studies remain rare, due to a lack of suitable empirical data (Kong et al. 2004; Fernandes et al. 2018).

## Evolution of recombination landscapes: conserved or dynamic?

A common observation is that the landscape of recombination can vary dynamically, even between closely related species (Stapley et al. 2017; Zelkowski et al. 2019). This variation can be at the broad-scale, where the recombination is affected by general features of meiotic chromosomes, or at the fine-scale, where recombination positioning is affected by local structure and DNA-binding proteins. Here, I discuss variation at both of these scales and the genetic factors associated with their evolution.

### **Broad-scale variation.**

Recombination landscapes are affected by the physical structure of meiotic chromosomes. During meiosis, DNA is tethered into chromatin loops along an axis structure, which is then

integrated into the synaptonemal complex, a protein structure that holds homologous chromosomes in close proximity during recombination (Henderson and Bomblies 2021). Larger loops and shorter axes/synaptonemal complexes are associated with lower crossover rates at the chromosome level (Lynn et al. 2002; Dumont and Payseur 2011; Ruiz-Herrera et al. 2017). In addition, recombination rates are often vary with their proximity to centromeres and telomeres (Coop and Przeworski 2007; Haenel et al. 2018), and can show large differences in these patterns between males and females, and between species (Figure 1).

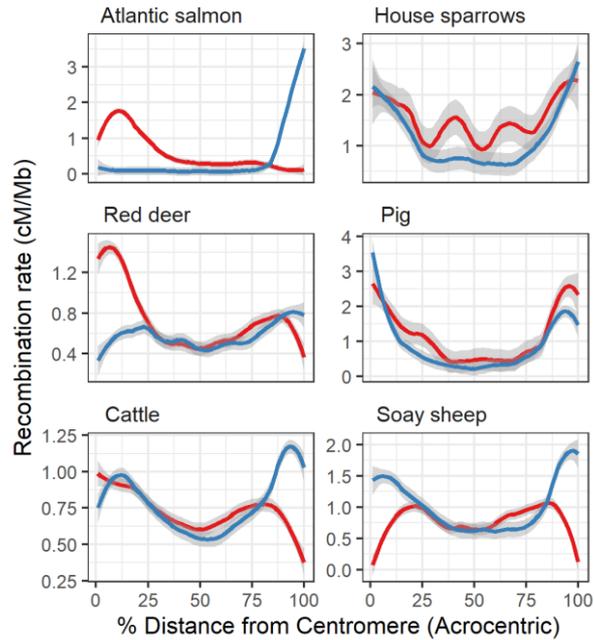
There is evidence that broad-scale patterning of recombination can be heritable, in terms of crossover positioning and crossover interference, although studies investigating genetic variation remain rare. The positions of individual crossovers per meiosis can be used to calculate the intra-chromosomal shuffling,  $\bar{r}$ , which is the rate at which two loci in the same chromosome are coupled or uncoupled by meiotic crossovers (Veller et al. 2019). Crossovers placed at the ends of chromosomes will lead to lower  $\bar{r}$ , whereas central crossovers will lead to increased  $\bar{r}$ ; this value can then be used as a proxy for crossover positioning across the whole genome. **Recent analysis in pigs shows that variation in  $\bar{r}$  can be heritable, and is driven by large effect variants at *MEI4* (Meiotic Double-Stranded Break Formation Protein 4), and *SYCP2* (Synaptonemal Complex Protein 2)(Brekke et al, *in prep*<sup>1</sup>).**  $\bar{r}$  has also been shown to be modestly heritable in house sparrows (McAuley et al. 2023) and Atlantic salmon (Brekke et al. 2023)<sup>2</sup>, although there are no large effect loci associated with this variation. Crossover positioning has a genetic basis in domesticated rye, where a major QTL was identified that increased the size of low-recombining regions in domesticated lines, with no change in the genome-wide rate (Schreiber et al. 2022).

Crossover interference (i.e. where crossover formation at one location suppressed the occurrence of crossovers nearby) can vary in its strength across chromosomes, and in turn have a a substantial impact on the rate and landscape recombination. It has been shown to be variable and heritable in cattle **and pigs**, driven by variants at the loci *NEK9* and *RNF212*, respectively (Wang et al. 2016)(Brekke et al, *in prep*). Similarly, a QTL analysis on the synaptonemal complex length in mice identified *RNF212* as a candidate quantitative trait locus (Wang et al. 2019). The identification of *RNF212* is interesting, as there is emerging evidence that the dosage and meiotic behaviour of *Hei10* (a locus in the same conserved family and with similar dynamics to *RNF212*) is highly associated with crossover interference in *Arabidopsis thaliana* (Morgan et al. 2021; Girard et al. 2023). However, studies on the genetic architecture of crossover interference remain challenging, as it relies on the observation of double crossovers, and so sample sizes required to accurately characterise remain difficult to achieve, with the exception of large pedigrees of model and domestic systems.

---

<sup>1</sup> ***NB: This has been presented at various conferences and we hope to preprint this before publication.***

<sup>2</sup> It may be worth noting that investigating  $\bar{r}$  has provided insights into the realised effects of heterochiasmy. In Atlantic salmon, there are distinct differences in recombination landscapes between females and males, where male recombination almost exclusive occurs in the sub-telomere (Figure 1). As a result, females have around 1.6x more crossovers, but have 8x more intra-chromosomal allelic shuffling. Therefore, most haplotypic diversity due to recombination is driven by females in this species.



**Figure 1:** Comparison of crossover distribution patterns in females (red) and males (blue) along chromosomes in six vertebrate species with high density linkage map information. Lines are Loess smoothed splines of recombination rates across all acrocentric autosomes (centromere to telomere) with a span parameter of 0.15, implemented in ggplot2 (Wickham 2016). The species included are Atlantic salmon (Brekke et al. 2023), house sparrows (McAuley et al. 2023), Red deer (Johnston et al. 2017), domestic pig (Brekke, Berg, et al. 2022), dairy cattle (Brekke, Johnston, et al. 2022), and Soay sheep (Johnston et al. 2016).

### ***Fine-scale variation - ancestral vs PRDM9-mediated hotspots.***

Population-based recombination mapping has shown a consistent pattern in many species for DSBs and crossover events to occur in recombination hotspots. In most species (and most likely the ancestral state), these hotspots tend to occur around functional elements such as gene promoter regions, and are often associated with nucleosome depletion, reduced DNA methylation and open chromatin (Brachet et al. 2012; Zekowski et al. 2019; Lian et al. 2022). These factors likely provide a window of opportunity for meiotic proteins such as SPO11 to bind to the DNA and initiate DSB formation more easily (Pan et al. 2011), and consequently, recombination can be higher in regions with higher gene densities (Zekowski et al. 2019; Lian et al. 2022). These hotspot positions are conserved over long evolutionary time periods, as demonstrated in birds (Singhal et al. 2015) and yeast (Tsai et al. 2010). Some species do not have recombination hotspots, such as *Drosophila spp.* (Smukowski Heil et al. 2015) and the nematode *Caenorhabditis elegans* (Kaur and Rockman 2014). Other fine-scale aspects of the genome have also been shown to be correlated with recombination rate variation, such as transposable element content, structural variation and histone H3 lysine K4 trimethylation marks (H3K4me3; (Kent et al. 2017; Morgan et al. 2017; Zekowski et al. 2019)). In particular, GC-content is often positively correlated with recombination rates and is likely due to GC-biased gene conversion (gBGC), where gene conversion events are more likely to be repaired with CG alleles rather than AT alleles (Duret and Galtier 2009). However, one of the most notable discoveries over the last 20 years is that of *PRDM9*, a rapidly-evolving locus that that determines recombination hotspot positioning in many vertebrate

species (Baudat et al. 2010; Baker et al. 2017). Unlike the ancestral hotspots above, PRDM9-mediated hotspots tend to be directed away from functional elements, and show remarkably little conservation within and between closely-related species (Berg et al. 2010; Baker et al. 2015; Stevison et al. 2016; Wooldridge and Dumont 2023). One key feature of PRDM9 is its zinc-finger (ZF) array, which binds to specific sequence motifs throughout the genome (Ségurel et al. 2011). Mutations in the ZF array can change the recognised sequence motifs, leading to the rapid loss and gain of recombination hotspots (Davies et al. 2016). Another notable feature of this system is that if there is asymmetry in hotspot sequence motifs (i.e. if a hotspot is heterozygous), then DSBs will be formed at the allele more likely to be bound by PRDM9, and repaired with the allele less likely to be bound by PRDM9 (Myers et al. 2008). This leads to a rapid loss of hotspots from the genome, referred to as the “hotspot paradox” (Coop and Myers 2007). This may result in a Red Queen scenario to replenish hotspots (Latrille et al. 2017), and indeed, in species where *PRDM9* is likely to be functional, it is one of the most rapidly evolving genes in the genome (Baker et al. 2017). The allelic diversity of *PRDM9* within species can be remarkable, with over 150 alleles identified in wild mice (Vara et al. 2019; Wooldridge and Dumont 2023), and 22 alleles identified in 19 corn snakes in a single study (Hoge et al. 2024). Variation in the abundance of hotspots recognised by *PRDM9* alleles may also affect the genome-wide rate of recombination; as mentioned in the previous section, variants at *PRDM9* have been associated with genome-wide crossover rates in humans, cattle, and pigs (Kong et al. 2014; Ma et al. 2015; Brekke, Berg, et al. 2022). *PRDM9* is also one of the few identified “speciation genes” in mice, and may be driven by allelic incompatibilities leading to sterility in hybrid males (Mukaj et al. 2020; Davies et al. 2021).

At this point in time, insights into the ubiquity and relative importance of PRDM9-mediated hotspots are still emerging. It was first shown to be the major driver of hotspot positioning in humans and mice (Baudat et al. 2010), with increasing evidence that it is associated with hotspots in nearly all mammals, some teleost fish, turtles, snakes, and lizards (Baker et al. 2017; Schield et al. 2020; Hoge et al. 2024; Raynaud et al. 2024); there is also emerging evidence that *PRDM9* could be functional in some insects (Everitt et al. 2024). However, *PRDM9* function has been lost in some groups, such as canids (Auton et al. 2013), birds, crocodiles and amphibians (Baker et al. 2017), reverting back to the stable, ancestral hotspots enriched at functional elements; this has been experimentally confirmed in *Prdm9*-knockout mice (Smagulova et al. 2016). Interestingly, more studies are beginning to show that the high fidelity of recombination to PRDM9-mediated hotspots in humans and mice may be the exception. A recent investigation of hotspots in 52 mammal species showed that many species in fact use both PRDM9-mediated and PRDM9-independent (i.e. ancestral) hotspots (Joseph et al. 2023), with a similar observation shown in rattlesnakes and corn snakes (Schield et al. 2020; Hoge et al. 2024).

## Are recombination rates adaptive, and are they evolving?

In this perspective, I have presented extensive evidence that variation in recombination rates and landscapes can be underpinned by genetic variation, meaning that they have the potential to evolve over short evolutionary timescales. Signatures of adaptive molecular evolution have been identified at meiotic genes in *Drosophila* (Brand et al. 2018) and mammals (Dapper and

Payseur 2019). Furthermore, evolution has been observed in small experimental populations of *Drosophila*, mice, and mustard, as an observed side-effect of strong selection on other traits such as geotaxis, wing length, and flowering time (reviewed in (Otto and Barton 2001)). This may have been due to indirect selection on recombination rate to overcome Hill-Robertson interference, as individuals with higher recombination rates are more likely to produce offspring with favourable haplotypes, who will in turn are more likely to inherit alleles associated with increased recombination rates (Otto and Barton 2001).

Domestication represents a scenario where strong selection may indirectly select for changes in recombination rates and landscapes. A long-held idea in the field was that this hypothesis explained why domestic mammals have higher recombination rates compared to other mammal species (Burt and Bell 1987). However, this was never explicitly tested, and subsequently countered by a study demonstrating no difference with rates in their wild progenitors (Muñoz-Fuentes et al. 2015). Indeed, given that recombination contributes relatively little to the shuffling of mammal genomes (Veller et al. 2019), selection for changes in recombination may be weak (Battagin et al. 2016; Gonen et al. 2017). On the other hand, plant species have more to gain from changes in recombination, due to their genome structure and breeding methods (Epstein et al. 2023), and indeed, studies from domesticated plants show evidence for evolution of recombination landscapes. In rye, the size of low-recombining regions has increased in domesticated lines, mediated by a major QTL at the locus *ESA1* (Schreiber et al. 2022); the authors hypothesises that this has arisen through indirect selection to achieve more homogeneous populations for agricultural use. In tomatoes, fine-scale alterations in recombination in specific genomic regions has observed between wild and domestic populations, with a loss of hotspots associated with selective sweeps (Fuentes et al. 2022), and in barley, domestication has led to reduced rates in interstitial chromosomal regions, but higher rates in distal regions (Dreissig et al. 2019).

Studies investigating selection on recombination rates phenotype remain rare, but with notable exceptions. First, a pedigree-based study in Icelandic humans found that oocytes with higher crossover rates increased the chance of a live birth, and that individuals with higher oocyte crossover rates tended to have more offspring (Kong et al. 2004); this is likely due to the direct effect of a reduced risk of non-disjunction leading to viable zygotes. Second, a population-based study of *Drosophila pseudoobscura* identified differences in the genome-wide rate of recombination between populations in Utah and Arizona, USA (Samuk et al. 2020). A QST-FST approach demonstrated that phenotypic difference were higher than expected than under neutrality, indicating that variation may be a consequence of local adaptation. Finally, it should be noted that substantial variation in recombination rates can exist with no apparent fitness cost. An experiment in *A. thaliana* combined mutants at three meiotic genes to increase the genome-wide recombination rates 7.8-fold, but this increase was not associated with any reduction in fertility (Fernandes et al. 2018), creating the possibility that recombination rate may be less constrained and more flexible to variation than previously thought.

## Future directions and open questions

This perspective has been a snapshot of developments in understanding the evolution of recombination rates over recent decades. One clear message is that the evolution of recombination rates is a multi-faceted and dynamic process, governed by genome structure, genetic variation, the presence or absence of PRDM9, plasticity and environmental effects, as well as selection on both the molecular and evolutionary fitness consequences of variation. Indeed, there is no one-size-fits-all canonical model of recombination rate evolution, illustrated by the scale of variation even between closely-related species. There remain a number of open questions on how and why recombination rate variation has evolved (Lenormand et al. 2016; Stapley et al. 2017; Zelkowski et al. 2019): Why does heritable variation in recombination persist, and is it under selection? What are the causes and consequences of heterochiasmy, in terms of rate and hotspot usage? What is the relative importance and mechanisms of variation in crossover positioning and interference? How is recombination rate coupled with fine-scale chromatin and gene function? Is recombination always adaptive, or flexible to variation? A clear message is that future progress will rely not only in further technological advances, but also on the synergy and inter-disciplinary research between molecular biologists, evolutionary biologists and theoreticians.

## Acknowledgements

Thanks to Deborah Charlesworth, Raphaël Mercier, Peter Keightley, Simon Martin, Cathrine Brekke, John McAuley and Bertrand Servin for helpful discussions.

## Funding

I am funded by a Royal Society University Research Fellowship (URF/R/211008).

## Data Availability

There is no data associated with this manuscript.

## Referenced Literature

- Adrion JR, Galloway JG, Kern AD. 2020. Predicting the landscape of recombination using deep learning. *Mol. Biol. Evol.* 37:1790–1808.
- Arter M, Keeney S. 2023. Divergence and conservation of the meiotic recombination machinery. *Nat. Rev. Genet.* [Internet]. Available from: <http://dx.doi.org/10.1038/s41576-023-00669-8>
- Auton A, Rui Li Y, Kidd J, Oliveira K, Nadel J, Holloway JK, Hayward JJ, Cohen PE, Greally JM, Wang J, et al. 2013. Genetic recombination is targeted towards gene promoter regions in dogs. *PLoS Genet.* 9:e1003984.
- Baker CL, Kajita S, Walker M, Saxl RL, Raghupathy N, Choi K, Petkov PM, Paigen K. 2015. PRDM9 drives evolutionary erosion of hotspots in *Mus musculus* through haplotype-specific initiation of meiotic recombination. *PLoS Genet.* 11:e1004916.

- Baker Z, Schumer M, Haba Y, Bashkirova L, Holland C, Rosenthal GG, Przeworski M. 2017. Repeated losses of PRDM9-directed recombination despite the conservation of PRDM9 across vertebrates. *Elife* [Internet] 6. Available from: <http://dx.doi.org/10.7554/elife.24133>
- Bascón-Cardozo K, Bours A, Manthey G, Durieux G, Dutheil JY, Pruisscher P, Odenthal-Hesse L, Liedvogel M. 2024. Fine-scale map reveals highly variable recombination rates associated with genomic features in the Eurasian blackcap. *Genome Biol. Evol.* [Internet] 16. Available from: <http://dx.doi.org/10.1093/gbe/evad233>
- Battagin M, Gorjanc G, Faux A-M, Johnston SE, Hickey JM. 2016. Effect of manipulating recombination rates on response to selection in livestock breeding programs. *Genet. Sel. Evol.* 48:44.
- Baudat F, Buard J, Grey C, Fledel-Alon A, Ober C, Przeworski M, Coop G, de Massy B. 2010. PRDM9 is a major determinant of meiotic recombination hotspots in humans and mice. *Science* 327:836–840.
- Berg IL, Neumann R, Lam K-WG, Sarbajna S, Odenthal-Hesse L, May CA, Jeffreys AJ. 2010. PRDM9 variation strongly influences recombination hot-spot activity and meiotic instability in humans. *Nat. Genet.* 42:859–863.
- Bomblies K, Higgins JD, Yant L. 2015. Meiosis evolves: adaptation to external and internal environments. *New Phytol.* 208:306–323.
- Booker TR, Payseur BA, Tigano A. 2021. Background selection under evolving recombination rates. *bioRxiv* [Internet]:2021.12.20.473549. Available from: <https://www.biorxiv.org/content/10.1101/2021.12.20.473549v1>
- Brachet E, Sommermeyer V, Borde V. 2012. Interplay between modifications of chromatin and meiotic recombination hotspots. *Biol. Cell* 104:51–69.
- Brand CL, Cattani MV, Kingan SB, Landeen EL, Presgraves DC. 2018. Molecular evolution at a meiosis gene mediates species differences in the rate and patterning of recombination. *Curr. Biol.* 28:1289-1295.e4.
- Brekke C, Berg P, Gjuvslund AB, Johnston SE. 2022. Recombination rates in pigs differ between breeds, sexes and individuals, and are associated with the RNF212, SYCP2, PRDM7, MEI1 and MSH4 loci. *Genet. Sel. Evol.* 54:33.
- Brekke C, Johnston SE, Gjuvslund AB, Berg P. 2022. Variation and genetic control of individual recombination rates in Norwegian Red dairy cattle. *J. Dairy Sci.* [Internet]. Available from: <http://dx.doi.org/10.3168/jds.2022-22368>
- Brekke C, Johnston SE, Knutsen TM, Berg P. 2023. Genetic architecture of individual meiotic crossover rate and distribution in Atlantic Salmon. *Sci. Rep.* 13:20481.
- Broman KW, Murray JC, Sheffield VC, White RL, Weber JL. 1998. Comprehensive human genetic maps: individual and sex-specific variation in recombination. *Am. J. Hum. Genet.* 63:861–869.
- Burt A, Bell G. 1987. Mammalian chiasma frequencies as a test of two theories of recombination. *Nature* 326:803–805.

- Campbell CL, Furlotte NA, Eriksson N, Hinds D, Auton A. 2015. Escape from crossover interference increases with maternal age. *Nat. Commun.* 6:6260.
- Campos JL, Halligan DL, Haddrill PR, Charlesworth B. 2014. The relation between recombination rate and patterns of molecular evolution and variation in *Drosophila melanogaster*. *Mol. Biol. Evol.* 31:1010–1028.
- Castellano D, Coronado-Zamora M, Campos JL, Barbadilla A, Eyre-Walker A. 2016. Adaptive evolution is substantially impeded by Hill-Robertson interference in *Drosophila*. *Mol. Biol. Evol.* 33:442–455.
- Cattani MV, Kingan SB, Presgraves DC. 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.
- Charlesworth B, Barton NH. 1996. Recombination load associated with selection for increased recombination. *Genet. Res.* 67:27–41.
- Charlesworth B, Betancourt AJ, Kaiser VB, Gordo I. 2009. Genetic recombination and molecular evolution. *Cold Spring Harb. Symp. Quant. Biol.* 74:177–186.
- Charlesworth B, Charlesworth D. 1975. An experimental on recombination load in *Drosophila melanogaster*. *Genet. Res.* 25:267–274.
- Charlesworth D. 2017. Evolution of recombination rates between sex chromosomes. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* [Internet] 372. Available from: <http://dx.doi.org/10.1098/rstb.2016.0456>
- Choi K, Henderson IR. 2015. Meiotic recombination hotspots - a comparative view. *Plant J.* 83:52–61.
- Coop G, Myers SR. 2007. Live hot, die young: transmission distortion in recombination hotspots. *PLoS Genet.* 3:e35.
- Coop G, Przeworski M. 2007. An evolutionary view of human recombination. *Nature Reviews Genetics* [Internet] 8:23–34. Available from: <http://dx.doi.org/10.1038/nrg1947>
- Creighton HB, McClintock B. 1931. A correlation of cytological and genetical crossing-over in *Zea Mays*. *Proc. Natl. Acad. Sci. U. S. A.* 17:492–497.
- Dapper AL, Payseur BA. 2018. Effects of demographic history on the detection of recombination hotspots from linkage disequilibrium. *Mol. Biol. Evol.* 35:335–353.
- Dapper AL, Payseur BA. 2019. Molecular evolution of the meiotic recombination pathway in mammals. *Evolution* 73:2368–2389.
- Davies B, Gupta Hinch A, Cebrian-Serrano A, Alghadban S, Becker PW, Biggs D, Hernandez-Pliego P, Preece C, Moralli D, Zhang G, et al. 2021. Altering the binding properties of PRDM9 partially restores fertility across the species boundary. *Mol. Biol. Evol.* 38:5555–5562.
- Davies B, Hatton E, Altemose N, Hussin JG, Pratto F, Zhang G, Hinch AG, Moralli D, Biggs D, Diaz R, et al. 2016. Re-engineering the zinc fingers of PRDM9 reverses hybrid sterility in mice. *Nature* 530:171–176.

- Dréau A, Venu V, Avdievich E, Gaspar L, Jones FC. 2019. Genome-wide recombination map construction from single individuals using linked-read sequencing. *Nat. Commun.* 10:4309.
- Dreissig S, Mascher M, Heckmann S. 2019. Variation in recombination rate is shaped by domestication and environmental conditions in barley. *Mol. Biol. Evol.* 36:2029–2039.
- Dumont BL, Payseur BA. 2011. Genetic analysis of genome-scale recombination rate evolution in house mice. *PLoS Genet.* 7:e1002116.
- Duranton M, Pool JE. 2022. Interactions between natural selection and recombination shape the genomic landscape of introgression. *Mol. Biol. Evol.* [Internet] 39. Available from: <http://dx.doi.org/10.1093/molbev/msac122>
- Duret L, Galtier N. 2009. Biased gene conversion and the evolution of mammalian genomic landscapes. *Annu. Rev. Genomics Hum. Genet.* 10:285–311.
- Epstein R, Sajai N, Zelkowski M, Zhou A, Robbins KR, Pawlowski WP. 2023. Exploring impact of recombination landscapes on breeding outcomes. *Proc. Natl. Acad. Sci. U. S. A.* 120:e2205785119.
- Everitt T, Rönneburg T, Elsner D, Olsson A, Liu Y, Larva T, Korb J, Webster MT. 2024. Unexpectedly low recombination rates and presence of hotspots in termite genomes. *bioRxiv* [Internet]:2024.03.22.586269. Available from: <https://www.biorxiv.org/content/10.1101/2024.03.22.586269>
- Felsenstein J. 1974. The evolutionary advantage of recombination. *Genetics* 78:737–756.
- Feng C, Wang J, Liston A, Kang M. 2023. Recombination variation shapes phylogeny and introgression in wild diploid strawberries. *Mol. Biol. Evol.* [Internet] 40. Available from: <http://dx.doi.org/10.1093/molbev/msad049>
- Fernandes JB, Séguéla-Arnaud M, Larchevêque C, Lloyd AH, Mercier R. 2018. Unleashing meiotic crossovers in hybrid plants. *Proc. Natl. Acad. Sci. U. S. A.* 115:2431–2436.
- Fisher R. 1930. *The Genetical Theory of Natural Selection*. The Clarendon Press
- Fuentes RR, de Ridder D, van Dijk ADJ, Peters SA. 2022. Domestication shapes recombination patterns in tomato. *Mol. Biol. Evol.* [Internet] 39. Available from: <http://dx.doi.org/10.1093/molbev/msab287>
- Gerton JL, Hawley RS. 2005. Homologous chromosome interactions in meiosis: diversity amidst conservation. *Nat. Rev. Genet.* 6:477–487.
- Girard C, Zwicker D, Mercier R. 2023. The regulation of meiotic crossover distribution: a coarse solution to a century-old mystery? *Biochem. Soc. Trans.* 51:1179–1190.
- Gonen S, Battagin M, Johnston SE, Gorjanc G. 2017. The potential of shifting recombination hotspots to increase genetic gain in livestock breeding. *Genet. Sel. Evol.* [Internet]. Available from: <https://link.springer.com/article/10.1186/s12711-017-0330-5>
- Gossmann TI, Santure AW, Sheldon BC, Slate J, Zeng K. 2014. Highly variable recombinational landscape modulates efficacy of natural selection in birds. *Genome Biol. Evol.* 6:2061–2075.

- Haenel Q, Laurentino TG, Roesti M, Berner D. 2018. Meta-analysis of chromosome-scale crossover rate variation in eukaryotes and its significance to evolutionary genomics. *Mol. Ecol.* 27:2477–2497.
- Halldorsson BV, Palsson G, Stefansson OA, Jonsson H, Hardarson MT, Eggertsson HP, Gunnarsson B, Oddsson A, Halldorsson GH, Zink F, et al. 2019. Characterizing mutagenic effects of recombination through a sequence-level genetic map. *Science* 363:eaau1043.
- Hassold T, Hunt P. 2001. To err (meiotically) is human: the genesis of human aneuploidy. *Nature Reviews Genetics* [Internet] 2:280–291. Available from: <http://dx.doi.org/10.1038/35066065>
- Hellsten U, Wright KM, Jenkins J, Shu S, Yuan Y, Wessler SR, Schmutz J, Willis JH, Rokhsar DS. 2013. Fine-scale variation in meiotic recombination in *Mimulus* inferred from population shotgun sequencing. *Proc. Natl. Acad. Sci. U. S. A.* 110:19478–19482.
- Henderson IR, Bomblies K. 2021. Evolution and plasticity of genome-wide meiotic recombination rates. *Annu. Rev. Genet.* 55:23–43.
- Henderson SA, Edwards RG. 1968. Chiasma frequency and maternal age in mammals. *Nature* 218:22–28.
- Hill WG, Robertson A. 1966. The effect of linkage on limits to artificial selection. *Genetical Research* [Internet] 8:269–294. Available from: <http://dx.doi.org/10.1017/s0016672300010156>
- Hinch R, Donnelly P, Hinch AG. 2023. Meiotic DNA breaks drive multifaceted mutagenesis in the human germ line. *Science* 382:eadh2531.
- Hoge C, de Manuel M, Mahgoub M, Okami N, Fuller Z, Banerjee S, Baker Z, McNulty M, Andolfatto P, Macfarlan TS, et al. 2024. Patterns of recombination in snakes reveal a tug-of-war between PRDM9 and promoter-like features. *Science* 383:eadj7026.
- Hunter CM, Huang W, Mackay TFC, Singh ND. 2016. The genetic architecture of natural variation in recombination rate in *Drosophila melanogaster*. *PLoS Genet.* 12:e1005951.
- Hunter N. 2015. Meiotic recombination: The essence of heredity. *Cold Spring Harb. Perspect. Biol.* [Internet] 7. Available from: <http://dx.doi.org/10.1101/cshperspect.a016618>
- Johnsson M, Whalen A, Ros-Freixedes R, Gorjanc G, Chen C-Y, Herring WO, de Koning D-J, Hickey JM. 2021. Genetic variation in recombination rate in the pig. *Genet. Sel. Evol.* 53:54.
- Johnston SE, Béréanos C, Slate J, Pemberton JM. 2016. Conserved Genetic Architecture Underlying Individual Recombination Rate Variation in a Wild Population of Soay Sheep (*Ovis aries*). *Genetics* 203:583–598.
- Johnston SE, Huisman J, Ellis PA. 2017. A High-Density Linkage Map Reveals Sexual Dimorphism in Recombination Landscapes in Red Deer (*Cervus elaphus*). *G3: Genes, Genomes* [Internet]. Available from: <https://academic.oup.com/g3journal/article-abstract/7/8/2859/6031530>

- Johnston SE, Huisman J, Pemberton JM. 2018. A Genomic Region Containing REC8 and RNF212B Is Associated with Individual Recombination Rate Variation in a Wild Population of Red Deer (*Cervus elaphus*). *G3* 8:2265–2276.
- Jones GH, Franklin FCH. 2006. Meiotic crossing-over: obligation and interference. *Cell* 126:246–248.
- Joseph J, Prentout D, Laverre A, Tricou T, Duret L. 2023. High prevalence of Prdm9-independent recombination hotspots in placental mammals. *bioRxiv* [Internet]. Available from: <https://www.biorxiv.org/content/10.1101/2023.11.17.567540.abstract>
- Josephs EB, Wright SI. 2016. On the trail of linked selection. *PLoS Genet.* 12:e1006240.
- Kadri NK, Harland C, Faux P, Cambisano N, Karim L, Coppieters W, Fritz S, Mullaart E, Baurain D, Boichard D, et al. 2016. Coding and noncoding variants in HFM1, MLH3, MSH4, MSH5, RNF212, and RNF212B affect recombination rate in cattle. *Genome Res.* 26:1323–1332.
- Kaur T, Rockman MV. 2014. Crossover heterogeneity in the absence of hotspots in *Caenorhabditis elegans*. *Genetics* 196:137–148.
- Kawakami T, Wallberg A, Olsson A, Wintermantel D, de Miranda JR, Allsopp M, Rundlöf M, Webster MT. 2019. Substantial heritable variation in recombination rate on multiple scales in honeybees and bumblebees. *Genetics* 212:1101–1119.
- Kent TV, Uzunović J, Wright SI. 2017. Coevolution between transposable elements and recombination. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* [Internet] 372. Available from: <http://dx.doi.org/10.1098/rstb.2016.0458>
- Koehler KE, Hawley RS, Sherman S, Hassold T. 1996. Recombination and nondisjunction in humans and flies. *Hum. Mol. Genet.* 5 Spec No:1495–1504.
- Kondrashov AS. 1988. Deleterious mutations and the evolution of sexual reproduction. *Nature* 336:435–440.
- Kong A, Barnard J, Gudbjartsson DF, Thorleifsson G, Jonsdottir G, Sigurdardottir S, Richardsson B, Jonsdottir J, Thorgeirsson T, Frigge ML, et al. 2004. Recombination rate and reproductive success in humans. *Nat. Genet.* 36:1203–1206.
- Kong A, Thorleifsson G, Frigge ML, Masson G, Gudbjartsson DF, Villemoes R, Magnusdottir E, Olafsdottir SB, Thorsteinsdottir U, Stefansson K. 2014. Common and low-frequency variants associated with genome-wide recombination rate. *Nat. Genet.* 46:11–16.
- Kosheleva K, Desai MM. 2018. Recombination alters the dynamics of adaptation on standing variation in laboratory yeast populations. *Mol. Biol. Evol.* 35:180–201.
- Kumar R, Bourbon H-M, de Massy B. 2010. Functional conservation of Mei4 for meiotic DNA double-strand break formation from yeasts to mice. *Genes Dev.* 24:1266–1280.
- Latrille T, Duret L, Lartillot N. 2017. The Red Queen model of recombination hot-spot evolution: a theoretical investigation. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 372:20160463.
- Lawrence EJ, Gao H, Tock AJ, Lambing C, Blackwell AR, Feng X, Henderson IR. 2019. Natural variation in TBP-ASSOCIATED FACTOR 4b controls meiotic crossover and germline transcription in *Arabidopsis*. *Curr. Biol.* 29:2676–2686.e3.

- Lenormand T, Dutheil J. 2005. Recombination difference between sexes: a role for haploid selection. *PLoS Biol.* 3:e63.
- Lenormand T, Engelstädter J, Johnston SE, Wijnker E, Haag CR. 2016. Evolutionary mysteries in meiosis. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* [Internet] 371. Available from: <http://dx.doi.org/10.1098/rstb.2016.0001>
- Li G, Figueiró HV, Eizirik E, Murphy WJ. 2019. Recombination-aware phylogenomics reveals the structured genomic landscape of hybridizing cat species. *Mol. Biol. Evol.* 36:2111–2126.
- Lian Q, Solier V, Walkemeier B, Durand S, Huettel B, Schneeberger K, Mercier R. 2022. The megabase-scale crossover landscape is largely independent of sequence divergence. *Nat. Commun.* 13:3828.
- Lichten M. 1995. Meiotic Recombination Hotspots. *Annu. Rev. Genet.* 29:423–444.
- Liu H, Jia Y, Sun X, Tian D, Hurst LD, Yang S. 2017. Direct determination of the mutation rate in the bumblebee reveals evidence for weak recombination-associated mutation and an approximate rate constancy in insects. *Mol. Biol. Evol.* 34:119–130.
- Lynn A, Koehler KE, Judis L, Chan ER, Cherry JP, Schwartz S, Seftel A, Hunt PA, Hassold TJ. 2002. Covariation of synaptonemal complex length and mammalian meiotic exchange rates. *Science* 296:2222–2225.
- Lyon MF. 1976. Distribution of crossing-over in mouse chromosomes. *Genet. Res.* 28:291–299.
- Ma L, O’Connell JR, VanRaden PM, Shen B, Padhi A, Sun C, Bickhart DM, Cole JB, Null DJ, Liu GE, et al. 2015. Cattle Sex-Specific Recombination and Genetic Control from a Large Pedigree Analysis. *PLoS Genet.* 11:e1005387.
- Malinovskaya L, Shnaider E, Borodin P, Torgasheva A. 2018. Karyotypes and recombination patterns of the Common Swift (*Apus apus* Linnaeus, 1758) and Eurasian Hobby (*Falco subbuteo* Linnaeus, 1758). *Avian Res.* [Internet] 9. Available from: <http://dx.doi.org/10.1186/s40657-018-0096-7>
- Martin HC, Christ R, Hussin JG, O’Connell J, Gordon S, Mbarek H, Hottenga J-J, McAloney K, Willemsen G, Gasparini P, et al. 2015. Multicohort analysis of the maternal age effect on recombination. *Nat. Commun.* [Internet] 6. Available from: <http://dx.doi.org/10.1038/ncomms8846>
- Martin SH, Jiggins CD. 2017. Interpreting the genomic landscape of introgression. *Curr. Opin. Genet. Dev.* 47:69–74.
- McAuley JB, Servin B, Hagen IJ, Niskanen AK, Husby A, Ringsby TH, Jensen H, Johnston SE. 2023. Sex-differences in the genetic architecture of individual recombination rates in wild house sparrows (*Passer domesticus*). *BioRxiv*:525019.
- Morgan AP, Gatti DM, Najarian ML, Keane TM, Galante RJ, Pack AI, Mott R, Churchill GA, de Villena FP-M. 2017. Structural variation shapes the landscape of recombination in mouse. *Genetics* 206:603–619.
- Morgan C, Fozard JA, Hartley M, Henderson IR, Bomblies K, Howard M. 2021. Diffusion-mediated HEI10 coarsening can explain meiotic crossover positioning in *Arabidopsis*. *Nat. Commun.* 12:4674.

- Mukaj A, Piálek J, Fotopulosova V, Morgan AP, Odenthal-Hesse L, Parvanov ED, Forejt J. 2020. Prdm9 intersubspecific interactions in hybrid male sterility of house mouse. *Mol. Biol. Evol.* 37:3423–3438.
- Muller HJ. 1932. Some genetic aspects of sex. *Am. Nat.* 66:118–138.
- Muller HJ. 1964. The relation of recombination to mutational advance. *Mutat. Res.* 106:2–9.
- Muñoz-Fuentes V, Marcet-Ortega M, Alkorta-Aranburu G, Linde Forsberg C, Morrell JM, Manzano-Piedras E, Söderberg A, Daniel K, Villalba A, Toth A, et al. 2015. Strong artificial selection in domestic mammals did not result in an increased recombination rate. *Mol. Biol. Evol.* 32:510–523.
- Myers S, Bottolo L, Freeman C, McVean G, Donnelly P. 2005. A fine-scale map of recombination rates and hotspots across the human genome. *Science* 310:321–324.
- Myers S, Freeman C, Auton A, Donnelly P, McVean G. 2008. A common sequence motif associated with recombination hot spots and genome instability in humans. *Nat. Genet.* 40:1124–1129.
- Olito C, Abbott JK. 2023. The evolution of suppressed recombination between sex chromosomes and the lengths of evolutionary strata. *Evolution* 77:1077–1090.
- Ortiz-Barrientos D, Engelstädter J, Rieseberg LH. 2016. Recombination rate evolution and the origin of species. *Trends Ecol. Evol.* 31:226–236.
- Otto SP, Barton NH. 2001. Selection for recombination in small populations. *Evolution* 55:1921–1931.
- Otto SP, Lenormand T. 2002. Resolving the paradox of sex and recombination. *Nat. Rev. Genet.* 3:252–261.
- Pan J, Sasaki M, Kniewel R, Murakami H, Blitzblau HG, Tischfield SE, Zhu X, Neale MJ, Jasin M, Succi ND, et al. 2011. A hierarchical combination of factors shapes the genome-wide topography of yeast meiotic recombination initiation. *Cell* 144:719–731.
- Peñalba JV, Wolf JBW. 2020. From molecules to populations: appreciating and estimating recombination rate variation. *Nat. Rev. Genet.* 21:476–492.
- Peterson AL, Miller ND, Payseur BA. 2019. Conservation of the genome-wide recombination rate in white-footed mice. *Heredity (Edinb.)* 123:442–457.
- Petit M, Astruc J-M, Sarry J, Drouilhet L, Fabre S, Moreno CR, Servin B. 2017. Variation in recombination rate and its genetic determinism in sheep populations. *Genetics* 207:767–784.
- Raynaud M-L, Sanna P, Joseph J, Clément J, Imai Y, Lareyre J, Laurent A, Galtier N, Baudat F, Duret L, et al. 2024. PRDM9 drives the location and rapid evolution of recombination hotspots in salmonids. *bioRxiv* [Internet]. Available from: <http://biorxiv.org/lookup/doi/10.1101/2024.03.06.583651>
- Reynolds A, Qiao H, Yang Y, Chen JK, Jackson N, Biswas K, Holloway JK, Baudat F, de Massy B, Wang J, et al. 2013. RNF212 is a dosage-sensitive regulator of crossing-over during mammalian meiosis. *Nat. Genet.* 45:269–278.

- Ritz KR, Noor MAF, Singh ND. 2017. Variation in recombination rate: Adaptive or not? *Trends Genet.* 33:364–374.
- Rousselle M, Laverré A, Figuet E, Nabholz B, Galtier N. 2019. Influence of recombination and GC-biased gene conversion on the adaptive and nonadaptive substitution rate in mammals versus birds. *Mol. Biol. Evol.* 36:458–471.
- Ruiz-Herrera A, Vozdova M, Fernández J, Sebestova H, Capilla L, Frohlich J, Vara C, Hernández-Marsal A, Sipek J, Robinson TJ, et al. 2017. Recombination correlates with synaptonemal complex length and chromatin loop size in bovids—insights into mammalian meiotic chromosomal organization. *Chromosoma* 126:615–631.
- Rybnikov SR, Frenkel Z, Hübner S, Weissman DB, Korol AB. 2023. Modeling the evolution of recombination plasticity: A prospective review. *Bioessays* 45:e2200237.
- Samuk K, Manzano-Winkler B, Ritz KR, Noor MAF. 2020. Natural selection shapes variation in genome-wide recombination rate in *Drosophila pseudoobscura*. *Curr. Biol.* 30:1517–1528.e6.
- Sardell JM, Kirkpatrick M. 2020. Sex differences in the recombination landscape. *Am. Nat.* 195:361–379.
- Schild DR, Pasquesi GIM, Perry BW, Adams RH, Nikolakis ZL, Westfall AK, Orton RW, Meik JM, Mackessy SP, Castoe TA. 2020. Snake recombination landscapes are concentrated in functional regions despite PRDM9. *Mol. Biol. Evol.* 37:1272–1294.
- Schreiber M, Gao Y, Koch N, Fuchs J, Heckmann S, Himmelbach A, Börner A, Özkan H, Maurer A, Stein N, et al. 2022. Recombination landscape divergence between populations is marked by larger low-recombining regions in domesticated rye. *Mol. Biol. Evol.* [Internet] 39. Available from: <http://dx.doi.org/10.1093/molbev/msac131>
- Schumer M, Xu C, Powell DL, Durvasula A, Skov L, Holland C, Blazier JC, Sankararaman S, Andolfatto P, Rosenthal GG, et al. 2018. Natural selection interacts with recombination to shape the evolution of hybrid genomes. *Science* 360:656–660.
- Ségurel L, Leffler EM, Przeworski M. 2011. The case of the fickle fingers: how the PRDM9 zinc finger protein specifies meiotic recombination hotspots in humans. *PLoS Biol.* 9:e1001211.
- Singhal S, Leffler EM, Sannareddy K, Turner I, Venn O, Hooper DM, Strand AI, Li Q, Raney B, Balakrishnan CN, et al. 2015. Stable recombination hotspots in birds. *Science* 350:928–932.
- Smagulova F, Brick K, Pu Y, Camerini-Otero RD, Petukhova GV. 2016. The evolutionary turnover of recombination hot spots contributes to speciation in mice. *Genes Dev.* 30:266–280.
- Smukowski Heil CS, Ellison C, Dubin M, Noor MAF. 2015. Recombining without hotspots: A comprehensive evolutionary portrait of recombination in two closely related species of *Drosophila*. *Genome Biol. Evol.* 7:2829–2842.
- Soni V, Pfeifer SP, Jensen JD. 2024. The effects of mutation and recombination rate heterogeneity on the inference of demography and the distribution of fitness effects. *Genome Biol. Evol.* [Internet]. Available from: <http://dx.doi.org/10.1093/gbe/evae004>

- Stapley J, Feulner PGD, Johnston SE, Santure AW, Smadja CM. 2017. Variation in recombination frequency and distribution across eukaryotes: patterns and processes. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 372:20160455.
- Stevison LS, Woerner AE, Kidd JM, Kelley JL, Veeramah KR, McManus KF, Great Ape Genome Project, Bustamante CD, Hammer MF, Wall JD. 2016. The time scale of recombination rate evolution in great apes. *Mol. Biol. Evol.* 33:928–945.
- Sturtevant AH. 1913. The linear arrangement of six sex-linked factors in *Drosophila*, as shown by their mode of association. *J. Exp. Zool.* 14:43–59.
- Theodosiou L, McMillan WO, Puebla O. 2016. Recombination in the eggs and sperm in a simultaneously hermaphroditic vertebrate. *Proc. Biol. Sci.* [Internet] 283. Available from: <http://dx.doi.org/10.1098/rspb.2016.1821>
- Tock AJ, Holland DM, Jiang W, Osman K, Sanchez-Moran E, Higgins JD, Edwards KJ, Uauy C, Franklin FCH, Henderson IR. 2021. Crossover-active regions of the wheat genome are distinguished by DMC1, the chromosome axis, H3K27me3, and signatures of adaptation. *Genome Res.* 31:1614–1628.
- Tsai IJ, Burt A, Koufopanou V. 2010. Conservation of recombination hotspots in yeast. *Proc. Natl. Acad. Sci. U. S. A.* 107:7847–7852.
- Vara C, Capilla L, Ferretti L, Ledda A, Sánchez-Guillén RA, Gabriel SI, Albert-Lizandra G, Florit-Sabater B, Bello-Rodríguez J, Ventura J, et al. 2019. PRDM9 diversity at fine geographical scale reveals contrasting evolutionary patterns and functional constraints in natural populations of house mice. *Mol. Biol. Evol.* 36:1686–1700.
- Veller C, Kleckner N, Nowak MA. 2019. A rigorous measure of genome-wide genetic shuffling that takes into account crossover positions and Mendel’s second law. *Proc. Natl. Acad. Sci. U. S. A.* 116:1659–1668.
- Wang RJ, Dumont BL, Jing P, Payseur BA. 2019. A first genetic portrait of synaptonemal complex variation. *PLoS Genet.* 15:e1008337.
- Wang S, Zickler D, Kleckner N, Zhang L. 2015. Meiotic crossover patterns: Obligatory crossover, interference and homeostasis in a single process. *Cell Cycle* 14:305–314.
- Wang Z, Shen B, Jiang J, Li J, Ma L. 2016. Effect of sex, age and genetics on crossover interference in cattle. *Sci. Rep.* [Internet] 6. Available from: <http://dx.doi.org/10.1038/srep37698>
- Webster MT, Hurst LD. 2012. Direct and indirect consequences of meiotic recombination: implications for genome evolution. *Trends Genet.* 28:101–109.
- Weng Z, Wolc A, Su H, Fernando RL, Dekkers JCM, Arango J, Settar P, Fulton JE, O’Sullivan NP, Garrick DJ. 2019. Identification of recombination hotspots and quantitative trait loci for recombination rate in layer chickens. *J. Anim. Sci. Biotechnol.* 10:20.
- Wickham H. 2016. About the ggplot2 Package. *J. Appl. Comput. Math.* [Internet] 5. Available from: <http://dx.doi.org/10.4172/2168-9679.1000321>

- Wooldridge LK, Dumont BL. 2023. Rapid evolution of the fine-scale recombination landscape in wild house mouse (*Mus musculus*) populations. *Mol. Biol. Evol.* [Internet] 40. Available from: <http://dx.doi.org/10.1093/molbev/msac267>
- Xie H, Li W, Guo Y, Su X, Chen K, Wen L, Tang F. 2023. Long-read-based single sperm genome sequencing for chromosome-wide haplotype phasing of both SNPs and SVs. *Nucleic Acids Res.* 51:8020–8034.
- Zelkowski M, Olson MA, Wang M, Pawlowski W. 2019. Diversity and determinants of meiotic recombination landscapes. *Trends Genet.* 35:359–370.
- Zickler D, Kleckner N. 1999. Meiotic chromosomes: integrating structure and function. *Annu. Rev. Genet.* 33:603–754.
- Ziolkowski PA, Underwood CJ, Lambing C, Martinez-Garcia M, Lawrence EJ, Ziolkowska L, Griffin C, Choi K, Franklin FCH, Martienssen RA, et al. 2017. Natural variation and dosage of the HEI10 meiotic E3 ligase control Arabidopsis crossover recombination. *Genes Dev.* 31:306–317.