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REVIEW

Recombination rate variation in closely related species

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Despite their importance to successful meiosis and various evolutionary processes, meiotic recombination rates sometimes vary within species or between closely related species. For example, humans and chimpanzees share virtually no recombination hotspot locations in the surveyed portion of the genomes. However, conservation of recombination rates between closely related species has also been documented, raising an apparent contradiction. Here, we evaluate how and why conflicting patterns of recombination rate conservation and divergence may be observed, with particular emphasis on features that affect recombination, and the scale and method with which recombination is surveyed. Additionally, we review recent studies identifying features influencing fine-scale and broad-scale recombination patterns and informing how quickly recombination rates evolve, how changes in recombination impact selection and evolution in natural populations, and more broadly, which forces influence genome evolution.
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Introduction

One of the main goals of evolutionary genetics is to understand how variation is created and maintained within and between species. Homologous meiotic recombination affects variation in the genome: differences in the rate of recombination determine the amount of genetic variation within populations and the rate at which new combinations of alleles are introduced into populations (Brooks and Marks, 1986; Coop and Przeworski, 2007). Indeed, in flies and humans, variability in recombination rate explains more than 50% of the variation in nucleotide heterozygosity across the genome (Nachman, 2002), and recombination may shape features of the genomic landscape such as codon bias, base composition and the distribution of repetitive elements and polymorphisms (Charlesworth *et al*., 1994; Comeron *et al*., 1999; Duret and Arndt, 2008; see section 'Molecular evolutionary consequences of recombination rate variation'). Recombination rates are also expected to mediate the effectiveness of natural and sexual selection on genome evolution because breakdown of linkage between nucleotide sites allows the sites to behave independently, permitting selection to act efficiently, eliminate mutations, reduce genetic hitchhiking and facilitate adaptive evolution by reducing interference between sites (Hill and Robertson, 1966).

Examining variation in recombination rates among closely related species may provide clues as to the evolutionary forces affecting recombination, and therefore offer insight into the forces shaping the genome over time. Studies across virtually all eukaryotic kingdoms have determined that the distribution of recombination events is non-uniform. Indeed, there is variation in recombination rate across the genome; extreme rates are known as 'hotspots' and 'coldspots' in yeast and mammals, and reflect more of a quantitative change in other organisms. Hotspots are conventionally defined as a significant increase in recombination rate from the background recombination rate, usually ranging on orders of magnitude, that takes place in a small percentage of the genome. In humans this translates to about 80% of the recombination taking place in less than 15% of the sequence (Myers *et al*., 2006). Although other organisms have not been assayed at the same resolution as yeast, mouse and humans, many studies observe regions with a several-fold increase above the background recombination rate. For example, in *Drosophila miranda*, several regions show recombination rates between 25 and 30 $cM\,Mb^{-1}$, several times the chromosomal average of $\sim 5\,cM\,Mb^{-1}$ (unpublished data; see also Cirulli *et al*., 2007; Stevison and Noor, 2010).

Recombination rates are variable between individuals, populations and species; however, the causative factors underlying this variation are largely unknown. Through comparison of fine-scale genetic maps of closely related species, it may be possible to identify features influencing fine-scale and broad-scale recombination patterns, as well as features that predict shifts in recombination landscapes between species. Such linkage map comparisons have the potential to answer questions such as how fast recombination rates change and how changes in recombination impact selection and evolution in natural populations. Theoretical work on the evolution of recombination and recombination modifiers has greatly contributed to these efforts, but this review will primarily focus on empirical work (for a review of theoretical considerations, see Charlesworth, 1990; Barton, 1995, 2010; Feldman *et al*., 1996; Lenormand and Otto, 2000; Martin *et al*., 2006).

The past few years have seen remarkable progress in the development of fine-scale maps and in revealing

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novel modifiers of recombination rate. However, some comparisons of recombination maps show seemingly contradictory results, particularly in relation to conservation and divergence of recombination rates. Therefore, in this review, we discuss conservation and divergence in homologous meiotic recombination rate between closely related species. We begin by briefly considering sequence and epigenetic features known to affect recombination and the molecular evolutionary consequences of recombination rate variation. We proceed to discuss several issues surrounding the generation and analysis of recombination maps to understand why we would see conservation or divergence between some species and not others. Similarly, we evaluate how constraints and regulating features could produce conflicting patterns of conservation and divergence when surveyed at different scales. Overall, we hope to highlight important questions pertaining to how recombination shapes genome evolution, and how studying closely related species can help answer them. Because the recombination literature is skewed toward humans, mice and yeast, this review places an emphasis on these taxa, but attempts to incorporate other organisms whenever possible.

Determinants and correlates

It is difficult to rigorously evaluate studies of recombination without considering various factors that may influence recombination rate. Control of recombination rate appears to be multifaceted, with molecular, environmental and demographic factors all having a role (for example, see Wilfert *et al*., 2007; see also section 'Why would we see conservation of recombination rates between some species and not others?' below). Attempts to elucidate the determinants of recombination have identified numerous factors of influence, many of which appear to be conserved across eukaryotes (Lichten and Goldman, 1995; Roeder, 1997; Hassold *et al*., 2000; Keeney, 2001; Petes, 2001; Page and Hawley, 2003). New hypotheses have emerged, for example, that variation in epigenetic features could explain the variation in the rates of recombination between closely related species (Myers *et al*., 2005, 2008; Ptak *et al*., 2005; Winckler *et al*., 2005). The continued study of recombination between closely related species has the potential to illuminate more decisive determinants and how they change over time. Here, we focus on molecular patterns and features that appear to be associated with or impact recombination.

At the chromosome level, the prevailing pattern across organisms is that a minimum number of crossovers must be achieved for proper segregation. In humans, the number of crossovers is strongly correlated with the number of chromosomes, where one crossover per chromosome ensures proper segregation at meiosis (Fledel-Alon *et al*., 2009). In other organisms, crossover rates range from one crossover per chromosome arm to as many as five per chromosome (Beye *et al*., 2006). Animals with numerous shorter chromosomes, such as the 'microchromosomes' found in many birds, tend to have higher recombination rates, again, likely as a result of ensuring proper disjunction (Groenen *et al*., 2009). Along chromosomes in many organisms, rates of recombination tend to be higher toward the distal portions of the chromosome and low around the centromere, perhaps because repression of meiotic recombination by the centromeric heterochromatin is also critical in proper segregation (Ellermeier *et al*., 2010).

At the genomic level, high recombination rates are positively and nearly ubiquitously associated with GC content, gene density, simple repeats, transposable elements and a number of different sequence motifs (Thuriaux, 1977; Gerton *et al*., 2000; Marais *et al*., 2001; Marais, 2003; Jensen-Seaman *et al*., 2004; Meunier and Duret, 2004; Myers *et al*., 2005; Groenen *et al*., 2009; Wong *et al*., 2010). In particular, it appears that a 13-mer degenerate motif may be responsible for recruiting recombination events in at least 40% of human hotspots (Myers *et al*., 2008). This motif binds to the zinc-finger protein PRDM9 in humans, and allelic variation controls hotspot activity in both humans and mice (Baudat *et al*., 2010; Berg *et al*., 2010). Relatedly, the *Drosophila* zinc-finger protein, Trade Embargo (*trem*), initiates double-strand breaks (DSBs) and is necessary for localization of the protein Mei-P22 to discrete foci on meiotic chromosomes, some or all of which are thought to mark sites for future DSBs (Lake *et al*., 2011). Thus, zinc-finger proteins and sequence motifs may be major determinants of high-recombination-rate locations and recombination rate intensities at these locations.

Observations of divergent hotspot locations and usage among human individuals, and between humans and chimpanzees, has sparked a rigorous analysis of how epigenetics is involved in meiotic hotspot determination (Myers *et al*., 2005; Ptak *et al*., 2005; Winckler *et al*., 2005; Neumann and Jeffreys, 2006). Subsequent studies show correlations between recombination hotspots and open chromatin, numerous histone modification patterns and DNA methylation in yeast, mice and humans (Berchowitz *et al*., 2009; Buard *et al*., 2009; Sigurdsson *et al*., 2009). Of particular note is the presence of a SET-methyltransferase domain in the *Prdm9* gene, which is responsible for the common chromatin feature trimethylation of lysine-4 of histone H3, or H3K4me3 (Baudat *et al*., 2010). H3K4me3 in yeast seems to be a prominent and pre-existing mark of active recombination sites (Borde *et al*., 2009), potentially creating a link between sequence and epigenetic features affecting recombination.

Continued analysis between individuals and species will surely lead to a greater understanding of existing features and the discovery of novel ones. For example, the analysis of *Prdm9* across species has already produced fascinating results. Chimpanzee PRDM9 has dramatically different predicted binding sequence than human PRDM9, and seems to be the most divergent of all orthologous zinc-finger proteins (Myers *et al*., 2010). Furthermore, *Prdm9* in other mammals shows rapid evolution, with variation in zinc-finger number and patterns of substitution suggestive of complex repeat shuffling (Oliver *et al*., 2009; Myers *et al*., 2010). Although there is no direct evidence that these changes have generated recombination rate differences, it is surely an intriguing area to be researched. If proven, this may provide an explanation as to how recombination hotspots are created and how they change over time (see section 'Why would we see recombination rate conservation at some scales and not others?' below). Closely related species present the unique opportunity to study the evolution of features regulating and influencing recombination rate, and should be central in future studies of this basic biological process.

The molecular evolutionary consequences of recombination rate variation

Recombination rate variation within and between closely related species allows evolutionary biologists to make conclusions as to whether selective or neutral forces are governing genomic landscapes. First postulated in a groundbreaking study, Begun and Aquadro (1992) found that recombination rate was positively correlated with nucleotide diversity in *Drosophila melanogaster*, but did not observe an association between recombination and *D. melanogaster–D. simulans* divergence. This pattern is interpreted to mean that natural selection, in particular selective sweeps and/or background selection, eliminates nucleotide variability in regions of low recombination (Smith and Haigh, 1974; Charlesworth *et al*., 1993), and is supported by studies in several organisms (see Table 1). However, a similar association between recombination rate and nucleotide diversity may be predicted if recombination is mutagenic, but fewer studies have detected a correlation between recombination and nucleotide divergence between species and so have not met the prediction of the mutagenic hypothesis (but, see empirical studies by Brown and Jiricny, 1987; Brown *et al*., 1989; Strathern *et al*., 1995; Papavasiliou and Schatz, 2000).

Additionally, the interpretations are complicated by conflicting results in several organisms surveyed (Payseur and Nachman, 2000; Baudry *et al*., 2001; Nachman, 2001; Huang *et al*., 2004; Yi *et al*., 2004; Yi and Li, 2005; Noor, 2008b; Tsai *et al*., 2010). Confounding factors that may lead to conflicting results are listed in Table 1, but there are several we would like to highlight here. First, conflicting results may simply reflect taxon-specific mutagenicity, but this hypothesis requires more empirical work. Second, correlations of diversity or divergence to recombination rate may change according to the scale with which recombination is assayed (Bussell *et al*., 2006; Spencer *et al*., 2006; Kulathinal *et al*., 2008; Noor, 2008a; Stevison and Noor, 2010), making it a priority to assess these measures using fine-scale recombination over varying magnitudes. Third, and most relevant to the primary topic of this review, many studies up to this point have only assayed recombination in one species of interest, assuming recombination rates are conserved. It remains unresolved as to whether the selection or mutagenic hypothesis primarily accounts for the observed pattern, but perhaps with increasing amounts of recombination and sequence data, we will be able to make firmer conclusions.

Conservation and divergence of recombination

Following the progressive discoveries in diverse species that recombination events are non-random across the genome, one of the most exciting and surprising findings has been the realization that recombination rates sometimes change, even within species or between closely related species. The fact that recombination rates are variable and heritable implies that recombination itself can evolve in response to natural selection (Chinnici, 1971; Charlesworth and Charlesworth, 1985; Otto and Michalakis, 1998). Furthermore, evidence from human recombination hotspots seems to show that this change can occur quickly on an evolutionary timescale, with hotspots emerging and disappearing in as little as 120 000 years, and certainly within the six million years human divergence from chimpanzee (Ptak *et al*., 2005; Winckler *et al*., 2005; Jeffreys and Neumann, 2009). However, conservation of recombination between closely related species has also been detected at varying scales (see Table 2), raising many questions: (1) How does the methodology by which recombination is measured affect estimates of recombination rate? (2) Why would we see conservation of recombination rates between some species and not others? (3) Why would we see conservation at some scales and not others? (4) Finally, and perhaps most fundamentally, should we expect to see conservation between closely related species? Here we comprehensively review empirical studies that compare recombination rates between closely related species, and speculate on the answers to these questions.

How does the methodology by which recombination is measured affect estimates of recombination rate?

The construction of a recombination map can dramatically affect the estimate of recombination rate depending on the methodology used (and associated biases). Three methods are commonly used for estimating recombination rate: linkage disequilibrium (LD) mapping, sperm typing and direct mapping using polymorphic markers (see Table 2 for examples of recombination maps generated with these approaches, and Table 3 for potential strengths and weaknesses). The first two methods are used primarily with human data (but see Guillon and de Massy, 2002; Ptak *et al*., 2004; Kim *et al*., 2007; Arguello *et al*., 2010), with the labor- and resource-intensive direct mapping applied more in other model organisms. Fundamentally, the major differences between these measures are (1) whether the recombination rates measured are current versus historical, and (2) whether the recombination rates measured reflect a population average or focus on a particular individual or set of individuals.

There has been some doubt as to whether LD consistently and accurately predicts hotspots (Jeffreys *et al*., 2005b; Reed and Tishkoff, 2006). For instance, Coop *et al*. (2008) estimated that 40% of crossovers occurred outside of LD-predicted hotspots, but Khil and Camerini-Otero (2010) suspect this may be an overestimate owing to the way hotspots were measured using particular populations. Khil and Camerini-Otero also found that 26–32% of crossovers happened outside of European population LD-predicted hotspots; however, this discrepancy disappeared when hotspot locations of other populations were taken into account. There are also specific examples of LD-predicted hotspots being absent when checked with sperm typing (Kauppi *et al*., 2005), although such inconsistencies appear to be the exception rather than the rule (Jeffreys *et al*., 2000, 2001; Yauk *et al*., 2003).

In pedigrees and controlled crosses, increasing sample size and marker coverage changes the way we measure and perceive recombination, similar to the 'Beavis effect' for mapping (Beavis *et al*., 1994; Beavis, 1996). For example, the original honeybee linkage map used 94–142 individuals and 365 markers for a total map length of 3450 cM (Hunt and Page, 1995); the newer map

Table 1 Relationships between recombination rate and measures of diversity and divergence

Species-1	*Species-2*	*Time since divergence (My)*	*Relationship between diversity and recombination*	*Relationship between divergence and recombination*	*Confounding factors*	*Claims support for natural selection or mutagenic hypothesis?*	*Source*
Human	Chimpanzee	5–6	Positive, $P=0.06$, $r=0.678$	Positive, $P=0.006$, $r=0.866$	Only surveyed PAR1; recombination rate only surveyed in humans	Claims support for mutagenic hypothesis for recombination	Bussell *et al.* (2006)
Human	Chimpanzee	5–6	Positive, $P=0.01$, $r=0.127$ (Stephens *et al.*, 2001); $P=0.037$, $r=0.257$ (SeattleSNPs); $P=0.032$, $r=0.249$ (NIEHS SNPs)	Positive, $P=0.037$, $r=0.259$ (Seattle); $P=10^{-6}$, $r=0.214$ (chimp shotgun); $P=4\times10^{-4}$, $r=0.289$ (chimp BAC); $P=0.204$, $r=0.264$ (Baboon BAC)	Recombination rate only surveyed in humans	Claims support for mutagenic hypothesis for recombination	Hellmann *et al.* (2003)
Human	Chimpanzee	5–6	Positive, $P<0.001$, $r=0.735$	Uncorrelated, $P=0.57$, $r=0.141$	Used recombination estimates from numerous studies, which used various methods to estimate recombination and may be imprecise; used SNPs in close proximity to exons, which may be influenced by other forces; recombination rate only surveyed in humans	Claims support for natural selection hypothesis for recombination	Nachman (2001)
Human	Chimpanzee	5–6	Positive, $P=0.041$, $r=0.775$	Uncorrelated, $P=0.726$, $r=0.164$	Recombination rate only surveyed in humans; based on small sample size (seven data points)	Claims support for natural selection hypothesis for recombination	Nachman *et al.* (1998)
Mus musculus	*Mus spicilegus*	3	Uncorrelated, $P=0.83$ (within subpopulations, $P=0.045$), $r=0.06$ (within subpopulations, positive, $r=0.46$)	Uncorrelated, $P=0.65$, $r=0.11$	Recombination estimates only from *M. m. domesticus*; used sequence data near functional genes; small sample size	Claims support for natural selection hypothesis for recombination	Takahashi *et al.* (2004)
Mus mus domesticus	*Mus caroli*	2.5	Positive, $P=0.0972$, $r=0.902$	Negative, $P=0.5663$, $r=0.434$	Imprecise estimates of recombination; small sample size; only surveyed at four loci	Inconclusive based on available data	Nachman (1997)
Saccharomyces cerevisiae	*Saccharomyces paradoxus*	5–20	NA, uncorrelated	NA, uncorrelated	Low frequency of sex and out-crossing	Inconclusive; suspect mutagenic effect of recombination swamped by the mutations occurring in intervening asexual generations	Tsai *et al.* (2010)
Drosophila melanogaster	*Drosophila simulans*	2.5–3.4	Positive, $P=0.0007$	Uncorrelated, $P=0.983$	Recombination only surveyed in *D. melanogaster*; low-quality estimates of recombination; only surveyed at 20 gene regions	Claims support for natural selection hypothesis for recombination	Begun and Aquadro (1992)
Drosophila simulans	*Drosophila melanogaster*	2.5–3.4	Positive, $P=8.5\times10^{-8}$	NA, $P=0.03$	Recombination only surveyed in *D. melanogaster*; low-quality map for *D. melanogaster;* only surveyed X chromosome	Claims support for natural selection hypothesis for recombination	Begun *et al.* (2007)

Table 1 (Continued)

Species-1	*Species-2*	*Time since divergence (My)*	*Relationship between diversity and recombination*	*Relationship between divergence and recombination*	*Confounding factors*	*Claims support for natural selection or mutagenic hypothesis?*	*Source*
Drosophila pseudoobscura	*Drosophila persimilis*	0.5–1	Positive, ⩽500-kb window: Intronic, $P=0.0156$, $r=0.488$; Inter-genic, $P=0.0020$, $r=0.588$ 2-Mb window: Intronic, $P=0.8322$, $r=0.045$; Inter-genic, $P=0.3260$, $r=0.205$	Positive, ⩽500-kb window: Inter-genic, $P=0.0006$, $r=0.635$ 2-Mb window: Inter-genic, $P=0.0013$, $r=0.607$	Shared ancestral polymorphism; hybridization; recombination only surveyed in *D. pseudoobscura*	Claims support for mutagenic hypothesis for recombination	Kulathinal *et al.* (2008)
Drosophila pseudoobscura	*Drosophila miranda*	2–3	Intronic, $P=0.004$, $r=0.333$; Inter-genic, $P=0.258$, $r=0.133$	Intronic, $P=0.128$, $r=0.180$; Inter-genic, $P=0.559$, $r=0.069$	Recombination only surveyed in *D. pseudoobscura*	Claims support for natural selection hypothesis for recombination	Stevison and Noor (2010)
Beta vulgaris maritima	*Beta macrocarpa*	NA	Positive, $P=0.007$, $r=0.226$ (based on number of distinct alleles); $P=0.084$, $r=0.117$ (based on heterozygosity); *calculated using θ	Negative, not significant, $r=-0.02$	Recombination estimates for *Beta vulgaris maritima* come from *B. vulgaris vulgaris*, which may not be an accurate assumption; recombination estimates are coarse	Claims support for natural selection hypothesis for recombination	Kraft *et al.* (1998)
Lycopersicon peruvianum	*Solanum ochranthum* or *Solanum lycopersicoides*	5.8–18.6	Positive, $P=0.089$, $r=0.471$; *calculated using θ	Uncorrelated, $P=0.640$, $r=0.159$	Demographic processes and life history traits may confound diversity and recombination estimates; genomic recombination rate used is based on a map from *Lycopersicon esculentum* × *Lycopersicon pennellii*, which may not be an accurate assumption	Demographic processes have a strong influence on shaping patterns in the genome in combination with mutation rate and/or selective constraint	Roselius *et al.* (2005) (see also, Stephan and Langley, 1998)
Lycopersicon chilense			Uncorrelated, $P=0.498$, $r=0.198$; *calculated using θ	Uncorrelated, $P=0.852$, $r=0.064$			
Lycopersicon hirsutum			Positive, $P=0.052$, $r=0.528$; *calculated using θ	Uncorrelated, $P=0.915$, $r=0.036$			
Zea mays mays	*Zea mays parviglumis*	7500–9000 years	Positive, $P=0.007$, $r=0.65$ (using $4Nc_{hud87}$); uncorrelated when recombination measured with physical measure R or $4Nc_{hud01}$; *calculated using θ	Uncorrelated, NA	Numerous studies produce different results; different recombination estimates produce different results; low power; complicated by demography	Inconclusive; not accounted for by demography model, selection has a role	Tenaillon *et al.* (2001, 2002, 2004)

A compilation of studies where measures of recombination rate are compared to measures of diversity (π, average number of pairwise differences, unless otherwise noted by an asterisk (*)) and to divergence (d, nucleotide divergence between species) using a linear regression. A positive correlation between recombination and diversity, but not divergence, is thought to be indicative of natural selection shaping the patterns of nucleotide diversity in the genome. A correlation of recombination to both diversity and divergence may indicate that the neutral theory of evolution has a role, suggesting recombination is associated with mutations. Correlations to diversity use diversity measured in Species-1, correlations to divergence use nucleotide differences between Species-1 and Species-2. Note that only studies in which both diversity and divergence are measured are included. Time since divergence is measured in millions of years (My) unless otherwise noted. NA denotes data were unavailable or not shown.

Table 2 A comparison of recombination rates between species pairs

Species-1	*Species-2*	*Time since divergence (My); approximate sequence divergence (%)*	*Region of genome surveyed*	*Approximate percentage of physical genome surveyed in between species comparison (%)*	*Methodology used to measure recombination rate*	*Number of markers*	*Marker distance*	*Size of intervals compared between species*	*Sample size*	*Conservation or divergence?*	*Source*
Human	Chimpanzee	5–6; 1	Several known hotspots; 3500-kb regions located on 4q26, 7q21, 7q31	<1	Linkage disequilibrium (LD)	Hotspot-specific	Hotspot-specific	Hotspot-specific	Hotspot-specific	15/18 hotspots are divergent; divergent in 10-kb windows; divergent in 14 additional 160-kb windows	Winckler *et al.* (2005)
Human	Chimpanzee	5–6; 1	Two regions totaling 14 Mb on Chr. 21	<1	Linkage disequilibrium (LD)	30 611 (11 642)	440 bp (1.2 kb)	50 kb	8 (71)	36/39 hotspots are divergent; significantly, but weakly correlated at 50 kb ($r = 0.276$); total recombination rates significantly, but weakly correlated ($r = 0.216$)	Ptak *et al.* (2005)
C57BL/6J × CAST/EiJ	Eight heterogeneous stock mice (A/J, AKR/J, BALB/cJ, DBA/2J, C57BL/6J, LP/J, I, RIIIS/J)	0.2375–0.475; <1	Chr. 1	7	SNP genotyping of controlled crosses	1059 (873)	225 kb (225 kb)	550 kb	6028 (2293)	Significant, but weak regional correlation ($r = 0.38$)	Paigen *et al.* (2008) (recombination data for HS mice from Shifman *et al.*, 2006)
Mus musculus domesticus × *Mus musculus musculus*	*Mus musculus domesticus* × *Mus musculus castaneus*	0.2375–0.475; <1	Genome-wide	84.8 (84.0)	SNP genotyping of controlled crosses	186 (197)	1.2–65.6 Mb (mean 15.8 Mb)	1.2–65.6 Mb (mean 15.8 Mb)	580 (554)	31/131 intervals divergent	Dumont *et al.* (2011)
Gallus gallus	*Taeniopygia guttata*	100; NA	Genome-wide	92	Pedigree SNP genotyping	1404 (9268)	800 kb (100 kb)	1 Mb	1079 (235)	Significantly correlated when comparing 275 intervals ($r = 0.5$)	Backstrom *et al.* (2010) (recombination data for chicken from Groenen *et al.*, 2009)
Gallus gallus	*Acrocephalus arundinaceus*	80–100; NA	Regions of nine chromosomes (ranging from 5 to 66% coverage)	26% of chicken genome	Pedigree SNP genotyping	46 (NA)	NA	NA	812 (NA)	Great reed warbler has a substantially shorter map than chicken	Dawson *et al.* (2007) (recombination data for chicken from http://www.ncbi.nlm.nih.gov/genome/guide/chicken/)
Drosophila pseudoobscura	*Drosophila persimilis*	0.5–1; NA	Chr. 2	23	SNP genotyping of controlled crosses	130 (50)	240 kb (average. 466 kb)	500 kb	1440 (1294)	Divergent in 5/38 intervals	Stevison and Noor (2010) (recombination data for *D. pseudoobscura* from Kulathinal *et al.*, 2008)
Apis mellifera	*Apis florea*	8–10; NA	Chr. 3 and Chr. 12	12.9	SNP genotyping	Chr. 3, 8; Chr. 12, 10 (2000 genome-wide)	Chr. 3, 1.2 Mb; Chr. 12, 780 kb (100 kb)	Chr. 3, 1.2 Mb; Chr. 12, 780 kb	120 (92–187)	Conservation in 19/19 intervals	Meznar *et al.* (2010) (recombination data for *A. mellifera* from Solignac *et al.*, 2007)

Table 2 (Continued)

Species-1	*Species-2*	*Time since divergence (My); approximate sequence divergence (%)*	*Region of genome surveyed*	*Approximate percentage of physical genome surveyed in between species comparison (%)*	*Methodology used to measure recombination rate*	*Number of markers*	*Marker distance*	*Size of intervals compared between species*	*Sample size*	*Conservation or divergence?*	*Source*
Saccharomyces cerevisiae	*Saccharomyces paradoxus*	5–20; 13	Chr. 3	3	Linkage disequilibrium (LD)	464 European, 232 Far East (52 000 genome-wide)	600 bp European, 1200 bp Far East (78 bp)	Hotspot-specific	20 strains (51 meioses; 204 spores)	6/10 hotspots are divergent	Tsai *et al.* (2010) (recombination data for *S. cerevisiae* from Buhler *et al.*, 2007; Mancera *et al.*, 2008)

A compilation of studies where recombination rates are compared between species pairs. The items in parentheses indicate measures used to create an independent recombination map in Species-1, the source of which is indicated in parentheses under the column heading Source. Hence, the column entitled 'Size of intervals compared between species' indicates intervals constrained by one species recombination map; it reflects the size of an interval in which there is recombination data in both species recombination maps. NA indicates that the data were unavailable or not shown.

used 541 markers and 283 individuals for a total length of 4061.2 cM (Solignac *et al.*, 2004). With more accurate technologies, the honeybee genome increased in length from 178 Mb in 1974 (Jordan and Brosemer, 1974) to 262 Mb in 2006 (The Honeybee Genome Consortium), thereby decreasing the average recombination rate from 19.38 to 16 cM Mb^{-1} today. Similarly, in chicken, the current map used 9268 markers for a total length of 3228 cM (Groenen *et al.*, 2009), substantially smaller than the 4200 cM previously estimated using 2261 markers (Schmid *et al.*, 2005). However, obtaining enough markers to detect fine-scale recombination is resource-intensive, thereby producing maps that range in scale from kilobases (hereafter referred to as 'fine scale'), to hundreds of kilobases (hereafter referred to as 'intermediate scale'), to tens of megabases (hereafter referred to as 'broad scale'), to whole genomes. This is relevant, as recombination rate conservation and divergence between species is scale-dependent (see below).

Other indirect quantitative approaches also exist, such as immunostaining as used by Dumont and Payseur (2011) in Murid rodents and Double Strand Break (DSB) mapping, most commonly used in yeast (Gerton *et al.*, 2000; Buhler *et al.*, 2007; Mancera *et al.*, 2008). Of course, choosing an approach is constrained by the organism and the resources available, and researchers must be aware of limitations when making generalizations and conclusions.

Why would we see conservation of recombination rates between some species and not others?

There are several pertinent issues to consider when comparing recombination rates between closely related species. First, differential action of selection, or selection in changing environments, could give rise to differences between species (Chinnici, 1971; Charlesworth and Charlesworth, 1985; True *et al.*, 1996). For example, artificial selection may have increased recombination rates in the domesticated species of chicken, honeybee and many plants (Rees and Dale, 1974; Burt and Bell, 1987; Otto and Barton, 2001; Ross-Ibarra, 2004; Wilfert *et al.*, 2007; Groenen *et al.*, 2009) in comparison with their wild progenitors.

Second, imprecise measures of physical distance can lead to inferred differences in recombination rate. Large insertions, deletions or inversions can affect the recombination fraction between two points in the genome because single crossover events may often lead to aneuploidy. Even if such changes do not change the actual recombination 'rate' (cM/Mb), if a large insertion is present in one taxon but not another, it may appear that recombination rates have diverged between species, when in fact recombination is being measured over intervals of unequal size. Moreover, chromosomal rearrangements, such as inversions, reduce the observed amount of recombination in heterokaryotypes (Hartl and Jones, 2004, pp 319–324). This repression of recombination associated with inversions extends several megabases (Mb) outside the inversion, thereby producing broader scale changes in recombination rate (Kulathinal *et al.*, 2009). Furthermore, inversion heterozygotes show increased recombination further outside the inverted region, known as the 'inter-chromosomal effect' (Schultz and Redfield, 1951). Large insertions and deletions have

Table 3 Comparison of three commonly used approaches to measure recombination rate

Approach	*Linkage disequilibrium*	*Sperm typing*	*Pedigrees and crosses*
Description	LD-based genetic maps use statistics to estimate historical recombination indirectly from patterns of allelic associations in samples from natural populations	Individual or pooled sperm is analyzed for linkage disequilibrium blocks using allele-specific PCR directed to heterozygous SNP sites	Genotype markers in pedigrees or controlled crosses
Current versus historical recombination	Historical	Current	Current
Application	Used in humans, chimpanzees; can be applied to other organisms depending on population history	Used in humans, mice	Used in mammals, birds, yeast, plants, insects
Potential strengths	A relatively quick and inexpensive way to assay whole genome	Direct assay of current recombination; looking at variation within and between individuals; looking at specific hotspots; detecting gene conversion events	Direct assay of current recombination; can be applied across whole genome; can obtain sex-specific rates for both sexes;
Potential weaknesses	Breaks in LD are not always hotspots; cannot necessarily detect recent recombination events; sex-averaged; made with heterogeneous populations; known to be influenced by genetic drift, demographic factors, natural selection, variable mutation rates and gene conversion	Male-specific (although this can also be a strength as it gives sex-specific information that LD cannot); labor-intensive; cannot assay whole genome or population	Sensitive to sample size; number of markers and unknown variation in genome size, structure and individual variation in recombination rate; difficult to achieve fine scale; labor- and resource-intensive
Further reading	Ardlie *et al*. (2002); Slatkin (2008); Clark *et al*. (2010)	Jeffreys *et al*. (2001); Jeffreys and Neumann (2002); Carrington and Cullen (2004)	Kong *et al*. (2010); see studies in Table 2

This table summarizes three methods used for estimating recombination rates: (1) Linkage disequilibrium; (2) sperm typing and (3) pedigrees and crosses. It gives a general overview of what each method is, which organisms it is most commonly used in, potential strengths and weaknesses, and suggestions for further reading. For specific examples, refer to the text and Table 2.

the potential to produce comparable outcomes to inversions. In comparing the same intervals between two closely related species in the absence of a genome sequence, one runs the risk of concluding increased divergence between species when in actuality, an inversion, insertion or deletion segregating in only one species is obscuring their comparable recombination rates.

Third, recombination is variable within individuals and populations (Brooks and Marks, 1986; True *et al*., 1996; Carrington and Cullen, 2004; Neumann and Jeffreys, 2006; Graffelman *et al*., 2007; Coop *et al*., 2008; Paigen *et al*., 2008; Cheng *et al*., 2009; Dumont *et al*., 2009; Kong *et al*., 2010 etc). This variation may stem from actual heritable variation in recombination rates among individuals; variation within an individual among regions of its genome (as discussed above) or from environmental variation. Because of potentially dramatic within-population variation, one must use caution in making generalizations about species as a whole or presumptions that a single linkage map describes the species. Without first surveying recombination within the populations, subspecies or species of interest, it will be impossible to conclude true conservation or divergence between groups. These potential challenges in estimating recombination rate can translate into real or perceived differences between closely related species.

Why would we see recombination rate conservation at some scales and not others?

Maps produced at varying scales provide an unexpected and seemingly contradictory view of conservation and divergence between species (see Table 2). In mice and humans, conservation of recombination rate was identified at a broad scale, but divergence of recombination hotspots was identified at a fine scale, suggesting that there may be differential regulation among the scales (Myers *et al*., 2005; Coop and Przeworski, 2007), or perhaps, simply that we do not understand the relationship between fine-scale and broad-scale recombination patterns.

Divergence of fine-scale recombination rates observed in yeast and humans is likely caused by the rapid turnover of hotspots owing to biased gene conversion and meiotic drive. In the process of DSB repair, one pathway leads to crossover and exchange of content between homologous chromosomes, whereas the other pathway leads to gene conversion (Boulton *et al*., 1997; Marais, 2003). Biased gene conversion favors one allele over the other, in which case the initiating hotspot is replaced by a copy of its homolog, effectively suppressing subsequent recombination. Simulations and empirical evidence have shown the self-destructive nature of hotspots through over-transmission of recombination-suppressing alleles (meiotic drive), creating what is known as 'the hotspot paradox' (Boulton *et al*., 1997; Jeffreys and Neumann, 2002).

Recent evidence might provide the elusive answer as to how new hotspots are created and regulated to counteract losses due to the hotspot paradox. The zinc-finger protein PRDM9, confirmed to have a significant role in recombination in human and mouse, contains a zinc-finger-encoding region with a minisatellite structure (Baudat *et al*., 2010). This particular structure may confer a strong potential to generate variability by recombination or replication slippage within the array. Indeed, studies documented variability in the contact residues predicting DNA binding between human populations (Baudat *et al*., 2010; Berg *et al*., 2010; Parvanov *et al*., 2010), and the number of zinc fingers and their contact residues vary significantly across rodents, primates and other Metazoans (Oliver *et al*., 2009). The changing of contact residues could create a new family of hotspots by the binding of the protein to new sequence motifs, thereby counteracting the loss of hotspots due to biased gene conversion. Regardless of the mechanism, it is clear by the constant flux of hotspots that the precise locations seem to be unconstrained, allowing divergence at the hotspot level.

It is believed that broad-scale recombination is controlled in a different, but potentially non-mutually, exclusive manner. Above all, the broad-scale rate is defined by the necessity of one crossover per chromosome to ensure proper disjunction (Hassold *et al*., 2004; Fledel-Alon *et al*., 2009). Other chromosomal properties, including size and number, are correlated with this trend. This selective constraint is likely a large influence on the conservation of broad-scale rates between closely related species. At the intermediate scale, conclusions are more vague. Regional recombination is decidedly influenced by crossover interference, where a crossover in one location prevents another crossover from occurring close by (Foss *et al*., 1993; Hillers, 2004; Stahl *et al*., 2004; Copenhaver, 2005). Regional properties of chromosomes have an impact as well, clearly shown by the lack of crossovers in the centromeric region and typically a high number of crossovers near the telomeres. Overall, perhaps these broader scale processes are more likely to be conserved, and hence preserve recombination at this scale as a byproduct.

The connection between the different scales is also unclear. In humans, there are an estimated 60 000–80 000 hotspots across the genome (Khil and Camerini-Otero, 2010), occurring in clusters every 60–90 kb, with individual hotspots separated by 1–7 kb within each cluster (Jeffreys *et al*., 2001; clustering also seen in mouse, Kelmenson *et al*., 2005) and no region greater than 200 kb in which recombination is absent (Myers *et al*., 2006). It appears that non-hotspot recombination is relatively rare, with sperm genotyping studies showing very low levels of background, non-hotspot recombination, most likely located in the weaker and polymorphic hotspots (Jeffreys *et al*., 1998, 2001, 2005b; Jeffreys and Neumann, 2002, 2005a). It is proposed that larger scale variation may be a product of the varying density or intensity of these hotspots in different regions of the genome (Nachman, 2002; Myers *et al*., 2006).

There are several hypotheses as to which selective pressures influence the overall process and distribution. Hey (2004) proposed that individual hotspots may arise as a byproduct of LD between genes that are being selected. If selection favors a recombinant haplotype, then it will favor chromosomes with high recombination between the two genes, thereby producing a variation in the location and the intensity of local recombination rates that fluctuate depending on the genes under selection and the LD patterns. Kauppi *et al*. (2004) put forward three hypotheses: the first stating that the distribution of recombination is governed by a balance between the need for recombination to ensure proper segregation during meiosis and the need to minimize the breakdown of favorable haplotypes, and the second and the third that state, more mechanistically, that restrictions on crossover position potentially facilitate the optimal mechanical/biochemical function of chiasmata in chromosome segregation, or that restrictions on position confine DSBs to regions that are most conducive to efficient assembly of machinery and repair.

The answer is plausibly a combination of all of these propositions. The continued analysis of recombination rates assayed at different scales, combined with theory that could test selective constraints at these scales, will help to determine why we would see conservation in recombination rate at some scales and not others.

Should we expect to see conservation between closely related species?

Just as we should expect to see conservation in sequence between closely related species, we should expect to see conservation in recombination (Dumont and Payseur, 2008). Presumably, with sequence similarity comes, on average, greater sharing of features that influence recombination. Divergence should be seen as departure from the null hypothesis, but only if there is a significant increase in divergence relative to variability of recombination within species, something rarely studied.

Organisms with resolution of recombination rate at the fine scale (for example human, mouse, and yeast) show that hotspots do indeed diverge over time. Other organisms with maps at an intermediate-to-broad scale generally portray a trend of conservation (see Table 2). From the evidence we have, we can determine that hotspots are not conserved owing to their transient nature. Over long periods of time, enough changes occur on the fine scale to produce a broad-scale change. Additionally, on a broad scale, shared constraints will hold the rate more constant, so that rates are more conserved between closely related species. These processes are compounded by changes in the genome such as inversions, translocations, insertions and deletions that lead to altered recombination rates over time.

Future studies should strive to confirm both these trends, and the mechanisms behind them, to better understand the impact recombination has on the genome, and which features of the genome regulate recombination. A combination of theoretical and empirical work will be necessary. Theoretically, models and simulations can inform the role of selective and neutral processes, and the different population parameters that could lead to the conservation or divergence of recombination rates. Empirically, in chimpanzees, comparisons of human–chimpanzee recombination rates should be extended beyond isolated regions of the genome. Recombination should also be surveyed in a broader

set of species, with particular attempt to obtain a resolution of less than 10 kb in order to observe the presence or absence of hotspots, albeit this is a major challenge in non-model systems. The ability to make cross-species generalizations about recombination rates will have an impact on our understanding of genome evolution, thereby implicating diverse topics such as human health, selection and neutrality in the genome, and speciation and mapping studies.

Conclusions

Several patterns emerge upon reviewing data from these recombination maps. First, labels such as conservation and divergence are somewhat misleading. No pair of species studied to date exhibits complete divergence or conservation of all studied hotspots or regions of high recombination, and furthermore, many studies report only a few intervals across the genome that can be categorized in these terms. Therefore, it is necessary to attempt to incorporate a standard, or at least explicitly defined, set of parameters when discussing divergence. Of course, the vast range of scales at which recombination has been, and continues to be, surveyed makes this difficult. Because recombination is considered a quantitative genetic trait showing variation and heritability that can be acted upon by natural selection, it shares features with other phenotypes and can be discussed in similar terms. A standard approach is to discuss sequence divergence as a percentage, and here we recommend recombination rate divergence to be treated in a similar manner. It is appropriate to express intervals conserved or diverged out of the total number surveyed, also citing the percentage of the total of the physical and recombination maps that was surveyed.

With more genome sequences becoming available, the decreasing cost of genotyping, and sophisticated software and technology at our fingertips, the detection of recombination can be completed with greater feasibility. These projects should be undertaken bearing several parameters in mind. First, recombination variation should be assayed within and across populations within species before making conclusions about differences between species. This is necessary to make conclusions regarding conservation or divergence between species, but will also provide a perspective on the speed at which recombination rate is changing. Second, genome sequences should be available for the populations or species involved, and particularly for the strains being surveyed. These data will ensure that no chromosomal rearrangements or insertions/deletions exist, and will facilitate analysis of features such as motifs, and measures of diversity and divergence. Surveying diversity and divergence will also provide a better understanding of the forces at work in the genome. Third, examining recombination at multiple scales will aid in the interpretation of different constraints influencing the distribution of recombination events, especially when compared between populations and species. Finally, in interpreting results, population history and the methodology used to infer recombination should be taken into account to avoid biases and complications.

Fine-scale recombination maps can help to address essential questions such as how variation is created and maintained within and between species. Recombination shapes the features of the genome and creates new allelic combinations that allow increased adaptability in all sexual organisms. However, many researchers have assumed that recombination rate is invariable among individuals and between species, which we now know is inherently false. Indeed, knowledge of fine-scale variation in crossover rate is essential in modeling genome evolution, population genetics studies, genome-wide association studies and inferring evolutionary processes. Thus, results indicating how recombination rate is distributed in the genome will have implications in human health, molecular evolution and the way we study genetics. The role of recombination in genome evolution is a fundamental issue in understanding basic biological processes, and although much progress has been made, many questions remain unanswered.

Conflict of interest

The authors declare no conflict of interest.

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