An evolutionary view of human recombination

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Abstract | Recombination has essential functions in mammalian meiosis, which impose several constraints on the recombination process. However, recent studies have shown that, in spite of these roles, recombination rates vary tremendously among humans, and show marked differences between humans and closely related species. These findings provide important insights into the determinants of recombination rates and raise new questions about the selective pressures that affect recombination over different genomic scales, with implications for human genetics and evolutionary biology.

Disjunction
The segregation of homologous chromosomes during meiosis.

Aneuploidy
Having more or less than the typical chromosome number (46 for humans).

Ectopic exchange
Homologous recombination between non-allelic copies.

Haplotype
The combination of alleles on a chromosome.

Synapsis
A process through which homologous chromosomes are brought into close alignment with one another.

Crossing over
A type of homologous-recombination event during which there is a reciprocal exchange of flanking regions. Also referred to as a crossover.

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In humans, recombination is subject to the dual constraints of ensuring accurate disjunction while maintaining genome integrity. Too little recombination or aberrant placements of recombination events along a chromosome can result in aneuploidy, a highly deleterious outcome[1,2], whereas ectopic exchange can lead to chromosomal rearrangements, many of which have been associated with disease[3]. Such considerations suggest that the locations and frequency of genetic exchange should be tightly regulated. Nonetheless, recent studies have shown large variation in recombination rates within humans, as well as marked differences between humans and other species[4]. These observations have yielded new insights into the determinants of human recombination. They also raise interesting questions about the genetic basis of recombination-rate variation and the selective pressures that influence recombination over different genomic scales.

In examining these questions, it might be important to consider selection on recombination independently of its role in meiosis. Recombination determines the rate at which new combinations of alleles are introduced into populations and change in frequency over time. As a result, selection for or against new haplotypes can indirectly select for alleles that modify recombination rates[5]. This argument suggests that the local recombination landscape is influenced by adaptation, as well as broad-scale constraints that stem from the role of recombination in meiosis. Understanding recombination therefore requires consideration of both molecular and evolutionary perspectives.

Our aim is to integrate these two viewpoints. We start by discussing the factors that constrain the recombination process in mammals and recent insights into the extent of heritable variation in human recombination rates. We then discuss models for selection on recombination rates and the experimental studies that have begun to reveal the relative importance of proposed selective mechanisms. Finally, we discuss recent findings about the evolution of recombination between closely related species. Our focus is human recombination, although we draw from studies of several other sexually reproducing species. Moreover, we concentrate on meiotic recombination, acknowledging that the involvement of meiotic recombination proteins in mitotic DNA repair[6] might impose another set of constraints. We do not address questions about the origin of sex or of recombination, nor do we describe the human recombination process in detail (for reviews of these topics, see REFS 5,4, respectively). Instead, our aim is to present an evolutionary perspective on recent discoveries about human recombination.

Recombination rates and their determinants

Recombination is subject to physical constraints that limit variability among individuals, and to selective pressures that stem from its role in meiosis. In mammals, as in many other organisms, recombination has two roles: Early in meiosis, it aids in homology recognition (leading to synapsis); at a later stage, crossing over binds the non-sister chromatids together, providing the tension that is needed for the spindle to pull the correct chromatids to the poles[7]. In the absence of appropriate resistance, proper disjunction might not occur. The result, aneuploidy, is highly deleterious in humans: autosomal monosomy is embryonic lethal, and embryos with trisomies either do not survive to full term or have severe developmental disabilities[2]. A mechanism that leads to proper segregation of chromosomes lacking a crossover exists in *Drosophila*[8], and the XY bivalent in marsupials segregates without a

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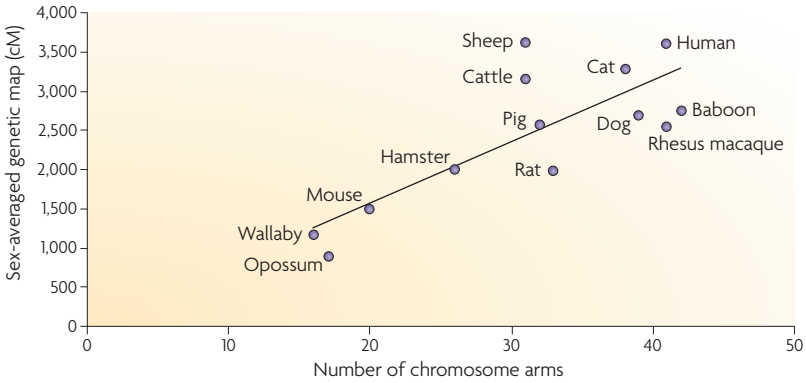

Figure 1 | **Genetic maps in mammals.** The *y*-axis shows an estimate of the total sex-averaged genetic-map length. The *x*-axis shows the total number of chromosomal arms in each species, excluding the small arms of acrocentric chromosomes. Also shown is the line of best fit. The baboon and rhesus macaque maps do not include sex chromosomes, but the others do. The sources for the genetic map estimates are: human (*Homo sapiens*), REF. 21; baboon (*Papio hamadryas*), REF. 130; rhesus macaque (*Macaca mulatta*), REF. 131; rat (*Rattus norvegicus*), REFS 90,132; Syrian hamster (*Mesocricetus auratus*), REF. 133; laboratory mouse (*Mus musculus*), REF. 134; cat (*Felis catus*), REF. 135; cattle (*Bos taurus*), REF. 136; sheep (*Ovis aries*), REF. 137; dog (*Canis familiaris*), REFS 90,138; pig (*Sus scrofa domesticus*), REF. 139; wallaby (*Macropus eugenii*), REFS 90,140; and laboratory oppossum (*Monodelphis domestica*), REF. 90. The number of chromosomal arms was taken from REF. 13 and supplemented with information from REFS 141,142.

crossover[9], but in Eutherian mammals, there is no known back-up system[10]. So, strong selective pressures are expected to keep human recombination rates above a minimum value.

Constraints on crossing over. Meiotic recombination is initiated by double-stranded breaks, the repair of which leads to the formation of a Holliday junction[11]. This junction is resolved as either a gene conversion event without the exchange of flanking markers, or as gene conversion accompanied by the exchange of flanking markers (crossing over or a crossover). Throughout the review, we focus on human crossing over, mainly because much more is known about it than about gene conversion.

Crossovers are subject to two main constraints, the first of which is often described as a need for one crossover for each bivalent. In humans, however, it seems that at least two crossovers occur on each metacentric chromosome (one on each arm), whereas one occurs on acrocentric chromosomes (for example, see REF. 12). Moreover, across mammals, the number of chromosomal arms (excluding short arms of acrocentric chromosomes) is a good predictor of genetic-map lengths[13] (FIG. 1), better so than the number of chromosomes.

However, one crossover on each arm is not sufficient to ensure correct segregation, as crossovers can be poorly positioned. For example, in humans, non-disjunction has been associated with crossovers that occur too close to the centromere or telomere (see REF. 2 and the references therein). Every human chromosome seems to have its own risk factors for aneuploidy in terms of the placement and number of crossovers[2], suggesting that selective constraints on large-scale recombination rates are chromosome-specific.

The second constraint on crossovers is that they do not occur independently along a chromosome. Instead, in humans, as in many other species, the distance between crossovers tends to be larger than would be predicted from the total recombination rate[14,15]. This positive interference is thought to lead to a more equal spread of crossovers over chromosomes, which reduces the risk of non-disjunction[16,17]. For example, in yeast, mutations that abolish interference lead to a high rate of non-disjunction[18]. Interference introduces dependence between levels of recombination in adjacent regions, with changes to the crossing-over rate in one segment affecting rates nearby.

Distribution of recombination rates along the genome. Sex-averaged recombination rates in humans (BOX 1) vary by an order of magnitude over the scale of megabases (FIG. 2), tending to be higher towards telomeres and lower near the centromere. Rates are strongly positively correlated with GC content, as in rodents and yeast[19,20], and with other genomic features, notably gene density[21,22]. Interestingly, both nucleotide diversity levels within humans and divergence between humans and other species increase with large-scale crossover rates[22,23]. These observations raise the possibility that recombination might be mutagenic, as reported for mitotic recombination in yeast[24]. However, a recent analysis suggests that the broad-scale associations are not causal, but instead arise from covariates such as GC content[25].

Even more striking heterogeneity in recombination rates is seen over the scale of 1–10 kb (FIG. 2). Indeed, recent sperm-typing studies of a dozen regions of the human genome have shown that most crossover resolutions are concentrated in short segments of 1–2 kb (REFS 26,27). These recombination hotspots vary greatly in intensity, from $4x10^{-4}$ cM to 0.14 cM (REF. 28). As expected from studies in fungi showing that gene conversion and crossing over are alternative outcomes of the same initiation events[29], hotspots experience increased gene conversion as well as crossing over, although the odds of the two resolutions vary substantially among regions[30,31]. Hotspots of 1–2 kb have also been characterized in *Saccharomyces cerevisiae*, *Schizosaccaromyces pombe*[11,29] and mice[11,20,28], and similar heterogeneity in recombination rate is seen in maize and *Arabidopsis thaliana* (see REF. 32 and the references therein). Interestingly, however, hotspots have not been reported in *Drosophila melanogaster* or *Caenorhabditis elegans*, two species in which synapsis precedes recombination[33].

In addition to sperm-typing, the past couple of years have seen the development of statistical approaches that allow the estimation of recombination-rate variation from patterns of linkage disequilibrium (LD), enabling large-scale studies of recombination at a much finer resolution than previously possible (BOX 2). The application to genome-wide genotyping data led to the identification of over 25,000 likely hotspots in humans[34]. The authors estimated that there is one hotspot every 50 kb or so, with 80% of crossover events occurring in 10–20% of the sequence[34] (FIG. 2).

Chromatid
An individual daughter chromosome after replication.

Bivalent
A pair of homologous chromosomes after replication; each chromosome consists of two chromatids.

Holliday junction
An intermediate step in homologous recombination; the point of exchange between four strands of DNA.

Gene conversion
Recombination that involves non-reciprocal exchange of a small segment of a chromosome. We note that this population-genetic definition differs from the more widespread definition, which is based on non-Mendelian segregation.

Metacentric
Chromosomes in which the centromere is not close to either end.

Acrocentric
Chromosomes in which the centromere is close to one end.

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Box 1 | **How we know what we know**

The most common approach to learning about recombination rates is to construct a linkage map, in which crossing-over events are inferred from the transmission patterns of polymorphic markers in a large pedigree (for example, REF. 40) or in extensive crosses. The rates of genetic exchange between markers are converted into a linkage map by use of a function that takes into account a model of crossover interference. Crossing-over rates are then obtained from a comparison of the genetic and physical maps. This approach can be used to make inferences about the strength of interference, and to characterize variation among individuals. However, it relies on estimates of recombination from transmitted chromosomes, and therefore does not allow one to observe half the crossover events that occur in meiosis, nor any gametes that are selected against. Moreover, even in the largest available pedigrees, accurate estimates of the genetic distances are only possible for markers that are 1–3 Mb apart[21]. Finally, genetic-map distances can be biased by low marker density, and the total length can be underestimated if a subset of regions is not covered by markers (notably telomeres).

Some of these difficulties are circumvented by looking directly at the chiasmata that are formed before meiotic divisions, in cytogenetic analyses of diakinesis-stage gametes[4]. This approach has been used extensively in mice but is impractical in humans because of the difficulty of obtaining samples from the appropriate stage. A recently developed alternative approach is an immunostaining assay that allows one to examine the distribution of MLH1 foci in pachytene-stage cells[103]. The MLH1 protein is thought to be a component of the recombination machinery that is required for crossover, so the foci serve as a marker for crossover locations. These two approaches allow one to learn about variation among individuals, and among oocytes or spermatocytes within an individual. However, it remains difficult to reliably visualize all the events and to pinpoint their locations, and large sample sizes might be needed to obtain accurate estimates of mean numbers of chiasma or MLH1 foci.

To learn about fine-scale rates, one approach is to estimate the rate of exchange by sperm typing (for reviews, see REFS 26,27). Briefly, the idea is to type markers in individual or pooled sperm to estimate the proportion of recombinants. Because large numbers of sperm can be assayed, the approach allows accurate estimation of recombination rates at fine scale (<1 kb, assuming that there are informative markers). Unfortunately, it is labour intensive, and has so far been applied to fewer than a dozen regions of the human genome. Moreover, the approach is, of course, only informative about recombination rates in males. As an alternative, a number of recent studies have estimated rates of recombination indirectly from patterns of allelic associations in samples from natural populations (see BOX 2).

Genetic map
A map of markers along the genome, in which the distance between markers reflects the recombination frequencies between them. The longer the total genetic map, the more recombination occurs in the genome. Also referred to as a linkage map.

Positive interference
The process through which a crossover event reduces the probability of a second such event in its neighborhood.

Recombination hotspot
A short segment of DNA that experiences much more recombination than the flanking regions.

The large number of candidate hotspots that have now been identified allows hypotheses about their regulation to be tested. In *S. cerevisiae*, hotspot activity is thought to require the chromatin to be accessible to the recombination machinery; other factors are also needed, including transcription-factor binding (but not transcription) for 'α-hotspots', nucleosome-excluding DNA sequences for 'β-hotspots', and high GC content for 'γ-hotspots'[20,35]. Support for the existence of α-hotspots stems, in part, from the observation that double-stranded breaks occur preferentially in promoter regions. In humans, the number of inferred hotspots is similar to the estimate of gene number, suggesting that α-hotspots might be common. However, Myers *et al.*[34] found that the population recombination rate tends to be higher 10^3–10^4 bp away from the start codon than in coding regions, indicating that crossovers favour more distant intergenic sites that might be less likely to be associated with promoter function. A caveat is that LD-based estimates are somewhat sensitive to levels of diversity (BOX 2), which tend to be lower in genes[36], so this finding awaits independent confirmation.

Strikingly, Myers *et al.* also identified a set of sequence motifs that are highly enriched in hotspots (inferred from LD) relative to coldspots[34]. For two of the top candidate motifs, their role in modulating hotspot activity was demonstrated in sperm-typing experiments (see below); the top motif alone is thought to have a role in over 10% of human hotspots. Therefore, in humans, as in fission yeast[37], hotspot intensities seem to be regulated, at least in part, by *cis*-sequence motifs.

Polymorphism analyses have also found evidence for biased gene conversion in humans[38]. Indeed, a recent study of polymorphism data on chromosome 20 showed that hotspots tend to have higher diversity levels than surrounding regions (but not higher divergence), and show a tendency for AT→GC mutations to segregate at higher frequency than GC→AT mutations. Both observations are consistent with a bias towards GC in the mismatch repair machinery that is used during the process of gene conversion[25].

Homology requirements and their consequences. Although the recombination machinery relies on sequence identity[3] to ensure that recombination takes place between homologous copies, ectopic exchange sometimes occurs between non-allelic regions of high identity. Ectopic crossing over can occur between distant or tandemly arrayed areas of homology, and can result in inversions, duplications and deletions of both small and large regions. These rearrangements have been associated with a range of disorders in humans[3], indicating that there might be strong selection against ectopic exchange. Although certain regions seem to experience such events recurrently, it is currently unknown whether hotspots for homologous recombination also serve as hotspots for non-allelic recombination (REF. 3 and the references therein; REFS 31,39).

Altogether, these studies show how recombination influences genome architecture through the rate of genomic rearrangements and by shaping diversity levels, as well as, possibly, base composition. Understanding the determinants of recombination is therefore crucial for the study of genome evolution.

Intraspecific variation in recombination rates

Despite the numerous constraints on recombination, recent studies suggest extensive heterogeneity in recombination rates among humans. Because such differences in recombination rates are likely to contribute to susceptibility to ectopic exchange and non-disjunction[2], characterizing the nature and extent of rate variation is an important medical challenge. It is also a key step in understanding how selective pressures might affect recombination.

Sex-differences in recombination rates. All human chromosomes have longer genetic maps in females than in males, by 1.6-fold on average (as determined on the basis of pedigrees)[21,40]. The distribution of crossover locations also differs between sexes, tending to be lower at the telomeres and higher near the centromere in females compared with males[40], whereas the strength of interference

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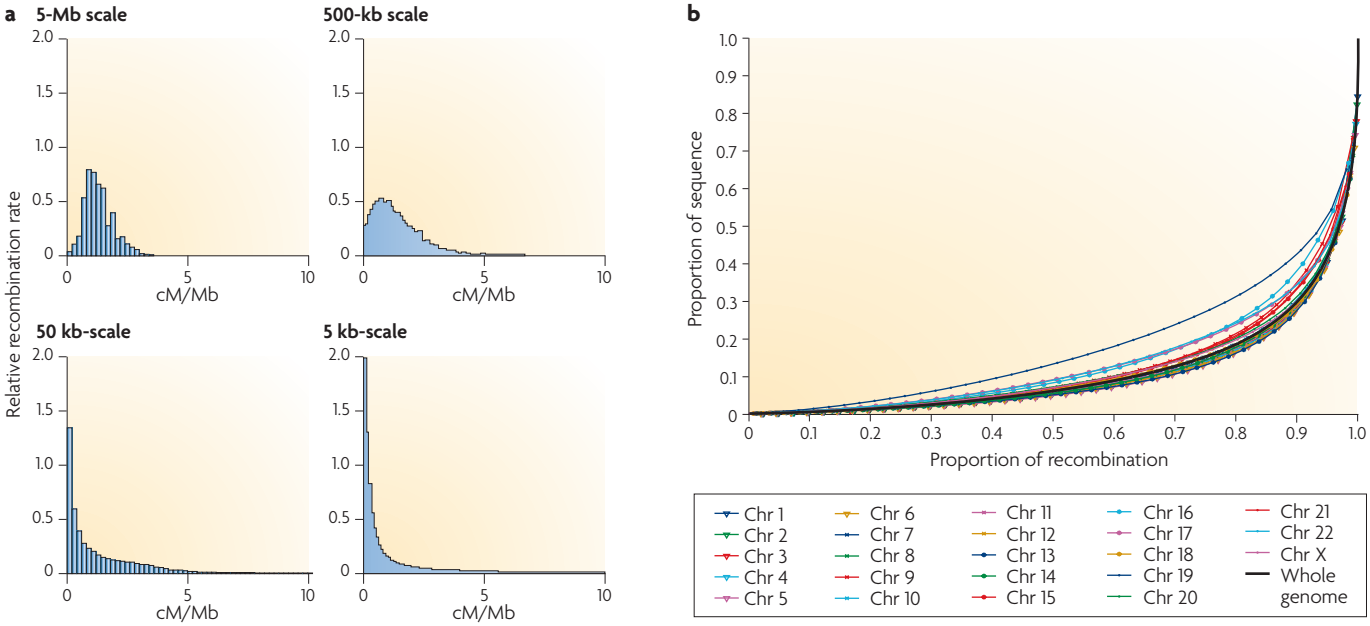

Figure 2 | **Heterogeneity in recombination rates along the human genome.** Rates are inferred from genome-wide linkage disequilibrium data. **a** | Recombination rates over different physical scales. **b** | The proportion of the total recombination rate that falls in a given percentage of the sequence. Modified with permission from REF. 34 © (2005) American Association for the Advancement of Science.

seems to be similar in the two sexes[14,15]. As pointed out previously[4,41], these observations cast doubt on the meaning of a sex-averaged genetic map, and on its utility for linkage mapping.

At a finer scale, comparisons of human LD patterns on the X chromosome (which only recombines in females) and autosomes indicate that hotspots are features of both male and female crossover landscapes[34], although the extent to which the two sexes use the same hotspots is unclear. Pedigree analyses of a few regions with elevated recombination indicate that they are active in both sexes[42,43], but a sex-specific hotspot has been reported in the mouse[44].

Despite the fact that males have fewer crossovers, they have a lower rate of aneuploidy: 1–2% of human spermatocytes are aneuploid, in contrast to ~20% of human ooyctes[2]. In part, this is likely to reflect differences in the stringency of the meiotic pathway. In human and mouse spermatocytes, meiosis is usually halted in the presence of synaptic or pairing errors[45]. By contrast, female meiosis in mice is often allowed to proceed under such conditions (in humans, it is not known whether this occurs)[45,46]. In general, mammalian meiosis proceeds differently in the two sexes[46]. Although spermatocytes are produced throughout a man's life, female meiosis begins in the fetal ovary, is suspended after crossovers have formed, and is only completed once fertilization occurs, up to 40 years later.

Variation in the total genetic-map length. Large-scale crossing-over rates vary among humans, as in model organisms (BOX 3). Indeed, pedigree and MLH1 studies (BOX 1) have identified variation in female crossing-over rates[21,40,47,48], and the heritability of the total recombination rate is estimated from female sibling pairs to be in the range of 30% (REF. 49). Furthermore, there is tentative evidence that the strength of interference differs between females[14,47].

Studies of MLH1 foci also show that there is tremendous variation in the number of crossovers among oocytes of the same female[48]. Strikingly, the number of crossovers in a large fraction (30%) of oocytes falls below the threshold that is required for correct segregation[48], potentially imposing a severe fitness cost. In this respect, it is interesting to note that the mean number of MLH1 foci in females is considerably lower than that expected from pedigree-based genetic maps[48,50] (FIG. 3). Because pedigree estimates are made on the basis of crossovers observed in offspring that survived the full term of pregnancy, whereas MLH1-foci counts reflect the number of crossovers before the potential mother is even born, many of the oocytes observed at the MLH1 stage might not lead to viable offspring. Alternatively, a subset of oocytes with too few crossovers could be discarded earlier if they are preferentially culled during the perinatal attrition of oocytes[48,50]. Therefore, the fitness consequences of variation among oocytes might not be as severe as it would at first seem.

Interestingly, in females, the rate of aneuploidy increases with age. Although only 2% of clinically recognized pregnancies are trisomies in women under the age of 20, this fraction rises to >10% for women in their late thirties[2], a phenomenon that is referred to as the 'maternal age effect'. This effect is not thought to be due to a decrease in crossover rates with age, leading to more achiasmatic chromosomes[51,52], but rather to age-related insults to the meiotic system[2].

Linkage disequilibrium
In a sample, an association of alleles at different loci beyond what would be expected by chance.

Chiasma
Connection between homologous chromosomes resulting from crossing over.

Population recombination rate
Usually defined as $4Nr$, where N is the effective population size and r the recombination rate per meiosis.

Biased gene conversion
A bias in the process of gene conversion in favour of one type of allele over another, also referred to as disparity of gene conversion.

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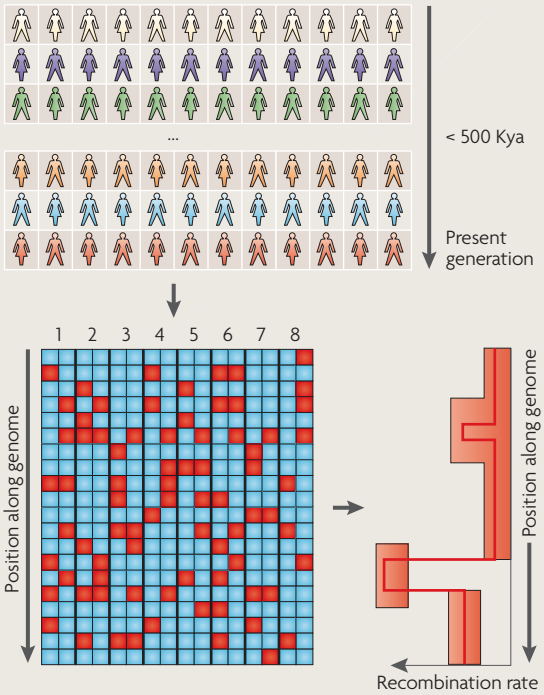
Box 2 | **Estimating recombination rates from patterns of linkage disequilibrium**



In the figure, the first panel depicts successive generations of humans leading to the present. A sample of extant individuals is surveyed for variation, and their genotypes are represented in the second panel. The columns correspond to haplotypes (two columns for each person) and the rows correspond to polymorphic sites at positions along the sequence (with blue denoting the ancestral allele and red denoting the non-ancestral one). These genetic variation data can be used to estimate the sex-averaged historical recombination rate along the genome, which is illustrated in the graph on the right, along with confidence intervals (shown as shaded regions).

Allelic associations that are observed in the sample reflect events that have affected the (male and female) ancestors of the individuals and, in particular, the recombination events that occurred in transmitted gametes[104]. A region of historically high recombination will tend to show low levels of allelic associations (or linkage disequilibrium (LD)) in the sample, and the opposite is true for regions of low recombination. Because the ancestry of randomly sampled humans extends back tens of thousands of generations, LD patterns in the sample reflect a huge number of meioses. They can be used to obtain an estimate of the sex-averaged (or for the X chromosome, female) recombination rate over very fine scales (for example, 1 kb)[105]. What one obtains is a population recombination rate, which is the product of the recombination rate for each meiosis and the effective population size.

LD-based estimation of crossover-rate variation has been shown to produce reliable results by comparison with genetic maps, sperm-typing results and simulation[93,97,106,107]. In principle, the approach can also be used to learn about relative rates of gene conversion (alone) versus crossing over, but simulation studies indicate that the estimates are associated with large errors[105].

Because LD-based methods estimate a population recombination rate, they cannot yield information about variation among individuals. Moreover, changes in the effective population size (for example, due to natural selection) along the genome, if they occur, will be confounded with recombination-rate variation. It should also be noted that the accuracy and reliability of the estimates depend on the sample size, marker density and allele frequencies, and estimates can be locally distorted by some modes of natural selection and/or biased by extreme demographic histories or marker ascertainment schemes[99,105,107,108]. Therefore, care must be taken when comparing LD-based estimates of recombination rates among populations or genomic regions that differ in these respects.

By sharp contrast, the length of male genetic maps that are constructed from pedigrees and from the observed number of MLH1 foci are similar[50,53]. The strength of interference has been reported to differ among males[54], and variation in the number of MLH1 foci was found among spermatocytes of the same male, as well as between males[12]. To date, however, variation in the mean recombination rate among men has not been detected in pedigree studies[21,40]; in any case, it is far less than that observed in females. The number of crossovers in males seems to be more tightly regulated to ensure that one crossover occurs on each chromosome arm (for example, REF. 12).

Variation in broad-scale recombination rates. Cytological differences can function as broad-scale recombination modifiers. For example, the fusion of two acrocentric chromosomes results in a decreased number of crossovers, which occur more distally than before[55]. Human chromosome 2 is one example of an acrocentric fusion, formed in the past ~6 million years. Rearrangements such as inversion polymorphisms (for example, of a couple of megabases in humans[56,57]) can also function as transient modifiers of the crossing-over rate. In a heterozygote for an inversion, a single crossover within the inversion is embryonic lethal. Because only double crossovers are possible, the recombination rate between the two inversion backgrounds is much reduced[43,57]. Interestingly, in *Drosophila*, heterozygotes for an inversion have higher rates of crossing over on other chromosomes[58]. Such an interchromosomal effect has not been reported in mammals[59]. An inversion in humans has been reported to increase genome-wide crossover rates, but more so in homozygotes than in heterozygotes[57].

Variation in fine-scale recombination rates. Sperm-typing studies have shown significant variation among males in the fine-scale rate of crossing over[26,60]. For instance, recombination rates were found to range by twofold in a study of a 25 Mb region[61], and by sixfold over 3.3 Mb of the MHC region[42]. Even within pseudoautosomal region 1, in which there is an obligate crossover in males,

Interchromosomal effect
In heterozygotes, the effect of an inversion on recombination rates on other chromosomes.

Pseudoautosomal region 1
A region of homology between the X and Y chromosomes that experiences obligate crossing over in males.

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Antagonistic pleiotropy
The case in which a single loci has multiple effects, some advantageous and some deleterious; for example, when a gene causes higher fitness early in life, but decreased fitness at older ages.

Negative disequilibrium
Two alleles are in negative linkage disequilibrium if they are found on different chromosomes more often than expected by chance.

Effective population size
Reflects the extent of genetic drift and can be far lower than the census population size.

there is variation in the recombination rate over a fine scale[62]. At the scale of individual hotspots, intensities have also been shown to differ significantly among males, sometimes over orders of magnitude (for example, REF. 63). In addition to the intensity of a hotspot, its location can also be polymorphic[64]. Given the small number of hotspots that have been examined experimentally, these findings suggest that a substantial fraction of hotspots vary in their intensity among individuals.

Variation in at least two male hotspots can be explained by single-site polymorphisms[65,66]. In two cases, the polymorphism disrupts a motif that is highly enriched in hotspots identified by LD analyses[34]. In other hotspots, the difference among males cannot be explained by a single sequence change in *cis*. For instance, Neumann and Jeffreys[63] found one hotspot that has a broad (50-fold) spectrum of intensities across males, whereas an adjacent hotspot is either present or absent. Examination of haplotypes in the region indicated that no local sequence variant underlies the variation in intensities. More generally, it is not known how much of the variation in hotspot activity is heritable, or whether there might also be environmental influences[35]. Moreover, almost nothing is known about variation in fine-scale rates among females, and whether it contributes to the risk of aneuploidy.

Which selective forces influence recombination?

The recombination process is likely to be subject to myriad selective pressures working over different genomic scales. Here we discuss forces that might be important in humans and the predictions that they make for the evolution of recombination in apes.

Selection related to the role of recombination in meiosis. A crossover rate that is too low is likely to be highly deleterious, as it will increase the rate of aneuploidy. Recent studies also found evidence of other selective pressures on recombination related to its effects on fertility. Indeed, Kong *et al.*[49] found that the offspring that a women bears later in life have, on average, slightly more crossing over. They speculated that viable offspring of older women require a higher number of crossovers to overcome the risk of aneuploidy due to the maternal age effect[67]. Consistent with this hypothesis, they showed that, in a large Icelandic pedigree, women with a higher crossing-over rate tend to have slightly more offspring[49]. These observations raise an obvious question: if a higher rate of crossing can reduce the rate of aneuploidy in females, why has the rate remained low?

Much of the selective advantage of increased recombination is to older mothers. Ageing theory suggests that there will be a decline in selection intensity with age, and selection will be ineffective at increasing the recombination rate[68]. Recombination rates might also be subject to antagonistic pleiotropy: if increasing the number of crossovers is somehow deleterious for younger mothers, for example, because it increases the risk of ectopic exchange, then what is favoured in older mothers will be deleterious for younger ones. In this case, selection will not increase recombination rate[69].

Selection to maintain genomic integrity. Certain regions of the genome, such as those flanked by segmental duplications[70], are prone to ectopic recombination, leading to changes in gene dosage and missense mutations, among other potentially harmful outcomes. In regions in which ectopic recombination is highly deleterious, modifiers that lower the recombination rate should be advantageous, and should eventually become fixed in the population. Therefore, the avoidance of ectopic exchange could influence local rates of crossing over. Modelling is needed to assess if this qualitative argument is plausible, given sensible recombination and selective parameters.

Selection on recombination modifiers. Increased crossing over can be favoured when an allele that modifies recombination is closely linked to two or more selected loci that are in negative disequilibrium. Many models for this type of indirect selection on crossover rates have been considered, although most have focused on the advantage of recombination versus no recombination (in order to explain the origin of sex and recombination), rather than on selective pressures that affect recombining regions. These models can be crudely split into three different categories, depending on the selective forces that are proposed to create the disequilibrium between selected alleles: epistatic interactions between loci; a spatially or temporally varying environment; and genetic drift due to the Hill–Robertson effect[71] (BOX 4). The classical theory of recombination modifiers tended to focus on very large populations, thereby concentrating on the role of epistasis (see REF. 72 and the references therein). However, when the effective population size is small, the most prevalent form of selection for increased crossing over is thought to be Hill–Robertson interference[5]. This form is likely to apply to human evolution, as the effective population size of humans and close evolutionary relatives is relatively small, in the tens of thousands (REF. 73).

Indirect selection on a recombination modifier can also reduce the crossing-over rate in a region. For example, if breaking up a combination of alleles is deleterious, a linked modifier allele that lowers the rate of crossing

Box 3 | **Heritable variation in recombination rates in model organisms**

Studies of model organisms have shown substantial variation in recombination rates within species: *Drosophila melanogaster* lines differ in the amount and distribution of crossovers (see REF. 109 and the references therein), as do strains of mice[110,111], fungi[109], and maize[112]. Natural populations are also known to harbour substantial variation[113,114]. In *D. melanogaster*, for example, rates of crossing over among lines were found to vary by >10% over a chromosome, and much more in specific regions[113]. This variation was mapped to the same or adjacent regions, as well as to other chromosomes[109].

A number of artificial selection experiments have also shown that one can increase or decrease the mean number of crossovers, demonstrating that this variability is at least somewhat heritable (reviewed in REF. 109). In individual experiments, the response tends to show a greater change in one direction (for example, a decrease), presumably due to the genetic variation that happened to be present in the original gene pool, and to the dominance of mutations in one direction. Selection for increased recombination led to an increase in all intervals considered, an increase in one and decrease in others, or had most pronounced effects locally[109]. In summary, in model organisms there are global and local modifiers of the recombination rate, and these reside both in *cis* and in *trans*.

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over will be favoured[74]. An extreme example is provided by the evolution of sex chromosomes, in which crossing over between sex-determining loci leads to sterility, and recombination is shut off[75].

Evidence for selection on recombination modifiers. Selection due to Hill–Robertson interference is expected to be strongest when many linked loci are repeatedly the target of selection. Therefore, all else being equal, regions or species that are under frequent selection should evolve towards higher recombination rates. An old observation, sometimes cited as an example, is that the genetic map is longer in domesticated species compared with wild species, after correction for the number of chromosomes[76] (see FIG. 1 for more recent data). Although this increase could be due to strong artificial selection for multilocus traits, a test of this hypothesis requires a comparison with the wild progenitors of the domesticated species (for example, REF. 77), for which rates are currently unknown.

Stronger evidence stems from several studies in *Drosophila*, which have shown that directional selection for a trait that is unrelated to recombination can alter the crossing-over rate. In these experiments, almost all significant changes were towards increased recombination (see REF. 74 and the references therein). Perhaps the best examples are selection for DDT resistance[78] and geotaxis[79] in *D. melanogaster*. In the first set of experiments, selection for DDT resistance led to a consistent, significant change in the recombination rate and, across chromosomes, larger responses were associated with larger increases[78]. In the second case, flies were selected for either positive or negative geotaxis, and both directions of selection led to a significant increase in crossing over[79]. A caveat of these selection experiments is that they involved small populations, such that genetic drift is likely to have a role. However, the consistent increase in crossover rates that are observed across this type of study (given that direct selection on the recombination rate can result in either an increase or a decrease; see BOX 3) indicates that drift alone is an unlikely explanation. So, these findings lend support to the hypothesis that selection on traits that are unrelated to meiosis can influence the evolution of crossing-over rates.

Several experiments have also been devised to test the converse — that differences in the recombination rate among individuals or genomic regions affect the efficacy of selection. To date, the results have been conflicting (see REF. 80 and the references therein). An indirect approach to evaluating this hypothesis is to compare rates of adaptive evolution across recombination environments. In *Drosophila*, in which most studies have been conducted, patterns of variation within and between species are consistent with a reduced efficacy of selection in regions of no recombination (for example, REF. 81) or low crossing over[82,83], but causality is hard to establish (for example, REF. 84).

Non-adaptive theories. Large-scale changes in chromosome morphology can also be subject to non-adaptive forces. In female meiosis, only one of the meiotic products is transmitted; the other three are discarded. As a consequence, chromosomal abnormalities can influence their chances of transmission, and so they experience a form of meiotic drive. If the abnormalities also affect recombination, they can result in large-scale changes to the recombination rate that are of no benefit to the organism[85].

Meiotic drive of recombination modifiers might also occur at a much finer scale. Indeed, the allele that initiates double-strand breaks does not serve as the donor for synthesis, but is instead converted to the allele on the other chromosome. Therefore, if an allele tends to initiate crossovers at higher rates (that is, if there is a conversion disparity), as has been observed in humans[65,66], it will experience a form of meiotic drive against it[86]. Over time, this drive will lead to the loss of the hotspot. Modelling indicates that, given the small contribution of an individual hotspot to the genetic-map length for a chromosome arm, direct selection to ensure disjunction is not enough to conserve specific hotspots (although it can shape their distribution along the genome) (S. Myers and G. Coop, unpublished observations). How hotspots arise and persist in the face of this form of meiotic drive is referred to as the 'hotspot paradox'[86,87].

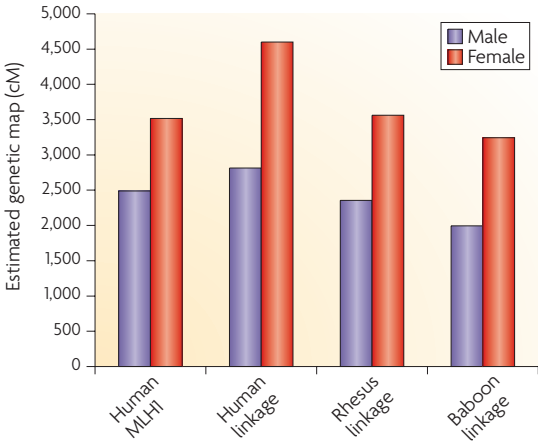

Figure 3 | **The genome-wide genetic map in humans and other primates.** The MLH1-based map estimates were obtained from the median number of MLH1 foci counts in studies summarized by Vallente *et al.*[50]; the MLH1 foci counts were transformed into an estimate of the genetic-map length by multiplying the number of foci by 50 cM (REF. 50). The human linkage-map lengths are from REF. 21, which is the most accurate genetic map that is currently available for humans. Note that linkage maps lead to a higher estimate of the average recombination rates than MLH1 counts. The sex-specific macaque linkage map for the rhesus macaque and the baboon were kindly provided by J. Rogers and M. Mahaney , respectively; sex-averaged genetic maps for these species are published in REFS 131,130. These maps do not include sex chromosomes and do not cover the entire genome; coverage is particularly incomplete for telomeres. Given that (in humans, at least) males tend to have higher rates of crossover in telomeres than females, the extent of the sex difference might be somewhat overestimated.

Meiotic drive
Any non-adaptive process that leads an allele to be over-transmitted in gametes during meiosis.

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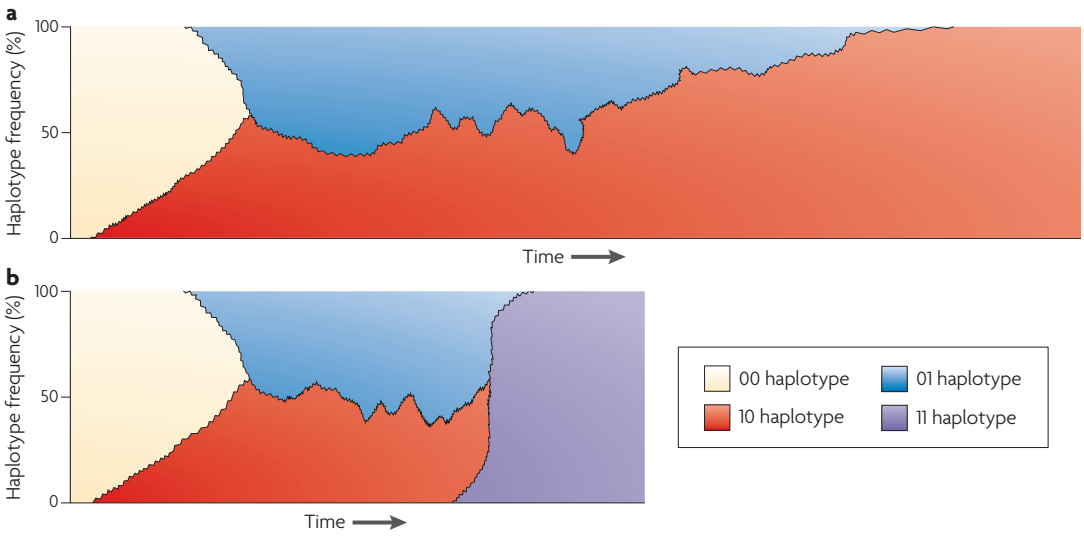
Interspecific variation in recombination rates

Cross-species comparisons allow the predictions of selection models to be tested. In particular, if the recombination process is highly constrained, rates should be conserved across species.

Changes in broad-scale recombination rates. Comparisons of genetic maps between closely related species of *Drosophila* show substantial differences in the number and location of crossover events (see REFS 88,89 and the references therein). In primates, there is less information about the evolution of broad-scale rates. Sex-averaged linkage maps were recently published for the rhesus macaque and the baboon, two Old World monkeys that share a common ancestor with humans ~25 million years ago. Although the number of arms in these species is similar to that of humans, the total genetic map of the two Old World monkeys is 20–30% shorter (FIG. 1). This difference is likely to be an overestimate, given the greater coverage and resolution of human maps (BOX 1), but it indicates that the sex-averaged recombination rates of humans might be elevated relative to other primates.

In spite of their relatively long genetic map, human females experience higher rates of non-disjunction than female mice, in which the rate of aneuploidy is only 1–2% (similar to that of human males, although higher than that of male mice)[2]. Part of this difference could be due to a more stringent control of crossovers in mice, as the variance in the number of crossovers seems

Box 4 | **Hill–Robertson interference and selection on recombination modifiers**



Imagine two loci, with two alleles (denoted 0 and 1) at each locus. Allele 0 is ancestral, and allele 1 has the same advantage over allele 0 at both loci. We assume, as is common in these models, that the fitness effects are multiplicative across loci. Plotted on the *y*-axis is the relative proportion of each haplotype in the population through time, for two runs of the evolutionary process. As will often be the case when two mutations arise in a short time period, the alleles that are denoted as 1 at the two loci do not occur on the same background.

In part **a**, the recombination rate between the two loci is low or zero. As a result, the two alleles are not brought together and one of the favoured alleles is eventually lost by drift. In part **b**, there is a higher rate of recombination between the two loci. Recombination brings the two favoured alleles onto the same background before one is lost, allowing both alleles to reach fixation in the population. In general, selection is less effective when the recombination rate is low, because beneficial alleles that arise on an unfavoured background (that is, are in negative disequilibrium with the beneficial allele at the other loci) are more likely to be lost. This phenomenon is called Hill–Robertson interference[71].

Now imagine a modifier allele at a closely linked third locus that increases the rate of recombination between the pair of selected loci. If the two 1 alleles arise on different backgrounds, the 11 recombinant is most likely to be generated on a background that carries the modifier. As the favoured 11 recombinant haplotype increases in frequency and fixes, the modifier will 'hitch-hike' along with it (see REFS 74,115,116 for more details).

In very large populations, Hill–Robertson interference has a much weaker effect, as there are enough individuals for the 11 haplotype to arise by mutation. Nonetheless, even in large populations, a modifier allele that increases recombination rates between many closely linked loci that are undergoing repeated beneficial substitutions will be indirectly favoured[117].

Although this argument has been phrased in terms of interference between beneficial mutations, modifiers of recombination might also be indirectly favoured in the presence of multiple deleterious alleles (because they can generate haplotypes that carry fewer of them)[118]. The efficacy of selection is also decreased when a beneficial mutation is linked to deleterious alleles[119], but little is known about the extent to which this scenario favours modifiers of the recombination rate. In general, selection on a recombination modifier is a second-order effect, so it is expected to be weak. When invoking these types of models to explain the observed differences in recombination rate, it is therefore important to evaluate whether the size of the effect is plausible.

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Heterogametic sex
The sex that has differently shaped sex chromosomes. In mammals, the heterogametic sex is male (XY) and homogametic sex is female (XX), whereas in other species, such as birds, the heterogametic sex is female (ZW).

to be smaller in female mice than in female humans (T. Hassold, personal communication). Tentative evidence further indicates that positive interference might be stronger in mice than in humans[15]. Whether primate species also differ in these respects is currently unknown.

In most mammals examined to date, including humans, baboons and rhesus macaques, female genetic maps are longer than those for males (FIG. 3). The evolutionary reasons for such sex differences are unclear, but some possibilities are discussed in BOX 5. In evaluating these theories, it is worth noting that a longer female map is not seen in all mammals; in sheep, the male map can be longer, and, in cattle, it is similar in the two sexes[90] — intriguingly, both are domesticated species. Moreover, the two existing marsupial maps are longer in males[90], in contrast to what is predicted by existing theories (BOX 5).

Box 5 | **Sex-specific recombination rates and their evolution**

Rates of crossing over differ between the two sexes in many species (for example, REF. 120), including in mammals. In the most extreme case, crossing over occurs in only one sex (for example, in almost all *Drosophila*), a trait that is believed to have evolved at least 25 times in dioecious animals[121]. Although this observation demonstrates that proper segregation can occur without recombination, in mammals, the absence of crossing over is highly deleterious (see text).

When one sex does not recombine, it is the heterogametic sex, an observation that is referred to as the Haldane–Huxley rule[122,123]. However, when both sexes recombine, heterogametism does not always predict which sex has the longer genetic map[120,121,124]. The mechanistic basis for sex-specific recombination rates in mammals is becoming clearer[46,47,125], but the selective pressures that influence this sexual dimorphism remain largely unknown.

In many species, males have lower recombination rates than females, whether or not they are the heterogametic sex (for example, REF. 126). A number of adaptive theories have been proposed to explain this observation, all of which implicitly assume that there are sex-specific recombination modifiers that exert their effects locally. Trivers[124] speculated that differences in the strength of sexual selection on the two sexes could result in greater selection on modifiers to decrease recombination rates in males. However, modelling indicates that sex-specific selection at the diploid life stage is ineffective at altering sex-specific rates of crossing over[127]. Instead, Lenormand and Detheil[120] suggested that selection at the haploid life stage is responsible. Indeed, in many organisms, selection is stronger during the haploid life stage of male versus female gametes (in mammals, female meiosis is only completed on fertilization, so the genome of the oocyte is not expressed in the haploid phase). This difference could lead to male-specific selection to maintain beneficial haplotypes and therefore to decrease the male recombination rate. Although this theory might account for sex-specific recombination rates in plants[120], the applicability to mammals in unclear, as relatively few genes are thought to be expressed in sperm. The theory also predicts that imprinted regions should have higher crossover rates and show greater differences between the sexes, with paternally imprinted genes having low male rates. Although there is some support for this in humans[128], differences in chromatin configuration in imprinted regions might also be responsible for the observations[129].

In mammals, an alternative explanation is that the female rate is higher to compensate for the apparently less stringent checkpoint for achiasmatic chromosomes compared with males (see text). If so, species in which the female meiotic pathway is more stringent should show smaller sex differences in the genetic map.

Finally, one sex might simply harbour more variation for crossing-over rates that can be selected. If so, (non sex-specific) selection for modifiers of recombination will tend to lead to a greater response in one sex.

In summary, a number of theories had been proposed to explain the initial observations, and these can now be re-evaluated with more extensive data. Whatever theory emerges must account for the existence of systematic differences in recombination landscapes across chromosomes (for example, higher male rates close to telomeres).

The evolution of recombination rates at finer scales. To examine the selective pressures that influence fine-scale recombination rates, recent studies have compared recombination rates that were estimated from LD data in humans and common chimpanzees (*Pan troglodytes*), which share 95–99% of their DNA. Interestingly, the conclusion was that hotspot locations are markedly different in the two species[91–94]. In fact, the hypothesis that hotspots are independently distributed along the two genomes could not be rejected[93]. One possible explanation for the rapid turnover of hotspots is meiotic drive against alleles that increase the recombination rate (see above). Alternatively, hotspot activity might be modulated by *trans*-acting factors or epigenetic modifications that have changed between the species.

The precise time frame over which hotspots evolve is unknown. Almost all hotspots that have been identified by sperm typing are also visible in patterns of LD[64,95,96], even though their intensities sometimes differ significantly[96]. This concordance indicates that, although hotspot locations have changed drastically over 6 million years, they persist for tens of thousands of generations (BOX 2). To further delimit the timescale over which hotspots evolve, a promising approach might be to use sperm typing to survey samples from different human populations.

Interestingly, at the scale of a megabase, LD-based estimates that reflect tens of thousands of generations are highly concordant with contemporary rates measured in pedigrees[97]. This observation indicates that recombination rates over a megabase are more conserved than expected from the sum of finer-scale rates[34], a prediction that can be tested by comparing larger genetic distances in humans and other primates.

Conservation of broad-scale recombination rates might arise in several ways, none of them mutually exclusive. It might occur if, as observed in yeast, hotspots within a genomic region are in competition, such that the removal of one leads to increased intensity of others (see REF. 87 and the references therein). Although this effect was reported for one region of the human genome[64], it was not seen at another pair of adjacent hotspots[63]; the effect could be weaker than in yeast because hotspots are less intense[28]. Large-scale physical constraints might also decrease the occurrence of recombination events in certain genomic regions[20]. Alternatively, recombination might occur, but be deleterious, resulting in stabilizing selection on rates over the megabase scale.

These observations indicate that mammalian species, even those that are closely related, differ in the length of the genetic map, the extent of sexual dimorphism for recombination rates and hotspot locations. They suggest that many aspects of the recombination process might not be under strong purifying selection. The question is whether evolutionary changes in recombination rates are neutral (that is, without fitness effects) or advantageous, and, if advantageous, what the benefits might be.

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Background selection
The effect of strong purifying selection on linked neutral variation.

Outlook

Although the past decade has seen immense progress in our characterization of recombination-rate variation among humans, little is known about its genetic basis. From 30-year-old experiments in *Drosophila*, we know that the answer is likely to lie with changes in *cis* and in *trans* (BOX 3); however, important questions remain. What is the relative contribution of the two, and how localized are their effects? Are many modifiers of crossing over sex-specific? What factors contribute to variation among females and to the maternal age effect? One way to investigate these questions would be to map loci that contribute to variation in recombination rates over different scales, taking advantage of the high-throughput genotyping arrays that are now available. Tools from molecular evolution can then be used to examine the selective pressures affecting these loci. Genome-wide mapping studies of recombination variation might be difficult given the imprecision of crossing-over measurements in a particular individual. One possibility is to take a candidate-loci approach, using genes that are known to be involved in recombination (for example, the homologue of the yeast gene *Spo11* (REF. 98) and *MLH1* (REF. 50)).

In addition to cytogenetic and sperm-typing approaches, the availability of cheap genotyping methods is likely to lead to the increasing use of LD-based methods for inferring recombination rates. In interpreting the results of such studies, it would be helpful to have a better understanding of possible biases in population recombination-rate estimates (for example, REF. 99), notably due to the effects of background selection[100]. LD-based estimates have already been used to identify one set of motifs that are associated with hotspot activity[34]. By comparing LD patterns across species, this approach will allow the determination of whether the same motifs modulate hotspot activity. If they do not, this will suggest that changes in *trans* have led to the rapid evolution of the motifs, providing a possible resolution to the hotspot paradox. Combining fine-scale genetic maps with extensive annotations of the human genome (for example, of epigenetic modifications) will help test other hypotheses about determinants of hotspot activity.

Characterizing heritable variation in recombination rates along the human genome would also allow an assessment of the selective forces that shape their evolution. Under a model in which differences in recombination rates have no fitness consequences, the rate of divergence between species should reflect the extent of within-species variation (see REF. 101 and the references therein). Less divergence than expected from within-species variation is indicative of stabilizing selection on recombination rates, whereas rapid divergence would be consistent with directional selection. In this respect, it is interesting to note that, in *Drosophila*, centromeric regions show extensive rate variation both within (for example, REF. 102) and between species[89].

In the shorter term, we can address questions about the evolution of recombination by taking advantage of the increasing availability of physical and genetic maps. Existing data indicate that humans have a longer genetic map than other primates, and a much higher frequency of aneuploidy than mice. With the accumulating comparative data on recombination, we can start narrowing down when these traits arose, and evaluate what selective factors might have influenced their evolution. For this, we need more theory as well as more data. Specifically, we need population-genetic models of selection on recombination modifiers that incorporate recent discoveries about meiotic recombination. We can also use existing data to assess the evidence for an association between recombination and the efficacy of selection. For example, we can examine whether regions with evidence of adaptive evolution in one species tend to be those that show differences in recombination rates between species (for example, REFS 82,83).

In conclusion, the increasing availability of genomic resources will enable us to address enduring questions about recombination, with important implications for human genetics and our understanding of adaptation. One of the challenges will be to bring together evolutionary and molecular perspectives to build a more complete understanding of the recombination landscape.

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Competing interests statement

The authors declare no competing financial interests.

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