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The Red Queen theory of recombination hotspots

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Abstract

Recombination hotspots are small chromosomal regions, where meiotic crossover events happen with high frequency. Recombination is initiated by a double-strand break (DSB) that requires the intervention of the molecular repair mechanism. The DSB repair mechanism may result in the exchange of homologous chromosomes (crossover) and the conversion of the allelic sequence that breaks into the one that does not break (biased gene conversion). Biased gene conversion results in a transmission advantage for the allele that does not break, thus preventing recombination and rendering recombination hotspots transient. How is it possible that recombination hotspots persist over evolutionary time (maintaining the average chromosomal crossover rate) when they are self-destructive? This fundamental question is known as the *recombination hotspot paradox* and has attracted much attention in recent years. Yet, that attention has not translated into a fully satisfactory answer. No existing model adequately explains all aspects of the recombination hotspot paradox. Here, we formulate an intragenomic conflict model resulting in Red Queen dynamics that fully accounts for all empirical observations regarding the molecular mechanisms of recombination hotspots, the nonrandom targeting of the recombination machinery to hotspots and the evolutionary dynamics of hotspot turnover.

Introduction

Crossover events are not uniformly distributed in the chromosomes of most eukaryotes (Myers *et al.*, 2005). They concentrate in small regions known as recombination hotspots, where the crossover frequency is 10–1000 times higher than the rest of the genome (Lichten & Goldman, 1995; Petes, 2001).

Recombination is initiated by a double-strand break (DSB), with the DNA sequence near the break site being first degraded and later repaired (Petes, 2001) (Fig. 1). As part of the repair process, crossover events and biased gene conversion may happen (Fig. 1). The allelic sequence that breaks is often repaired using the sequence in its homologous chromosome as a template (Lichten & Goldman, 1995; Petes, 2001) (Fig. 1). Thus, recombination results in the over-transmission of the allelic sequence that does not break.

If a DNA sequence can affect its probability of experiencing a DSB, the over-transmission of the allelic sequence that does not break (and prevents recombination and crossover) becomes systematic (Boulton *et al.*, 1997). The strength of biased gene conversion will be at its highest in recombination hotspots. In this sense, recombination hotspots are self-destructive, and their persistence presents an evolutionary puzzle referred to as the *recombination hotspot paradox* (Boulton *et al.*, 1997) The essence of the paradox is that recombination hotspots and the rate of chromosomal crossover are sustained in spite of the fact that biased gene conversion systematically eliminates individual hotspots (Boulton *et al.*, 1997; Dumont & Payseur, 2008).

In this article, we present a model that resolves the recombination hotspot paradox, while qualitatively accounting for all of the empirical patterns observed in recombination hotspots. Our model relies on the idea that there is intragenomic conflict between allelic

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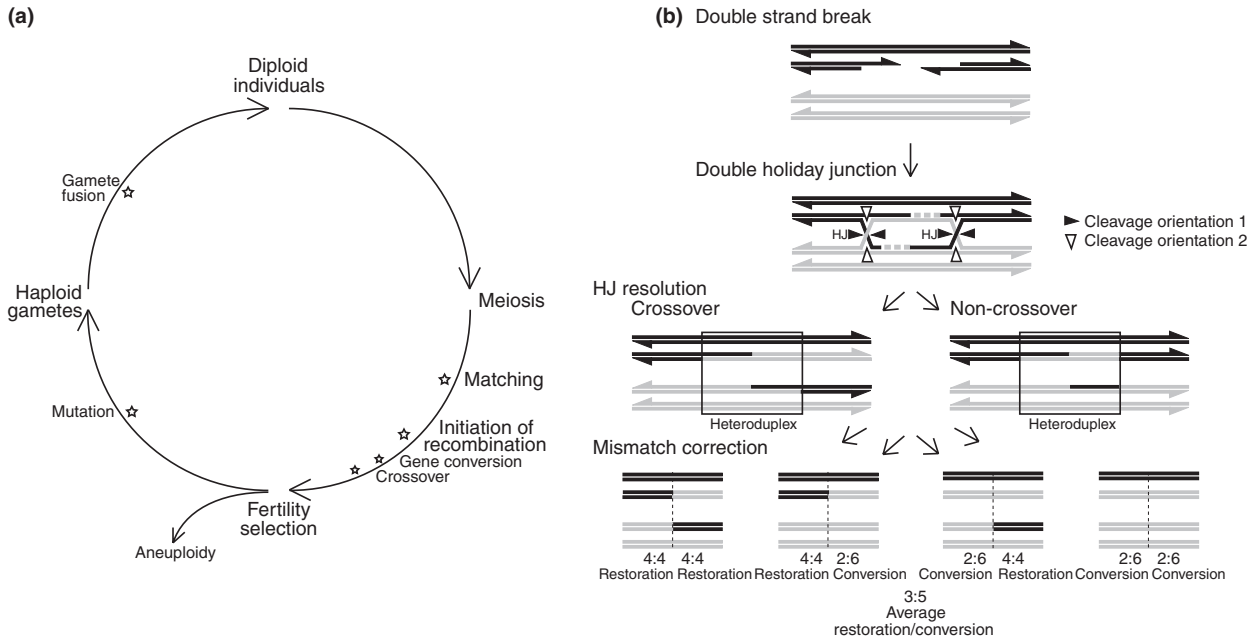

Fig. 1 Life cycle and double-strand break (DSB) repair model for the initiation of recombination. (a) Life cycle of the simulated population and (b) canonical DSB repair model (Szostak *et al.*, 1983; Sun *et al.*, 1991). We use black and grey colours to represent the chromosome that breaks and does not break, respectively. We present the sequence of steps leading from a DSB to crossover and bias gene conversion.

sequences resistant to DSBs and modifiers of resistance acting at the genome level. In particular, we model intragenomic conflict between allelic sequences (at target loci) that determine their own probability of experiencing a DSB, and genes (at a modifier locus) encoding recombinogenic proteins that recognize those target sites.

Biased gene conversion favours allelic sequences that can evade recognition by the recombinogenic protein. However, this comes at a fertility cost to the individual. Escaping recognition results in lower chromosomal crossover rate and higher probability of defective chromosome segregation (aneuploidy). Thus, fertility selection drives the evolution of the recognition site on the recombinogenic molecule to counteract the effect over the chromosomal crossover rate of selfish alleles (alleles that promote their own transmission at the expense of the fitness of the individual) at target sites. Notice, however, that fertility selection does not act to preserve susceptible allelic sequences at specific target sites, but to maintain the chromosomal crossover rate. The result is a Red Queen dynamic (van Valen, 1973) somewhat analogous to what has been described in predator–prey (Dieckmann *et al.*, 1995; Dercole *et al.*, 2010) or host–parasite systems (Decaestecker *et al.*, 2007; Koskella & Lively, 2009; Paterson *et al.*, 2010).

In our model, the twin dynamics of recognition evasion by allelic sequences at recombination hotspots and selection on the recombinogen to match sequences result in a dynamic equilibrium. Individual recombination hotspots are created and destroyed rapidly, but at nearly equal rates, such that the overall level of crossover in the chromosome is maintained indefinitely. Thus, our model is able to account not only for the maintenance of chromosomal crossover rate in the face of biased gene conversion but also for the turnover of individual recombination hotspots (the instability of the recombinatorial landscape) and the apparent rapid evolution of the sequence motifs associated with recombination hotspots.

We believe that ours is the first model that is consistent with all of the empirical patterns associated so far with recombination hotspots. Several previous models have suggested partial resolutions to the paradox, but each of these has failed to account for one or more empirical observations. Prior to presenting the results of our model, we briefly describe each of the empirical observations that must be accommodated and how our model differs from those that have been proposed.

Empirical observations

Trans-acting recombinogenic molecules target specific DNA sequence motifs

Recombinogenic DSBs are highly enriched at sequence motifs that are thought to be recognized by particular recombinogenic molecules. The *PRDM9* locus in humans encodes a protein containing 13 zinc fingers with a tandem repeat structure similar to that observed in the

12-zinc-finger mouse homolog, *Prdm9* (Baudat *et al.*, 2010). A degenerate 13-base pair motif found in approximately 40% of human recombination hotspots (CCNCCNTNNCCNC) (Myers *et al.*, 2008; Webb *et al.*, 2008) is specifically targeted by the human PRDM9 protein (Baudat *et al.*, 2010), and biased gene conversion is eliminating the motif from the genome (Myers *et al.*, 2010).

Other studies have also shown that the location of recombination sites depends on *cis*-acting and *trans*-acting elements, consistent with the involvement of sequence-specific interactions in the initiation of recombination (Neumann & Jeffreys, 2006; Grey *et al.*, 2009; Parvanov *et al.*, 2009). Most recently, genetic variation at the PRDM9 locus has been shown to modify recombination activity in sperm and can cause new recombination hotspots to form (Berg *et al.*, 2010).

Hotspot recognition motifs are not stable

Comparison of the *Prdm9* cDNA sequences in two mouse subspecies (*Mus mus molossinus* and *Mus mus domestica*) revealed a high level of polymorphism, concentrated particularly in the zinc-finger array responsible for targeting the Prdm9 protein to specific sequence motifs (Baudat *et al.*, 2010). In fact, *Prdm9* shows evidence of consistently accelerated evolution across a range of taxa. The evidence for strong directional selection is greatest in rodents and primates, but it appears that directional selection on this gene may be an ancient feature among metazoans (Oliver *et al.*, 2009). Note that this sort of pattern – consistent directional selection over very long times – is difficult to reconcile with adaptive evolution towards a fixed target. However, it is consistent with Red Queen dynamics, where the evolutionary target is consistently changing. In fact, it has been suggested that a rapidly evolving target sequence is necessary to explain the molecular evolution of *Prdm9* (Thomas *et al.*, 2009).

Recombination-resistant alleles are over-transmitted

Sperm genotyping studies at polymorphic recombination hotspots differentiate between *hot alleles* (allelic sequences showing higher frequency of crossover rate in homozygotes) and *cold alleles* (allelic sequences showing lower frequency of crossover rate in homozygotes) (Jeffreys & Neumann, 2002, 2005). These studies show that in heterozygotes, hot alleles are under-transmitted, whereas cold alleles are over-transmitted as a consequence of recombination events (Jeffreys & Neumann, 2002, 2005) (Fig. 2). Consistent with this pattern of biased gene conversion and transmission, and with a role for sequence specificity in the interaction between *cis*-acting and *trans*-acting elements, the over-transmitted (cold) alleles in humans are those that match less well to the 13-bp *PRDM9* recognition sequence (Myers *et al.*, 2010).

RHS	DNA2	NID1
SNPs	FG11A FG11G	M-57.8C M-57.8T
	Crossover rate	
■■	26.0×10^{-4}	16.2×10^{-4}
■□	37.4×10^{-4}	5.5×10^{-4}
TD	74%	76%
□□	4.0×10^{-4}	3.2×10^{-4}

Fig. 2 Over-transmission of cold alleles. Crossover rate corresponding to each genotype and transmission of cold alleles in two hotspots (*DNA2* and *NID1*) in humans obtained using sperm genotyping techniques (Jeffreys & Neumann, 2002, 2005). We use black and grey to represent the hot and cold alleles, respectively. Notice that a homozygote for the hot allele shows greater hotspot crossover rate than and homozygote for the cold allele. A heterozygote shows high hotspot crossover rate in one hotspots and low in the other. The cold allele is over-transmitted (75%) in both hotspots.

Recombination hotspots are transient

The locations of specific recombination hotspots are transient and appear to change at a rate much faster than other features of the genome. Statistical analysis of fine-scale recombination patterns in humans and chimpanzees indicates that recombination hotspots are rarely found in the same position in the two species (Ptak *et al.*, 2004, 2005; Winckler *et al.*, 2005). Furthermore, even within humans, the locations of recombination hotspots can vary among different populations (Winckler *et al.*, 2005; Arnheim *et al.*, 2007; Coop *et al.*, 2008).

The chromosomal crossover rate is maintained by fertility selection over long periods of time

Even though biased gene conversion acts at the level of each recombination hotspot, fertility selection acts on the chromosomal crossover rate at the level of the organism. Proper segregation of the chromosomes during meiosis requires at least one crossover per chromosome arm, and excessively low rates of chromosomal crossover often result in aneuploidy (Coop & Przeworski, 2007). An excessively high rate of chromosomal crossover is not beneficial either, and stabilizing selection has maintained a crossover rate slightly above one crossover per chromosome arm across a broad range of taxa (de Villena & Sapienza, 2001; Dumont & Payseur, 2008). Consistent with a role for *Prdm9* in maintaining proper chromosome segregation, and the potential efficacy of fertility selection, mutations in this gene have been associated with azoospermia through meiotic arrest (Miyamoto *et al.*, 2008; Irie *et al.*, 2009).

Previous models

The recombination hotspot paradox has received a great deal of attention from both molecular and theoretical biologists as it was first identified (Boulton *et al.*, 1997; Archetti, 2003; Pineda-Krch & Redfield, 2005; Calabrese, 2007; Coop & Myers, 2007; Friberg & Rice, 2008; Peters, 2008). Genes can interact in three different manners: *cis*-acting, *trans*-acting or a combination of both (Fig. 3). Furthermore, allelic sequences can code for tolerance to DSBs or resistance to DSBs. In this section, we consider modifiers coding for tolerance to DSBs and targets coding for resistance to DSBs. However, under particular circumstances, it is expected that modifiers coding for resistance evolve. These circumstances are described in the discussion section.

The *recombination hotspot paradox* assumes that allelic sequences at recombination hotspots act in *cis* to determine their own probability of experiencing a DSB (Fig. 3a1) (Boulton *et al.*, 1997). The problem remains unsolved when selection acts on individuals to sustain the crossover rate in specific hotspots (Boulton *et al.*, 1997; Pineda-Krch & Redfield, 2005; Peters, 2008). Mathematical models show that the strength of selection (either fertility or viability) necessary to prevent biased gene conversion from removing hot alleles from the population is far too strong to be realistic, and the chromosomal crossover rate declines rapidly under realistic parameter values (Boulton *et al.*, 1997; Pineda-Krch & Redfield, 2005; Peters, 2008).

Acting in cis on a neighbouring sequence

Mathematical models indicate that a modifier acting in *cis* on a neighbouring sequence and coding for susceptibility to DSBs (Fig. 3a2) could be maintained in the population if crossing over has a selective advantage (Coop & Myers, 2007; Peters, 2008). By acting on its neighbour, this modifier gains the individual advantage derived from crossing over, but limits the cost of under-transmission to the cases in which it lies close enough to its target site to be affected by gene conversion. This form of action reduces the strength of selection necessary to maintain recombination hotspots in the population (Peters, 2008). However, this model cannot explain

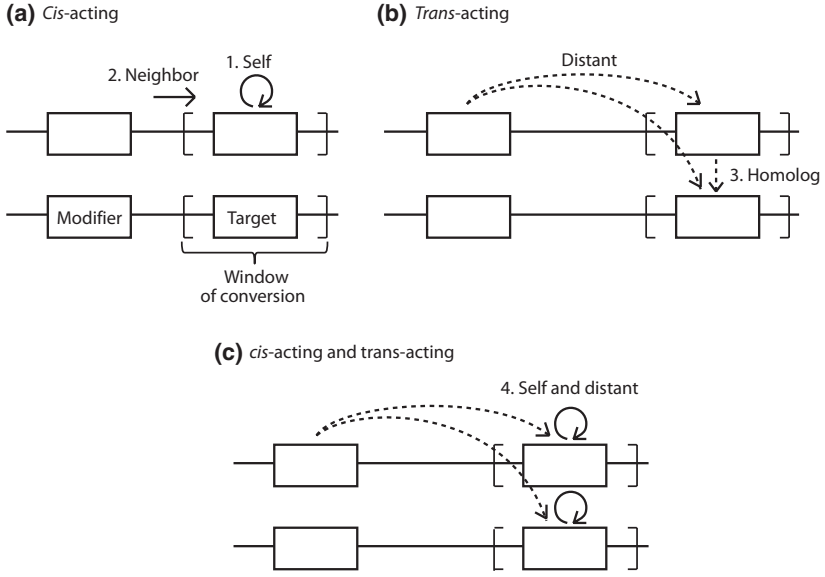

Fig. 3 Modes of action of modifier and target loci. Rectangles joined by a line represent genes in a chromosome. The first gene corresponds to a modifier of the second gene, a target. The target locus is susceptible to double-strand breaks (DSBs) and part of the DNA sequence around it is converted during break repair (window of conversion). Arrows indicate actions. The origin of each arrow indicates who is the actor and the end of the arrow who is it action on. (a) *cis*-acting target or modifier. The term *cis*-acting refers to genes affecting the activity of genes in the same DNA strand. These loci generally do not encode a protein, thus acting on its neighbouring sequences. Regarding recombination hotspots, it has been used to refer to genes acting on themselves or acting on another gene in its proximity in the same DNA strand. (a.1) Target locus acts in *cis* to determine its own probability of suffering a DSB. This is the assumption leading to the recombination hotspot paradox. (a.2) Modifier locus acts in *cis* to determine the probability of the target sequence to experience a DSB. This modifier might be inside or outside of the gene conversion window. (b) *trans*-acting target or modifier. The term *trans*-acting refers to a genes acting on other genes in either their own DNA strand or its homologous strand. These loci encode a diffusible protein thus able to act on distant genes. Regarding recombination hotspots, it has been used to refer to genes acting on their homologs or on a distant genes (b.3) Target locus acts in *trans* on its homolog to determine the probability of its homolog's target sequence to experience a DSB. (c) *cis*-acting target and *trans*-acting modifier. (c.4) Target locus acts in *cis* to determine its own probability of experiencing a DSB, but modifier locus acts in trans to modify this probability.

either the over-transmission of a particular sequence (there are no hot or cold alleles at the target site) or the transient nature of recombination hotspots (each hotspot remains hot indefinitely, and the recombinatorial landscape is static).

Acting in trans

A second class of mathematical models suggests that an allelic sequence acting specifically in *trans* on its homolog and coding for susceptibility to DSBs could enter the population and be maintained (Fig. 3b3), even in the absence of any selection favouring crossovers (Archetti, 2003). By acting on its homolog, this *trans*-acting allele is directly favoured by being over-transmitted. However, this model results in the over-transmission of the hot allele (which is contrary to the existing empirical evidence) and cannot explain the transient nature of recombination hotspots (the recombinatorial landscape is static).

Acting in cis and trans

A final class of mathematical models considers an allelic sequence acting in *cis* to determine its own resistance to DSBs and a modifier acting in *trans* to modify the resistance of its target (Peters, 2008) (Fig. 3c4).

In particular, Peters (2008) models a *trans*-acting modifier that makes the target locus either active or inactive. In a population fixed at the modifier locus for the inactivating allele, alleles at the target locus are neutral. Target alleles that are susceptible to DSBs may increase in frequency through drift, and active alleles at the modifier locus are favoured when crossing over provides a selective advantage to the individual (Peters, 2008). This model requires that the modifier locus be far enough from the target locus to evade gene conversion (Peters, 2008).

Similarly, Friberg & Rice (2008) consider a *trans*-acting modifier that determines the susceptibility of the target locus to DSBs. In a population fixed at the target locus for a resistant allele, negative linkage disequilibrium between flanking regions is built up because of the lack of local recombination. When negative linkage disequilibrium is large enough, alleles at the modifier locus coding for tolerance to DSBs will be favoured by hitchhiking with the most fit genetic background (Friberg & Rice, 2008). The argument of Friberg & Rice (2008) requires that the modifier locus be far enough from the target site to avoid gene conversion, but close enough to hitchhike with its genetic background. Eventually a resistant allele at the target locus evolves. No formal analysis of this idea has been undertaken.

The essence of the recombination hotspot paradox is that recombination hotspots and the chromosomal crossover rate will be maintained over long periods of time in spite of biased gene conversion. In the existing models of *cis*-acting alleles and *trans*-acting modifiers proposed, cold alleles eventually become fixed at the target locus. A successful model needs to provide a specific mechanism that allows the regeneration of hotspots and to assess the strength of selection necessary to maintain the chromosomal crossover rate. These steps are missing in previous models of interaction between *cis*- and *trans*-acting alleles.

Although our model falls into the general category of *cis*- and *trans*-acting modifiers, it provides a mechanism (driven by intragenomic conflict between modifier and target loci) that maintains the chromosomal crossover rate indefinitely for a wide range of strengths of fertility selection. Furthermore, our model is able to explain not only the maintenance but also the origin of recombination hotspots.

Model

We simulate a population of N diploid individuals ($N/2$ males and $N/2$ females) and nonoverlapping generations. We assume that each individual carries a single linear acrocentric chromosome consisting of one locus that encodes a recombinogenic molecule (modifier locus) capable of initiating recombination at any of the $L = 100$ loci that are potential target sites (target loci).

Initiation of recombination

Recombination is initiated by the production of a recombinogenic molecule that potentially acts on a target locus. The modifier and each target locus are modelled as a sequence of 40 sites, where each site can take on one of four distinct states, corresponding to four possible nucleotides.

The probability that a recombinogenic molecule initiates recombination at a particular target locus is a function of the number of sites at which the recombinogenic and target sequences match. We assume that the probability of initiating recombination at a target locus is 0 if the sequences match at 12 or fewer sites, and is $1/L = 0.01$ if the sequences match at 18 or more sites. Between 12 and 18, the probability of initiation increases linearly with the number of matches. These match values were chosen to reflect the typical motif length (~13 bp) observed in human recombination hotspots (Myers *et al.*, 2008).

The probability of initiation of recombination is evaluated independently for each pairwise combination of modifier and target allele. That is, the probability is calculated as described earlier for each of 400 possible comparisons (2 modifier alleles × 2 target alleles × 100 target loci). Recombination is initiated at a particular target allele if a pseudorandom number (uniform between 0 and 1) is smaller than the probability defined by the number of matches. Recombination probabilities are rescaled to preclude the possibility that both alleles at a single target locus suffer DSBs during the same meiosis.

Biased gene conversion and crossover

Once recombination has been initiated, we follow the canonical DSB repair model (Szostak *et al.*, 1983; Sun *et al.*, 1991) (Fig. 1b). We assume that when a DSB occurs, with probability 1/2, the allele that breaks is converted into the allele that does not break, but is restored to its original form otherwise. Although this assumption follows the canonical form of the DSB repair model, recent work shows that not all four products of the mismatch correction process will be produced with equal probability. There is often conversion in one side of the DSB but rarely conversion, or restoration, in both sides (Birmingham *et al.*, 2004; Jessop *et al.*, 2005) (Fig. 1b). However, even eliminating these two products, the probability of conversion remains 1/2. The unbroken allele is thus transmitted with probability 5/8 (62.5%) (notice that the sister chromatids that do not participate in the recombination process may also be transmitted) (Fig. 1b). We assume that neighbouring target loci are separated by sufficient distance that gene conversion initiated at one locus never affects neighbouring loci. We assume that the modifier locus is close to the 10th target locus along the chromosome (starting from the centromere), and gene conversion at this locus also results in gene conversion at the modifier locus.

When a DSB occurs, we assume that the aligned chromatids experience crossover independently of whether there is gene conversion. This assumption deviates from the canonical form of the DSB repair model, which assumes that a crossover event follows a DSB with probability 1/2. The reason is that research shows that shortly after a DSB takes place, there is an early differentiation between two pathways, one of which generally results in a crossover event, whereas the other does not (Foss *et al.*, 1999; Allers & Lichten, 2001; Birmingham *et al.*, 2004; Jessop *et al.*, 2005). Thus, our model focuses on the pathway leading to crossover (Fig. 1b). The exchange of chromatids happens to the right (the telomeric side) of the sequence that determines the recombination probability at a target locus. The position of the locus encoding the recombinogen is not expected to affect the results, as gene conversion (as opposed to meiotic drive) does not result in linkage disequilibrium between pairs of loci (Bengtsson & Uyenoyama, 1990). Consistent with this prediction, altering the position of the recombinogen-encoding locus does not affect the behaviour of the model (results not shown). What is relevant is whether the locus encoding the recombinogen is affected by gene conversion from the neighbouring target loci.

Fertility selection

In our model, individual fitness is determined by proper chromosome segregation during gametogenesis (fertility selection). A random individual is chosen from the parental population. The number and location(s) of crossover events in an individual's gametes are determined probabilistically as described in the previous section. The probability that this individual contributes a gamete to the next generation is determined by the number of crossover events that took place in the meiosis giving rise to that individual's gamete. We assume that the greater the number of crossover events the greater the fertility of an individual, but that having too many crossover events reduces fertility (Fig. 4). Our selection scheme reflects the empirical observation that too few or too many crossover events are associated with fitness costs for the individual (Hassold *et al.*, 2000; Louis & Borts, 2003). We concentrate our attention on functions that show maximum fertility for the range of 1–4 crossover events per chromosome, corresponding to

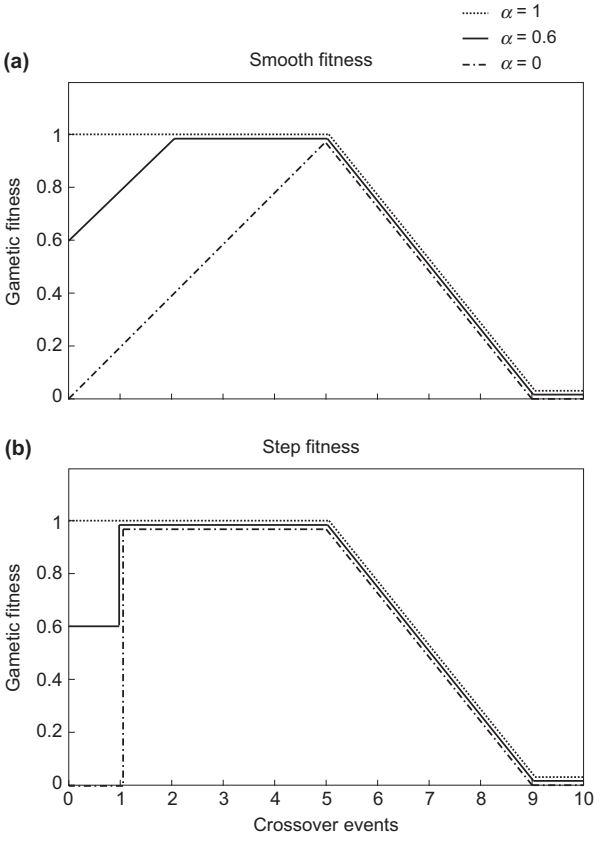

Fig. 4 Fitness function. The horizontal axis represents the number of crossover events in the chromosome. The vertical axis represents the probability of proper chromosome segregation during gametogenesis (and thus the probability that a gamete is viable). Two classes of stabilizing fitness function are considered: (a) smooth fitness and (b) step fitness functions. The variable α corresponds to the probability of proper chromosome segregation with zero crossover events.

the observation that on average there is one recombination event per chromosome arm (Dumont & Payseur, 2008).

We vary the strength of selection in the context of two different functional shapes. First, we consider a family of fitness functions where the survival probability of a gamete is equal to α if there are no crossover events. Each additional crossover increases the fitness by 0.2, up to a maximum 1 (*smooth fitness*) (Fig. 4a). For this family of functions, reducing the fitness of a gamete with no crossover events (α) has the simultaneous effect of increasing the number of crossover events required to achieve maximum fitness (Fig. 4a). We also consider a family of fitness functions where the survival probability of a gamete increases abruptly from a minimum α at zero crossover events to a maximum 1 at more than zero crossover events (*step fitness*) (Fig. 4b). In both families, fitness declines if there are more than five crossover events, with decrements of 0.25 for each additional crossover to a minimum fitness of 0 for the case of nine or more crossovers.

The chromosome carried by a gamete is constructed as follows. One of the two homologous chromosomes in the parent is chosen at random, and the new chromosome is generated by copying each target locus in order (starting at the centromeric end), switching to the other chromosome at each site where a recombination event occurs. If a pseudorandom number (between 0 and 1) is less than the gamete fitness (as determined by the total number of crossovers), the gamete is accepted and passed to the gamete pool. Sampling of parents continues until $2N$ male gametes and $2N$ female gametes have successfully been generated.

Mutation

Mutations are introduced randomly following gametogenesis. The mutation rate per locus per generation is μ_M at the modifier locus and μ_T at each target locus. If an allele mutates, one of the 40 sites in its sequence is randomly picked and changed to one of the possible four states. Notice that the probability that a mutation occurs at a particular site is (1/40) (1−0.25) = 0.01875 times the nominal mutation rate for the locus, as the locus consists of 40 sites, and a mutation at a site has a 0.25 probability of leaving the site unchanged. Finally, male and female gametes are paired randomly to generate the *N/2* male and *N/2* female diploid genomes of the next generation (Fig. 1a).

Results

Our results are presented in Figs 5–7. Owing to computational constrains, results correspond to a population of $N = 2000$ individuals. However, the robustness of the main result has been tested for $N = 4000$ and $N = 8000$ without finding any significant difference for the maintenance of the chromosomal crossover rate but a significant reduction of its variance.

Our results show that fertility selection can maintain the chromosomal crossover rate indefinitely despite gene conversion (Fig. 5a). Even weak fertility selection can sustain chromosomal crossover rates that are significantly higher than those found in the absence of fertility selection (Fig. 5b). This is true for at least two different families of stabilizing selection functions (smooth and step) (Fig. 5b). These results also hold for the corresponding families of directional selection functions (where there is no fitness cost associated with having too many crossover events), as the strong effects of biased gene conversion result in the equilibrium crossover rate being maintained at a level where fertility selection is favouring, increasing the number of crossovers (Fig. 5b). We show that the greater the strength of fertility selection, the greater the chromosomal crossover rate at equilibrium (Fig. 5b).

Although the chromosomal crossover rate is held at a constant level, this steady state represents a dynamic equilibrium that emerges from intragenomic conflict between the recombinogen and target sequences. This dynamic equilibrium is characterized by the rapid turnover of individual hotspots, where the rate of hotspot elimination through biased gene conversion matches the rate at which new hotspots are formed because of adaptive evolution of the recombinogen (Fig. 6). That is, the effect of biased gene conversion is sufficiently strong that target loci rapidly evolve away from sequences that are recognized by the recombinogen. Fertility selection favours alleles at the recombinogenic locus that are able to bind target sites. However, fertility does not require that the recombinogen continue to bind to the same target sites (by 'mimicking' or 'chasing' the cold alleles that are increasing in frequency because of biased gene conversion). At some frequency, new recombinogen alleles will be created that bind to target sites that were not previously hotspots, as is seen in mouse crosses (Grey *et al.*, 2009) and in human variants (Berg *et al.*, 2010). Thus, the combination of fertility selection and biased gene conversion drives an evolutionary chase between alleles at the recombinogenic and target loci (Fig. 6). The resulting Red Queen dynamics produces a highly dynamic recombinatorial landscape (Fig. 6) that explains the lack of shared hotspots between humans and chimpanzees, and the variability even among different populations of the same species (Ptak *et al.*, 2004, 2005; Winckler *et al.*, 2005; Arnheim *et al.*, 2007; Coop *et al.*, 2008).

Recombination hotspots form spontaneously in our model in a way that depends on sequence specificity. Starting with a uniform distribution of crossover events along the chromosome, crossover events quickly become clustered, creating recombination hotspots (Fig. 6). This clustering depends on the specificity of the interaction between recombinogenic molecules and target sites.

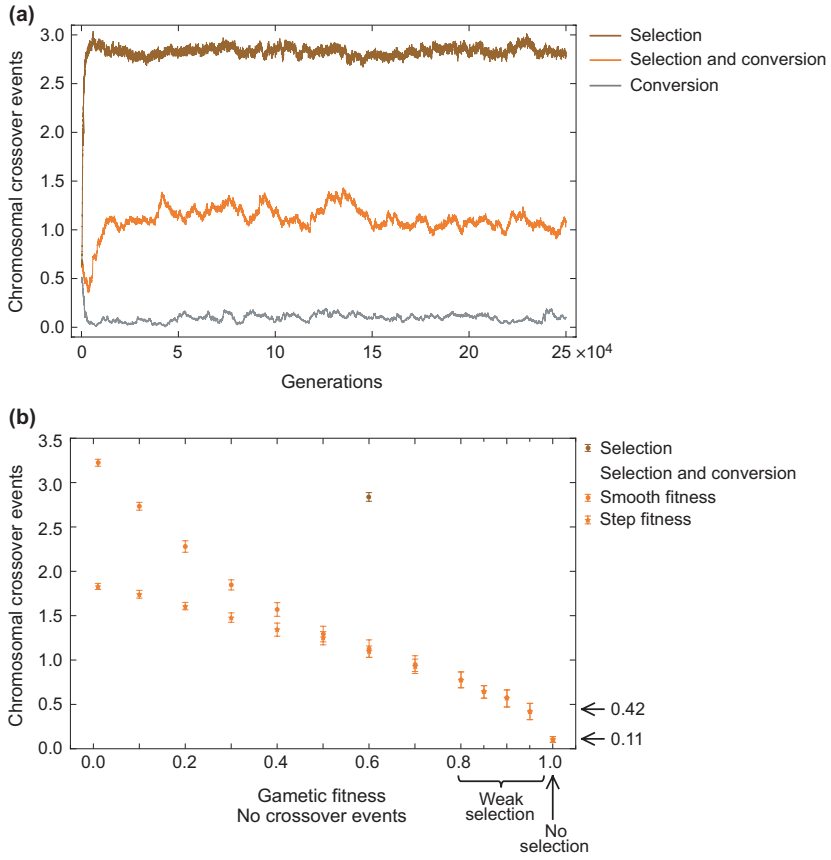

Fig. 5 Chromosomal crossover rates. This figure represents the chromosomal crossover rates at equilibrium. (a) The horizontal axis represents the number of generations as multiple of 10 000. The vertical axis represents the crossover rate per chromosome per generation. The three cases presented correspond to gene conversion without selection favouring crossovers (grey, mean 0.11), selection favouring crossovers without gene conversion (brown, mean 2.84), and a combination of gene conversion and selection for crossovers (orange, mean 1.13). These results were obtained using a smooth fitness function with $\alpha = 0.6$ (see Fig. 4), mutation rates $\mu_M = 10^{-3}$, $\mu_T = 10^{-4}$ and population size $N = 2000$. The figure shows that with conversion and selection, the chromosomal crossover rate becomes stable and fluctuates around its average (1.13) for a large number of generations (> 200 000). This equilibrium rate lies between the corresponding ones in the absence of selection (0.11) and in the absence of gene conversion (2.84). Notice that the fluctuation for the case of conversion and selection (standard deviation 0.0984) is twice as large as either the cases of conversion (0.0324) or selection (0.0465). (b) The horizontal axis represents gametic fitness with no crossover events (α), which measures the strength of selection favouring crossover events; values of α in the range (0.0, 0.8) correspond to strong selection, values of α in the range (0.8, 1.0) correspond to weak selection, and when α takes the value 1, there is no selection. The vertical axis represents the chromosomal crossover rate per generation. Each value of α corresponds to a different fertility fitness function with two variants (both in orange) corresponding to the smooth function (circles) and the step function (stars). For each condition, either circles or stars indicate the mean chromosomal crossover rate over the last 200 000 generations of the simulation, after the rate has reached its equilibrium level. Error bars corresponding to the standard deviation are provided for each value. The additional data point in brown at $\alpha = 0.6$ indicates the case of no gene conversion illustrated in (a), whereas the value at $\alpha = 1$ indicates the case of no selection illustrated in (a). The chromosomal crossover rate sustained by the lowest selection strength considered ($\alpha = 0.95$) is almost four times larger and significantly different (0.4200 ± 0.0917) from the rate observed without selection (0.1051 ± 0.0324).

Simulations in which the recombinogen activity is independent of the sequence at the target locus showed no hotspot formation (results not shown).

We find that chromosomal crossover rates at equilibrium are higher when the mutation rate at the modifier locus is greater than the mutation rate at the target loci (Fig. 7). That is, in the Red Queen dynamics resulting from intragenomic conflict, the rate at which target loci evolve to evade recognition and the rate at which the recombinogen locus evolves to target new sequences both appear to be mutation limited. The chromosomal crossover rate at equilibrium depends most strongly on the ratio of the two mutation rates (μ_M and μ_T) (Fig. 7). Increasing the mutation rate for the target loci enhances their ability to evade recognition by the recombinogen, resulting in a reduced crossover rate. Similarly, increasing the recombinogen

mutation rate enhances its ability to pursue target loci through sequence space and to identify new targets (Fig. 7). When mutation rates are low, for a given value of the ratio of μ_M to μ_T, lower mutation rates result in an increase in the chromosomal crossover rate at equilibrium (Fig. 7), suggesting that in our model, target loci are more mutation limited than is the recombinogen. When mutation rates are very high, mutational effects swamp out the effects of biased gene conversion and fertility selection, and the chromosomal crossover rate at equilibrium declines. The resolution of the conflict between modifier and target loci is thus determined by the mutation rates at modifier and target loci.

Interestingly, the region of the *PRDM9* locus that encodes its binding sequence contains a minisatellite structure. Minisatellites produce a high intrinsic mutation rate of the genes containing them (Ellegren, 2004; Baudat *et al.*, 2010). This high mutation rate can be explained, in part, by the number of repetitions of the sequence forming the minisatellite structure (Ellegren, 2004). This minisatellite structure consists of 12 repeats in humans (Baudat *et al.*, 2010) and 8–13 repeats in other mammals (Oliver *et al.*, 2009). The mutation rate in microsatellites in the human genome ranges between 10^{-4} and 10^{-2} (Ellegren, 2004). According to the results of the model presented here, elevating the mutation rate of the binding sequence of the recombinogenic molecule enhances the ability of that molecule to maintain a high rate of chromosomal crossovers in the face of the destruction of hotspots by biased gene conversion. Current evidence suggests that *PDRM9* may be the primary contributor to the formation of recombinogenic DSBs. We suggest that its minisatellite structure, and the resulting elevation in its mutation rate, may provide it with a competitive advantage in the intragenomic conflict with its target sequences. This advantage leads to a resolution of the conflict that is closer to the interests of the recombinogen and farther from the interests of the selfish alleles at the target loci.

Discussion

In this article, we present a computational model of the evolution of recombination hotspots inspired by the existing molecular evidence. We model a modifier locus producing a recombinogenic protein that induces DSBs at multiple potential target loci. The probability of a DSB in a particular allele depends on the match between the recognition sequence of the allele at the target locus and the binding sequence of the recombinogenic protein determined by alleles at the modifier locus (Baudat *et al.*, 2010). We follow the crossover pathway of the DSB repair model for the initiation of recombination (Szostak *et al.*, 1983; Allers & Lichten, 2001) to derive the probability of biased gene conversion. We assume that crossover events are favoured by fertility selection (Hassold *et al.*, 2000; Kong *et al.*, 2004; Ferguson *et al.*, 2007), due to the fact that the probability of proper chromosome segregation is a function of the number of crossover events (Hassold *et al.*, 2000). Fitness is maximized for intermediate numbers of crossover events per chromosome, with fitness costs associated with having either too few or too many crossovers, as suggested by empirical data (Hassold *et al.*, 2000; Louis & Borts, 2003).

Owing to biased gene conversion, allelic sequences at target loci rapidly evolve away from the recombinogen's binding sequence, thereby reducing the chromosomal crossover rate. At the same time, fertility selection creates a selective pressure on alleles at the modifier locus to bind the recognition sequence of enough target loci to maintain a certain level of chromosomal crossing over. We show that the combined effect of biased gene conversion and fertility selection mediated by a matching mechanism (all of which are well supported by empirical data) is sufficient to explain the formation and rapid turnover of recombination hotspots, and the maintenance of the chromosomal crossover rate indefinitely, thus, offering a solution to the recombination hotspot paradox. This model is consistent with evidence for the under-transmission of hot alleles and the rapid evolution of *trans*-acting modifiers.

Our results are compatible with previous models, indicating that realistic values of fertility selection cannot maintain *cis*-acting hot alleles in the population in the face of biased gene conversion (Boulton *et al.*, 1997; Pineda-Krch & Redfield, 2005). In our model, realistic fertility selection is not able to maintain hot alleles at any particular target locus. Rather, fertility selection drives the evolution of a *trans*-acting modifier that turns previously neutral alleles at other target loci into hot alleles. Our results are also compatible with previous mathematical models, suggesting that a combination of *cis*-acting targets and *trans*-acting modifiers can explain the maintenance of recombination hotspots (Peters, 2008). However, those previous models of *cis*-acting targets and *trans*-acting modifiers are limited, as they do not provide a mechanism through which the chromosomal crossover rate can be maintained for long periods of time. Our model overcomes this limitation by introducing explicit sequence specificity, which allows the recombinogen to spontaneously generate new hotspots and to maintain the chromosomal crossover rate indefinitely. We provide the first formal model of such a process and in this sense, a novel complete solution to the recombination hotspots paradox.

Ours is a model of intragenomic conflict with selfish genes acting in *cis* to promote their own transmission at the expense of the fitness of the individual, whose chromosomal crossover rate decays. This creates the selective pressure for a *trans*-acting modifier to evolve, increasing the individual fitness by enhancing the chromosomal crossover rate. Notice that conflict exists over the chromosomal crossover rate; although there is selective pressure to maintain the overall crossover

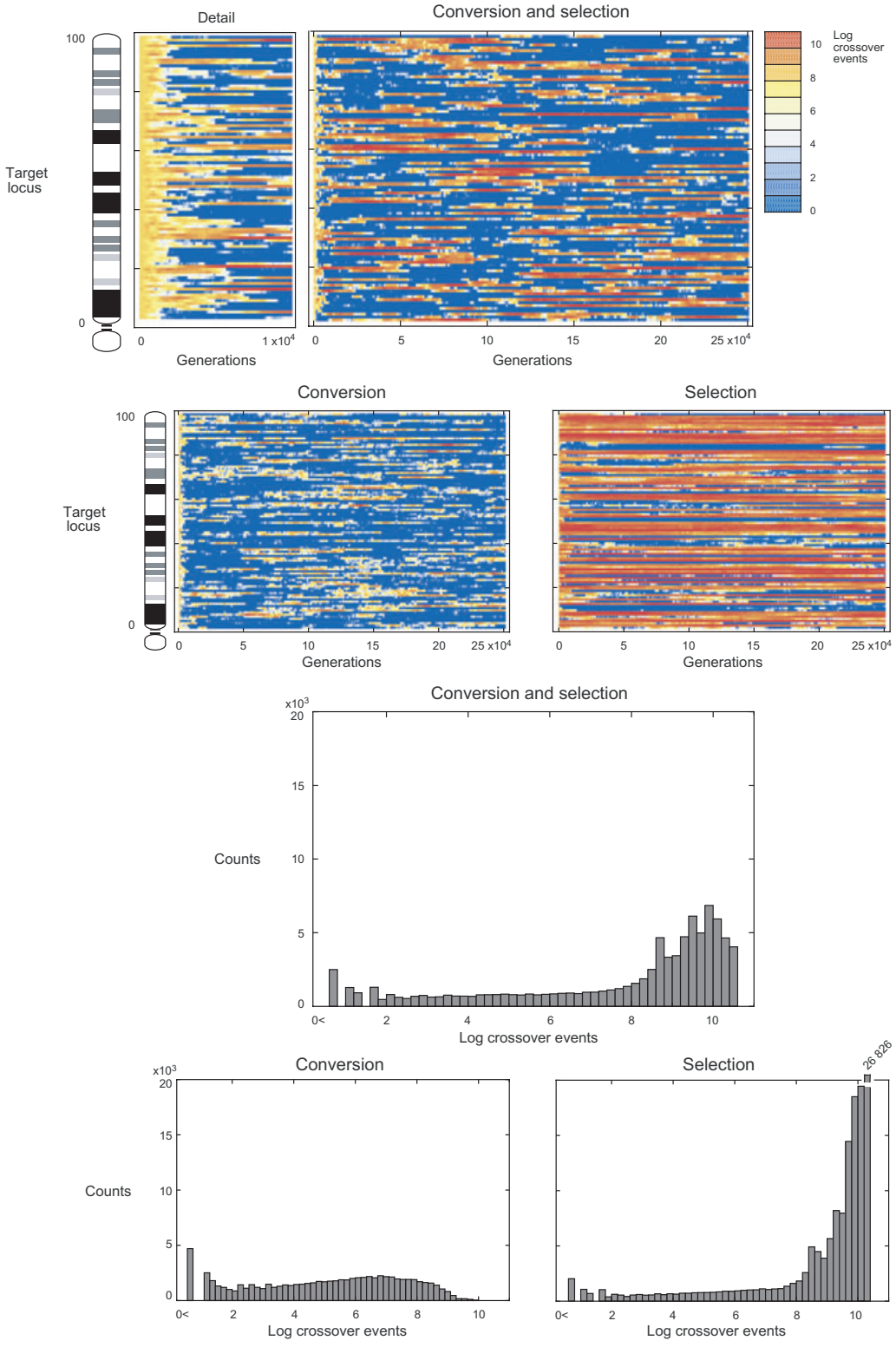

Fig. 6 Genome recombinatorial landscape. This figure presents the location and the distribution of recombination hotspots. Results correspond to a smooth fitness function with $\alpha = 0.6$, mutation rates $\mu_M = 10^{-3}$, $\mu_T = 10^{-4}$, and population size $N = 2000$. (a) The horizontal axis represents time (generations). The vertical axis indexes the 100 target loci along the chromosome. Each pixel represents the log-transformed number

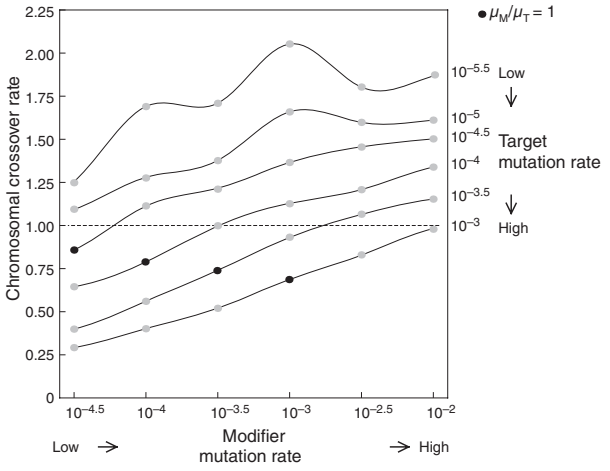

Fig. 7 Mutation rates. Variation of mutation rates at modifier and target loci. Results in Figs 5 and 6 were obtained assuming mutation rates $\mu_M = 10^{-3}$ and $\mu_T = 10^{-4}$ at modifier and target loci. The data presented in this figure illustrate the effects of changes in these mutation rates. The horizontal axis represents the mutation rate at the modifier locus (μ_M). The vertical axis represents the chromosomal crossover rate. Each line corresponds to the same mutation rate at target loci (μ_T). Dots in each line represent the average number of crossovers per chromosome at equilibrium (over the last 200 000 generations of the simulation). Black dots correspond to the case in which the mutation rate at the modifier locus is equal to the mutation rate at target loci. Notice that to maintain a chromosomal crossover rate close to or above 1, it is necessary that the mutation rate at the modifier locus is greater than the mutation rate at the target locus, $\mu_M > \mu_T$, which corresponds dots above the line formed by black dots. Notice also that when the ratio of the two mutation rates is held constant, it is the lower mutation rates that can maintain higher levels of chromosomal crossover rates.

activity, there is no selective pressure to maintain specific recombination hotspots. Such intragenomic conflict leads to Red Queen dynamics (van Valen, 1973) where recombinogenic alleles chase the most abundant of the target alleles, switching to a new target allele when the first allele becomes rare because of biased gene conversion. The chromosomal crossover rate associated with the resolution of this conflict is determined by the mutation rate of the recombinogenic locus relative to the mutation rate at the target loci. Recombinogenic loci with mutation rates greater than the mutation rates at target sites have the upper hand in the resolution of this conflict.

Our model maintains the chromosomal crossover rate only if there is a conflict between modifier and target locus. That is, the modifier cannot be copied with its target locus during gene conversion. If modifier and target locus are within the window of gene conversion, their interest aligns, and there will be no intragenomic conflict. The alignment of interests between modifier and target results in the modifier being selected to code for resistance to DSB as the target is. There are other circumstances in which intragenomic conflict between recombinogenic and target alleles may become extinct. If there is no constraint on a modifier over its mode of action (*cis*-acting or *trans*-acting), it will be selected to evolve *cis*-acting and code for resistance when it is within the window of gene conversion around the target locus. If there is no limit to the specificity of a modifier, it will be selected to act on a single locus that corresponds to its closest target and code for resistance when it is within the window of gene conversion around that target locus.

In both cases discussed earlier, most modifiers in the genome will be outside the window of gene conversion of a particular target locus and are, thus, selected to increase the fitness of the individual by acting in *trans* and coding for susceptibility. Using the metaphor of Leigh (1971), the genome would act as a parliament, and the largest group of genes with the same interests has a greater chance to solve the conflict to its favour. Thus, a modifier acting in *trans* over multiple loci (which is always in conflict with multiple targets) has a greater chance to evolve. Hence, we would expect that gene *PRDM9* lies in a region where the presence of target loci is reduced.

Although this model is consistent with our current understanding of the molecular mechanisms underlying recombination hotspots, future findings may require the model to be modified or discarded altogether. Even

of crossover events [1 + ln (number of crossovers)] that take place in 100 generations in surviving gametes in the population. The first 10 000 generations (detail) shows how recombination hotspots evolve from a uniform distribution of crossover events arising from the random sequences used to initialize the simulation. (a.1) Selection and conversion; the system quickly evolves to its dynamic equilibrium, with rapid creation and destruction of hotspots maintaining a relatively constant chromosomal crossover rate. (a.2) Conversion but no selection; recombination hotspots are rarely observed as they are rapidly destroyed, resulting in an extremely low chromosomal crossover rate. (a.3) Selection but no conversion; recombination hotspots are easily observed as they are quickly created and seldom destroyed, which results in an extremely high chromosomal crossover rate, but little turnover of individual hotspots. (b) The horizontal axis represents the log transform of the number of crossover events that take place at a locus for the entire population over a period of 100 generations [corresponding to one pixel in (a)]. The vertical axis indicates the number of times a particular axis value is observed. These histograms represent a summary of the distribution of crossover rates across all loci for the last 200 000 generations of the simulation (after the recombination rate stabilizes around its equilibrium value). (b.1) Selection and conversion; most loci show a high crossover rate but with values not as extreme as the case of selection only. (b.2) Conversion but not selection; most loci show a very low crossover rate per generation (notice that $0 < x < 9$ corresponds to a crossover rate of < 0.0075). (b.3) Selection but not conversion; most loci show a very high recombination rate per generation ($9 < x < 10.6$ corresponds to a crossover rate between 0.0075 and 0.06).

under the present circumstances, and within the framework of intragenomic conflict, there are additional phenomena that beg both evolutionary and molecular explanations. For example, the recombinogenic PRDM9 protein appears to be responsible for only ~40% of the recombination hotspots. The mechanism(s) responsible for the remainder of the hotspots remain to be identified, and additional modelling may be required to understand the evolutionary dynamics of the genes involved.

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References

Allers, T. & Lichten, M. 2001. Differential timing and control of noncrossover and crossover recombination during meiosis. *Cell* **106**: 47–57.

Archetti, M. 2003. A selfish origin for recombination. *J. Theor. Biol.* **223**: 335–346.

Arnheim, N., Calabrese, P. & Tiemann-Boege, I. 2007. Mammalian meiotic recombination hot spots. *Annu. Rev. Genet.* **41**: 369–399.

Baudat, F., Buard, J., Grey, C., Fledel-Alon, A., Ober, C., Przeworski, M. *et al.* 2010. PRDM9 Is a major determinant of meiotic recombination hotspots in humans and mice. *Science* **327**: 836–840.

Bengtsson, B.O. & Uyenoyama, M.K. 1990. Evolution of the segregation ratio – modification of gene conversion and meiotic drive. *Theor. Popul. Biol.* **38**: 192–218.

Berg, I.L., Neumann, R., Lam, K.W.G., Sarbajna, S., Odenthal-Hesse, L., May, C.A. *et al.* 2010. PRDM9 variation strongly influences recombination hot-spot activity and meiotic instability in humans. *Nat. Genet.* **42**: 859–863.

Birmingham, E.C., Lee, S.A., McCulloch, R.D. & Baker, M.D. 2004. Testing predictions of the double-strand break repair model relating to crossing over in mammalian cells. *Genetics* **168**: 1539–1555.

Boulton, A., Myers, R.S. & Redfield, R.J. 1997. The hotspot conversion paradox and the evolution of meiotic recombination. *Proc. Natl Acad. Sci. USA* **94**: 8058–8063.

Calabrese, P. 2007. A population genetics model with recombination hotspots that are the population heterogeneous across. *Proc. Natl Acad. Sci. USA* **104**: 4748–4752.

Coop, G. & Myers, S.R. 2007. Live hot, die young: transmission distortion in recombination hotspots. *PLoS Genet.* **3**: 377–386.

Coop, G. & Przeworski, M. 2007. An evolutionary view of human recombination. *Nat. Rev. Gen.* **8**: 23–34.

Coop, G., Wen, X.Q., Ober, C., Pritchard, J.K. & Przeworski, M. 2008. High-resolution mapping of crossovers reveals extensive variation in fine-scale recombination patterns among humans. *Science* **319**: 1395–1398.

Decaestecker, E., Gaba, S., Raeymaekers, J.A.M., Stoks, R., Van Kerckhoven, L., Ebert, D. *et al.* 2007. Host–parasite 'Red Queen' dynamics archived in pond sediment. *Nature* **450**: 870–873.

Dercole, F., Ferriere, R. & Rinaldi, S. 2010. Chaotic Red Queen coevolution in three-species food chains. *Proc. R. Soc. B-Biol. Sci.* **277**: 2321–2330.

Dieckmann, U., Marrow, P. & Law, R. 1995. Evolutionary cycling in predator–prey interactions – population-dynamics and the red queen. *J. Theor. Biol.* **176**: 91–102.

Dumont, B.L. & Payseur, B.A. 2008. Evolution of the genomic rate of recombination in mammals. *Evolution* **62**: 276–294.

Ellegren, H. 2004. Microsatellites: simple sequences with complex evolution. *Nat. Rev. Gen.* **5**: 435–445.

Ferguson, K.A., Wong, E.C., Chow, V., Nigro, M. & Ma, S. 2007. Abnormal meiotic recombination in infertile men and its association with sperm aneuploidy. *Hum. Mol. Genet.* **16**: 2870–2879.

Foss, H.M., Hillers, K.J. & Stahl, F.W. 1999. The conversion gradient at HIS4 of *Saccharomyces cerevisiae*. II. A role for mismatch repair directed by biased resolution of the recombinational intermediate. *Genetics* **153**: 573–583.

Friberg, U. & Rice, W.R. 2008. Cut thy neighbor: cyclic birth and death of recombination hotspots via genetic conflict. *Genetics* **179**: 2229–2238.

Grey, C., Baudat, F. & de Massy, B. 2009. Genome-wide control of the distribution of meiotic recombination. *PLoS Biol.* **7**: 327–339.

Hassold, T., Sherman, S. & Hunt, P. 2000. Counting cross-overs: characterizing meiotic recombination in mammals. *Hum. Mol. Genet.* **9**: 2409–2419.

Irie, S., Tsujimura, A., Miyagawa, Y., Ueda, T., Matsuoka, Y., Matsui, Y. *et al.* 2009. Single-nucleotide polymorphisms of the PRDM9 (MEISETZ) gene in patients with nonobstructive azoospermia. *J. Androl.* **30**: 426–431.

Jeffreys, A.J. & Neumann, R. 2002. Reciprocal crossover asymmetry and meiotic drive in a human recombination hot spot. *Nat. Genet.* **31**: 267–271.

Jeffreys, A.J. & Neumann, R. 2005. Factors influencing recombination frequency and distribution in a human meiotic crossover hotspot. *Hum. Mol. Genet.* **14**: 2277–2287.

Jessop, L., Allers, T. & Lichten, M. 2005. Infrequent co-conversion of markers flanking a meiotic recombination initiation site in *Saccharomyces cerevisiae*. *Genetics* **169**: 1353–1367.

Kong, A., Barnard, J., Gudbjartsson, D.F., Thorleifsson, G., Jonsdottir, G., Sigurdardottir, S. *et al.* 2004. Recombination rate and reproductive success in humans. *Nat. Genet.* **36**: 1203–1206.

Koskella, B. & Lively, C.M. 2009. Evidence for negative frequency-dependent selection during experimental coevolution of a freshwater snail and a sterilizing trematode. *Evolution* **63**: 2213–2221.

Leigh, E.G. 1971. *Adaptation and Diversity*. Freeman, Cooper & Company, San Francisco.

Lichten, M. & Goldman, A.S.H. 1995. Meiotic recombination hotspots. *Annu. Rev. Genet.* **29**: 423–444.

Louis, E.J. & Borts, R.H. 2003. Meiotic recombination: too much of a good thing? *Curr. Biol.* **13**: R953–R955.

Miyamoto, T., Koh, E., Sakugawa, N., Sato, H., Hayashi, H., Namiki, M. *et al.* 2008. Two single nucleotide polymorphisms in PRDM9 (MEISETZ) gene may be a genetic risk factor for

Japanese patients with azoospermia by meiotic arrest. *J. Assist. Reprod. Genet.* **25**: 553–557.

Myers, S., Bottolo, L., Freeman, C., McVean, G. & Donnelly, P. 2005. A fine-scale map of recombination rates and hotspots across the human genome. *Science* **310**: 321–324.

Myers, S., Freeman, C., Auton, A., Donnelly, P. & McVean, G. 2008. A common sequence motif associated with recombination hot spots and genome instability in humans. *Nat. Genet.* **40**: 1124–1129.

Myers, S., Bowden, R., Tumian, A., Bontrop, R.E., Freeman, C., MacFie, T.S. *et al.* 2010. Drive against hotspot motifs in primates implicates the PRDM9 gene in meiotic recombination. *Science* **327**: 876–879.

Neumann, R. & Jeffreys, A.J. 2006. Polymorphism in the activity of human crossover hotspots independent of local DNA sequence variation. *Hum. Mol. Genet.* **15**: 1401–1411.

Oliver, P.L., Goodstadt, L., Bayes, J.J., Birtle, Z., Roach, K.C., Phadnis, N. *et al.* 2009. Accelerated evolution of the Prdm9 speciation gene across diverse metazoan taxa. *PLoS Genet.* **5**: 1–14.

Parvanov, E.D., Ng, S.H.S., Petkov, P.M. & Paigen, K. 2009. Trans-regulation of mouse meiotic recombination hotspots by Rcr1. *PLoS Biol.* **7**: 340–349.

Paterson, S., Vogwill, T., Buckling, A., Benmayor, R., Spiers, A.J., Thomson, N.R. *et al.* 2010. Antagonistic coevolution accelerates molecular evolution. *Nature* **464**: 275–278.

Peters, A.D. 2008. A combination of cis and trans control can solve the hotspot conversion paradox. *Genetics* **178**: 1579–1593.

Petes, T.D. 2001. Meiotic recombination hot spots and cold spots. *Nat. Rev. Gen.* **2**: 360–369.

Pineda-Krch, M. & Redfield, R.J. 2005. Persistence and loss of meiotic recombination hotspots. *Genetics* **169**: 2319–2333.

Ptak, S.E., Roeder, A.D., Stephens, M., Gilad, Y., Paabo, S. & Przeworski, M. 2004. Absence of the TAP2 human recombination hotspot in chimpanzees. *PLoS Biol.* **2**: 849–855.

Ptak, S.E., Hinds, D.A., Koehler, K., Nickel, B., Patil, N., Ballinger, D.G. *et al.* 2005. Fine-scale recombination patterns differ between chimpanzees and humans. *Nat. Genet.* **37**: 429–434.

Sun, H., Treco, D. & Szostak, J.W. 1991. Extensive 3′-overhanging, single-stranded-DNA associated with the meiosis-specific double-strand breaks at the Arg4 recombination initiation site. *Cell* **64**: 1155–1161.

Szostak, J.W., Orrweaver, T.L., Rothstein, R.J. & Stahl, F.W. 1983. The double-strand-break repair model for recombination. *Cell* **33**: 25–35.

Thomas, J.H., Emerson, R.O. & Shendure, J. 2009. Extraordinary molecular evolution in the PRDM9 fertility gene. *PLoS ONE* **4**: 1–7.

van Valen, L. 1973. A new evolutionary law. *Evol. Theory* **1**: 1–30.

de Villena, F.P.M. & Sapienza, C. 2001. Nonrandom segregation during meiosis: the unfairness of females. *Mamm. Genome* **12**: 331–339.

Webb, A.J., Berg, I.L. & Jeffreys, A. 2008. Sperm cross-over activity in regions of the human genome showing extreme breakdown of marker association. *Proc. Natl Acad. Sci. USA* **105**: 10471–10476.

Winckler, W., Myers, S.R., Richter, D.J., Onofrio, R.C., McDonald, G.J., Bontrop, R.E. *et al.* 2005. Comparison of fine-scale recombination rates in humans and chimpanzees. *Science* **308**: 107–111.

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