Modeling Recombination Rate as a Quantitative Trait Reveals New Insight into Selection in Humans

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Abstract

Meiotic recombination is both a fundamental biological process required for proper chromosomal segregation during meiosis and an important genomic parameter that shapes major features of the genomic landscape. However, despite the central importance of this phenotype, we lack a clear understanding of the selective pressures that shape its variation in natural populations, including humans. While there is strong evidence of fitness costs of low rates of recombination, the possible fitness costs of high rates of recombination are less defined. To determine whether a single lower fitness bound can explain the variation in recombination rates observed in human populations, we simulated the evolution of recombination rates as a sexually dimorphic quantitative trait. Under each scenario, we statistically compared the resulting trait distribution with the observed distribution of recombination rates from a published study of the Icelandic population. To capture the genetic architecture of recombination rates in humans, we modeled it as a moderately complex trait with modest heritability. For our fitness function, we implemented a hyperbolic tangent curve with several flexible parameters to capture a wide range of existing hypotheses. We found that costs of low rates of recombination alone are likely insufficient to explain the current variation in recombination rates in both males and females, supporting the existence of fitness costs of high rates of recombination in humans. With simulations using both upper and lower fitness boundaries, we describe a parameter space for the costs of high recombination rates that produces results consistent with empirical observations.

Key words: meiotic recombination, humans, quantitative trait, forward-in-time simulations, selection.

Significance

Meiotic recombination is an important cellular process required for proper chromosomal segregation and a fundamental genomic parameter that shapes major features of the genomic landscape. However, despite the central importance of this phenotype, we lack a clear understanding of the selective pressures that shape its variation in natural populations, including humans. In our manuscript, we model recombination rates as a quantitative trait under a wide range of fitness landscapes and test the resulting predictions using a large, published data set on recombination rates in humans. We make new inferences about the selection pressures that shape the variation in recombination rates in humans and produce empirically testable predictions.

Introduction

Meiotic recombination, alongside mutation, generates and maintains the diversity of life on Earth. Crossover events increase genetic diversity among offspring by creating new combinations of alleles not present in the parental genomes, thereby modulating the efficacy of selection (Muller 1964; Hill and Robertson 1966). Recombination is also vital to successful reproduction in most eukaryotes. The physical binding between sister chromatids that occurs during a crossover event provides the tension required to pull the

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correct complement of chromatids into each pole (Roeder 1997). Errors result in aneuploid gametes that typically do not produce fertile offspring (Hassold and Hunt 2001).

The recombination rate, the number of crossover events in the genome per meiosis, is not evolutionarily conserved (Stapley et al. 2017). Rapid divergence of the genome-wide recombination rate has been repeatedly documented between closely related species (Smukowski and Noor 2011; Burri et al. 2015) and subspecies (Dumont et al. 2011; Peterson and Payseur 2021). Within populations, the recombination rate can vary dramatically between sexes (Burt et al. 1991; Sardell and Kirkpatrick 2020) and between individuals (Broman et al. 1998; Kong et al. 2010). Importantly, heritable genetic differences between individuals underlie this variation, indicating that the recombination rate can evolve (Fledel-Alon et al. 2011; Johnston et al. 2016; Kawakami et al. 2019). Genome-wide association studies (GWAS) demonstrate that the recombination rate is a moderately complex quantitative trait with a modest component of additive genetic variance (Kong et al. 2008, 2014; Chowdhury et al. 2009; Dapper and Payseur 2017). In humans, at least 13 autosomal loci contribute to the variation in recombination rates (Kong et al. 2014), and narrow-sense heritability (h^2) is estimated to be 0.18 and 0.30 for males and females, respectively (Fledel-Alon et al. 2011). However, this is likely an underestimate, as GWAS is limited by statistical power to find all loci that influence a trait.

While any trait with heritable variation may evolve, selection can only act if this variation impacts fitness. Understanding how selection acts on recombination rates is notoriously tricky because the recombination rate may impact fitness both directly, due to its impact on gamete viability (Hassold and Hunt 2001), and indirectly, due to its impact on genotypic variability among offspring (Barton 1995a; Otto and Lenormand 2002). Theoretical and empirical studies have identified a suite of potential selective pressures that stem from the direct and indirect consequences of recombination rates and can favor both higher and lower rates (Feldman et al. 1980; Hassold and Hunt 2001; Otto and Lenormand 2002; Halldorsson et al. 2019). While recent studies suggest that differences in recombination rates between populations may be adaptive (Samuk et al. 2017, 2020; Dumont 2020; Neupane and Xu 2020), no conclusion has been reached on which selective pressures predominantly shape the observed variation.

Aneuploidy represents the most dramatic and direct fitness consequence of variation in recombination rates. In humans, this fitness cost manifests, in most cases, as the spontaneous abortion of aneuploid embryos (Hassold and Jacobs 1984; Hassold and Hunt 2001). The mechanistic requirement of at least one crossover per chromosome, coupled with the evolution of genome size and structure, has been proposed to explain the broad, taxonomic patterns of variation in the trait (Lynch 2006). While it is clear that recombination rates below one crossover per chromosome experience strong fitness consequences, generating a discrete lower fitness bound on the trait, the direct fitness consequences of high rates of recombination are not well defined. Recombination involves damaging DNA, then repairing the damage using its homologous chromosome as a template (Gray and Cohen 2016; Crickard and Greene 2018), which can lead to mutations (Arbeithuber et al. 2015; Halldorsson et al. 2019). High recombination rates can also pose threats to genomic integrity. Certain regions of the genome are susceptible to ectopic recombination, which can change gene dosage and generate missense mutations. Both outcomes are highly deleterious (Coop and Przeworski 2007).

Theoretical models demonstrate that the pressure to decrease or increase recombination rates may also arise from indirect selection, the pressure exerted on the recombination rate due to its impact on the evolution of other traits. Recombination generates new combinations of alleles, allowing beneficial alleles to escape an otherwise suboptimal genetic background (Muller 1964; Hill and Robertson 1966). If a population is in a rapidly changing environment, higher recombination rates may increase the efficacy of selection on other traits (Charlesworth et al. 1993; Barton 1995a, 1995b; Kondrashov and Yampolsky 1996; Otto and Barton 1997; Otto and Feldman 1997). On the other hand, recombination can also break apart beneficial allele combinations and can introduce deleterious variants into an otherwise highly fit genetic background (Barton 1995a). Under stable environmental conditions, this fitness cost of recombination results in selection against recombination, a concept known as the Reduction Principle (Feldman et al. 1980, 1996; Feldman and Liberman 1986; Otto and Lenormand 2002). The intensity and direction of selective pressures generated by these indirect effects are determined by environmental (i.e., heterogeneity in selection) and genetic features (i.e., sign and magnitude of epistasis) that are difficult to accurately measure, limiting our ability to make explicit, empirical predictions at the genome level.

Each of the selective hypotheses described above makes predictions about the fitness landscape of variation in recombination rates within populations. To test these predictions, we simulated the evolution of recombination rates as a moderately heritable, quantitative trait under a broad range of fitness landscapes. We compare the resulting distribution of trait values in our simulated populations with the distribution of recombination rates measured in a single human population (Halldorsson et al. 2019) to ask the following: 1) Is the selective pressure to ensure one crossover per chromosome sufficient to explain the observed variation in recombination rates in a human population? 2) Is there evidence of fitness costs to high rates of recombination? 3) If so, at what recombination rate do we predict to observe significant fitness costs for each sex? Our

framework also allows us to ask whether sex-specific differences in the heritability of recombination rates are sufficient to explain the degree of heterochiasmy observed in humans without assuming sex-specific fitness landscapes. We show that in our model, selective pressures to ensure one crossover per chromosome are insufficient to explain the observed variation in human recombination rates. We find that assuming additional fitness consequences of high recombination rates is necessary to simulate populations that are consistent with empirical data, providing evidence for fitness costs of high rates of recombination in humans. While we find that sex-specific differences in heritability significantly impact the predicted evolutionary trajectories, we also find support for the hypothesis that fitness costs of high rates of recombination are stronger in males. From our simulated data, we identify a discrete range at which high rates of recombination are predicted to have negative fitness consequences in each sex. In summary, our results support that while the pressure to ensure one crossover per chromosome is a component of the evolution of recombination rates, it likely exists in conjunction with the pressure that limits high rates of recombination in humans.

Results

We modeled the evolution of recombination rates as a quantitative trait using forward-in-time simulations with a modified version of the open-source software forqs (Forward-in-time Simulation of Recombination, Quantitative Traits, and Selection) (Kessner and Novembre 2014). We compared the predicted range of trait distributions generated under a range of fitness landscapes with an empirical data set quantifying recombination rate variation in humans, allowing us to distinguish between two alternative hypotheses: 1) Fitness costs are associated only with low rates of recombination, and 2) fitness costs are incurred by individuals with recombination rates that are either too high or too low. Due to the observed sexual dimorphism in recombination rates in humans, we simulated selection on male and female recombination rates completely separately. This assumption of our model differs from the known shared architecture of recombination rate variation in humans (Kong et al. 2014). However, the strength of this approach is that it allows us to use currently available tools to predict the consequences of selective landscapes on male and female recombination rates independently from one another in the absence of intralocus constraint or conflict. This approach allows us to test whether the same selective hypotheses explain the variation in recombination rates among males and females when taking sex-specific differences in heritability into account.

Modeling Selection on Recombination Rates

Fitness landscapes are functions that describe an individual's likelihood of reproducing (W) as a function of their phenotype or trait value (z). To model fitness landscapes that are consistent with existing hypotheses on the evolution of recombination rates, we added a new fitness function to forqs (Kessner and Novembre 2014) that meets three important criteria: 1) It allows the user to apply truncation selection based upon an individual's absolute trait value (rather than their trait value relative to other individuals in the population), 2) it allows the user to set the curvature (width) of a fitness bound such that slight deviations from the center of the boundary affect fitness as gradually as necessary, and 3) it allows the user to flexibly specify both upper and lower fitness boundaries separately, allowing them to be asymmetrical (fig. 1). To accommodate these requirements, we selected the double hyperbolic tangent function as our fitness function:

$$W = \frac{1}{2} * \left(\left(1 + \tanh\left(\frac{z - b_l}{a_l} \right) \right) - P_u * \left(1 + \tanh\left(\frac{z - b_u}{a_u} \right) \right) \right). \quad (1)$$

The width of the curve (a) controls how sharply fitness decreases as the trait value nears each bound (b) and can be set separately for the upper and lower bounds. The inflection point (b) of the curve determines the center of the fitness boundary ($W(b) = 0.5$), and the toggle P_u can be set to zero to remove the upper fitness boundary. If the width is near zero, slight changes in trait values near each bound have dramatic fitness consequences and large changes in trait values far from each bound have no fitness consequences. As the width parameter increases, fitness changes more gradually as trait values move away from each bound. This fitness landscape may also be applicable to other traits responding to stabilizing selection, allowing our model to be used to study the evolution of these traits (fig. 1).

Fitness Costs of Low Rates of Recombination

To determine whether the selective cost of aneuploidy is sufficient to explain the observed variation in a human population, we simulated the evolution of recombination rates in males and females under a wide range of fitness landscapes that modeled costs associated only with low rates of recombination ($b_l = 0$–1.2, $a_l = 0.1$–0.9). In every case we examined, our simulated results predicted the evolution of higher rates of recombination than observed in a human population (fig. 2). For example, when we simulated a sharp decrease in fitness when an individual's recombination rate decreased below one crossover per chromosome ($b_l = 1$, $a_l = 0.1$), our simulations predicted an average of 4.99 crossovers per chromosome ($\overline{XO/chr}_{sim}$) (equivalent to ~2.5 breakpoints per

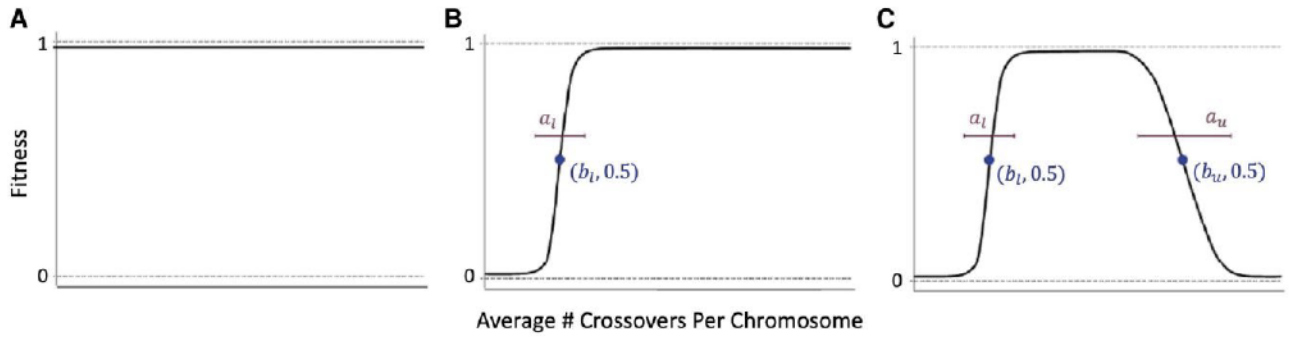

FIG. 1.—We modeled the relationship between the fitness and the recombination rate using a double hyperbolic tangent curve. (*A*) All individuals are equally fit, that is, no selection. (*B*) Individuals with recombination rates above a lower threshold (specified by the coefficients a_l and b_l) are most fit, that is, selection to increase recombination rates. (*C*) Individuals with recombination rates between an upper (b_u) and lower (b_l) threshold (or boundary) are most fit, that is, selection to maintain intermediate recombination rates. The width of the upper and lower boundaries is determined separately (a_u and a_l, respectively).

chromosome), which is 1.9 standard deviations above that observed among human females ($\overline{XO/chr}_{obs} = 3.8$, *or* ~ 1.9 breakpoints per chromosome). Note that here, and throughout this article, we are quantifying recombination rates as the number of crossover events per pair of homologous chromosomes ($\overline{XO/chr}$), not as the frequency of resulting recombined chromosomes (fig. 3). Under the same fitness landscape, our simulations predicted an average male recombination rate of 2.7 standard deviations above that observed among human males, $\overline{XO/chr}_{sim} = 3.33$ (~1.7 breakpoints per chromosome) versus $\overline{XO/chr}_{obs} = 2.38$ (~1.19 breakpoints per chromosome). Our simulations consistently predict higher rates of recombination in females than males. Interestingly, the relative increase in recombination rates was larger for males than females in this case, indicating that the fitness costs were higher for males at the starting trait distribution.

To determine the likelihood of observing a trait distribution similar to that observed among humans under each fitness landscape, we made three statistical comparisons: 1) We asked how often the mean recombination rate in our simulated populations exceeded the mean recombination rate observed in humans, 2) we measured the percentage overlap (intersection) of the simulated and empirical distributions, and 3) we found the difference in simulated means and the empirical mean in units of standard deviations. Under most of the parameter space investigated, we found that the mean of the empirical data was lower than the mean of all simulated populations (percentile = 0; fig. 2*A* and *B*). We did identify a small region of the parameter space in which more than 5% of the simulated populations had mean recombination rates equal to or less than that observed in the human data set ($b_l = 0$–0.7 [females], $b_l = 0$–0.5 [males]; fig. 2*A* and *B*). However, this parameter space models scenarios that are much more permissive of aneuploidy than current empirical evidence supports (i.e., less than a 50% reduction in fitness when a recombination event is happening only on every other chromosome).

Additionally, we do not categorize these fitness landscapes as consistent with empirical data (tables 1 and 2) because they do not meet both of our two additional conditions: 1) The empirical mean falls within one standard deviation of the mean of simulated means, and 2) at least 50% of simulated distributions have at least 90% overlap with the empirical distribution (tables 1 and 2). These statistical approaches capture additional differences between the variances in the trait distribution between the simulated and empirical data. However, it is worth noting that the variances in trait values are likely more sensitive to assumptions of our model, such as the number of loci contributing to the variation in recombination rates and the lack of recurrent mutation, than the mean trait value.

To determine whether a given selective scenario predicts the evolution of higher or lower recombination rates than we currently observe among humans, we matched the starting trait distribution to the empirical data set and incorporated observed sex differences in heritability ($V_E = 0.13$ and 0.41, male and female, respectively) (Fledel-Alon et al. 2011). To accomplish this, we fine-tuned the starting allele frequency (p) and the additive allelic contribution to the recombination rate (α) (male: $p = 0.4$ and $\alpha = 0.15$, female: $p = 0.38$ and $\alpha = 0.25$) to generate starting trait distributions with means and variances that match empirical observations. As follows, the minimum possible recombination rate is 0 $\overline{XO/chr}$ for both sexes and the maximum recombination rate was 6 $\overline{XO/chr}$ and 10 $\overline{XO/chr}$ for males and females, respectively. While sex differences in the starting allele frequency are not realistic with a shared genetic architecture, it is appropriate for our goal of determining the extent to which a given fitness landscape will exert directional selection on the observed phenotypic distribution.

Additionally, to determine whether the assumptions we made about our starting conditions may have also contributed to the outcomes of our simulations, we repeated our analyses with low starting allele frequencies ($p = 0.05$ at all loci) and intermediate allele frequencies ($p = 0.5$ at all loci).

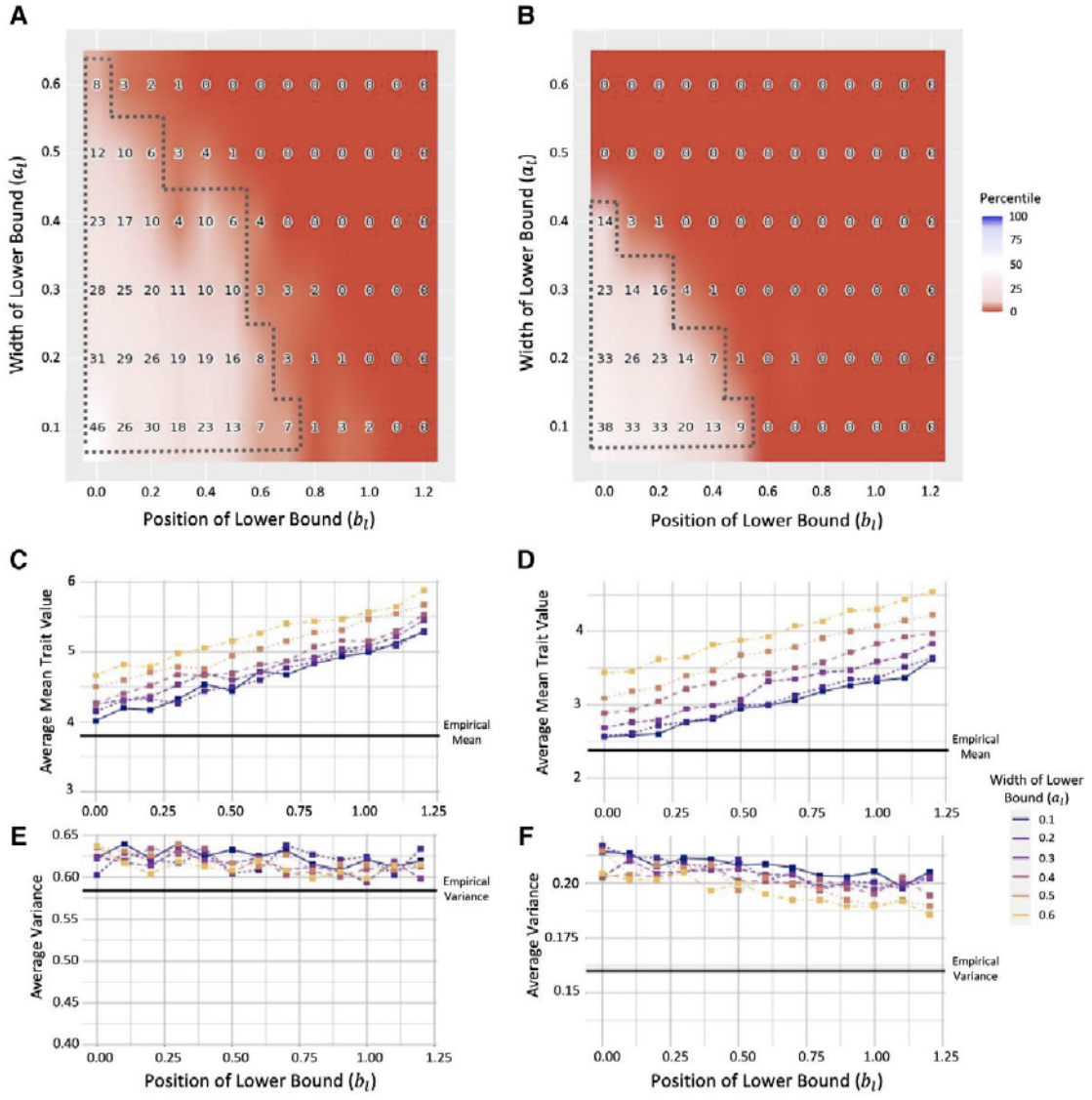

FIG. 2.—Simulations that modeled only fitness costs to low rates of recombination poorly match the distribution of recombination rates in a human population. (*A*, *B*) Heatmaps show the number of simulated means (out of 100) that are less than or equal to the empirical sex-specific mean or the percentile of the empirical mean in the distribution of simulated means for females and males, respectively. The dashed box indicates the parameter space where at least 5% of simulations predicted mean trait values equal to or less than the empirical mean. (*C*, *D*) The mean of simulated means under each fitness landscape (parameterized by the position b_l and width a_l of the lower bound) for females and males, respectively. (*E*, *F*) The mean of simulated variances under each fitness landscape (parameterized by the position b_l and width a_l of the lower bound) for females and males, respectively. The horizontal lines in (*C*)–(*F*) are the sex-specific empirical values.

Importantly, this second case represents the maximum starting additive genetic variance and the greatest opportunity to observe an evolutionary response to selection. We found that our simulations predicted higher rates of recombination (farther away from the empirical mean) when simulations started with higher additive genetic variance for recombination rates in both males and females (supplementary fig. S3, Supplementary Material online). As we were careful to run our simulations long enough to capture the entire response to selection, these results suggest that additive genetic variance is a limiting factor in the evolutionary response. Importantly, while this is a constraint of our approach, it strengthens, rather than weakens, our inference that recombination rates in human populations are lower than expected due to the costs of aneuploidy. An influx of genetic variation through mutational processes would only result in the evolution of even higher average recombination rates in our simulated populations.

To determine how sensitive our results are to estimates of the heritability of recombination rates, which may not

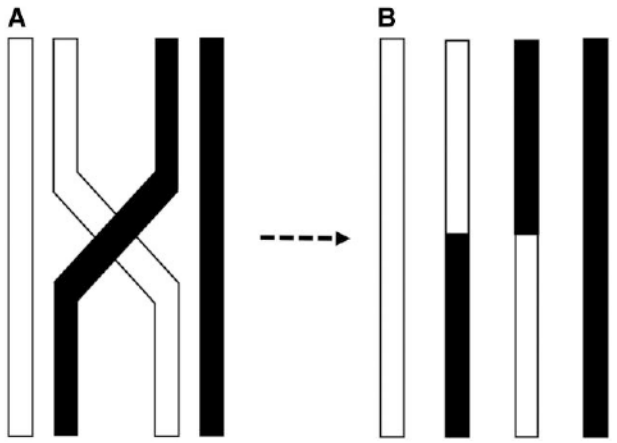

FIG. 3.—Schematic representation of a single crossover event. (*A*) A recombination event with exactly one crossover per pair of homologous chromosomes (1 XO/chr). The black and white chromosomes denote maternal and paternal inheritance. During recombination, one copy of each parental chromosome crosses over with the other parental chromosome, resulting in a hybrid (recombinant) chromosome. (*B*) Output of one crossover per pair of chromosomes: equal ratios of recombined and nonrecombined gametes (each rectangle is one gamete) ($r = 0.5$).

Table 1
Upper Fitness Boundaries Predicted to Produce Populations with Distributions of Recombination Rates Consistent with Empirical Observations in Females

Starting Allele Frequency (p)	Environmental Variance (V_E)	Position of the Upper Bound (b_u)	Width of the Upper Bound (a_u)
0.38	0.41	6.5	0.1–0.3
		7.0	0.3–0.5
		7.5	0.6–0.8
		8.0	0.7–0.9
0.38	0.3	None	None
0.38	0.5	6.5	0.1–0.2
		7.0	0.3–0.6
		7.5	0.6
0.05	0.41	6.5	0.1–0.2
		7.0	0.3–0.5
		7.5	0.5–0.6
0.5	0.41	6.5	0.1–0.2
		7.0	0.3–0.6
		7.5	0.6

be precise or consistent across all populations, we repeated our analyses after modifying only the contribution of environmental variances (V_E) to differences in recombination rates between individuals. In females, increasing heritability (by lowering the component of environmental variance) lowered the expected average recombination rate in our simulations (supplementary fig. S11, Supplementary Material online). Conversely, decreasing heritability (by increasing the component of environmental variance)

Table 2
Upper Fitness Boundaries Predicted to Produce Populations with Distributions of Recombination Rates Consistent with Empirical Observations in Males

Starting Allele Frequency (p)	Environmental Variance (V_E)	Position of the Upper Bound (b_u)	Width of the Upper Bound (a_u)
0.4	0.13	4.0	0.2–0.3
		4.5	0.5
		5.0	0.7
		5.5	0.8–0.9
0.4	0.2	4.0	0.4
0.4	0.3	None	None
0.05	0.13	4.0	0.2–0.3
		4.5	0.5
0.5	0.13	4.0	0.2–0.3
		4.5	0.5

increased the expected average recombination rate in our simulations, pushing it away from the empirical mean (supplementary fig. S13, Supplementary Material online). For example, using the same values as above ($b_I = 1$, $a_I = 0.1$), when $V_E = 0.3$, our simulations predicted a mean recombination rate of ~4.76 $\overline{\text{XO/chr}}$ (~2.38 breakpoints per chromosome) among females, and when $V_E = 0.5$, our simulations predicted a mean recombination rate of ~5.14 $\overline{\text{XO/chr}}$ (~2.57 breakpoints per chromosome) among females. We observed the same relationship between environmental variances and predicted recombination rates in males (supplementary figs. S15 and S17, Supplementary Material online). Thus, differences in heritability likely contribute to sex differences in predicted recombination rates we observed in our simulations and could drive heterochiasmy in natural populations.

However, it is also important to note that modifying the heritability of the trait changed not only the predicted mean but also the predicted within-population variance. In cases where we considered a smaller component of environmental variance (supplementary fig. S11, Supplementary Material online), the predicted trait variance was much lower than that observed in a human population. Likewise, in cases where we increased V_E (supplementary figs. S12, S15, and S17, Supplementary Material online), the predicted variation in recombination rates within populations far exceeded the empirical observation.

Fitness Costs of High Rates of Recombination

To determine whether additional costs of high rates of recombination could explain the distribution of recombination rates observed in humans, we simulated the evolution of recombination rates with fitness landscapes that simultaneously modeled fitness costs of both high and low rates of recombination. For these simulations, we

kept the fitness costs of low rates of recombination constant ($b_l = 1$, $a_l = 0.1$), consistent with the costs of aneuploidy, and considered a wide range of fitness costs associated with high rates of recombination (male: $b_u = 3.5–5.5$ $\overline{XO/chr}$, female: $b_u = 6–8$ $\overline{XO/chr}$, $a_u = 0.1–0.9$).

When applying selective pressures on both high and low recombination rates, our simulation produced results consistent with empirical data for both females and males under a narrow range of the parameter space (tables 1 and 2). This parameter space is shaped by the interaction between the position (b_u) and the width (a_u) of the upper fitness bound. For example, when the upper bound centered around lower recombination rates, narrow bound widths result in distributions matching the empirical data ($b_u = 6.5$, $a_u = 0.1$; females). As the bound position increases such that higher rates of recombination are associated with lower fitness costs, the width of the bound must also increase to maintain similarity to the empirical distribution ($b_u = 8.0$, $a_u = 0.8$; females) (fig. 4*A* and *B*). When the costs of elevated recombination rates are more severe (lower and/or wider upper bound), the mean of simulated results falls below the empirical mean, predicting lower rates of recombination than observed empirically. Conversely, when the fitness costs of elevated recombination rates are less severe (higher and/or narrower upper bound), the mean of simulated results falls above the empirical mean, predicting higher rates of recombination than observed empirically.

Our simulations predict that the costs of high rates of recombination are less severe in females than males. For example, when we modeled a female fitness landscape with a moderate drop-off in fitness ($a_u = 0.5$) centered around an average of seven crossovers per chromosome (~4.5 breakpoints per chromosome), our simulated results were largely consistent with empirical observations (70% of simulations overlapping 90% or more with the empirical data [intersection ≥ 90% empirical distribution], supplementary fig. S2*A*, Supplementary Material online; and the empirical mean was only 0.4 standard deviations away from the mean of simulated means, supplementary fig. S2*C*, Supplementary Material online). However, when modeling the evolution of male recombination rates under the same fitness landscape, our simulations predict much higher rates of recombination among males than observed among humans. In contrast, considering a moderately gradual drop-off in fitness ($a_u = 0.5$) centered around an average of 4.5 crossovers per chromosome (~2.25 breakpoints per chromosome) produces results that are highly consistent with our observations in males but predicts much lower female recombination rates than observed. Thus, again, differences in heritability were not sufficient to explain the observed degree of heterochiasmy in humans, supporting sex differences in selective pressures on recombination rates.

To determine how sensitive our results are to estimates of the heritability of recombination rates, we repeated our analyses, exploring a range of environmental variances (V_E). Modifying heritability did not shift the parameter space of the fitness landscape under which our simulated means matched empirical observations, but the variance shifted in the direction of the change (i.e., higher heritability led to lower variance and vice versa) (supplementary figs. S11–S18, Supplementary Material online). However, we did observe that the parameter space expanded slightly when the environmental variance decreased and, conversely, slightly narrowed when the environmental variance increased. In other words, if the recombination rate is more heritable than we previously estimated, a slightly wider range of selective pressures may explain the distribution of recombination rates in humans.

To determine whether the starting allele frequency shaped the outcome of our simulations, we repeated our analyses under two different scenarios (starting allele frequencies $p = 0.05$ and $p = 0.5$). When we simulated populations responding to both costs of high and low rates of recombination, we found little to no change in the predicted mean and variance for both females and males (tables 1 and 2). These results suggest that the starting allele frequency did not significantly impact the outcome of these simulations.

Discussion

These results constitute a novel use of forward-in-time simulations to assess the possible selective pressures acting on the evolution of recombination rates as a quantitative trait in humans. Our simulations show that under the assumptions of our model, the empirical distribution of recombination rates in the Icelandic population is lower than we would expect, given the direct fitness costs of aneuploidy alone. None of the simulations that modeled only costs to low rates of recombination (lower bound) produced a parameter space consistent with empirical observations of recombination rates in humans, in either males or females, and all predicted the evolution of substantially higher rates of recombination than observed empirically (tables 1 and 2, fig. 1).

There are three potential explanations for this observation. First, it is possible that the fitness costs of aneuploidy are overestimated, especially in males. While the impact of improper chromosomal segregation and reduced fertility in humans is well documented (Hassold and Hunt 2001; Sun et al. 2008; Gruhn et al. 2019; Hassold et al. 2021), mechanisms of crossover assurance may buffer fitness costs of low rates of recombination (Deshong et al. 2014; Krishnaprasad et al. 2015). Studies in mice provide evidence that crossover assurance checkpoints are likely much more stringent in males than females (Nagaoka

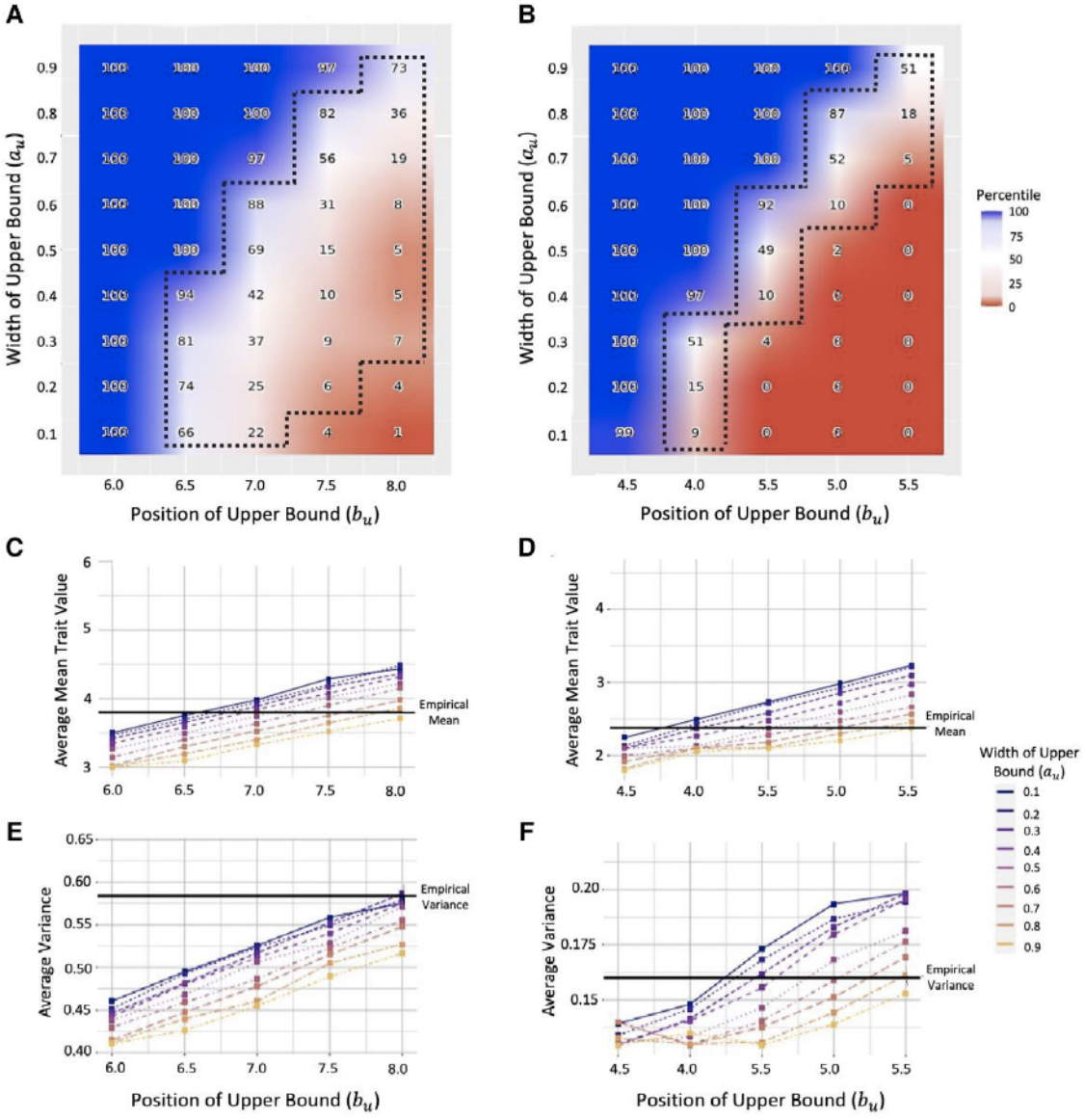

FIG. 4.—Simulations that modeled fitness costs to low and high rates to sufficiently match the distribution of recombination rates in a human population under certain parameters. (*A*, *B*) Heatmaps show the number of simulated means (out of 100) that are less than the empirical sex-specific mean or the percentile of the empirical mean in the distribution of simulated means for females and males, respectively. The red region is the parameter space that predicted mean recombination rates higher than observed empirically, the white region produced mean recombination rates consistent with empirical data, and the blue region predicted lower rates of recombination than observed among human females and males, respectively. The dashed box indicates the parameter space in which 5–95% of the simulation results predicted mean recombination rates lower than observed empirically. (*C*, *D*) The mean of simulated means under each fitness landscape (parameterized by the position b_u and width a_u of the upper bound) for females and males, respectively. (*E*, *F*) The mean of simulated variances under each fitness landscape (parameterized by the position b_u and width a_u of the upper bound) for females and males, respectively. The horizontal lines in (*C*)–(*F*) are the sex-specific empirical values. In all simulations represented in this figure, the lower fitness boundary was held constant ($b_l = 1$ $\overline{XO/chr}$, $a_l = 0.1$).

et al. 2012; Cloutier et al. 2016). However, two lines of evidence suggest that crossover assurance checkpoints are unlikely to buffer the fitness effects of low rates enough to explain the discrepancy between the observed distribution of recombination rates in humans and the predictions of our model. First, a recent study of human fetal ovaries ($n = 160$) observed a surprisingly high level of recombination failure (7.3% of a total of 7,396 scored oocytes) that was correlated with the genome-wide recombination rate (Hassold et al. 2021). Second, our simulations suggest that the fitness costs associated with recombination failure must be very, very small (i.e., less than a 50% reduction in

fitness when a recombination event is happening only on every other chromosome, $b_1 = 0.5$) to produce populations with mean recombination rates similar to that we observe in humans. Taken together, it seems unlikely that crossover assurance mechanisms are effective enough in humans to minimize the fitness costs to the necessary degree.

An alternative possibility is that the human population is currently experiencing selection for higher rates of recombination and has not yet reached its fitness peak. Given the strong evidence that genetic variation for recombination rates is currently segregating in human populations (Kong et al. 2008, 2014; Chowdhury et al. 2009; Dapper and Payseur 2017), this explanation predicts a slow but consistent increase in average recombination rates from generation to generation. Additionally, given the intensity of the selective pressure, we should also expect to observe genetic signatures of strong, persistent directional selection on genes that modify recombination rates. It is worth noting that our simulations predict the relatively rapid evolution of recombination rates (on the order of a couple hundred thousand years), suggesting that there has been sufficient time for human recombination rates to evolve in response to the selective pressure exerted by aneuploidy.

A third possibility is that our results provide evidence that selective costs of high rates of recombination exist in human populations. By including an upper fitness boundary in our simulations, we identified fitness landscapes that produced distributions of recombination rates very similar to those observed in the Icelandic population, providing further support for the existence of fitness costs of high recombination rates. Our approach here does not allow us to identify the source of these costs. These selective pressures may be due to direct consequences of meiotic recombination, such as elevated rates of chromosomal nondisjunction, or indirect consequences, such as breaking apart beneficial alleles (Feldman et al. 1980). Alternatively, the selective cost could result from pleiotropic effects on other cellular processes rather than as a consequence of the high crossover number itself.

Our results provide explicit, and testable, predictions of the recombination rates above which significant fitness costs may be incurred in humans. For example, our simulations predict that fitness costs are incurred in human females when the recombination rate exceeds an average of 6.5–8.0 crossovers per pair of homologous chromosomes (~3.25–4 breakpoints per chromosome per meiosis) and an average of 4.0–5.5 (~2.0–2.75 breakpoints per chromosome per meiosis) in males (tables 1 and 2). We identified this parameter space by comparing our simulated trait distributions with the observed trait distribution (Halldorsson et al. 2019) in terms of the mean, variance, and degree of overlap (intersecting area of the two curves). It is important to note that the overall shape of the distribution, as captured by the variance and overlap, is likely sensitive to some of our modeling assumptions. In particular, the number of loci modeled (20), their additive contribution, and the lack of recurrent mutation can impact genetic variance and thus the total phenotypic variance in a population.

Heritability had a large impact on the predictions of our simulations. Increasing the environmental variance slightly (compared with empirical estimates) (Fledel-Alon et al. 2011), thus decreasing heritability, narrowed the range of fitness landscapes that produced mean trait values similar to the empirical distribution of recombination rates in both the male and female data sets (supplementary figs. S14 and S16, Supplementary Material online) and elevated the predicted trait variance in simulated populations. This result was likely observed because decreasing heritability increased the likelihood that random perturbations could push individuals with acceptable "genetic" recombination rates outside of the optimal range. Interestingly, when considering both the mean and the variance, simulations with components of environmental variance similar to those estimates for humans—or slightly higher—produced predicted distributions most similar to empirical observations. Thus, our results provide support to the estimates of the environmental variance of recombination rates in humans (Fledel-Alon et al. 2011).

Consistent with the direction of heterochiasmy in humans, our simulations predict that the costs of high rates of recombination are more severe in males than females. Future work should explore whether this result holds outside humans and may help explain the variation in the direction and degree of heterochiasmy with and between species (Burt et al. 1991; Brandvain and Coop 2012; Cooney et al. 2021; Peterson and Payseur 2021). Additionally, this result should be interpreted carefully in light of two important assumptions of our model. First, we assumed that the fitness costs of low rates of recombination are incurred equally in males and females. However, more stringent crossover assurance checkpoints in male meiosis may lessen the impact of errors in recombination rates compared with females, leading us to overestimate the fitness costs of high rates of recombination in males. Interestingly, the existence of more robust crossover assurance mechanisms in males may, itself, be evidence of more severe costs of high rates of recombination in males. Future models should aim to determine whether this cost is likely to arise from mechanistic differences in male and female meiosis (Petkov et al. 2007; Brick et al. 2018) or sex-specific differences in indirect selection on recombination rates (Lenormand 2003; Lenormand and Dutheil 2005; Sardell and Kirkpatrick 2020).

Second, in our model, we simulated the evolution of male and female recombination rates separately. While this approach was practical and had several advantages, it assumes that the genetic control of recombination rates is

not shared between sexes. However, while some variants identified in humans and other mammals are sex-specific (Ma et al. 2015), we know that a significant proportion of the genetic architecture of recombination is shared between sexes. Thus, selection pressures on one sex may limit or constrain the evolution of the trait in response to selection pressures that differ in magnitude or direction in the other sex (i.e., intralocus sexual conflict). When considering only costs to low rates of recombination, predicted recombination rates were significantly higher than empirical measurements in both sexes. Thus, under this scenario, both sexes are predicted to be experiencing strong selection for higher rates of recombination, limiting the opportunity for conflict between sexes. Therefore, we do not expect bias due to genetic architecture to change our conclusion that fitness costs of low rates of recombination alone do not explain the distribution of this trait in human populations. When considering fitness costs to both high and low recombination rates, conflict over a shared genetic architecture could result in higher than optimal recombination rates in males or lower than optimal recombination rates in females. Thus, by modeling the trait separately, we may be overestimating the sensitivity of females to fitness costs of high rates of recombination or underestimating the sensitivity of males. In other words, the sexual dimorphism in the fitness landscape of recombination may be more extreme than what our model predicts.

To simplify our model and make our results more tractable, we assumed a simple genomic architecture with 20 identical chromosomes, each with a genetic locus that contributes to the average recombination rate per pair of homologous chromosomes. This approach did not explicitly capture the variation in chromosome size that is present in the human genome nor the variance in the crossover number per chromosomal pair. For example, the largest chromosomes in the human genome often have 5–6 crossovers, while the smallest chromosomes typically have only 1–2 and are at highest risk of lacking a crossover altogether at low recombination rates (Hassold et al. 2021). Thus, it is very likely that the effective rate of recombination on these smallest chromosomes most strongly drives the cost of low rates of recombination due to the risk of aneuploidy. As a result, a genome-wide average of one crossover per chromosome may not be sufficient to ensure that at least one crossover occurs on every chromosome. In this case, we may be overestimating the tolerance for low rates of recombination in our simulations and, as follows, underestimating the predicted constraints on high recombination rates.

We also did not explicitly model sex chromosomes in our simulations. However, given that most loci influencing recombination rates are on autosomes (Kong et al. 2008, 2014; Chowdhury et al. 2009; Dapper and Payseur 2017), the absence of sex chromosomes should not significantly bias our results. By excluding sex chromosomes, we did not explicitly model pseudoautosomal regions (PAR). PAR1 and PAR2 are short segments of homology that allow crossovers and proper disjunction of the differentiated X and Y sex chromosomes in human males (Rouyer et al. 1986; Freije et al. 1992; Flaquer et al. 2009). Both regions have recombination rates that are significantly higher than the genome-wide average (i.e., the male crossover rate in PAR1 is elevated 17-fold) (Hinch et al. 2014). This localized elevation is likely necessary to ensure that at least one crossover occurs per meiosis and is not inconsistent with the general conclusions of our simulations, which focus on the potential fitness costs of chromosome-wide increases in the number of crossovers.

To make inferences about how selection may be acting on recombination rates in human populations, we compared our simulations with empirical measurements of recombination rates in a human population (Halldorsson et al. 2019), calculated by genotyping parent–offspring pairs. Thus, the recombination rate was inferred only from viable offspring, potentially biasing estimates by excluding aneuploid gametes. For example, no individual was recorded with a recombination rate of less than one crossover per chromosome for either sex. Both the female and male data sets are normally distributed with means closer to the lower bound than their predicted upper bounds; therefore, it is more likely that the population estimates of recombination rates are overestimates than underestimates. Additionally, because the tails of the distributions are more likely to be affected by this imprecision than the center, the variation in both male and female recombination rates may also be underestimated. This potential source of bias does not impact our inference that recombination rates in humans are lower than expected due to the fitness costs of low rates of recombination alone. However, it does have the potential to shift our estimates of the fitness costs of high rates of recombination.

We applied a novel quantitative modeling approach to test predictions about the selective landscape shaping variation in recombination rates in humans. The results we present are consistent with the hypothesis that the recombination rate evolves in response to selective pressures to both increase above a minimum threshold and decrease below another maximum threshold. We present evidence suggesting that it is unlikely that the distribution of recombination rates observed in humans arose only from the selective pressure to increase recombination rates above one crossover per chromosome. We further provide a parameter space of upper bounds on recombination rates at which fitness costs are likely to be incurred (tables 1 and 2). Our general conclusions are robust to the variation in both the heritability of recombination rates and the allele frequency of the contributing alleles, parameters that are difficult to estimate in human populations. Future

applications of this approach are likely to lead to new insight by incorporating more complex genomic features thought to be important in the evolution of recombination rates, such as epistasis and intralocus sexual conflict. Future studies should also aim to refine the thresholds at which high and low recombination rates decrease fitness costs in humans. While our model assumes that recombination rates of less than one crossover per chromosome lead to fitness costs, an average of one may still be deleterious as many gametes (half under a normal distribution) would lead to inviable offspring. Further, while we suggest a range of upper fitness boundaries on recombination rates, more investigation is needed to better understand exactly where this boundary exists in humans and its mechanistic foundations.

Materials and Methods

Simulations

For each simulation, we specified the shape of the fitness landscape and modeled the evolution of recombination rates, tracking changes in the distribution of trait values in the population over time. We performed 100 replicates for each parameter set and ran each simulation for 10,000 generations. To allow for more accurate comparisons with the empirical data set, we matched the effective population size as 5,000 for all simulations, consistent with the estimated effective population size of Iceland (Bataillon et al. 2006). To capture the moderate complexity of the genetic architecture of recombination rates in humans, we modeled 20 additive recombination rate loci. Each locus was mapped to a distinct chromosome to simplify our analysis by preventing the accumulation of linkage disequilibrium between sites. At each locus, we modeled two alleles, one that does not contribute to the recombination rate ($z + 0$) and another that increases the recombination rate additively ($z + \alpha$). In the simulation, each individual's trait value (recombination rate) was determined by the additive contribution of alleles at each locus along with environmental variance (described below). The contribution of this allele to an individual's trait value (α) was assumed to be equal for each locus.

Due to the significant levels of heterochiasmy and sex differences in the underlying genetic architecture in humans (Kong et al. 2004; Fledel-Alon et al. 2011), we modeled the evolution of recombination rates separately for males and females. For each sex, we matched the heritability and environmental variance of recombination rates to empirical estimates in humans (males: $H^2 = 0.18$; females: $H^2 = 0.3$) (Fledel-Alon et al. 2011). Broad-sense heritability of mean recombination rates was estimated in human females from sibpairs ($H^2 = 0.3$, Kong et al. 2004). We conservatively approximated a comparable measure of broad-sense heritability of male mean recombination from the available estimate of narrow-sense heritability ($H^2 = 0.14$, Fledel-Alon et al. 2011). We converted estimates of broad-sense heritability to environmental variance, $V_E = V_P\ (1 - H^2)$, to parameterize our simulations (males: $V_E = 0.13$, females: $V_E = 0.41$). The component of environmental variance in males is lower than that of females, despite lower heritability, due to lower overall phenotypic variance.

To determine whether a given selective scenario predicts the evolution of higher or lower recombination rates than we currently observe among humans, we matched the starting trait distribution to the empirical data set. To accomplish this, we modified the starting allele frequency (p) and the additive allelic contribution to the recombination rate (α) (male: $p = 0.4$ and $\alpha = 0.15$, female: $p = 0.38$ and $\alpha = 0.25$).

To determine whether fitness costs associated with high recombination rates are necessary to explain the variation in recombination rates seen in humans today, we considered two broad categories of selective landscapes: 1) those with fitness costs associated only with low rates of recombination (lower bound; $P_u = 0$) and 2) those with fitness costs associated with both high and low rates of recombination (double bound). For the lower bound simulations, we varied the position ($b_l = 0$–$1.2\ \overline{XO/chr}$, by intervals of 0.1) and width ($a_l = 0.1$–0.6, by intervals of 0.1) of the lower fitness boundary (78 total parameter combinations and 7,800 total simulations per sex). For the double bound simulations, the lower boundary was held constant ($b_l = 1\ \overline{XO/chr}$, $a_l = 0.1$), and we varied the position (male: $b_u = 3.5$–$5.5\ \overline{XO/chr}$, female: $b_u = 6$–$8\ \overline{XO/chr}$; in intervals of 0.5) and width ($a_u = 0.1$–0.9; in intervals of 0.1) of the upper boundary (45 total parameter combinations and 4,500 total simulations per sex). Due to computational costs, we focused only on relevant upper bound positions (those producing trait distributions in the vicinity of that observed in humans). As a result, we explored different parameter spaces for each sex.

As a control comparison, we also simulated the evolution of recombination rates without selection (fig. 1*A*), capturing the effects of genetic drift alone. These sets of simulations were considered a null case for the purpose of assessing the presence of directional selection. When variation between generations of a simulation was less than or equal to the variation in this null case, the simulation was considered to no longer be responding to directional selection. When modeling the female population with only fitness costs to low rates of recombination, the population reached this point by 10,000 generations. We used this 10,000-generation maximum as the number of generations for simulations to run to avoid excessive computational costs.

Empirical Data Set

To test the predictions generated in our simulations under various selective scenarios, we compared each simulated trait distribution with that observed in a human population. Halldorsson et al. (2019) measured the variation in recombination rates in the Icelandic population of humans through the sequencing of 126,407 parent–child pairs using SNP-chip genotyping, capturing 70,086 and 56,321 maternal and paternal meiosis, respectively. Crossover positions were given by Halldorsson et al. (2019) for each chromosome of each child and the origin of the crossover (maternal or paternal). From here, we counted the number of crossovers associated with each chromosome for each mother and father, excluding the X chromosome (Y was not measured/reported). When a crossover occurs, only half of the resulting gametes inherit the recombined chromosomes (fig. 3). To account for this, we multiplied these rates by two to produce a distribution of the number of recombination events for females and males. As expected, we found that the mean number of crossovers per chromosome in the male and female data sets (2.38 and 3.80, respectively) was significantly different ($P < 2.2e{-}16$) using a two-sample *t*-test.

Statistics

To test our hypotheses, we used a statistical framework to determine whether the empirical distribution of recombination rates in humans is consistent with the population-level trait distributions predicted in our simulations. For each simulation, we recorded the mean, variance, skewness, and kurtosis of the final distribution of recombination rates ($n = 5{,}000$). To determine the similarity between the predicted and observed population-level trait distributions, we calculated the percent overlap of the simulated and empirical distributions. To do so, we compared a normal curve with the mean and variance matching the simulated data with a normal curve with the mean and variance corresponding to the empirical data. We calculated the area of overlap between these curves by integration using R (R Core Team 2020) with the assumption that the area under a normal curve is always one. The assumption of normality was assessed using the skewness and kurtosis of each trial because the sample sizes were too large for an informative assessment using the Shapiro test. The skewness of every trial was between −1 and 1, while the excess kurtosis was between −2 and 2 in most trials (96%). High kurtosis should not significantly impact the use of overlap between distributions because kurtosis is heavily influenced by outliers, which produce almost no area under the density curve. Further, errors due to the assumption of normality would bias results toward less overlap, indicating a more stringent test of similarity.

For each set of parameters, we calculated the mean and variance for each replicate simulation ($n = 100$). To determine how likely a given set of parameters produced a predicted population with a similar rate of recombination to that observed in humans, we asked what percentage of simulations produced a mean trait value greater than or equal to the empirical mean (percentile). We also determined how many standard deviations the empirical mean was from the mean of simulated means. These are useful statistics because they allow us to quantify similarity using a single value, capturing both the mean and the variance. We considered, for a given parameter set, the empirical data to be consistent with the predictions if 1) the empirical mean is less than one standard deviation away from the mean of simulated means and 2) at least 50% of the simulations predict trait distributions that overlap at least 90% with the empirical distribution of recombination rates.

Heritability

Our estimates of the environmental variance associated with recombination rates in humans are based on a pedigree analysis. The data set used to generate these estimates was reasonably large, but because each nuclear family size is very small, the estimates may be imprecise (Fledel-Alon et al. 2011). We modeled the evolution of recombination rates under a range of environmental variances to account for possible inaccuracies in the estimates used. We performed the same simulations with different environmental variances ($V_E = 0.2$ and 0.3 for males and $V_E = 0.3$, 0.5, 0.8, and 1.0 for females) to determine how errors in current estimates of environmental variance might impact the direction and magnitude of the response to selective pressures. These modifications also allow us to test the robustness of our model and determine how heritability impacts our results.

Starting Allele Frequencies

Our simulations considered the starting allele frequencies of 0.4 and 0.38 for males and females, respectively. These values were selected because they produce a starting population-level trait distribution that most closely matched the empirical data. To assess the robustness of our model to changes in starting allele frequencies, we considered two additional cases for each sex: 1) low starting frequency of high recombination alleles (0.05) such that the recombination rate starts out lower than empirical estimates and 2) intermediate allele frequency of high recombination alleles (0.5) such that the recombination rate starts out higher than empirical estimates while holding all other parameters constant. These additional analyses also allowed us to determine whether the total additive genetic variance for recombination rates in the simulated populations influenced the outcomes of the simulations.

Supplementary Material

Supplementary data are available at *Genome Biology and Evolution* online (http://www.gbe.oxfordjournals.org/).

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Data Availability

The modified version of forqs (https://bitbucket.org/dkessner/forqs/src/master/) used in this work is available at https://github.com/drurya96/forqs_mod.

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