Local adaptation and the evolution of inversions on sex chromosomes and autosomes

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Spatially varying selection with gene flow can favour the evolution of inversions that bind locally adapted alleles together, facilitate local adaptation and ultimately drive genomic divergence between species. Several studies have shown that the rates of spread and establishment of new inversions capturing locally adaptive alleles depend on a suite of evolutionary factors, including the strength of selection for local adaptation, rates of gene flow and recombination, and the deleterious mutation load carried by inversions. Because the balance of these factors is expected to differ between X (or Z) chromosomes and autosomes, opportunities for inversion evolution are likely to systematically differ between these genomic regions, though such scenarios have not been formally modelled. Here, we consider the evolutionary dynamics of X-linked and autosomal inversions in populations evolving at a balance between migration and local selection. We identify three factors that lead to asymmetric rates of X-linked and autosome inversion establishment: (1) sex-biased migration, (2) dominance of locally adapted alleles and (3) chromosome-specific deleterious mutation loads. This theory predicts an elevated rate of fixation, and depressed opportunities for polymorphism, for X-linked inversions. Our survey of data on the genomic distribution of polymorphic and fixed inversions supports both theoretical predictions.

This article is part of the theme issue ‘Linking local adaptation with the evolution of sex differences’.

1. Introduction

Widely distributed species are often fragmented into subpopulations, each of which must cope with a unique set of abiotic stresses [1] and biotic challenges imposed by local competitor species, natural enemies, and conspecific competitors for resources and mates [2,3]. The unique conditions faced by each population generate selection for local adaptation, which favours genetic and phenotypic diversification among populations of the species, and potentially sets the stage for speciation [4–6].

Gene flow is central to the process of adaptation in fragmented populations, and has several well-known beneficial consequences: it bolsters population genetic diversity, alleviates harmful effects of genetic drift and inbreeding depression, and increases the evolutionary capacity of populations within the species’ range [7–9]. On the other hand, gene flow also inhibits genetic divergence between populations, and thereby constrains their potential to locally adapt. The establishment and maintenance of local adaptations depends on the balance between gene flow and local selection [4,10]. Even under the best circumstances, sustained migration results in perpetual maladaptation in populations receiving...
Box 1. Processes of inversion evolution.

Comparative genomic studies show that closely related species exhibit extensive differences in gene order, and these differences arise through the spread of inversions (e.g. [26,27]). Although the specific processes accounting for inversion fixation are not well known, four general processes potentially contribute. These include: (1) genetic drift; (2) positive selection on beneficial inversions; (3) linked positive selection on inversions that carry beneficial genetic variation; and (4) segregation distortion in favour of inversions over wild-type chromosomes. We provide a brief overview of these scenarios below. Readers seeking a broader review of theory and empirical examples should consult the references [23,28,29].

**Genetic drift of (nearly) neutral and under-dominant inversions.** Neutral and slightly deleterious inversions may fix solely by genetic drift [29]. Under-dominant inversions—in which inversion heterozygotes have reduced fitness relative to homozygotes of inversion and wild-type chromosomes—become fixed by a combination of genetic drift and positive selection; drift can allow an initially rare inversion to reach a high enough frequency in the population for positive selection to subsequently drive it to fixation [30,31].

**Positive selection of beneficial inversions.** An inversion may directly improve fitness of its carriers by favourably altering the expression of genes within the inversion, or of genes that flank inversion break points [23,29]. Standard evolutionary models for adaptive substitution can be applied in such cases, including evolutionary models contrasting X-linked and autosomal divergence [22,30].

**Indirect positive selection due to linkage.** Selection can favour inversions that become associated with beneficial genetic variation, though the inversion is not beneficial per se. Inversions may spread within the population if they carry alleles within them that are individually beneficial [23], or epistatically beneficial in combination [32]. Inversions may also spread when they are free of deleterious alleles that are maintained within the population by recurrent mutation [33], or by maladaptive gene flow from other regions of the species’ range [23]. Our models focus on the latter two scenarios, which are illustrated in figure 1.

**Meiotic drive.** Inversions can spread within the population if they become associated with meiotic drive, i.e. in heterozygotes for inversion and wild-type chromosomes, the preferential meiotic segregation of inversions into gametes. Whether a driving inversion eventually becomes fixed will also depend on whether it is saddled with deleterious fitness consequences in individuals homozygous for the inversion (as in the Segregation Distorter or SD system in *Drosophila* [34]), or the inversion causes sex-ratio distortion [35]. In both cases, selection against the inversion will intensify as it increases in frequency in the population, limiting its likelihood of fixation.

A range of evolutionary scenarios can potentially trigger the evolutionary spread and fixation of new inversions (box 1). Most models—including current theories of inversion evolution during local adaptation—focus on autosomal inheritance, where the dynamics of inversions and of local adaptation depend on the average intensity of selection and migration in females and males of the species. By contrast, the evolutionary dynamics of sex chromosomes are heavily influenced by sex differences in selection, mutation, migration, recombination and demography, which collectively lead to fundamentally different patterns of evolution at autosomal and X-linked genes [36,37]. These sex differences are widespread [38] and can lead to different contributions of the X and autosome to: (i) genetic admixture and population differentiation [20,39,40], (ii) molecular population genetic diversity and divergence between species [22,41], and (iii) genetic variation for fitness [42–44]. Although previous models have considered the spread of X-linked inversions with under-dominant fitness effects (see [30]) and inversions promoting divergence between sex chromosomes (between the X and Y, or the Z and W; see [45–47]), current theory has so far ignored the role of sex linkage in the evolution of locally adapted inversions. This is somewhat surprising given the extensive development of theory on the individual roles of inversions and X-linked inheritance in adaptation and speciation [22,48–50], as well as the wealth of inversion data that is currently available for species with sex chromosomes [26,28,30,51,52].

Here, we extend Kirkpatrick & Barton’s [23] model for the evolution of locally adapted inversions, and characterize the relative rates of establishment of inversions on the X and autosomes. We focus on the impacts of sexual dimorphism in
mutation, selection and migration on the evolutionary dynamics of inversions, as well as the consequences of local adaptation for the evolution of structural changes in different regions of the genome (figure 1). Our aim is to identify drivers of inversion evolution on the X and autosomes, and conditions leading to different rates of inversion accumulation on each chromosome type. Finally, we evaluate predictions of our models by reviewing current empirical data on polymorphic and fixed inversions on sex chromosomes and autosomes.

2. Material and methods

Our analytical framework follows that of Kirkpatrick & Barton [23], who characterized the evolutionary dynamics of rare inversions in a focal population receiving a steady flow of migrants from a much larger external population. Following their model, we assume that loci responding to local selection have independent effects on fitness (i.e. there is no epistasis between loci). Generations are non-overlapping and migration and selection parameters are small (see below for details). Prior to the origin of inversions, recombination between loci is high relative to the strength of selection per locus. We refer readers to Charlesworth & Barton [25] for a rigorous analysis of inversion dynamics under arbitrary linkage. Our simulations relax many of our analytical assumptions and allow us to explore effects of tight linkage on inversion dynamics.

We present models focusing on contrasts between X-linked and autosomal inversions, though our results also apply to species with Z-linked inheritance, in which females represent the heteromorphic sex (the equivalent to males in species with X chromosomes). All of our models focus on species with heteromorphic sex chromosomes, where X-linked and Z-linked genes are haploid in the heteromorphic sex. Although we do not consider the evolution of locally adapted inversions in species with undifferentiated (homomorphic) sex chromosomes (see [53]), we note that the dynamics of such inversions should be similar to those of autosomal inversions, with the added consequence that X-linked and Z-linked inversions that span the sex-determination region would suppress recombination on Y and W chromosomes, and thereby promote differentiation and degeneration between homomorphic X and Y, or Z and W, chromosome pairs.

(a) Migration—selection balance prior to the origin of inversions

In each generation, a fixed proportion of females and males are migrants: $m_i$ and $m_m$, respectively. Accounting for the relative contributions of maternal and paternal genetic transmission to the inheritance of autosomal and X-linked genes, the effective migration rates for autosomes and the X, respectively, are $m_A = 1/2 (m_i + m_m)$ and $m_X = 1/2 (2m_i + m_m)$ [20,38].

Each locus (arbitrarily labelled locus i) has two alleles: an $A_i$ allele which is fixed in the external population, and $a_i$, which isfavoured in the focal population. Locally adapted alleles increase fitness by $s_{a_i}$ and $s_{a_m}$ in female and male homozygotes, and $s_{A_i}h_i$ and $s_{a_m}h_i$ in heterozygotes, where $h_i$ is the dominance coefficient for the ith locus ($0 < h_i < 1$, with $h_i = 1/2$ corresponding to partial recessivity of the locally adaptive allele, $h_i > 1/2$ to partial dominance and $h_i = 1/2$ to additivity; we assume there are no selection differences in allelic frequencies); see table 1 for a complete list of model notation used throughout the paper.

Following Charlesworth & Charlesworth ([54] ch. 4), when migration and selection parameters are small (e.g. $1 \gg s_{a_i}, s_{a_m}$; $1 \gg m_A, m_X$), the equilibrium frequency of a maladaptive allele at an autosomal locus can be approximated as:

\[
\begin{align*}
\hat{q}_i & = \frac{(1 - h_i)}{2(1 - 2h_i)} \left( 1 - \frac{8(1 - 2h_i)m_A}{(1 - h_i)^2(s_{a_i} + s_{a_m})} \right) \\
& \approx \frac{2m_A}{(1 - h_i)(s_{a_i} + s_{a_m})} \\
& (2.1a)
\end{align*}
\]
and the equilibrium for an X-linked locus is

\[ \hat{q}_i = \frac{(2u_i(1 - h_i) + s_{im})}{4s_{if}(1 - 2h_i)} \left( 1 - \sqrt{1 - \frac{8u_i(1 - 2h_i)3m_X}{(2u_i(1 - h_i) + s_{im})^2}} \right) \]

\[ \approx \frac{3m_X}{2s_{im}(1 - h_i) + s_{im}} \]  

(2.1b)

(see the electronic supplementary material, Appendix I). The final approximations, which we use extensively in the analytical results, imply that locally maladaptive alleles are rare within the focal population. These approximations are valid when selection against locally maladaptive alleles in heterozygotes is strong relative to the migration rate \((s_{im}(1 - h_i) \gg m_X, m_Y)\); the more exact results apply for arbitrary migration relative to selection.

(b) Selection on rare inversions

The expected rate of increase of a rare inversion depends on the marginal fitness associated with the inversion compared to the mean fitness of all genotypes in the population. Kirkpatrick & Barton [23] modelled inversion dynamics within a focal population that experiences one-way migration from a source population in which the alleles that are locally maladaptive for the focal population are fixed. Here, the invasion fitness of a rare inversion within the focal population is

\[ \lambda = (1 + s_i) = (1 - m) \frac{W_i}{W}, \]  

(2.2)

where \(s_i\) is the rate of frequency change for a rare inversion in a deterministically evolving population (essentially, the selection coefficient for a rare inversion; see [25]), \(m\) is the rate of migration, \(W_i\) is the marginal fitness of the inversion and \(W\) is the mean fitness of the population. Selection favours the invasion’s spread within the population when \(\lambda > 1\) (\(s_i > 0\)); selection acts against the inversion when \(\lambda < 1\) (\(s_i < 0\)).

To account for sex-linked inheritance and sex differences in selection and migration, we modify equation (2.2) as follows (see the electronic supplementary material, Appendix II). Invasion fitness of a rare autosomal inversion becomes

\[ \lambda_A \approx (1 - m_A) \left( \frac{W_{fA}}{2W_f} + \frac{W_{mA}}{2W_m} \right), \]  

(2.2a)

where the \(f\) and \(m\) subscripts distinguish the marginal and mean fitnesses of each sex. Invasion fitness of an X-linked inversion becomes

\[ \lambda_X \approx (1 - m_X) \left( \frac{2W_{fX}}{3W_f} + \frac{W_{mX}}{3W_m} \right). \]  

(2.2b)

These expressions take into account the fractions of autosomal and X-linked genes that are maternally and paternally inherited, and follow standard population genetics theory for autosomal and X-linked evolutionary dynamics under weak selection [36,55] (see the electronic supplementary material, Appendix II). Kirkpatrick & Barton [23] further developed approximations for \(W_i\) and \(W\) in equation (2.2), which apply when the ancestral rate of recombination between loci is high relative to the strength of selection for local adaptation at individual loci (see [25]). We extend their approach to incorporate effects of sex-specific selection and X-linked inheritance. Consider a new inversion that captures locally adaptive alleles at a set of \(L\) loci within the larger set of \(I\) total loci that span the inversion. Under the stated assumptions (weak selection and migration; loose linkage between loci in the ancestral population; no epistasis), female selection on an autosomal or X-linked inversion is given by

\[ \frac{W_{fA}}{W} = \frac{\prod_{i \in I} [1 + s(f_i)(1 - h_i)]}{\prod_{i \in I} [1 + s(f_i)(1 - h_i)(1 - \hat{q}_i)]} \left[ \prod_{i \in (1-1)} [1 + s(f_i)(1 - h_i)] \right]. \]  

(2.3a)

The above equation also applies for male selection on an autosomal inversion (i.e. \(W_{mA}/W\), with \(m\) subscripts replacing \(f\)
subscripts in equation (2.3a)). Male selection under X-linked inheritance is
\[
\frac{W_m}{W_n} = \frac{\prod_i (1 + s_m + q)}{\prod_i (1 + s_n)} .
\]
(2.3b)

Approximations of equations (2.3a) and (2.3b), used in the main analytical results below, are provided in the electronic supplementary material, Appendix III.

(c) The distribution of fitness effects and establishment probability of new inversions

When many loci segregate independently at migration—selection balance, and each has a small effect on fitness, we can approximate the distribution of fitness effects and establishment probabilities of new X-linked or autosomal inversions that span a given set of loci at migration—selection balance, and that capture a random sample of locally adaptive and maladaptive alleles within the set of loci (see the electronic supplementary material, Appendix III).

With many independent loci, each having a small fitness effect, the distribution of fitness effects of random inversions (the distribution of \(s_j\)) will be approximately normal with mean and variance of \(s_1\) and \(\sigma^2\), respectively (see the electronic supplementary material, Appendix III). Assuming that the population size is large and selection coefficients are small (1 \(\gg s_j\) \(\gg 1/N\), where \(N\) is the population size), inversion establishment probabilities are approximately 2\(s_1\) when \(s_1 > 0\) and zero otherwise (e.g. [56]). The probability of inversion establishment is
\[
\Pi = \int_0^\infty 2s_1 f(s_1) ds_1 = s_1 \left[ 1 - \text{erf} \left( -\frac{s_1}{\sqrt{2\sigma^2}} \right) \right] + \frac{2\sigma^2}{\pi} \exp \left( -\frac{s_1^2}{2\sigma^2} \right) .
\]
(2.4)

where \(f(s_1)\) is the probability density function for inversion selection coefficients (see the electronic supplementary material, Appendix III).

(d) Simulations

To complement our analytical results, we carried out stochastic simulations to rigorously explore the behaviour of a two-locus version of the model, with arbitrary ancestral linkage between them. Exact recursions follow the life cycle: (1) birth, (2) selection, (3) migration, (4) recombination and random mating of adults and (5) death. The recombination rate between loci was \(r_1\) and \(r_2\), for females and males, respectively, with no X-linked recombination in males.

For each simulation run, we iterated deterministic recursions to convergence to the exact migration—selection equilibrium for the two-locus system with the inversion absent from the population. We then introduced a single copy of an inversion that captured locally adaptive alleles at both loci and, carried out Wright-Fisher forward simulations using the deterministic recursions and multinomial sampling of genotype frequencies for each sex among a pool of \(N\) breeding adults, per generation. For simplicity, we assume a constant number of adults in each generation with an equal sex ratio (i.e. selection is ‘soft’ in that the size of the focal population is independent of its genetic composition). Each simulation run lasted until the inversion was lost from the population or crossed a threshold frequency \(p = p^*\) that corresponds to an establishment probability of \(0.9997\), where \(p^* = 2/(N m_A)\) for the autosomal model and \(p^* = 8/(3 N m_X)\) for the X. To confirm that successfully established inversions eventually increase towards fixation, we carried out additional simulations for 4\(N\) generations, allowing sufficient time for inversions to approach fixation. Complete simulation code can be found at https://github.com/colin-olito/XvAutosomeInversions.

3. Results and discussion

Our results and discussion are divided into four major sections. First, we provide a full characterization of the simplest version of our model: the evolution of an inversion that spans two loci and captures the locally adaptive alleles at both. We explore how dominance and partial linkage between loci affect the establishment of X-linked and autosomal inversions. Second, we explore the dynamics of rare inversions spanning many loci, where each locus has a small effect on local adaptation. Here, establishment probabilities of new inversions take into account the different proportions of locally adaptive and maladaptive alleles that are captured by X-linked versus autosomal inversions. Third, we consider how X/autosome differences in the standing load of deleterious mutations affect the establishment of inversions on each chromosome type. Finally, we review data on X-linked and autosomal inversions, and discuss the relation between empirical patterns and predictions of our models.

(a) Two-locus evolutionary dynamics

Previous theory has shown that when selection is strong relative to migration and locally adaptive loci are loosely linked in the ancestral population, the rate of spread of a rare inversion that captures the locally adaptive alleles is proportional to the migration rate [23–25]. In the electronic supplementary material, Appendix III, we show that these conclusions apply under both autosomal and X-linked inheritance. With two loci at migration—selection balance, selection coefficients for rare inversions that capture locally adapted alleles at both loci \(s_1\) are
\[
s_{1A} = \lambda_A - 1 \approx m_A + O(m_A^2) ,
\]
and
\[
s_{1X} = \lambda_X - 1 \approx m_X + O(m_X^2) ,
\]
for autosomal and X-linked inversions, respectively. With weak migration (i.e. ignoring higher-order terms of \(m_X\) and \(m_A\)), the establishment probabilities of autosomal and X-linked inversions will be \(\Pi_A \approx 2s_{1A} \approx 2m_A\) and \(\Pi_X \approx 2s_{1X} \approx 2m_X\), respectively, and sex-specific migration patterns determine the relative establishment probabilities of inversions. With no sexual dimorphism in migration, establishment probabilities will be equal between the X and autosomes (\(m_A = m_X\)). Male-biased migration leads to a higher establishment probability on autosomes, and female-biased migration causes a higher probability on the X. In the extremes—with sex-limited migration—autosomal establishment probabilities are 50% higher when males are the migrating sex (\(\Pi_A/\Pi_X \approx 3/2\)); X-linked probabilities are approximately 33% higher when females are the migrating sex (\(\Pi_A/\Pi_X \approx 3/4\)).

The approximations in equations (3.1a) and (3.1b) compare well with more exact numerical results using equations (2.1) and (2.2), and evaluated across the full range of dominance for locally adaptive alleles (figure 2a). Equations (3.1a) and (3.1b) also perform well against stochastic simulations of inversions with local adaptation, as long as selection for local adaptation is weak relative to the ancestral recombination rate between loci (i.e. \(r \gg s\), as predicted by previous theory [25]; figure 2b; electronic supplementary material, figure S1). The simulations confirm that \(2m_A\) and \(2m_X\) provide useful approximations for inversion establishment probabilities under loose linkage in the ancestral population (as predicted in [23,25]). In addition,
2000, with supplementary material, figures S1 and S2. Each inversion spans a specific set of alleles. In reality, new inversions are expected to capture a single-copy inversion that eventually becomes established at migration–selection balance equilibrium. L represents the set of loci in an inversion (L is a subset of I) that carry the locally adaptive allele.

With many segregating loci, each with small fitness effects and loose ancestral linkage between them, the distribution of fitness effects of new autosomal inversions is approximately normal with mean and variance of \( \sigma^2 \approx nmA\), where \( n \) is the number of loci within the inversion and \( j \) is the average heterozygous fitness cost of a maladaptive allele (the average value of \( \frac{1}{2}(s_j + s_m)(1 - h_j) \) for the set of loci in the inversion; see the electronic supplementary material, Appendix III). Under X-linked inheritance, the mean and variance of new inversion fitness effects will be \( j \approx nmX \) and \( \sigma^2 \approx nmX^2 \), where \( j_X \) is the average value of \( \frac{1}{2}(s_j(1 - h_j) + s_m) \) (see the electronic supplementary material, Appendix III). By incorporating these expressions into equation (2.4), we obtain the ratio of establishment probabilities for new autosomal versus new X-linked inversions:

\[
\frac{\Pi_A}{\Pi_X} \approx \frac{m_A}{m_X} \left( \frac{\sqrt{2nA/m_A} - 1}{\sqrt{mX/m_X} - 1} \right) \approx \frac{m_A}{m_X}. \tag{3.2}
\]

with the last approximation applicable when \( \bar{r}_A, \bar{r}_X \gtrsim m_A, m_X \) (as we assume throughout). Equation (3.2) reveals that the establishment probabilities depend on an interaction between dominance, sex-biased migration and sex-specific selection. Each factor influences the pre-inversion equilibrium frequencies of locally adaptive alleles, and thereby mediates the distributions of adaptive and maladaptive alleles captured by random inversions.

To evaluate the effects of dominance and sex-specific selection and migration on \( \Pi_A/\Pi_X \), we suppose that dominance is constant among loci (\( h = h_l \)), and the distribution of selection coefficients (\( s_j \) and \( s_m \)) is equal between chromosomes. With selection equal between the sexes, equation (3.2) simplifies to

\[
\Pi_A/\Pi_X \approx \sqrt{3mA(1 - h_l)/mX(3 - 2h_l)} \approx \sqrt{3mA/4mX}.
\]

These results are plotted in figure 3, which shows that \( \Pi_A/\Pi_X \) declines with the dominance of locally adaptive alleles, provided there is some selection through males (\( \Pi_A/\Pi_X \) is unaffected by dominance when selection is limited to females). This makes intuitive sense: with increased masking of migrant alleles, maladaptive alleles reach higher equilibrium frequencies on autosomes, and X-linked inversions capture larger proportions of locally adaptive alleles and become established more readily than autosomal inversions.

(c) Deleterious mutations and inversion dynamics

New inversions can vary in the proportions of locally adaptive alleles that they capture, as well as their loads of deleterious mutations. Deleterious mutations can hinder the spread of inversions by dampening or overwhelming positive selection arising in the context of local adaptation. As deleterious alleles typically reach different equilibrium frequencies on the X and autosomes, they may disproportionately affect inversion dynamics on the two chromosome types. As the bulk of deleterious mutations are expressed in heterozygotes [57,58], we first consider the effects of incompletely recessive mutations on the establishment probabilities of X-linked and autosomal inversions. We later consider how completely recessive mutations potentially impact the dynamics of autosomal inversions.

\[\text{Figure 2. Effects of dominance and recombination on the establishment of inversions that capture two locally adapted alleles. (a) Effects of dominance on selection for rare inversions. Solid lines show the ratio of X and autosome approximations, based on equations (3.1a) and (3.1b), for three idealized scenarios of sex-specific migration: male-limited migration (blue), equal migration (black) and female-limited migration (red). Open circles show numerical evaluation of exact equations (2.1) and (2.2), with \( s_j + s_m/2 = 0.01 \), and a dominance coefficient of \( h_l = h \) at both loci. (b) A representative comparison between analytical approximations for X and autosome establishment probabilities (broken line, based on equations (3.1a) and (3.1b), with \( m_l = m_m \) and stochastic simulations of inversion establishment in a Wright-Fisher population of size \( N = 500000 \), with \( s = s_j = s_m = 0.005 \), \( m_l = m_m = 0.0002 \), and sex-specific recombination rates of \( r = r_l = r_m \) with no X-linked recombination in males; \( j \) refers to the mode of inheritance \( \{j, X\} \). Each circle shows the fraction of \( 10^6 \) single-copy inversions that eventually become established in the population. Analytical, numerical and simulation results are based on the two-locus model of local adaptation in which inversions capture locally adaptive alleles at both loci. For additional simulation results, see electronic supplementary material, figures S1 and S2.)\]
Figure 3. Establishment probabilities of autosomal and X-linked inversions that span many loci with small effects on local adaptation. Curves show the special cases of equation (3.2) (see text following equation (3.2)), which assume that dominance of locally adaptive alleles is constant across the set of loci captured by the inversion \( h = h_0 \), and distributions of selection coefficients among loci are the same for the X and autosomes \( \left( f_x = f_0 \right) \). Values greater than one correspond to higher establishment probabilities for autosomal inversions; values less than one correspond to greater X-linked establishment probabilities.

(i) Incompletely recessive deleterious mutations

To characterize the effects of deleterious mutations on establishment of X-linked and autosomal inversions, we focus on the simplest case where each inversion captures only locally adaptive alleles at a set of \( n \) loci that were loosely linked prior to the origin of the inversion (as before, selection and migration are assumed to be weak). We suppose that the inversion also spans a set of loci at mutation–selection balance equilibrium; there is no epistasis or linkage disequilibrium between the deleterious mutations. Nei et al. [33] previously considered the evolution of inversions that are favoured because they carry fewer mutations than most other haplotypes in the population. Following their model, we assume that inversions cannot invade the population unless they are free of deleterious mutations; this assumption is reasonable as long as the benefit of the inversion for local adaptation and the cumulative mutation rate across loci are both modest (i.e. less than \( s_h h_0 \), the heterozygous fitness cost of a deleterious mutation; see [33]). Following standard theory, mutation–selection equilibrium at a locus \( i \) is \( q_i^* \sim u_i / d_i \), where \( u_i \) is the mutation rate and \( d_i \) is the effective strength of purifying selection against deleterious alleles at the locus \( (d_i \gg u_i) \). Chromosome-specific definitions for \( u_i \) and \( d_i \) are provided in table 1.

In the electronic supplementary material, Appendix IV, we derive selection coefficients for a rare inversion that is free of deleterious mutations and that captures only the locally adaptive alleles at all \( n \) loci at mutation–selection balance. After also taking into account the probability that random inversions carry no deleterious mutations, we obtain a general expression for the relative probability of establishment for autosomal

![Figure 4. Deleterious mutations dampen establishment probabilities of autosomal inversions.](https://example.com/figure4)

Figure 4. Deleterious mutations dampen establishment probabilities of autosomal inversions. The y-axis shows how deleterious mutations reduce the establishment probability of autosomal inversions relative to those on the X. Results are based on equation (3.3), with \( \alpha = u_m / u_h \), \( \beta = s_{d,m} / s_{d,h} \), \( U_i = 0.01 \), \( m_f (n - 1) = m_f (n - 1) = 0.01 \).

versus X-linked inversions:

\[
\frac{\Pi_A}{\Pi_X} \approx \exp \left( \frac{U_i}{s_{d,h}} \right) \left( \frac{2 + \alpha}{2d_h + \beta} - \frac{1 + \alpha}{H(1 + \beta)} \right) \left( \frac{U_i(1 + \alpha) + m_A(n - 1)}{U_i(2 + \alpha) + m_X(n - 1)} \right),
\]

(3.3)

where \( (s_{d,h})_i \) is the harmonic mean deleterious selection coefficient in females, \( U_i \) is the total rate of mutation in females (i.e. across the set of mutation–selection balance loci within an inversion). For simplicity, equation (3.3) assumes that dominance coefficients and ratios of sex-specific mutation and selection parameters are constant across loci \( (h_{d,i} = h_{d,i}; \alpha = u_m / u_h, \beta = s_{d,m} / s_{d,h}) \). Evaluation of equation (3.3) shows that deleterious mutations within inversions can severely dampen the probability of inversion establishment, with deleterious mutations having a greater impact on autosomal than X-linked inversions (figure 4). The greater impact of deleterious mutations on autosomal inversions reflects the higher load of deleterious mutations carried by autosomes compared to the X, and consequently, the lower probability that a given autosomal inversion will be mutation-free. In the simplest case, where mutation, selection and migration parameters are equal between the sexes, \( \Pi_A / \Pi_X \) is always less than one—and establishment probabilities are greater on the X—across the entire plausible range of dominance \( (0 < h_d < 1) \); see the electronic supplementary material, Appendix IV. The quantitative discrepancy between inversions on the X and autosomes can be substantial: \( \Pi_A / \Pi_X \) is likely to be small when mutation rates are male-biased \( (\alpha > 1) \) and deleterious mutations are partially recessive \( (h_d < 0.5) \), as shown in figure 4. Modest sex differences in the fitness effects of deleterious mutations (see [59,60]) have a comparatively small impact on the results.

(ii) Recessive deleterious mutations

Although the vast majority of mutations are partially expressed in heterozygotes (with \( h_d = 1/4 \), on average; see [57,58]), a small subset of deleterious alleles is completely recessive.
Because recessive mutations are completely masked in heterozygotes, they will not hinder the initial spread of autosomal inversions, which may ultimately become established even when they carry one or more strongly deleterious recessive alleles. Such inversions will not fix because their spread is eventually counteracted by selection against low-fitness homozygotes of the inversion, which express the full fitness cost of deleterious mutations [23]. This mechanism for inversion polymorphism is unfeasible for X-linked inversions because X-linked recessives are fully expressed in males.

Assuming that completely recessive mutations have no impact on the establishment of autosomal inversions, the fraction of autosomal inversions that carry one or more recessive deleterious alleles may be approximated as

\[ G \approx 1 - \exp\left(-\frac{U_0 \sqrt{s_d}}{\sqrt{\langle s^2 \rangle_H}}\right), \]  

(equation 3.4) provides an upper limit for this case: approximately 8% of large (chromosome-spanning) autosomal inversions capture recessive lethals; this proportion should decrease for smaller inversions. However, if we take into account non-lethal recessives—those causing sterility, or having milder fitness effects—then the 8% benchmark could underestimate the true fraction of autosomal inversions that carry one or more deleterious recessive alleles. Such inversions may invade the population when rare, and persist as polymorphisms maintained by associative overdominance (see [23]).

(d) Comparison between theoretical predictions and inversion data

Our models predict that three factors should influence the evolutionary accumulation of inversions on sex chromosomes relative to autosomes. Compared to autosomes, the higher efficacy of selection at X- and Z-linked genes is expected to increase the frequencies of locally adapted alleles and decrease the load of deleterious mutations. As a result, sex-linked inversions tend to ‘capture’ higher-fitness genotypes, and experience higher establishment probabilities. Sex-biased migration can modify these predictions somewhat, with higher migration in the homogametic sex (e.g. females in XX/XY species) increasing inversion biases towards the sex chromosomes; higher migration in the heterogametic sex should decrease the bias. Finally, because recessive deleterious alleles are more likely to generate associative overdominance on autosomes, we predict a higher proportion of polymorphic inversions on the autosomes compared to the X or Z.

We conducted a review of the chromosomal locations of inversions by searching the literature for evidence of polymorphic and fixed inversions. Much of the data were obtained from reviews of cytological data [30,52] and taxon-specific comparative genomics datasets [27,51]. We expanded the data collection beyond these studies by searching Google Scholar and Pubmed for relevant search terms (inversion, rearrangement, polymorphism, fixed, polytene, local adaptation, sex chromosomes, autosomes) in conjunction with clade names where known genomic or cytological studies have been conducted. As sex chromosomes and autosomes make up different proportions of the genome, and these proportions vary among species, we focused on the numbers of polymorphic and fixed inversions on each chromosome type, relative to their proportional contributions to the genome. All data refer to paracentric inversions unless otherwise stated.

Two clear patterns emerged from the inversion data. First, fixed inversions show consistent enrichment on X and Z chromosomes relative to their sizes (electronic supplementary material, table S1; figure 5), which is consistent with our theoretical predictions. Analysis of 12 Drosophila genomes suggests an approximately 1.2-fold enrichment of fixed inversions on the X [27,62], which corroborates previous observations of X-linked enrichment for fixed inversions in Drosophila and other insects [30]. Likewise, across 16 species of Anopheles mosquitoes, rearrangement rates are approximately 2.7 times higher on the X relative to autosomes [51]. The X also shows an excess of fixed inversions between humans and chimpanzees compared to similarly sized autosomes [63]. Finally, across 81 clades of passerine birds, Hooper and Price [52] reported pericentric inversions fix at a rate approximately 1.4 times higher on the Z chromosome relative to autosomes.

Second, although data on inversion polymorphisms are less readily available than those on fixed inversions, species from which data are sufficient to contrast the X and autosomes suggest that polymorphic inversions are typically more common on autosomes (electronic supplementary material, table S2; figure 5). This pattern could reflect our prediction that segregating autosomal inversions can harbour recessive deleterious mutations that generate balancing selection via associative overdominance. A recent high-resolution genomic analysis of Drosophila melanogaster shows no bias between the X and autosomes, relative to their proportions of the genome [26]; of 27 inversions detected, 22% are X-linked, corresponding to the approximately 18% of the genome that is X-linked. However, extensive cytological
data from the *Drosophila* and *Anopheles* clades show a clear excess of polymorphic inversions on autosomes.

5. Conclusion

We have shown that the evolutionary fates of inversions differ when they arise on sex chromosomes versus autosomes. In our model, inversions are favoured because they facilitate local adaptation, and inversion establishment probabilities are typically higher on the X (or Z) than on autosomes. This sex chromosome bias is strongest when migration is higher in the homogametic sex, locally adapted alleles are strongly expressed in heterozygotes, and inversions are large enough to span many loci evolving at migration-selection and mutation-selection balance (as is widely observed in classical cytology data, e.g. [30,52]). Deleterious mutations appear to have the strongest impact on the dynamics of X-linked and autosomal inversions; the higher burden of deleterious mutations on autosomes can impose a strong constraint to the invasion and fixation of autosomal inversions. These predictions are consistent with empirical patterns of fixed and polymorphic inversions (figure 5).

The observed excess of fixed inversions on X and Z chromosomes most probably reflects the greater efficiency of purifying selection on X and Z chromosomes (i.e. against locally maladaptive or unconditionally harmful alleles). Several lines of empirical evidence, spanning genomics to quantitative genetics data, suggest that sex linkage facilitates the removal of deleterious genetic variation (e.g. [37,59,64]). The possible role of sex-biased migration in inversion evolution is less clear. Data on sex-specific migration in arthropods are sparse, though mark–recapture studies in *Drosophila* suggest that sex-specific migration may range from female-biased to male-biased in the genus [65–69]. It has long been recognized that migration rates are typically higher for the heterogametic sex in birds and mammals (i.e. females and males, respectively [70]), which should, if anything, dampen the preferential accumulation of inversions on Z and X chromosomes. A fine-scaled phylogenetic comparative analysis of correlations between the degree of sex-biased migration and the magnitude of inversion bias towards the X or Z would help clarify the impact of migration on genomic patterns of inversion accumulation.

While our models provide a compelling explanation for empirical patterns of fixed and polymorphic inversions on sex chromosomes and autosomes, they do not preclude the role of other factors in driving non-random genomic patterns of inversion evolution. Several other mechanisms, including positive selection on inversions, meiotic drive and fixation of under-dominant inversions by genetic drift, may also contribute to inversion evolution (see box 1), and each mechanism may play out differently on the X and autosomes. Direct, positive selection on inversions (e.g. due to position effects of genes) could lead to a faster-X pattern if inversions are intrinsically beneficial and partially recessive [22,30,71]. Under-dominant inversions are more likely to fix on the X than the autosomes, because directional selection in males on X-linked inversions can overwhelm any under-dominant fitness costs to heterozygous females [22]. Finally, idiosyncratic features of sex chromosome composition, including repeat abundance, may lead to mutational biases in the formation of new inversions [62,72]. High-resolution data on polymorphic and fixed inversions, along with tests of neutrality for inversion polymorphisms [73] may help shed further light on these possibilities.

References


APPENDIX I. Migration-selection balance at single loci

We assume that selection and migration are weak ($m_f$, $m_m$, $s_f$, $s_m << 1$), that reproduction involves random mating among adults, and dominance ($h_i$) is equal between the sexes (see Table 1). In these cases, genotype frequencies at birth are approximately equal between the sexes, and at Hardy-Weinberg equilibrium [26, 55]. Let $q_i$ represent the frequency of the locally maladapted allele at locus $i$; we assume that migrants carry locally maladaptive alleles at the $i$th locus. For ease of presentation, we drop the $i$ subscript in deriving the migration-selection balance equilibria for X-linked and autosomal loci.

Under weak selection and migration (i.e., ignoring second-order and higher terms of migration and selection), the allele frequency change per generation is approximately:

$$\Delta q_i = \Delta q_{i,mig} + \Delta q_{i,sel}$$  \hspace{1cm} (A1.1)

where $\Delta q_{i,mig}$ and $\Delta q_{i,sel}$ represent the expected frequency changes due solely to migration and selection, respectively (see chapter 4 of [54]).

**Autosomal inheritance**

**Frequency change due to migration.** In the $j$th sex ($j = \{f, m\}$), the frequencies of the three genotypes after migration are:

$$f_{AA,ij} = q_i^2 (1 - m_j) + m_j$$  \hspace{1cm} (A1.2)

$$f_{Aa,ij} = 2q_i (1 - q_i)(1 - m_j)$$

$$f_{aa,ij} = (1 - q_i)^2 (1 - m_j)$$

The change in frequency due to migration in the $j$th sex is:

$$\Delta q_{ij}^M = q_i^2 (1 - m_j) + m_j + q_i (1 - q_i)(1 - m_j) - q_i = m_j (1 - q_i)$$  \hspace{1cm} (A1.3)

The total change in frequency due to migration is:

$$\Delta q_{i,mig} = \frac{\Delta q_{ij}^M + \Delta q_{im}^M}{2} = \frac{m_f + m_m}{2} (1 - q_i)$$  \hspace{1cm} (A1.4)

**Frequency change due to selection.** Allele frequency change due to selection in the $j$th sex is:

$$\Delta q_{ij}^s = -s_{ij} q_i (1 - q_i) [1 - h_i - q_i (1 - 2h_i)] + O(s_{ij}^2)$$  \hspace{1cm} (A1.5)

The total change in frequency due to selection is:

$$\Delta q_{i,sel} = \frac{\Delta q_{ij}^s + \Delta q_{im}^s}{2} \approx -\frac{s_{if} + s_{im}}{2} q_i (1 - q_i) [1 - h_i - q_i (1 - 2h_i)]$$  \hspace{1cm} (A1.6)
**Migration-selection balance equilibrium.** At equilibrium ($\Delta q_{\text{mig}} = -\Delta q_{\text{sel}}$), the frequency of the locally maladaptive allele is:

$$q_i = \frac{(1 - h_i) - \sqrt{(1 - h_i)^2 - 4(1 - 2h_i)\left(\frac{m_f + m_m}{s_{if} + s_{im}}\right)}}{2(1 - 2h_i)}$$

(A1.7)

which corresponds to eq. (1a) in the main text. With weak migration relative to selection, eq. (A1.7) reduces to eq. (A3.4), used in Appendix III.

**X-linked inheritance**

**Frequency change due to migration.** The frequency changes due to migration are:

$$\Delta q_{if}^M = m_f(1 - q_i)$$

$$\Delta q_{im}^M = m_m(1 - q_i)$$

in females and males, respectively. The total change in frequency due to migration is:

$$\Delta q_{i,mig} = \frac{2\Delta q_{if}^M + \Delta q_{im}^M}{3} = \frac{2m_f + m_m}{3}(1 - q_i)$$

(A1.9)

**Frequency change due to selection.** Allele frequency change due to selection in females is:

$$\Delta q_{if}^S = -s_{if}q_i(1 - q_i)[1 - h_i - q_i(1 - 2h_i)] + O(s_{if}^2)$$

(A1.10)

The frequency change due to selection in males is:

$$\Delta q_{im}^S = -s_{im}q_i(1 - q_i) + O(s_{im}^2)$$

(A1.11)

The total change in frequency due to selection is:

$$\Delta q_{i,sel} = \frac{2\Delta q_{if}^S + \Delta q_{im}^S}{3} \approx -q_i(1 - q_i)\frac{2s_{if}[1 - h_i - q_i(1 - 2h_i)] + s_{im}}{3}$$

(A1.12)

**Migration-selection balance equilibrium.** At equilibrium ($\Delta q_{i,mig} = -\Delta q_{i,sel}$), the frequency of the locally maladaptive allele is:

$$q_i = \frac{(2s_{if}(1 - h_i) + s_{im})}{4s_{if}(1 - 2h_i)}$$

$$-\sqrt{\left(\frac{(2s_{if}(1 - h_i) + s_{im})^2 - 8s_{if}(1 - 2h_i)(2m_f + m_m)}{4s_{if}(1 - 2h_i)}\right)}$$

(A1.13)

which corresponds to eq. (1b) in the main text. With weak migration relative to selection, eq. (A1.7) reduces to eq. (A3.13), used in Appendix III.
APPENDIX II. Spread of a rare inversion that captures locally adapted alleles

Following the basic framework of Kirkpatrick and Barton [23], we consider the rate of spread of an inversion that spans an arbitrary set of loci responding to local adaptation. To incorporate sexually dimorphic evolutionary parameters, and allow for different modes of inheritance of the inversions, we adjust Kirkpatrick and Barton’s general framework by incorporating functions for the effective strength of selection and migration for each chromosome type. These functions take into account sex-specific patterns of selection and dispersal.

In Kirkpatrick and Barton’s original formulation, the invasion fitness of a rare inversion is:

\[ \lambda = (1 + s_I) = (1 - m) \frac{W_I}{\bar{W}} \]  (A2.1)

where \( s_I \) is the geometric rate of change of a rare inversion in a deterministically evolving population, \( m \) is the rate of migration, \( W_I \) is the marginal fitness of the inversion, and \( \bar{W} \) is the mean fitness of the population. Selection favours the inversion’s spread within the population provided \( \lambda > 1 \) \((s_I > 0)\); selection acts against the inversion when \( \lambda < 1 \).

**Effective migration rates.** Taking into account the rates of transmission through each sex for the X and autosomes, the effective migration rates for the two chromosome types are captured by the following expressions:

\[ m_X = \frac{2m_f + m_m}{3} \]  (A2.2)

for the X, and

\[ m_A = \frac{m_f + m_m}{2} \]  (A2.3)

for the autosomes (Hedrick 2007; for a more general model, see Goldberg and Rosenberg 2015).

**Fitness benefits of rare inversions.** Following standard population genetics theory of sex-dependent selection (e.g., Kidwell et al. 1977), allele frequency change of a rare autosomal allele depends equally on the allele’s rate of increase in females and males of the population. In the context of inversion evolution, the invasion fitness of a rare autosomal inversion with arbitrary fitness in each sex is:
\[ \lambda_A = (1 - m_f) \frac{W_{lf}}{2W_f} + (1 - m_m) \frac{W_{lm}}{2W_m} \]  
\[ = (1 - m_A) \left( \frac{W_{lf}}{2W_f} + \frac{W_{lm}}{2W_m} \right) + \frac{1}{4} (m_m - m_f) \left( \frac{W_{lf}}{W_f} - \frac{W_{lm}}{W_m} \right) \]

where \( W_{lf} \) and \( W_{lm} \) are the marginal fitnesses of inversions in females and males, and \( W_f \) and \( W_m \) represent mean relative fitness of each sex in a population at migration-selection balance with no inversions. Expressions for \( W_{lf}/W_f \) and \( W_{lm}/W_m \) are presented in the main text. Since \( \left( \frac{W_{lf}}{W_f} - \frac{W_{lm}}{W_m} \right) \) is \( O(s_{fi}, s_{sm}) \), then to first order in migration and selection, eq. (A2.4) reduces to:

\[ \lambda_A \approx (1 - m_A) \left( \frac{W_{lf}}{2W_f} + \frac{W_{lm}}{2W_m} \right) \]  
\[ \text{(A2.4a)} \]

which corresponds to eq. (2a) in the main text.

Each X-linked allele is transmitted one-third of the time through fathers and two-thirds of the time through mothers. Therefore, with weak selection (as assumed here), the invasion fitness for an X-linked inversion is given by:

\[ \lambda_X = (1 - m_f) \frac{2W_{lf}}{3W_f} + (1 - m_m) \frac{W_{lm}}{3W_m} \]  
\[ = (1 - m_X) \left( \frac{2W_{lf}}{3W_f} + \frac{W_{lm}}{3W_m} \right) + \frac{2}{9} (m_m - m_f) \left( \frac{W_{lf}}{W_f} - \frac{W_{lm}}{W_m} \right) \]

Once again, with weak selection and migration, we can approximate eq. (A2.5) to first order in the migration rate and the strength of selection, yielding:

\[ \lambda_X \approx (1 - m_X) \left( \frac{2W_{lf}}{3W_f} + \frac{W_{lm}}{3W_m} \right) \]  
\[ \text{(A2.5)} \]

which corresponds to eq. (2b) in the main text.
APPENDIX III. Distributions of fitness effects for rare inversions

Autosome model. As noted in the main text, the invasion fitness of an inversion that captures the locally adaptive allele at a set of \( L \) loci within a larger set of \( I \) loci that span the inversion is:

\[
\lambda_A = \frac{(1 - m_A)}{2} \left( \frac{W_{if}}{W_f} + \frac{W_{im}}{W_m} \right)
\]  
(eq. (2a) from the main text), where:

\[
\frac{W_{if}}{W_f} = \frac{\prod_{i \in L} [(1 - \tilde{q}_i)(1 + s_{if}) + \tilde{q}_i(1 + h_i s_{if})] \prod_{i \notin (L-L)} [(1 - \tilde{q}_i)(1 + h_i s_{if})] + \tilde{q}_i]}{\prod_{i \in I} [(1 - \tilde{q}_i)^2(1 + s_{if}) + 2\tilde{q}_i(1 - \tilde{q}_i)(1 + h_i s_{if}) + \tilde{q}_i^2]}
\]

and

\[
\frac{W_{im}}{W_m} = \frac{\prod_{i \in E} [(1 - \tilde{q}_i)(1 + s_{im}) + \tilde{q}_i(1 + h_i s_{im})] \prod_{i \notin (I-L)} [(1 - \tilde{q}_i)(1 + h_i s_{im})] + \tilde{q}_i]}{\prod_{i \in I} [(1 - \tilde{q}_i)^2(1 + s_{im}) + 2\tilde{q}_i(1 - \tilde{q}_i)(1 + h_i s_{im}) + \tilde{q}_i^2]}
\]

To first order in the migration and selection coefficients \((s_{ji}, m_A << 1)\), eq. (A3.1) reduces to:

\[
\lambda_A \approx 1 - m_A + \frac{1}{2} \sum_{i \in L} (s_{if} + s_{im}) \tilde{q}_i [1 - h_i - \tilde{q}_i(1 - 2h_i)]
\]  
\[+ \frac{1}{2} \sum_{i \in (I-L)} (s_{if} + s_{im}) [1 - h_i - \tilde{q}_i(1 - 2h_i)]
\]  
\[= \frac{m_A}{t_{Ai}}
\]  
(see eq. (A1.7)), where \( m_A = (m_f + m_m)/2 \) is the effective migration rate, and \( t_{Ai} = (1 - h_i)(s_{if} + s_{im})/2 \) is the effective strength of selection, in heterozygotes, for the locally adaptive allele at the \( i \)th locus. Substituting eq. (A3.4) into eq. (A3.3), we obtain an approximation for the selection coefficient acting on a rare autosomal inversion:

\[
s_i = \lambda_A - 1 \approx m_A(n - 1) - \sum_{i \in L} k_i t_{Ai} \left[ 1 - \tilde{q}_i \frac{(1 - 2h_i)}{(1 - h_i)} \right] + O(m_A^2)
\]  
(A3.5)
where \( n \) is the number of loci within the set \( I \), \( k_i = 0 \) for all loci in the inversion that carry the locally adaptive allele, and \( k_i = 1 \) for loci in the inversion that carry the locally maladaptive allele.

Suppose that each new inversion captures a random draw of alleles at the set of loci evolving under migration-selection balance. Given our assumption that locally maladaptive alleles segregate independently of each other, and each locus evolves to the deterministic migration-selection balance equilibrium, denoted by eq. (A3.4), then the set of \( k_i \) terms in eq. (A3.5) can be modelled as independent Bernoulli random variables: \( k_i \sim \text{Bernoulli} \left( \frac{m_A}{\bar{t}_A} \right) \). We can therefore calculate the mean and variance of \( s_I \) for random inversions that span the set of \( I \) loci as follows. The mean fitness effect of a random inversion is:

\[ \bar{s}_I \approx -m_A \quad (A3.6) \]

and the variance of fitness effects is:

\[ \sigma^2 \approx nm_A \bar{t}_A \quad (A3.7) \]

where \( \bar{t}_A = E[t_{\bar{A}_i}] \) represents the mean effective strength of purifying selection against locally maladaptive alleles. Both results neglect terms of \( O(m_A^2) \).

The above expressions will eventually break down as \( h \) approaches one. When maladaptive alleles are completely recessive (\( h = 1 \)), the migration-selection balance equilibrium is:

\[ \hat{q}_i \approx \sqrt{\frac{2m_A}{(s_{if} + s_{im})}} \quad (A3.8) \]

The invasion fitness of an autosomal inversion becomes:

\[ \lambda_A \approx 1 - m_A + \frac{1}{2} \sum_{i \in I} (s_{if} + s_{im}) \hat{q}_i^2 - \frac{1}{2} \sum_{i \in (I-L)} (s_{if} + s_{im}) \hat{q}_i \]

\[ \approx 1 + m_A(n - 1) - \frac{1}{2} \sum_{i \in I} k_i (s_{if} + s_{im}) \hat{q}_i \]

where the \( k_i \) take values of 0 or 1, as above. Assuming independent segregation of the locally maladaptive alleles, with each segregating at the equilibrium in eq. (A3.8), then the \( k_i \) are independent Bernoulli random variables: \( k_i \sim \text{Bernoulli} \left( \sqrt{\frac{2m_A}{(s_{if} + s_{im})}} \right) \). In this case, the mean and variance of the distribution of fitness effects of new inversions is:

\[ \bar{s}_I \approx -m_A \quad (A3.10) \]
\[
\sigma^2 \approx m_A \sum_{i \in I} \text{var}(k_i) \frac{1}{2} (s_{if} + s_{im}) \approx n(m_A)^3 \varphi + O(m_A^2)
\]

Where \( \varphi \) is the average value of \( \sqrt{\frac{1}{2} (s_{if} + s_{im})} \) across the set of migration-selection balance loci in the inversion. Note that the mean fitness effect of an inversion is unaffected by dominance, yet the variance differs from the expression obtained above for incompletely recessive maladaptive alleles (\( h < 1 \)). The question is whether masking (by dominance) of maladaptive alleles increases or decreases the variance of fitness effects of new inversions. To evaluate how dominance impacts the variance in fitness effects of new inversions, assume that fitness parameters are constant across the set of loci spanning the inversion (\( s_{if} = s_f; s_{im} = s_m; h_i = h \)). The ratio of the variance of fitness effects with \( h = 1 \) versus \( h << 1 \) is:

\[
\frac{\sigma^2(h = 1)}{\sigma^2(h << 1)} \approx \frac{1}{(1 - h)} \left( 1 - \frac{2m_A}{s_f + s_m} \right)
\]

When selection is strong relative to migration – a condition underlying all of the derivations that we have considered – then the term in the square root will be small, and thus, we expect \( \sigma^2(h = 1) \ll \sigma^2(h << 1) \).

**X-linked model.** Using the same general approach as above, we approximate the invasion fitness of an X-linked inversion as:

\[
\lambda_{X} = (1 - m_X) \left( \frac{2W_{if}}{3W_f} + \frac{1W_{im}}{3W_m} \right)
\]

\[
\approx 1 - m_X
\]

\[
+ \frac{1}{3} \sum_{i \in I} [2s_{if} \tilde{q}_i(1 - h_i) + s_{im} \tilde{q}_i - 2s_{if} \tilde{q}_i^2 (1 - 2h_i)]
\]

\[
- \frac{1}{3} \sum_{i \in I} k_i [2s_{if} (1 - h_i) + s_{im} - 2s_{if} \tilde{q}_i (1 - 2h_i)]
\]

where \( k_i = 0 \) for all loci in the inversion that carry the locally adaptive allele, and \( k_i = 1 \) for loci in the inversion that carry the locally maladaptive allele.

Supposing that each new inversion captures a random draw of alleles at the set of loci evolving under migration-selection balance, then \( k_i \sim \text{Bernoulli}(\tilde{q}_i) \), with \( \tilde{q}_i \) representing the equilibrium frequency of the maladaptive allele at the \( i \)th X-linked locus. With incomplete masking of locally maladaptive alleles and strong local selection relative to migration (\( h, \tilde{q}_i << 1 \)), we can approximate the migration-selection balance equilibrium (from eq. (A1.13)): 
\[ \hat{q}_i \approx \frac{m_X}{t_{Xi}} \]  
(A3.13)

where \( m_X = (2m_f + m_m)/3 \) and \( t_{Xi} = (2s_if(1 - h_i) + s_{im})/3 \). Selection on a rare inversion becomes:

\[ s_i = \lambda_A - 1 \approx m_X(n - 1) - \sum_{i \in I} k_i \left[ t_{Xi} - \frac{2}{3}s_if(1 - 2h_i) \right] + O(m_X^2) \]  
(A3.14)

With independent segregation of loci in the ancestral population, the mean and variance of selection on new inversions that span the set of \( I \) loci will be:

\[ \bar{s}_i \approx -m_X \]  
(A3.15)

and

\[ \sigma^2 \approx nm_X\bar{\ell}_X \]  
(A3.16)

where \( \bar{\ell}_X \), which is the mean value of \( t_{Xi} \) across the set of loci, represents effective strength of purifying selection against locally maladaptive alleles on the X chromosome. Both of the final results neglect terms of \( O(m_X^2) \).

**The special case of two loci.** Consider the specific case of two loci, with the inversion capturing locally adaptive alleles at both \( (n = 2; I = L) \). With strong selection relative to migration (using the migration-selection balance approximation for each mode of inheritance), we obtain the following results:

\[ \lambda_A \approx 1 - m_A + \frac{1}{2} \sum_{i \in I} (s_{if} + s_{im})(1 - h_i)\hat{q}_i + O(m_A^2) \approx 1 + m_A \]  
(A3.17)

and

\[ \lambda_X \approx 1 - m_X + \frac{1}{3} \sum_{i \in I} [2s_{if}(1 - h_i) + s_{im}]\hat{q}_i + O(m_X^2) \approx 1 + m_X \]  
(A3.18)

which correspond to eqs. (5a-5b) in the main text.

**Fixation probabilities of inversions.**

Following standard branching process theory for beneficial mutations (e.g., [56]), we can use the following approximations for the establishment probability of a single-copy inversion with selection coefficient \( s_I \). If the inversion is beneficial \((s_I > 0)\), then the establishment probability is roughly \( 2s_I \). The establishment probability is zero, otherwise (i.e., for \( s_I \leq 0 \)).
The total probability of establishment for inversions that arise on the X or autosomes must take into account the distribution of selection coefficients among random inversions that arise by mutation. Using the branching process approximation, we can model the fixation probability for a given mode of inheritance as:

$$\Pi = \int_{0}^{\infty} 2s_{I} f(s_i) ds_{I}$$

(A3.19).

where $f(s_i)$ is the probability density function for the distribution of fitness effects of new inversions under the given mode of inheritance.

With many independent loci of small individual fitness effects, then we can approximate the distribution of $s_i$ as normal, with expressions for mean and variance as calculated above, i.e.: $\bar{s}_i$ and $\sigma^2$ based on eqs. (A3.6-A3.7) for autosomal linkage, or eqs. (A3.15-A3.16) for X-linkage. In this case $f(s_i)$ is the probability density function for the normal distribution. In this case, eq. (A3.19) evaluates to:

$$\Pi = \int_{0}^{\infty} 2s_{I} f(s_i) ds_{I} = \bar{s}_i \left[ 1 - \text{erf} \left( -\frac{\bar{s}_i}{\sqrt{2}\sigma^2} \right) \right] + \frac{2\sigma^2}{\sqrt{\pi}} \exp \left( -\frac{\bar{s}_i^2}{2\sigma^2} \right)$$

(A3.20).

$$= \bar{s}_i + \frac{2\sigma^2}{\sqrt{\pi}} + O(\bar{s}_i^2)$$

where $O(\bar{s}_i^2)$ collects all 2nd-order and higher order terms of $\bar{s}_i$. Eq. (A3.20) corresponds to eq. (4) of the main manuscript.
APPENDIX IV. Impact of deleterious mutations on inversion establishment

Following the frameworks of Nei et al. [50] and Kirkpatrick and Barton [23], we make the following simplifying assumptions: (1) The total mutation rate in the sequence captured by the inversion is modest to small, so that \( \sum_{i=1}^{ld} u_i \ll 1 \), where and \( ld \) is the number of mutation-selection balance loci in the inversion, and \( u_i \) is the effective rate of mutation at the \( i \)th locus (see Table 1); (2) deleterious mutations are sufficiently harmful that inversions that bear one or more of them are not favoured by selection; (3) fitness is multiplicative across loci (there is no epistasis); and (4) prior to the origin of the inversion, locally adaptive alleles and deleterious mutations segregate at deterministic migration-selection balance and mutation-selection balance (respectively), with loose linkage between them. Finally, we assume, for simplicity, that inversions capture only locally adaptive alleles. With respect to loci at migration-selection balance, the pattern of selection on a rare inversion becomes \( s_{I,A} = m_A(n-1) \) and \( s_{I,X} = m_X(n-1) \), where \( n \) is the number of loci at migration-selection balance; these results follow from setting \( k_i = 0 \) in eqs. (A3.5) and (A3.14) of Appendix III.

Under the stated conditions, it can be shown that the probability that an inversion is free of deleterious mutations is \( f_0 \approx e^{-U/(d)_H} \), where \( U = \sum_{i=1}^{ld} u_i \) is the total deleterious mutation rate across the \( ld \) loci at mutation-selection balance, and \( \langle d \rangle_H \) is the harmonic mean of \( d_i \) for the set of loci (see Orr 2000). We apply this expression for \( f_0 \) in the following models of autosomal and X-linked inversion establishment (i.e., using chromosome specific terms, \( \langle d_X \rangle_H \) and \( \langle d_A \rangle_H \), for the X and autosomes, respectively).

**Autosome model.** The total invasion fitness of an inversion, taking into account both deleterious mutations and locally adaptive alleles, is:

\[
\lambda_{d,A} (1 + s_{I,A})
\]

(A4.1)

where \( 1 + s_{I,A} = \lambda_d \) is the invasion fitness of an autosomal inversion with respect to loci at migration-selection balance (i.e., based on eq. (2b) of the main manuscript, which neglects effects of deleterious mutations); \( \lambda_{d,A} \) is the invasion fitness of the inversion with respect to the loci at mutation-selection balance:

\[
\lambda_{d,A} = \left( \frac{W_{d,ff}}{2W_{d,f}} + \frac{W_{d,lm}}{2W_{d,m}} \right)
\]

(A4.2)

The terms in (A4.2) parallel those from eq. (2a) in the main text, though in this case, mean fitness and marginal fitness of the inversion (per sex) are functions of the deleterious mutation load in the inversion and within the population as a whole. Following standard mutation-
selection balance theory, the mean fitness of females in the base population, with respect to loci at mutation-selection balance, is:

$$W_{d,f} = \prod_{i=1}^{l_d} \prod_{i=1}^{l_d} \left( 1 - 2\hat{q}_i h_{d,i} s_{d,if} - \hat{q}_i^2 s_{d,if} (1 - 2h_{d,i}) \right)$$

$$\approx \exp \left( -\sum_{i=0}^{l_d} [2\hat{q}_i h_{d,i} s_{d,if} + \hat{q}_i^2 s_{d,if} (1 - 2h_{d,i})] \right)$$

$$\approx \exp \left( -2 \sum_{i=0}^{l_d} \hat{q}_i h_{d,i} s_{d,if} \right) \approx \exp \left( -2 \frac{(1 + \alpha)}{(1 + \beta)} U_f \right)$$

where $U_f = \sum_{i=1}^{l_d} u_{i,f}$ is the haploid mutation rate in females across the set of $l_d$ loci, and additional terms are defined in Table 1 of the main text; $\hat{q}_i$ is the equilibrium frequency of the deleterious allele at the $i$th locus:

$$\hat{q}_i \approx \frac{u_{i,f} + u_{i,m}}{h_{d,i}(s_{d,if} + s_{d,im})} = \frac{u_{i,f} (1 + \alpha)}{h_{d,i} s_{d,if} (1 + \beta)} = \frac{u_{i,f} (1 + \alpha)}{h_{d,i} s_{d,im} (1 + 1/\beta)}$$

(A4.4)

where $\alpha = u_{im}/u_{if}$, $\beta = s_{d,im}/s_{d,if}$.

Following Nei et al. [50], the fitness of a new inversion, with respect to deleterious genetic variation, is:

$$W_{d,if} \approx \exp \left( - \sum_{i=1}^{l_d} P_{d,i} s_{d,if} h_{d,i} \right) \exp \left( -\frac{(1 + \alpha)}{(1 + \beta)} U_f \right)$$

(A4.5)

where $P_{d,i} = 1$ if the inversion carries the deleterious allele at the $i$th locus, and $P_{d,i} = 0$ otherwise. For inversions that are completely mutation free, $P_{d,i} = 0$ across the entire set of loci. The mean fitness of males with respect to deleterious variation in the base population, and prior to the origin of the inversion, is:

$$W_{d,m} = \prod_{i=1}^{l_d} W_{mi} \approx \exp \left( - \sum_{i=0}^{l_d} 2\hat{q}_i h_{d,i} s_{d,im} \right) \approx \exp \left( -2 \frac{(1 + \alpha)}{(1 + 1/\beta)} U_f \right)$$

(A4.6)

The inversion’s fitness in males, with respect to deleterious genetic variation, is:

$$W_{d,im} \approx \exp \left( - \sum_{i=1}^{l_d} P_{d,i} s_{d,im} h_{d,i} \right) \exp \left( -\frac{(1 + \alpha)}{(1 + 1/\beta)} U_f \right)$$

(A4.7)

Substituting eqs. (4.3-4.7) into eq. (4.2), we obtain the general expression for inversion invasion fitness:
\[
\lambda_{d,A} = \frac{1}{2} \left( \exp \left( - \sum_{i=1}^{l_d} P_{d,i} s_{d,i} h_{d,i} \right) \exp \left[ \frac{(1 + \alpha)}{(1 + \beta)} U_f \right] 
+ \exp \left( - \sum_{i=1}^{l_d} P_{d,i} s_{d,in} h_{d,i} \right) \exp \left[ \frac{(1 + \alpha)}{(1 + 1/\beta)} U_f \right] \right)
\]

\[
\approx 1 + \frac{(1 + \alpha) U_f}{2} + s_{l,A}
\]

with the final expression applying when \( U_f \) and \( s_{l,A} \) are both small. The effective strength of selection on a rare, mutation-free, inversion becomes:

\[
s^*_I \approx \lambda_{d,A} (1 + s_{l,A}) - 1 \approx \frac{(1 + \alpha) U_f}{2} + s_{l,A}
\]

When mutation rates are the same in female and males, the first term of the approximation reduces to eq. (6) of Nei et al. \[50\], as expected.

The probability of establishment of a mutation-free chromosome is \( 2s^*_I \), and the probability of the autosomal inversion being mutation free is:

\[
f_{0,A} \approx \exp \left( - \frac{\sum_{i=0}^{l_d} \frac{1}{2} (u_{i,f} + u_{i,m})}{\langle d_A \rangle_H} \right) = \exp \left( - \frac{(1 + \alpha) U_f}{2\langle d_A \rangle_H} \right)
\]

To evaluate \( \langle d_A \rangle_H \), we assume for simplicity that dominance is fixed across loci \( (h_d = h_{d,i}) \), leading to:

\[
\langle d_A \rangle_H = \frac{l_d}{\sum_{i=1}^{l_d} \frac{1}{d_i}} = \frac{1}{2} h_d (1 + \beta) \frac{l_d}{\sum_{i=1}^{l_d} \frac{1}{s_{d,if}}} = \frac{1}{2} h_d (1 + \beta) \langle s_{d,f} \rangle_H
\]

where \( \langle s_{d,f} \rangle_H \) is the harmonic mean selection coefficient in females. Therefore, the probability of the inversion being mutation free and becoming established is:

\[
\Pi_A = 2s^*_I f_{0,A} \approx \exp \left( - \frac{U_f (1 + \alpha)}{h_d (1 + \beta) \langle s_{d,f} \rangle_H} \right) \left( (1 + \alpha) U_f + 2s_{l,A} \right)
\]

Since we are only concerned with inversions that are mutation free (as noted above, we assume that inversions with deleterious mutations will not become established), we quantify the invasion fitness of a mutation-free inversion \((P_{d,i} = 0)\):

\[
\lambda_{d,A} (1 + s_{l,A}) = \frac{1}{2} \left( \exp \left[ \frac{(1 + \alpha)}{(1 + \beta)} U_f \right] + \exp \left[ \frac{(1 + \alpha)}{(1 + 1/\beta)} U_f \right] \right) (1 + s_{l,A})
\]

\[
\approx 1 + \frac{(1 + \alpha) U_f}{2} + s_{l,A}
\]
**X-linked model.** Following the same general approach as above total invasion fitness of an inversion, taking into account both deleterious mutations and locally adaptive alleles, is:

\[
\lambda_{d,X}(1 + s_{l,X})
\]  

where \(1 + s_{l,X} = \lambda_X\) is the invasion fitness of an X-linked inversion based on eq. (2b) of the main manuscript, which neglects effects of deleterious mutations; \(\lambda_{d,X}\) represents the impact of deleterious mutations on the relative fitness of the X-linked inversion:

\[
\lambda_{d,X} \approx \left(\frac{2 W_{d,lf}}{3 W_{d,f}} + \frac{1 W_{d,lm}}{3 W_{d,m}}\right)
\]  

(A4.15).

The terms in eq. (A4.15) are:

\[
\bar{W}_{d,f} \approx \exp \left(-2 \sum_{i=0}^{l_d} \hat{q}_i h_{d,i} s_{d,if}\right) \approx \exp \left(-2(2 + \alpha) \sum_{i=0}^{l_d} \frac{u_{i,f} h_{d,i}}{2 h_{d,i} + \beta}\right)
\]

\[
W_{d,lf} \approx \exp \left(-\sum_{i=1}^{l_d} P_{d,i} s_{d,if} h_{d,i}\right) \exp \left(-(2 + \alpha) \sum_{i=0}^{l_d} \frac{u_{i,f} h_{d,i}}{2 h_{d,i} + \beta}\right)
\]

\[
\bar{W}_{d,m} = \prod_{i=1}^{l_d} \left(1 - \hat{q}_i s_{d,im}\right) \approx \exp \left(-\sum_{i=0}^{l_d} \hat{q}_i s_{d,im}\right) \approx \exp \left(-\sum_{i=0}^{l_d} \frac{u_{i,f} (2 + \alpha)}{1 + 2 h_{d,i} / \beta}\right)
\]

\[
W_{d,lm} \approx \exp \left(-\sum_{i=1}^{l_d} P_{d,i} s_{d,im}\right)
\]

where the equilibrium frequency of X-linked deleterious alleles at locus \(i\) is:

\[
\hat{q}_i \approx \frac{2u_{i,f} + u_{i,m}}{2 s_{d,if} h_{d,i} + s_{d,im}} = \frac{u_{i,f} (2 + \alpha)}{s_{d,if} (2 h_{d,i} + \beta)} = \frac{u_{i,f} (2 + \alpha)}{s_{d,im} (1 + 2 h_{d,i} / \beta)}
\]  

(A4.16)

Focusing only on those inversions that are free of deleterious mutations \((P_{d,i} = 0)\), and dominance fixed across loci \((h_d = h_{d,i})\), the total invasion fitness becomes:

\[
\lambda_{d,X}(1 + s_{l,X}) \approx \left[\frac{2}{3} \exp \left(\frac{h_d (2 + \alpha) U_f}{(2 h_d + \beta)}\right) + \frac{1}{3} \exp \left(\frac{(2 + \alpha)}{(1 + 2 h_d / \beta)} U_f\right)\right] (1 + s_{l,X}) \approx 1 + \frac{U_f (2 + \alpha)}{3} + s_{l,X}
\]  

(A4.17)

Total selection on a rare, mutation-free inversion on the X chromosome becomes:

\[
s_{l,X}^* = \lambda_{d,X} (1 + s_{l,X}) - 1 \approx \frac{U_f (2 + \alpha)}{3} + s_{l,X}
\]  

(A4.18)
The probability of establishment of a mutation-free X chromosome is $2s_{I,X}^*$, and the probability of the inversion being mutation free is:

$$f_{0,X} \approx \exp \left( -\frac{\frac{1}{3} \sum_{i=0}^{d} (2u_{i,f} + u_{i,m})}{(s_{X})_{H}} \right) = \exp \left( -\frac{(2 + \alpha)U_f}{3(d_{X})_{H}} \right)$$  \hspace{1cm} (A4.19)

with the final expression applicable under the assumption of constant dominance across the set of loci. The probability of the inversion being mutation free and becoming established is:

$$\Pi_x \approx \exp \left( -\frac{(2 + \alpha)U_f}{(2h_d + \beta)(s_{d,f})_{H}} \right) \left( \frac{2}{3} U_f (2 + \alpha) + 2s_{I,X} \right)$$  \hspace{1cm} (A4.20)

The ratio of autosome to X-linked establishment probabilities is:

$$\frac{\Pi_A}{\Pi_X} \approx \exp \left( \frac{U_f}{(s_{d,f})_{H}} \left[ \frac{2 + \alpha}{2h_d + \beta} - \frac{1}{h_d (1 + \beta)} \right] \right) \frac{U_f}{2} \left( 1 + \alpha \right) + m_A(n - 1)$$ \hspace{1cm} (A4.21)

When mutation and selection and migration parameters are the same in females and males ($\alpha = \beta = m_m/m_f = 1$), the ratio reduces to:

$$\frac{\Pi_A}{\Pi_X} \approx \exp \left( \frac{U_f}{(s_{d,f})_{H}} \left[ \frac{3}{2h_d + 1} - \frac{1}{h_d} \right] \right)$$ \hspace{1cm} (A4.22)

in which case, autosomal inversions are always less likely to become established than X-linked inversions ($\Pi_A/\Pi_X < 1$ for the entire plausible range of dominance for deleterious mutations: $0 < h_d < 1$).

**Recessive deleterious mutations on autosomes.** The above expression for the autosome inversion establishment probability is expected to break down when deleterious mutations are completely recessive. In this case, mutations will not hinder the initial spread of autosomal inversions, since such mutations will be completely masked in individuals that are heterozygous for a rare inversion. An inversion carrying one or more recessive mutations may therefore become established, though it will not fix, because the spread of the inversion is eventually counteracted by selection against low-fitness homozygotes for the inversion; such homozygotes express the full fitness cost of the deleterious mutations within the inversion. In contrast, as long as deleterious alleles are expressed in males, the above approximation for
establishment of X-linked inversions should remain applicable when mutations are completely recessive.

We can quantify the fraction of autosomal inversions that carry recessive deleterious alleles. Such inversions, once established, can persist as inversion polymorphisms. The proportion of autosomal inversions that carry at least one completely recessive mutation is:

\[ G = 1 - \prod_{i=1}^{l_0} \left( 1 - \frac{u_i}{\sqrt{s_{di}}} \right) \approx 1 - \exp \left( - \frac{\sqrt{U_0}}{\langle \sqrt{s_d} \rangle_H} \right) \]  

(A4.23)

where \( l_0 \) refers to the set of loci that mutate to completely recessive alleles, \( U_0 \) is the total mutation rate (within the inversion) to recessive alleles, and \( \langle \sqrt{s_d} \rangle_H \) is the harmonic mean of the square root of selection coefficients for recessive mutations.

**ADDITIONAL REFERENCES**


$N = 3 \times 10^4$
Figure S1. Effects of recombination on the establishment of inversions that capture two locally adapted alleles: additional simulation results. See the Fig. 1 legend for additional details. Here we present additional results comparing analytic approximations of establishment probabilities (dashed line, based on eqs. (5a-5b), with \( m_f = m_m \)) and stochastic simulations for inversion establishment on the X (red symbols) and autosomes (grey symbols). Simulations were carried out in a Wright-Fisher population with effective population size of \( N = 30,000 \) (panels A-I) and \( N = 5 \times 10^5 \).
= 500,000 (panels J–R), and for three dominance scenarios for the locally adaptive alleles (h = 0 in the left-hand column; h = ½ for the middle column; h = 1 for the right-hand column). For each combination of h and N, we performed simulations corresponding to equal (circles), female-limited (squares), and female-limited (diamonds) parameterizations of migration rate (m_f, m_m), selection (s_f, s_m), and recombination rate (r_f, r_m, with no X-linked recombination in males). The sex-averaged rate of migration and strength of selection were held constant across simulations. For simplicity, we present results in which we explore the effects of sex-bias in only one of the three parameters at a time. For simulations using N = 30,000, we set \( \bar{m} = (m_f + m_m)/2 = 0.002 \) and \( \bar{s} = (s_f + s_m)/2 = 0.05 \). For simulations using N = 500,000, we set \( \bar{m} = (m_f + m_m)/2 = 0.0002 \) and \( \bar{s} = (s_f + s_m)/2 = 0.005 \). Hence, panels A–C and J–L explore effects of equal migration (where \( m_f = m_m = \bar{m} \)), female-limited migration (\( m_f = 0; m_m = 2\bar{m} \)), and male-limited migration (\( m_f = 0; m_m = \bar{m} \)), with equal selection and recombination between sexes (\( s_f = s_m = \bar{s}; r_f = r_m = r \)). Panels D–F and M–O show results explore effects of equal selection (\( s_f = s_m = \bar{s} \), female-limited selection (\( s_f = 0; s_m = 2\bar{s} \)), and male-limited selection (\( s_f = 0; s_m = 2\bar{s} \)), with equal migration and recombination between sexes (\( m_f = m_m = \bar{m} \); \( r_f = r_m = r \)). Panels G–I and P–R explore effects of equal recombination (\( r_f = r_m = r \)), female-limited recombination (\( r_m = 0; r_f = r \)), and male-limited recombination (\( r_f = 0; r_m = r \)), with equal migration and selection between sexes (\( m_f = m_m = \bar{m} \); \( s_f = s_m = \bar{s} \)). The j in the establishment probability, \( \Pi_j \), refers to the mode of inheritance (\( j = \{A, X\} \)). Each data point shows the fraction of 10^6 single-copy inversions that eventually become established in the population. Analytical, numerical and simulation results are based on the two-locus model of local adaptation in which inversions capture locally adaptive alleles at both loci.
Figure S2. Long-run evolutionary dynamics of inversions. Instead of using frequency thresholds to delineate inversions that successfully invade the population, we ran forward simulations for $4N$ generations – a sufficient number of generations for the population to reach migration-selection-drift equilibrium. Data points show the results for $5 \times 10^4$ replicate simulations, each of which was run until a new inversion was lost or $4N$ generations had passed. Panels A and B show the proportion of inversions that are not lost from the population. Panels C and D show the mean frequency, at generation $4N$, of inversions that became established in the population. We present
results for Wright-Fisher populations of size $N = 30,000$ with $s = s_f = s_m = 0.05$, $m_f = m_m = 0.002$ (panels A, C) and $N = 500,000$ with $s = s_f = s_m = 0.005$, $m_f = m_m = 0.0002$ (panels B, D), with recombination rates between the sexes ($r = r_f = r_m$, and no X-linked recombination in males). Fitness effects of locally adaptive alleles are additive ($h = h_f = h_m = 0.5$). The dashed line in Panels A and B show the analytic approximation for inversion establishment probability, based on eqs. (5a-5b), with $m_f = m_m$. Note, in Panels C-D, that the simulation results show that the average frequency of established X-linked inversions is slightly higher than the average frequency for autosomal inversions, though inversions are nearly fixed under both modes of inheritance.
Table S1. The number of fixed inversions found on the X or Z chromosome and autosomes for a given species pair is shown, as well as the relative lengths (in Mb) of X-linked, Z-linked and autosomal genetic material. Primary data were generated by Feuk et al. (2005), von Grotthus et al. (2010), Neafsey et al. (2015) and Hooper and Price (2017). For passerine birds (*), the number of polymorphic inversions was collated across 81 clades, the autosomal lengths represent branch lengths (in million years), and the inversions recorded are pericentric.

<table>
<thead>
<tr>
<th>Species 1</th>
<th>Species 2</th>
<th>Autosomal inversions</th>
<th>X- or Z-linked inversions</th>
<th>Autosomal length (Mb)</th>
<th>X- or Z-linked length (Mb)</th>
<th>Per-Mb enrichment on X or Z</th>
<th>Study</th>
</tr>
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<tr>
<td>D. erecta</td>
<td>D. melanogaster</td>
<td>17</td>
<td>3</td>
<td>103.2</td>
<td>21.3</td>
<td>0.88</td>
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<td>D. yakuba</td>
<td>D. melanogaster</td>
<td>29</td>
<td>6</td>
<td>116.4</td>
<td>21.8</td>
<td>1.09</td>
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<td>D. melanogaster</td>
<td>348</td>
<td>159</td>
<td>99</td>
<td>31.5</td>
<td>1.30</td>
<td>von Grotthuss et al. 2010</td>
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<tr>
<td>D. pseudoobscura</td>
<td>D. melanogaster</td>
<td>592</td>
<td>198</td>
<td>108.7</td>
<td>20.3</td>
<td>1.59</td>
<td>von Grotthuss et al. 2010</td>
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<td>D. willistoni</td>
<td>D. melanogaster</td>
<td>1243</td>
<td>381</td>
<td>125.2</td>
<td>27.9</td>
<td>1.29</td>
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<tr>
<td>D. virilis</td>
<td>D. melanogaster</td>
<td>997</td>
<td>298</td>
<td>118.2</td>
<td>30.5</td>
<td>1.12</td>
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<td>1.10</td>
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<td>1.25</td>
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<td>A. gambiae</td>
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<td>84.87</td>
<td>7.97</td>
<td>2.78</td>
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<td>Passerine birds*</td>
<td>Passerine birds*</td>
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<td>194.15*</td>
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<td>1.45</td>
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</table>
The number of polymorphic inversions found on the X chromosome and autosomes for a given species, or species group, are shown. The table builds upon a similar review by Charlesworth et al. (1987) and includes more recent analyses. The table also reports the proportion of the genome which is composed of autosomal vs. X-linked genetic material. For species where a full genome assembly was available, the relative proportions were derived from the UCSC Genome Browser. When such information was lacking, we used either the proportion of mapped scaffolds from Table 1 of Schaeffer et al. (2008) and Table S14 of Neafsey et al. (2015), or approximations from polytene chromosome analyses. Adjusted enrichment is the ratio of the number of X-linked to autosomal inversions, scaled by their corresponding proportion of genetic material.

<table>
<thead>
<tr>
<th>Clade</th>
<th>Species (or species group)</th>
<th>Autosomal inversions</th>
<th>X-linked inversions</th>
<th>Proportion autosomal genetic material</th>
<th>Proportion X-linked genetic material</th>
<th>Adjusted enrichment on X</th>
<th>Study</th>
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<td><em>Drosophila melanogaster</em></td>
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<td>(genomic analysis)</td>
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<td><em>Drosophila melanogaster</em></td>
<td>305</td>
<td>23</td>
<td>0.82</td>
<td>0.18</td>
<td>0.39</td>
<td>Lemeunier and Au- lard 1992</td>
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<td></td>
<td>(polytene chromosome analysis)</td>
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<td>35</td>
<td>6</td>
<td>~0.6</td>
<td>~0.4</td>
<td>0.37</td>
<td>Levitan 1982</td>
</tr>
<tr>
<td></td>
<td>(6 species)</td>
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<td><em>Picture-wing Hawaiian Drosophila</em> (103 species)</td>
<td>73</td>
<td>13</td>
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<td>0.19</td>
<td>0.80</td>
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<td>51</td>
<td>6</td>
<td>0.79</td>
<td>0.21</td>
<td>0.50</td>
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<td>61</td>
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<td>~0.6</td>
<td>~0.4</td>
<td>0.59</td>
<td>Levitan 1982</td>
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<td></td>
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<td>8</td>
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<td>0.51</td>
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<td>Species Count</td>
<td>X Chromosome Mismatch</td>
<td>Y Chromosome Mismatch</td>
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<td>Ref.</td>
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<td>2</td>
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<td>Cordeiro et al. 2014</td>
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<td>(6 species)</td>
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<td>Wasserman 1982</td>
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<td>24</td>
<td>0.62</td>
<td>0.38</td>
<td>Dobzhansky et al. 1950</td>
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<tr>
<td><em>Drosophila subobscura</em></td>
<td>58</td>
<td>8</td>
<td>~0.8</td>
<td>~0.2</td>
<td>Krimbas 1992</td>
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<td><em>Drosophila funebris</em></td>
<td>8</td>
<td>0</td>
<td>~0.8</td>
<td>~0.2</td>
<td>Dubinin et al. 1937</td>
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<td><em>Drosophila pseudoobscura</em></td>
<td>9</td>
<td>0</td>
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<td>0.39</td>
<td>Anderson et al. 1975</td>
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<td>Dia et al. 2000.</td>
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<td></td>
<td>Coluzzi et al. 2002</td>
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<td></td>
<td></td>
<td></td>
<td>al. 2014</td>
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<td><em>Actinopterygii</em></td>
<td>5</td>
<td>1</td>
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<td>0.04</td>
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<td>Jones et al. 2012</td>
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<td>Unknown</td>
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<td>Kirubakaran et al. 2016</td>
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REFERENCES


