How Selection Acts on Chromosomal Inversions

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Chromosomal inversions are structural mutations that invert the orientation and thus the sequence of a chromosomal segment; in diploid heterozygous individuals, when one chromosome carries the inverted segment and the other homologous chromosome is noninverted, recombination is strongly or even completely suppressed. Most inversions are deleterious or neutral, but occasionally they are beneficial. Positive selection can establish a new, initially rare inversion via indirect (linked) selection (e.g. when the inversion captures a locally adaptive haplotype and then 'hitchhikes' with it) or via direct positive selection (e.g. when a beneficial mutation arises fortuitously at the breakpoints). After their establishment, adaptive inversions often seem to be maintained by balancing selection in a polymorphic state, that is, they are neither lost nor do they become fixed at 100% frequency. Such balancing selection acting on inversion polymorphisms might involve overdominance, associative overdominance, negative frequency-dependent selection, spatially and/or temporally varying selection.

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Introduction

Chromosomal inversions are rare, structural mutations that reverse the orientation and thus the gene order of a chromosomal segment, first discovered in 1919 by Sturtevant in the vinegar fly *Drosophila melanogaster* (Sturtevant, 1919). Inversions can be small (<1 kb) or large (>1 Mb) and include or exclude the centromere (peri- vs. paracentric inversions) (**Figure 1a**) (Kirkpatrick, 2010). In contrast to homozygous individuals that either carry two noninverted chromosomes (so-called 'standard' homokaryotypes) or two inverted chromosomes (inverted homokaryotypes), inversion heterozygotes (so-called heterokaryotypes) have major problems with proper pairing of chromatids during meiosis, thus causing a strongly reduced frequency of crossing-over and recombination (**Figure 1b–d**) (Kirkpatrick, 2010). The major genetic property of inversions is, therefore, that they effectively suppress or at least strongly reduce 'gene flux', that is, the genetic exchange between homologous chromosomes when in heterozygous state. This can have major consequences for evolutionary processes, as we shall see below. **See also**: **Genomic Rearrangements: Mutational Mechanisms**

Like other mutations (e.g. single nucleotide changes), a large fraction of newly arisen inversions is expected to be deleterious, for example when they generate structural problems with meiosis, when their breakpoints disrupt functionally important genes and/or when they negatively impact gene expression, as is the case for several genetic diseases in humans (Castermans *et al*., 2007; Feuk, 2010; Kirkpatrick 2010; Puig *et al*., 2015). Purifying (negative) selection will thus act to eliminate such deleterious inversions from the population. In some cases, however, underdominant inversions with deleterious effects can become fixed by random genetic drift, for instance when the effective population size is low for a long time and/or when selection against heterokaryotypes is sufficiently weak (Lande, 1984; Kirkpatrick and Barton, 2006; Kirkpatrick, 2010). Another large fraction of

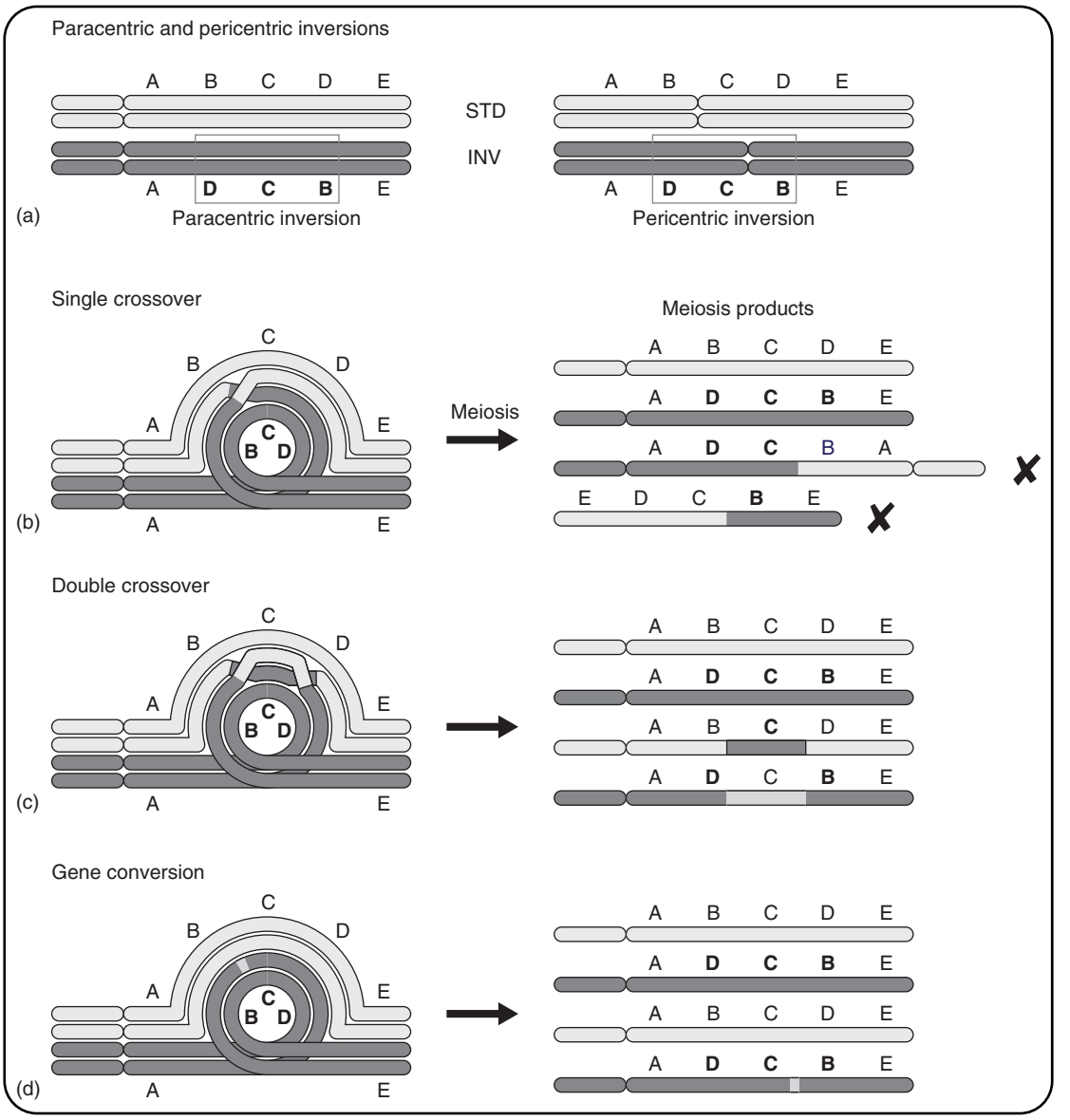

Figure 1 Suppression of recombination and gene flux in the context of inversions. (a) Inversions can be either paracentric (i.e. both breaks occur on one chromosomal arm) or pericentric (i.e. breaks occur on two chromosomal arms and inversions span a centromere). In paracentric inversion heterozygotes, homologous chromosomes form a loop during meiosis (b–d). Single cross-overs (b) result in the formation of four products: standard (STD) and inverted (INV) nonrecombinant gametes, as well as an acentric fragment lacking a centromere and a dicentric bridge harbouring two centromeres. The former is lost and the latter is torn apart during centromere migration to the cell poles, which results in two nonviable recombinant gametes (indicated by black crosses). In the case of pericentric inversions (not shown here, see Wellenreuther and Bernatchez, 2018 for details), meiosis also produces four products: viable STD and INV nonrecombinant gametes as for paracentric inversions, and two nonviable recombinant gametes harbouring large deletions or duplications. (b) Modified from Wellenreuther and Bernatchez L (2018). Exchange of genetic material between STD and INV chromosomal arrangements (gene flux) can nevertheless happen via double crossovers (c) and gene conversion events (d), especially away from the breakpoints (see Korunes and Noor, 2019 for details). (d) Modified from Korunes and Noor, (2019).

inversions is likely to be selectively neutral, for example when they are very small and/or occur in intergenic regions, and might thus be lost by drift from the population (Kirkpatrick, 2010). Yet, occasionally, inversions might also be subject to positive selection (see **Glossary**), causing them to spread and to become established in the population, starting from an initially very low frequency (e.g. if an inversion arises by mutation in a single individual its initial frequency is $1/2N$, where N is the number of diploid individuals in the population); below we shall focus on this case.

Here, we discuss the mechanisms whereby positive selection leads, directly or indirectly, to the spread and establishment of inversions (Dobzhansky, 1937, 1970; Charlesworth and Charlesworth, 1973; Kirkpatrick and Barton, 2006; Hoffmann and Rieseberg, 2008; Kirkpatrick, 2010; Charlesworth, 2016;

Charlesworth and Barton, 2018; Kapun and Flatt, 2019). Once established, inversions can become fixed (i.e. reach a frequency of 100%) by positive directional selection or they remain polymorphic, being maintained by balancing selection (Kirkpatrick and Barton, 2006). Our treatment mainly follows the syntheses by Kirkpatrick and Barton (2006) and Kapun and Flatt (2019); for other reviews, we refer to papers by Hoffmann and Rieseberg (2008), Kirkpatrick (2010), Faria *et al*. (2019), and Wellenreuther and Bernatchez (2018). **See also: Inversions and Evolution**; **Inversions and Evolution of the Human Genome**

How Newly Arisen Inversions Spread by Positive Selection

Different types of positive selection that might act on newly arisen inversion can be distinguished, including indirect and direct positive selection (Kirkpatrick and Barton, 2006; Faria *et al.,* 2019; Charlesworth and Barton, 2018; Kapun and Flatt, 2019) (**Figure 2a–c**). We first discuss indirect selection acting on inversions – such mechanisms include different kinds of linked selection that depend on the effects of the inversion on recombination (additive linked selection, positive epistatic selection) (Charlesworth and Charlesworth 1973; Kirkpatrick and Barton, 2006; Charlesworth, 2016; Charlesworth and Barton, 2018; Kapun and Flatt, 2019). **See also: Fitness and Selection**

Indirect positive selection for chromosomal inversions arises because they prevent recombination (i.e. increase linkage) between alleles at two or more loci whose combination is advantageous but where recombinants involving other alleles are disadvantageous, thereby reducing recombination load (Charlesworth and Charlesworth, 1973; Charlesworth, 2016). Thus, an inversion can spread by selection because it suppresses crossing-over in the heterokaryotype and reduces the likelihood that recombination breaks up an advantageous haplotype. Importantly, this might occur even when the inversion itself is selectively neutral or weakly deleterious; what is required is the pre-existence of a multi-locus haplotype that has higher fitness than other recombinant haplotypes and which then gets 'captured' by a newly arisen inversion.

The main condition for the spread of a new inversion is that linkage disequilibrium (LD; see **Glossary**) is present among the selected loci before the inversion has arisen; the effect of the inversion is to further increase the LD among the selected loci and thus to hitchhike with the adaptive haplotype (Charlesworth and Charlesworth, 1973; Charlesworth and Barton, 2018). The initial positive LD among the selected loci should not be too large: the selective advantage of the inversion is very small if the loci are already tightly linked and effective recombination rate is small (Kirkpatrick and Barton 2006; Charlesworth and Barton 2018). **See also: Linkage Disequilibrium**

In one theoretical scenario, investigated by Kirkpatrick and Barton (2006) and Charlesworth and Barton (2018), we can imagine that an inversion has captured a locally adaptive haplotype and might then spread along with that haplotype to near fixation because it protects the adapted loci from recombination and maladaptive gene flow from neighbouring populations

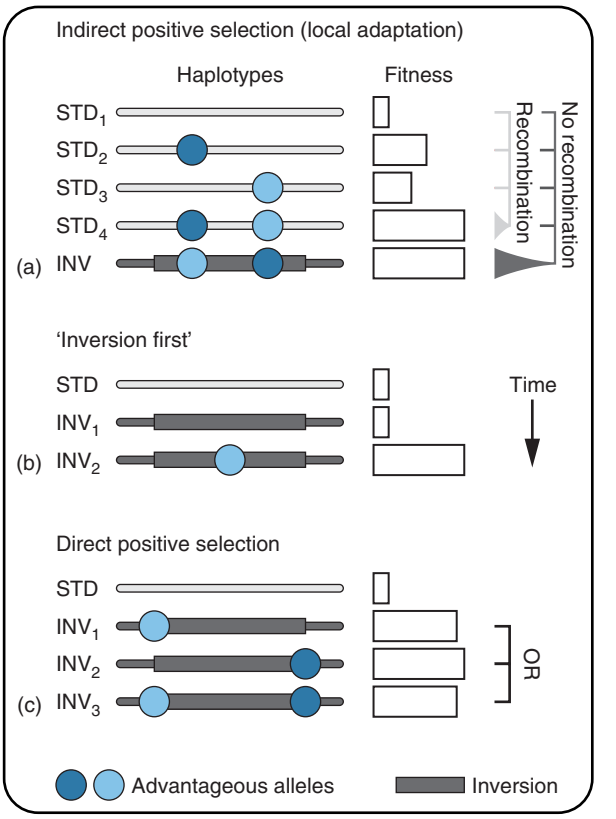

Figure 2 Selective mechanisms leading to the establishment of inversions. (a) An inversion (INV) captures a locally adapted high-fitness haplotype (STD_4) and protects it from recombing with maladaptive low-fitness haplotypes (STD_{1-3}). In this 'local adaptation' scenario, positive selection acts on locally adapted alleles within the inversion and indirectly on the inversion itself. This mechanism is similar to the 'coadaptation' scenario; see main text for details. (b) A neutral inversion (INV_1) spreads to intermediate frequency by drift before picking up a beneficial mutation by chance (INV_2), which causes the inversion to raise to high frequency via hitchhiking. As in the local adaptation model (a), positive selection acts on the beneficial mutation and not on the inversion itself. (c) Gene disruption caused by an inversion can by chance cause beneficial mutations at either one (INV_1 or INV_2) or both of the breakpoints (INV_3). Here, positive selection directly targets the inversion and its breakpoints instead of its allelic content.

(migration load) which tend to break down LD. This mechanism is commonly referred to as the 'local adaptation' or 'Kirkpatrick–Barton' model; it can operate either with additivity or epistasis among selected loci, but epistasis is clearly not required (Kirkpatrick and Barton, 2006; Charlesworth and Barton, 2018) (**Figure 2a**). **See also**: **Role of Natural Selection in Chromosomal Speciation**; **Epistasis**

A conceptually similar model, first developed by Dobzhansky, assumes the existence of epistatic combinations of beneficial, locally adapted alleles whereby the heterokaryotype has a higher fitness than expected from the contributions of the individual loci, thus giving rise to 'cumulative' multi-locus heterosis (Dobzhansky, 1947, 1950; Haldane, 1957; Wasserman, 1968; Charlesworth and Charlesworth, 1973; Schaeffer *et al*., 2003; Kirkpatrick and Barton, 2006). This scenario thus not only requires positive

epistasis (see **Glossary**) among the selected loci but also that at least two inversion-linked loci are subject to overdominant selection (Dobzhansky, 1947, 1950; Haldane, 1957; Kirkpatrick and Barton, 2006). This mechanism of epistatic selection (see **Glossary**) is often called Dobzhansky's 'coadaptation' or 'coadapted gene complex' model (sometimes also called the 'supergene' model) (Wasserman, 1968; Charlesworth, 2016).

As in the Kirkpatrick–Barton model, we imagine that a newly arisen inversion captures an adaptive haplotype whose positively epistatically interacting loci are in LD with each other (Charlesworth and Charlesworth, 1973; Charlesworth and Barton, 2018). By suppressing recombination and increasing LD among the epistatically interacting loci, the inversion experiences a selective advantage and might spread to fixation (Charlesworth and Charlesworth, 1973; Kirkpatrick and Barton, 2006; Charlesworth and Barton, 2018). Thus, similar to the Kirkpatrick–Barton model, the inversion invades because it prevents recombination (and/or migration) from disrupting the locally favoured epistatic haplotype (Haldane, 1957; Wasserman, 1968). Although this model is often thought to involve local selection, the epistatic selection invoked by it could in principle be acting uniformly across a broad geographic range (Charlesworth and Charlesworth, 1973).

Both of the above-mentioned models of selection assume that a new inversion captures an already existing adaptive haplotype with some positive (but not too strong) LD present among the selected loci (Charlesworth and Barton, 2018). It is, however, also possible that locally adaptive alleles accumulate inside the inversion after it has become established in the population by random drift (the 'inversion first' or 'hitchhiking' scenario; e.g. Noor *et al*., 2001; Navarro and Barton, 2003; Kirkpatrick and Barton, 2006; Charlesworth and Barton, 2018). Under this scenario, the neutral inversion drifts up to intermediate frequency in the population, picks up a rare beneficial mutation by chance, and then spreads to high frequency because of hitchhiking with the positively selected site (see discussion in Kirkpatrick and Barton, 2006; Charlesworth and Barton, 2018) (**Figure 2b**). Again, this mechanism is one of indirect, linked selection. This scenario might not be so likely because it requires that the initially rare inversion is not lost by drift and, once it has reached some appreciable frequency, to pick up a novel, initially rare beneficial mutation (Kirkpatrick and Barton, 2006). **See also**: **Drift: Introduction**

The inversion might also be subject to direct positive selection – this can occur because the inversion lesion might have direct beneficial fitness consequences (Kirkpatrick and Barton 2006). For example, the chromosome break caused by a new inversion might by chance induce a beneficial mutation or alter gene expression in the breakpoint region. Depending on the degree of dominance of the beneficial mutation, this mechanism might lead to the fixation of the inversion or, if the fitness effect is overdominant, to a stable polymorphism (**Figure 2c**).

In practice, these different adaptive scenarios are difficult to distinguish from each other. Coalescent models developed by Guerrero *et al*. (2012) suggest that, under both the Kirkpatrick–Barton model and the coadaptation model, we might observe a deviation from neutral expectation (**Figure 3a**), with pronounced peaks of genetic divergence between the noninverted and inverted karyotype away from the breakpoints and centred on the selected loci (**Figure 3b**). Such adaptive centre peaks inside the body of inversion arise from the interaction of selection and genetic exchange (gene flux) between noninverted and inverted chromosomes. Gene flux, due to double cross-over or gene conversion events (**Figure 1c,d**), occurs at a rate of $\sim 10^{-2}$ to 10^{-8} per nucleotide and generation (Navarro *et al*., 1997; Andolfatto *et al*. 2001); thus, if the inversion is sufficiently old ($>N_e$ generations), gene flux is predicted to break up the initially strong LD and homogenise differences between noninverted and inverted chromosomes (Guerrero *et al*., 2012). Under selection, this homogenising gene flux reduces neutral divergence towards the centre of the inversion, with the exception of the centre regions where selection opposes this homogenisation and of the breakpoints (where recombination is completely suppressed) (Guerrero *et al*., 2012).

Observations that are qualitatively consistent with these predictions have for example been made in *Drosophila pseudoobscura*, *D. melanogaster*, *Anopheles gambiae* and *Rhagoletis pomonella* (**Figure 3c,d**; see discussion and references in Guerrero *et al*., 2012; Cheng *et al*. 2012; Kapun *et al*., 2016). A particularly clear example seems to be the *In(3R)Payne* inversion polymorphism in *D. melanogaster* which is subject to spatially varying (clinal) selection across latitude (Kapun *et al*. 2016; **Figure 3c**; also see below). However, centre peaks of divergence can also arise nonadaptively from demographic changes (e.g. bottlenecks) and the stochastic nature of the coalescent process. At least in principle, phased deoxyribonucleic acid (DNA) sequence data carry the necessary information to distinguish between nonadaptive and adaptive inversion evolution (Guerrero *et al*., 2012). Yet, even if selection on centre peaks can be established from such data, it will be practically difficult to determine whether selection involves fitness additivity or positive epistasis (coadaptation).

Another issue is that adaptive variants that have accumulated after an inversion has become established are expected to leave the same pattern of genomic divergence than pre-existing adaptive loci that were subsequently captured by the inversion. Distinguishing whether the selected polymorphisms predate the origin of the inversion (as assumed under both the Kirkpatrick–Barton and the coadaptation model) or not ('hitchhiking' or 'inversion first' scenario) would, therefore, require identifying the adaptive loci inside the inversion, dating their ages relative to the inversion origin, and then demonstrating that the inversion is younger or older than the selected variants (Kirkpatrick, 2010).

Beyond these cases of indirect selection, inferring direct selection acting on the breakpoints of the inversion from sequence data is also not trivial. This is because the expected pattern of divergence between the noninverted and the inverted karyotype for a sufficiently old inversion looks very similar under neutrality versus direct selection: the pattern resembles a 'suspension bridge', with maximal divergence at the breakpoints where recombination is completely suppressed but low divergence towards the centre of the inversion (**Figure 3a**; Navarro *et al*., 1997; Guerrero *et al*., 2012). There is qualitative evidence that this type of mechanism might apply to the *In(3L)P* inversion in *D. melanogaster* (Wesley and Eanes, 1994). Like *In(3R)Payne* inversion mentioned above, this inversion is also subject to clinal selection, but its pattern

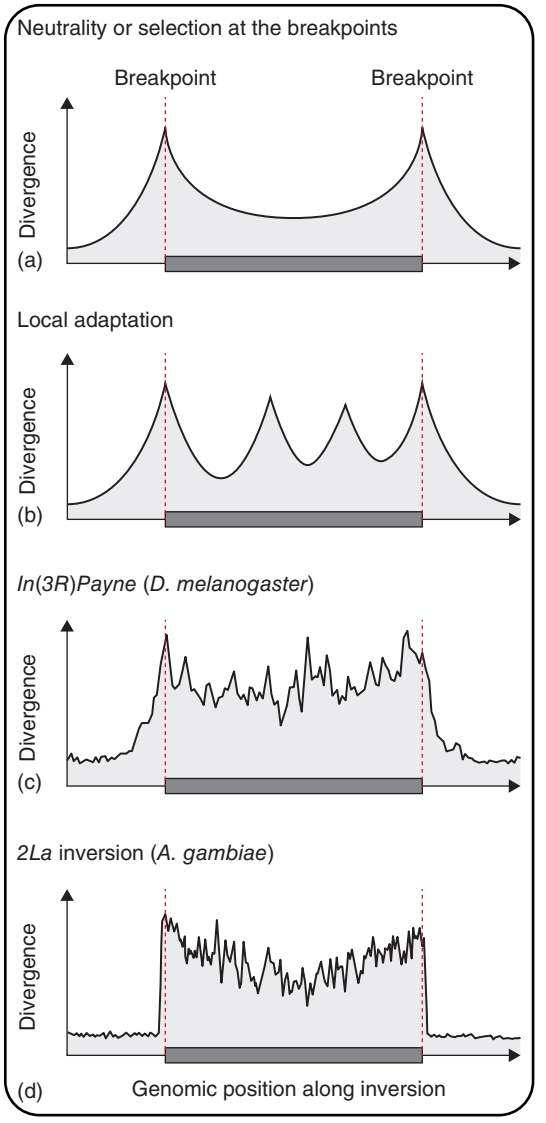

Figure 3 Expected patterns of genetic divergence (for example as measured by F_{ST} or D_{xy}) between standard and inverted chromosomal arrangements. Inversion breakpoints positions are depicted with dashed orange lines. (a) Under neutrality, divergence is expected to be low at the centre of the inversion, where gene flux between arrangements is maximal, and high at the breakpoints, where gene flux is strongly reduced. Importantly, this 'suspension bridge' pattern might also reflect strong selection at the breakpoints. (b) Under the 'local adaptation' and the 'coadaptation' models, we expect to see additional peaks of high divergence in the centre of the inversion and away from the breakpoints: these peaks are centred on locally adapted loci that are maintained by selection despite homogenising gene flux. This pattern has been observed for the *In(3R)Payne* inversion in the fruit fly *D. melanogaster* (c) (Kapun *et al.* 2016) and, to a lesser extent, for the *2La* inversion in the mosquito *A. gambiae* (d) (Cheng *et al.* 2012). Source: Kapun *et al.* (2016), Cheng *et al.* (2012), Kapun and Flatt (2019).

of divergence closely resembles the 'suspension bridge' pattern (Kapun *et al.* 2016).

How Inversion Polymorphisms Are Maintained by Balancing Selection

Once positive selection has established an inversion at some appreciable frequency, and depending on the details of the circumstances (Kirkpatrick and Barton 2006), it might go to fixation or be maintained at some intermediate frequency by balancing selection (e.g. Dobzhansky, 1954; Dobzhansky, 1970; Kirkpatrick and Barton, 2006; Hoffmann and Rieseberg, 2008; Schaeffer, 2008; Wellenreuther and Bernatchez, 2018; Faria *et al.*, 2019). Indeed, a large body of work has shown that adaptive inversion polymorphisms are often maintained by some form of balancing selection, with numerous examples from *Drosophila* but also from many other organisms (e.g. reviewed in Dobzhansky, 1970; Kirkpatrick and Barton, 2006; Schaeffer, 2008; Kapun and Flatt, 2019; and see references therein). Many of these empirical examples indicate that heterokaryotypes are fitter than the homokaryotypes, thus suggesting that the inversion polymorphisms in question might be maintained by heterozygote advantage (see **Glossary**) but in most cases, the actual genetic mechanisms involved have not been worked out. **See also**: **Heterozygous Advantage**

Heterozygote advantage for an inversion could arise through classical, single-locus overdominance (OD), for example caused by an overdominant mutation at the breakpoints or from an overdominant locus inside the inversion body, with one allele being fixed on the ancestral standard arrangement chromosome and the other one fixed on the inverted chromosome (Kirkpatrick 2010) (**Figure 4a**). Alternatively, in the coadaptation model, the inversion might experience 'cumulative' heterozygote advantage, with at least two overdominant loci being involved (Haldane, 1957). Both these mechanisms could potentially lead to the spread of the inversion and stabilise it at some intermediate frequency.

Another interesting hypothesis is 'associative' overdominance (AOD; sometimes also called 'pseudo-overdominance'; see **Glossary**) (Sved, 1968; Ohta and Kimura, 1970; Sved, 1972; Crow, 2000; Kirkpatrick and Barton, 2006; Zhao and Charlesworth, 2016; Charlesworth and Charlesworth, 2018) (**Figure 4b**). This type of 'OD' typically refers to heterozygotes at neutral loci that experience 'apparent heterozygote advantage' because they are linked to sites under selection, but this mechanism obviously has a direct bearing on the 'effective' heterosis of the linked region beyond the neutral loci. AOD arises if alleles at the selected loci are subject to classical OD **(Figure 4a)**, or if they segregate for partially or fully recessive deleterious alleles maintained by mutation pressure (**Figure 4b**), so that homozygotes at the neutral loci, which are linked to the selected loci, have lower fitness values on average than the heterozygotes (Charlesworth and Charlesworth, 2018). In the latter case, the fitness effects of deleterious alleles at the selected loci are thus covered up by partially or fully dominant alleles on mutually complementary haplotypes (**Figure 4b**). The haplotypes are thus in negative LD with each other, which generates an excess of repulsion double heterozygotes (see 'coupling and repulsion phase', **Glossary**).

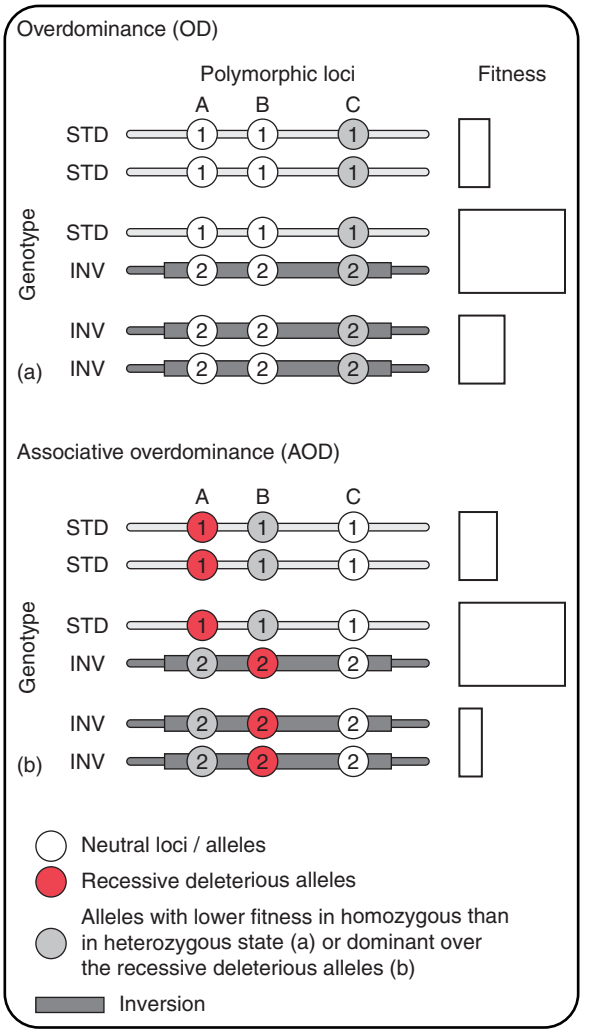

Figure 4 Two forms of heterozygote advantage that can maintain inversion polymorphisms. (a) Fitness overdominance (OD) occurs when heterozygotes at a given locus (for example locus C) enjoy a greater fitness than both STD and INV homozygotes. This heterozygote advantage might result from a single overdominant mutation, either at the breakpoints or within the inversion body, whereas in more complex scenarios (e.g. the 'coadaptation' model), it might arise from 'cumulative' effects of two or more overdominant mutations. (b) Associative overdominance (AOD) refers to heterozygotes at a neutral locus that experience an 'apparent' heterozygote advantage because the neutral locus is linked to sites under selection. For example, heterozygotes at the neutral locus C appear to have a greater fitness than STD and INV homozygotes because of negative selection against the linked recessive deleterious mutations A1 and B2 at loci A and B, respectively. In inversion heterozygotes, the negative effects of A1 and B2 are 'balanced' by the dominant or partially dominant alleles A2 and B1, thus rendering the STD and INV haplotypes 'complementary'. AOD can also occur when a neutral locus is linked to a single overdominant locus, as shown in (a): heterozygotes at the neutral B locus have greater fitness than homozygotes because the B locus is linked to the overdominant C locus, the latter being under positive selection.

How might this mechanism affect the frequency dynamics of an inversion polymorphism? Under some fairly delicate conditions, this mechanism can stabilise allele frequencies at the linked loci and retard the loss of variability; however, under other conditions, loss of variability might be accelerated (Zhao and Charlesworth, 2016; Charlesworth and Charlesworth, 2018). One potential difficulty with the AOD mechanism is that, if the inversion is initially rare and will thus most frequently find itself in heterokaryotypic state, it is somewhat difficult to see how a sufficient amount of heterosis could be generated in heterokaryotypes, unless the inversion carries a very large number of weakly selected deleterious alleles and there is a substantial amount of genetic drift in a small population, allowing the inversion to gain a foothold. Another possibility might be that the inversion is initially favoured by positive selection when rare, with the inversion subsequently capturing recessive deleterious alleles at other loci and thus with AOD building up over time. The inversion would then spread up to a point where the recessive deleterious homozygotes in the homokaryotypes have become sufficiently frequent for the initial selective advantage to be offset, thereby resulting in a balanced inversion polymorphism (Kirkpatrick and Barton, 2006). This scenario is – at least qualitatively – consistent with quite many

inversion polymorphisms that seem to be stably maintained at intermediate frequencies in natural populations (Kirkpatrick and Barton, 2006; Kapun and Flatt, 2019). Some form of AOD might also be qualitatively consistent with the relatively high proportion of lethality observed in iso-chromosomal homokaryotypes when isolating inverted chromosomes from natural populations of *D. melanogaster* (our unpublished observations). However, it is probably fair to say that there is not yet much strong empirical evidence for AOD being involved in maintaining inversion polymorphisms. Nonetheless, recent advances in studying AOD using genomic data, albeit not yet in the context of inversions, are promising (Becher *et al*., 2020; Gilbert *et al*., 2020). **See also**: **Genetic Load**

Net heterozygote advantage for fitness can also arise from antagonistic pleiotropy (AP; see **Glossary**) with dominance reversal, that is, when one allele has a dominant effect on one fitness component, whereas the other allele has a dominant effect on another fitness component (Curtsinger *et al*., 1994). Indeed, there is some recent evidence suggesting that this mechanism might be at play in maintaining a chromosomal inversion polymorphism in the seaweed fly *Coelopa frigida* (Mérot *et al*., 2020).

In addition to these various forms of heterozygote advantage, other important, not mutually exclusive types of balancing selection can contribute to maintaining inversion polymorphisms, including frequency-dependent selection, spatially varying (clinal) selection, and temporally varying (fluctuating) selection (Dobzhansky, 1943; Wright and Dobzhansky, 1946; Haldane, 1948; Alvarez-Castro and Alvarez, 2005; Kirkpatrick and Barton, 2006; Schaeffer, 2008; Kapun *et al*., 2016; Wittmann *et al*., 2017; Faria *et al*., 2019).

For example, models applied to empirical data from *Drosophila subobscura and D. pseudoobscura* suggest that negative frequency-dependent selection (NFDS; see 'Frequency-dependent selection', **Glossary**), that is, a situation where a genotype or allele is selectively favoured when rare, might lead to the maintenance of balanced inversion polymorphisms (Alvarez-Castro and Alvarez, 2005). Similarly, a study by Nassar *et al*. (1973) indicates that the *In(3R)Payne* inversion in *D. melanogaster* mentioned above might be subject to NFDS, with the highest fitness being observed when the inversion is at low to intermediate frequency, whereas its advantage vanishes when its frequency is high. Recent work has also found that a combination of NFDS and positive frequency-dependent selection maintains a polymorphic mimicry supergene (involving several distinct inversions) in the toxic, mimetic Amazonian butterfly *Heliconius numata* (Chouteau *et al*., 2017). Overall, however, evidence that NFDS maintains inversion polymorphisms remains scarce. **See also**: **Selection: Frequency-dependent**

Like frequency-dependent selection, spatially and/or temporally varying selection also involve variable (nonconstant) fitness values and can contribute to maintaining polymorphisms (see discussion in Faria *et al*. 2019; Kapun and Flatt, 2019). The importance of spatially varying selection acting on inversion polymorphisms is particularly well supported by empirical evidence, especially in *Drosophila*. For instance, several inversion polymorphisms in *D. melanogaster* exhibit pronounced frequency gradients across latitude (so-called 'clines') on multiple continents, typically with inverted arrangements being more common in subtropical/tropical climates and with standard arrangements being more frequent in temperate, seasonal climates (Kapun and Flatt, 2019; Kapun *et al*., 2016). Population genomic evidence suggests that several of these clinal inversion polymorphisms are indeed stably and nonneutrally maintained by selection (Kapun *et al*., 2016; Kapun *et al*., 2020).

Finally, some inversion polymorphisms in *D. pseudoobscura*, famously studied by Dobzhansky, and in *D. melanogaster* have also been found to fluctuate seasonally, potentially consistent with temporally varying selection (Dobzhansky, 1943; Wright and Dobzhansky, 1946; Kapun *et al*., 2016). A recent model by Wittmann *et al*. (2017), involving fluctuating selection and AP with dominance reversal, suggests that the conditions whereby temporally varying selection can maintain polymorphisms are less restrictive than previously thought.

Conclusions

As we have discussed in this article, different forms of positive selection can be invoked to explain the spread and the maintenance of chromosomal inversion polymorphisms. While several of these selective mechanisms are consistent with observational or experimental evidence, firmly demonstrating which mechanisms are causally involved remains a major empirical challenge. A related difficulty is that many of the mechanisms mentioned above are not mutually exclusive (Faria *et al*., 2019). Yet, at the same time, inversion polymorphisms provide a fascinating opportunity for improving our understanding of natural selection, in particular, the nature of balancing selection. Current advances in genomics and modelling, in conjunction with experimental data, promise to make progress in this direction (Guerrero *et al*., 2012; Wellenreuther and Bernatchez, 2018; Faria *et al*., 2019; Kapun and Flatt, 2019).

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Glossary

Antagonistic pleiotropy (AP) In terms of fitness-related traits, antagonistic pleiotropy means that a single gene or allele has positive effects on one fitness component but negative effects on another.

Associative overdominance (AOD) AOD refers to a sort of multi-locus heterozygote advantage caused by the effects of linked loci; this net heterozygote advantage of a multi-locus haplotype can even arise when the loci involved are not subject to overdominance. AOD is sometimes also called pseudo-overdominance. Strictly speaking, it refers to the 'apparent' heterozygote advantage at a nonselected (neutral)

locus which is linked to a selected locus but here we use the term more broadly to describe multi-locus heterozygote advantage caused by linkage.

Coupling and repulsion phase A double heterozygote is in 'coupling phase' if the two linked heterozygous loci occur in the arrangement *A B* / *a b*, whereas 'repulsion phase' means that the heterozygous gene pair occurs in the arrangement *A b* / *a B* (where *A* is fully or partly dominant over *a*, and where *B* is fully or partly dominant over *b*).

Epistasis and epistatic selection Epistasis describes the interaction between alleles at two or more loci whereby the allelic effects at one locus depend upon the effects at the other locus or loci (in contrast to additive or multiplicative effects across loci). Epistatic selection refers to selection acting on a combination of alleles at two or multiple loci whose fitness values interact.

Frequency-dependent selection Under frequency-dependent selection, the fitness (selection coefficient) of a genotype or allele depends upon the frequency of that genotype or allele in the population. With negative frequency-dependent selection, the genotype or allele has a selective advantage when rare, whereas with positive frequency-dependent selection the genotype or allele has an advantage when common. Only negative frequency-dependent selection can maintain a balanced polymorphism.

Heterozygote advantage Heterozygote advantage means that the heterozygote at a single locus or a heterozygous multi-locus genotype has higher fitness than the homozygotes. In the former case, this is called overdominance (OD); in the latter case, this is sometimes called associative overdominance or pseudo-overdominance. Heterozygote advantage can also arise through antagonistic pleiotropy with dominance reversal of allelic effects with regard to fitness components. Heterozygote advantage is sometimes also called heterosis, even though heterosis can also refer to 'hybrid vigour', that is, the situation where the F1 hybrids have higher fitness than the parental stocks or genotypes.

Linkage disequilibrium (LD) LD is a statistical, nonrandom association of alleles at two or more loci. It implies that certain haplotypes are more or less frequent as compared to the situation where the allele frequencies at these loci evolve independently. LD can be caused, for example, by physical linkage, however, any statistically nonrandom association of alleles across loci is called LD, no matter what the cause (e.g. epistatic or correlational selection, drift, etc.).

Positive selection Under diploidy, positive directional selection implies that individuals homozygous for one allele have a greater fitness than the heterozygote and individuals homozygous for the other allele. Positive balancing selection (or simply balancing selection) refers to a situation where the heterozygote has higher fitness than the homozygotes, a situation called overdominance.

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