Revisiting the Impact of Inversions in Evolution: From Population Genetic Markers to Drivers of Adaptive Shifts and Speciation?

Ary A. Hoffmann[1] and Loren H. Rieseberg[2]

[1]Centre for Environmental Stress and Adaptation Research, Department of Genetics, University of Melbourne, Parkville, Victoria 3010 Australia; email: ary@unimelb.edu.au

[2]Botany Department, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada; email: lriesebe@interchange.ubc.ca

Key Words

Abstract

There is a growing appreciation that chromosome inversions affect rates of adaptation, speciation, and the evolution of sex chromosomes. Comparative genomic studies have identified many new paracentric inversion polymorphisms. Population models suggest that inversions can spread by reducing recombination between alleles that independently increase fitness, without epistasis or coadaptation. Areas of linkage disequilibrium extend across large inversions but may be interspersed by areas with little disequilibrium. Genes located within inversions are associated with a variety of traits including those involved in climatic adaptation. Inversion polymorphisms may contribute to speciation by generating underdominance owing to inviable gametes, but an alternative view gaining support is that inversions facilitate speciation by reducing recombination, protecting genomic regions from introgression. Likewise, inversions may facilitate the evolution of sex chromosomes by reducing recombination between sex determining alleles and alleles with sex-specific effects. However, few genes within inversions responsible for fitness effects or speciation have been identified.

INTRODUCTION

Inversions can be paracentric, involving one chromosome arm, or less commonly, pericentric, encompassing the centromere region. Paracentric inversions may segregate with noninverted arrangements in populations, and these polymorphisms provided early evidence for genetic markers under selection through the pioneering work of Dobzhansky and his colleagues on *Drosophila pseudoobscura* (Dobzhansky 1970). Evidence for selection on inversion polymorphisms has now been obtained in several other organisms including mice (Lyon 2003) and humans (Stefansson et al. 2005). Early literature on inversions also focused on their role in genetic isolation based on reports of meiotic abnormalities and partial sterility in plants heterozygous for inverted and noninverted arrangements (known as inversion "heterozygotes" or "heterokaryotypes"), followed by similar observations in *Drosophila*, grasshoppers, and ducks (reviewed in Darlington 1937, Sturtevant 1938). However, it was clear even at this very early stage that inversion heterozygosity had a larger impact on fertility in plant hybrids than in *Drosophila* (Dobzhansky 1933).

In this review, we focus on recent data and models that aim to understand the impact of inversions and inversion polymorphisms on evolution. After an inversion arises in a population, it may be lost or spread to fixation, or else remain in a polymorphic state. We consider recent theory and data that addresses the conditions favoring their spread and their potential role in speciation. We examine the extent to which inversions maintain areas of disequilibrium (nonrandom association) among alleles at loci located within or near inversions, providing them with a role in adaptive evolution particularly along environmental gradients. Phenotypes associated with inversions are reviewed, along with progress in establishing the genetic basis of these phenotypes. We examine the long-term fate of inversion polymorphisms in populations and the role of deleterious mutations in maintaining polymorphisms.

INCIDENCE AND ORIGIN OF INVERSIONS AND INVERSION POLYMORPHISMS

Inverted regions that distinguish species and inversion polymorphisms within species have traditionally been identified cytologically from observations of meiotic configurations. Polymorphisms in large inversions were traditionally identified in *Drosophila* and other diptera like midges by examining the salivary glands of adults where polytene chromosomes were located; inversion polymorphisms were recognized by loops in polytene chromosomes that reflected chromosomal pairing between large inverted and noninverted arrangements. Inverted regions were identified from banding patterns of chromosomes even among phylogenetically distant species groups and used to reconstruct phylogenies as in several *Drosophila* (Krimbas & Powell 1992).

Recently, molecular techniques have been developed to score known inversion polymorphisms, either through primers that span the breakpoint region of the inversions or through single nucleotide polymorphisms (SNPs) and other polymorphisms in disequilibrium with the inversions (Matzkin et al. 2005, White et al. 2007b). Unusual patterns of linkage disequilibrium (LD) among alleles from high-density markers provide one avenue for identification, such as in the case of human SNP data (Bansal et al. 2007). Inversions can also be detected by looking at the linear map order of molecular markers in crosses or by comparing sequenced genomes. The comparative genetic mapping approach was pioneered in the plant family, Solanaceae, where it was shown that the tomato and potato genomes differ by three paracentric inversions (Bonierbale et al. 1988). More recently, the approach was used by Feder et al. (2003b) to identify inverted regions on three chromosomes of *Rhagoletis pomonella* fruitflies. There are other cases where coinheritance suggests paracentric inversions, such as in the marine snail *Littorina fabalis* where genetic markers and size are associated (Johannesson & Mikhailova 2004). However, with the advent of next-generation

sequencing platforms, direct sequencing represents the most promising and accurate approach for inversion detection. For example, characterization of inversion events in six hemiascomycetous yeast lineages, which represent more than 500 million years of divergence, identified between 100 and 800 inversions within major synteny blocks (Fischer et al. 2006)

Inversions that differentiate species tend to accumulate at different rates in lineages. In *Drosophila* species, the majority of genes in different species are located on the same chromosomes, but extensive shuffling often involving paracentric inversion rearrangements has occurred within chromosome arms. Rearrangement rates within chromosome arms differ between *Drosophila* lineages. For example, the recent 12 genome comparison revealed 29 inversions between *D. melanogaster* and *D. yakuba*, of which 28 were fixed in the *D. yakuba* lineage (*Drosophila 12 Genomes Consortium 2007*). Likewise, in yeast, the inversion rate in the clade leading to cryotolerant *Debaryomyces hansenii* is approximately 10 times that of most other lineages (Fischer et al. 2006).

Genomic comparisons across species may assist in identifying inversion polymorphisms within species. In a comparison of human and chimpanzee genomes, 66 inversions more than 25 kb in length were detected, often flanked by duplications of DNA segments (Feuk et al. 2005). Three out of 23 regions were subsequently found to be polymorphic in the human genome, varying from 1 kb to 730 kb in length.

However, in other cases polymorphisms may be maintained by different processes from those leading to rearrangements; this seems to be the case for *Drosophila miranda* and *D. pseudoobscura*, which are differentiated through numerous paracentric inversion events in all chromosomes, while most inversion polymorphisms in *D. pseudoobscura* are restricted to one of the chromosomes (Bartolome & Charlesworth 2006). Inversion polymorphisms within species may also be identified through reiterated DNA sequences that are targets for nonallelic homologous recombination. Flores et al. (2007) focused on identical repeats located in reverse orientation to locate three chromosomal inversions in somatic human tissue.

Inversions that segregate as polymorphisms can be large; common inversions in *Drosophila* can cover a substantial part of a chromosome arm and might be around 10,000 kb (Krimbas & Powell 1992). Other segregating inversions are much smaller and may cover only a few kb. In humans numerous small inversions segregate in populations, but also larger ones to 1000 kb (Bansal et al. 2007, Feuk et al. 2005).

The incidence of inversion polymorphisms can differ markedly among related species. *Drosophila melanogaster* has more than 500 inversion polymorphisms, whereas its sibling species *D. simulans*, which has a similar distribution, has only 14 (Aulard et al. 2004). Many *Drosophila melanogaster* inversions display strong geographic clines, whereas these have not been found for *D. simulans*. *Drosophila virilis* lacks natural polymorphic inversions, whereas the related *D. montana* has more than 40 (Morales-Hojas et al. 2007). The incidence of inversion polymorphisms varies among populations as well as species. In *Drosophila*, a repeatable pattern established more than two decades ago is the higher incidence of polymorphisms in populations that are centrally located within a species' distribution compared to marginal populations (Krimbas & Powell 1992, Stocker et al. 2004).

One reason why species might differ in the incidence of inversion polymorphisms is variation in the activity of transposable elements (TEs). These elements often occur close to breakpoints of inversions in *Drosophila* (e.g., Andolfatto et al. 1999, Evgen'ev et al. 2000) and may generate inversions at least in laboratory stocks (Evgen'ev et al. 2000), although not all breakpoints are associated with TEs (e.g., Wesley & Eanes 1994). Also the presence of some TEs at inversion breakpoints might be a consequence of the inversion event rather than responsible for it. In *D. buzzatii*, several TEs at the breakpoints of inversions *2j* and *2q*(7) appear to be secondary effectors rather than being responsible for the inversion event (Casals et al. 2003, 2006). TEs

have also been found at breakpoints of one inversion in mosquitoes of the *Anopheles gambiae* complex (Mathiopoulos et al. 1998), although the precise role of TEs in generating inversions is unclear for another inversion in this complex (Sharakhov et al. 2006).

Recent analysis of breakpoints for the 29 inversions differentiating the *D. melanogaster* and *D. yakuba* genomes has cast further doubt on the role of TEs in generating inversions (Ranz et al. 2007). Only five pairs of breakpoint regions had similar repetitive sequences at the two breakpoints. Instead, the majority of the inversions (18 of 29) were associated with duplicated regions at the co-occurring breakpoints. These duplicated sequences generally were not found elsewhere in the genome, and with only one exception, occurred in reverse orientation. Ranz et al. (2007) argued that the inverted duplications most likely result from staggered breaks rather than ectopic exchange between inverted repetitive sequences.

Apart from TEs, another reason why the incidence of polymorphisms in large inversions might differ among species relates to the meiotic cost of infertility in inversion heterozygotes. When single crossovers occur in these heterozygotes, the recombinant gametes are unbalanced. However, in *Drosophila* females, three of the four gametes become polar cells and only one forms the egg; the recombinant gamete is less likely to become the egg because it migrates more slowly, reducing any cost associated with recombinant gametes. This factor coupled with the absence of recombination in males might explain the persistence of inversion polymorphisms in *Drosophila melanogaster* and other species, although it does not explain the high incidence of inversion polymorphisms in species where there is some male recombination (Krimbas & Powell 1992).

Inversions might be introduced into populations through hybridization. Perhaps the most convincing case of introduction following hybridization concerns *Anopheles gambiae* and *A. arabidiensis* (Besansky et al. 2003). The former species is polymorphic for two chromosome 2 inversions, 2Rb and 2La. Based on molecular similarity, it appears that *A. gambiae* acquired 2Rb and 2La from *A. arabidiensis* following hybridization, allowing colonization of more arid areas where these inversions are at a high frequency. The introduction of inversions through hybridization is supported experimentally through the results of introgression experiments (dellaTorre et al. 1997). Hybridization has also been implicated in the acquisition of climate-adapted inversions by *Rhagoletis pomonella* (Feder et al. 2003a) and it seems certain that many more cases will emerge as additional molecular comparisons are completed.

SPREAD OF INVERSIONS IN POPULATIONS

There are six main explanations for the spread and distribution of inversions in populations (**Table 1**). Two focus on the impact that inversions have on maintaining LD between loci located within the inversions. Inversions maintain LD because pairing among chromosomes is affected, decreasing the production of recombinants, and also because single crossovers between inverted and noninverted arrangements result in unbalanced products during meiosis. The latter can be averted when there are double crossovers within the inverted region of the chromosome. Gene conversion can also occur within inversions, at least away from the breakpoints. Some recombination therefore does occur between inverted and noninverted sequences but it is greatly reduced when compared to recombination within the inverted (or noninverted) sequences. Recombination might be almost completely suppressed with a series of overlapping inversions along a chromosome.

In the traditional explanation for the spread of an inversion proposed by Dobzhansky, alleles at loci within the inversion are assumed to have epistatic effects on fitness; combinations of alleles at these loci are assumed to be "coadapted" by having a higher fitness than predicted from the sum of their independent effects (Dobzhansky 1970). Theoretical models and computer simulations

Table 1 Factors contributing to the spread of inversions in populations[a]

Explanation	Fate of inversion	Supporting evidence
Reduced recombination and local selection	Near fixation	Multiple areas of inversion under selection and/or contributing to traits
Reduced recombination and epistatic selection	Fixation	Indirect evidence based on fitness of *Drosophila* following inter- and intrapopulation crosses
Inversion itself is under selection	Depends on fitness effects caused by breakpoints or position effects	Changed expression levels of genes associated with human diseases
Inversion is neutral	Depends on genetic drift in populations and migration	Inversion polymorphisms that behave like neutral markers in populations
Overdominance	Balanced polymorphism	Excess of heterokaryotypes, such as in some *Drosophila* populations and seaweed flies
Underdominance	Fixation or loss	Recovery of chromosome pairing and fertility in plants following genome doubling

[a]Partly based on Kirkpatrick & Barton 2006.

indicate that these types of interactions favor selection for areas of low rates of recombination where the interacting loci reside (Nei 1967, Pepper 2003). Because inversion polymorphisms generate low recombination rates among the standard (noninverted) and inverted arrangements, they facilitate the spread of the coadapted alleles. Inversions carrying favorable alleles then spread to fixation unless there is migration or counteracting selection to prevent fixation.

An alternative hypothesis is that inversions are favored because they bring together locally adapted alleles even without epistasis. This hypothesis was recently promoted by Kirkpatrick & Barton (2006), and builds on theory showing that modifier alleles decreasing recombination are favored even when loosely linked to locally adapted genes that act additively (Charlesworth & Charlesworth 1979). Kirkpatrick & Barton (2006) pointed out that inversions are favored in a population at migration-selection balance whenever an inversion captures an advantageous haplotype whose frequency is decreased by recombination. They then derived conditions for the invasion of an inversion and showed that when recombination is strong relative to selection, the inversion will spread at a rate of $(n–1)/m$, where n is the number of loci under local selection captured in the inversion and m is the migration rate. The inversion will then spread close to fixation, with polymorphism only being maintained via migration or deleterious genes captured within the inversion.

A third hypothesis is that inversions are favored because of direct selection for the inversion event that generates a mutation at the breakpoint. Under this hypothesis, the inversion itself is the target of selection, rather than any effects that it might have on recombination. In humans, genetic disorders may be caused by inversion breakpoints disrupting gene expression through position effects or direct disruption of a gene (Castermans et al. 2007, Tadin-Strapps et al. 2004). However, there is little direct evidence that phenotypes associated with inversions segregating in populations are caused by gene disruption at breakpoints.

A fourth hypothesis is that inversions are neutral, and their probability of fixation or loss depends purely on population size and migration. Many small inversions segregating in populations might be neutral but it is too early to determine what fraction of inversions fall into this category. In water beetles, intraspecific variation in chromosomal rearrangements largely follows Hardy-Weinberg (HW) equilibrium, suggesting that there is no strong selection on the rearrangements (Aradottir & Angus 2004). There is also no evidence of deviations from HW in inversion polymorphisms from blackflies (Kuvangkadilok et al. 2003). However, deviations from HW are a weak test for the

absence of selection. *Drosophila* data show that frequencies of large inversion usually vary clinally and/or seasonally and therefore are influenced by selection in at least some environments (Krimbas & Powell 1992).

The fifth and sixth hypotheses for the spread of inversions involve overdominance and underdominance. Overdominance occurs when inversion heterozygotes have a higher fitness than either homozygote inverted or noninverted ("standard") arrangement, whereas underdominance refers to the situation where inversion heterozygotes have a lower fitness than either of the other arrangements. Overdominance can arise from deleterious alleles in the region covered by an inversion. If the inverted arrangement carries a deleterious allele and the standard arrangement carries a different deleterious allele, there will be heterokaryotype advantage. However, it is hard to see how this situation could develop in a population unless it was tied to another mechanism like local adaptation. Different deleterious alleles might accumulate in isolated populations fixed for alternative arrangements, and these arrangements could then exhibit heterokaryotype advantage if the populations come together again. Nevertheless, any advantage is expected to be transitory as recombination generates haplotypes in the inverted or standard arrangement without the deleterious alleles.

Underdominance might occur if single crossovers are frequent within the inversion, leading to the production of unbalanced and inviable gametes. This appears to be the case for many inversions that differentiate plant species, but not seemingly in most animals (Coyne & Orr 2004, Rieseberg 2001), and this process does not maintain inversion polymorphism in populations. The most convincing evidence for chromosomal underdominance comes from recovery of chromosome pairing and fertility following genome doubling of structural heterozygotes, reported in many plant species (Stebbins 1958). In one such test performed in animals, involving hybrids of *Drosophila pseudoobscura* and *D. persimilis*, no such recovery was observed (Dobzhansky 1933). As explained by Dobzhanksy (1933), polyploidy furnishes an exact homologue to every chromosome, thereby eliminating chromosomal sterility. In contrast, sterility caused by the action of complementary genetic factors should not be changed by genome doubling. Other evidence consistent with the underdominance of inversions includes mapping of underdominant quantitative trait loci (QTLs) to inversion breakpoints in several plant species (e.g., Lai et al. 2005), although this also can result from the accumulation of Bateson-Dobzhansky-Muller (BDM) incompatibilities within inversions (Noor et al. 2001). BDM incompatibilities occur when different incompatibility alleles become fixed in populations that then exhibit incompatibility when crossed.

Several factors may contribute to the higher fixation rates of underdominant rearrangements in plants. First, rates of chromosomal evolution appear to be highest in annual plants (Burke et al. 2004, Levin 2002), which are prone to dramatic fluctuations in population size and high levels of population turnover (Harrison et al. 2000). These population dynamics are favorable for the establishment of underdominant rearrangements through drift in small, inbred populations (Hedrick 1981, Walsh 1982), as well as their spread through repeated bouts of local extinction and recolonization (Lande 1985). Second, many plant species can self, at least at some low frequency, whereas this is not possible in most animals. Because selfing greatly increases the fixation probability of underdominant mutations, Coyne & Orr (2004) argued that this is the most important explanation for this pattern. Although selfing must be important, it is not the full explanation because the highest rates of chromosomal evolution in plants or animals are in annual sunflowers (Burke et al. 2004, Lai et al. 2005), which are obligate outcrossers. A third explanation was put forward by Rieseberg (2001), who speculated that the lack of degenerate sex chromosomes in plants might be partially responsible for this pattern. Degenerate sex chromosomes, which are common in many animals, facilitate both the accumulation of gene incompatibilities (Masly & Presgraves 2007) and their expression in heterogametic hybrids (if partially recessive), reducing the opportunity for chromosomal speciation.

PATTERNS OF MOLECULAR VARIATION AND LINKAGE DISEQUILIBRIUM ACROSS INVERSIONS

Patterns of LD between alleles at loci located within the inverted arrangements reflect the history of an inversion and gene flux since its formation. Levels of LD should fall away from the inversion breakpoints toward its center where multiple crossovers and gene conversion are more common (Laayouni et al. 2003, Navarro et al. 1997). These processes decrease levels of divergence between arrangements and help explain low levels of nucleotide divergence away from the breakpoints as found in many *Drosophila* studies (Andolfatto et al. 2001), although this is not always the case (Munte et al. 2005). The extent of loss of LD depends on the time elapsed since an inversion first arose. The rate of gene conversion and crossing over in the center of the inversions is 10^{-4} to 10^{-5} in *Drosophila*, and this rate is expected to decrease LD to low levels over some tens or hundreds of thousand generations (Andolfatto et al. 2001). Thus little LD would be expected in inversions that developed hundreds of thousands of years ago given the relatively short generation times of *Drosophila*. The origin of inversions can be aged from levels of nucleotide variation at breakpoints as well as levels of divergence from standard arrangements. On this basis, *D. melanogaster* inversions like *In(2L)t* and *In(3L)P* appear relatively recent at one or a few hundred thousand years (Andolfatto et al. 1999, Hasson & Eanes 1996). Inversions in *Drosophila buzzatii* also appear to be relatively recent in origin (Laayouni et al. 2003).

Patterns of nucleotide variation provide another signature of the evolutionary history of an inversion. Variation is expected to be lowest in derived inversions around the breakpoint when compared to their center, as long as the inversions do not represent an old polymorphism because nucleotide variation might then be high around breakpoints (Andolfatto et al. 1999, Navarro et al. 1997). This is largely consistent with the *Drosophila* data where nucleotide variation is low around breakpoints even though divergence between inverted and standard arrangements in this region is high (Andolfatto et al. 1999, Laayouni et al. 2003).

Although empirical studies indicate a decrease in LD away from breakpoints (Kennington et al. 2006, Schaeffer et al. 2003), there is good evidence of LD across inversions consistent with selection. An extreme case concerns meiotic drive. Alleles that generate meiotic drive are transmitted to more than half of offspring (unlike under Mendelian segregation) often by influencing processes associated with sperm. For instance, segregation distorter (SD) in *Drosophila melanogaster* causes preferential transmission of the SD chromosome from SD/SD+ males because of sperm dysfunction associated with a signaling pathway (Kusano et al. 2003). Because drive systems usually involve interacting alleles, they are expected to spread only in populations if located in regions with low recombination like inversion regions in *D. melanogaster* and mice (Kusano et al. 2003, Lyon 2003). An extreme case of LD associated with meiotic drive has recently been described in *Drosophila recens*, where there is suppression of recombination across the entire X chromosome owing to a series of inversions (Dyer et al. 2007). The driver is polymorphic in *D. recens* populations and persists despite the X chromosome carrying a deleterious mutation.

Other cases of LD across inversions but away from the breakpoints suggest regions within inversions under selection. Areas of high LD between markers and inversions interspersed with areas of low LD have been found in both *D. pseudoobscura* and *D. melanogaster* (Kennington et al. 2006, Schaeffer et al. 2003). LD is evident among loci within the inversion as well as between the loci and the inversion, suggesting that LD reflects selection rather than historical processes. In some inversions like the O_3 inversion system of *D. subobscura*, there is strong LD across the entire region covered by the inversion (Munte et al. 2005). In other inversions like those found in *A. funestus*, no LD has yet been found among loci within the inversion or between the loci and the inversion (Cohuet et al. 2004). Patterns of LD might be detected in such systems with a higher

density of markers, although it is also possible that inversion polymorphisms in *A. funestus* are being maintained by direct selection on breakpoints rather than on alleles within the inversions.

As well as involving loci located within inversions, patterns of LD may extend to markers outside inversions. These might include other inversions, genes, or even mtDNA variants (Oliver et al. 2002) and arise because of selection for particular combinations of alleles/inversions. Patterns of LD between inversions and markers may change seasonally in a predictable manner (Rodriguez-Trelles 2003) and reflect changing selection pressures throughout the year.

Several studies have examined nucleotide variation at genes within inversions to detect a signature of selection using measures like Tajima's D. Schaeffer & Anderson (2005) detected one region in a *D. pseudoobscura* inversion with a very low level of polymorphism suggestive of selection, in contrast to regions with a high level of polymorphism nearby. However, no clear signature of selection was detected in genes in the 2La inversion of *Anopheles gambiae* by White et al. (2007a), even though these genes were located in regions that were differentiated between chromosomal arrangements as identified through oligonucleotide microarray analysis.

The location of polymorphic inversions in a genome when compared to the location of fixed differences that distinguish species has been used as a test of neutrality of inverted arrangements. If chromosome polymorphisms are neutral, an association between these locations might be expected. In the case of polymorphic inversions in *D. montana*, the location of polymorphic inversions is significantly different from that of fixed inversion differences that distinguish this species from its relative *D. virilis* (Morales-Hojas et al. 2007). The locations of polymorphic inversions in *D. pseudoobscura* also do not match fixed differences with a related species (Bartolome & Charlesworth 2006), as noted above.

FREQUENCY CHANGES IN POPULATIONS

Soon after their initial discovery, *Drosophila* inversion polymorphisms were found to be under strong selection because inversion frequencies changed rapidly in cage and natural populations and often returned to their original values following perturbations (Dobzhansky 1970, Krimbas & Powell 1992). Changes in inversion frequencies were often interpreted in terms of inversion heterozygote advantage, particularly as an excess of heterokaryotypes was found in several population samples. This pattern has also been observed in population samples of *Anopheles gambiae* mosquitoes (Brooke et al. 2002) and *Coelopa frigida* flies (Butlin & Day 1989).

Heterokaryotype advantage can arise when there are different deleterious alleles in inverted and standard arrangements. However, as discussed above, LD within arrangements breaks down quite rapidly over time, and this advantage is unlikely to be maintained unless deleterious genes are located near breakpoints. Heterokaryotype advantage is therefore often likely to be transient following founder events. For instance, the O_5 inversion of *D. subobscura* in the Americas is in complete LD with a lethal gene even though this inversion is common in populations (Sole et al. 2000). The tight LD is probably the result of a founder event when *D. subobscura* populations colonized the Americas in small numbers from Europe in the late 1970s, because European O_5 inversions with the same apparent breakpoint do not carry the same lethal gene (Zivanovic & Mestres 2000).

When inversion frequencies return to intermediate levels after perturbation, frequency-dependent selection rather than heterozygote advantage might be involved. Recently, Alvarez-Castro & Alvarez (2005) proposed frequency-dependent selection as a general mechanism for maintaining inversion polymorphisms in populations, based on the observation that arrangements in *D. subobscura* and *D. pseudoobscura* tended to have a higher fitness when they were relatively uncommon in populations. However, these patterns were based on a limited number of experimental

data points—a rigorous test of frequency dependence, particularly in natural populations, has not yet been undertaken.

Geographic patterns in inversion polymorphisms in *Drosophila* have often been interpreted in terms of climatic selection (Lee et al. 2002), although the selective factors involved are poorly understood. Inversion frequencies are typically linked to climate data from weather stations but these data might not reflect conditions experienced by flies and larvae from different parts of the geographic range. Geographic studies typically consider only linear clinal patterns, whereas high density sampling of a cline might reveal a nonlinear pattern as in the case of markers within the *In(2L)t* inversion in *D. melanogaster* (Umina et al. 2006).

Several *Drosophila* studies on chromosome inversion polymorphisms have linked changes in inversion frequencies to recent climate change, suggesting that widespread species may undergo adaptive shifts in response to the unprecedented 0.2°C increase in temperature per decade in the past 30 years (IPCC 2007). Changes in inversion frequencies have now been related to the direct or indirect effects of temperature shifts in three species: *D. subobscura*, *D. melanogaster*, and *D. robusta*.

In *D. subobscura*, Balanya et al. (2006) contrasted historic frequencies of over 21 chromosome inversion polymorphisms, gathered over an average of 24 years, to contemporary frequencies. They then compared these with monthly mean temperature records during this time period; consistent with predictions of climatic natural selection on these markers, there was a highly significant correlation between the indices used for chromosomes and for climate across all three continents. Temperature had increased in 22 of the 26 sites examined across the three continents, and chromosome frequencies had shifted toward a more low-latitude pattern in 21 of these 22 sites. This shift was comparable to moving the historical population approximately 1° of latitude closer to the equator. Surveys of Spanish populations (Rodriguez-Trelles & Rodriguez 1998) have also indicated that inversion arrangements typical of warm latitudes had increased in frequency at a local level. Whether temperature is directly responsible for these shifts is unclear. Santos et al. (2005) found that inversion frequencies changed consistently across replicate laboratory populations of *D. subobscura* held at different temperatures, but the chromosomal arrangements favored at the high laboratory temperature were not necessarily the same as the arrangements common at warmer latitudes.

In *D. melanogaster*, changes in clinal patterns exhibited by the *In(3R)P* inversion have been detected along the eastern coast of Australia over more than 20 years (Anderson et al. 2005, Umina et al. 2005). This inversion increases sharply from a low frequency in the temperate south of Australia to be close to fixation in tropical populations. The inversion shows parallel clines on different continents consistent with selection. The elevation of the clinal association (but not the slope) has changed markedly, such that inversion frequencies have increased around 20% on average.

Finally, long-term monitoring of *D. robusta* from the Smoky Mountains in North America has indicated shifts in inversion frequencies that match climate change. These shifts were first reported by Levitan (2001) and have since been documented more extensively by Etges, Levitan, and coworkers (Etges et al. 2006, Etges & Levitan 2004). Inversion polymorphisms in *D. robusta* exhibited similar altitudinal clines in different mountains, suggesting that they are under selection (Levitan 2001). In the 1980s, inversion frequencies changed in a manner consistent with the cooler conditions prevalent at that time, whereas since that period the high-altitude forms have decreased in frequency, consistent with more recent warmer conditions.

When changes in inversion frequencies at a site or geographic patterns are detected, there is always a danger that these patterns can be spurious and reflect random processes or gene flow rather than selection (Vasemagi 2006). This issue can be addressed by comparing patterns for

markers inside inversions with those outside them. In *D. melanogaster* from eastern Australia, clinal patterns were evident for several microsatellites within inversions but rare outside them (Gockel et al. 2001, Kennington et al. 2003), suggesting geographic selection on areas within the inversion. In *Anopheles gambiae*, microsatellite loci located within polymorphic chromosomal inversions show higher levels of genetic structuring than those outside them (Onyabe & Conn 2001), again consistent with selection. However, in another malaria vector, *Anopheles funestus*, this difference was not found, suggesting that the inversions might not be under selection (Cohuet et al. 2004).

Although there is considerable evidence for shifts in inversion frequencies in populations, the fitness components affected by the inversions have rarely been identified. One exception involves a 900-kb inversion at chromosomal location 17q21.31 in humans. This inversion is absent in African populations but at a high frequency of around 20% in European populations (Stefansson et al. 2005). In Iceland, carriers of the inversion have around 3% more offspring than noncarriers. The genome-wide recombination rate is higher in carrier females, particularly when females are homokaryotypic for the inversion, and this feature has previously been linked to female offspring number (Stefansson et al. 2005). These patterns suggest that the inversion should spread in human populations, although fitness effects may depend on environmental conditions as the inversion is present at a low frequency in some populations.

CANDIDATE TRAITS

A large number of traits have been associated with inversion polymorphisms; in *Drosophila* lists were given in Sperlich & Pfriem (1986) and Hoffmann et al. (2004) and an updated list is provided in **Table 2**. Traits include wing and thorax size, thermal resistance, starvation resistance, development time, fecundity, longevity, wing shape, and male mating success. Trait-inversion associations have been identified from correlated selection responses as well as association studies (Yadav & Singh 2006, 2007).

Inversion polymorphisms have been linked to several traits in nondrosophilids (**Table 2**). In blackflies and seaweed flies, they influence development time. In seaweed flies they also influence size and viability, although trait effects vary with environmental conditions including density (Butlin & Day 1989). Chromosome inversions also influence sperm displacement in seaweed flies; when females mate rapidly with males carrying the same or different karyotypes, sperm from males with the opposite karyotype to the female are favored, resulting in a higher number of heterokaryotypic offspring (Blyth & Gilburn 2005).

Pericentric inversions influence body size features in the New World grasshopper *Trimerotropis pallidipennis* (Colombo 2002). Higher latitude or altitude individuals are smaller and have higher frequencies of standard sequences. Moreover, inversion frequencies change between samples taken at the start and end of the adult lifespan, reflecting selection on the polymorphisms (Colombo 2003). A pericentric inversion also influences size in another grasshopper, *Sinipta dalmani* (Pensel & Remis 2007), and this trait in turn influences male survival (Remis 2002).

Polymorphic inversions in *Rhagoletis pomonella* fruitflies contain alleles that are associated with eclosion time, which dictates the diapause timing of pupae (Feder et al. 2003b). This trait contributes to isolation between hawthorn and apple races of *Rhagoletis*. Nuclear and mtDNA data suggest that the inversions that contribute to diapause arose in Mexico and probably spread into the United States where hawthorn and apple races separated at a later date (Feder et al. 2003a).

Inversion polymorphisms may contain genes influencing insecticide resistance. The *Anopheles gambiae* complex has two widespread paracentric inversions (2La and 2Rb) associated with dieldrin resistance (2La) and DDT resistance (2Rb) (Brooke et al. 2002). However, dieldrin resistance is

Table 2 List of traits associated with chromosomal polymorphisms[a]

Taxon	Traits associated with inversion polymorphism
Drosophila (various species)	Body size including wing and thorax size
	Wing shape and wing loading
	Resistance to heat and cold
	Longevity
	Development time
	Larval to adult viability
	Male mating success
	Fecundity
	Competitive ability
	Male and female fertility
	Starvation resistance
Seaweed fly (*Coelopa frigida*)	Body size
	Development time
	Viability
	Sperm displacement
Blackfly (*Wilhelmia paraequina puri*)	Male development
Grasshopper (*Trimerotropis pallidipennis*)	Body size
Grasshopper (*Sinipta dalmani*)	Body size and male survival
Fruitfly (*Rhagoletis pomonella*)	Eclosion time and diapause
Mosquito (*Anopheles gambiae*)	Aridity responses
	Insecticide resistance
Midge (*Chironomus ramosus* and others)	Nematode resistance
	Body size
Fungus (*Neurospora crassa*)	Self recognition

[a]Based on references in Sperlich & Pfriem 1986, Hoffmann et al. 2004, and text.

not associated with 2La in at least one African population (Brooke et al. 2006). In the tropical midge, *Chironomus ramosus*, inversion heterozygotes have lower rates of nematode infection than either of the inverted or noninverted homozygotes (Hardikar & Nath 2001). Inversions in midges have also been associated with larval size (Werle et al. 2004).

Patterns of nonself recognition that control cell fusion in *Neurospora crassa* are controlled by several factors, one of which consists of a complex of two genes (*un24* and *het-6*) in strong LD that are contained within the *In*(*het-6*) paracentric inversion (Micali & Smith 2006). The strong LD between these loci reflects the fact that the genes are located near the inversion breakpoints; there is only evidence for recombination in the center of the inversion. The allele combinations held together by the inversion have a higher fitness than the other combinations, which produce fewer viable progeny when generated artificially. When an allele from either *un24* or *het-6* isolated from one background was introduced into a different background, there was incompatibility and a reduction in fitness, suggesting that alleles combine to influence fitness in a particular background (Micali & Smith 2006). This case may represent a rare example of epistatic fitness effects maintaining an inversion polymorphism (**Table 1**).

The relative importance of inversions in the adaptive evolution of traits has rarely been addressed. It is therefore usually not clear if inversions play a critical role in adaptive shifts or if they only have a minor effect. One exception concerns the *In(3R)P* inversion of *D. melanogaster*, which

influences geographic variation in body size. By comparing genetically determined changes in size along a latitudinal gradient with the mean difference in size associated with *In(3R)P* genotypes within a population, Rako et al. (2006) found that 60% of the size cline in males and 30% in females was because of the *In(3R)P* inversion. In this case the inversion appears to have a substantial effect on the evolution of size along a gradient.

CANDIDATE GENES

Although a large number of traits have now been associated with inversions, there has been little progress in isolating the genetic basis of these associations. One reason is that traditional QTL mapping through crosses and recombinants cannot be easily undertaken owing to the low number of recombinants recovered from inversion heterozygotes. Mapping then produces broad areas where QTLs are located that reflected the position of the inversion (Calboli et al. 2003). Instead, association studies can be used to link marker variation within the inversion to quantitative traits, as long as LD within inversions is weak away from breakpoints. For instance, by associating size with microsatellite variation inside *In(3R)P* of *D. melanogaster*, Kennington et al. (2007) mapped two peaks away from the inversion breakpoints that contained genes influencing size. This approach can be used for mapping traits within large inversions that have been established for some time.

When there are geographic patterns exhibited by genes within inversions as well as the inversions themselves, and LD is not complete, it is possible to separate out the inversion effects statistically or by examining clinal patterns of the alleles within inverted and standard arrangements. Recent examples of this approach in *D. melanogaster* include Fryenberg et al. (2003), who showed that clinal patterns in one of the small heat shock proteins (*hsp 26*) persisted when only patterns within the *In(3L)P* inversion were considered, and Umina et al. (2006), who separated the effects of *In(2L)t* from the *Gpdh* polymorphism.

When a number of loci are examined across an inversion, it is possible to identify regions of the inversion that show strong clinal patterns and are therefore likely to be under clinal selection. Patterns of variation in genes and inversions are compared to determine regions of the inversion that covary with traits and regions away from breakpoints where clinal patterns are maintained. In the *In(3R)P* inversion of *D. melanogaster*, Kennington et al. (2007) found that two regions away from breakpoints but in strong LD with the inversion contained microsatellites that showed the strongest clinal patterns. These regions may contain loci that interact epistatically or act independently to maintain LD across the inversion. These alternatives can only be tested by estimating the fitness of different combinations of alleles across the inverted and standard arrangements (e.g., Micali & Smith 2006).

Genes underlying traits may eventually be identified from microarray analyses, high-resolution mapping, mutagenesis, RNAi, and other approaches, ideally supported by manipulations through techniques like homologous recombination to test the effects of specific alleles on traits in the same genetic background. We are unaware of these approaches successfully identifying allele-trait associations segregating with inversions, even though there are increasing numbers of examples in the literature for specific genes being linked to environmental changes (Reusch & Wood 2007). Associations between specific genes in inversions and traits have been postulated, such as the involvement of insulin receptor genes located inside *In(3R)P* in *Drosophila* size clines (De Jong & Bochdanovits 2003), but supporting evidence has not yet been provided.

Microarrays have been used to compare patterns of gene expression for loci located within and between inversions. In *D. subobscura* lines evolving in different thermal selection regimes (between 13°C and 22°C), populations diverged in a repeatable manner for inversion frequencies as well as life history and morphological traits (Laayouni et al. 2007). When gene expression patterns were

compared using cDNA microarrays, 6.6% of cDNAs were differentially expressed and the cDNAs with significant expression differences tended to be more commonly found inside than outside the inversions. These results indicate a complex evolutionary response to thermal regimes involving a number of genes nonrandomly distributed in the genome, and suggest candidates exist inside the inversions for future screening. Hybridization patterns with microarrays have also been used to identify regions of the 2La inversion in *Anopheles gambiae* that show a high level of differentiation from other arrangements and where candidate genes associated with aridity are likely to be located.

INVERSIONS AND SPECIATION

There are two main classes of chromosomal speciation models, closely aligned to alternative explanations given above for the establishment and spread of inversions. In the traditional underdominance models (King 1993, White 1978), recombination between rearranged chromosomes (e.g., between inverted and noninverted arrangements) is assumed to generate gametes carrying chromosomal duplications or deficiencies. These unbalanced gametes (or the zygotes produced from them) may be inviable, thereby creating a partial sterility barrier between populations or species that differ for the rearrangement. Underdominance models have been criticized on theoretical grounds, because a rearrangement that causes a large reduction in the fitness of heterozygotes is unlikely to become established in the first place, except under special conditions. For inversions, these conditions include meiotic drive (King 1993, White 1978), drift in small ($N_e < 50$), inbred populations (Hedrick 1981, Lande 1985, Walsh 1982), and possibly, strong selection favoring locally adapted alleles in populations connected by migration (Kirkpatrick & Barton 2006). Rearrangements that are neutral or weakly underdominant are more easily fixed in populations, but they also will be ineffective as isolating barriers.

Because of these theoretical concerns, as well as observations that inversions often fail to reduce fitness (Bardhan & Sharma 2000, Coyne et al. 1993, John 1981), a second class of chromosomal speciation models has been developed based on the other main property of inversions—reduced recombination between inverted and noninverted genomic regions (Noor et al. 2001, Rieseberg 2001). As was mentioned earlier, a reduction in effective recombination rates may be achieved through reduced pairing and crossing over between inverted regions, as well as by selection against recombinant gametes.

The reduced recombination associated with inversions may facilitate speciation in several ways (Kirkpatrick & Barton 2006, Navarro & Barton 2003a, Ortiz-Barrientos et al. 2002, Rieseberg 2001). If an allele causing significant reproductive isolation is associated with an inversion, the size of the genomic region protected from introgression will be considerably larger than for an allele housed in a collinear segment. Gene flow near a locus that contributes to isolation should be inversely proportional to the selection:recombination ratio (Barton 1979), so the effectiveness of an inversion at limiting gene flow will depend mostly on the rate of double crossovers or gene conversion within the inversion. Although these rates are rarely exactly known, they appear to be several orders of magnitude below recombination rates in collinear regions (Navarro et al. 1997).

Inversions may facilitate the accumulation of alleles that contribute to reproductive isolation between populations connected by gene flow. This is particularly true for Bateson-Dobzhansky-Muller (BDM) incompatibilities; otherwise, the ancestral, compatible genotype would be favored (Noor et al. 2001). Analytical models of parapatric speciation confirm that BDM incompatibilities are more likely to accumulate at species boundaries in the presence of inversions than in the presence of genetic barriers that do not reduce recombination (Navarro & Barton 2003a). If alleles that contribute to reproductive isolation are also locally adapted, their establishment may

occur either during the initial fixation of the inversion (Kirkpatrick & Barton 2006) or afterward (Feder et al. 2003a).

Lastly, inversions may promote sympatric or parapatric speciation by creating associations between alleles under divergent natural selection and those that cause assortative mating (Butlin 2005, Hauffe & Searle 1993, Trickett & Butlin 1994). Also, if the inversion (or incompatibilities associated with it) causes some degree of postzygotic isolation, then selection may favor alleles that increase the strength of prezygotic reproductive barriers (i.e., reinforcement), but only where populations are in contact (Butlin 2005, Servedio & Noor 2003).

Empirical data also favor the recombination model, at least outside of the plant kingdom. As discussed earlier, most inversions in animals do not have detectable effects on fitness when heterozygous (Bardhan & Sharma 2000, Coyne & Orr 2004, John 1981). Also, even in plants, it might be that the effects of inversions on recombination are more important than their effects on fitness (Rieseberg 2001). For example, by tracking the movement of species-specific markers across three recently arisen hybrid zones in sunflowers, Rieseberg et al. (1999) showed that rates of introgression across chromosomes carrying translocations and/or inversions were about half that for collinear linkage groups. In a follow-up study, Yatabe et al. (2007) assessed historical patterns of gene flow between the same pair of hybridizing species for a random set of markers. They found that the effects of the chromosomal rearrangements on genetic differentiation were limited to ~5 cM from chromosomal breakpoints, indicating significant recombination and gene flow across the rearranged chromosomes since the species diverged approximately one million years before the present. In contrast, male sterility QTLs in collinear chromosomes had no effect on the introgression of adjacent markers, at least at the scale of resolution examined by Yatabe et al. (2007). Thus, the sunflower data remain consistent with reduced recombination models, although the effects of the rearrangements are more local than previously believed. Support for the reduced recombination model also comes from parapatric species of tomato, in which expressed sequence tags (ESTs) within an inversion on chromosome 10 exhibited significantly greater sequence divergence than those from collinear chromosomes (Livingstone & Rieseberg 2004).

The strongest evidence for the reduced recombination models comes from *Drosophila*. Loci that contribute to both prezygotic and postzygotic isolation map to inversions in the sympatric species pair, *Drosophila pseudoobscura* and *D. persimilis* (Brown et al. 2004, Noor et al. 2001). In addition, sequence data suggest much lower introgression (measured by migration rate) within the inversions (and 1–2 Mb outside them) than for the rest of the genome (Machado et al. 2002, 2007; **Figure 1**). In contrast, no such association is observed for the allopatric species, *D. pseudoobscura bogotana* and *D. persimilis* (Brown et al. 2004, Chang & Noor 2007). Also, allozymes that show frequency differences between the hawthorn and apple races of *Rhagoletis* map to inversions, as do QTLs that contribute to an important prezygotic barrier, diapause timing (Feder et al. 2003b).

There is some support for reduced recombination models of chromosomal speciation in *Anopheles gambiae* (the malaria vector in Africa) and related species (Ayala & Coluzzi 2005). As predicted by the model, fixed inversions occur between sympatric, but not allopatric, species in the group (Coluzzi et al. 2002). Also, sets of inversions characterizing possible incipient species exhibit significant LD (Guelbeogo et al. 2005), and molecular differentiation within or linked to inversions in these incipient species appears to be higher than that for collinear chromosomes (Michel et al. 2005).

A high-profile study of sequence divergence in 115 genes from collinear versus rearranged chromosomes between humans and chimpanzees reported that rates of protein evolution were higher in rearranged chromosomes (Navarro & Barton 2003b). This result was interpreted as evidence that inversions facilitated adaptive evolution in the presence of gene flow (Navarro & Barton 2003b, Rieseberg & Livingstone 2003; although see Hey 2003). However, a more
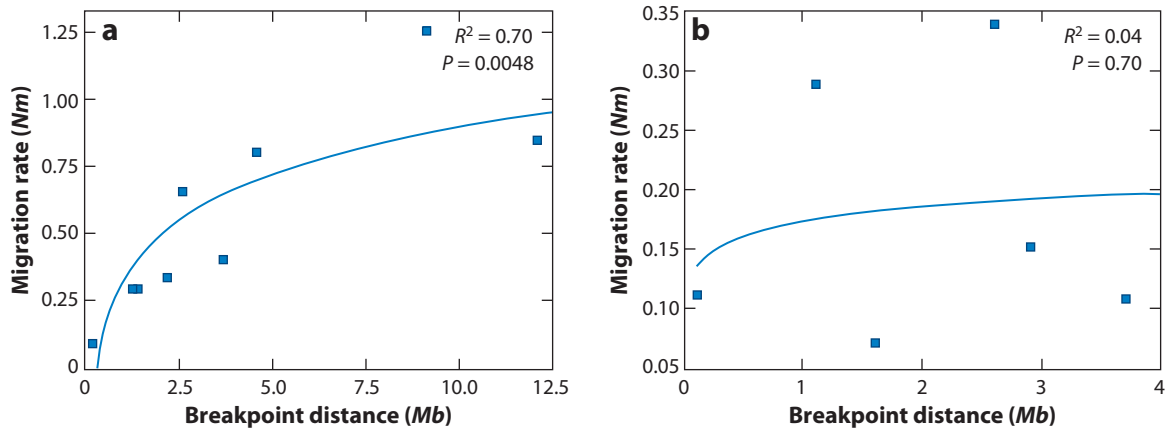
Figure 1

Plot of migration rate (*Nm*) as a measure of introgression versus distance to an inversion breakpoint on the second chromosome of *Drosophila pseudoobscura* and *D. persimilis* for markers outside (*a*) or inside (*b*) the inversion. Adapted with permission from Machado et al. (2007).

comprehensive analysis involving the full genome sequence of both species failed to confirm this result (The Chimpanzee Sequencing and Analysis Consortium 2005).

INVERSIONS AND SEX CHROMOSOME EVOLUTION

An early step in the evolution of sex chromosomes is the suppression of recombination between sex-determining regions (Ming & Moore 2007). This leads to the degeneration of nonrecombinant portions of the heterogametic sex chromosome, and to the recruitment of alleles that are beneficial to one sex and detrimental to the other. Selection to maintain LD between sex-determining alleles and alleles with sex-specific benefits/detriments may favor expansion of recombination suppression, until the entire heterogametic sex chromosome is nonrecombining (reviewed in Charlesworth et al. 2005).

Recombination suppression in sex chromosomes may increase through the spread of alleles that modify local recombination rates or through chromosomal rearrangements such as inversions (Charlesworth et al. 2005, Fraser & Heitman 2005). The possible role of inversions is best studied in recently evolved sex-determination systems, because the initial cause(s) of suppressed recombination may no longer be evident in older, more degenerate systems. Fishes and plants, in particular, are characterized by multiple independent origins of chromosomal sex determination and wide variation in the ages of sex chromosomes. Differentiation of sex chromosomes in neotropical fishes appears to involve inversions in 10 of 34 species that have been examined cytogenetically (da Rosa et al. 2006). Likewise, cytogenetic studies of the young Y chromosome of stickleback fishes indicate that it is heteromorphic and differs from the X chromosome by multiple inversions (C.L. Peichel, personal communication). However, inversions do not appear to contribute to recombination suppression between homomorphic sex chromosomes in medaka fishes, although local duplications may contribute to reductions in recombination (Nanda et al. 2002). In some fish species, sex determination appears to have moved between nonhomologous chromosomes (Mank et al. 2006). Recent theoretical work suggests that this may occur if an autosomal inversion captures a sex-change mutation and an allele with sex-specific benefits or detriments (van Doorn & Kirkpatrick 2007).

In plants, large inversions have been reported on the Y-chromosomes of *Rumex acetosa* and *Silene latifolia*. The *Silene* inversion contains a wide gradient in silent site divergence values, suggesting that it probably arose after recombination arrest (Zluvova et al. 2005). However, there is evidence that restricted recombination in *Silene latifolia* evolved in several steps (Nicolas et al. 2005), and it might be that smaller inversions contributed to this stepwise pattern, similar to that suspected for the mammalian Y-chromosome (Lahn & Page 1999). Inversions do not appear to be associated with sex chromosome evolution in papaya, although the male-specific region on the Y-chromosome is characterized by extensive local sequence duplication (Yu et al. 2007) similar to that observed in sticklebacks (Peichel et al. 2004).

Inversions also have been reported to contribute to sex chromosome differentiation in spiny eels (Liu et al. 2002) and *Dysdercus* bugs (Bressa et al. 1999), as well as to neo-sex chromosomes in grasshoppers (Bidau & Marti 2000) and *Drosophila* (McAllister 2003). In the latter study, an inversion that suppresses recombination between the neo-X and neo-Y appears to have been favored by natural selection, a result predicted by theoretical models for the evolution of sex chromosomes.

CONCLUDING REMARKS

The past few years have seen a resurgence in interest in inversions as genomic comparisons have highlighted the large number of inverted regions that distinguish species, and as new mapping efforts have indicated the presence of inversion polymorphisms in many organisms. Theoretical models and empirical data have emphasized the importance of reduced recombination as a process that promotes the spread of inversions in populations, potentially facilitating climatic adaptation and the evolution of reproductive isolation. Recent molecular and mapping studies have highlighted that areas within inversions well away from breakpoints can be in strong LD with each other. These regions are likely to contain the genes that are under strong selection and responsible for the spread and eventual fixation of inversions in populations. Further progress will come from mapping these genes and using genetic manipulations to create different combinations of alleles between loci. This type of information may eventually allow a rigorous test of the coadaptation hypothesis of Dobzhansky and an assessment of the role of alleles with deleterious and beneficial effects in driving the dynamics of inversions within populations. Recent speciation models have emphasized that speciation is facilitated in several ways by the effect of inversions on reducing recombination, allowing alleles at different loci that influence reproductive isolation to accumulate. The detailed genetic analysis of reproductive isolation and associated loci under natural selection should help to clarify the importance of these effects when compared to more traditional models of underdominance.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

Alvarez-Castro JM, Alvarez G. 2005. Models of general frequency-dependent selection and mating-interaction effects and the analysis of selection patterns in *Drosophila* inversion polymorphisms. *Genetics* 170:1167–79

Anderson AR, Hoffmann AA, McKechnie SW, Umina PA, Weeks AR. 2005. The latitudinal cline in the *In(3R)Payne* inversion polymorphism has shifted in the last 20 years in Australian *Drosophila melanogaster* populations. *Mol. Ecol.* 14:851–58

Andolfatto P, Depaulis F, Navarro A. 2001. Inversion polymorphisms and nucleotide variability in *Drosophila*. *Genet. Res.* 77:1–8

Andolfatto P, Wall JD, Kreitman M. 1999. Unusual haplotype structure at the proximal breakpoint of *In(2L)t* in a natural population of *Drosophila melanogaster*. *Genetics* 153:1297–311

Aradottir GI, Angus RB. 2004. A chromosomal analysis of some water beetle species recently transferred from *Agabus* Leach to *Ilybius* Erichson, with particular reference to the variation in chromosome number shown by *I. montanus* Stephens (Coleoptera: Dytiscidae). *Hereditas* 140:185–92

Aulard S, Monti L, Chaminade N, Lemeunier F. 2004. Mitotic and polytene chromosomes: comparisons between *Drosophila melanogaster* and *Drosophila simulans*. *Genetica* 120:137–50

Ayala FJ, Coluzzi M. 2005. Chromosome speciation: Humans, *Drosophila*, and mosquitoes. *Proc. Natl. Acad. Sci. USA* 102:6535–42

Balanya J, Oller JM, Huey RB, Gilchrist GW, Serra L. 2006. Global genetic change tracks global climate warming in *Drosophila subobscura*. *Science* 313:1773–75

Bansal V, Bashir A, Bafna V. 2007. Evidence for large inversion polymorphisms in the human genome from HapMap data. *Genome Res.* 17:219–30

Bardhan A, Sharma T. 2000. Meiosis and speciation: a study in a speciating *Mus terricolor* complex. *J. Genet.* 79:105–11

Bartolome C, Charlesworth B. 2006. Rates and patterns of chromosomal evolution in *Drosophila pseudoobscura* and *D. miranda*. *Genetics* 173:779–91

Barton NH. 1979. Gene flow past a cline. *Heredity* 43:333–39

Besansky NJ, Krzywinski J, Lehmann T, Simard F, Kern M, et al. 2003. Semipermeable species boundaries between *Anopheles gambiae* and *Anopheles arabiensis*: Evidence from multilocus DNA sequence variation. *Proc. Natl. Acad. Sci. USA* 100:10818–23

Bidau CJ, Marti DA. 2000. Meiosis and the Neo-XY system of *Dichroplus vittatus* (Melanoplinae, Acrididae): a comparison between sexes. *Genetica* 110:185–94

Blyth JE, Gilburn AS. 2005. The effect of an inversion system and the time interval between matings on postcopulatory sexual selection in the seaweed fly, *Coelopa frigida*. *Heredity* 95:174–78

Bonierbale MW, Plaisted RL, Tanksley SD. 1988. Rflp map based on a common set of clones reveal modes of chromosomal evolution in potato and tomato. *Genetics* 120:1095–103

Bressa MJ, Papeschi AG, Mola LM, Larramendy ML. 1999. Meiotic studies in *Dysdercus* Guerin Meneville 1831 (Heteroptera: Pyrrhocoridae). I. Neo-XY in *Dysdercus albofasciatus* Berg 1878, a new sex chromosome determining system in *Heteroptera*. *Chromosome Res.* 7:503–8

Brooke BD, Hunt RH, Chandre F, Carnevale P, Coetzee M. 2002. Stable chromosomal inversion polymorphisms and insecticide resistance in the malaria vector mosquito *Anopheles gambiae* (Diptera: Culicidae). *J. Med. Entomol.* 39:568–73

Brooke BD, Hunt RH, Matambo TS, Koekemoer LL, Van Wyk P, Coetzee M. 2006. Dieldrin resistance in the malaria vector *Anopheles gambiae* in Ghana. *Med. Vet. Entomol.* 20:294–99

Brown KM, Burk LM, Henagan LM, Noor MAF. 2004. A test of the chromosomal rearrangement model of speciation in *Drosophila pseudoobscura*. *Evolution* 58:1856–60

Burke JM, Lai Z, Salmaso M, Nakazato T, Tang SX, et al. 2004. Comparative mapping and rapid karyotypic evolution in the genus *Helianthus*. *Genetics* 167:449–57

Butlin RK. 2005. Recombination and speciation. *Mol. Ecol.* 14:2621–35

Butlin RK, Day TH. 1989. Environmental correlates of inversion frequencies in natural populations of seaweed flies (*Coelopa frigida*). *Heredity* 62:223–32

Calboli FCF, Kennington WJ, Partridge L. 2003. QTL mapping reveals a striking coincidence in the positions of genomic regions associated with adaptive variation in body size in parallel clines of *Drosophila melanogaster* on different continents. *Evolution* 57:2653–58

Casals F, Caceres M, Ruiz A. 2003. The Foldback-like transposon Galileo is involved in the generation of two different natural chromosomal inversions of *Drosophila buzzatii*. *Mol. Biol. Evol.* 20:674–85

Casals F, Gonzalez J, Ruiz A. 2006. Abundance and chromosomal distribution of six *Drosophila buzzatii* transposons: BuT1, BuT2, BuT3, BuT4, BuT5, and BuT6. *Chromosoma* 115:403–12

Castermans D, Vermeesch JR, Fryns JP, Steyaert JG, Van de Ven WJM, et al. 2007. Identification and characterization of the TRIP8 and REEP3 genes on chromosome 10q21.3 as novel candidate genes for autism. *Eur. J. Hum. Genet.* 15:422–31

Chang AS, Noor MAF. 2007. The genetics of hybrid male sterility between the allopatric species pair *Drosophila persimilis* and *D. pseudoobscura bogotana*: dominant sterility alleles in collinear autosomal regions. *Genetics* 176:343–49

Charlesworth D, Charlesworth B. 1979. Selection on recombination in clines. *Genetics* 91:581–89

Charlesworth D, Charlesworth B, Marais G. 2005. Steps in the evolution of heteromorphic sex chromosomes. *Heredity* 95:118–28

Cohuet A, Dia I, Simard F, Raymond M, Fontenille D. 2004. Population structure of the malaria vector *Anopheles funestus* in Senegal based on microsatellite and cytogenetic data. *Insect Mol. Biol.* 13:251–58

Colombo PC. 2002. Chromosome inversion polymorphisms influence morphological traits in *Trimerotropis pallidipennis* (Orthoptera). *Genetica* 114:247–52

Colombo PC. 2003. Inversion polymorphisms and natural selection in *Trimerotropis pallidipennis* (Orthoptera). *Hereditas* 139:68–74

Coluzzi M, Sabatini A, della Torre A, Di Deco MA, Petrarca V. 2002. A polytene chromosome analysis of the *Anopheles gambiae* species complex. *Science* 298:1415–18

Coyne JA, Meyers W, Crittenden AP, Sniegowski P. 1993. The fertility effects of pericentric inversions in *Drosophila melanogaster*. *Genetics* 134:487–96

Coyne JA, Orr HA. 2004. *Speciation*. Sunderland, MA: Sinauer

Darlington C. 1937. *Recent Advances in Cytology*. Philadelphia: Blakiston

da Rosa R, Bellafronte E, Filho OM, Margarido VP. 2006. Constitutive heterochromatin, 5S and 18S rDNA genes in *Apareiodon* sp. (Characiformes, Parodontidae) with a ZZ/ZW sex chromosome system. *Genetica* 128:159–66

De Jong G, Bochdanovits Z. 2003. Latitudinal clines in *Drosophila melanogaster*: body size, allozyme frequencies, inversion frequencies, and the insulin-signalling pathway. *J. Genet.* 82:207–23

della Torre A, Merzagora L, Powell JR, Coluzzi M. 1997. Selective introgression of paracentric inversions between two sibling species of the *Anopheles gambiae* complex. *Genetics* 146:239–44

Dobzhansky T. 1933. On the sterility of interracial hybrids in *Drosophila pseudoobscura*. *Proc. Natl. Acad. Sci. USA* 19:397–403

Dobzhansky T. 1970. *Genetics of the Evolutionary Process*. New York: Columbia Univ. Press

Drosophila 12 Genomes Consort. 2007. Evolution of genes and genomes on the *Drosophila phylogeny*. *Nature* 450:203–18

Dyer KA, Charlesworth B, Jaenike J. 2007. Chromosome-wide linkage disequilibrium as a consequence of meiotic drive. *Proc. Natl. Acad. Sci. USA* 104:1587–92

Etges WJ, Arbuckle KL, Levitan M. 2006. Long-term frequency shifts in the chromosomal polymorphisms of *Drosophila robusta* in the Great Smoky Mountains. *Biol. J. Linn. Soc.* 88:131–41

Etges WJ, Levitan M. 2004. Palaeoclimatic variation, adaptation and biogeography of inversion polymorphisms in natural populations of *Drosophila robusta*. *Biol. J. Linn. Soc.* 81:395–411

Evgen'ev MB, Zelentsova H, Poluectova H, Lyozin GT, Veleikodvorskaja V, et al. 2000. Mobile elements and chromosomal evolution in the *virilis* group of *Drosophila*. *Proc. Natl. Acad. Sci. USA* 97:11337–42

Feder JL, Berlocher SH, Roethele JB, Dambroski H, Smith JJ, et al. 2003a. Allopatric genetic origins for sympatric host-plant shifts and race formation in *Rhagoletis*. *Proc. Natl. Acad. Sci. USA* 100:10314–19

Feder JL, Roethele FB, Filchak K, Niedbalski J, Romero-Severson J. 2003b. Evidence for inversion polymorphism related to sympatric host race formation in the apple maggot fly, *Rhagoletis pomonella*. *Genetics* 163:939–53

Feuk L, MacDonald JR, Tang T, Carson AR, Li M, et al. 2005. Discovery of human inversion polymorphisms by comparative analysis of human and chimpanzee DNA sequence assemblies. *PloS Genet.* 1:489–98

Fischer G, Rocha EPC, Brunet F, Vergassola M, Dujon B. 2006. Highly variable rates of genome rearrangements between hemiascomycetous yeast lineages. *PloS Genet.* 2:253–61

Flores M, Morales L, Gonzaga-Jauregui C, Dominguez-Vidaña R, Zepeda C, et al. 2007. Recurrent DNA inversion rearrangements in the human genome. *Proc. Natl. Acad. Sci. USA* 104:6099–106

Fraser JA, Heitman J. 2005. Chromosomal sex-determining regions in animals, plants and fungi. *Curr. Opin. Genet. Dev.* 15:645–51

Fryenberg J, Hoffmann AA, Loeschcke V. 2003. DNA sequence variation and latitudinal associations in hsp23, hsp26 and hsp27 from natural populations of *Drosophila melanogaster*. *Molec. Ecol.* 12:2025–32

Gockel J, Kennington WJ, Hoffmann AA, Goldstein DB, Partridge L. 2001. Nonclinality of molecular variation implicates selection in maintaining a morphological cline of *Drosophila melanogaster*. *Genetics* 158:319–23

Guelbeogo WM, Grushko O, Boccolini D, Ouedraogo PA, Besansky NJ, et al. 2005. Chromosomal evidence of incipient speciation in the Afrotropical malaria mosquito *Anopheles funestus*. *Med. Vet. Entomol.* 19:458–69

Hardikar AA, Nath BB. 2001. Chromosomal polymorphism is associated with nematode parasitism in a natural population of a tropical midge. *Chromosoma* 110:58–64

Harrison S, Maron J, Huxel G. 2000. Regional turnover and fluctuation in populations of five plants confined to serpentine seeps. *Conserv. Biol.* 14:769–79

Hasson E, Eanes WF. 1996. Contrasting histories of three gene regions associated with *In(3L)Payne* of *Drosophila melanogaster*. *Genetics* 144:1565–75

Hauffe HC, Searle JB. 1993. Extreme karyotypic variation in a *Mus musculus domesticus* hybrid zone—the tobacco mouse story revisited. *Evolution* 47:1374–95

Hedrick PW. 1981. The establishment of chromosomal variants. *Evolution* 35:322–32

Hey J. 2003. Speciation and inversions: chimps and humans. *BioEssays* 25:825–28

Hoffmann AA, Sgro CM, Weeks AR. 2004. Chromosomal inversion polymorphisms and adaptation. *Trends Ecol. Evol.* 19:482–88

Johannesson K, Mikhailova N. 2004. Habitat-related genetic substructuring in a marine snail (*Littorina fabalis*) involving a tight link between an allozyme and a DNA locus. *Biol. J. Linn. Soc.* 81:301–6

John B. 1981. Chromosome change and evolutionary change: a critique. In *Evolution and Speciation. Essays in Honor of MJD White*, ed. W Atchley, D Woodruff, pp. 23–51. Cambridge, UK: Cambridge Univ. Press

Kennington WJ, Gockel J, Partridge L. 2003. Testing for asymmetrical gene flow in a *Drosophila melanogaster* body-size cline. *Genetics* 165:667–73

Kennington WJ, Hoffmann AA, Partridge L. 2007. Mapping regions within cosmopolitan inversion *In(3R)Payne* associated with natural variation in body size in *Drosophila melanogaster*. *Genetics* 177:549–56

Kennington WJ, Partridge L, Hoffmann AA. 2006. Patterns of diversity and linkage disequilibrium within the cosmopolitan inversion *In(3R)Payne* in *Drosophila melanogaster* are indicative of coadaptation. *Genetics* 172:1655–63

King M. 1993. *Species Evolution*. Cambridge, UK: Cambridge Univ. Press

Kirkpatrick M, Barton N. 2006. Chromosome inversions, local adaptation and speciation. *Genetics* 173:419–34

Krimbas C, Powell JR. 1992. *Drosophila Inversion Polymorphism*. Boca Raton, FL: CRC Press

Kusano A, Staber C, Chan HYE, Ganetzky B. 2003. Closing the (Ran)GAP on segregation distortion in *Drosophila*. *BioEssays* 25:108–15

Kuvangkadilok C, Boonkemtong C, Phayuhasena S, Baimai V. 2003. Larval polytene chromosomes of black flies (*Simulium*) from Thailand. I. Comparison among five species in the subgenus *Gomphostilbia* Enderlein. *Genetica* 118:69–81

Laayouni H, García-Franco F, Chávez-Sandoval BE, Trotta V, Beltran S, et al. 2007. Thermal evolution of gene expression profiles in *Drosophila subobscura*. *BMC Evol. Biol.* 7:42

Laayouni H, Hasson E, Santos M, Fontdevila A. 2003. The evolutionary history of *Drosophila buzzatii*. XXXV. Inversion polymorphism and nucleotide variability in different regions of the second chromosome. *Mol. Biol. Evol.* 20:931–44

Lahn BT, Page DC. 1999. Four evolutionary strata on the human X chromosome. *Science* 286:2273

Lai Z, Nakazato T, Salmaso M, Burke JM, Tang SX, et al. 2005. Extensive chromosomal repatterning and the evolution of sterility barriers in hybrid sunflower species. *Genetics* 171:291–303

Lande R. 1985. The fixation of chromosomal rearrangements in a subdivided population with local extinction and colonization. *Heredity* 54:323–32

Lee BS, Kim NW, Rim NR. 2002. Chromosome inversion—environment relationships in Korean populations of *Drosophila melanogaster*. *Korean J. Genet.* 24:9–20

Levin D. 2002. *The Role of Chromosomal Change in Plant Evolution*. Oxford: Oxford Univ. Press

Levitan M. 2001. Studies of linkage in populations. XIV. Historical changes in frequencies of gene arrangements and arrangement combinations in natural populations of *Drosophila robusta*. *Evolution* 55:2359–62

Liu JD, Yi MS, Zhao G, Zhou F, Wang DQ, Yu QX. 2002. Sex chromosomes in the spiny eel (*Mastacembelus aculeatus*) revealed by mitotic and meiotic analysis. *Cytogenet. Genome Res.* 98:291–97

Livingstone K, Rieseberg L. 2004. Chromosomal evolution and speciation: a recombination-based approach. *New Phytol.* 161:107–12

Lyon MF. 2003. Transmission ratio distortion in mice. *Annu. Rev. Genet.* 37:393–408

Machado CA, Haselkorn TS, Noor MAF. 2007. Evaluation of the genomic extent of effects of fixed inversion differences on intraspecific variation and interspecific gene flow in *Drosophila pseudoobscura* and *D. persimilis*. *Genetics* 175:1289–306

Machado CA, Kliman RM, Markert JA, Hey J. 2002. Inferring the history of speciation from multilocus DNA sequence data: The case of *Drosophila pseudoobscura* and close relatives. *Mol. Biol. Evol.* 19:472–88

Mank JE, Promislow DEL, Avise JC. 2006. Evolution of alternative sex-determining mechanisms in teleost fishes. *Biol. J. Linn. Soc.* 87:83–93

Masly JP, Presgraves DC. 2007. High-resolution genome-wide dissection of the two rules of speciation in *Drosophila*. *PLoS Biol.* 5:1890–98

Mathiopoulos KD, della Torre A, Predazzi V, Petrarca V, Coluzzi M. 1998. Cloning of inversion breakpoints in the *Anopheles gambiae* complex traces a transposable element at the inversion junction. *Proc. Natl. Acad. Sci. USA* 95:12444–49

Matzkin LM, Merritt TJS, Zhu CT, Eanes WF. 2005. The structure and population genetics of the breakpoints associated with the cosmopolitan chromosomal inversion *In(3R)Payne* in *Drosophila melanogaster*. *Genetics* 170:1143–52

McAllister BF. 2003. Sequence differentiation associated with an inversion on the neo-X chromosome of *Drosophila americana*. *Genetics* 165:1317–28

Micali CO, Smith ML. 2006. A nonself recognition gene complex in *Neurospora crassa*. *Genetics* 173:1991–2004

Michel AP, Guelbeogo WM, Grushko O, Schemerhorn BJ, Kern M, et al. 2005. Molecular differentiation between chromosomally defined incipient species of *Anopheles funestus*. *Insect Mol. Biol.* 14:375–87

Ming R, Moore PH. 2007. Genomics of sex chromosomes. *Curr. Opin. Plant Biol.* 10:123–30

Morales-Hojas R, Päällysaho S, Vieira CP, Hoikkala A, Vieira J. 2007. Comparative polytene chromosome maps of *D. montana* and *D. virilis*. *Chromosoma* 116:21–27

Munte A, Rozas J, Aguade M, Segarra C. 2005. Chromosomal inversion polymorphism leads to extensive genetic structure: A multilocus survey in *Drosophila subobscura*. *Genetics* 169:1573–81

Nanda I, Kondo M, Hornung U, Asakawa S, Winkler C, et al. 2002. A duplicated copy of *DMRT1* in the sex-determining region of the Y chromosome of the medaka, *Oryzias latipes*. *Proc. Natl. Acad. Sci. USA* 99:11778–83

Navarro A, Barton NH. 2003a. Accumulating postzygotic isolation genes in parapatry: A new twist on chromosomal speciation. *Evolution* 57:447–59

Navarro A, Barton NH. 2003b. Chromosomal speciation and molecular divergence—Accelerated evolution in rearranged chromosomes. *Science* 300:321–24

Navarro A, Betran E, Barbadilla A, Ruiz A. 1997. Recombination and gene flux caused by gene conversion and crossing over in inversion heterokaryotypes. *Genetics* 146:695–709

Nei M. 1967. Modification of linkage intensity by natural selection. *Genetics* 57:625–41

Nicolas M, Marais G, Hykelova V, Janousek B, Laporte V, et al. 2005. A gradual process of recombination restriction in the evolutionary history of the sex chromosomes in dioecious plants. *PLoS Biol.* 3:47–56

Noor MAF, Grams KL, Bertucci LA, Reiland J. 2001. Chromosomal inversions and the reproductive isolation of species. *Proc. Natl. Acad. Sci. USA* 98:12084–88

Oliver P, Castro JA, Picornell A, Ramon MM, Sole E, et al. 2002. Linkage disequilibria between mtDNA haplotypes and chromosomal arrangements in a natural population of *Drosophila subobscura*. *Heredity* 89:133–38

Onyabe DY, Conn JE. 2001. Genetic differentiation of the malaria vector *Anopheles gambiae* across Nigeria suggests that selection limits gene flow. *Heredity* 87:647–58

Ortiz-Barrientos D, Reiland J, Hey J, Noor MAF. 2002. Recombination and the divergence of hybridizing species. *Genetica* 116:167–78

Peichel CL, Ross JA, Matson CK, Dickson M, Grimwood J, et al. 2004. The master sex-determination locus in threespine sticklebacks is on a nascent Y chromosome. *Curr. Biol.* 14:1416–24

Pensel SM, Remis MI. 2007. Variation in adult female body size related to chromosome polymorphism and female mating success in *Sinipta dalmani* (Orthoptera: Acrididae). *Ann. Entomol. Soc. Am.* 100:283–88

Pepper JW. 2003. The evolution of evolvability in genetic linkage patterns. *Biosystems* 69:115–26

Rako L, Anderson AR, Sgro CM, Stocker AJ, Hoffmann AA. 2006. The association between inversion *In(3R)Payne* and clinally varying traits in *Drosophila melanogaster*. *Genetica* 128:373–84

Ranz JM, Maurin D, Chan YS, von Grotthuss M, Hillier LW, et al. 2007. Principles of genome evolution in the *Drosophila melanogaster* species group. *PloS Biol.* 5:1366–81

Remis MI. 2002. Differential adult survival and phenotypic variation in a chromosomally polymorphic population of the grasshopper *Sinipta dalmani*. *Hereditas* 136:155–58

Reusch TBH, Wood TE. 2007. Molecular ecology of global change. *Mol. Ecol.* 16:3973–92

Rieseberg LH. 2001. Chromosomal rearrangements and speciation. *Trends Ecol. Evol.* 16:351–58

Rieseberg LH, Livingstone K. 2003. Evolution—Chromosomal speciation in primates. *Science* 300:267–68

Rieseberg LH, Whitton J, Gardner K. 1999. Hybrid zones and the genetic architecture of a barrier to gene flow between two sunflower species. *Genetics* 152:713–27

Rodriguez-Trelles F. 2003. Seasonal cycles of allozyme-by-chromosomal-inversion gametic disequilibrium in *Drosophila subobscura*. *Evolution* 57:839–48

Rodriguez-Trelles F, Rodriguez MA. 1998. Rapid microevolution and loss of chromosomal diversity in *Drosophila* in response to climate warming. *Evol. Ecol.* 12:829–38

Santos M, Cespedes W, Balanya J, Trotta V, Calboli FCF, et al. 2005. Temperature-related genetic changes in laboratory populations of *Drosophila subobscura*: Evidence against simple climatic-based explanations for latitudinal clines. *Am. Nat.* 165:258–73

Schaeffer SW, Anderson WW. 2005. Mechanisms of genetic exchange within the chromosomal inversions of *Drosophila pseudoobscura*. *Genetics* 171:1729–39

Schaeffer SW, Goetting-Minesky MP, Kovacevic M, Peoples JR, Graybill JL, et al. 2003. Evolutionary genomics of inversions in *Drosophila pseudoobscura*: Evidence for epistasis. *Proc. Natl. Acad. Sci. USA* 100:8319–24

Servedio MR, Noor MAF. 2003. The role of reinforcement in speciation: Theory and data. *Annu. Rev. Ecol. Evol. Syst.* 34:339–64

Sharakhov IV, White BJ, Sharakhova MV, Kayondo J, Lobo NF, et al. 2006. Breakpoint structure reveals the unique origin of an interspecific chromosomal inversion (2La) in the *Anopheles gambiae* complex. *Proc. Natl. Acad. Sci. USA* 103:6258–62

Sole E, Mestres F, Balanya J, Arenas C, Serra L. 2000. Colonization of America by *Drosophila subobscura*: spatial and temporal lethal-gene allelism. *Hereditas* 133:65–72

Sperlich D, Pfriem P. 1986. Chromosomal polymorphism in natural and experimental populations. In *The Genetics and Biology of Drosophila*, ed. M Ashburner, HL Carson, JN Thompson Jr, 3e:257–309. New York: Academic

Stebbins G. 1958. The inviability, weakness, and sterility of interspecific hybrids. *Adv. Genet.* 9:147–215

Stefansson H, Helgason A, Thorleifsson G, Steinthorsdottir V, Masson G, et al. 2005. A common inversion under selection in Europeans. *Nat. Genet.* 37:129–37

Stocker AJ, Foley B, Hoffmann A. 2004. Inversion frequencies in *Drosophila serrata* along an eastern Australian transect. *Genome* 47:1144–53

Sturtevant AH. 1938. Essays on evolution. III. On the origin of interspecific sterility. *Q. Rev. Biol.* 13:333–35

Tadin-Strapps M, Warburton D, Baumeister FAM, Fischer SG, Yonan J, et al. 2004. Cloning of the breakpoints of a de novo inversion of chromosome 8, inv (8)(p11.2q23.1) in a patient with Ambras syndrome. *Cytogenet. Genome Res.* 107:68–76

The Chimpanzee Seq. Anal. Consort. 2005. Initial sequence of the chimpanzee genome and comparison with the human genome. *Nature* 437:69–87

Trickett AJ, Butlin RK. 1994. Recombination suppressors and the evolution of new species. *Heredity* 73:339–45

Umina PA, Hoffmann AA, Weeks AR, McKechnie SW. 2006. An independent nonlinear latitudinal cline for the sn-glycerol-3-phosphate (α-Gpdh) polymorphism of *Drosophila melanogaster* from eastern Australia. *Genet. Res.* 87:13–21

Umina PA, Weeks AR, Kearney MR, McKechnie SW, Hoffmann AA. 2005. A rapid shift in a classic clinal pattern in *Drosophila* reflecting climate change. *Science* 308:691–93

van Doorn GS, Kirkpatrick M. 2007. Turnover of sex chromosomes induced by sexual conflict. *Nature* 449:909–12

Vasemagi A. 2006. The adaptive hypothesis of clinal variation revisited: Single-locus clines as a result of spatially restricted gene flow. *Genetics* 173:2411–14

Walsh JB. 1982. Rate of accumulation of reproductive isolation by chromosome rearrangements. *Am. Nat.* 120:510–32

Werle SF, Klekowski E, Smith DG. 2004. Inversion polymorphism in a Connecticut River *Axarus* species (Diptera: Chironomidae): biometric effects of a triple inversion heterozygote. *Can. J. Zool.-Rev. Can. Zool.* 82:118–29

Wesley CS, Eanes WF. 1994. Isolation and analysis of the breakpoint sequences of chromosome inversion *In(3L)Payne* in *Drosophila melanogaster*. *Proc. Natl. Acad. Sci. USA* 91:3132–36

White BJ, Hahn MW, Pombi M, Cassone BJ, Lobo NF, et al. 2007a. Localization of candidate regions maintaining a common polymorphic inversion (2La) in *Anopheles gambiae*. *PloS Genet.* 3:e217

White BJ, Santolamazza F, Kamau L, Pombi M, Grushko O, et al. 2007b. Molecular karyotyping of the 2La inversion in *Anopheles gambiae*. *Am. J. Trop. Med. Hyg.* 76:334–39

White M. 1978. *Modes of Speciation*. San Francisco: W.H. Freeman

Yadav JP, Singh BN. 2006. Evolutionary genetics of *Drosophila ananassae*. I. Effect of selection on body size and inversion frequencies. *J. Zool. Syst. Evol. Res.* 44:323–29

Yadav JP, Singh BN. 2007. Evolutionary genetics of *Drosophila ananassae*: evidence for trade-offs among several fitness traits. *Biol. J. Linn. Soc.* 90:669–85

Yatabe Y, Kane NC, Scotti-Saintagne C, Rieseberg LH. 2007. Rampant gene exchange across a strong reproductive barrier between the annual sunflowers, *Helianthus annuus* and *H. petiolaris*. *Genetics* 175:1883–93

Yu QY, Hou SB, Hobza R, Feltus FA, Wang X, et al. 2007. Chromosomal location and gene paucity of the male specific region on papaya Y chromosome. *Mol. Genet. Genomics* 278:177–85

Zivanovic G, Mestres F. 2000. Lethal genes in O_5 chromosomes of *Drosophila subobscura* from Europe and America. *J. Zool. Syst. Evol. Res.* 38:123–26

Zluvova J, Janousek B, Negrutiu I, Vyskot B. 2005. Comparison of the X and Y chromosome organization in *Silene latifolia*. *Genetics* 170:1431–34

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Ecology, Evolution, and Systematics*
articles may be found at http://ecolsys.annualreviews.org/errata.shtml