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Chromosomal inversions in human populations: A review from an evolutionary perspective

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ABSTRACT

Inversion polymorphisms provided critical case studies in the early development of population genetics. Recently, interest in their evolution has been re-invigorated by the discovery of inversion polymorphism in many animal and plant species using genomic approaches and by new theoretical developments. In parallel, genomic approaches are providing new insights into the origin, prevalence and consequences of inversions in human populations. In this article, I consider how observations on human inversions fit into the prevailing view of inversion polymorphism in the evolutionary biology community. Surveys in humans have revealed many small inversions that are missed in animal and plant studies. These surveys show a mix of origins via non-allelic homologous recombination and non-homologous end-joining processes. Importantly, homologous recombination can lead to recurrent origins with significant evolutionary consequences. Direct selection operates against inversion heterozygotes via both breakpoint and recombination effects. Both fields infer the maintenance of common polymorphisms by balancing selection, arising due to linkage disequilibrium between inversions and the loci they contain, but it remains difficult to identify the underlying causes. Research on non-human species tends to concentrate on large inversions and those maintained at high frequency. As a result, the evolutionary field has much to learn from work on humans about inversion origins and the pathological effects of rare variants. Medical research on inversions may benefit from considering the evolutionary processes underlying their behaviour in human populations.

Introduction

Inversions are structural mutations in which a section of chromosome is reversed in orientation, resulting in a change in gene order but no change in copy number. They were originally detected as suppressors of recombination in *Drosophila*[1] but then quickly connected to cytologically visible reversals of chromosome banding patterns[2]. A century later, modern sequencing approaches have demonstrated that inversion polymorphism is widespread among animal and plant species, including humans. However, there is only limited contact between the evolutionary biology and medical genetics communities, potentially allowing divergence in the way that the biology of inversions is understood. In this article, I consider human inversions from an evolutionary biologist's perspective, aiming to find ways in which each field can learn from recent developments in a different research community.

Evolutionary background

The first population geneticists expected inversions to be selectively neutral and set out to use them to test the expectations of Sewall Wright's theory of genetic drift. However, they quickly found evidence for selection on polymorphic inversions in *Drosophila pseudoobscura*. They found repeatable altitudinal clines and regular seasonal cycles in arrangement frequencies, while laboratory populations with different starting frequencies tended to converge on the same equilibrium frequencies[3]. In many species, there is also evidence that arrangement frequencies are strongly influenced by natural selection, often balancing selection that maintains stable intermediate frequencies[4].

What is the source of natural selection on inversions? There are two possibilities: selection might be the result of changes inherent to the structural mutation, or it might be due to association (linkage disequilibrium, LD) between the structural mutation and alleles at loci within the inverted region or nearby. When a mutation occurs, the derived arrangement (Box 1) captures a single haplotype from the population. This haplotype tends to be maintained intact because effective recombination is suppressed in the region of the inversion and for some distance beyond its breakpoints. If the new arrangement persists and spreads, new mutations in either arrangement tend to remain associated with the inversion resulting in strong LD among loci, typically extending beyond the breakpoints, which is a hallmark of polymorphic inversions. However, it is now clear that the suppression of recombination is incomplete: both double crossovers and gene conversion can result in the transfer of alleles between arrangements (collectively known as 'gene flux'). Therefore, the two arrangements evolve only partially independently, akin to a pair of populations that experience a low rate of gene flow[5].

Box 1. Terminology

The term 'inversion' is used here either for the mutational event or for the chromosomal region in which the gene order is altered. An inversion creates two 'arrangements', one ancestral and one derived. Each arrangement might contain multiple 'haplotypes' consisting of the combination of alleles at the loci included in the inversion. Individuals carrying two different arrangements for an inversion are 'heterokaryotypes' while those carrying two copies of the same arrangement are 'homokaryotypes'.

Inversions are 'balanced variants' in the sense that they do not change copy number. They might experience 'balancing selection', which is any form of selection that tends to maintain intermediate arrangement frequencies, such as when the heterokaryotype is the most fit karyotype (heterosis) or where selection favours rare variants (negative frequency dependence).

Gene flux is the exchange of alleles between arrangements (analogous to gene flow between populations). It is the result of double cross-over events and gene conversion in heterokaryotype individuals. Because flux is expected to be lower close to breakpoints than in the centre of an inversion, it can generate a 'suspension bridge' pattern of differentiation between arrangements.

What is the likely fate of a newly arisen inversion? As for any type of mutation, the mostly likely outcome is that it is lost stochastically within a few generations, regardless of its effects on fitness. Many new arrangements will have deleterious effects and will be removed from the population by selection. If the ancestral and derived arrangements have similar fitness, polymorphism might persist for many generations, and the derived arrangement might even become fixed. If the new arrangement is beneficial in the heterokaryotype and escapes stochastic loss, it will increase in frequency and may fix, if the derived homokaryotype also has an advantage, or reach a stable equilibrium if there is some form of balancing selection (Box 1). Relative fitnesses may be environment-dependent, generating polymorphisms that are maintained by the interaction between selection and gene flow. All of this is in common with any mutation, but the fate of inversions is more complex. This is because the set of alleles associated with each arrangement evolves over time: new alleles are introduced by mutation and gene flux, and allele frequencies change due to drift and selection within each arrangement population. These changes alter the relative fitnesses of the karyotypes and so their frequencies, potentially creating complex feedbacks (discussed below).

While these principles are clear, many details remain unknown. From the evolutionary biologist's perspective, inversions in the human population potentially provide unique insights because of the combination of high-quality reference assemblies, very large population samples, data on traits related to fitness and functional information on the genes included within inversions. Reciprocally, it may be that evolutionary interpretations of the features of inversions can help the medical researcher or practitioner. Here, I briefly consider inversion prevalence and origin, and the ways in which selection might act on inversions, with these reciprocal benefits in mind.

Inversion prevalence

Until recently, detection of inversions in both humans and other organisms depended on cytogenetic approaches and was limited to large rearrangements. Genomic methods have transformed understanding of their prevalence[6]. In evolutionary biology, genotyping and short-read sequencing approaches have mainly been used to detect blocks of LD or of differentiation in population samples, often without direct confirmation that they are caused by inversions. This has demonstrated that inversions are widespread taxonomically and can cover substantial proportions of the genome in some species (even >40%[4]). As long-read data become more widely available, inversion status is usually confirmed, although rearrangements may turn out to be more complex than previously imagined (e.g.[7]). However, these approaches remain biased towards detecting long inversions (130kb to >100Mb, mean 8.4Mb, in one survey[4]) at intermediate frequencies, which may, in turn, bias towards old inversions that are maintained by balancing selection (see below). The prevalence of inversion polymorphism varies widely among species but the reasons for this variation are not understood[5,8]. Long-read sequencing and pangenome analysis methods are starting to reveal the true prevalence and range of characteristics of inversions in natural populations[9], and the characteristics of their breakpoints[10,11], but this resolution remains the exception rather than the rule.

The study of inversions in humans has a rather different history. Early work also used cytogenetic approaches but was complemented by focused studies of pathologies, and so on rare variants[12]. One of the best studied human inversions, 17q21.31, was first identified as a block of LD around the MAPT locus and only later shown to be an inversion[13], mirroring animal and plant studies. More recent genomic approaches have been dominated by high-resolution analyses of small samples: for example, Ebert et al found[14] 316 inversions in a sample of 70 haplotypes using a combination of strand-seq, long-read and optical mapping approaches (but still noting that inversions remain difficult to detect and validate compared to structural variants that alter copy number). The great majority of these inversions were <0.5Mb long and their mean frequency was around 17%. Porubsky et al report[15] 729 inversions in 44 individuals, ranging in size from 50bp to 23.2Mbp and covering, on average, 0.4% of the genome. Many of these were internal to L1 mobile element insertions (330) but 292 were confidently assigned to balanced inversions in genomic DNA. A high proportion of the inversions detected in studies like these would be invisible in most population genomic work on other organisms because of their small size or low frequency.

Surveys of large samples are less common, because inversions are difficult to call reliably in high-throughput screens. However, Giner-Delgado et al surveyed[16] more than 500 individuals from 7 populations, world-wide, for 45 previously identified inversions with minor allele frequency (MAF) >5%. These inversions were smaller (83 – 415kb) than most inversions studied in other taxa. They covered the full range of MAFs and provided important opportunities to test for functional and fitness effects (see below).

Fixed inversion differences characterise closely related species in many taxa (e.g. *Drosophila*[17]). This is also true for the great apes. Yoo et al found[18] >1000 inversions in complete genome comparisons, of which >600 were homozygous in their samples and potentially fixed different between species. When 311 homozygous inversions were assigned to an ape phylogeny, the numbers of origins per branch were corelated with branch length, although the 5 origins observed on the human branch were fewer than expected. There are multiple reasons to expect inversions to contribute to speciation[19-21] but there is also a clear expectation that chromosomal differences will accumulate after speciation, in relation to branch length (ref. [22], pp.260-261). Therefore, there is an open question about the role of inversions in great ape speciation.

The mutation process

Most inversions are thought to result from one of two types of process: non-allelic homologous recombination (NAHR) or non-homologous end joining (NHEJ) [23]. NAHR requires substantial stretches of homologous sequence and is mostly associated with segmental duplications (SDs, also known as low copy repeats) that are 10s of kilobases long and have high sequence similarity (>95%). Inversions that originate by NAHR should carry signatures of these repeats around their break points, usually in the form of long inverted repeats (Figure 1A). However, these repeats make assembly and mapping difficult with short-read sequencing data and so it has only been in recent years that breakpoint resolution has become possible.

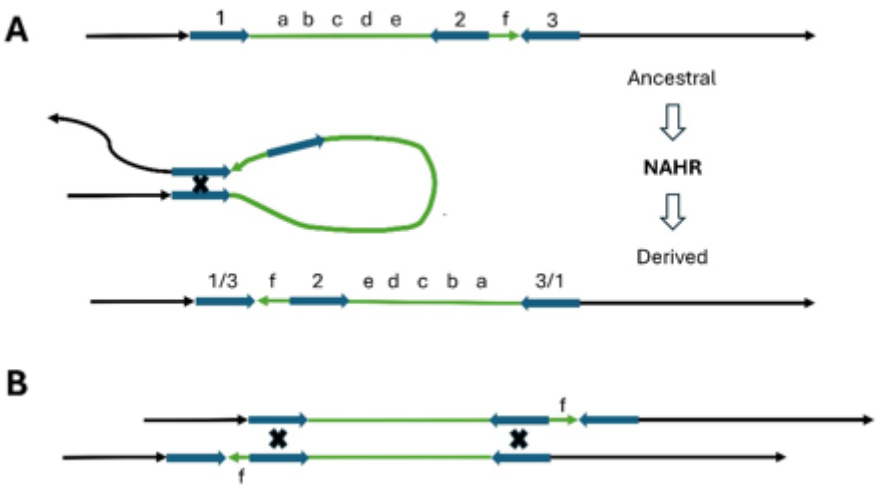

Figure 1. The origin of an inversion by non-allelic homologous recombination (A). In this case, there are three repeats (1-3) that vary in orientation. A cross-over (X) between repeats in different orientations generates an inverted sequence of genes a-f. In an individual heterozygous for the ancestral and derived arrangements repeats can misalign (B), cross-over at either of the positions marked X will then generate gametes with a deletion or a duplication of gene f.

In non-human systems, breakpoint resolution remains rare. Harringmeyer and Hoekstra described[11] 21 inversions in *Peromyscus* deer mice and were able to localise breakpoints for 13 of them. Twelve out of these 13 had 500 to 50kb inverted repeats flanking the breakpoints, strongly suggesting a role for NAHR. This also explains a strong tendency for breakpoints to be concentrated in repeat-rich regions near centromeres and telomeres. In *Drosophila*, both NHEJ and NAHR mechanisms have been described, the latter frequently mediated by transposable elements, as well as more complex mechanisms (e.g.[24]). The association with repeats likely explains the clustering of inversion breakpoints seen in *Drosophila*[25]. Hoff et al found[7] that breakpoint regions of multiple inversions within and among species of cod have elevated

densities of transposable element derived repeats, consistent with a role for NAHR in their origin.

Genomic approaches in humans have mapped many inversion breakpoint regions, although it often remains difficult to define mutational events with precision because of the presence of complex repeats. The two best known human polymorphic inversions, 17q21.31 and 8p23.1 are both flanked by complex segmental duplications indicating that they originated by NAHR[26,27]. However, the 45 polymorphic inversions studied by Giner-Delgado et al included[16] 24 with inferred NAHR origins and 21 with NHEJ origins. The NAHR inversions were flanked by inverted repeats ranging from 650bp to 24kbp. Their methods could not include inversions with longer flanking repeats and so the proportion of NAHR inversions might have been underestimated. Importantly, the two classes of inversions differed in many properties (discussed below).

Population genetic theory has typically assumed that the mutation events leading to inversions are so rare that the derived state for each polymorphic inversion can be considered to have a unique origin (e.g. [5]). The derived arrangement initially contains a single haplotype and gradually accumulates variation over time by a combination of new mutations and gene flux[28] (Box 1). SNPs shared between arrangements are expected to be rare unless an inversion polymorphism is old, especially close to break points where flux is weaker. Divergence between the arrangements will accumulate over time but will be opposed by flux in the centre of long inversions leading to the so-called 'suspension bridge' pattern (e.g.[29]; Figure 2).

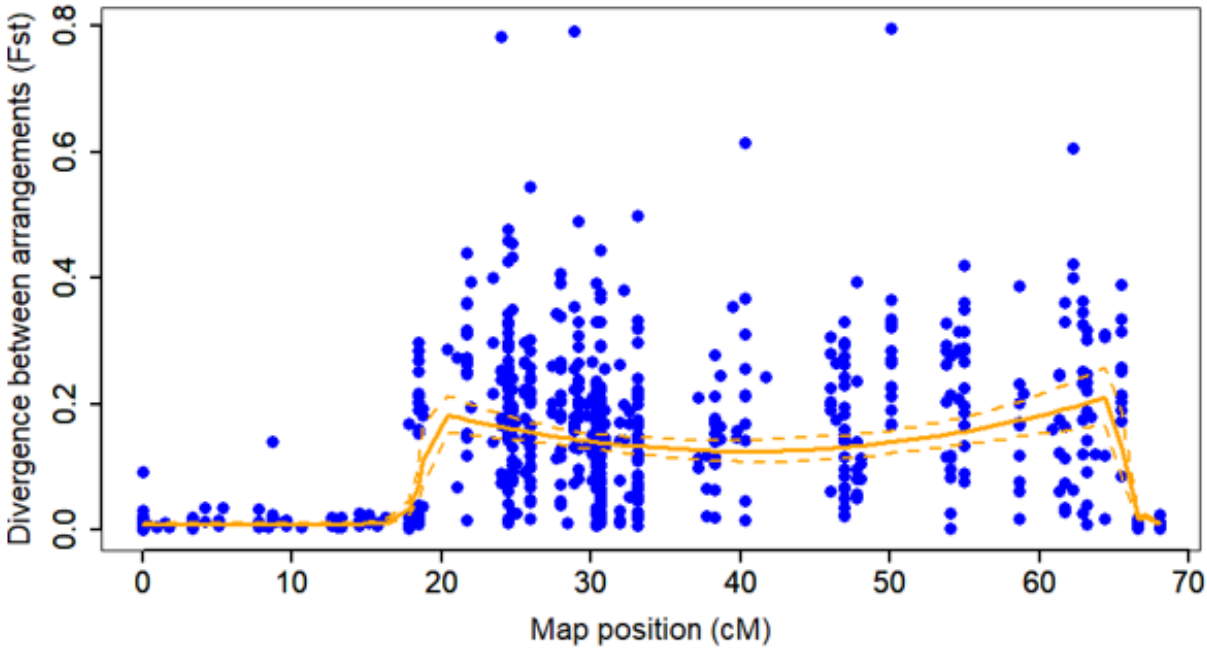

Figure 2. An example of the suspension bridge pattern of genetic divergence between arrangements, in this case for a very large inversion on linkage group 3 in the marine snail *Littorina fabalis*. Blue points are mean divergence (F_{ST}) for individual genomic contigs. The solid orange line is a fitted mean divergence and the dashed lines indicate the 95% plausible range for the mean. Data from[29].

Mutation rates for NHEJ inversions appear to be low enough to be consistent with this theory. All NHEJ inversions studied by Giner-Delgado et al[16] had a single origin in humans and none was shared with chimp or gorilla. Nearly all had some SNPs in complete LD with the inversion and polymorphisms shared between arrangements were rare. All of this is consistent with a single origin for each polymorphism and suppression of recombination both within the inversion and in flanking regions extending up to 20kb outside the breakpoints. However, NAHR inversions showed strongly contrasting patterns: SNPs in complete LD with the inversion were generally absent and shared SNPs were common such that the two arrangements did not cluster separately in distance-based analyses. Of 21 NAHR inversions with data available, 14 were also polymorphic in chimpanzees, gorillas or both. Up to 7 recurrent origins were inferred in humans, and the mutation rate for a Y-linked inversion was estimated to be greater than 5×10^5 per generation. Since the precise positions of breakpoints remain difficult to resolve, it is possible, indeed likely, that recurrent inversions have distinct boundaries within the segmental duplications that promote their origin. Nevertheless, provided that the bulk of the

sequence included is in the same orientation, normal recombination is expected among haplotypes of the same arrangement but different origins. Therefore, each arrangement will function as a single population regardless of the number of origins.

These results are consistent with previous studies that have also found evidence for recurrent origins of human NAHR inversions (e.g.[30]). Breakpoint re-use has also been observed in other species, including cod[7], but in the origin of distinct (overlapping or adjacent) inversions.

The study by Giner-Delgado et al was focused[16] on common polymorphic inversions (as is most work in non-human species). More intensive analyses have shown that recurrence rates can be higher still for smaller inversions. Among 316 inversions detected in 70 human haplotypes using long-read data[14], inversions flanked by repeats tended to be longer than those that were not, were clustered in the genome, and showed evidence for repeated changes in orientation. The 729 inversions detected by Porubsky et al[15] ranged in size from 50bp to 23.2Mbp. Among short inversions (<2kb), 85% were associated with L1 transposition. Among 183 larger, sequence-resolved inversions, 72% were flanked by segmental duplications, L1 or Alu elements, consistent with NAHR. Around one third of inversions showed evidence of recurrence, with a wide range of re-orientation rates from ~10^{-6} for 17q21.31 to 1.1 x 10^{-3} (up to 15 inferred events in humans). Recurrent inversions were characterised by many shared polymorphisms (so called 'toggling-indicator' SNPs), tended to be flanked by longer repeats and were more common on the X chromosome than on the autosomes. Because recurrent events do not use exactly the same break points, they lead to increasing complexity in the repeat regions around the breakpoints.

Evolutionary expectations need to be modified to account for recurrent re-orientation of inversions. For example, when the mutation rate, u, is very low, an inversion with a disadvantage, s, in the carrier (heterokaryotype) is expected to have a frequency of u/s. With weak selection of s = 0.01, the range of inversion rates found by Porubsky et al[15] implies frequencies from 10^{-4} to 0.1. Back-mutation would reduce these expectations slightly. Without selection, the arrangement frequencies would depend on the forward and backward mutation rates, but with a strong effect of drift. Recurrence might explain why inversions have higher average MAF than other structural variants[15]. Each new origin introduces new alleles at sites within the inversion to the population of the derived arrangement. Unlike gene flux, this would be uniform along the inversion and so would not generate a suspension-bridge pattern of divergence between arrangements. This suggests an approach to distinguish between shared polymorphism due to recurrence versus flux that has not yet been applied to human inversions. Both processes oppose the accumulation of deleterious alleles unique to each arrangement and promote the exchange of adaptive alleles between arrangements, thus altering the long-term fate of an inversion polymorphism. Therefore, it will be important for future work in humans and other species to determine the factors that promote both recurrence and gene flux.

The mutational process contributes to the observed difference between the human inversion length distribution and the length distribution reported in other organisms. This is because the size of an inversion influences the probabilities of its loss, retention in a polymorphic state or spread to fixation[31]. Human data include rare inversions, that are likely to be lost, through a combination of detection via pathological effects and intensive sequence-based survey. Data for most other organisms focus on common polymorphisms and fixed differences between populations or species, missing this rare class and biasing towards longer inversions. This is similar to comparisons between X-ray induced and naturally polymorphic, or between rare and common inversions in *Drosophila* (references in[31]).

Inherent fitness effects

Inversions can influence fitness in one of two ways: either through effects of the rearrangement itself or through linkage disequilibrium between the rearrangement and the loci within it that results from suppressed recombination. Effects inherent to the arrangement itself are considered here in two categories – breakpoint effects and recombination effects. It is possible that large inversions also result in conformational changes[32], which might influence fitness either via gene expression or by impacting meiosis. Conformation might also influence patterns of inversion origin[33].

BREAKPOINT EFFECTS

Inversion breakpoints may disrupt genes or separate coding regions from some of their control elements. In principle, these disruptions might be advantageous, but most are expected to be deleterious. In natural populations, those with deleterious effects are unlikely to be observed because they will occur in single individuals or families, or they might persist for short periods at low frequency if their effects are mild. However, in human populations, investigations of pathogenic symptoms have been a major driver for the discovery of inversions, leading to an expectation that breakpoint effects are more likely to be described in humans than in other species.

There are few examples of breakpoint effects in non-human systems, probably because of the focus on common polymorphisms. An early study of inversion In(3L)Payne in *Drosophila melanogaster* showed disruption of gene expression by one of the breakpoints[34] but this is unlikely to be the only, or even the main source of selection on this polymorphism[6]. The recent survey[11] of inversions in deer mice found 2 of 13 inversions to have breakpoints within protein-coding genes (a significant under-representation relative to the coding component of the genome), while the survey in cod[5] found no breakpoints within genes. There are other cases where breakpoint effects seem unlikely, at least as causes for the major adaptive effects of inversions (e.g.[35]).

In humans, disruption of coding sequences has been reported in several cases, often associated with pathogenic effects. For example, disruption of the AP3B1 gene by an inversion on chromosome 5 manifests as the autosomal recessive disorder Hermansky–Pudlak syndrome[36] and an inversion on the X chromosome disrupts the XIAP and TMEM47 genes and results in immunodeficiency and mental retardation[37]. The small (16.6kb) 16q23.1 inversion results in the exchange of exon-1 between two related genes, CTRB1 and CTRB2, that are present in reverse orientation[38]. The minor arrangement for this inversion is widespread and at high frequency in some populations suggesting that the gene disruption has little or no negative effect. A deletion covering part of CTRB2 occurs only on the inverted arrangement, apparently arising from a separate mutational event: care is needed to avoid attributing pathogenic effects to breakpoints without first excluding the possible effects of such arrangement-specific variants.

Disruption of expression regulation by inversions has also been reported. For example, an inversion on the X chromosome separates the POU3F4 gene from its regulatory elements, leading to hearing loss in affected individuals[39]. Inversions on chromosome 7 separate the DLX5 and DLX6 genes from their regulatory elements[40] and sonic hedgehog from enhancer elements[41], with pathological effects in both cases. These examples are important but there are much more widespread effects of inversions on gene expression via LD (see below).

RECOMBINATION EFFECTS

The suppression of effective recombination by inversions can occur either because pairing failure prevents the formation of chiasmata or because cross-overs within inversions generate unbalanced gametes that result in inviable zygotes. In *Drosophila*, there is no recombination in males and the arrangement of female meiosis leads to the regular segregation of unbalanced meiotic products to polar bodies[42]. In other taxa, it is generally not clear whether or how the cost of unbalanced gametes is avoided (see[43], for example). In humans, these crossover effects would be expected to reduce the fertility of heterokaryotypic individuals or the health of their offspring. There is evidence for these effects in terms of reduced fertility, increased miscarriage or children with unbalanced karyotypes, and the effects are stronger for pericentric than for paracentric inversions and for longer inversions, as expected (e.g. [44] and references therein).

In addition to these costs, inversion heterozygotes also have increased risks of offspring suffering from microdeletion and microduplication syndromes (reported for more than 50 inversions[45]). For example, Williams-Beuren syndrome is caused by a 1.5Mb deletion in chromosome 7 and an inversion in this region has a frequency of 12.4% in the parents of affected individuals but only 2.9% in the general population[46]. Microdeletions and duplications are attributed to the presence of repeats that are brought into the same orientation in inversion heterozygotes whereas they would be in inverted orientation in homozygotes for either arrangement. This increases the risk of mismatched recombination, which generates gametes with either deletions or duplications and the possibility

of pathologies in offspring, especially for deletions of genes where a single copy is insufficient. A possible structure is illustrated in Figure 1B. In the situation shown, mispairing of repeats is also possible in inversion homozygotes but problems with chromosome alignment in the inverted region in heterozygotes might make mispairing more likely. Microdeletion syndromes are more common in recurrent inversions, presumably because of the complex repeat structures that they generate around breakpoints[15]. This is a form of selection against heterokarotypes for NAHR inversions that is also likely to occur in other species and may be hard to distinguish from the effects of unbalanced gametes due to allelic recombination within inversions.

Fitness effects due to linkage disequilibrium

The suppression of recombination in and near inversions slows down the decay of linkage disequilibrium. LD is generated by the capture of a specific set of alleles at the origin of a new arrangement and subsequently by mutation, drift and selection operating partly independently for the populations of the two arrangements[5]. These populations are only partly independent because of the transfer of alleles by gene flux (double recombination events and gene conversion) plus recurrence events, which move entire haplotypes from one population to the other.

Here, I will consider the effects of LD on the realised fitness of inversion genotypes (i.e. the direct fitness effects of the inversion, as discussed above, plus the indirect effects of loci in LD with the inversion) in terms of five possibilities: recessive deleterious alleles, epistatic interactions, loci of large effect, polygenic effects and expression effects. This classification is largely for convenience: boundaries are unclear, the effects are difficult to separate, and they may well occur together in many cases.

RECESSIVE DELETERIOUS ALLELES

One possible reason for the initial spread of a new arrangement is because it happens to capture a haplotype with an unusually low load of recessive deleterious alleles[47]. Subsequently, the two arrangements will tend to accumulate recessive deleterious alleles independently and may achieve an equilibrium load that is higher than outside the inversion because each arrangement has a lower effective population size than the colinear genome (due to lower census size, especially for the less-common arrangement, and the suppression of recombination). The process can also generate complex feedbacks because the rarer arrangement suffers greater accumulation, lower fitness and, therefore, further decreases in population frequency[48]. One possible outcome is to generate a higher fitness for the heterokaryotype than for either of the homokaryotypes, because fewer deleterious alleles are homozygous[49]. This is a form of 'associative overdominance'. All else being equal, it will tend to maintain the inversion polymorphism. However, the effectiveness of this process depends on the dominance coefficients of deleterious mutations and the extent of gene flux, and it is most likely to be effective in small populations[5].

Balancing selection has frequently been inferred for inversions[4] but the form of this selection (heterokaryotype advantage or negative frequency-dependent selection) and its source (i.e. the genes and environmental conditions that generate fitness differences) are rarely known. Very strong heterokarytoype advantage is seen in the seaweed fly, *Coelopa frigida*, and this might be partly due to accumulation of deleterious recessive alleles[50]. Non-synonymous substitutions and repeat sequences appear to have accumulated within inversions in *Heliconius* butterflies[51] but the evidence for accumulation of load in animal and plant species is generally mixed[5].

At least 19 missense mutations are known in the human 17q21.31 inversion[52]. This has not been specifically compared to a background expectation, but it is high for a region of only about 700kb. In general, the contribution of the accumulation effect to selection on human inversions is unknown. For recurrent inversions, it is less likely to be important because of lower LD.

EPISTASIS

Early work on polymorphic inversions in *Drosophila* emphasised the concept of coadaptation[3]. Selection can favour suppressed recombination between loci with epistatic effects on fitness, and this can cause a new inversion arrangement to spread[53]. However, it is very difficult to demonstrate fitness interactions among loci within inversions. Indirect evidence comes from the maintenance of allelic associations between loci

within inversions, despite gene flux[54], and from the special case of an inversion involved in sex ratio distortion[55]. In humans, there seems to be no such evidence. Widespread impacts of inversions on gene expression (see below) are likely to generate epistatic interactions, both between genes and their control regions and among genes, but they will be hard to document.

LOCI OF LARGE EFFECT

Evidence for selection on inversions often comes from temporal or spatial patterns. Dobzhansky observed repeated seasonal cycles and replicated altitudinal clines in inversion frequencies in *Drosophila pseudoobscura* that could not be explained without invoking selection[3]. Much recent work has shown similar patterns in other species, such as replicated latitudinal clines in *Drosophila subobscura*[56] or steep clines at habitat boundaries in the intertidal snail, *Littorina saxatilis*[57]. These steep clines are of particular interest because they generate a tension between selection and gene flow. Because gene flow allows recombination to disrupt locally-advantageous combinations of alleles, this tension can provide an advantage to recombination suppression in the absence of epistasis[58]. The rapid spread of a young inversion can provide strong evidence for positive selection (e.g. *In(1)Be* in *Drosophila melanogaster*[59]). However, restricted recombination makes it difficult to pin down the loci that underlie these fitness effects. Progress in non-human systems has been slow, with very few examples identifying loci of large effect (e.g.[60]).

In humans, geographic variation in inversion frequencies also provides evidence for selection, although this has to be distinguished from strong effects of recent population expansion (e.g.[61]). This type of evidence can be combined with associations to known pathologies and interpreted in the light of the high-quality genome assembly and functional annotation, leading to a promise of more progress. The 17q21.31 inversion is one of the best studied cases[52]. The H2 haplotype group can reach a frequency of 30% in some European populations while frequencies are much lower in Africa and the arrangement carrying this haplotype is virtually absent in Asia. The inversion contains 15 genes and ncRNAs, with a further 22 genes in the area of reduced recombination around the inversion. Of these, MAPT (microtubule associated protein tau) has received much attention because its known role in axonal microtubule stability, neuronal survival and maturation correlates with increased risk of neurodegenerative disease for some haplotypes and reduced risk for others (reviewed in[52]). However, there are also duplications and deletions of parts of the KANSL1 genes associated with the inversion, missense mutations in other genes and impacts on gene expression. Some phenotypic effects are not obviously connected to the MAPT function. Therefore, it is likely that MAPT contributes to fitness differences among inversion genotypes along with multiple other loci. The net result appears to be balancing selection, maintaining intermediate frequencies in European populations, but selection against the H2 arrangement elsewhere.

The situation is similar for many other human inversions. The survey by Giner-Delgado et al[16] of 45 common polymorphic inversions found evidence for a contribution of selection to differences in inversion frequencies among geographic populations in 16 cases and evidence for balancing selection in 11 cases (note that these two forms of selection are not mutually exclusive[20]). Seven of the inversions were known to be associated with gene mutations but causal links remain difficult to establish. Surprisingly, evidence for selection was not stronger or more widespread for NHEJ than for NAHR inversions, despite the difference in LD between these two groups.

POLYGENIC EFFECTS

Inversions are commonly identified as quantitative trait loci in association analyses. In itself, this says little about the numbers of loci within inversions that have phenotypic or fitness effects. However, there are many examples where the same inversion influences multiple traits, indicating that these inversions maintain associations among loci contributing to fitness in different ways, or where multiple inversions, along with loci in the colinear genome, contribute to a single trait, suggesting that loci of small effect contribute to the fitness effects of inversions. In *Drosophila melanogaster*, at least three inversions influence thermal tolerance (*In(3R)C*, *In(3R)Mo* and *In(2L)t*) and In(3R)Payne influences both body size and coloration[8]. The large chromosome 1 inversion in *Coelopa frigida* influences body size, development time, larval survival and mating behaviour[62,63].

Many inversions are polymorphic in *Littorina saxatilis* and contribute to variation in multiple adaptive traits[64]. Inversions contain QTL for multiple phenotypic traits in stickleback, *Gasterosteus aculeatus*[65] and monkeyflowers, *Mimulus guttatus*[66].

A recent study on brain morphology[67] illustrates the similar position in humans. An association analysis including 35 common polymorphic inversions found 5 of them to have influences across multiple morphological traits. The strongest effect was for 17q21.31. The inversion regions are also hotspots for neuropsychiatric conditions. More generally, inversion regions have an increased probability of harbouring QTL across a range of studies and commonly have associations with multiple diseases or traits[16].

EXPRESSION EFFECTS

Gene expression patterns commonly differ among inversion genotypes. For example, the chromosome 1 inversion genotypes in adult *Coelopa frigida*, were found to differ in expression for ~300 genes[68]. Cis-regulatory effects were suggested by the observation that 80% of differentially expressed genes were located within the inversion. Similar results have been reported for multiple inversions in *Drosophila*[8]. This expression divergence seems likely to be the result of divergence between inversion arrangements affecting regulatory elements of many genes.

Wang et al followed up their findings[67] of significant associations between inversions and brain morphology by examining data in the BrainSpan Developmental Transcriptome database. All inversions with significant associations contained genes that are highly expressed in the brain, often with distinct developmental patterns. Specifically for 17q21.31, the strongest association, multiple genes showed differential expression between carriers and non-carriers, with MAPT showing the strongest effect. The inversion was an eQTL for multiple genes within and close to the inverted region and carriers also showed differences in methylation and splicing. Many of the genes involved have known neurodevelopmental or physiological functions, helping to link the inversion to the phenotypes it affects. Widespread effects of inversions on expression patterns appear to be typical: Giner-Delgado et al found[16] either differential expression or eQTL signals associated with 15 of 42 inversions using published data sets.

Conclusions

Evolutionary theory leads to the clear expectation that the properties of segregating inversions will vary with their age. For young inversions, the derived arrangement will have low diversity and little divergence from the ancestral arrangement. Older inversions will be more divergent, and divergent at more loci, but with similar diversity in the derived and ancestral arrangements. Inversions may be old, i.e. have persisted in the polymorphic state for a long time, because they are selectively neutral but persistence is much more likely if there is balancing selection or divergent selection between populations that is countered by gene flow[5]. Evolutionary studies of non-human species tend to focus on common polymorphic inversions: this generates a bias towards older inversions and the common inference of balancing selection or local adaptation[2,18]. Surveys of inversions in human populations may have been biased in the past towards inversions with deleterious effects, but recent genomic approaches provide a much more complete picture, especially when high-intensity studies (e.g.[14]) are combined with broader population surveys (e.g.[16]).

Comparing human and non-human results shows, as expected, that inversion mutations commonly have deleterious effects, leading to a class of rare variants in mutation-selection balance that is missed in most non-human studies. However, it also reveals important processes that have been neglected in the evolutionary biology literature. One of these is the distinction between inversions generated by NAHR and those generated by other process that do not involve long inverted repeats. Recurrence of NAHR inversions can have profound effects on their evolution and so the consequences of inversions by reducing LD between the inversions and the loci they contain. In addition, complex repeats around breakpoints can introduce an additional selection pressure against inversion heterozygotes (seen as microdeletion syndromes in humans) that is not accounted for in evolutionary theory.

Costs experienced by heterozygotes for new inversion arrangements must be overcome by advantageous effects if the arrangements are to become common. In some cases, these benefits may be unconditional, in which case, the new arrangement may spread to fixation, contributing

to the widespread differences seen between related species, including humans and other apes. In others, the benefit may be conditional on the genotype (as in heterokaryotype advantage), the frequency of the variant (potentially leading to balancing selection if fitness declines with increasing frequency) or the environment (potentially leading to polymorphism maintained by a balance between divergent selection and gene flow). For common polymorphic inversions in humans and other species, there is widespread evidence for effects on fitness-related phenotypes and for the operation of these forms of selection. Indeed, polymorphic inversions often influence multiple phenotypes and appear to be subject to multiple forms of selection, deriving from a mix of direct effects and effects due to LD with multiple loci. In humans, the 17q21.31 inversion is a good example of these multifarious effects[52]. Progress towards pinning down the key genetic effects and their connections to fitness has been limited. Perhaps it is possible only for very small inversions. Even if it were successful, it might not reveal the original reason for the spread of an arrangement because of the many layers of divergence added during the evolution of the polymorphism.

From the clinical perspective, inversions might be considered to fall into three classes. The first group comprises rare mutational events that disrupt genes or have other direct pathological effects, either as heterokaryotypes or in males when X-linked. These inversions behave very like single-locus mutations. Recurrent inversions and the overlapping group of inversions associated with microdeletion syndromes can reach higher frequencies and can have effects on offspring rather than carriers but still have defined pathologies, typically associated with genes at or near their breakpoints. Finally, there is the group of polymorphic inversions, with a composition that varies among human populations. Carriers can be common but typically have complex patterns of increased or decreased susceptibility, perhaps to a range of related conditions: they are risk factors for polygenic effects rather than determinants of specific pathologies. This last group is the hardest to understand, but it is something that we share with many other species.

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