JOURNAL OF Evolutionary Biology

doi: 10.1111/jeb.13101

COMMENTARY

Genome evolution, structural rearrangements and speciation

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Ravinet *et al.* (2017) focus their review on the genomic landscape of speciation, in particular on the identification of barrier loci. However, here we wish to direct attention towards the evolution of structural rearrangements of the genome. By this, we refer to structural changes in the genome, including deletions, insertions, duplications, inversions and translocations, which alter the genome organization of individuals and result in structural variations within populations and structural differences between species. Within this short comment, we touch on three aspects of this subject, by no means attempting a comprehensive review of the topic. We aim to highlight that genome structure, as well as its sequence, evolves and point out some intrinsic differences between small sequence mutations, including single nucleotides and indels usually smaller than 50 bp, and larger structural variants (SVs) often much larger than 1 kb. The three aspects we judge particularly relevant for considering structural variations in a speciation context and want to review here are (i) the evidence for adaptive SVs, (ii) indications of incompatibilities due to SVs and (iii) the effects of SVs on recombination.

Evidence for adaptive structural variants

Structural variants frequently occur, are widely spread along the length of the genome and based on their size (total base pair count) account for more variation than point mutations (Conrad *et al.*, 2010; Feulner *et al.*, 2013). Evidence from mutation accumulation lines further suggests that the per-locus mutation rates of some types of SVs, specifically gene duplications, are higher than those of point mutations (Katju & Bergthorsson, 2013). After arising in the genome, the evolutionary fate of SVs might largely depend on their genomic position (Hurles *et al.*, 2008). Although SVs falling into intergenic regions are less likely to affect phenotypes, SVs overlapping genic or promoter regions have the potential to effect phenotype and fitness. To a large extent, these SVs are likely to be deleterious and therefore get pruned by selection. As a result, these SVs are rare or entirely absent in natural populations. The detrimental effects of CNVs, which might not destroy genes but change the gene copy number, can largely be explained by the dosage sensitivity of many genes (Rice & McLysaght, 2017). In *Drosophila*, such CNVs encompassing whole genes generally experience strong purifying selection, and only very few rise to high frequency, which suggests they are under positive selection (Emerson *et al.*, 2008). But similar to other variants, which to a large proportion are neutral, variation patterns of SVs within and between populations match well with population history and structure (Conrad & Hurles, 2007; Chain *et al.*, 2014). Although most SVs appear to be neutral and highly detrimental variants, some proportion of SVs might still be beneficial and thus contribute to adaptation (Iskow *et al.*, 2012; Kondrashov, 2012). In mice, evidence suggests that large-effect variants are more likely to be SVs than smaller variants (Keane *et al.*, 2011). The notion that SVs might be more likely to cause larger phenotypic effects is especially interesting if considered in a speciation context. Under adaptation without migration, the expected distribution of allele effect sizes is exponential and large-effect mutations are expected to be rare (Orr, 1998). However, adaptation with migration tends to result in concentrated genetic architectures with fewer variants of large effect (Yeaman & Whitlock, 2011). One well-documented example is a deletion variant that has been causally linked to a major phenotypic effect (namely the loss of the pelvic spine), which is distinct for different freshwater stickleback populations (Chan *et al.*, 2010). This provides evidence of the adaptive role of large-effect SVs in population differentiation and potentially speciation.

Indications of incompatibilities due to structural variants

Aside from potentially being adaptive, divergent evolution of SVs has also been suggested as a plausible and powerful genetic isolation mechanism, concordant with the postulations of the Bateson-Dobzhansky-Muller (BDM) model of speciation (Orr, 1996). Genomic incompatibilities might result from chromosomal rearrangements, which lead to mis-segregation during meiosis in hybrids (but see section below) or from epistatic interactions that act as loss-of-function alleles in hybrid backgrounds (Lynch & Force, 2000). During whole-genome duplications (WGD), thousands of duplicated genes arise simultaneously. The divergent resolution of parts of this genomic redundancy, that is one population loses one copy of a paralog and another population loses the second copy at a different genomic location, leads to gametes of hybrids completely lacking

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any copy of the duplicated pair, reducing hybrid fitness and contributing to the evolution of reproductive isolation (Lynch & Force, 2000). In yeast (Scannell *et al.*, 2006) and *Paramecium* (McGrath *et al.*, 2014), divergent resolution of paralogs following WGD has been associated with the evolution of reproductive isolation between rapidly evolving lineages. Interestingly, in rice, which has many duplicated genes resulting from both an ancient WGD as well as recent, smaller, duplications, only one epistatically interacting locus pair causing incompatibilities could be identified (Mizuta *et al.*, 2010). This shows that the evolution of such genic isolation mechanism is not constrained to large numbers of simultaneously arising paralogs resulting from WGD, but is also consistent with other, locally constraint, duplications of only a few genes. In *Drosophila*, BDM incompatibility has been associated with not only a paralog (Ting *et al.*, 2004), but also a divergently fixed transposition (Masly *et al.*, 2006). This observation points out the mutational effect of transposable elements and its potential to create structural variations, which promote the evolution of isolation mechanisms. An idea supported by studies on whitefish showing that retrotransposons can become re-activated in hybrids (Symonová *et al.*, 2013; Dion-Côté *et al.*, 2015).

Effect of structural variants on recombination

In contrast to structural rearrangements that change the copy numbers of loci (i.e. deletions and duplications), inversions are less likely to provide a plausible genic mechanism for incompatibilities, as they have been observed to have little fitness effects and are difficult to fix due to their strong underdominance (Rieseberg, 2001). However, they have received special attention due to their potential suppression of recombination in heterokaryotypes, as alleles within the inversions are protected from getting lost due to recombination and gene flow (Noor *et al.*, 2001). Further, especially if inversions capture locally favoured alleles at two or more loci, they can readily spread to high frequencies (Kirkpatrick & Barton, 2006). However, genic (BDM incompatibilities) and nongenic (suppression of recombination) factors might not be mutually exclusive and instead could be incorporated into one mechanistic framework (Faria & Navarro, 2010). Aside from the above-mentioned models, which suggest that rearrangements facilitate the evolution of reproductive isolation, others, including individual-based simulations, have shown that structural rearrangements can evolve during divergence with gene flow at realistic time scales (Yeaman, 2013). This suggests that the genome structure might be shaped by the speciation process, as rearrangements which move adaptive loci closer together will be selected for. Hence, structural rearrangements act as modifiers of recombination that create more subtle patterns of recombination rate variation across the genome (Ortiz-Barrientos *et al.*, 2016). This suggest yet another way, in which structural rearrangements can facilitate divergence in the face of gene flow including the early stages of divergence as well as the persistence of species after secondary contact. Empirical data from various study systems strongly suggest that chromosomal inversions should play a major role during speciation with gene flow. In diverging sister taxa of *Drosophila pseudoobscura* and *Drosophila persimilis*, inversions have been shown to reduce recombination to maintain areas of high divergence in the face of hybridization and have done so for a substantial period of time (McGaugh & Noor, 2012). Studies on *Mimulus* suggest that an inversion encapsulating loci involved in local adaptation has protected those loci from recombination and getting lost by gene flow (Twyford & Friedman, 2015). In addition to these two examples, four more case studies have characterized a heterogenous genomic landscape of differentiation, highlighted in table 1 (Ravinet *et al.*, 2017), and provide further evidence of inversions co-occurring with some regions of increased differentiation or divergence (in total six of 11 studies). Both theoretical predictions as well as empirical data therefore point towards an important role of inversions during speciation.

In summary, structural variations have been identified as interesting and important aspects of the speciation process and therefore deserve more dedicated attention. SVs not only influence the genomic landscape but also intrinsically provide genetic mechanisms to restrict gene flow. Fortunately, further evaluations are now technically and financially feasible and hopefully future empirical studies investigating the role of SVs in the speciation process across many different systems will continue to inform our understanding of speciation at a genomic level.

Acknowledgment

We thank Frederic Chain for his helpful comments and suggestions on an earlier version of this article.

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Received 26 March 2017; accepted 12 April 2017