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Going beyond SNPs: the role of structural genomic variants in adaptive evolution and species diversification

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Introduction

Although single-nucleotide polymorphism (SNPs) were initially thought to make-up the majority of selectable variation (Morin *et al.* 2004; Sachidanandam *et al.* 2001), it is becoming increasingly recognized that structural variation represents a significant, yet often poorly understood, source of genetic variation. It is only within the past 10 years, aided by the development of genomic technologies such as high-throughput and later 3rd generation sequencing, that the extent of intra- and interspecific structural variation has been investigated in a number of non-model species (Chain & Feulner 2014; Fan & Meyer 2014).

The term structural variation is used to define a region of DNA that shows a change in copy number (deletions, insertions and duplications), orientation (inversions) or chromosomal location (translocations, fusions) between individuals. Structural variation may occur both in coding and non-coding gene region of the genome, including in highly repetitive elements, such as transposons. In other words, structural variants can be balanced and show no specific loss or gain of DNA information, such as inversions of a genetic fragment or translocations of a stretch of DNA within or between chromosomes, or they can be unbalanced, where a part of the genome is lost (insertions/deletions) or duplicated (duplications), which is termed copy number variation (CNV).

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This Special Issue in *Molecular Ecology* provides a platform to showcase and highlight the very recent progress in understanding the role of genomic structural variants in adaptive evolution and species diversification. The contributions are varied, covering both animals and plants, and range from comparison of different kind of structural variants in the genome to bioinformatic approaches that can be used to characterize structural variants, experimental approaches that test the role of structural variants in adaptation and diversification to population-level studies that document the ecological determinants of structural variants and their adaptive significance in nature.

A short history of structural variants

The history of structural variants goes back to the beginning of this century, many years before scientists even had an understanding of what DNA was. It all started with the discovery of inversions, DNA regions that are flipped in orientation, which leads to the suppression of recombination in inversion heterozygotes (Butlin 2005; Dobzhansky & Sturtevant 1938). The discovery of inverted chromosomal regions was made when Alfred Sturtevant compared the chromosome maps of *Drosophila melanogaster* with those of *D. simulans,* a closely related species that he had described earlier (Sturtevant 1913). He found that the interspecies chromosome maps were similar, except for a genomic region on the third chromosome, where one large part of the sequence was inverted (Sturtevant 1921). In the years to follow, Sturtevant was able to obtain a sufficient numbers of mutants with the various inversion-containing chromosomes of *D. melanogaster* to establish that the dominant cross-over suppressors were indeed inversions (Sturtevant & Mather 1938). Afterwards, additional structural variants were discovered in a variety of species, with the notable discovery of transposable elements in maize (e.g. McClintock 1931, 1950). McClintock's work was revolutionary in that it suggested that an organism's genome is not a stationary entity, but rather is subject to alteration and rearrangement and changed the way scientists think about genetic patterns of inheritance. At the time the concept that was met with criticism from the scientific community, however, the role of transposons eventually became widely appreciated and the community started to accept that genomic replication does not always follow a consistent pattern. McClintock was awarded the Nobel Prize in 1983 in recognition of this and her many other contributions to the field of genetics (Ravindran 2012).

Yet, starting in the 1970s, this rich literature largely sank from view with the rise of molecular genetics and the development of other markers, including microsatellites, AFLPs and more recently SNPs. In particular, the latest techniques provide cheap, high-throughput methods for genotyping many SNP markers (e.g. Elshire *et al.* 2011), leading to studies of genetic variation being largely dominated by SNP variation. However, structural variants are present at significant frequencies in many populations and may contribute to important processes. For example, evidence is accumulating that gene dosage can be heavily affected by CNV with a profound effect on the functionality and the resulting evolutionary trajectories (Ha *et al.* 2009). Yet, CNVs go mostly undetected by standard SNP genotyping methods. Likewise, young inversions may go undetected in sequencing analyses, because merely the linear order of DNA bases is changed initially and only the breakpoints carry SNP variants, however, the consequences on recombination in a species can be pronounced and have long-term effects on the fitness of specific inversion genotypes (Wellenreuther & Bernatchez 2018).

Structural variants in the genomics era

The study of the structural variation of the genome has recently gained momentum as we are currently witnessing major advances in the field of computational genomics with increasingly high quality whole-genome data and assemblies becoming available for non-model species. Furthermore, advances in long-read sequencing, optical mapping and novel assembly algorithms now provide incredible resolution to study the presence and absence of a variety of structural variants (Chakraborty *et al.* 2018; Lee *et al.* 2016). This is accompanied by simultaneous fast improvements in computational and statistical tools that together allow the extraction of reliable information of the location and effect of structural variants on the phenotype (e.g. Boetzer & Pirovano 2014; Koren & Phillippy 2015; Koren *et al.* 2017). Using these genomic and bioinformatics advances we can now dissect the nucleotide variation contained within these structural variants as well as their ecological and evolutionary significance with unprecedented detail. As a consequence of these discoveries, a growing number of geneticists and evolutionary biologists have recently shifted their attention from SNP markers towards bigger and more complex alterations in the genomic architecture thus going back to some of the oldest genetic markers. For example, we have recently witnessed a dramatic increase in the number of studies reporting the involvement of complex structural variants in several genomic disorders (Sanchis-Juan *et al.* 2018; Xia *et al.* 2017).

Contributions and overview of the Special Issue on structural variants

The 24 articles in this Special Issue of Molecular Ecology, which embody a diverse collection of approaches and study systems, offer valuable lessons about the role of structural genomic variation in adaptation and species diversification. The contribution by Catanach *et al.* (2019) highlights the frequent nature of structural variants and their non-random distribution in the genome, thus underscoring the emergent tenet that structural variants offer important sources of genetic fuel for evolutionary processes. Specifically, they use replicate genome assemblies of the Australasian snapper *Chrysophrys auratus* to quantify the locations and prevalence of SNPs and structural variants of varied sizes, and showed that while SNPs were most common, that the number of base pairs affected by structural variants was almost three times higher compared to SNPs. The high number of structural variants indicates that some may have an impact on the phenotype and this was further supported by the finding that a sizeable portion of the structural variants were located in regions under putative selection, and that a third intersected in some way with genes. The prevalence of genome-wide structural variants was also investigated by Lucek *et al.* (2019) using a mate-pair sequencing and a population genomics framework in the stick insect *Timema cristinae.* The authors were able to describe numerous inversions, deletions, duplications throughout the genome. Although not detected by the mate-pair approach, the study also considers one large structural variant that has formerly been described, which shows reduced recombination and harbours genes controlling colour-pattern and therewith leads to an accentuated differentiation between ecotypes. This study is a prime example of the need to go beyond the mere measure of SNPs when studying evolutionary processes and that knowledge of structural variants can be relevant to understand variation at the intra-specific level or during early divergence. They also highlight that while not all structural variants would be expected *a priori* to be involved in ecotype differentiation, that some variant characteristics, such as large size and being able to protect regions from gene flow (e.g. inversions) would increase the likelihood of them being involved in adaptive processes compared to others.

Many inversions fulfil these criteria and this is partly the reason why inversions have seen a surge in popularity over the last decade due to their clear association with adaptive phenotypes, behaviour, mating strategies and speciation (Wellenreuther & Bernatchez 2018). The first contribution on inversions by Cheng and Kirkpatrick (2019) investigates the intriguing observation in varied taxa that inversions fix at a faster rate on the X chromosome compared to autosomes. Using the *Drosophila* system they show that X-linked inversions are often larger than their autosomal counterparts and capture a staggering 67% more genes than autosomal inversions. They combine this empirical result with a population genetic model showing that the same conditions that favour higher fixation rates of inversion on the X chromosome also favour larger inversions. Together these results indicate that inversions on the X chromosome may strongly influence the evolution of sex chromosomes. Hooper *et al.* (2019) also explore inversions on sex chromosomes by studying two subspecies of long-tailed finches and integrating population genomics with phenotype data associated with fitness differences, such as bill colour. With this, they are able to detail Z-linked inversion related differentiation between the two subspecies, however they also find that the frequency cline does not coincide with the autosome nor bill-colour; a major phenotypic difference between the subspecies. They integrate these findings to argue that inversions on the sex chromosome could serve as good candidates for structural variants that are tightly linked to reproductive isolation.

In their contribution to this special issue, Kapun and Flatt (2019) revisit the species where inversions where first described, the vinegar fruitfly *Drosophila melanogaster.* Since the original discovery, significant advances in the field have come from the same system and they provide an in-depth and thorough review of the rich work until today. In particular, they also include a meta-analysis of the geographic distribution of four major cosmopolitan inversions, and worldwide patterns of clinality. The evidence that they put together suggests that large cosmopolitan inversions in this species have an adaptive significance and are under balancing selection. Fuller *et al.* (2019) provide a complementary review on the history of inversion research in *D. pseudoobscura* and *D. persimilis,* notably going also over the details by which recombination is suppressed in inversion heterozygotes. By summarizing the large body of work on the inversions both at the intra-specific and inter-specific level, the review concludes that inversions often underlie adaptation to heterogeneous environments, are governed by balancing selection, and how this can transition to fixed differences between species. Korunes and Noor (2019) work on the same species pair to measure non-crossover gene conversion rates in intra- and interspecific crosses. They detect that the gene conversion rate can be high within inversions, and this holds true even near breakpoints. However, conversion rate is considerably lower in regions of high divergence, yet the rate is still higher than in similar regions of collinear genome. Korunes and Noor (2019) claim that these findings force us to rethink the extent that recombination is reduced in inversions and how this may affect the build-up of divergence. Specifically, they argue for a more nuanced view as some exchange is still occurring, even at the inter-specific level. That being said, the extent of homogenisation remains limited because the length of the fragments homogenized by gene conversion is still very short compared to the size of the overall rearrangement, or compared to the extent of genetic exchange due to true cross-overs. Puig Giribets *et al*. (2019) examine the role of inversions in the evolutionary responses to heat shock variation in *Drosophila subobscura* to understand why flies homokaryotypic for the warm-climate chromosomal arrangement exhibit basal Hsp70 protein levels after a heat shock treatment similar to those attained by their cold-climate counterpart. They detected a mostly common pattern of cytological location, number of cis-regulatory elements and gene copies among these inversions and

found that they evolve in concert through gene conversion. The pattern of concerted evolution, however, is strongly structured and idiosyncratic across lineages as expected from the barriers to interchromosomal genetic exchange. This finding points to a previously unrealized link between inversions and concerted evolution, with potentially major implications for understanding genome evolution. Newly arisen inversions could disrupt existing patterns of concerted evolution via altering the relative orientation and distance between genes, which may impose constraints on their location, position and size. Or alternatively, newly derived inversions could be positively selected for if they promote specific adaptive patterns of intrachromosomal concerted evolution through their interchromosomal recombination suppression effects.

A key problem with many inversion systems is that the genes under selection inside the inversion are hard to identify because the regions typically shows strong linkage disequilibrium. A technically challenging study by Ayala and co-workers (2019) tries to address this issue, and applies a GWAS approach to dissect the causative genes inside an inversion of the malaria vector *Anopheles gambiae.* They do this by measuring phenotypes for desiccation resistance within homokaryotypes and performing pool-seq on the phenotypically extreme individuals. By doing so they are able to characterize the putative basis of adaptation to desiccation and provide a proof-of-concept for an original method to characterize the genotype-phenotype link and the genetic basis of adaptation within a rearrangement. Similar, Coughlan and Willis (2019) empirically investigate the phenotypic effects of an inversion known to differentiate between annual and perennial forms of the yellow monkeyflower *Mimulus guttatus*. In particular, they tested the hypothesis that that loci contributing to local adaptation should predate the inversion, as theoretically predicted by the recombination suppression hypothesis (Kirkpatrick & Barton 2006). To test this, they mapped QTLs for life history traits that differ between annual *M. guttatus* and a more distantly related, collinear perennial species. Interestingly, they found a chromosomal region containing at least two adaptive QTLs that were associated with life history in the absence of the inversion. With this, the contribution by Coughlan and Willis provides one of the few cases were empirical support for the recombination suppression hypothesis could be found to date.

Another long-standing challenge when describing new inversions system has been the characterisation of the inversion breakpoints. Christmas *et al.* (2019) study the inversion breakpoints characteristics with a combination of long-read and short-read in the honeybee *Apis mellifera*. By comparing inversions associated with high-and lowland populations they found that the haplotypes were well-conserved, indicating that inversions are likely ancient and associated with adaptation to altitude, and detected an additional rearrangement on the same chromosome. The detected breakpoints were mostly composed of repeat sequences and transposable elements, in line with a formation process that is governed by non-allelic homologous recombination. Faria et al. (2019) address yet another difficulty commonly encountered in inversion research, that is the biased discovery and reporting of structural variants because typically only the largest major inversions are reported, which makes it difficult to assess their prevalence and biological importance in evolutionary change. Using a method based on linkage disequilibrium which combines the analysis of recombination in controlled crosses and patterns of diversity in the field, Faria and co-workers detected no less than 17 polymorphic rearrangements in the coastal marine snail *Littorina saxatilis*. Most of these rearrangements showed clinal variation in frequency between habitats, suggestive of a role in local adaptation. Although the approach does not allow to rigorously confirm that these rearrangements are indeed inversions, it nevertheless represents an efficient means to detect

multiple structural variants at a relatively low cost. It should be noted, however, that the association between inversions and ecotypes is not always that straightforward to map, particularly not in species characterized by large effective population size and high gene flow, such as the Atlantic cod *Gadus morhua*. Barth et al. (2019) test the idea that chromosomal inversions are an important mechanism for maintaining reproductive isolation between ecotypes in the face of gene flow. They found that frequencies of the inversions differed between the genetically distinct groups but they could not tie these differences to reproductive isolation leading them to suggest that thus multiple other processes likely contributed to reproductive divergence in this system. This contribution highlights the need to use more holistic approaches to study selection and demonstrates that sometimes rearrangements are one of many factors working together to generate divergence. Arostegui *et al.* (2019) provide another example associating ecotype specialisation with an inversion polymorphism by studying the complex migratory behaviour in the fluvial and adfluvial ecotypes of the rainbow trout *Oncorhynchus mykiss.* To do this, they sampled wild rainbow trout occupying connected stream and lake habitats and they detected that the chromosomal inversion on Omy05 contains many genes exerting control over migratory behaviour and its haplotypes were present at different frequencies between trout in streams and those that had migrated to a lake. This indicates that the inversion is associated with the migratory behavioural phenotype and likely sustains ecotypic diversity but also that the direct link is not straightforward.

Inverted genomic regions are commonly associated with so called supergenes. Here, Avril *et al.* (2019) investigate the large supergene associated with divergent social behaviour in the Alpine silver ant *Formica selysi,* where colonies are either headed by a single or multiple queens. The supergene haplotypes of this species differs by multiple inversions, but it is not yet clear whether inversions are a cause or consequence of the arrest of recombination. Their results reveal that asymmetry between social forms in the degree of assortative mating generates unidirectional male-mediated gene flow from the monogynous to the polygynous social forms. As such, this study convincingly demonstrates that supergene variants may control social organization and multiple components of the mating system which influence the population dynamics in this species.

Chromosomal fusions are also featured in this Special Issue, and Wellband *et al*. (2019) investigates the chromosomal fusion between chromosomes 8 and 29, which is polymorphic in some Atlantic salmon (*Salmo salar)* populations. Such fusions are intriguing because they can act akin to inversions and reduce the rate of recombination in some crosses. They use Atlantic salmon populations residing in the tributaries of the Miramichi River (Canada) to resolve the genetic contribution of SNPs vs the chromosomal fusions to the genetic relationships between populations. They report extremely weak overall population structuring using SNPs ($F_{st} < 0.01$) and fail to support a hierarchical structure between the river's two main branches. However, when investigating patterns of variation of the chromosomal fusion, they found high linkage disequilibrium, reduced heterozygosity in the fused homokaryotypes and strong divergence between the fused and the unfused rearrangement. Moreover, the population structure based on fusion karyotypes was five times stronger compared to the neutral variation and the frequency of the fusion was associated with summer precipitation. This association strongly implicates that this rearrangement may contribute local adaptation despite weak neutral differentiation. This indicates that adaptive processes, independent of major river branching, may be more important than neutral processes for structuring populations.

Another common structural variant is CNVs and their main role in influencing the path of evolution stems from their effect on gene dosage and by reshaping gene structure. The contribution by Nelson *et al.* (2019) dissects the role of tRNA ligase gene CNV in adaptation of the yellow monkeyflower *Mimulus guttatus* and provides empirical evidence that copy number variants of this type are associated with multiple phenotypes that are under fluctuating selection. Their work suggests that plant tRNA ligases mediate stress-responsive life-history traits, and introduces a novel system for investigating the molecular mechanisms of gene amplification. Prunier *et al.* (2019) use genomic sequence data from the black cottonwood tree *P. trichocarpa* to design a custom hybridization array to detect CNV of coding regions in the closely related balsam poplar genome *P. balsamifera*, and to relate that variation to several phenological characters. They used 34 individuals from two mixed-parentage families from northern Quebec and southern Saskatchewan and found CNV in 1,721 of the ca. 20,000 genes tested, and identified 23 of the CNVs as having significant connections to eco-physiological or phenological traits. They attribute the significant variation to selection for resistance to disease in the south and to abiotic stress in the north. A such, this work represents an important advance in genomic analysis, particularly of intra-specific structural variation, both by demonstrating that CNV is much more common than previously expected (ca. 9% of coding genes), and by identifying potential physiological and ecological roles for several of the variants detected.

Another process that can lead to the generation of duplicated sequences is driven by transposable elements (TEs), ubiquitous sequences that are present in virtually all eukaryotes and that can move (or jump) from one location in the genome to another. While next-generation sequencing methods have opened the opportunity to study TE population dynamics at the genome-wide scale, most of the studies so far comprised the analysis of a limited number of populations. Dennenmoser *et al.* (2019) studied the genome-wide distribution of transposon insertions in a young hybrid fish lineage ("invasive *Cottus*") and its parental species *Cottus rhenanus* and *Cottus perifretum* using a reference genome assembled from long single molecule PacBio reads. They used this data to test the relative contribution of transposition bursts versus recombination-based mechanisms in evolutionary adaptation. The data revealed that the transposon copy numbers in the hybrid lineage increased significantly, suggesting that they have proliferated within a few hundred generations since admixture began. Most transposons appeared to be added to repetitive regions of the genome that remain difficult to assemble, making it difficult to ascertain whether recombination-based mechanisms or genome-wide transposition can explain the transposon proliferation in the hybrid lineage. Lerat *et al.* (2019) took advantage of the European *Drosophila* population genomics consortium sequencing dataset to document the dynamics of TEs in a large sample of *Drosophila melanogaster* natural populations. This allowed them to show that while the "mobilome landscape" is population specific, no clear geographical structure was observed for transposable element abundance or divergence. Yet, they identified several TEs that were present at high frequencies and located in genomic regions with a high recombination rate, which could be candidate targets of positive selection. Moreover, their results revealed parallel patterns of association between the frequency of TEs insertions and some geographical and temporal variation between European and North American populations, further suggesting that at least some of the TEs they identified could play a role in local adaptation across continents. Adrion *et al*. (2019) investigated TEs along the classic *Drosophila* cline in North America by sampling six populations of *D. melanogaster* and nine populations of *D. simulans* from multiple latitudes across North America. The authors find a nearly twofold excess of TEs in *D. melanogaster* relative to *D. simulans*, but no effect of latitude on either

total TE abundance or average TE allele frequencies in either species. Despite the absence of clinal variation, the authors argue that this does not necessarily imply a limited role for TEs in adaptation and uncovered a complex relationship between the presence of TEs, recombination rate and chromatin state that calls for further investigation. The work by Schrader and Schmitz (2019) on TEs further examines the ways in which they can contribute to adaptation and by disentangling the basic molecular mechanisms by which the underlying genetic changes arise. They also discuss how the defence mechanisms against TE activity are affected by environmental challenges, which might be particularly relevant in understanding how invasive, pathogenic or parasitic species quickly adapt to new environments. Choudhury *et al.* (2019) study the Alpine rock-cress (*Arabis alpina*) to test to what extent the enrichment of TEs in recombinationally inert regions reflects their inefficient removal by purifying selection and whether the presence of polymorphic TEs can modify the local recombination rate. To do this, they measure how TEs and recombination interact at a fine scale along chromosomes. The detected 28 linkage disequilibrium blocks of up to 5.5Mb in length and found that a majority of these blocks were enriched in genes related to ecologically relevant functions such as responses to cold or salt stress. This is consistent with strong evidence of selective sweeps at a few loci through either site frequency spectrum or haplotype structure. These results are consistent with the hypothesis that TEs modify recombination landscapes and thus interact with selection in driving blocks of linked adaptive loci in natural populations

Lastly, a study by Yoshida et al. (2019) provides an important contribution to better understand how selfish genetic elements may drive intragenomic conflict and lead to reproductive isolation. They show that hybrid sterility between Japan Sea (*Gasterosteus nipponicus)* and Pacific Ocean sticklebacks (*G. aculeatus)* maps to a gene encoding a heterochromatin-binding protein and gene expression test indicated that over-expression of at least two retrotransposons, hence providing strong evidence for a role of transposons in the generation of hybrid sterility.

Future outlook

The increasing awareness that structural genomic variants provide raw genetic material that provides a key resources to fuel important evolutionary processes, from mating systems to adaptation and speciation, is slowly changing the way that researchers dissect and analyse the genomic landscape of species. Whereas structural variants were previously considered to be rare, they are now recognized as the largest source of inter-individual genetic variation that can affect more bases than SNPs, variable number tandem repeats and other small genetic variants. The contributions in this Special Issue highlight that the inclusion of structural variants in evolutionary genetics and molecular ecology will provide a more complete view of the role of genetic variants in adaptation and diversification. On one hand, an increasing number of studies show that inversions are critical in isolating species (Hooper *et al.* 2019), that they may facilitate the coexistence of several ecotypes (Arostegui *et al.* 2019; Christmas *et al.* 2019; Lucek *et al.* 2019), and can contain adaptive loci (Ayala *et al.* 2019; Coughlan & Willis 2019; Puig Giribets *et al.* 2019). On the other hand, these studies also highlight that the link between structural variants and adaptation is not always straightforward. New studies showcased in this special issue also show that while inversions have an overall reduction in recombination rate, gene conversion is still a potent force that should be accounted for (Korunes & Noor 2019). When studying all structural variants (TEs, or different sizes and types of structural variants such as deletions, duplications and inversions) the evidence for a link

with adaptation can indeed be mixed (Adrion *et al.* 2019; Barth *et al.* 2019; Catanach *et al.* 2019; Lucek *et al.* 2019), with some outliers in putatively adaptive regions and plenty of possibly neutral variants elsewhere in the genome.

While much remains to be learned about their evolutionary role in nature, it is becoming increasingly clear that structural variants are important to consider when studying genetic diversity and genome evolution, and as such, they simply can no longer be ignored. Therefore, improvements in structural variant detection and analysis should be a priority to better evaluate the impact of these types of variants on evolution, something that will become increasingly feasible with improvements and cost reduction of long-read sequencing technologies. Most current methods are poor at defining breakpoints at a fine scale, making it difficult to determine the mechanism that lead to variant formation which is a key aspect to help understand the processes that lead to the evolution and spread of structural variants. Accumulating evidence points towards a disproportionate role of large inversions in adaptation, but whether this is because of a detection bias or because they span a larger number of potentially adaptive genes is still unclear and deserves some future attention. Moreover, the ability to accurately genotype structural variants would allow for a population genetic framework analysis that can make use of allele frequency changes to determine the evolutionary dynamics similar to the framework used for SNPs. Despite these limitations, essentially any organism can now be screened for structural variants, which will allow us to gain better knowledge of their ecological and evolutionary implications.

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