

1 **A roadmap for understanding the evolutionary**
2 **significance of structural genomic variation**

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23 ABSTRACT

24 Structural genomic variants (SVs) are ubiquitous and play a major role in adaptation and
25 speciation. Yet, comparative and, later, population genomics have focused predominantly
26 on gene duplications and large-effect inversions. The lack of a common framework for
27 studying all SVs is hampering progress towards a more systematic assessment of their
28 evolutionary significance. Here we 1) review how different types of SVs affect ecological
29 and evolutionary processes, 2) suggest unifying definitions and recommendations for future
30 studies, and 3) provide a roadmap for the integration of SVs with eco-evolutionary studies.
31 In doing so, we lay the foundation for population genomics, theoretical, and experimental
32 approaches to understand how the full spectrum of SVs impacts ecological and
33 evolutionary processes.

34 **Beyond SNPs: structural variation plays a key role in adaptive evolution and**
35 **speciation**

36 The study of **structural variants (SVs)** (see Glossary, Figure 1) has a long history going
37 back to the discovery of **chromosomal inversions** in *Drosophila* fruit flies in the early 20th
38 century [1], followed by **transposable elements (TEs)** in maize (*Zea mays*) [2], and **gene**
39 **duplications** in *Drosophila* [3]. Yet, this rich knowledge from comparative genetics was not
40 widely integrated into the field of molecular population genetics, which rose in the 1970s.
41 Since then, predominant attention has been on molecular markers that quantify patterns
42 defined by one or few base pairs, such as **SNPs**, **AFLPs**, and **microsatellites**. However,
43 diverse forms of SVs have reemerged in population-level studies owing to advances in
44 genomic technologies. Mounting evidence suggests that they are taxonomically ubiquitous
45 [4–7] and key contributors to a multitude of evolutionary processes (Box 1; [8]).

46 *Considering the full spectrum of structural variants*

47 Large inversions — spanning 100 kb to several Mb — are the most frequent SVs
48 associated with adaptive phenotypes and the maintenance of differentiation [9,10]. The
49 strong association is largely due to their ease of detection and their ability to reduce
50 recombination in inversion heterozygotes (**heterokaryotypes**), and hence to preserve
51 linkage between alleles despite gene flow. Although they have received less attention,
52 other SVs such as chromosomal **fusions** and **translocations** also interfere with
53 recombination and promote differentiation. For example, a chromosomal fusion
54 polymorphism in some Atlantic salmon (*Salmo salar*) populations in Canada is associated
55 with precipitation and harbors five times stronger differentiation than neutral SNP variation
56 [11]. The fusion of several chromosomes in *Heliconius* butterflies is associated with a
57 higher speciation rate [12]. Indeed, karyotype engineering shows that chromosome fusions
58 lead to the rapid emergence of reproductive isolation in *Saccharomyces cerevisiae* yeast
59 [13]. Translocations can also be involved in speciation: in the house mouse *Mus musculus*,
60 four incipient species with different karyotypes coexist in the Swiss-Italian Alps [14].

61 Gene duplication, and the subsequent evolution of novel functions, is probably the
62 best documented effect of **Copy Number Variants (CNVs)** on adaptation and

63 diversification [15]. However, CNVs encompass a much wider class of variants, including
64 **insertions/deletions (indels)**, tandem repeats (**mini- and microsatellites**), and variation
65 in copy number for a given coding or non-coding sequence. They represent the most
66 common SV type and can modify gene dosage and reshape gene structure [16]. A large
67 CNV linked to plumage dimorphism and thermal adaptation in common murrelets (*Uria*
68 *lomvia*) appears to suppress recombination locally [17]. Copy number variation associated
69 with toxin resistance has also been demonstrated multiple times, indicating that CNVs may
70 enable rapid adaptation to environmental stressors [18]. Micro- and minisatellite data, used
71 predominantly as neutral markers in the past (but see [19]), also represent a common type
72 of SV with demonstrated functional impact [20,21].

73 **Transposable elements (TEs)** are major modifiers of genome structure [22] and
74 drivers of adaptation and reproductive isolation [23]. TEs represent a type of translocation
75 and/or duplication and a source of indels because they ‘jump’ from one location to another.
76 TE insertions also lead to segmental duplications and inversions, due to **non-allelic**
77 **homologous recombination** [24]. TEs can change during an individual’s lifetime, which
78 makes them an important variant in rapidly changing environments [25].

79 *A better understanding of how structural variants affect evolutionary processes is needed*

80 While recent studies provide exciting insights into the role of SVs in adaptation and
81 diversification, they also reveal limitations that hamper progress. For example, many
82 studies investigating the genomic basis of traits from sequence data have found a link
83 between a phenotype and a SV, most often a large inversion or gene duplication (e.g.,
84 [18,26–28]). Whether such examples are representative of the global importance of SVs or if
85 their prevalence is biased by their relative ease of detection is still unclear. However, with
86 ever-improving sequencing and analytical methods, we can now adopt a bottom-up
87 approach and explore genomes independently from phenotypes to identify SVs of different
88 types and sizes that could be associated with different evolutionary processes. Generally,
89 synthesis in the field is slowed by a lack of unified definitions and the absence of a
90 framework to synthesize information from SVs and SNPs in population genomics. We
91 suggest definitions and focus points to guide future investigations and propose a roadmap
92 to integrate SVs into evolutionary genomics (Figure 2).

93 **Defining and detecting structural variants of all types and sizes**

94 *Sequence and structural variation exist along a continuous spectrum*

95 Definitions of biological phenomena reflect the thoughts and methods in the field that
96 coined them. 'Chromosomal rearrangement' was used to describe inversions, fusions, and
97 translocations detected at a microscopic scale using cytogenetics. The term 'structural
98 variation' emerged in 2004 with its characterization in the human genome [29] and now
99 generally refers to smaller-scale variants detected from sequence data. However,
100 sequence and structural variation exists on a size spectrum ranging from **Single**
101 **Nucleotide Variants (SNVs)**, including SNPs and single nucleotide indels, up to large SVs
102 affecting hundreds of Mb (Figure 1).

103 SVs are also classified according to how they alter the genome, i.e. whether they
104 add, delete, or change the position or orientation of DNA (Figure 1). As highlighted by
105 recent reviews on inversions [9,10,30], most studies focus on only one type of SV rather
106 than considering their diversity. For example, CNVs and TEs are often not considered
107 'chromosomal rearrangements', resulting in an oversight of similarities shared among SVs.
108 We argue that the field would benefit from jointly considering the full diversity of SVs and
109 advocate for a wider adoption of the term 'structural variant' to encompass all changes in
110 position or direction, as well as gains or losses of sequence, without imposing a size limit,
111 to enable synthesis across studies.

112 *Systematic characterization of structural variants of all types and sizes is needed*

113 Regions of elevated differentiation linked to phenotypic variation and exhibiting signatures
114 of **linkage disequilibrium (LD)** (Box 2) are often ascribed to inversions. However, such
115 **blocks of differentiation**, or **haploblocks**, can likewise result from other types of SVs
116 (e.g., CNVs [17], fusions [11]) or be due to selective sweeps [31] or introgression [32].
117 Follow-up analyses are needed to definitively associate a haploblock with a SV. Moreover,
118 indirect identifications are biased towards large SVs (> 1 Mb) with large phenotypic effect
119 and/or high sequence divergence, and overlook small, neutral, and recently established
120 SVs.

121 Recent developments in sequencing and computational methods have enabled
122 direct genome-wide characterization of SVs, providing information on SV position,
123 frequency, breakpoints, and gene content [33,34] (Box 2). However, challenges remain.
124 High-quality, chromosome-level reference genomes are seldom available, yet are helpful to
125 localize and characterize SVs. Sampling enough individuals to capture the geographic,
126 phenotypic, and sexual population variation is needed to characterize structural diversity
127 [35], but can be logistically and financially prohibitive. Further, the sensitivity of different
128 detection methods varies with respect to SV size [7,33] and is not generally reported. To
129 enable comparisons and syntheses and identify best practices (e.g., data type, software,
130 settings), we need simulations and benchmarking to test how detection power varies by
131 analytical approach, SV type, and type of sequence data (Figure 2).

132 **A framework for understanding the evolutionary significance of structural variation**

133 *Structural variants are missing pieces to the puzzle of genomic variation*

134 SVs might explain some of the ‘missing heritability’ in many genotype-phenotype
135 association studies [36]. In the crow *Corvus corone*, a retrotransposon indel of 2.25 kb
136 explained an additional 10% in plumage colouration variance between two subspecies
137 compared to SNP variation only [7]. **eQTL** studies that integrate CNVs and SNPs in
138 humans identified several SVs that cause gene expression changes, often with larger effect
139 sizes than SNPs [37,38]. Signatures of population structure can also vary depending on the
140 type of marker. In modern humans, CNVs and deletions show different signatures of
141 population structure and selection, with the former revealing a stronger spatial signature
142 [39]. Moreover, SVs can encompass two to five times more bases of the genome than
143 SNPs [4,40]. SVs also follow different evolutionary trajectories. For instance, some large
144 inversions are under long-term balancing selection and are involved in interspecific
145 introgression [41], while TEs and microsatellites commonly evolve rapidly [21,25].
146 Therefore, accounting for the range of genetic variation requires going beyond SNPs and
147 integrating SVs into studies investigating genome evolution, levels of standing genetic
148 variation, population structure, demography, phenotype-genotype associations, and the
149 genomic basis of adaptation and speciation.

150 *Population genomics can reveal the roles of SVs in evolutionary processes*

151 Cost-effective ways to analyse SVs at larger scales in non-model species are emerging.
152 For example, CNVs and large inversions can be genotyped, directly or indirectly (Box 2),
153 using low-coverage whole-genome sequencing [42] or RAD-seq [27,43,44]. Complex and
154 large SVs are better characterized by long-range information (Box 2), but these methods
155 can be expensive. New tools are necessary to leverage information from a subset of
156 diverse and well-sequenced genomes to genotype SVs in larger datasets.

157 Some analytical methods developed for traditional markers may be used to mine
158 information on SVs from existing population-scale datasets. For instance, population
159 genomics based on CNVs uses an extension of the F_{ST} index of differentiation called V_{ST}
160 [45]. Coding SVs similarly to SNPs and genotyping different SVs for large numbers of
161 individuals is a challenge. CNVs can be relatively easily summarized in a matrix of read
162 depths, but expressing genotypes as numbers of copies remains difficult. For balanced SVs
163 (Figure 1), analyses can either focus on SNPs genotyped within the rearranged region [5]
164 or consider the SV as an individual locus, with the latter being a more powerful approach to
165 finding associations with phenotypic and environmental variation [46].

166 The joint analysis of SNPs and SVs in a population genomics framework will allow
167 us to test whether sequence differentiation associated with SVs has adaptive value or is
168 due to demographic and population structure (e.g. [44]). Systematic analysis of SVs will
169 address the detection bias towards large inversions and help to unveil how different
170 features of SVs (e.g., size, position, content, type, breakpoints) influence evolutionary
171 trajectories (e.g., [47]). Comparing SNPs and different kinds of SVs will reveal factors
172 causing variability in evolutionary rates across the genome. Finally, comparing numbers
173 and distributions of SVs among populations connected by varying levels of gene flow will
174 improve our understanding of how gene flow-selection balance affects the genomic
175 architecture of adaptive traits [48]. Altogether, such studies will enable us to shed light on
176 when and how SVs form, persist, and spread among populations and species (e.g., *de*
177 *novo* formation or introgression, drift, balancing or fluctuating selection).

178 *Theoretical approaches are needed to predict evolutionary patterns specific to SVs*

179 Theoretical models have been pivotal to developing hypotheses on why SVs might follow a
180 different evolutionary pathway compared to SNPs [49–51]. Models have shed light on TE
181 dynamics [52] and the role of recombination suppression in adaptation with gene flow,
182 particularly in inversions [49–51]. Less is known about the evolutionary significance of other
183 features of SVs, such as the multi-allelic characteristics of CNVs, the impacts of reduced
184 effective population sizes (N_e) of inversions and deletions, and differences in mutation rates
185 within SVs. Theoretical studies targeting a wider variety of SVs are needed to understand
186 how different features relate to their origin and maintenance, and the relative contribution of
187 selective and neutral processes in their evolution.

188 Forward individual-based simulations are a promising tool to account for SV
189 complexity under realistic evolutionary scenarios. For instance, the program *SLiM* 3 [53]
190 models population genetic processes and includes genetic variation based on SNPs and
191 TEs, and information on LD. Such simulations enable evaluating the relative effects of
192 migration, drift, and selection on SV dynamics (e.g., [54]) and, reciprocally, to predict the
193 conditions under which SVs represent relevant architectures for adaptation and
194 differentiation [51]. Forward simulations can model expected signatures of selective and
195 demographic processes, enabling comparisons between simulated and empirical data to
196 identify the specific processes and range of conditions that explain SV distributions in
197 natural populations. Simulated genomic data are also useful for testing the performance of
198 genome-scan methods [55], especially regarding the effects of SVs on detecting putative
199 targets of selection [56].

200 Backward simulations based on coalescent theory can also contribute to our
201 understanding of SV evolution. Comparing demographic models sheds light on the
202 evolutionary history of SVs [41,57]. Such simulations enable comparisons of coalescence
203 times across different parts of the genome, or between different variant types, populations,
204 or species. They provide a projection of the expected polymorphism frequencies under
205 neutrality, against which the distribution of SVs can be contrasted [58]. Thus, backward
206 simulations are another way of disentangling the contributions of demographic and
207 selective processes to creating observed SV frequencies.

208 *Experiments can reveal the mechanisms by which SVs impact phenotypes*

209 Common garden and reciprocal transplant experiments comparing groups with different SV
210 genotypes are classic approaches for demonstrating adaptation [59,60]. However, care
211 must be taken to account for differences in genomic background. Combining numerous
212 artificial crosses with statistical modelling can help to separate the effects of SVs from the
213 rest of the genome, yet genetically modifying SVs into alternate genomic backgrounds in a
214 full factorial design would be ideal.

215 Experimental evolution approaches can test theoretical predictions about the
216 genomic architecture of polygenic traits. This approach revealed alternate genomic
217 architectures underlying the evolution of growth rate in the marine fish *Menidia menidia*
218 following size-selective harvesting. An extended haploblock was implicated in the evolution
219 of smaller sizes in one experimental population but not its replicate, where evolutionary
220 changes were associated with unlinked SNPs [61].

221 Analyses of gene expression can shed further light on the adaptive roles of SVs and
222 has supported the **recombination suppression hypothesis** [49,60,62] and direct gene
223 effects near breakpoints [63] (Box 1). Strong support for the recombination suppression
224 hypothesis was found in *D. melanogaster* by comparing gene expression patterns between
225 natural inversions, which influenced expression genome-wide, and genetically engineered
226 synthetic inversions, which had negligible effects on expression [64]. Gene expression
227 analyses can reveal gene dosage effects of CNVs on associated phenotypes [16].
228 Experimental knockdown of genes inside rearrangements can be used to functionally
229 annotate SVs [28].

230 There is a pressing need for experiments directed towards understanding the effects
231 of SVs on recombination. High resolution sequencing of offspring, heterozygous for the SV
232 of interest, can be used to measure recombination rates of regions within and proximal to
233 SVs [65]. Note that the effects of recombination suppression can be diluted by **gene**
234 **conversion**, whose rates within SVs can be quantified using a similar approach [66].

235 **Concluding remarks and future perspectives**

236 The field of structural genomic variation has matured to move beyond the most easily
237 detected variants and to investigate the mechanisms underlying the relevance of all SVs for
238 evolution. As more high-quality genome assemblies become available, we expect SVs to
239 be investigated in an increasing number and diversity of non-model organisms.

240 Future syntheses of these studies will provide new insights into several outstanding
241 questions regarding the respective roles of structural and sequence variation in evolution,
242 differences in abundances and distributions of SVs among taxa, how SVs relate to
243 ecological specialization, and how they affect recombination. By cataloguing the whole
244 spectrum of genetic variation, we will gain insights into the mechanisms that create
245 genomic hotspots of diversity. Because evolutionary dynamics of SVs differ from other
246 parts of the genome, they will help us tease apart evolutionary and demographic effects on
247 genome evolution that were hitherto hidden. Resurrecting classic micro- and minisatellite
248 data and treating them as SVs might facilitate a better understanding of the role of these
249 variants in evolutionary processes (but see [67]). Further, systematic inclusion of SVs in
250 both empirical and theoretical studies will enable a better understanding of the roles of
251 selection, drift, and gene flow in SV maintenance and how population connectivity across
252 large and small scales impacts SV distribution and evolution.

253 In the future, SVs will be integrated into ecological and evolutionary applications
254 such as conservation genomics, plant and animal breeding, and global change biology, as
255 well as applications based on ancient and environmental DNA. It is therefore fundamental
256 that we enable future comparisons across studies and taxa by developing generalizable
257 tools and best practices in order to maximize the ecological and evolutionary insights
258 provided by the joint analysis of genome sequence and structure.

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451

452 FIGURES

453 **Figure 1. The diversity of structural variants.** Genetic variants vary in size from a single
454 nucleotide to hundreds-of-Mb-long structural variants (SVs). SVs are classified according to
455 how they change the genome sequence. Balanced SVs change the position and/or order of
456 genomic areas. Unbalanced SVs involve a gain or loss of sequence. Note that
457 transposable elements can cause translocations, indels, and/or duplications. SNV = Single
458 Nucleotide Variant, including SNPs and single nucleotide indels; MNV = Multiple Nucleotide
459 Variant; CNV = Copy Number Variant.

460 **Figure 2 (Key Figure): A roadmap for understanding the evolutionary significance of**
461 **structural genomic variation.** Colors indicate different steps toward understanding the
462 role of SVs in adaptation and speciation, from top to bottom.

463 **Figure I (in Box 1). The effects of SVs on adaptation and speciation at multiple levels**
464 **of biological organization.** From bottom to top and left to right: CELL: Example
465 mechanisms by which SVs impact the genome, from DNA sequence to chromosome.
466 Effects of SVs on gene expression include changes in the distance between genes and
467 their regulatory elements, chromatin state, and gene dosage. ORGANISM: Multiple copies
468 of tRNA ligase in the yellow monkeyflower *Mimulus guttatus* are associated with shorter
469 flowering time, leading to differential survival in dry years and variation in seed production
470 [26] (photo by D. Lowry). A large CNV in the common murre *Uria aalge* is associated with
471 differences in plumage and thermal adaptation [17] (drawings by J. Ditner). A 25 Mb
472 inversion in the seaweed fly *Coelopa frigida* affects a life-history trade-off between larval
473 survival and reproductive success [74] (photo by M. Wellenreuther). DIVERSIFICATION:
474 The crab- and wave-ecotypes of *Littorina saxatilis* periwinkles harbour more than 17
475 chromosomal inversions whose frequencies vary between the two microhabitats despite
476 gene flow, suggesting that they are involved in local adaptation [76] (photo by F. Pleijel).
477 Two subspecies of European crow, *Corvus corvus corvis* and *C. corvus corone*, differ by a
478 2.25 kb retrotransposon insertion that affects plumage, a trait involved in pre-mating
479 isolation [7] (photos by R. Burri). Genomic incompatibilities leading to reduced hybrid
480 fitness and reproductive isolation between the bluefin (*Lucania goodei*) and rainwater (*L.*
481 *parva*) killifish are associated with a Robertsonian fusion of the sex chromosome [54]
482 (photos by A. Terceira).

483

484 **Figure II (in Box 2). Overview of complementary approaches for SV detection**

485 *Sequencing:* Reduced-representation sequencing (RRS) approaches target a fraction of
486 the genome (e.g., RAD-seq and SNP-chips). WGS = whole-genome sequencing. CMS =
487 connected molecule strategies. A chromosome-level genome assembly is usually
488 necessary for the analyses of SVs (but see alternative approaches in [44,57]).

489 *Indirect detection:* “Local PCA” refers to principal component analyses performed on
490 windows along the genome. The PCA in the haploblock region highlights a typical pattern
491 with three clusters of individuals, corresponding to the three haploblock variant
492 combinations [11,27,46,76,78]. In contrast, the PCA outside the haploblock shows no
493 clustering.

494 *Direct detection:* SV detection algorithms are based on sequencing depth, read orientation,
495 and read splitting of short and long reads [4,5,34,35]. RRS provides information on
496 sequencing depth, enabling detection of CNVs [44,45]. Long-reads provide high resolution
497 of SV breakpoints [86]. Hi-C links are chromatin contacts between pairs of loci represented
498 by a triangular heatmap of the number of links. Accumulation of links between distant loci
499 reveals SVs between the target sample and reference [46,81]. Linked-reads are short
500 reads tagged with the same barcodes when originating from the same original DNA
501 fragment (up to 100 kb). SVs can be detected from the long-range information carried by
502 barcoded linked-reads [40]. The comparison of genetic maps [27,76], optical maps [7], or
503 full assemblies [6,7] enables the detection of both intra- and inter-chromosomal
504 rearrangements. We refer to “large SV” when >100 kb (Figure 1).

505

506

507 TEXT BOXES

508 **Box 1: Structural variants affect the evolution and maintenance of adaptive traits and**
509 **reproductive barriers at several levels of biological organization (Figure I).**

510 At the genome level, structural variants (SVs) necessarily alter the linear structure (i.e.,
511 sequence) of DNA. These changes can affect the order and proximity of genetic elements
512 and disrupt functionality of extant genes, or form new ones, by coupling or uncoupling
513 promoters and coding regions [68]. Changes to DNA sequence can affect three-
514 dimensional genome structure by altering folding patterns and histone interactions. SVs
515 can form secondary structures during meiosis in heterozygotes that can interfere with
516 recombination to varying degrees [65,69]. Suppression of recombination can occur through
517 production of unbalanced meiotic products and by displacement of crossing-overs away
518 from SVs [70]. Some SVs (e.g., fissions and fusions) change the number and size of
519 chromosomes, thereby impacting recombination rates even within homokaryotypes.

520 SV impacts the transcriptome in several ways. An underappreciated mechanism,
521 **Position-Effect Variegation (PEV; [71])**, occurs when changes in the spatial proximity of
522 the DNA sequence to telomeres and centromeres, and thus heterochromatic regions, alters
523 the expression levels of nearby genes. SVs can also change the proximity of regulatory
524 elements to genes, potentially affecting gene expression across the genome [64]. Changes
525 in the positions of genetic elements relative to histones and interactions among
526 topologically associated domains can affect the exposure of transcription binding sites,
527 thereby silencing or enhancing transcription [72]. Local effects of SVs on expression
528 include changes in gene dosage [16], expression of *de novo* genes [68], loss of expression
529 of genes disrupted by SV breakpoints or deletions, and alterations of the epigenetic
530 environment near breakpoints [63,73]. If the SV is associated with reduced recombination,
531 it can maintain LD among genes and regulatory elements [73].

532 SVs underlie diverse morphological, physiological, behavioural, and life history traits
533 [8] and impact fitness through effects on survival and reproduction [74]. When SVs affect
534 recombination, heterokaryotypes can experience partial sterility due to the formation of
535 lethal or inviable recombinant products during meiosis [30]. A lack of recombination

536 prevents purging of deleterious mutations, resulting, over time, in higher fitness of
537 heterokaryotypes [54,75].

538 SVs are frequently associated with various stages of diversification, including local
539 adaptation [76], pre-mating isolation [7], and speciation [9,54]. Blocks of differentiation are
540 predicted to be favoured under adaptation with gene flow [48] and are expected to alter the
541 evolutionary trajectory of polygenic traits under selection as they resemble single loci of
542 large effect, rather than many loci of small effect [77].

543

544

545 **Box 2: Moving from indirect evidence to the direct detection of SVs (Figure II)**

546 *Indirect evidence: haploblocks of differentiation*

547 An increasing number of studies are uncovering genetic differentiation driven by a subset of
548 co-localized linked SNPs using unsupervised methods such as Principal Component
549 Analysis (PCA) [76,78]. The combination of high differentiation and LD suggests that these
550 SNPs may be associated with a SV reducing recombination. Based on this observation,
551 sliding-window PCAs along the genome were employed to screen for these signatures
552 across *Helianthus* sunflower ecotypes, which identified 37 haploblocks [46]. Similarly,
553 inversions associated with two periwinkle (*Littorina saxatilis*) ecotypes were identified
554 based on clusters of SNPs in LD [76]. Complementary evidence, including higher
555 heterozygosity in putative heterokaryotypes, and recombination and heritability estimates
556 based on genetic maps, can support the presence of an inversion [27].

557 *Direct evidence: making the best of different sequencing methods to catalog SVs*

558 Standard shotgun libraries (i.e., with short insert size, generally < 1 kb) sequenced with
559 Illumina short reads are the most common type of sequencing data and can be used to
560 directly detect SVs (reviewed in [79]). However, they are not necessarily the best for
561 identifying SVs, particularly large ones. Mate-pair libraries have more power than shotgun
562 libraries to detect SVs because their paired reads have larger insert sizes (> 1 kb) and are
563 more likely to span SV boundaries [5]. Additionally, SVs are often associated with repeats
564 and duplications that are difficult to assemble or map to with short reads [17]. Annotations
565 of repetitive elements, such as TEs, in the reference genome is the first step when
566 targeting this class of SVs and understanding their role in the formation of more complex
567 SVs [80]. Long-read sequencing, such as Pacific Biosciences SMRT (PacBio) and Oxford
568 Nanopore Technology (ONT) can help identify SVs and characterize breakpoints,
569 especially in complex SVs [33].

570 Emerging methods for SV detection also include linked-reads, such as 10x
571 Genomics, which provide long-range information across reads up to 100 kb or longer (e.g.,
572 [40]), or Strand-Seq, which preserves strand directionalities, but is mostly used in humans

573 (e.g., [81]). Chromosome conformation capture techniques like Hi-C provide long-range
574 information at the chromosomal, and even inter-chromosomal, scale and are a powerful
575 tool for characterizing complex SVs [46]. Compared to long reads, Hi-C data provide
576 additional information about the potential effect of SVs on chromatin architecture, including
577 enhancer-promoter contacts and consequent changes in gene expression [82], which is
578 useful for linking genotype and phenotype. Optical mapping, based on visualization of
579 restriction enzyme cut sites, or genetic mapping, based on linkage between genetic
580 markers, are also valuable tools to validate large-scale SVs within or between
581 chromosomes (e.g., [62,83]). Finally, comparison of *de novo* assemblies remains an
582 important tool for SV detection, even within species, and can promote the creation of a pan-
583 genome reference or a graph-based reference that includes major SVs from several
584 individuals [6,84,85].

585

586 **GLOSSARY**

587 **Amplified Fragment Length Polymorphism (AFLP):** genomic marker obtained by amplification of
588 a short fragment of DNA cut by restriction enzymes. Polymorphism is characterized by variable
589 lengths.

590 **Chromosomal inversion:** a genomic structural variant in which a segment of DNA is reversed end-
591 to-end relative to a reference sequence.

592 **Copy number variant (CNV):** a genomic structural variant in which a segment of DNA is
593 represented in different numbers of copies. The segment can be absent (*deletion*) or present in two
594 or more copies (*duplication[s]*) relative to a reference.

595 **Expression Quantitative Trait Locus (eQTL):** a genomic region that explains variation in mRNA
596 transcript abundance.

597 **Gene conversion:** process by which one DNA sequence replaces a homologous sequence such
598 that the sequences become identical after the conversion event.

599 **Gene duplication:** a genomic structural variant, example of CNV, in which a region of DNA that
600 contains a gene is duplicated.

601 **Haploblock (block of differentiation):** region of reduced recombination, characterized by high LD,
602 and often associated with high local differentiation between genetic groups.

603 **Heterokaryotypes/homokaryotypes:** individuals that are heterozygous/homozygous for a
604 structural variant when it is considered as a single locus. The alleles are the different possible
605 haplotypes (e.g., the inverted and non-inverted states for an inversion).

606 **Insertion/deletion (indel):** a genomic structural variant in which a segment of DNA varies in
607 presence or absence relative to a reference. Indels include CNVs and non-reciprocal translocations.

608 **Linkage Disequilibrium (LD):** non-random association of alleles at different loci.

609 **Microsatellites/minisatellites:** a genomic structural variant, example of CNV, constituted by a tract
610 of DNA motifs (1-10 bp for micro-, 10-60 bp for mini-) repeated 10 to 50 times. Also referred to as
611 *tandem repeats* and *simple sequence repeats*.

612 **Non-Allelic Homologous Recombination:** a form of homologous recombination that occurs
613 between two lengths of DNA that have high sequence similarity, but are not alternate alleles, such
614 as TE copies.

615 **Recombination suppression hypothesis:** a model in which an inversion is indirectly favoured by
616 natural selection because it suppresses recombination between sets of alleles, whereby alleles
617 within a set are favoured in similar contexts and each set is favored in a different context.

618 **Single Nucleotide Polymorphism (SNP):** a single base-pair substitution.

619 **Single Nucleotide Variant (SNV):** genomic variant affecting a single base pair, including SNPs and
620 single base-pair indels.

621 **Structural Variant (SV):** genomic variation between individuals affecting the presence, position,
622 and/or direction of a nucleotide sequence (Figure 1).

623 **Translocation:** a genomic structural variant in which a segment of DNA is in a different position
624 relative to a reference. Translocations can be either reciprocal or non-reciprocal (generating indels)
625 and affect whole chromosome arms, such as in whole-arm reciprocal translocations. The
626 translocation of a segment of chromosome can result in a change in the total number of
627 chromosomes, either by joining two chromosomes in one (*fusion*) or splitting a chromosome into
628 two (*fission*). When fusions/fissions and translocations occur at the centromeres, they are called
629 *Robertsonian*.

630 **Transposable Element (TE or transposon):** a segment of DNA that can change its position in the
631 genome by either a cut-and-paste mechanism (DNA transposons) or a copy-and-paste mechanism
632 (retrotransposons). TEs are a form of translocation, indel, and/or duplication.

633

HIGHLIGHTS

1. Structural genomic variants (SVs) take diverse forms and are ubiquitous drivers of ecological and evolutionary processes.
2. Most studies of SVs focus on the adaptive significance of gene duplications and large inversions. Future studies should catalogue SVs of all types and sizes and systematically test their evolutionary implications.
3. We propose a roadmap and definitions for the study of SVs in ecological and evolutionary genomics.
4. Best practices for SV detection are needed to facilitate comparisons across studies.
5. Integrating population genomic, theoretical, and experimental approaches to SVs will more comprehensively characterize genomic variation, uncover the adaptive and neutral processes shaping the evolutionary trajectory of SVs, and identify the mechanisms by which SVs impact adaptation and speciation.

OUTSTANDING QUESTIONS

- How can we develop appropriate bioinformatic tools to detect structural variants (SVs) of all sizes and genotype them in a large number of samples?
- What are the abundances, diversities, and distributions of SVs in natural populations and across taxonomic groups?
- How do SVs interact with sequence (e.g., SNP) variation and with each other? To what extent do different SVs predispose the offspring of carriers to more SVs?
- What are the roles of different types of SVs in evolutionary processes? For instance, which characteristics make some SVs particularly involved in adaptation and speciation? Conversely, how do neutral and adaptive processes determine the evolutionary trajectory of SVs?
- What is the relative influence of different types of SVs and sequence variation at different points along the speciation continuum and among systems with varying levels of gene flow?
- What are the proximate mechanisms (e.g., through linkage, effects on recombination, effects on 3D genome structure and gene expression, etc.) by which SVs influence evolution by natural and sexual selection?
- How can the unique properties of different types of SVs be harnessed for use as genetic markers to contribute to new understandings in population genomics and demography? What is the evolutionary rate of different SVs?
- How can SV markers be applied to agriculture, selective breeding programs, resource management, and conservation?



A continuum of variation in size

SNV
1 bp

SV
> 50 bp

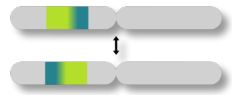
2-50 bp
MNV

>100 kb
Large SV

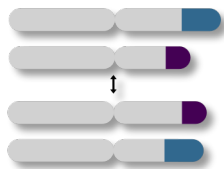


Balanced SVs
(change in position or order)

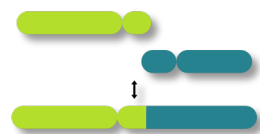
Inversion



Translocation

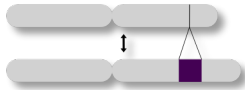


Fusion/fission

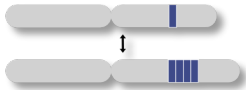


Unbalanced SVs
(gain/loss of DNA)

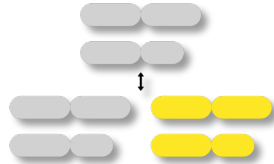
CNV:
Insertion/deletion



CNV:
duplications, tandem repeats



Polyploidy



Identification and characterization of SVs

Indirect methods

Patterns of differentiation and LD

Direct methods

Explicit mining of sequencing data

Objectives

Develop best practices to allow synthesis and comparison among studies

Assess sequencing/bioinformatic tools to select appropriate approaches depending on available resources

Account for population/species standing variation by enabling detection in large datasets

Understanding evolution and function of SVs

Population genomics

SV distribution & frequency

Differences among

populations/species

Associations with environment

and/or phenotype

Evolutionary simulations

Simulate effects on genome evolution

Population genetic simulations of SVs distribution and evolution

Experimental validation

Common garden and reciprocal transplant experiments

Experimental evolution

Differential gene expression

Gene knockdown/editing

Objectives

Acknowledge SVs as standing genetic variation

Describe evolutionary processes

Identify candidate SVs for adaptation & speciation

Objectives

Predict evolutionary trajectory

Disentangle effects of neutral and selective processes on SVs

Objectives

Validate candidate SVs for adaptation

Understand effects on phenotypes/recombination

Comparisons and meta-analyses among studies and across taxa

Comparative genomics - Phylogenomics

Synthesis of similarities and differences among studies and taxa

Objectives

Increase reproducibility and reliability of findings

Characterize SVs (e.g., number, position, size, breakpoints)

Assess frequency & distribution of SVs within and across species

Understand how SVs form, evolve, and persist

Ecological and evolutionary applications

New markers for genetic structure, environmental DNA, ancient DNA

Delineating evolutionarily significant units for conservation and management

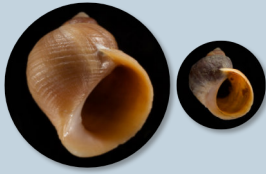
Predicting population and species responses to global change

Agriculture and aquaculture breeding program design

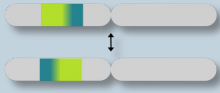
GROUP

DIVERSIFICATION

Local adaptation

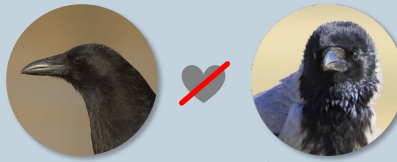


Littorina saxatilis
Wave/Crab ecotypes

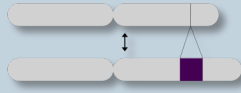


17 inversions

Pre-mating isolation

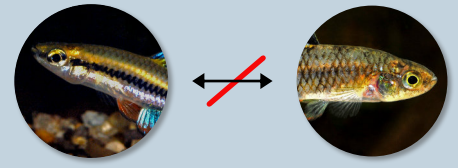


Corvus corone corone *Corvus corone cornix*



2.25-kb TE indel

Reproductive isolation



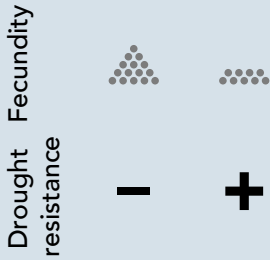
Lucania goodei *Lucania parva*



Robertsonian fusion

ORGANISM

FITNESS



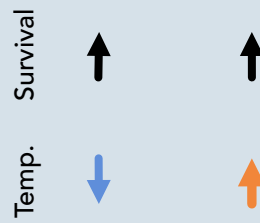
Flowering time



Mimulus guttatus



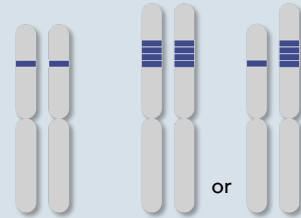
CNV (x 300)



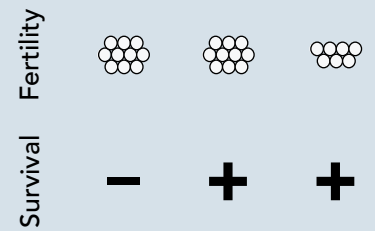
Plumage linked to thermal adaptation



Uria aalge



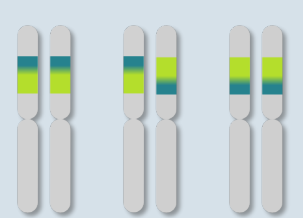
CNV (of a 60 kb region)



Adult size & development time



Coelopa frigida

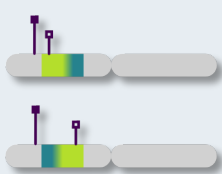


Inversion (25 Mb)

CELL

TRANSCRIPTOME

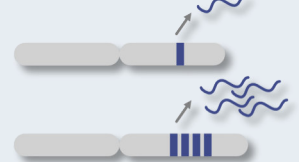
Gene-regulation decoupling



Position-effect variegation

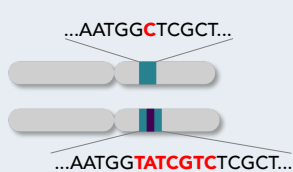


Gene dosage



GENOME

Linear sequence



Recombination



Karyotype divergence

