the geneticssociety

www.nature.com/hdy

EDITORIAL

Structural variation in context: mechanisms, functions and selection regimes across the tree of life

Genomic structural variants (SVs) are central to modern genetics. However, they do not fit easily into the simple classifications and analytical frameworks that work well for single-nucleotide polymorphisms (SNPs). The papers in this special issue underscore that SVs cannot be treated as a homogeneous class, nor can their evolutionary consequences be inferred directly from their structural category alone. Instead, they compel us to engage explicitly with mutational mechanism, genomic context, and selection regime, and to recognize that the structural category only weakly predicts their functional and evolutionary impact.

Heredity (2026) 135:121–125; https://doi.org/10.1038/s41437-026-00832-x

WHY STRUCTURAL VARIATION DEMANDS A DIFFERENT FRAMEWORK

Structural variants typically span kilobases to megabases and can influence multiple functional elements simultaneously, overlapping smaller genetic variants, altering local recombination rates, and reshaping three-dimensional (3D) genome architecture (Conrad and Hurles 2007; Kirkpatrick 2010; Spielmann et al. 2018). Because of this complexity, an SV is often better viewed as a multi-locus haplotype or genomic segment rather than a single biallelic variant (Charlesworth and Charlesworth 1973). This presents a challenge, as much of classical population genetics was developed for biallelic loci and is often presented, at least in its simplest formulations, under assumptions of additivity at a locus and weak interactions among loci, assumptions that are especially likely to be violated by SVs. In practice, a given phenotypic effect or inferred selection coefficient on SV can have a functional impact through numerous underlying processes, for example changes in gene dosage (Rice and McLysaght 2017), altered cis-regulatory architecture (Spielmann et al. 2018), modified chromatin contacts (Fudenberg and Pollard 2019), or shifts in segregation patterns (meiotic drive) (Courret et al. 2019), rather than a single, easily interpretable causal change.

Moreover, SVs are not rare exceptions at the tail of the mutational spectrum; in many genomes they affect more base pairs than SNPs (Karageorgiou et al. 2024), and individual SVs often perturb multiple genes at once (Chiang et al. 2017; Berdan et al. 2024). In humans and other primates, SVs frequently define species- or population-specific segments and have been repeatedly implicated in adaptive traits, disease risk, and genomic innovation (Soto et al. 2023; Pajic and Gokcumen 2026). In plants and crops, SVs contribute substantially to heritability and can reveal trait associations that SNP-only GWAS completely miss (Li et al. 2024; Zhang et al. 2024). These observations motivate a conceptual shift; from treating SVs as outliers in a SNP-centric model, to thinking first about functional effects and selection/constraint, and only then about their mechanistic labels.

SV CATEGORIES: USEFUL BUT INSUFFICIENT

We still rely on broad categories of SVs (inversions, deletions, duplications and other copy number variants (CNVs), insertions, mobile element insertions, translocations, fissions and fusions, as well as, more complex configurations such as nested inversions) to describe how genomes differ from one another. At the same time, detailed models now link specific breakpoint architectures to underlying mutational processes, including non-allelic homologous recombination (NAHR), non-homologous end joining (NHEJ), replication-based mechanisms, and transposon activity (Kidd et al. 2010; Currall et al. 2013; Carvalho and Lupski 2016). Yet across taxa, neither structural class nor mutational mechanism reliably predicts functional outcome (Hurles et al. 2008; Karageorgiou et al. 2024). A nominally "balanced" inversion may be dosage-neutral and act primarily as a recombination modifier with subtle life-history effects, or it may disrupt genes and carry substantial recessive load (Kirkpatrick and Barton 2006; Hoffmann and Rieseberg 2008; Charlesworth and Flatt 2021); likewise, duplications with similar structure can be tolerated, dosage-beneficial, or lethal, depending on their genomic context (Kuzmin et al. 2022).

Even within a single structural category, the same type of event can mediate local adaptation, contribute to intrinsic incompatibilities, or drift neutrally, and these roles may change over time (Todesco et al. 2020; Saitou et al. 2021). The contributions in this issue collectively show that meaningful inference requires moving beyond labels to consideration of (i) the mutational mechanism and breakpoint context, (ii) the genomic context affected (genes, regulatory elements, centromeres, topologically associating domains (TADs)), and (iii) the ecological and demographic context in which the SV segregates.

TECHNOLOGICAL ADVANCES TRANSFORMING SV DISCOVERY AND INTERPRETATION

The study of structural variation has its roots in classical cytogenetics, which first revealed chromosomal inversions and large karyotypic differences (Sturtevant 1921), and has since expanded through molecular and genome-wide approaches. Early work in systems such as *Drosophila* (Dobzhansky and Sturtevant 1938), *Coelopa* (Butlin and Day 1985), and holocentric insects (White 1973) made clear that chromosomal rearrangements could underlie local adaptation, reproductive isolation, and dramatic karyotype evolution, but cytogenetic methods could resolve only

Received: 14 February 2026 Revised: 24 February 2026 Accepted: 24 February 2026
Published online: 7 March 2026

their approximate positions and sizes, not nucleotide-level breakpoints or detailed gene content.

Short-read sequencing enabled population-scale SV discovery, but with major blind spots; complex rearrangements, multi-allelic CNVs, repeat-rich regions, and large insertions were systematically undercalled (Goodwin et al. 2016). Long-read platforms (PacBio HiFi, Oxford Nanopore), coupled with graph-based and telomere-to-telomere assemblies, now routinely span repetitive regions and complex breakpoints, revealing far more SVs and structural complexity within each locus (Mahmoud et al. 2019). Crucially, nucleotide-level breakpoint resolution allows us to infer mutational mechanism, NAHR on segmental duplications, transposable element (TE)-mediated ectopic recombination, replication slippage, and to connect these mechanisms to mutational spectra, genomic "hotspots" and diverse phenotypes (Lin and Gokcumen 2019; Karageorgiou et al. 2025). It also enables direct mapping of SVs onto regulatory annotations and 3D genome architecture, making it possible to identify SVs that overlap enhancers, promoters, CpG-rich regulatory regions, or architectural elements such as TAD boundaries, and to test whether these events are associated with changes in chromatin contacts or gene regulation in specific cases. The GWAS SVatalog study by Chirmade et al. (2025) in this issue exemplifies how integrating long-read SV catalogs with GWAS summary statistics can uncover putatively causal regulatory SVs that explain association signals previously attributed to noncoding SNPs. Advances in genomics act as a bridge from "where are the SVs?" to "how did they form?", "what do they change?" and "under what neutral or selection regimes do they persist?".

FUNCTIONAL IMPACTS ACROSS THE TREE OF LIFE: PERSPECTIVES FROM THIS SPECIAL ISSUE

Rather than organizing this special issue by structural class, we emphasize four broad categories of functional impact that recur across taxa and mechanisms. In this section, we highlight how structural variants shape function across the animal tree of life, drawing on case studies in insects (*Drosophila*, *Coelopa frigida*, the black soldier fly, and other Stratiomyidae), teleost fishes (Zoarcoidei and threespine stickleback), and humans.

Gene dosage and expression modulation

Copy-number changing SVs, duplications, deletions, multi-allelic CNVs, and tandem array expansions, directly reshape gene dosage and regulatory context. Gene duplication remains a major source of evolutionary novelty: duplicated genes may confer an adaptive increase in dosage, undergo subfunctionalization, neofunctionalize under relaxed constraint, or pseudogenize (Ohno 1971; Force et al. 1999). The paper by Zhou et al. (2025) in this issue shows how lineage-specific gene family expansions in the black soldier fly, occurring in a TE-rich genomic background, have amplified immune and olfactory functions, while Stratiomyidae more broadly show duplicated gene families enriched for digestive and metabolic functions, plausibly contributing to higher decomposer efficiency and the ecological success of *Hermetia illucens*.

In polar fishes, Moosman et al. (2025) illustrate how copy-number variation in antifreeze proteins can be highly heterogeneous even within individuals. By developing haplotype-aware tools to control for assembly uncertainty and switch errors in phased long-read genomes, they show that type III AFP arrays in Zoarcoidei harbor substantial haplotype-level CNV, with intra-individual differences of several to more than ten copies, providing the standing variation on which temperature-related selection can act.

Across taxa, dosage-modifying SVs have been tied to traits ranging from variation in amylase copy number that appears advantageous in starch-rich diets (Bolognini et al. 2024; Yilmaz et al. 2024; Scheer et al. 2025) to herbicide resistance mediated by EPSPS amplification (Gaines et al. 2010) and to human brain evolution and neurodevelopmental disorders (Dennis et al. 2012; Soto et al. 2025). The GWAS SVatalog compiled in Chirmade et al. (2025) highlights how relatively small indels in UTRs or introns, such as deletions in *TF*, *KCNQ5*, and *TMEM106B*, can modulate transcription factor binding and chromatin marks, thereby providing plausible causal variants for disease-associated GWAS loci that could not be mechanistically explained by nearby SNPs alone.

Structural reorganization and recombination effects

Balanced rearrangements, especially inversions, alter the recombination landscape and thereby change the effective linkage among loci. Inversion heterokaryotypes experience suppressed crossing-over within the inverted segment, which can maintain beneficially adapted alleles together in the face of gene flow, accumulate deleterious recessive variants, and modulate gene flow between ecotypes or incipient species (Kirkpatrick 2010; Faria et al. 2019; Berdan et al. 2023).

Several inversion case studies in this issue illustrate these principles. In an ecological context, Nicolas et al. (2025) investigated the polymorphic *Cf-Inv(4.1)* inversion in *Coelopa frigida*, which displays parallel latitudinal clines in frequency across North America and Europe that closely track thermal gradients. Experimental work revealed that this inversion affects egg-to-adult viability in interaction with temperature and genetic background, and is associated with differences in female fecundity between karyotypes, despite having no detectable impact on classical cold-tolerance measures. The authors suggest that fitness differences are shaped by subtle life-history trade-offs whose relative advantage varies with climate, rather than by tolerance to thermal extremes.

In an experimental set-up, Rodríguez-Fuentes et al. (2025) tested the fitness consequences of three paracentric inversions that consistently differentiate marine and freshwater threespine stickleback populations. Controlled crosses revealed no deviations from Mendelian ratios and no strong lethality or intrinsic underdominance at any of the three inversions, but heterozygotes at the chromosome I inversion had reduced body condition specifically in the freshwater treatment, hinting at environment-dependent fitness trade-offs and possible genic incompatibilities between inversion orientations.

Complementing these systems, Paris et al. (2025) demonstrate that the cosmopolitan *In(3 R)Payne* inversion in *Drosophila melanogaster* behaves as a supergene affecting a suite of life-history, stress-resistance, and survival traits, with the heterokaryotype showing overdominance for multiple pre-adult fitness components and male desiccation resistance, and with context-dependent dominance shifts across traits, sexes, and temperatures consistent with multiple forms of balancing selection, further complicated by genotype-by-environment interactions and parental effects.

In concert with other recent work, these examples reinforce that inversions could be viewed as recombination modifiers with diverse and often context-dependent fitness effects, sometimes strongly adaptive, sometimes nearly neutral, sometimes burdened by mutation load or involved in associative overdominance (Kapun and Flatt 2019; Berdan et al. 2022; Schaal et al. 2022).

Chromosomal rearrangements and genome architecture

At larger scales, translocations and chromosome fissions/fusions reconstruct karyotypes, change linkage groups, and modify 3D genome organization (Álvarez-González and Ruiz-Herrera 2025). The review by Diblasi and Saitou (2025) in this issue synthesizes emerging work showing how fissions, fusions, and translocations alter recombination patterns, centromere behavior, meiotic segregation, and sex chromosome evolution, often in ways that feed back into adaptation and speciation.

Chromosome fusions can reduce the number of linkage groups, facilitating the co-inheritance of locally adapted alleles, while fissions can increase chromosome number and reshape recombination landscapes; both can interact with meiotic drive acting on centromere number and strength to bias transmission (Malik and Henikoff 2002). Translocations and neo-sex chromosome formation can link sex-determining loci with sexually antagonistic alleles or relocate genes into new regulatory neighborhoods, changing dosage and expression. High-resolution Hi-C and assembly work in mammals and insects shows that such rearrangements can distort long-range chromatin contacts and sometimes, though not always, perturb TAD structure and regulatory interactions (Álvarez-González et al. 2022). These observations extend the traditional view of karyotype evolution beyond a purely cytological description, emphasizing its mechanistic and functional consequences for gene regulation, 3D genome architecture, and the rate at which populations can respond to selection (Vara et al. 2021).

Population-level consequences and signatures of selection

Across these mechanistic and functional categories, selection regimes acting on SVs are heterogeneous. Examples include:

- Strong positive selection on specific SVs underlying herbicide resistance (Gaines et al. 2010), insecticide resistance (Gimenez et al. 2020), or rapid local adaptation in plants (Hämälä et al. 2021; Wilson et al. 2025), invertebrates (Villoutreix et al. 2023; Gompert et al. 2025), and vertebrates (Hager et al. 2022; Liang et al. 2024; Sridharan et al. 2025).
- Balancing selection maintaining polymorphic inversions or SV hotspots that harbor alternative ecological strategies (Joron et al. 2011; Lamichhaney et al. 2016; Mérot et al. 2020; Matschiner et al. 2022; Kapun et al. 2023), immune functions (Fang and Edwards 2024), or oxygen transport variants (Leffler et al. 2017).
- Purifying selection eliminating deleterious rearrangements (Kondrashov et al. 2002; Kondrashov and Kondrashov 2006), particularly those disrupting essential genes or regulatory architecture (Zhang et al. 2011; Uddin et al. 2014; Gardner et al. 2019; Saxena and Baer 2025), with surviving SVs often biased toward gene-poor or functionally buffered regions (Lin and Gokcumen 2019; Igolkina et al. 2025).
- Nearly neutral or drift-dominated dynamics, especially in repeat-rich regions where recurrent formation and loss produces high turnover without clear phenotypic associations (Charlesworth et al. 1994; Mularoni et al. 2010; Palazzo and Koonin 2020).

Importantly, elevated frequency or wide geographic spread of an SV does not automatically imply positive selection or adaptation. Recurrent structural variants at mutational hotspots, biased segregation (meiotic drive), or demographic processes can all elevate SV frequencies without conferring fitness benefits. The stickleback experiments in this issue are particularly instructive. Inversions that consistently differentiate marine and freshwater populations show minimal fitness differences under the salinity regimes assayed, suggesting that salinity alone is unlikely to explain their evolution, and that either other selective forces or more subtle, context-dependent fitness effects may be involved (Rodríguez-Fuentes et al. 2025).

EXPANDING BEYOND MODEL ORGANISMS

These papers suggest that emerging technologies are gradually loosening the field's long-standing dependence on a few classical model systems. Chromosome-level assemblies and long-read resequencing are increasingly available for non-model taxa with diverse karyotypes, life histories, and ecological niches, from soldier flies and robber flies to a growing set of vertebrates and plants (Rhie et al. 2021; Zhou et al. 2025). This broader coverage is beginning to reveal a wider range of SV mechanisms, sizes, and genomic contexts, including many that would be difficult to detect with short-read data alone (Sedlazeck et al. 2018; Moosman et al. 2025; Chirmade et al. 2025). As sampling expands across the tree of life, it becomes more feasible to ask which patterns–such as TE-associated genome expansions, inversion-mediated local adaptation, or fusion-associated changes in sex chromosomes–are common versus lineage-specific (Diblasi and Saitou 2025). Non-model systems also provide comparative settings where similar ecological challenges seem to have been resolved by distinct SV architectures, creating valuable opportunities for comparative inference. Population-scale sampling remains a major challenge. Pangenome initiatives in humans, domestic animals, and crops show that haplotype-specific sequences and SVs contribute substantially to adaptive and economically important traits and the same will likely prove true across the tree of life (Qin et al. 2021; Liao et al. 2023). Designing SV studies that span multiple populations and environmental niches will be essential for understanding the functional consequences of structural variation.

ON PREDICTING FUNCTION

The central message emerging from this special issue is that SV type does not equate to SV impact. The same mechanistic class, for instance a paracentric inversion, can be neutral, adaptive, or deleterious, depending on which genes and regulatory elements are involved, how recombination is altered, and under which ecological and demographic conditions the variant segregates. Conversely, very different structural events can converge on similar functional outcomes; duplications, TE insertions, and fusions can all create new regulatory environments or alter gene dosage for the same pathways.

To move toward prediction, we need a comprehensive approach that explicitly links:

1. Mechanism and structure: what mutational process generated the SV, what is its precise structure, and how stable is it (e.g., propensity for rearrangements)?
2. Molecular and cellular function: which genes, regulatory elements, chromatin domains, and centromeres are altered, and how does this affect expression, chromatin state, and recombination?
3. Population-genetic dynamics: what are the fitness effects across environments, the dominance relationships (including load and overdominance), and the null expectations under neutral processes?
4. Macroevolutionary consequences: how do SVs contribute to long-term phenotypic innovation, karyotype evolution, and lineage diversification?

CONCLUSIONS AND OUTLOOK

The studies gathered here present a snapshot of the diversity of mechanisms, functions, and selection regimes through which SVs shape genomes and phenotypes. They demonstrate that SVs are not peripheral outliers but major contributors to gene regulatory variation, gene family evolution, genome architecture, and local adaptation across taxa. They also show that simple inferences from structural class or frequency are insufficient; understanding SVs demands attention to mechanism, context, and ecology. Several future directions seem particularly pressing. First, improved theoretical models for the population genetics of SVs, incorporating recombination suppression, multi-locus linkage, mutation load, and heterogeneous environments, are needed to

interpret empirical patterns and to predict when inversions, fusions, or CNVs have been favored. Second, population-scale pangenomes and long-read resequencing across diverse lineages or populations will be essential to capture the full spectrum of SVs and to integrate them into GWAS, eQTL, and selection scans on equal footing with SNPs, moving from a handful of well-characterized loci to genome-wide maps of structural haplotypes and the evolutionary processes acting on them. Third, functional follow-up, from reporter assays and/or CRISPR editing of structural haplotypes to comparative phenotyping of engineered karyotypes, will be required to move from correlation to causation.

Genomics will be most effective when structural variants are treated not as a separate category, but as an integral part of models describing how genomes encode, regulate, and evolve phenotypes. The work showcased in this issue takes important steps in that direction, and invites us to rethink our theoretical and empirical approaches accordingly.

Charikleia Karageorgiou[1]✉, Ellen M. Leffler[2]✉, Megan Y. Dennis[3,4]✉ and Omer Gokcumen[1]✉

[1]*Department of Biological Sciences, University at Buffalo, Buffalo, NY, USA.* [2]*Department of Human Genetics, University of Utah School of Medicine, Salt Lake City, UT, USA.* [3]*Department of Biochemistry & Molecular Medicine, MIND Institute, University of California, Davis, CA, USA.* [4]*Genome Center, University of California, Davis, CA, USA.*
Associate editor: Aurora Ruiz-Herrera.
✉*email: charikle@buffalo.edu; leffler@genetics.utah.edu; mydennis@ucdavis.edu; omergokc@buffalo.edu*

REFERENCES

Álvarez-González L, Ruiz-Herrera A (2025) Evolution of 3D chromatin folding. Annu Rev Anim Biosci 13:49–71.

Álvarez-González L, Arias-Sardá C, Montes-Espuña L, Marín-Gual L, Vara C, Lister NC et al. (2022) Principles of 3D chromosome folding and evolutionary genome reshuffling in mammals. Cell Rep 41:111839.

Berdan EL, Blanckaert A, Butlin RK, Flatt T, Slotte T, Wielstra B (2022) Mutation accumulation opposes polymorphism: supergenes and the curious case of balanced lethals. Philos Trans R Soc Lond B Biol Sci 377:20210199.

Berdan EL, Barton NH, Butlin R, Charlesworth B, Faria R, Fragata I et al. (2023) How chromosomal inversions reorient the evolutionary process. J Evol Biol 36:1761–1782.

Berdan EL, Aubier TG, Cozzolino S, Faria R, Feder JL, Giménez MD et al. (2024) Structural variants and speciation: multiple processes at play. Cold Spring Harb Perspect Biol 16:a041446.

Bolognini D, Halgren A, Lou RN, Raveane A, Rocha JL, Guarracino A et al. (2024) Recurrent evolution and selection shape structural diversity at the amylase locus. Nature 634:617–625.

Butlin RK, Day TH (1985) Genie and karyotypic selection on an inversion polymorphism in the seaweed fly, Coelopa frigida. Heredity (Edinb) 54:267–274.

Carvalho CMB, Lupski JR (2016) Mechanisms underlying structural variant formation in genomic disorders. Nat Rev Genet 17:224–238.

Charlesworth B, Charlesworth D (1973) Selection of new inversions in multi-locus genetic systems. Genet Res (Camb) 21:167–183.

Charlesworth B, Flatt T (2021) On the fixation or nonfixation of inversions under epistatic selection. Mol Ecol 30:3896–3897.

Charlesworth B, Sniegowski P, Stephan W (1994) The evolutionary dynamics of repetitive DNA in eukaryotes. Nature 371:215–220.

Chiang C, Scott AJ, Davis JR, Tsang EK, Li X, Kim Y et al. (2017) The impact of structural variation on human gene expression. Nat Genet 49:692–699.

Chirmade S, Wang Z, Mastromatteo S, Sanders E, Thiruvahindrapuram B, Nalpathamkalam T, et al. (2025) GWAS SVatalog: a visualization tool to aid fine-mapping of GWAS loci with structural variations. Heredity (Edinb): 1–12. (In This Issue).

Conrad DF, Hurles ME (2007) The population genetics of structural variation. Nat Genet 39:S30–6.

Courret C, Chang C-H, Wei KH-C, Montchamp-Moreau C, Larracuente AM (2019) Meiotic drive mechanisms: lessons from Drosophila. Proc Biol Sci 286:20191430.

Currall BB, Chiangmai C, Talkowski ME, Morton CC (2013) Mechanisms for structural variation in the human genome. Curr Genet Med Rep 1:81–90.

Dennis MY, Nuttle X, Sudmant PH, Antonacci F, Graves TA, Nefedov M et al. (2012) Evolution of human-specific neural SRGAP2 genes by incomplete segmental duplication. Cell 149:912–922.

Diblasi C, Saitou M (2025) Beyond inversions and deletions: the evolutionary and functional insights from translocations, fissions, and fusions in animal genomes. Heredity (Edinb): 1–12. (In This Issue).

Dobzhansky T, Sturtevant AH (1938) Inversions in the chromosomes of Drosophila pseudoobscura. Genetics 23:28–64.

Fang B, Edwards SV (2024) Fitness consequences of structural variation inferred from a House Finch pangenome. Proc Natl Acad Sci 121:e2409943121.

Faria R, Johannesson K, Butlin RK, Westram AM (2019) Evolving inversions. Trends Ecol Evol 34:239–248.

Force A, Lynch M, Pickett FB, Amores A, Yan YL, Postlethwait J (1999) Preservation of duplicate genes by complementary, degenerative mutations. Genetics 151:1531–1545.

Fudenberg G, Pollard KS (2019) Chromatin features constrain structural variation across evolutionary timescales. Proc Natl Acad Sci USA 116:2175–2180.

Gaines TA, Zhang W, Wang D, Bukun B, Chisholm ST, Shaner DL et al. (2010) Gene amplification confers glyphosate resistance in Amaranthus palmeri. Proc Natl Acad Sci USA 107:1029–1034.

Gardner EJ, Prigmore E, Gallone G, Danecek P, Samocha KE, Handsaker J et al. (2019) Contribution of retrotransposition to developmental disorders. Nat Commun 10: 4630.

Gardner EJ, Prigmore E, Gallone G, Danecek P, Samocha KE, Handsaker J et al. (2019) Contribution of retrotransposition to developmental disorders. Nat Commun 10:4630.

Gimenez S, Abdelgaffar H, Goff GL, Hilliou F, Blanco CA, Hänniger S et al. (2020) Adaptation by copy number variation increases insecticide resistance in the fall armyworm. Commun Biol 3:664.

Gompert Z, Feder JL, Parchman TL, Planidin NP, Whiting FJH, Nosil P (2025) Adaptation repeatedly uses complex structural genomic variation. Science 388:eadp3745.

Goodwin S, McPherson JD, McCombie WR (2016) Coming of age: ten years of next-generation sequencing technologies. Nat Rev Genet 17:333–351.

Hager ER, Harringmeyer OS, Wooldridge TB, Theingi S, Gable JT, McFadden S et al. (2022) A chromosomal inversion contributes to divergence in multiple traits between deer mouse ecotypes. Science 377:399–405.

Hämälä T, Wafula EK, Guiltinan MJ, Ralph PE, dePamphilis CW, Tiffin P (2021) Genomic structural variants constrain and facilitate adaptation in natural populations of Theobroma cacao, the chocolate tree. Proc Natl Acad Sci USA 118: e2102914118.

Hoffmann AA, Rieseberg LH (2008) Revisiting the impact of inversions in evolution: From population genetic markers to drivers of adaptive shifts and speciation? Annu Rev Ecol Evol Syst 39:21–42.

Hurles ME, Dermitzakis ET, Tyler-Smith C (2008) The functional impact of structural variation in humans. Trends Genet 24:238–245.

Igolkina AA, Vorbrugg S, Rabanal FA, Liu H-J, Ashkenazy H, Kornienko AE et al. (2025) A comparison of 27 Arabidopsis thaliana genomes and the path toward an unbiased characterization of genetic polymorphism. Nat Genet 57:2289–2301.

Joron M, Frezal L, Jones RT, Chamberlain NL, Lee SF, Haag CR et al. (2011) Chromosomal rearrangements maintain a polymorphic supergene controlling butterfly mimicry. Nature 477:203–206.

Kapun M, Flatt T (2019) The adaptive significance of chromosomal inversion polymorphisms in Drosophila melanogaster. Mol Ecol 28:1263–1282.

Kapun M, Mitchell ED, Kawecki TJ, Schmidt P, Flatt T (2023) An ancestral balanced inversion polymorphism confers global adaptation. Mol Biol Evol 40:msad118.

Karageorgiou C, Gokcumen O, Dennis MY (2024) Deciphering the role of structural variation in human evolution: a functional perspective. Curr Opin Genet Dev 88:102240.

Karageorgiou C, Ruhl S, Gokcumen O (2025) Convergent evolution through independent rearrangements in the primate amylase locus. bioRxivorg: 2025.08.14.670395.

Kidd JM, Graves T, Newman TL, Fulton R, Hayden HS, Malig M et al. (2010) A human genome structural variation sequencing resource reveals insights into mutational mechanisms. Cell 143:837–847.

Kirkpatrick M (2010) How and why chromosome inversions evolve. PLoS Biol 8: e1000501.

Kirkpatrick M, Barton N (2006) Chromosome inversions, local adaptation and speciation. Genetics 173:419–434.

Kondrashov FA, Kondrashov AS (2006) Role of selection in fixation of gene duplications. J Theor Biol 239:141–151.

Kondrashov FA, Rogozin IB, Wolf YI, Koonin EV (2002) Selection in the evolution of gene duplications. Genome Biol 3: RESEARCH0008.

Kuzmin E, Taylor JS, Boone C (2022) Retention of duplicated genes in evolution. Trends Genet 38:59–72.

Lamichhaney S, Fan G, Widemo F, Gunnarsson U, Thalmann DS, Hoeppner MP et al. (2016) Structural genomic changes underlie alternative reproductive strategies in the ruff (Philomachus pugnax). Nat Genet 48:84–88.

Leffler EM, Band G, Busby GBJ, Kivinen K, Le QS, Clarke GM et al. (2017) Resistance to malaria through structural variation of red blood cell invasion receptors. Science 356:eaam6393.

Li X, Wang Y, Cai C, Ji J, Han F, Zhang L et al. (2024) Large-scale gene expression alterations introduced by structural variation drive morphotype diversification in Brassica oleracea. Nat Genet 56:517–529.

Liang X, Duan Q, Li B, Wang Y, Bu Y, Zhang Y et al. (2024) Genomic structural variation contributes to evolved changes in gene expression in high-altitude Tibetan sheep. Proc Natl Acad Sci USA 121: e2322291121.

Liao W-W, Asri M, Ebler J, Doerr D, Haukness M, Hickey G et al. (2023) A draft human pangenome reference. Nature 617:312–324.

Lin Y-L, Gokcumen O (2019) Fine-scale characterization of genomic structural variation in the human genome reveals adaptive and biomedically relevant hotspots. Genome Biol Evol 11:1136–1151.

Mahmoud M, Gobet N, Cruz-Dávalos DI, Mounier N, Dessimoz C, Sedlazeck FJ (2019) Structural variant calling: the long and the short of it. Genome Biol 20: 246.

Malik HS, Henikoff S (2002) Conflict begets complexity: the evolution of centromeres. Curr Opin Genet Dev 12:711–718.

Matschiner, Barth M, Tørresen JMI, Star OK, Baalsrud B, Brieuc MSO HT et al. (2022) Supergene origin and maintenance in Atlantic cod. Nat Ecol Evol 6:469–481.

Mérot C, Llaurens V, Normandeau E, Bernatchez L, Wellenreuther M (2020) Balancing selection via life-history trade-offs maintains an inversion polymorphism in a seaweed fly. Nat Commun 11: 670.

Moosman OW, Kelley JL, Bogan SN (2025). Mitigating assembly and switch errors in phased genomes of polar fishes reveals haplotype diversity in copy number of antifreeze protein genes. Heredity (Edinb): 1–13. (In This Issue).

Mularoni L, Ledda A, Toll-Riera M, Albà MM (2010) Natural selection drives the accumulation of amino acid tandem repeats in human proteins. Genome Res 20:745–754.

Nicolas LA, Berdan EL, Wellenreuther M, Colinet H, Clouard A, De Wit P, et al. (2025). Parallel clines of chromosomal inversion frequencies in seaweed flies are associated with thermal variation. Heredity (Edinb): 1–12. (In This Issue).

Ohno S (1971) *Evolution by Gene Duplication*. Springer: New York, NY.

Pajic P, Gokcumen O (2026) Evolutionary balancing of genetic consequence and innovation in mammals through variable number tandem repeats. Genome Biol Evol 18: evaf250.

Palazzo AF, Koonin EV (2020) Functional long non-coding RNAs evolve from junk transcripts. Cell 183:1151–1161.

Paris M, Durmaz Mitchell E, Kerdaffrec E, Rubin D, Spichtig C, Zurbriggen F, et al. (2025) Multiple forms of balancing selection maintain inversion polymorphism. Heredity (Edinb): 1–14. (In This Issue).

Qin P, Lu H, Du H, Wang H, Chen W, Chen Z et al. (2021) Pan-genome analysis of 33 genetically diverse rice accessions reveals hidden genomic variations. Cell 184:3542–3558.e16.

Rhie A, McCarthy SA, Fedrigo O, Damas J, Formenti G, Koren S et al. (2021) Towards complete and error-free genome assemblies of all vertebrate species. Nature 592:737–746.

Rice AM, McLysaght A (2017) Dosage sensitivity is a major determinant of human copy number variant pathogenicity. Nat Commun 8: 14366.

Rodríguez-Fuentes J, Nesvadba N, Saladin V, Roesti M, Peichel CL (2025) Experimental test of the fitness effects of divergent marine-freshwater chromosomal inversions in stickleback under different salinity conditions. Heredity (Edinb): 1–10. (In This Issue).

Saitou M, Resendez S, Pradhan AJ, Wu F, Lie NC, Hall NJ et al. (2021) Sex-specific phenotypic effects and evolutionary history of an ancient polymorphic deletion of the human growth hormone receptor. Sci Adv 7: eabi4476.

Saxena AS, Baer CF (2025) High rate of mutation and efficient removal by selection of structural variants from natural populations of Caenorhabditis elegans. https://doi.org/10.1101/2025.03.22.644739.

Schaal SM, Haller BC, Lotterhos KE (2022) Inversion invasions: when the genetic basis of local adaptation is concentrated within inversions in the face of gene flow. Philos Trans R Soc Lond B Biol Sci 377:20210200.

Scheer K, Landau LJB, Jorgensen K, Karageorgiou C, Siao L, Alkan C, et al. (2025). Adaptive increase of amylase gene copy number in Peruvians driven by potato-rich diets. bioRxiv: 2025.03.25.644684.

Sedlazeck FJ, Rescheneder P, Smolka M, Fang H, Nattestad M, von, Haeseler A et al. (2018) Accurate detection of complex structural variations using single-molecule sequencing. Nat Methods 15:461–468.

Soto DC, Uribe-Salazar JM, Shew CJ, Sekar A, McGinty SP, Dennis MY (2023) Genomic structural variation: A complex but important driver of human evolution. Am J Biol Anthropol 181(Suppl 76):118–144.

Soto DC, Uribe-Salazar JM, Kaya G, Valdarrago R, Sekar A, Haghani NK et al. (2025). Human-specific gene expansions contribute to brain evolution. Cell 188:5363-5383.

Spielmann M, Lupiáñez DG, Mundlos S (2018) Structural variation in the 3D genome. Nat Rev Genet 19:453–467.

Sridharan S, Lou RN, Ferguson S, Rocha JL, De-Kayne R, Mitchell MW et al. (2025). Recurrent structural variation and recent turnover at the 17q21.31 locus in humans and great apes. https://doi.org/10.1101/2025.08.15.670618.

Sturtevant AH (1921) A case of rearrangement of genes in Drosophila. Proc Natl Acad Sci USA 7:235–237.

Todesco M, Owens GL, Bercovich N, Légaré J-S, Soudi S, Burge DO et al. (2020) Massive haplotypes underlie ecotypic differentiation in sunflowers. Nature 584:602–607.

Uddin M, Tammimies K, Pellecchia G, Alipanahi B, Hu P, Wang Z et al. (2014) Brain-expressed exons under purifying selection are enriched for de novo mutations in autism spectrum disorder. Nat Genet 46:742–747.

Vara C, Paytuví-Gallart A, Cuartero Y, Álvarez-González L, Marín-Gual L, Garcia F et al. (2021) The impact of chromosomal fusions on 3D genome folding and recombination in the germ line. Nat Commun 12: 2981.

Villoutreix R, de Carvalho CF, Feder JL, Gompert Z, Nosil P (2023) Disruptive selection and the evolution of discrete color morphs in Timema stick insects. Sci Adv 9:eabm8157.

White MJD (1973) *Animal Cytology and Evolution*, 3rd edn. Cambridge University Press: Cambridge, England.

Wilson J, Bieker VC, van Boheemen L, Connallon T, Martin MD, Battlay P et al. (2025) Copy number variation contributes to parallel local adaptation in an invasive plant. Proc Natl Acad Sci USA 122:e2413587122.

Yilmaz F, Karageorgiou C, Kim K, Pajic P, Scheer K, Human Genome Structural Variation Consortium, et al. (2024) Reconstruction of the human amylase locus reveals ancient duplications seeding modern-day variation. Science 386:eadn0609.

Zhang Y, Romanish MT, Mager DL (2011) Distributions of transposable elements reveal hazardous zones in mammalian introns. PLoS Comput Biol 7:e1002046.

Zhang Z, Gomes Viana JP, Zhang B, Walden KKO, Müller Paul H, Moose SP et al. (2024) Major impacts of widespread structural variation on sorghum. Genome Res 34:286–299.

Zhou W, Kunz D, Jiggins CD (2025) Comparative analysis of gene family evolution demonstrates expansion of digestive, immunity and olfactory functions in the black soldier fly (Hermetia illucens) lineage. Heredity (Edinb): 1–12. (In This Issue).

ACKNOWLEDGEMENTS

We thank Aurora Ruiz-Herrera for inviting us to edit this special issue. EML was supported by the National Institute of General Medical Sciences of the National Institutes of Health (R35GM147709). MYD was supported by the National Science Foundation (CAREER 2145885) and the National Institute of Mental Health of the National Institutes of Health (R01MH132818). OG was supported by the National Science Foundation (2049947, 2123284) and the National Institute of General Medical Sciences of the National Institutes of Health (R35GM156519).

COMPETING INTERESTS

The authors declare no competing interests.