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INVITED REVIEW

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How structural variants shape avian phenotypes: Lessons from model systems

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Abstract

Despite receiving significant recent attention, the relevance of structural variation (SV) in driving phenotypic diversity remains understudied, although recent advances in long-read sequencing, bioinformatics and pangenomic approaches have enhanced SV detection. We review the role of SVs in shaping phenotypes in avian model systems, and identify some general patterns in SV type, length and their associated traits. We found that most of the avian SVs so far identified are short indels in chickens, which are frequently associated with changes in body weight and plumage colouration. Overall, we found that relatively short SVs are more frequently detected, likely due to a combination of their prevalence compared to large SVs, and a detection bias, stemming primarily from the widespread use of short-read sequencing and associated analytical methods. SVs most commonly involve non-coding regions, especially introns, and when patterns of inheritance were reported, SVs associated primarily with dominant discrete traits. We summarise several examples of phenotypic convergence across different species, mediated by different SVs in the same or different genes and different types of changes in the same gene that can lead to various phenotypes. Complex rearrangements and supergenes, which can simultaneously affect and link several genes, tend to have pleiotropic phenotypic effects. Additionally, SVs commonly co-occur with single-nucleotide polymorphisms, highlighting the need to consider all types of genetic changes to understand the basis of phenotypic traits. We end by summarising expectations for when long-read technologies become commonly implemented in non-model birds, likely leading to an increase in SV discovery and characterisation. The growing interest in this subject suggests an increase in our understanding of the phenotypic effects of SVs in upcoming years.

KEYWORDS
Avian model systems, chromosomal rearrangements, genotype/phenotype associations, pangenomes, structural variants

1 | INTRODUCTION

Avian model species, including the chicken and the Wild Turkey, vary in plumage colour and patterns, beak morphology, vocalisations and behaviours, as well as in economically relevant traits such as body size, immune response and egg production. Significant resources have been invested to understand how these phenotypes associate with genomic variation, especially in species where such knowledge is of economic relevance. Therefore, avian model systems can shed light on the underlying genomic mechanisms shaping such traits, offering insights applicable to both model and non-model species. The methods most commonly used

to establish links between genomic variants and phenotypes are genome-wide association studies (GWAS, Uffelmann et al., 2021) and genetic linkage analysis; the latter often involves quantitative trait loci (QTL) mapping for quantitative traits, which is based on the co-inheritance of genetic markers and phenotypic traits among pedigreed individuals (Broman, 2001). Most research on the genetic basis of phenotypic traits has focused on single-nucleotide polymorphisms (SNPs, see Glossary) and relatively small (<50 bp) genetic rearrangements such as short insertion/deletion (indel) mutations (e.g. Lan et al., 2021; Minvielle et al., 2010). The impact of larger structural variants (SVs) on avian phenotypes, even in model systems, remains understudied despite their potential importance. SVs (Box 1), which include insertions, deletions, inversions and duplications, traditionally describe genomic alterations involving DNA regions longer than 50 bp (Bickhart & Liu, 2014). However, SVs shorter than 50 bp can still have significant impact on phenotypes, for instance they underlie plumage colouration in Japanese Quail (Hiragaki et al., 2008; Minvielle et al., 2010) and chickens (Adetula et al., 2020), as well as impacting egg production in both species (Lan et al., 2021; Manoharan et al., 2021; Vinh et al., 2021). Additionally, transposable elements (TEs), which encompass various classes of mobile genetic elements, can be considered a form of SV (see below). TEs contribute to genetic variation through translocation, indel formation and duplication events, generating structural genomic changes that can impact phenotypes (Mérot et al., 2020). Therefore, as proposed by Mérot et al. (2020), we advocate for an SV concept that encompasses both the full size-range, from single-nucleotide SVs (i.e. 1 bp indels but not 1 bp substitutions) to megabases, without an arbitrary size threshold and the full diversity of SVs including TEs.

SVs can affect gene structure and function (Mérot et al., 2020), although knowledge gaps in our understanding of the effect of SVs on phenotype remain, likely due to a combination of methodological challenges in detecting SVs, the complex genetic basis of most traits and the lack of highly contiguous reference genomes. Many SVs are hard to detect and genotype, requiring third-generation sequencing techniques (i.e. long-read technologies such as Pacific Biosciences (PacBio) and Oxford Nanopore Technologies sequencing), chromosome conformation capture techniques like Hi-C (Belton et al., 2012), and the implementation of robust analytical tools (van Dijk et al., 2023). The more widely used short-read technologies are unable to assemble highly repetitive regions, leading to challenges in genome assembly and hindering the identification of longer SVs. Additionally, even with long-read technologies, the detection of small SVs remains challenging within repetitive regions of the genome: long-read sequencing technologies show a higher susceptibility to introducing indel errors, particularly within homopolymer regions (Sacristán-Horcajada et al., 2021). Despite these challenges, significant improvements have been achieved through technological advancements such as PacBio HiFi and ONT Duplex, which have substantially reduced the sequencing error rate to less than 1% (Mahmoud et al., 2024). Additionally, when mapping population-level data against a reference genome, SVs might be overlooked if they are absent from the reference sequence. Despite the generally conserved synteny and architecture of bird genomes (Singhal et al., 2015; Zhang, Li, et al., 2014), several examples from both model and non-model species illustrate that SVs, chromosomal rearrangements and TEs are ubiquitous in this taxonomic group (Kapusta & Suh, 2017; Taylor & Campagna, 2016). However, relatively few large SVs have been associated with phenotypic traits (e.g. Küpper et al. 2016; Sanchez-Donoso et al., 2022; Tuttle et al., 2016), and it is still unclear whether this can be attributed to limitations in detection power or to the genomic stability of bird genomes. Moreover, SVs can interact with multiple genes to shape complex and polygenic traits, further complicating the ability to pinpoint the individual effects on a given phenotype of genes within, and interacting with, SVs. Additionally, other factors such as the frequency of the SV in the population and the sampling effort affect detection power. These challenges must be addressed in order to understand how SVs are linked to avian phenotypic evolution.

In this review, we explore some of the ways in which SVs shape phenotypes in avian model systems, and compare their effects to what is known for other types of genetic variation, such as SNPs. As noted above, our understanding of how SVs shape phenotypes is linked to the advancements in sequencing technologies such as third-generation sequencing and telomere-to-telomere genomes, and advances in bioinformatics, and we thus expect a significant increase in studies uncovering the influence of SVs on avian phenotypes in the coming years, including in non-model species. However, linking SVs with phenotypes also requires measuring and genotyping a large number of individuals for robust association studies. We focus on avian model systems for various reasons. First, their commercial value combined with the ease of conducting research due to their domestication and husbandry provides large sample sizes and attracts many research resources, setting them apart from other avian species. Second, the longer-standing availability and superior quality of reference genomes for avian model species, along with the availability of pedigrees and genetic mapping techniques, facilitates the identification of phenotype/genotype associations. The first avian studies utilising long-read sequencing were therefore conducted on model species (e.g. He et al., 2022; Wang et al., 2022; Warren et al., 2017). In this review, we focus on seven model species: chicken (*Gallus gallus*), Zebra Finch (*Taeniopygia guttata*), Wild Turkey (*Meleagris gallopavo*), domestic Mallard duck (*Anas platyrhynchos*), domestic pigeon (*Columba livia*) and the Common and Japanese Quails (*Coturnix coturnix* and *Coturnix japonica*) because these have been the most extensively studied. We also discuss how the insights gained on the role of SVs in model systems can be extrapolated to non-model systems irrespective of taxonomic group. The outline of this review is organised around seven major topics: (1) the phenotypic effects of SNPs compared to SVs, (2) how TEs contribute to modifying genomic structure and shaping phenotypes, (3) the type and length of SVs associated with phenotypic traits in avian model systems, (4) common methods implemented to detect SV genotype–phenotype associations, (5) the genetic mechanisms by which SVs generate phenotypic variation, (6) the current pangenome availability and relevance, and (7) the SV-phenotypic associations in non-model avian species.

1.1 | Systematic review of phenotype-associated SVs in avian model systems

We conducted a systematic search in Web of Science and Google Scholar using the terms shown in Table S1, which yielded 2005 studies. From these, we identified only 103 articles reporting SVs associated with phenotypic traits in avian model systems. We discarded the remaining studies as they involved only subsets of our search terms and did not establish SV/phenotype associations. We categorised the studies based on SV type: insertions/deletions (indels), duplications, copy number variants (CNVs, which involve changes in the number of repeats of a certain sequence in a population, resulting from both deletions and duplications), inversions, or complex rearrangements (Box 1). SV lengths were subsequently classified into the following intervals: <50 bp, 50 bp to 1 kb, 1–10 kb, 10–100 kb, >100 kb or unknown. When a study reported multiple SVs, we used the mean length for our analysis (provided in 9 of 12 cases); otherwise, we classified it as unknown. When possible, we also recorded whether the inheritance was recessive or dominant, its impact on coding and/or non-coding regions (encompassing subcategories such as upstream/downstream of coding regions, untranslated region, promoter, intergenic, intron or enhancer), and whether it encompassed one or several genes. We differentiated between gene-associated upstream/downstream regions, which are specific regions that are close to the gene's coding sequence, and intergenic regions, which are the larger spaces between genes on a chromosome. Additionally, we examined the nature of the identified phenotypic traits associated with the variants, distinguishing between quantitative and discrete traits. Furthermore, we documented the detection method used, the genetic mechanism involved (e.g. gene disruption) and whether the reported phenotypic associations underwent further validation. If a study reported multiple SVs associated with different phenotypes, we treated them as distinct entities for analysis. Moreover, when a study documented multiple SVs of the same type that were associated with the same phenotype, we counted one occurrence for our analysis. Additionally, only the initial study among several that described the same SV was included; consequently, five studies out of the 103 were excluded. Among the remaining 98 studies, 10 of the 11 that focused on characterising SVs among breeds or populations were excluded from the analysis, as they reported numerous SVs related to broad traits such as domestication or multiple inter-breed differences. After this initial revision, 88 studies remained in our summary (see a full list in Table S1).

2 | THE PHENOTYPIC EFFECTS OF SNPs VERSUS SVs

Structural variants likely surpass the phenotypic impact of SNPs owing to their larger size and capacity to encompass multiple functional genetic elements (Alonge et al., 2020; Wellenreuther et al., 2019). Notably, SVs have a greater likelihood of significantly altering gene expression and thus modifying phenotypes due to their large-scale perturbations of genes and cis-regulatory regions (Alonge et al., 2020). This difference in their effect on the phenotype could explain why SNPs appear to be much more common than SVs, for example, studies of the human pangenome and European starlings (*Sturnus vulgaris*) suggest that SVs are three orders of magnitude less common than SNPs (Liao et al., 2023; Stuart et al., 2023). Even though SNPs and some SV types can be tightly linked (Geibel et al., 2022), the patterns of genetic diversity derived from each type of variant may differ at the individual and the population level. This dissimilarity can arise from factors such as the distribution of each type of variant along chromosomes: while SNPs are more evenly distributed, SVs tend to be concentrated at the ends of the chromosomes, although this could be due to a detection bias (e.g. erroneous SV calls at chromosome ends as a result of higher repeat densities), or to an actual higher SV density at chromosome ends resulting from an increased mutation rate in these highly repetitive regions. Additionally, at the population level, SNPs and SVs may occur at different frequencies, with potential consequences for the discovery of lower frequency variants (Stuart et al., 2023). The contrast between the larger size of SVs and the higher abundance of SNPs suggests that while SVs may have a more pronounced individual effect on traits, the cumulative effect of SNPs could also be substantial due to their higher prevalence. Understanding the independence or interplay between SNPs and SVs will provide a comprehensive view of the genomic landscape. However, their frequent co-occurrence, and possible interactions, will likely pose a challenge in distinguishing their individual effects on traits.

3 | HOW TEs CONTRIBUTE TO MODIFYING GENOME STRUCTURE AND SHAPING PHENOTYPES IN AVIAN MODEL SYSTEMS

Transposable elements are mobile genetic elements that play a significant role in shaping genome structure, adaptation and the development of reproductive barriers (Bourque et al., 2018). TEs have the potential to alter the structural architecture of the genome, as their insertion, deletion, duplication or rearrangement can lead to gene modifications, altered recombination patterns and the formation of other SV types. The latter, arising from TE activity, are commonly referred to as TE-related SVs. As emphasised by Mérot et al. (2020), in essence, TEs are SVs—specifically, translocations, duplications and/or indels. As TEs jump and insert into other regions, they can also lead to segmental duplications and inversions. TEs can generate phenotypic variation through alterations in gene expression patterns due to the introduction of regulatory elements such as promoters, silencers, or enhancers, or by modifying the spacing between these Cis-regulatory elements (CREs) elements and promoters (Bourgeois & Boissinot, 2019). Notably, the domestic duck pangenome (see Glossary) revealed that the phenotypic impact of TE-related SVs can be important, exemplified by a Ty3 family long terminal repeat element (LTR,

see Glossary) insertion in the promoter region of the IGF2BP1 gene, that accounts for a large proportion (27.61%) of the variation in body mass (Wang et al., 2023). Moreover, the domestic duck pangenome and the numerous inversions in the Zebra Finch have shown an accumulation of TEs at the breakpoints of SVs (i.e. the start and end points on the DNA where the SV occurs), suggesting a potential correlation between TEs and the generation of additional SVs (Boman et al., 2019; Wang et al., 2023). Specifically, the presence of endogenous retrovirus LTR retrotransposons is relatively common among avian model systems, and associates with different phenotypic traits such as blue eggshell in chickens (Altgilbers et al., 2022) and domestic duck body size and plumage colouration (Wang et al., 2023). Boman et al. (2019) reported 4.5 Mb of LTRs in the Zebra Finch genome, likely associated with

BOX 1 Structural variants (SVs) and their phenotypic effect.

Structural variants encompass a wide range of genomic alterations, ranging in size from small changes (~50 bp) to large-scale modifications spanning megabases. Traditionally, changes involving less than 50 bp have not been considered SVs, although we note that this size threshold is arbitrary (as discussed in more detail in the main text). These mutations can be classified into two categories. Unbalanced changes lead to alterations in DNA content. These changes include insertions and deletions (indels), which are small-scale genetic changes involving the insertion or deletion of one or more nucleotides; copy number variants (CNV) involving both deletions and duplications of a DNA segment; and presence/absence variants (PAV) that represent changes related to the presence or absence of larger genomic segments. Such mutations result in the loss or gain of DNA information. Secondly, balanced changes, such as inversions and inter or intra-chromosomal translocations, impact the orientation or location of DNA without altering the overall genetic content. Additionally, in a broader sense, SVs include insertions of TEs, tandem and segmental duplications, as well as complex rearrangements involving combinations of all these mutations, for example, inverted duplications (Figure I).

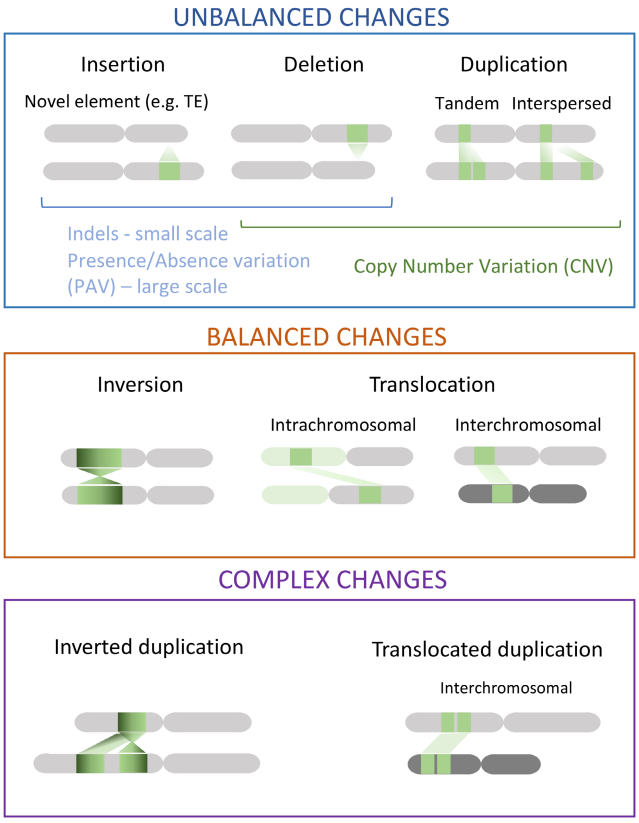


FIGURE I. Graphical representation of structural variants (SVs). SVs are categorised into unbalanced changes, which include insertions, deletions and duplications; balanced changes, such as inversions and translocations; and complex changes that are a combination of the previous types.

the numerous inversions present in this species. However, the causality between the presence of LTRs at the breakpoints and the generation of these inversions (Knief et al., 2016, 2017) remains to be established. Overall, more effort is needed to annotate and characterise the TE diversity and abundance in avian genomes, a challenging process that has likely led to their underreporting (Kapusta & Suh, 2017). TEs represent a type of SV, yet their relative importance and role within the broader landscape of SVs remains to be understood. Investigating the impact of TEs in avian model systems, as well as their interactions with other genetic elements and environmental factors, will provide valuable insights on how SVs shape phenotypic diversity.

4 | TYPE AND LENGTH OF SVs ASSOCIATED WITH PHENOTYPIC TRAITS IN AVIAN MODEL SYSTEMS

A range of types and sizes of SVs are implicated in shaping phenotype, from less than 50 bp all the way to megabases. However, the most commonly detected SVs are indels and duplications, and they tend to be short (<1 kb; Figure 1a,b). Most of the articles that informed this review (except one, Zhu et al., 2021) relied primarily on short-read sequencing, which introduces a bias towards short SV detection due to the challenges in identifying long SVs from short reads (Mahmoud et al., 2019). It remains to be determined if the higher frequency of short SV detection may also be attributed to short SVs being more prevalent than large ones. As the use of long-read sequencing technologies becomes more prevalent, long SV identification may increase due to a higher likelihood of detection. In total, the 88 reviewed articles collectively identified 95 SVs that were associated with phenotypic changes. While many of the detected SVs (31.6%) were shorter than 50 bp, 46.4% ranged between 50 bp and 100 kb (combining percentages from several size classes), whereas only 13.7% of SVs were over 100 kb (Figure 1a).

The diversity of reported SV types in each model species is likely constrained by research effort. In the case of the Zebra Finch, only inversions have been reported but we only reviewed three articles reporting SVs associated with phenotypic traits in this species, and two of them report the same SV (Kim et al., 2017; Knief et al., 2016, 2017) compared to the 66 studies we found on chickens. Similarly, for the turkey, only deletions and duplications have been documented in three studies (Table S1). Conversely, Japanese Quail and chicken, which were the subjects of a higher number of studies included in the review–8 (9.2%) and 66 (74.7%), respectively, show higher SV diversity (Figure 1c,d). Although we included both Common and Japanese Quails in our analyses, eight of nine studies focused on the Japanese Quail. The disparity in the number of studies among species is likely due to the allocation of more research resources to commercially valuable species, such as chickens. In contrast, species studied mostly without an applied research purpose, like the Zebra Finch, show findings related to conspicuous genetic changes, such as large inversions, rather than comprehensive characterisations of all SVs. Moreover, it is easier to sample a higher diversity of populations/breeds in commercial species like the chicken or the quail than in wild species like Zebra Finches.

We found several relationships between SV length and type: insertions are typically shorter, while deletions and duplications show the highest length variability (ranging from a few bases to over 100 kb, Figure 1b). The reported inversions and complex SVs are longer, always exceeding 10 kb (Figure 1b), yet there are relatively few examples of these SVs. This pattern is most likely a product of detectability and reduced discovery, rather than indicating that inversions and complex rearrangements are uncommon SVs, which is consistent with the limitations of detecting long SVs using the prevailing short-read sequencing methods.

5 | IDENTIFYING ASSOCIATIONS BETWEEN SVs AND PHENOTYPIC TRAITS

The reviewed studies employed various methods to associate phenotypes with SVs in avian model systems. GWAS identify links between genetic loci across the genome and phenotypic traits (e.g. Lin et al., 2023) by analysing how genotypes covary with phenotypes across individuals. Crossing and segregation experiments involve the controlled mating of individuals with different genetic backgrounds or traits to investigate the inheritance pattern and the distribution of the traits in their offspring (Li, Chen, et al. 2021; Li, Lee, et al. 2021). Linkage analyses aim to pinpoint markers associated with specific traits by identifying genetic loci and assessing the likelihood of their co-inheritance with the phenotypic trait (Shinomiya et al., 2012). Finally, CNV calling consists of assessing the frequency of these SVs among individuals or populations that show clear phenotypic differentiation (Sohrabi et al., 2018). CNV calling is usually complemented with validation through qPCR or other indirect evidence such as previous knowledge of QTLs (regions of the genome associated with variation in quantitative traits) and/or selective sweep detection (regions under selection detected through the reduction of genetic variation around beneficial mutations).

The predominant approach in the studies we reviewed was GWAS (~66.5%), followed by crossing and segregation experiments (~14.7%). Additionally, linkage analysis and CNV calling combined either with qPCR validation or with previous QTL and/or selective sweep detection were fairly common methods (7.4% each), while F_{ST} outlier analysis (2.1%) and genetic fine mapping (1%) are less frequently used. Among all the SVs reported to be associated with phenotypic traits, 70% were validated. Several validation methods were used, but the predominant one is the use of qPCR or RT-PCR to detect changes in expression, whereas functional validation (e.g., retrovirus-mediated expression) and transcriptome analyses were less common (Table S1).

Among all the studies reviewed, we observed a comparable prevalence of discrete and quantitative traits associated with SVs (46% vs. 47% respectively). In over 55% of the studies, the mode of inheritance of traits is either unreported or unknown. Among the remaining 45%, 20 articles (21%) reported dominant traits, 11 (11.6%) incompletely dominant, 7 (7.4%) recessive and 4 (4.2%)

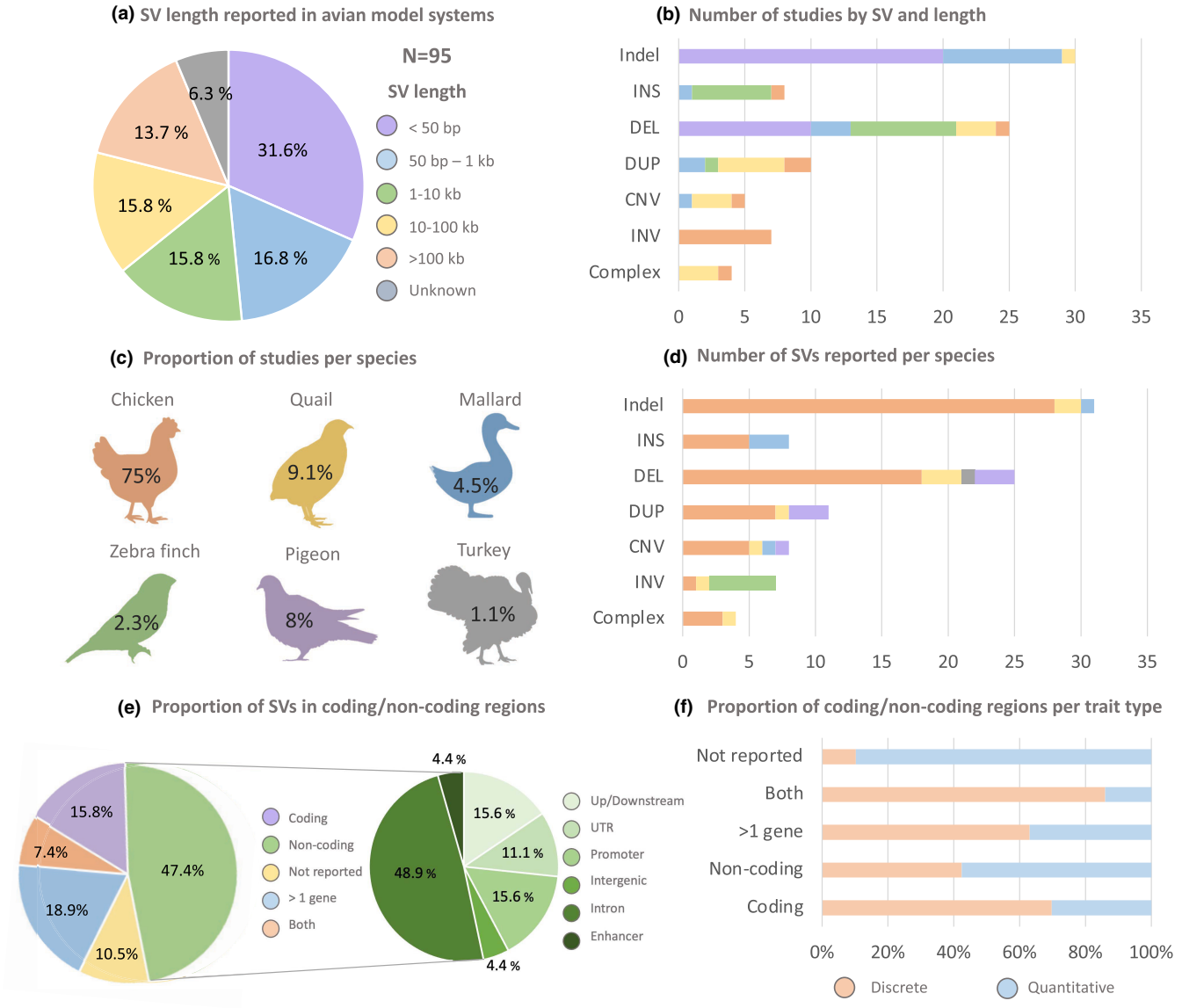


FIGURE 1 Summary of structural variants (SVs) associated with phenotypic traits in avian model systems. (a) Length distribution of SVs associated with phenotypic traits categorised in the following intervals: <50 bp, 50–100 bp, 1–10 kb, 10–100 kb, >100 kb and unknown length. (b) Number of studies by SV type and their length distribution. The SV types include indels, insertions (INS), deletions (DEL), duplications (DUP), copy number variation (CNV) that encompass both deletions and duplications, inversions (INV) and complex rearrangements. The colour of the bars represent different SV lengths as in (a). (c) Proportion of studies reporting SVs associated with phenotypic traits per species, including the chicken, the Common and Japanese Quails, the domestic Mallard duck, the Zebra Finch and the Wild Turkey. (d) Number of studies by SV type reported per species (colour-coded as in c), including the same SV types than those shown in (b). (e) Proportion of SVs reported in coding and non-coding regions. Non-coding regions are further categorised by genomic feature including: upstream and downstream regions near genes, promoters, intergenic regions, introns and enhancers. (f) Proportion of coding and non-coding regions according to the discrete or quantitative nature of the associated phenotypic trait.

sex-linked. Among the 42 studies reporting inheritance (45%), 32 articles (76.2%) pertained to discrete traits, while only 8 (19%) were related to quantitative traits. The remaining 4.8% corresponded to two studies (Bed'hom et al., 2012; Imsland et al., 2012) implicating both discrete and quantitative traits simultaneously, mediated by a complex rearrangement and an inversion with pleiotropic effects respectively.

To date the most common associations found between SVs and phenotypes in avian model systems underlie traits related to body size and weight (e.g. Han et al., 2019; Hirwa et al., 2010; Li et al., 2022; Li, Chen, et al., 2021; Lin et al., 2021; Qin et al., 2023; Ren et al., 2020; Sohrabi et al., 2018; Wang, Wang, et al., 2020; Wei et al., 2020; see remaining references in Table S1 under phenotype category 'Bodyweight') followed by plumage colouration and pigmentation (e.g. Bruders et al., 2020; Domyan et al., 2014; Han et al., 2011; Krishnan & Cryberg, 2019; Krishnan, 2019; Maclary et al., 2023; Shen et al., 2022; Vickrey et al., 2018; Wang et al., 2013; see remaining references in

Table S1 under phenotype category 'Plumage Colouration and Pigmentation'). There are examples in quails of both trait categories being affected by the same SV (Bed'hom et al., 2012; Sanchez-Donoso et al., 2022). There are many studies, mostly in chickens, that show associations between SVs and feathering phenotypes (Chen, Xi, et al., 2022; Derks et al., 2018; Domyan et al., 2016; Dong et al., 2018; Elferink et al., 2008; Li et al., 2020; Li, Lee, et al., 2021; Mou et al., 2011; Ng et al., 2012; Shen et al., 2023); comb, muff and beard traits (Dorshorst et al., 2015; Guo et al., 2016; Imsland et al., 2012; Moro et al., 2015; Sato et al., 2010; Wang et al., 2017; Wright et al., 2009; Yang et al., 2020, 2021); and egg production (Cui et al., 2006; Huang et al., 2018; Lan et al., 2021; Manoharan et al., 2021; Vinh et al., 2021). Although less common, there are also associations between SVs and behaviour and domestication (Abe et al., 2013; Chen, Bai, et al., 2022; Falker-Gieske et al., 2023; Khatri et al., 2019; Komiyama et al., 2014; Krause et al., 2019; Rubin et al., 2010; Seol et al., 2019; Zhou et al., 2018; Zhu et al., 2021). Other uncommon traits associated with SVs are craniofacial deformities (Bai et al., 2018; Chang et al., 2014; Gu et al., 2017), fertility (Gu et al., 2017), muscle glycogen content (Liu et al., 2020), number of vertebrae (Xu et al., 2022) and aldehyde flavour (Yuan et al., 2022). Most of the traits implicated are economically relevant, such as body size and egg production, and/or conspicuous, such as plumage colouration. This could be due to a detection bias that leads to the under-representation of harder to study traits, such as immune responses.

6 | GENETIC MECHANISMS INVOLVED IN SHAPING SV-MEDIATED PHENOTYPIC TRAITS

6.1 | SVs in coding versus non-coding regions

The genomic regions affected by SVs in avian model systems are predominantly non-coding, found in 45 cases (47.4%). These non-coding regions include many genomic features, of which introns are most frequently implicated (22 studies, 50% of all non-coding examples), followed by upstream or downstream of genes and promoter regions (Figure 1e). In contrast, SVs in coding regions, specifically exons, are reported in 15 studies (15.8%). In seven instances (7.4%), the SV spanned both coding and non-coding regions, and in 18 studies (19%) SVs encompassed more than one gene. When looking at differences between discrete and quantitative traits (Figure 1f), the genomic feature affected by the SV is more commonly reported for discrete traits. Discrete traits more frequently involve SVs in coding regions, while the opposite is true for quantitative traits, which mostly implicate SVs in non-coding regions. Further investigation is necessary to confirm this pattern and understand the underlying mechanisms and their evolutionary implications. Non-coding regions can include gene regulatory networks, which may be more important for the generation of phenotypic diversity than coding regions (Fagny & Austerlitz, 2021).

6.2 | Same traits across different species: Diverse SVs in a single gene

The same phenotype in different species can be achieved by modifying the same gene in various ways. For instance, the late feathering trait in both chickens (Shen et al., 2023) and turkeys (Derks et al., 2018), which is a sex-linked phenotype used for sexing birds at an early age, involves SVs in the Prolactin receptor gene (PRLR). In chickens, the SV is a partial duplication of the PRLR and SPEF2 genes that affects gene expression and dosage of PRLR (Luo et al., 2012), while in turkeys, a 5 bp deletion in the PRLR terminal exon results in a truncated protein lacking 98 C-terminal amino acids (Figure 2a). Moreover, deletions in different regions of the Prolactin gene (PRL) influence egg production in both chickens and Japanese Quails (Cui et al., 2006; Lan et al., 2021; Figure 2b). Similarly, larger body size in commercial chicken (Wang et al., 2021) and Mallard duck breeds (Wang et al., 2023) has been associated with two different SVs in the promoter region of the IGF2BP1 gene that results in increased gene expression: in chickens, the SV is a deletion, whereas in ducks, it involves a Ty3 family LTR TE insertion, and both mutations lead to higher body mass (Figure 2c). In contrast, more complex traits, such as body size and growth, are commonly linked to multiple genes and SVs. Given their polygenic nature, similar changes in these traits can be achieved through various genetic mechanisms (e.g. Fernandes et al., 2021; Fu et al., 2020; Jing et al., 2020; Rao et al., 2016; Wang et al., 2020b).

6.3 | Same traits across different species: Diverse SVs in different genes

Our comparison across studies also shows that the same phenotype can be obtained through different types and lengths of SVs in different genes. For instance, the white plumage phenotype in chickens (Adetula et al., 2020) and domestic ducks (Wang et al., 2023) is attributed to a 4-bp deletion in the RAI14 transcription factor binding site and a 6-kb insertion in the MITF gene, respectively. In white chickens, the deletion is accompanied by three SNP alleles within 100 kb of the candidate genes (TYR, RAI14 and GTDC1). The TYR gene is involved in white pigmentation in other chicken breeds (Chang et al., 2006) and RAI14 has been shown to enhance melanoma cell differentiation in vitro (Huang et al., 2003). In Pekin and Cherry Valley ducks, white plumage results from a Ty3 family LTR TE insertion that generates a novel MITF transcript lacking 39 amino acids, which in turn affects the expression of four downstream genes including the TYR gene (Figure 2d).

6.4 | Many genetic mechanisms for modifying a single trait

Within species, the same trait can be modified by either different mutations in a single gene or mutations in different genes. For instance, in Japanese Quails, Fawn-2-beige and yellow plumage colouration arise from a tandem duplication and a deletion in a single gene (ASIP), respectively (Robic et al., 2019; Figure 2e). In contrast, different chicken combs, such as the pea-comb (Wright et al., 2009), V-shape, buttercup (Dorshorst et al., 2015) and Rose comb (Wang et al., 2017), are strongly linked to SVs in different genes. The pea and V-shape combs are associated with duplications in the SOX5 and EOMES genes, respectively, whereas the Rose comb is associated with an inversion that affects expression of the MNR2 gene. This gene is not within the inversion but located adjacent to its breakpoints. In all these cases, the SVs lead to the ectopic expression of the affected genes, likely impacting comb development and resulting in their phenotypic diversity (Figure 2f). Moreover, the same genetic variant can have pleiotropic effects on several traits, for example, the inversion causing the rose comb phenotype also affects sperm mobility (Wang et al., 2017).

6.5 | Supergenes

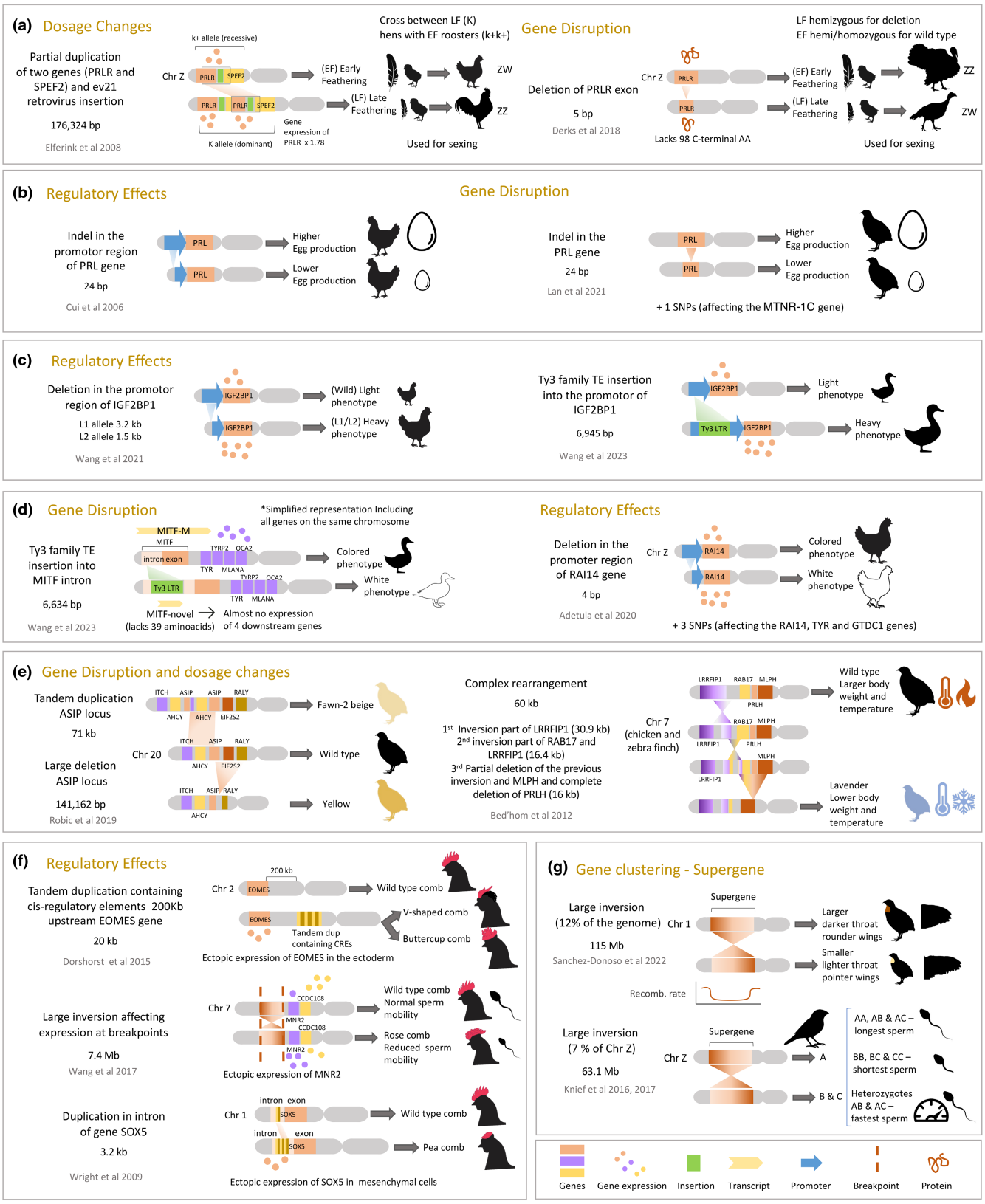
Additionally, the same phenotype can be achieved by similar types of SVs in different genes. In both Zebra Finches and chickens, sperm mobility is influenced by an inversion, but the inversion is on chromosome Z in the Zebra Finches and chromosome 7 in chickens (Figure 2f,g; Kim et al., 2017; Knief et al., 2017; Wang et al., 2017). In Zebra Finches, the SV clusters several genes into a supergene. Supergenes involve inversions which link genes by reducing the recombination rate, causing blocks of multiple genes to be transmitted as a unit, with the potential for co-adaptation. Because these supergenes include several genes, this type of SV may result in more complex phenotypic variation, such as changes in behaviours, compared to what may be generated by other genetic variants affecting a single gene (Taylor & Campagna, 2016). Moreover, the typically large size of such SVs, which generally involve multiple genes, complicates the accurate identification of the specific genomic regions that are causally linked to the phenotype. Two such supergenes have been reported in avian model systems: the aforementioned one in Zebra Finches (Kim et al., 2017), plus one in Common Quails (Sanchez-Donoso et al., 2022). These supergenes have different and pleiotropic phenotypic effects across species. In quails the supergene is associated with geographically isolated populations that differ in several traits, including body size, throat colour and wing shape, whereas the Zebra Finch supergene affects sperm morphology and swimming speed in outbred and in artificially selected birds from a domesticated population (Figure 2g).

6.6 | Complex rearrangements

Complex rearrangements involve combinations of different types of SVs within a specific genomic region. Only four complex rearrangements have been reported in avian model systems, and due to their large size, they typically impact multiple genes, potentially shaping multiple phenotypic traits. For example, in quails two inversions and a partial deletion that affect four genes result in changes in plumage colouration, body weight and temperature (Bed'hom et al., 2012; Figure 2e). Two studies on hyperpigmentation (Dorshorst et al., 2011; Shinomiya et al., 2012) and two studies on muff and beard development (Guo et al., 2016; Yang et al., 2020) in chickens have reported SVs implicating the same genes in each trait category (EDN3 for hyperpigmentation and HOXB8 for muff and beard development). Interestingly, the initial two studies for each trait (Dorshorst et al., 2011; Guo et al., 2016) identified complex SVs, but were later followed by the second set of studies (Shinomiya et al., 2012; Yang et al., 2020) that tried to narrow down the genomic mechanism and subsequently reported only duplications. These studies illustrate the complexity of both characterising SVs and understanding the genetic causes underlying a specific trait.

Most of the traits have a complex genetic basis, and SVs are often associated with phenotypes in conjunction with other types of genetic variation, such as SNPs (e.g. Adetula et al., 2020; Guo et al., 2016; Yang et al., 2020). Therefore, in non-model systems,

FIGURE 2 Examples of structural variants (SVs) affecting phenotypic traits in different avian model systems. (a) Different SVs affecting the PRLR gene in chickens (Elferink et al., 2008) and turkeys (Derks et al., 2018) that lead to changes in feathering time. This trait is linked to the Z sex chromosome and can be used for sexing in specific breads because females are heterogametic (ZW) and males homogametic (ZZ). (b) Indel in the PRL gene or its promoter in chickens (Cui et al., 2006) and Japanese Quails (Lan et al., 2021) that affects egg production. (c) Different SVs affecting the IGF2BP1 promotor in chicken (Wang et al., 2021) and domestic ducks (Wang et al., 2023) modulate body weight in both species. (d) Different SVs in different genes generate the white phenotype in domestic ducks (Wang et al., 2023) and chickens (Adetula et al., 2020), but in both cases the TYR gene is implicated. In the duck example the representation is simplified, including all the genes on the same chromosome, yet in reality some genes are found on different chromosomes. (e) Different SVs in the ASIP gene generate variation in quail plumage colouration (Robic et al., 2019) and a large complex rearrangement affecting several genes modify several traits in quail, including plumage colouration, body weight and temperature (Bed'hom et al., 2012). (f) Different SVs affect many genes and lead to their ectopic expression generating chicken comb diversity (Dorshorst et al., 2015; Wang et al., 2017; Wright et al., 2009). (g) Large inversions in quail (Sanchez-Donoso et al., 2022) and the Zebra Finch (Knief et al., 2016, 2017) result in supergenes affecting different traits in each species.



certain traits that have been initially linked to SNPs, due to the current prevailing short-read methodologies, might actually have a more complex genetic basis also involving SVs. Overall, given the genetic complexity underlying phenotypic traits, it is important to account for multiple types of genetic variation when establishing associations between phenotypes and genotypes.

6.7 | Cross-breed comparisons and independent origins of the same trait

Among the 11 articles reporting multiple SVs, seven described SVs found across different chicken breeds and populations (Chen, Bai, et al., 2022; Drobik-Czwarno et al., 2018; Fan et al., 2013;

Han et al., 2014; Rao et al., 2016; Sohrabi et al., 2018; Zhang, Du, et al., 2014), along with two each on turkey (Strillacci et al., 2019, 2021) and domestic ducks (van Dijk et al., 2023; Zhou et al., 2018). Exploring diverse breeds or populations within a species offers an opportunity to examine whether similar phenotypes stem from comparable genetic mechanisms. For instance, the Creeper trait, which involves abnormally short legs, is associated with the IHH gene in two chicken breeds. The IHH gene is completely deleted in Chinese Xingyi Bantam Chickens (Jin et al., 2016), while a complex rearrangement involving deletions and an insertion affects both the IHH and NHEJ1 genes in Japanese bantam chickens (Kinoshita et al., 2020). Additionally, there are instances where identical or nearly identical SVs in the same gene lead to the same phenotype, for example, the frizzle feather trait is caused by a 15-bp deletion in the KRT75L4 gene in both Kirin Chickens (Dong et al., 2018) and Xiushui Yellow Chickens (Chen, Xi, et al., 2022). The same trait is observed in crosses between a heterozygous frizzle rooster and wild-type hens, generated by a 69-bp deletion with autosomal incomplete dominant inheritance in the same gene (Ng et al., 2012). Another example is blue egg colouration in Araucana, Chinese and European chicken breeds (Wang et al. 2013; Wragg et al., 2013). In these breeds, blue eggs are caused by the insertion of a ~4.2-kb retrovirus (EAV-HP) in the promoter region of the SLCO1B3 gene, leading to ectopic expression in the shell glands of the uterus. However, the integration site differs between the Asian breed and the Araucana and European breeds, suggesting two independent origins (reviewed in Campagna & Toews, 2022). Notably, similar SVs can also yield diverse phenotypic outcomes, exemplified by a SOX10 gene deletion generating both dark brown and yellow colouration in different chicken breeds (Gunnarsson et al., 2011; Zhu et al., 2022).

7 | THE ROLE OF PANGENOMES IN DETECTING SVs

The study of SVs is closely linked to the pangenome concept. Traditional reference-based genome studies have predominantly focused on a single reference genome, leading to the underrepresentation of SVs, as sequences from individuals which possess the SV may not map against reference genomes which lack them. Pangenomes integrate information from multiple genomes within a species or a group of related organisms, thus revealing a more comprehensive landscape of genetic variation, including SVs (Gong et al., 2023). Pangenomes aim to uncover the full spectrum of genetic variation, including both small and large-scale SVs, capturing the core genome shared among all individuals from that species and the accessory or variable genome containing non-reference sequences. While it is possible to construct pangenomes from short-read genome assemblies, the best resolution is achieved by generating pangenomes from high-quality reference genomes derived from long reads, ideally telomere-to-telomere, because short-read assemblies may not capture important variants such as long repeats. Pangenomics is an emerging research field, and its adoption in eukaryotes has been slow, primarily attributed to the challenges of transitioning the approach from the simpler and shorter bacterial genomes (where they were first developed) to effectively capture the genomic complexity of eukaryotes (see review by Gong et al., 2023). Other major challenges include the computationally demanding analytical and storage requirements. However, the field is anticipated to grow substantially in the coming years, driven by the increased affordability of third-generation sequencing, along with the development of bioinformatic tools supporting this approach. The implementation of the pangenome as the reference genome in population-level genome re-sequencing studies (as opposed to using a single genome as reference), will allow researchers to capture a more complete picture of the genetic variation in a population or species. This approach will enable leveraging existing and new whole-genome sequencing data for genotyping and characterising SVs across a large number of individuals. Through pangenomic approaches, researchers have been able to detect and characterise previously unknown SVs that play a significant role in shaping phenotypic diversity (e.g. Li et al., 2023; Liao et al., 2023).

Pangenomes remain most prevalent in bacteria and plants, but there is an increasing effort to generate pangenomes in other organisms (Gong et al., 2023). Currently, the chicken (Rice et al., 2023; Wang et al., 2021) and the domestic duck (Wang et al., 2023) are the only avian model species with an available pangenome. This approach revealed new SVs associated with phenotypic traits, highlighting the power of using pangenomes to study the complex genomic basis of phenotypic diversity. Moreover, the publication of the first pangenome in a non-model avian species, the barn swallow (*Hirundo rustica*; Secomandi et al., 2023), demonstrates that advances in sequencing and bioinformatics are enabling the implementation of this approach in diverse organisms. The pangenomes themselves will also improve as larger numbers of individuals (and from different populations) are incorporated, leading to the increased detection of rare or population-specific variants.

8 | SVs/PHENOTYPE ASSOCIATIONS IN NON-MODEL BIRDS

Although genotype–phenotype associations have most commonly involved SNPs (Campagna & Toews, 2022), there are also examples of SVs which mediate traits in non-model birds. These studies show an improved understanding of the genetic bases of phenotypes when SVs, which involve a larger portion of the genome, are included (e.g. Delmore et al. 2023; Knief et al., 2019). For example, supergenes have been implicated in modifying complex behaviours in both model and non-model organisms. In the Common Quail (Sanchez-Donoso et al., 2022) a supergene is associated with changes in migratory behaviour; similarly, a supergene, likely a TE-related inversion, is also associated with migration in the Willow Warbler (*Phylloscopus trochilus*; Caballero-López et al., 2022; Lundberg et al., 2023). The same trait can be modified in multiple ways, as a 710-bp deletion on chromosome 27

in the Eurasian Blackcap (*Sylvia atricapilla*) also shapes migratory phenotypes (Delmore et al., 2023). Other complex behavioural traits are mediated by supergenes in the Ruff (*Philomachus pugnax*; Küpper et al., 2016) and the White-throated sparrow (*Zonotrichia albicollis*; Tuttle et al., 2016). In both cases, the inversion is associated with different male morphs and their mating strategies. In a phylogenetic context, He et al. (2021) studied the importance of duplications in generating variation at the major histocompatibility complex (MHC), loci that are central to shaping the immune response. Long-read sequencing allowed researchers to study the MHC, despite the highly repetitive nature of this region, across 34 birds that included both model and non-model species. This study shows an unprecedentedly high level of duplication in passerines, highlighting the need for long-read sequencing to characterise the genomic architecture of highly repetitive, yet phenotypically relevant, regions like the MHC.

LTR retrotransposon insertions can also shape phenotypic traits in non-model avian species in a manner similar to that seen in the chicken (Altgilbers et al., 2022) and the domestic duck (Wang et al., 2023). Plumage colouration differences in European crow populations are associated with a 2.25-kb LTR retrotransposon insertion (Weissensteiner et al., 2020). Additionally, Suh et al. (2018) using whole-genome resequencing data characterised ~12,000 polymorphic TE insertions in *Ficedula* flycatchers, with potential phenotypic effects that have been likely overlooked and still need to be determined. The implementation of emerging techniques to study SVs, such as performing GWAS analysis with SV genotypes and creating pangenomes, will contribute to developing our understanding of the significance of SVs in the evolutionary history of natural populations.

9 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Our comprehensive exploration of the SVs reported in avian model systems reveals a diverse landscape of genetic mechanisms influencing phenotypic traits. Non-coding regions, particularly introns, are commonly impacted by SVs, while SVs are less commonly identified within coding regions. The diverse genomic features affected by SVs emphasise the complex regulatory networks shaping phenotypic diversity. Different types of SVs, both in the same and in different genes, can result in the same phenotype across species, highlighting the possibility of phenotypic convergence through several genomic mechanisms. Moreover, the modification of the same gene in different ways can lead to a variety of phenotypes, underscoring the high flexibility of SVs and genes in contributing to phenotypic diversity. Complex rearrangements and supergenes usually result in diverse and pleiotropic phenotypic outcomes. The co-occurrence of SVs with other genetic variants, such as SNPs, emphasise the need for an integrative approach to unravel the genetic basis of phenotypic traits.

Despite the growing body of literature on avian SVs, there remain relatively few studies associating SVs with phenotypic traits, and most examples detect small variants (<50 bp) in chickens (Figure 1a,b). The number of identified links between SVs and phenotypes is likely influenced by the requirements of third-generation sequencing and robust analytical methods for long SV detection. With the increased affordability of long-read sequencing methods, the continuous improvement of bioinformatics to detect and characterise SVs, and the emergence of pangenomic approaches, we anticipate a shift in focus in the coming years. The current widespread emphasis on genetic variants identified from SNPs will likely be increasingly replaced by a more integrative approach that investigates different types of genetic variants and their interactions, incorporating the detection of SVs and the evaluation of their role in shaping phenotypic traits. Many studies have initially associated certain phenotypes to specific SNPs, yet the underlying reality might be more complex: unidentified SVs may actually be influencing these phenotypes, and uncovering these associations will provide a deeper understanding of such traits. Moreover, understanding the intricate relationship between TEs and the rest of SVs is crucial for comprehending the genetic basis underlying evolutionary processes. Further research is needed to elucidate the specific mechanisms by which TEs and other SVs interact, including the impact of TEs on other SV formation and the influence of SVs on TE behaviour. This will provide a better understanding of the functional significance of SV-TE interactions and their contributions to phenotypic diversity in various organisms, including avian model and non-model systems.

The adoption of an integrative approach that studies multiple forms of genetic variation holds great potential to clarify how different types of variants contribute and interact to generate the wide diversity of phenotypic traits observed in avian species. Avian model systems provide an opportunity to understand the roles of SVs and their interrelationships with, for example, SNPs and TEs (see Box 2). These systems can serve as a valuable resource to help disentangle the complex genetic mechanisms underlying phenotypic diversity, ultimately leading to a better understanding of gene regulation and expression. As the different techniques discussed in this review become more widely available, we anticipate a significant improvement in the detection and characterisation of SVs in both model and non-model avian systems. This enhanced characterisation is likely to reveal previously obscured associations between SVs and phenotypes, providing a more comprehensive understanding of the genomic basis of avian traits.

In chickens, SV occurs in both coding and non-coding regions of the genome and the presence of these variants is positively correlated with chromosome size (Zhang et al., 2022). Furthermore, due to SVs involving larger stretches of the genome compared to SNPs, they have the potential to significantly impact phenotype (Chiang et al., 2017; Zhang et al., 2021). SVs can affect gene expression through many mechanisms, including gene disruption, alteration of gene dosage, position effects, and disruption of gene expression at breakpoints (Wang et al., 2017). SVs can also directly affect genes leading to the production of non-functional proteins or causing failures/modifications in mRNA translation or expression. Gene dosage alterations occur due to CNVs which cause

BOX 2 Outstanding questions box.

- How do SVs contribute to the remarkable diversity of phenotypes observed in avian species, and what are the specific genetic mechanisms underlying this variation? Model species suggest SVs have a strong effect on phenotype and we expect the same to be true in non-model avian systems. Once the study and detection of SVs becomes more prevalent, these relationships are likely to be uncovered.
- What is the extent of structural variation in the avian genome, and how does it compare to other forms of genetic variation (e.g. SNPs), in terms of frequency and phenotypic impact? Do certain genomic regions consistently exhibit a higher propensity to accumulate SVs, taking into account factors such as recombination rate? Additionally, how do SVs interact with other sources of genetic variation, such as SNPs, TEs or regulatory elements, to shape complex phenotypic traits?
- What is the impact of TEs on other SV formation and how do SVs influence TE behaviour?
- Considering both model and non-model species, to what extent do SVs play a role in complex avian phenotypes, such as mating displays, vocalisations, or migratory patterns, and how do they influence social interactions and reproductive success?
- What are the evolutionary forces driving the maintenance or elimination of SVs in avian populations, and how do they contribute to the generation of genetic diversity?
- How can the insights gained from studying SVs in avian model systems be translated to improve conservation initiatives, breeding programmes and our understanding of the genetic basis of phenotypic traits in other avian species? Furthermore, what is the contribution of SVs to adaptations in avian populations, particularly in response to environmental changes such as habitat fragmentation and climate change? What is the relative contribution of SVs to mutational load?

changes in the number of gene copies, subsequently leading to modifications in gene expression. Gene expression could also be modified through position effects due to shifts in a gene's genomic location or changes in its surrounding chromatin environment that affect gene accessibility and expression. For instance, SVs are likely to alter the position of CREs, such as promoters and enhancers. Not only can the SVs impact gene expression, but also their breakpoints (the edges at the 5′ and 3′ ends of the SV) can affect the expression of nearby genes (Mérot et al., 2020; Spielmann et al., 2018; Zhang et al., 2021).

Glossary

Cis-regulatory elements (*CREs*): Non-coding DNA regions, including promoters, enhancers and silencers, that regulate the transcription of genes located in the same chromosome or neighbouring genomic region.

Ectopic Expression: Atypical expression of a gene in a cell type, tissue or developmental stage where it is normally inactive. This results from genetic or regulatory changes activating the gene in a novel context.

Enhancers: Sequences that can increase transcription by interacting with the transcription machinery and can be located either upstream, downstream or within the intronic regions of the gene.

Exon: Coding region of a gene that contains the instructions for producing a part of the final protein or functional RNA. Exons are interspersed with introns within a gene, and they are retained and joined together in the mature mRNA after splicing.

Gene expression: A dual process that involves transcription, where the gene's DNA sequence is copied into mRNA, and translation, where mRNA directs the assembly of amino acids into proteins.

Ty3 family Long Terminal Repeat (*LTR*) *Transposable Element*: A type of TE that belongs to the class of retrotransposons, possesses long terminal repeats (LTR) at both ends and can transpose within a genome via an RNA intermediate.

Intron: Non-coding regions of a gene between exons. During gene expression, introns are removed from the RNA transcript through RNA splicing.

Pangenome: A collection of representative DNA sequences from a species, including both the sequences shared among all individuals (core genome) and specific sequence information unique to subsets of individuals (variable genome).

Polygenic traits: Phenotypes that are influenced by multiple genes, each contributing a small effect, in combination with environmental factors.

Promoters: Sequences that provide a binding site for transcription factors and RNA polymerase, which initiate gene transcription and are usually located upstream of the gene's coding region.

Silencers: Sequences that can modulate the transcription process by binding to repressors, effectively preventing transcription and leading to lower gene expression.

Single-Nucleotide Polymorphism (*SNP*): Genetic variation that occurs at a single position in the DNA sequence, where only one nucleotide differs among individuals.

Supergene: Closely linked genes on a chromosome, inherited as a unit due to reduced recombination that results from being captured within an inversion. These genes often evolve together to control complex traits facilitating local adaptation.

Transcription factor (*TF*): A protein that regulates gene expression by binding to specific DNA sequences, such as promoters, enhancers or silencers and recruiting the transcription machinery.

Transposable Element (*TE*): TEs, also known as 'jumping genes', are DNA segments that can move within a genome. They can contribute

to genetic variability by causing mutations, influence gene regulation, and have significant evolutionary implications. They are a form of SV but can also contribute to the formation of more complex SVs.

AUTHOR CONTRIBUTIONS

MR conducted the literature review and was primarily responsible for drafting the manuscript. LC conceptualized the review, provided critical analysis of the literature, and contributed to writing and revising the manuscript. Both authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

No new data were generated from this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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