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Review

The influence of transposable elements on animal colouration

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Transposable elements (TEs) are mobile genetic sequences present within host genomes. TEs can contribute to the evolution of host traits, since transposition is mutagenic and TEs often contain host regulatory and protein coding sequences. We review cases where TEs influence animal colouration, reporting major patterns and outstanding questions. TE-induced colouration phenotypes typically arise via introduction of novel regulatory sequences and splice sites, affecting pigment cell development or pigment synthesis. We discuss if particular TE types may be more frequently involved in the evolution of colour variation in animals, given that examples involving long terminal repeat (LTR) elements appear to dominate. Currently, examples of TE-induced colouration phenotypes in animals mainly concern model and domesticated insect and mammal species. However, several influential recent examples, coupled with increases in genome sequencing, suggest cases reported from wild species will increase considerably.

Highlights

Increasing studies report an influence of transposable elements (TEs) on animal colouration. Current cases are dominated by mammals and insects, lab models, and domestic species.

Recent studies reveal an influence of TEs on colouration in wild species, associated with fitness benefits including increased reproductive success, decreased predation risk, and optimised resource allocation.

Most TE types influence animal colouration, but long terminal repeat/endogenous retrovirus elements are involved more often, potentially due to variation in insertion preferences or inclusion of regulatory sequences.

Common genetic mechanisms involve TE-mediated regulatory change in domestic and wild species and disrupted splicing in lab strains.

Accumulating genomic data will enable analyses across animal diversity, allowing testing of whether TEs are general contributors to the evolution of animal colouration and their importance relative to other forms of genetic variation.

TEs as contributors to the evolution of animal colouration

Colouration is a striking form of variation among animals and study of its underlying genetic bases and ecological and evolutionary significance are major research fields. An increasing number of studies, examining diverse animal lineages and colouration pathways, have recognised an influence of TEs on animal colouration (Figure 1, see Table S1 in the supplemental information online). TEs are selfish genetic elements that can mobilise and proliferate in host genomes (Box 1). While most TE insertions are detrimental to the host, TE sequences represent a major source of genetic variation that can be co-opted during host evolution [1,2]. However, to our knowledge, the specific relevance of TEs for animal colouration remains poorly considered. Consequently, the extent to which TEs contribute to the evolution of animal colouration, and the patterns and processes involved, are little described.

Here, we review the role of TEs in animal colouration, discussing outstanding questions, and examining emergent patterns. Given the recent proliferation of high-quality genome sequence data, and ongoing massive-scale sequencing initiatives [3,4], we anticipate substantial growth in studies reporting TE-induced influences on animal colouration. This offers great potential to improve understanding of the mechanisms by which TEs influence animal colouration and, ultimately, to elucidate their relative importance compared with other forms of genetic variation. We organise our review according to five major outstanding questions, discussed in turn later. (i) Are certain animal taxa more frequently affected by TE-induced changes in colouration? (ii) Are specific types of TE more frequently involved in animal colouration? (iii) Are TE-induced influences on animal colouration biased towards particular mechanisms of action? (iv) Are any animal colouration developmental stages or gene pathways more prone to contributions from TEs? (v) Do different forms of selection affect the influence of TEs on animal colouration? Animal colouration is primarily due to the reflection and absorption of light by structural features and chemical pigments [5,6].

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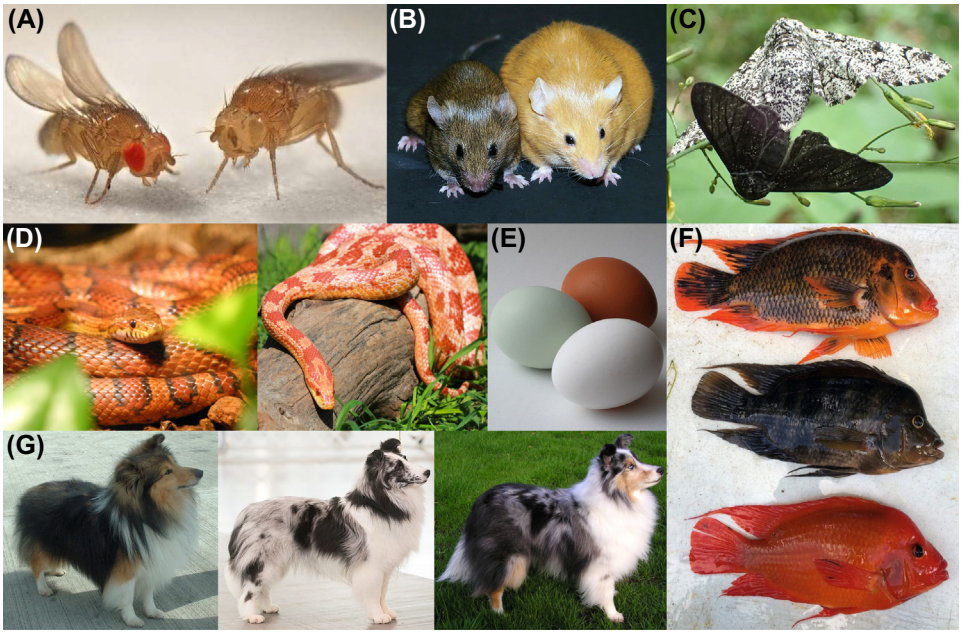


Figure 1. Examples of the influence of transposable elements (TEs) on animal colouration. (A) Wild type fruit fly eye colouration (left) versus TE-induced white mutant. (B) Wild type mouse colouration (left) versus TE-induced viable yellow mutant. (C) Wild type peppered moth (top) versus TE-induced *carbonaria* morph. (D) Wild type corn snake colouration (left) versus TE-induced amelanism. (E) White and brown chicken eggs versus TE-induced blue-shelled mutant (left). (F) Wild type Midas cichlid colouration versus TE-induced goldentouch mutant (bottom). (G) Standard Shetland sheepdog colouration (left) versus TE-induced 'Merle' or 'dapple' patterning. Figure credits: (A) Poli.mara (CC-BY-SA-4.0); (B) Randy Jirtle/Dana Dolinoy (CC-BY-3.0); (C) Siga (CC-BY-SA-4.0); (D) Mwx (Public Domain); Lietuvos zoologijos sodas (CC-BY-SA-4.0); (E) Gmoose1 (Public Domain); (F) U.S. Geological Survey (Public Domain); (G) Ellen Levy Finch (CC-BY-SA-3.0); Brad DoChara (CC-BY-SA-4.0); Sannse (CC-BY-SA-3.0).

Structural colouration involves the diffraction and scattering of light by complex nano- and micro-structures, producing iridescence, and a major drive to understand its genetics has only begun recently [7,8]. Thus, here we limit consideration to pigment-based colouration.

Animal taxa where colouration is affected by TEs

Reported cases where TEs influence animal colouration are currently restricted to vertebrates and insects, with most examples from mammals and flies (Figure 2A). Within these groups, there is a strong bias towards: (i) laboratory models, such as the laboratory mouse and *Drosophila* fruit flies; (ii) domesticated animals, including agriculturally important species, such as cattle, pigs, and chickens, and pets, such as cats and dogs (see Table S1 in the supplemental information online). In contrast, relatively few cases concern wild research models, with just three examples in vertebrates (wolves/dogs, haplochromine cichlid fish and heroine cichlid fish) and seven examples in insects (*Heliconius*, *Limenitis*, and *Colias* butterflies, the peppered moth, and three in *Drosophila*).

We do not anticipate that TE-induced influences on colouration are restricted to vertebrates and insects. Rather, we suggest that current cases are limited to these taxa due to historical study bias. Similarly, laboratory and domesticated species are foci of human attention. For example, most reported cases of TE-induced changes in laboratory species relate to novel colour mutations within a strain, where variants are likely to be detected and are obvious targets for research. Meanwhile, domesticated animals were often specifically selected for desirable novel colour patterns, resulting in a rich diversity of colouration among domesticated animal breeds [9].

Box 1. A brief overview of transposable elements (TEs) and their mutagenic properties

TEs are selfish genetic elements able to move location (transpose) within host genomes [87]. TEs comprise a large proportion of many animal genomes (e.g., 47% of the human genome [88], 20% of the *Drosophila melanogaster* genome [89], 16% of the chicken genome [90]). Self-replicating TEs are referred to as autonomous elements, whereas those that rely on the machinery of other TEs are referred to as non-autonomous elements. TEs are classified into two major groups according to their method of transposition: Class I elements mobilise via replicative 'copy-and-paste' mechanisms, whereby the TE is copied and the copy is inserted elsewhere; Class II elements are mobilised largely through 'cut-and-paste' mechanisms, whereby the TE is excised and re-inserted elsewhere (Figure I).

Class I TEs are divided into long terminal repeat (LTR) elements and non-LTR elements. LTR elements include LTR retrotransposons, endogenous retroviruses (ERVs), and *Dictyostelium* intermediate repeat sequences (DIRS), which transpose using enzymatic products from the polymerase gene (*pol*). Additionally, some LTR retrotransposons and ERVs possess an envelope gene (*env*), and DIRS possess a tyrosine recombinase gene (*YR*). Non-LTR elements include *Penelope*-like elements and long interspersed nuclear elements (LINEs), which transpose using enzymes encoded by their reverse transcriptase (*RT*) and endonuclease (*EN*) genes; and short interspersed nuclear elements (SINEs), which are non-autonomous elements that utilise LINE proteins for mobilisation, with a 5′ head derived from a tRNA or sRNA (red), and a 3′ tail derived from a LINE (black).

Class II elements are divided into four subclasses based on their method of mobilisation. DDE TEs and Crypton elements use DDE transposases or tyrosine recombinases (YR), respectively, to mobilise. Helitrons appear to replicate through a 'peel-and-paste' mechanism, excising one strand of DNA, which is inserted elsewhere. Structural similarities between Polintons and adenoviruses suggest that Polintons likely self-synthesise.

TE insertions can affect coding sequence, gene regulation, and genome structure. Most insertions are considered nearly neutral [91]. Some are more deleterious, directly disrupting coding or regulatory regions, leading to diseases including cancers [92]. A small fraction may provide host benefits, through mechanisms including donation of coding sequence, regulatory change, or facilitating genomic rearrangements [93].

Retrogenes are intronless gene copies formed via reverse transcription of mature mRNA by reverse transcribing TEs [26,93]. Retrogenes lack introns, but possess a poly-A tail and target site duplications formed during insertion. Though retrogenes are not TEs, they can also alter host gene function and contribute to host evolvability.

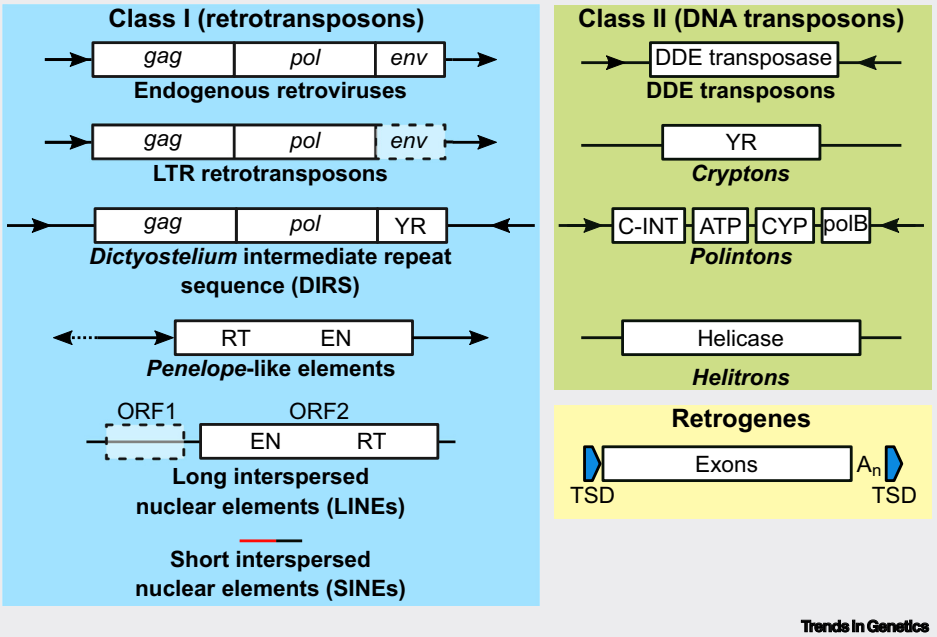
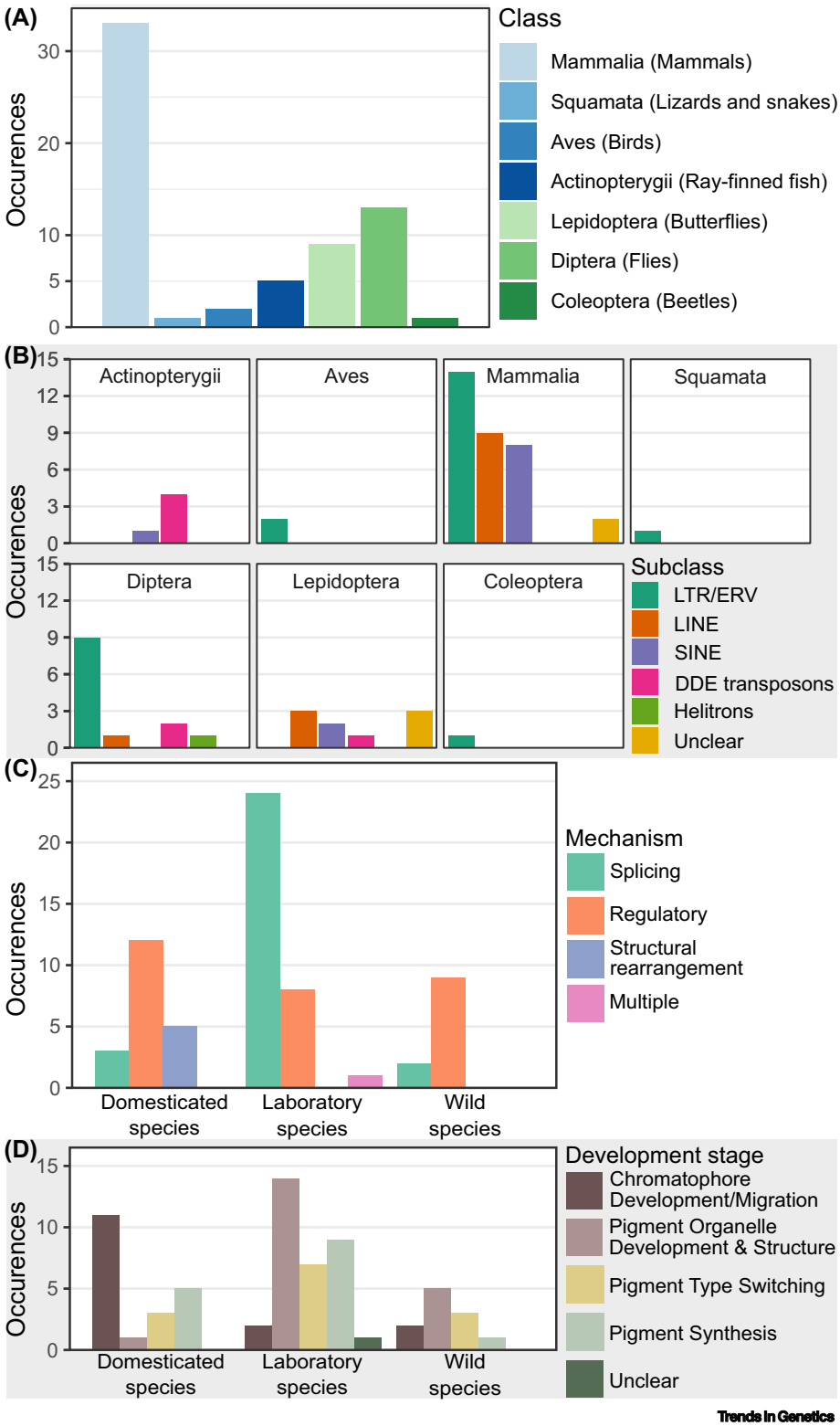


Figure I. The structure and classification of the major types of transposable elements, and the structure of retrogenes. Abbreviation: TSD, target site duplication.



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Studies describing TE-induced influences on colouration appear to show a temporal pattern: most laboratory cases were reported from the 1980s to the 2000s; most examples from domesticated species occur from 2010 onwards, while examples from wild species are largely restricted to the last 6 years. This apparent trend is likely due to the increasing influence of genome sequencing in facilitating detailed genetic studies on non-model species. Previously, focussed research on a small number of laboratory species enabled the early identification of TEs in these taxa. While, due to their agricultural and medical relevance, domesticated species were among the earliest non-model animals to have their genomes sequenced [10,11]. More recently, rapidly decreasing sequencing costs have allowed researchers to extend consideration to less studied domestic species [12,13], and wild species [14]. Thus, as increasing numbers of non-model animal genomes are sequenced, we predict many more cases of TE-induced influences on animal colouration will be identified across animal diversity.

Types of TE involved in animal colouration

Most major TE subtypes are reported to influence animal colouration (Figure 2B). However, LTR/endogenous retrovirus (ERV) elements appear to be over-represented compared with other TE subtypes. This is despite LTR/ERV elements constituting a relatively minor proportion of the repeat landscapes of mammalian genomes [2] (mammals display the majority of reported TE-induced colouration changes, Figure 2A). Instead, long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs) account for the greatest proportion of mammalian TE sequences and are the most active TEs in these genomes [2]. Nevertheless, LTR/ERV elements account for more reported cases than LINEs and SINEs combined (Figure 2B). For example, in the mouse genome, most reported TE insertions affecting colouration are ERVs, even though the genome contains a much greater proportion of active LINEs and SINEs [15]. This is consistent with a recent systematic review, which found that ERVs cause 82% of germline mutations observed in mice [16] and may partially arise due to preferential accumulation of different TE classes in contrasting regions of the mouse genome. For example, VL30 LTR retrotransposons preferentially insert into introns, 3′ gene flanks, and near transcription start sites [17], SINEs preferentially insert into GC-rich sequences, and LINEs preferentially insert into AT-rich sequences [18]. Another explanation is the number and diversity of enhancer elements frequently present within LTR/ERV elements, which can alter host gene regulation in complex ways, including modulating expression of specific splice variants and inducing tissue-specific expression patterns [19–21]. In Diptera, most reported instances of TE-induced influences on colouration involve LTR elements (invertebrates lack ERVs), but, unlike mammalian genomes, LTR elements are the dominant TE type in dipteran genomes [22,23].

LINEs, SINEs, and DDE elements also frequently influence animal colouration (Figure 2B). In the case of LINEs and SINEs, this is likely due to their dominance within mammalian genomes and their possession of regulatory sequences (although to a lesser extent than LTR/ERV elements [24]). However, while full-length LINEs contain internal regulatory sequences in their 5′

Figure 2. Summary of major taxonomic, mechanistic, and physiological patterns associated with transposable element (TE)-induced influences on animal colouration. (A) Distribution of TE-induced colouration changes across animal classes, with vertebrates depicted in blue and arthropods in green. (B) Occurrences of TE insertions influencing colouration in major clades of invertebrates and vertebrates split by TE subclass. We did not identify any reports of *Penelope*, *Crypton*, or *Polinton* elements altering animal colouration. (C) The mechanisms underlying examples of TE-induced colour change split according to domestic, laboratory, and wild animals. Compared with other mechanisms, a greater number of regulatory mutations underlie TE-induced colour change in both wild and domestic animals, while mutations causing aberrant splicing are much more frequent in lab animals. (D) The developmental stage at which TE insertions influence colour change, split according to domestic, laboratory, and wild animals. Abbreviations: ERV, endogenous retrovirus; LINE, long interspersed nuclear element; LTR, long terminal repeat; SINE, short interspersed nuclear element.

untranslated region (UTR), LINE insertions are frequently 5′ truncated due to poor processivity of their reverse transcriptase [2]. Consequently, most LINE insertions lack regulatory sequences. Meanwhile, in addition to reverse transcribing their own transcripts, LINEs (and other reverse transcribing TEs) sometimes reverse transcribe mature host mRNA, leading to the integration of retrogenes [25,26]. While not strictly TEs, retrogenes can also influence colouration, as reported in poodles [27]. DDE transposons are no longer active in most mammalian genomes [28] and do not account for any reported cases of TE-mediated effects on colouration in mammals, but are involved in other taxa (Figure 2B) [22,23].

Mechanisms by which TEs influence animal colouration

Three main mechanisms appear to underlie the influence of TEs on animal colouration (Box 2): (i) splicing effects leading to truncated proteins, via the introduction of premature stop codons, novel splice sites, exon skipping, and frameshifts; (ii) regulatory effects on gene expression, via the co-option of TE sequences as novel promoters and enhancers, or as a consequence of interference with existing regulatory elements; (iii) structural rearrangements, via the duplication of colouration genes through processes such as non-allelic homologous recombination (NAHR). The prevalence of these mechanisms varies among studies reporting TE-induced influences on colouration in wild, domesticated, and laboratory animals (Figure 2C). Specifically, most reported TE-induced colouration changes in wild and domesticated animals are due to influences on gene regulation, while those in laboratory animals are due to altered mRNA splicing (Figure 2C), with many insertions leading to truncated proteins (see Table S1 in the supplemental information online). A possible explanation may be that gene truncations more frequently lead to negative fitness consequences, which may be partially masked in highly artificial laboratory environments [29]. However, given the few reported instances, it remains unclear if this reflects a general pattern.

Variation in TE involvement among development stages and colouration pathways

The influence of TE insertions on colouration depends on the affected developmental stage and genetic pathway. A multitude of genetic pathways influence animal colouration at various stages of development, but most can be categorised into: (i) chromatophore differentiation and migration, (ii) pigment organelle development, (iii) pigment type switching, (iv) pigment synthesis within pigment organelles, and (v) intercellular pigment transfer (Box 3).

Box 2. Genetic mechanisms underlying changes in colouration

Transposable elements (TEs) alter the function of colouration genes in three main ways: (A) splicing effects, (B) regulatory effects, and (C) structural rearrangements (Figure I). Additionally, (D) reverse transcription of mature mRNA by reverse transcribing TEs leads to the formation of retrogenes, which can also alter the function of colouration genes. Figure I illustrates an example of each mechanism, with untranslated exons shown in blue, coding exons in light green, coding regions of nearby genes in dark green, and TEs in yellow. (A) In the *red egg* silkworm strain, an unspecified non-autonomous TE insertion in exon 9 of the *BGIBMGA003497-1* gene causes a frameshift, leading to exon skipping during splicing [94]. The translated protein lacks the transmembrane domain necessary for transporting precursor molecules used in the synthesis of the ommochrome pigment into the pigment granules. (B) Compared with *agouti* dogs and wild type grey wolves, *dominant yellow* and *shaded yellow* dogs and wolves have a novel SINE insertion upstream of the ventral hair promotor of *ASIP*, and *dominant yellow* have an additional SINE insertion upstream of the hair cycle promoter (HCP) [40]. These SINE insertions increase expression of the ventral and hair cycle *ASIP* transcript variants, leading to *dominant yellow* dogs and wolves having completely red/yellow/white coats, and *shaded yellow* dogs and wolves having lighter coats compared with the darker coats of *agouti* dogs and wild type grey wolves [40]. (C) A silencing mutation within the *ASIP* promoter of Merino sheep prevents *ASIP* expression in sheep with a single copy of the gene. Non-allelic homologous recombination (NAHR) between two SINE insertions, upstream of the coding exons of *ASIP* and *ITCH*, respectively, commonly leads to a ~190 kb tandem duplication [42]. The resultant fusion of the *ITCH* promoter and *ASIP* coding region in Merino sheep with this duplication promotes expression of *ASIP*, leading to white wool. The various *ITCH-ASIP* fusion transcript variants each contain noncoding exons from *ITCH* (It and It') in addition to *ASIP* noncoding and coding exons. (D) A retrocopy of *SNN* is present 2.8 kbp upstream of *GPR22* in red and apricot poodles [27]. *SNNL1* disrupts the regulation of *GPR22* regulation in skin tissue, leading to darker coats compared with the standard white coat.

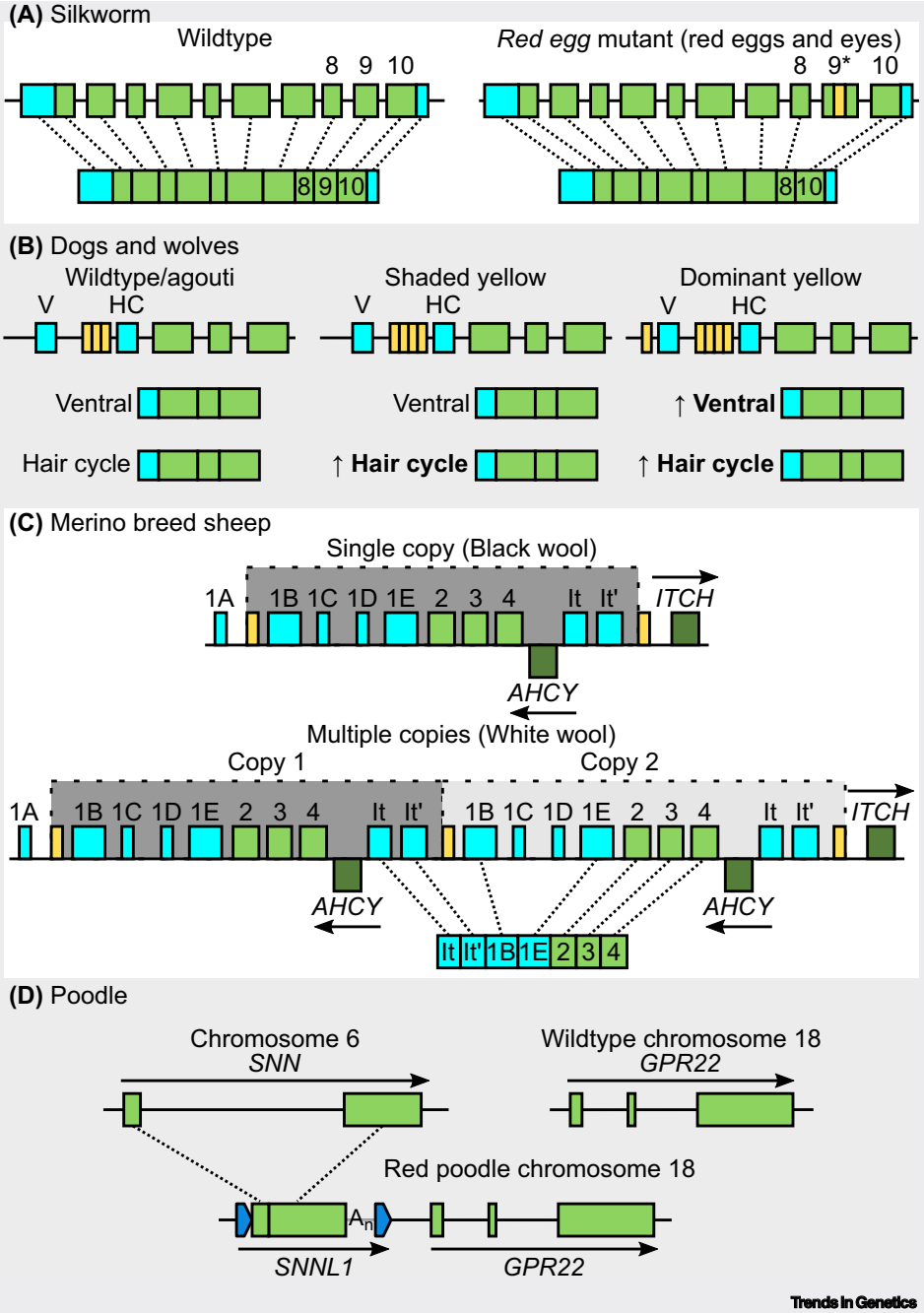

Figure I. Schematic of genetic mechanisms by which transposable elements and retrogenes alter colouration.

Chromatophore development and migration

TE insertions that disrupt chromatophore (pigment producing cells) development and/or migration, limit, or even prevent, pigment production due to the reduction or absence of mature chromatophores. For example, in mammals, KIT and MITF are key proteins involved in melanocyte (melanin-producing cell) differentiation from neural crest cells and their migration to the epidermis

and hair follicles [30,31]. Cases where TE insertions affect *KIT* and *MITF* genes cause a patchy distribution or complete lack of melanocytes in the epidermis and hair follicles, resulting in patchy or complete loss of pigmentation [21,32–35]. However, outside of domesticated species, reports of this class of mutation are uncommon (Figure 2D).

Pigment organelle development and function within mature chromatophores

Reports of TE insertions that disrupt the development and function of pigment organelles within chromatophores are more frequent than those that disrupt chromatophore development and/or migration (Figure 2D). These either alter pigment organelle structure or truncate transmembrane proteins. Two examples of TE-induced mutations that significantly alter melanosome (melanin-synthesising organelles) shape occur in mice, limiting melanosome trafficking within melanocytes [36,37]. Meanwhile, TE-induced transmembrane protein mutations can limit the trafficking of pigment precursors into pigment granules [38], or prevent maintenance of suitable pH for pigment synthesis [39].

Pigment type switching

Many reported TE insertions cause pigment type switching (a change in the type of pigment produced). For example, mammals produce two types of melanin, yellow/red pheomelanin and

Box 3. The influence of transposable element (TE) insertions on colouration over multiple developmental stages

Most TE-induced colour changes in vertebrates are due to disruptions to one of four pathways: chromatophore development and migration; pigment organelle development within mature chromatophores; pigment type switching; and cellular production and transport of enzymes/precursor molecules for pigment synthesis. We discuss these next using examples from mice and medaka (Figure I).

Chromatophore development and migration

Disruptions to chromatophore development and/or migration during embryogenesis lead to patchy or complete colour loss. For example, the mouse piebald mutation (*s*) is caused by an ETn LTR retrotransposon insertion into *EDNRB* intron 1. A splice acceptor site and stop codon in the retrotransposon can cause truncation of *EDNRB*, resulting in lower abundance of the standard *EDNRB* transcript variant in piebald (*s/s*) mice embryos, disrupting melanocyte development and causing patchy epidermal melanocyte distribution [95]. Similarly, the black-eyed white mutation results from a LINE L1 insertion into *MITF* intron 3 interfering with the melanocyte-specific promoter. Lack of melanocyte-specific MITF prevents melanocytes from developing and migrating, leading to lack of pigmentation [21].

Pigment organelle development

TE insertions may affect pigment-synthesising organelles within chromatophores, altering the number or structure of pigment organelles. An example in mice is the beige phenotype, caused by LINE L1 insertion into *LYST* intron 25. The LINE L1 insertion contains a stop codon and two splice donors, leading to two abnormal splice variants, both containing premature stop codons. The truncated LYST protein causes abnormally large melanosomes, limiting trafficking from melanocytes to keratinocytes in skin/fur [96].

Pigment type switching

TE insertions can alter colouration through switches in synthesised pigment type. For example, the murine *hypervariable yellow* mutation results from an ERV insertion into *ASIP* noncoding exon 1C. A sequence within the ERV acts as a novel methylation-dependent promoter, with the type of melanin produced dependent on its methylation. Higher methylation lowers *ASIP* expression, leading to increased eumelanin production and darker brown-black skin/fur, while lower methylation increases *ASIP* expression, leading to increased pheomelanin production and lighter yellow skin/fur [19].

Pigment synthesis

Several TE mutations directly affect pigment synthesis pathways, for example, by preventing the production of enzymes that modify precursor molecules. Albinism in the i^{1} medaka mutant results from a DDE transposon insertion into tyrosinase exon 1, introducing a stop codon [48]. Tyrosinase is a key enzyme at several stages in melanin synthesis from tyrosine. As truncated tyrosinase cannot its perform enzymatic function, i^{1} medaka are unable to synthesise melanin.

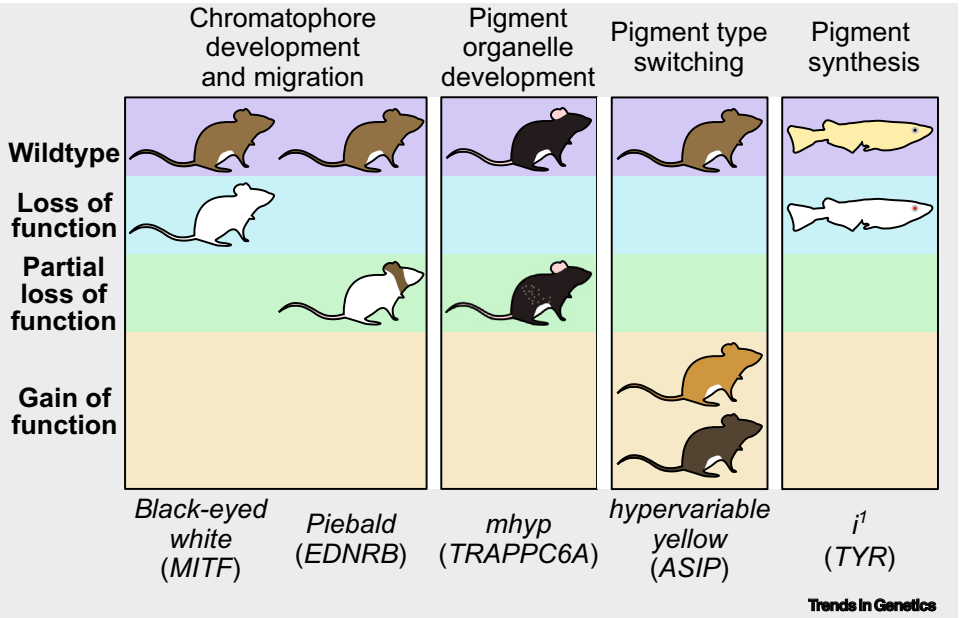

Figure I. Examples of how transposable elements alter colouration gene function at different developmental stages.

brown/black eumelanin, dependent on the binding of agouti signalling protein (ASIP) to the Melanocortin 1 receptor (MC1R). Almost half of reported TE-induced colour variants identified in mammals are due to mutations that alter either the expression level or coding sequence of *ASIP* [19,20,40–47]. TE insertions that increase *ASIP* expression cause higher levels of pheomelanin to be synthesised compared with wild type and hence skin/fur to be lighter; while those that decrease expression or result in aberrant transcripts lead to higher expression of eumelanin and darker skin/fur.

Pigment synthesis

There are multiple examples of TEs directly disrupting pigment synthesis, mostly due to impacts on pigment synthesis enzymes (see Table S1 in the supplemental information online). For example, a DDE transposon insertion into exon 1 of *tyrosinase* (*TYR*) in albino medaka fish acts as a premature stop codon [48]. During melanin synthesis, tyrosinase catalyses the oxidation of tyrosine to DOPA and DOPA to DOPAquinone [49]. Aberrant tyrosinase cannot performoxidation, preventing melanin synthesis (Figure 2D). Other TE-induced mutations directly impact splicing or expression of genes encoding enzymes utilised in the synthesis of pigments from precursor molecules, including tyrosinase in chicken [50,51] and medaka fish, [52], and tyrosine hydroxylase and aspartate decarboxylase in silkworm [53,54].

Intercellular pigment transfer

Pigments are often trafficked from chromatophores to other cell types. For example, in mammals and birds, melanin is transferred from melanocytes to keratinocytes in skin and fur and feather follicles [55,56]. No examples of TEs influencing pigment transfer between cells were identified. However, this may be due to poor understanding of the molecular mechanisms underlying pigment trafficking [56,57].

Do certain forms of selection favour TE-induced influences on colouration?

Reported cases of TE-induced change in animal colouration are strongly biased towards domesticated species and model laboratory species (Figure 2C). Both groups have a history of maintenance under artificial selection. In domesticated species, TE-induced influences on colouration have largely arisen following domestication and were often selected by humans as desirable new colour phenotypes. Similarly, reported cases in laboratory models generally originated in inbred laboratory lineages maintained under artificial selection. Considering the lower frequency of cases in wild species, an emergent question is whether TE-induced influences on animal colouration: (i) occur more rarely in wild species, (ii) are less likely to be maintained under natural selection, or (iii) are simply less well studied in wild species? Arguments presented earlier suggest that (iii) is partially responsible for this pattern, while we discuss (i) and (ii) later.

Do TE-induced influences on animal colouration occur less frequently in wild species?

Several population and genetic factors may interact to determine the likelihood of novel TE-induced insertions affecting colouration, including: (i) the number and type of active TEs present in a genome, (ii) genome size and compactness, (iii) the number and complexity of colouration loci, and (iv) host population size and structure. These factors vary greatly among taxa, both wild and captive, and it is unlikely that they underlie the lower number of cases reported in wild species.

Artificial environments differ considerably from natural environments and likely exert various stressors on captive wild species, at least during early stages of adaptation to captivity [58]. The influence of host stress on TE activity remains contentious, but evidence suggests that stress can affect host TE-repression mechanisms, resulting in increased TE activity [59]. However, environmental stressors, such as temperature, and exposure to pathogens and xenobiotics, also operate in wild environments. Horizontal transposon transfer (HTT) can introduce TEs into naive host genomic backgrounds, resulting in bursts of activity in new hosts [60,61]. Artificial environments frequently bring new combinations of species together, potentially facilitating HTT. However, HTT also occurs in the wild via natural processes such as introgressive hybridisation and host–parasite interactions [62,63].

Are TE-induced influences on animal colouration less likely to be maintained?

Under natural conditions, novel TE-induced colouration changes may be lost due to drift, or actively purged via natural selection. For example, changes in colouration may have negative fitness consequences if they elevate the likelihood of predation [64], or aggression from conspecifics [65]. Meanwhile, under artificial conditions, animal breeders/researchers often selectively maintain novel mutations. Thus, due to human interest in novel colouration patterns, artificial selection may favour the maintenance of TE-induced colouration changes. Nevertheless, we note that TE-induced changes in colouration can result in fitness benefits and be maintained under natural selection. Examples of TE-induced colouration change maintained under natural selection are currently most frequent in Lepidoptera (Box 4), while we identified two cases in fish and one in wolves/dogs, which are discussed later.

Two examples of fitness benefits arising from the influence of TEs on colouration under natural selection concern cichlid fishes. In the heroine Midas cichlid a *piggyBac* DDE transposon insertion induces a golden morph through a proposed regulatory mutation, apparently beneficial in avoiding bird predation in clear water compared with the black morph, but detrimental in avoiding fish predation in murky water [66]. Meanwhile in haplochromine cichlids, a SINE insertion acts as a tissue-specific enhancer for the expression of egg spots on the anal fins of male fish, whereby increased expression of *fhl2b* leads to increased egg spot pigmentation [67]. Egg spots are present on the anal fins of ~1500 haplochromine cichlid species and while their exact benefit is debated and may vary between species, studies suggest a sexual selection advantage [68].

Box 4. TE-induced colouration change maintained under natural selection in Lepidoptera

Two colour morphs are stable in *Colias* (clouded sulphur) butterflies: yellow/orange and white Alba [97]. During pupation, Alba morphs redirect resources from expensive wing pigment granules to developmental processes, increasing fecundity while decreasing pupal maturation time [97]. Alba morphs are more successful in cold and resource-poor conditions [72]. However, coloured morphs are maintained, since the yellow/orange wings of females are important mate recognition cues, resulting in mating bias against white females, despite their increased reproductive fitness [72]. The mechanism underlying colour polymorphism in *Colias crocea* (clouded yellow) is a *Jockey*-like LINE retrotransposon insertion downstream of homeobox transcription factor *BarH-1*, switching on *BarH-1* expression, suppressing pigment granule formation, and dramatically decreasing wing pteridine pigment synthesis [72]. Consequently, here a TE insertion apparently underlies evolution of a complex trait involved in an ecologically relevant alternative life-history strategy. Other efforts to elucidate the genetic bases of alternative life history strategies have implicated supergenes [98,99]. The extent to which TEs are involved in such cases is unclear, but facilitating NAHR represents one potential influence. For example, region 3 of the BC supergene, which underlies warning-colouration variation in the African monarch butterfly (*Danaus chrysippus*), shows elevated TE content, which may have facilitated accumulation of segmental duplications in the region [100].

In several lineages of *Heliconius*, a yellow-barred hindwing phenotype acts as warning colouration, signalling toxicity to potential predators [101]. The yellow-bar appears to occur due to disruption of a *cortex* gene enhancer by a *Helitron*-like TE, with evidence that the mutation has spread among co-mimetic morphs via adaptive introgression [73]. Meanwhile, in the mimetic red-spotted purple (*Limenitis arthemis astyanax*), a LINE insertion in the first intron of the signalling ligand gene *WntA* may underlie differential expression of a *WntA* 5′-UTR sequence during late larval development, leading to white wing band loss.

The black *carbonaria* form of the peppered moth (*Biston betularia*) became dominant over the pale *typica* form during the industrial revolution [102]. The *carbonaria* form arises due to regulatory change at the *cortex* gene, resulting from a DDE TE insertion in its first intron [71]. The specific mechanism by which the TE increases melanisation remains unclear, but it apparently increases expression of specific *cortex* isoforms during rapid wing disc morphogenesis during prepupation [71]. This case suggests TEs may be involved in the origin of melanic morphs that have increased in abundance during industrialisation in many other moth species [103].

A complex example of TEs altering colouration to provide both a fitness benefit in a wild species and a desirable trait in a domesticate occurs in grey wolves and domestic dogs [40]. Compared with the *agouti* coat pattern typical of North American and Eurasian wolves, Arctic wolves have fully white coats, due to SINE insertions in the ventral promoter (VP) and hair cycle promoter (HCP) of *ASIP*, increasing expression of each transcript and the resultant production of pheomelanin across the entire coat (see Figure IB in Box 2). Some North American, Eurasian, and Arctic wolves carry the SINE insertion in HCP, but lack the insertion in VP, leading to elevated expression of only the hair cycle transcript. These wolves have lighter coats compared with the *agouti* phenotype, but noticeably darker coats than Arctic wolves. The high prevalence of white coats in Arctic wolves, but near and complete absence from North American and Eurasian wolves, respectively, indicates strong natural selection to optimise coat patterning according to habitat. The same TE insertions are present in many domestic dog breeds and are responsible for dominant yellow and shaded yellow coat patterns [40].

Collectively, reported cases demonstrate that TE-induced influences on colouration can be maintained under natural selection. Even if such influences are less frequent than under artificial selection, given the small fraction of laboratory and domesticated species compared with wild species, we anticipate considerable increases in the identification of cases in wild species over coming years. Additionally, we note that for most examples under natural selection, rather than the novel TE-induced colour variant going to fixation, alternative morphs are retained. This may suggest that the often-pronounced colouration mutations arising from the action of TEs are typically beneficial only under certain ecological conditions. Additionally, in situations involving maintenance of multiple colour morphs, it is possible that the identity of co-opted TEs may differ among host populations (or sets of related species), depending on the specific effect of the TE on colouration and the optimum phenotype favoured by natural selection at each location. Interrogating such patterns may reveal fundamental mechanistic insights into major outstanding

questions, such as the molecular bases underlying the repeatability of evolution, and so influence our capacity to infer its predictability.

Concluding remarks

Considering the huge variation in colouration across animal diversity, relatively few reported examples of the involvement of TEs currently exist. However, rather than indicating a limited influence of TEs on animal colouration, we suggest this reflects the comparative paucity of studies that have thoroughly dissected the genetic bases of animal colouration, particularly in wild species. Thus, as genomic resources accumulate, and as further studies determine the detailed genetic mechanisms underlying animal colouration, we anticipate many additional reports supporting a role for TEs in the generation of novel colour phenotypes in animals.

Currently, mammals and insects dominate reported cases, likely due to the over-representation of these taxa among domesticated and laboratory species. Meanwhile, very few cases of the influence of TEs on colouration are known in several diverse clades of highly visual animals that display great colour variation. For example, reported cases in birds and reptiles are limited to the chicken and cornsnake [39,50,69]. Similarly, cases are reported from just three fish genera [48,52,67,70] and five lepidopteran genera [53,54,71–74], which also represent highly speciose clades, famous for their vibrant colouration.

Reports suggest that most TEs can influence animal colouration. However, LTR/ERV elements appear to play a more frequent role. This may be due to their relative richness in host regulatory elements, or because of differences in insertion preferences among TEs [75]. Testing these patterns and their underlying mechanisms are key directions for future research. TEs can alter colouration via varied mechanisms and act on diverse colouration pathways and stages. Meanwhile, TE-induced changes in animal colouration can also affect additional phenotypic aspects, including causing deafness in the Japanese house mouse black-eyed white mutation [21], modifying scale morphology in the *Heliconius* yellow-bar mutation, and initiating vacuolation of the central nervous system in the Syrian hamster black tremor mutation [76].

Certain ecological situations may be more likely to yield cases of TE-induced colouration polymorphism and species with ranges encompassing pronounced climatic or other environmental clines may be particularly promising candidates for consideration. Many animals display intraspecific differences in colouration as adaptations to novel environments [77,78], or seasonal responses to major environmental changes (e.g., snowfall [79], day length [80]). While many such colour variants likely arise due to changes in gene expression, the precise underlying mechanisms remain to be determined in most cases. Since TEs are frequently co-opted as species-specific regulatory elements such as transcription factor binding sites [81], further investigation is likely to reveal additional TE involvement.

While we identify just two cases in which TEs are responsible for colour variants through enabling NAHR [32,42], multiple recent studies have identified copy number variants (CNVs) arising through NAHR to be the cause of coat colour phenotypes. However, most do not investigate how the CNVs occurred, by considering translocation enabling sequences at the breakpoints [82–85]. A more complex example of TE-enabled duplications affecting colouration is reported from Belgian Blue and Brown Swiss cattle, whereby serial interchromosomal translocations through circular intermediates enabled by TEs led to the lineback phenotype [86]. Thus, going forward we encourage authors to investigate breakpoints of both simple and complex structural rearrangements for evidence of enablement by TEs.

Outstanding questions

As whole genome assemblies of an increasingly diverse range of animal species become available, will current patterns in the taxa affected by TE-induced influences on colouration remain, or will other patterns become apparent?

Will the current trend of LTR/ERV elements being most frequently involved in cases of TE-induced influences on colouration persist once more species are analysed and, if so, why? What genetic mechanisms underlie biases in the influence of certain TE types on colouration? Are certain TE-borne regulatory elements more frequently co-opted than others, or is variation in insertion preferences more relevant?

Will current mechanistic biases involved in TE-induced influences on animal colouration be upheld across a larger sample size? Specifically, are TEs more frequently involved in colouration mutations affecting gene regulatory change in domesticated and wild animals, while those occurring in laboratory strains are more likely to involve modified RNA splicing? And if so, is this due to the relaxation of negative fitness effects in laboratory environments, such as masking of negative pleiotropy, or other factors?

Do TE-induced influences on colouration maintained under natural selection typically exist as alternative morphs that convey fitness benefits only under certain ecological conditions and, if so, why? In cases of colouration polymorphism involving TEs, is it more common that similar TEs are co-opted at similar positions in colouration loci among separate populations/related species, or are different TEs and mechanisms involved, according to their particular influence on colouration and associated selective benefits in different host lineages?

Will increased understanding of the genetic bases of structural colouration reveal similar patterns concerning the role of TEs to those observed for pigment-based colouration?

To what extent are TEs important general contributors to the evolution of novel colouration phenotypes in

animals, and what are their relative contributions compared with other forms of genetic variation?

Notably, none of the reported studies identifying TEs in colouration change set out to explicitly investigate their role. Meanwhile, species where TEs are reported to influence animal colouration typically represent intensively studied model systems, where the colouration differences involved were striking. Thus, targeted bioinformatic exploration of organisms that display colour variation will likely provide a rich source of further examples. Additionally, current large-scale efforts to sequence the earth's biodiversity [3,4] combined with decreases in the cost of computing time, offer exciting new opportunities to screen for the involvement of TEs in colouration pathways, *en masse*, across large swathes of animal diversity, instead of directing efforts at single species. Data arising from such studies will facilitate interrogation of the detailed evolutionary patterns and processes associated with the involvement of TEs in animal colouration within a comparative framework (see Outstanding questions). Ultimately, this will enable evaluation of the extent to which TEs are important general contributors to the evolution and diversity of animal colouration and their relative significance compared with other forms of genetic diversity.

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Declaration of interests

The authors have no conflicts of interest to declare.

Supplemental information

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