Eukaryote hybrid genomes

Anna Runemark¹*, Mario Vallejo-Marin², Joana I. Meier³⁴

¹ Department of Biology, Lund University, Lund, Sweden, ² Biological and Environmental Sciences, University of Stirling, Stirling, Scotland, United Kingdom, ³ St John’s College, Cambridge, Cambridge, United Kingdom, ⁴ Department of Zoology, University of Cambridge, Cambridge, United Kingdom

* Anna.Runemark@biol.lu.se

Abstract

Interspecific hybridization is the process where closely related species mate and produce offspring with admixed genomes. The genomic revolution has shown that hybridization is common, and that it may represent an important source of novel variation. Although most interspecific hybrids are sterile or less fit than their parents, some may survive and reproduce, enabling the transfer of adaptive variants across the species boundary, and even result in the formation of novel evolutionary lineages. There are two main variants of hybrid species genomes: allopolyploid, which have one full chromosome set from each parent species, and homoploid, which are a mosaic of the parent species genomes with no increase in chromosome number. The establishment of hybrid species requires the development of reproductive isolation against parental species. Allopolyploid species often have strong intrinsic reproductive barriers due to differences in chromosome number, and homoploid hybrids can become reproductively isolated from the parent species through assortment of genetic incompatibilities. However, both types of hybrids can become further reproductively isolated, gaining extrinsic isolation barriers, by exploiting novel ecological niches, relative to their parents. Hybrids represent the merging of divergent genomes and thus face problems arising from incompatible combinations of genes. Thus hybrid genomes are highly dynamic and undergo rapid evolutionary change, including genome stabilization in which selection against incompatible combinations results in fixation of compatible ancestry block combinations within the hybrid species. The potential for rapid adaptation or speciation makes hybrid genomes a particularly exciting subject of evolutionary biology. Here we summarize how introgressed alleles or hybrid species can establish and how the resulting hybrid genomes evolve.

Background

Genetic exchange between species can impede the evolution of biodiversity because gene flow between diverging species can lead to loss of genetic adaptations or species fusion[1]. Traditionally, zoologists have viewed interspecific hybridization as maladaptive behaviour[2] which can result in breaking up co-adapted gene complexes[3]. In contrast, plant biologists recognized early on that hybridization can sometimes be an important evolutionary force, contributing to
increasing biodiversity[4][5]. Recently, evidence has been accumulating showing that hybridization is also an important evolutionary process in animals[1][6][7]. Interspecific hybridization can enrich the genetic diversity of introgressed taxa, lead to introgression of beneficial genetic variation or even generate new hybrid species[1]. Hybridization is now also known to contribute to the evolutionary potential in several textbook examples of adaptive radiation, including the *Geospiza* Galapagos finches[8], African cichlid fishes[9], *Heliconius* butterflies[10][11][12] and Hawaiian *Madiinae* tarweeds and silverswords[13]. Here we review the evolutionary outcomes of interspecific hybridization and the properties of genomes of hybrid genomes. Many of the discussed topics also apply to hybridization between different subspecies or populations of the same species, but here we focus on interspecific hybridization (referred to as hybridization in this review).

**Evolutionary outcomes of hybridization**

There are several potential evolutionary outcomes of hybridization (Fig 1). If early generation hybrids are not viable or sterile, hybridization may reduce the reproductive success of the parent species[14][15]. This could potentially lead to reinforcement, selection to strengthen premating isolation[16] or if the species fail to evolve premating isolation, it could increase their extinction risk due to wasted reproductive effort[14]. If the fitness of early generation hybrids is non-zero and that of some later generation hybrids is as high or even higher than the fitness of one or both parent taxa, hybrids may displace the parent taxa and the hybridizing taxa may fuse (speciation reversal[17][18], Fig 1). If the fitness of early generation hybrids is reduced

![Fig 1. Potential evolutionary outcomes of hybridization.](https://doi.org/10.1371/journal.pgen.1008404.g001)
but non-zero, hybrid zones may emerge in the contact zone of the taxa[19]. If hybrids are fertile, hybridization may contribute novel variation through rare hybrids backcrossing with parental species. Such introgressive hybridization may enable neutral or selectively beneficial alleles to be transferred across species boundaries even in species pairs that remain distinct despite occasional gene flow[20][21]. Hybrid fitness may vary with divergence time between the hybridizing taxa. This pattern has been shown for a variety of taxa including *Drosophila*, birds[23] and fish[24]. Hybrid fitness may also differ with cross direction[25], between first generation and later generation hybrids[26], and among individuals within generations of the same cross-type[27][28]. In some cases hybrids may evolve into new hybrid species with reproductive isolation to both parent taxa[29][30]. Below we describe the evolutionary outcomes of hybridisation that result in persistent hybrid genomes.

**Adaptive introgression**

When rare hybrids backcross with parent species alleles coding for traits that are beneficial for both parental species can be transferred across species boundaries, even if parent species remain distinct taxa. This process is referred to as adaptive introgression (a somewhat misleading term because backcrossing itself may not be adaptive, but some of the introgressed variants may be beneficial[1]). Simulations suggest that adaptive introgression is possible unless hybrid fitness is substantially reduced[31][32], or the adaptive loci are tightly linked to deleterious ones[33]. Examples of adaptive traits that have been transferred via introgression include an insecticide resistance gene that was transferred from *Anopheles gambiae* to *A. coluzzii*[21] and the red warning wing colouration trait in *Heliconius* butterflies that is under natural selection from predators and introgressed from *H. melpomene* to *H. timareta* [34] and other *Heliconius* species[20]. In the plant *Arabidopsis arenosa* some of the alleles conferring adaptation to drought and phytotoxic levels of metal have introgressed from *A. lyrata*[35]. Even in humans there is evidence for adaptive introgression of e.g. immunity alleles, skin pigmentation alleles and alleles conferring adaptation to high altitude environments from Neanderthal and Denisovans[36]. If traits important for species recognition or reproductive isolation introgress into a population of another species, the introgressed population may become reproductively isolated against other populations of the same species. Examples of this include *Heliconius* butterflies, where selective introgression of wing pattern genes between diverged lineages occurs (see e.g.[37]), and wing patterns contribute to reproductive isolation in some species pairs with low (e.g. between *H. t. florencia* and *H. t. linearesi*) and intermediate levels (e.g. *H. c. galanthus/H. pachinus*) of divergence[38]. See also Box 1.

**Box 1. Detecting and studying hybridization with genomic tools**

Many empirical case studies start with exploratory detection of putative hybrid taxa or individuals with genomic clustering approaches, such as STRUCTURE[142], ADMIXTURE[143] or fineSTRUCTURE[144]. These methods infer a user-specified number of genetic groups from the data and assign each individual to one or a mix of these groups. They can be applied to closely related taxa without having to preassign individuals to taxa and may thus be particularly useful in the study of closely related taxa or species complexes. However, uneven sampling of the parental taxa or different amounts of drift in the included taxa may lead to erroneous conclusions about evidence for hybridization[145]. If genomic data of multiple species is available, phylogenetic methods may be
better suited to identify introgression. Introgessive hybridization leads to gene trees that are discordant from the species tree, whereby introgressed individuals are phylogenetically closer to the source of introgression than to their non-introgressed conspecifics. Such discordant gene trees can also arise by chance through incomplete lineage sorting, particularly if the species compared are still young. Therefore, discordant gene trees are only evidence of introgression if a gene tree produced by excess allele sharing between the hybridizing taxa is strongly overrepresented compared to alternative discordant gene trees. An entire suite of methods have been developed to detect such excess allele sharing between hybridizing taxa, including Patterson’s D statistics or ABBA-BABA tests[146] [147][148] or f-statistics[149][150]. Modified versions of these tests can be used to infer introgressed genomic regions[151], the direction of gene flow[152][153] or the amount of gene flow[150]. For datasets with a large number of taxa it may be difficult to compute all possible test of hybridization. In such cases, graph construction methods may be better suited[154][155][156]. These methods reconstruct complex phylogenetic models with hybridization that best fit the genetic relationships among the sampled taxa and provide estimates for drift and introgression. Other phylogenetic network methods that account for incomplete lineage sorting and hybridization may also help[157][158]. Methods based on linkage disequilibrium decay or methods inferring ancestry tracts can be used to date recent admixture or introgression events as over time ancestry tracts are continuously broken down by recombination[155][159][160][161][162]. With increasing genome stabilization, individuals should vary less in local ancestry. Levels of genome stabilization can thus be assessed by computing the ancestry proportions (e.g. with \( f_d[151] \)) in genomic windows and testing if these correlate across individuals. Additionally, if hybridization is still ongoing, ancestry proportions should vary across individuals and in space. A different approach is to use demographic modelling to find the simplification of the evolutionary history of the studied taxa[163]. Demographic modelling should only be applied to small sets of taxa because with increasing number of taxa model complexity increases and the number of model parameters such as timing, amounts and direction of gene flow, and population sizes and split times can quickly become too high. The fit of the demographic models to the data can be assessed with the site frequency spectrum[164][165] or with summary statistics in an Approximate Bayesian Computation framework[166]. It is also possible to gain more power by combining information from linkage disequilibrium decay patterns and the allele frequency spectrum[167].

What is a hybrid species?

One of the potential evolutionary outcomes of hybridisation is the establishment of a novel, reproductively isolated lineage, i.e., hybrid speciation[1][29]. A hybrid species has an admixed genome and forms stable genetically distinct populations[29]. Some researchers argue that evidence of a hybridization-derived basis for reproductive isolation should be an additional defining criterion for hybrid speciation[39] but see[40]. This stricter definition includes polyploid hybrid taxa but only encompasses a handful of well studied cases of homoploid hybrid speciation, e.g. *Heliconius heurippa*[10][11][12], *Passer italiae*[28], and three *Helianthus* sunflower species[41] because for most suggested examples of homoploid hybrid speciation, the genetic basis of reproductive isolation is still unknown[39].
Hybrid species can occupy an ecological niche different to those of the parents and may be isolated from the parent species primarily through pre-mating barriers (hybrid speciation with external barriers, c.f. [42]). Hybrid species may also be reproductively isolated from the parent species through sorting of incompatibilities leading to new combinations of parental alleles that are incompatible with both parent species but compatible within the hybrid taxon (recombinational hybrid speciation)[29]. A recombinational hybrid taxon typically also has a substantial proportion of the genome derived from the donor of introgressed material, although variation exists both between taxa and within lineages of hybrid taxa (see e.g.[43][44]).

Homoploid and polyploid hybrid speciation

In general, hybrid species can arise from two major types of hybrid speciation, defined by whether the speciation event is associated with genome duplication (polyploidy) or not. Homoploid hybrid speciation is defined as the evolution of a new hybrid species with reproductive isolation to both parent taxa without change of ploidy, i.e. number of chromosome sets (Fig 2)[1]. The genomes of homoploid hybrid species are mosaics of the parent genomes as ancestry tracts from the parent species are broken up by recombination[40][41][45][46][47][48][49]. In the case of polyploid hybrid speciation, hybridisation is associated with genome duplication (polyploidy) leading to new combinations of parental alleles that are incompatible with both parent species but compatible within the hybrid taxon (recombinational hybrid speciation)[29].

Fig 2. Schematic representation of homoploid and allopolyploid hybrid speciation. As an example of a homoploid hybrid genome we present a schematic figure of the mosaic genome of the Italian sparrow which is a hybrid resulting from the anthropogenic house sparrow *P. domesticus* which spread across the Mediterranean with agriculture and encountered and hybridized with local populations of Spanish sparrow *P. hispaniolensis* [44,47,85]. As allopolyploid example we use the monkeyflower *Mimulus peregrinus*, an allohexaploid species that has evolved independently at least twice and which involves an intermediate, sexually-sterile but clonally vigorous F1 hybrid [115]. Sterile F1 hybrids have given rise to allopolyploids in other taxa (e.g. *Spartina* and *Senecio*), but allopolyploids can also form via fertile intermediate hybrids (e.g. *Tragopogon*).
duplication, resulting in an allopolyploid with increased ploidy compared to their parental taxa (Fig 2). In contrast to allopolyploids, autopolyploids are characterised by genome duplication within the same species and are thus not discussed further in the context of this review. Allopolyploid speciation is more common in plants than in animals[50]. Polyploid hybrids can be instantly isolated from their parental species through chromosome number differences [50].

Reproductive isolation against parental species

Sufficient reproductive isolation from both parental species is required for the successful establishment of a hybrid species[1][39][51]. Reproductive isolation against parent species is harder to achieve for homoploid hybrids where karyotype differences do not contribute to intrinsic isolation. Reproductive isolation between a hybrid species and its parental species can arise from a variety of reproductive barriers either before or after fertilization (prezygotic or postzygotic, respectively), which may themselves be dependent or independent of environmental conditions (extrinsic or intrinsic barriers, respectively)[52]. For example, intrinsic postzygotic barriers cause hybrid inviability or sterility regardless of the environment in which they occur, while extrinsic postzygotic barriers result in hybrids of low fitness due to maladaptation to specific environments[30].

Prezygotic intrinsic and extrinsic differences have also been shown to be important in isolating hybrids from their parent species. In plants, pollinator-mediated isolation resulting from changes in floral characteristics may be an important extrinsic prezygotic ecological barrier[53][54][55][56]. Strong extrinsic pre-zygotic barriers have been shown to isolate the hybrid species Senecio eboracensis from its parent species, where hybrids are virtually absent in the wild, although a fraction of hybrid offspring are fertile in lab experiments[57]. Lowe & Abbott conclude that selfing, timing of flowering and characters involved in pollinator attraction likely contribute to this external isolation[57]. Prezygotic mate preference driven isolation generated from intrinsic assortative mating between hybrids has also been reported in several taxa. In African cichlid fish, experimental hybrids displayed combinations of parental traits and preferences which resulted in hybrids predominantly mating with other hybrids[58]. A similar pattern was found in Geospiza Galapagos finches where a specific hybrid song resulted from the transgressive beak morphology[8], and hybrid Heliconius butterflies preferred the hybrid wing patterning over that of both parental species[12]. Intrinsic differences in habitat use[59] or in phenology[60] may result in some degree of reproductive isolation against parental species if mating is time and habitat-specific. For example the apple host race in Rhagoletis pomonella maggot flies evolved after introgression of diapause related genes from Mexican altiplano flies that allowed a switch from the ancestral host hawthorne to the later flowering apple [61][62] and isolated the two host races via allochronic intrinsic pre-zygotic isolation. In Xiphophorus swordtail fish strong ancestry-assortative mating maintained a hybrid genetic cluster separate for 25 generations, but disappeared under manipulated conditions[63]. Hence, prezygotic reproductive barriers to gene flow may be environment dependent.

Postzygotic isolating barriers have also been shown to be important in a variety of hybrid lineages. Work on Helianthus sunflowers has revealed that intrinsic postzygotic can cause reproductive isolation against the parent species. The postzygotic barriers consist in pre-existing structural differences[47][64], in combination with hybridization induced structural differences[47]. Sorting of incompatibilities between parent species, where one subset of these isolates the hybrid taxon against one parent and a different subset isolates it against the other parent, has resulted in intrinsic postzygotic isolation between the Italian sparrow Passer italiae and its parent species[28]. Simulation studies show that the likelihood of hybrid speciation
through this mechanism depends on the divergence time between parent species[65], the population size of the hybrid species[66], the nature of selection acting on hybrids, and linkage among incompatibilities to each other and to adaptive variants[67]. Extrinsic ecological barriers against parent species may arise as by-products of ecological differentiation if mating is time and/or habitat specific. Hybrid species have been shown to adapt to novel ecological niches through transgressive phenotypes[59], or through novel combinations of ecological traits from the parent species[68], and ecological selection against parent-hybrid cross phenotypes would result in extrinsic postzygotic isolation.

**Stabilization of hybrid genomes**

Hybridization can have many different outcomes. Hybrid speciation results in reproductive isolation against both parent species and genomes that evolve independently from those of the parent species. Introgressive hybridization can transfer important novel variants into genomes of a species that remains distinct from the other taxa in spite of occasional gene flow. Here we refer to both types of hybridization-derived genomes as persistent hybrid genomes. Following initial hybridization, introgression tracts, the genetic blocks inherited from each parent species, are broken down with successive generations and recombination events. Recombination is more frequent in homoploid hybrid genomes than in allopolyploid hybrid genomes. In allopolyploids, recombination can destabilize the karyotype and lead to aberrant meiotic behaviour and reduced fertility, but may also generate novel gene combinations and advantageous phenotypic traits[69] as in homoploid hybrids. Once hybridization between the hybrid taxon and its parent taxa ceases, different ancestry blocks or introgression tracts may become fixed, a process referred to as "genome stabilization"[45]. Some introgression tracts are removed by selection against incompatibilities and others are fixed. Theoretical models on hybrid zones suggest that the breakdown of ancestry blocks through recombination is suppressed near genes conferring reproductive isolation due to lower fitness of recombinant hybrids[70]. The strength of the suppression is affected by the form of selection, dominance, and whether the locus is situated on an autosome or sex chromosome[70]. The time to genome stabilization is variable. Fixation of ancestry blocks was found to be rapid in experimental hybrid Helianthus sunflower species genomes[71], and the genome stabilization of hybrid sunflower species is estimated to take hundreds of generations[45]. In Zymoseptoria fungi genomes were stabilized within ca. 400 generations[72] and hybrid Xiphophorus swordtail genomes[73] genome stabilization was achieved after ca. to 2500 generations. Few Neanderthal regions have fixed in human genomes during the ca. 2000 generations after hybridization[74], and segregating incompatibilities are present in the hybrid Italian sparrow approximately 5000 generations after the initial hybridization event[75].

Given time, genetic drift will eventually stochastically fix blocks derived from the two parent species in finite isolated hybrid populations[45]. Selection against incompatibility loci may accelerate the process of fixation of parental alleles as hybrids that possess alleles that are less likely to cause incompatibility will have higher fitness and favourable alleles will spread in the population. Fixation of recessive weakly deleterious alleles in the parent taxa may, however, also result in hybrids retaining both parental alleles: because hybrids with haplotypes from both parents are not homozygous for any weakly deleterious alleles, they have higher fitness than hybrids with only one parental haplotype. This associative overdominance[76][77], may slow down the process of fixation of parental alleles through favouring retention of both parental haplotypes. The effect of associative overdominance is strongest in low recombination regions, including inversions[78]. The balance between alleles and allelic combinations providing favourable phenotypic characters and the strength of selection against incompatibilities
determine what introgression tracts will be inherited from which parent species upon hybridization (Fig 3)[21][79][80]. An insecticide resistance region was retained following a hybridization event in *Anopheles coluzzi*[21], suggesting a role for selection in maintaining favourable introgressed regions. The local recombination rate is important for the likelihood of introgression because in the case of widespread incompatibilities, introgressed alleles are more likely to recombine away from incompatibilities in high recombination regions. This pattern has been detected in monkeyflowers *Mimulus*[81], in *Mus domesticus* house mice[82], in *Heliconius* butterflies[80] and in *Xiphophorus* swordtail fish[43].

Genome-wide incompatibilities have been identified in *Xiphophorus* fish,[83] chimeric genes and mutations of orthologous genes cause incompatibilities in early generation experimental Cyprinidae goldfish—carp hybrids[84] and mito-nuclear incompatibilities are found to have a key role e.g. in Italian sparrows[49][85], fungus[86] and cyto-nuclear incompatibilities in *Mimulus* plants[87]. Evidence from altered expression patterns in synthetic hybrids and missing gene combinations in a hybrid species also suggest that DNA-repair[49][84][88] and genes involved in mutagenesis and cancer related pathways[84] may cause incompatibilities in hybrids. Genome formation in hybrid species is shaped by selection against incompatible combinations[43][73][79].

**Altered genome properties in hybrid taxa**

The hybrid origin may affect genome structure and properties. It has been shown to increase mutation rates[52][89][90], to activate transposable elements[91][92][93], and to induce
chromosomal rearrangements\cite{94}\cite{95}. Increased transposon activation, as proposed in McClintock’s ‘genomic shock’ theory, could result in alterations to gene expression\cite{95}. Transposable elements may, in addition to altering gene products if inserted into a gene, also alter promoter activity for genes if inserted upstream of the coding regions, or may induce gene silencing as a result of gene disruption\cite{96}\cite{97}. For allopolyploid genomes chromosomal rearrangements may result from the genomic shock induced by hybridisation, with more distantly related species being more prone to genome reorganisations e.g. in *Nicotiana*\cite{98}.

Chromosomal rearrangements resulting from either genomic shock or recombination events between non-homologous subgenomes may cause genome sizes to either increase or decrease \cite{99}. Both increases and decreases were found in the *Nicotiana* genus, and were not related to the age since hybridization\cite{100}.

Following genome duplication in allopolyploids, the genome goes through diploidization, which is a process in which the genome is rearranged to act as a meiotic diploid \cite{101}\cite{102}. After such diploidization, much of the genome is lost due to genome fractionation, the loss-of-function of one or the other of the newly duplicated genes\cite{102}\cite{103}. In a meta analysis, Sankoff and collaborators found evidence consistent with reduction-resistant pairs and a concentration of functional genes on a single chromosome and suggest that the reduction process partly is constrained\cite{103}.

A related allopolyploid specific phenomenon is subgenome dominance. For example, in the octoploid *Fragaria* strawberry, one of the four subgenomes is dominant and has significantly greater gene content, more frequently has its genes expressed, and exchanges between homologous chromosomes are biased in favour of this subgenome, as compared with the other subgenomes\cite{104}. This study also showed that certain traits, e.g. disease-resistance, are controlled by the dominant subgenome to a high extent\cite{104}. A proposed mechanism of how subgenome dominance arises, suggests that relative dominance is related to the density of transposable elements in each subgenome. Subgenomes with higher transposable element density tend to behave submissively relative to the other subgenomes when brought together in the allopolyploid genome\cite{102}\cite{105}. Interestingly, subgenome dominance can arise immediately in allopolyploids, as shown in synthetic and recently evolved monkeyflowers\cite{105}.

In addition to these changes to genome structure and properties, studies of allopolyploid rice and whitefish suggest that patterns of gene expression may be disrupted in hybrid species \cite{106}\cite{107}. Studies of synthetic and natural allopolyploids of *Tragopogon miscellus* show that gene expression is less strictly regulated directly after hybridization, and that novel patterns of expression emerge and are stabilized during 40 generations\cite{108}. While expression variation in miRNAs alters gene expression and affects growth in the natural allopolyploid *Arabidopsis suecica* and experimental lineages, inheritance of siRNAs is stable and maintains chromatin and genome stability\cite{109}, potentially buffering against a transcriptomic shock.

**What factors influence the likelihood of formation of persistent hybrid genomes?**

Whereas hybridization is required for the generation of persistent hybrid genomes, it is not sufficient. For the persistence of hybrid genomes in hybrid species they need to be sufficiently reproductively isolated from their parent species to avoid species fusion. Selection on introgressed variants allows the persistence of hybrid genomes in introgressed lineages. Frequency of hybridization, viability of hybrids, and the ease at which reproductive isolation against the parent species arises or strength of selection to maintain introgressed regions are hence factors influencing the rate of formation of stable hybrid lineages.
Few general conclusions about the relative prevalence of hybridization can be drawn, as sampling is not evenly distributed across the tree of life, even if there is evidence for hybridization in an increasing number of taxa. One pattern that emerges is that hybridization is more frequent in plants where it occurs in 25% of the species, whereas it only occurs in 10% of animal species[110]. Most plants, as well as many groups of animals, lack heteromorphic sex chromosomes[111]. The absence of heteromorphic sex chromosomes results in slower accumulation of reproductive isolation[112][113], and may hence enable hybridization between phylogenetically more distant taxa. Haldane’s rule[114] states that “when F1 offspring of two different animal races one sex is absent, rare, or sterile, that sex is the heterozygous sex”. Empirical evidence supports a role for heteromorphic sex chromosomes in hybrid sterility and inviability. A closely related observation is the large X effect stating that there is a disproportionate contribution of the X/Z-chromosome in fitness reduction of heterogametic hybrids [22]. These patterns likely arise as recessive alleles with deleterious effects in hybrids have stronger impacts on the heterogametic than the homogametic sex, due to hemizygous expression[115]. In taxa with well-differentiated sex chromosomes, Haldane’s rule has shown to be close to universal, and heteromorphic sex chromosomes show reduced introgression on the X in XY (see [116] for a review). In line with a role for heteromorphic sex chromosomes in constraining hybrid genome formation, elevated differentiation on sex chromosomes has been observed in both ZW and XY systems[117]. This pattern may reflect the lower effective population sizes and higher susceptibility to drift on the sex chromosomes[118], the elevated frequency of loci involved in reproductive isolation[119] and/or the heightened conflict on sex chromosomes[120]. Findings of selection for uniparental inheritance of e.g. mitonuclear loci residing on the Z chromosome in hybrid Italian sparrows[49] is consistent with compatible sex chromosomes being important for the formation of a viable hybrid genomes.

There are also several ecological factors that affect the probability of hybridization. Generally, hybridization is more frequently observed in species with external fertilization including plants but also fishes, than in internally fertilized clades[4]. In plants, high rates of selfing in some species may prevent hybridization, and breeding system may also affect the frequency of heterospecific pollen transfer[121][122]. In fungi, hybrids can be generated by ameiotic fusion of cells or hyphae[123] in addition to mechanisms available to plants and animals. Such fusion of vegetative cells and subsequent parasexual mating with mitotic crossover may generate recombined hybrid cells[123].

For hybrid species to evolve, reproductive isolation against the parental species is required. The ease by which such reproductive isolation arises is thus also important for the rate at which stable hybrid species arise. Polyploidisation and asexual reproduction are both mechanisms that result in instantaneous isolation and may increase the rate of hybrid lineage formation. The ability to self-pollinate may also act in favour of stabilising allopolyploid taxa by providing a compatible mate (itself) in the early stages of allopolyploid speciation when rare cytotypes are at a reproductive disadvantage due to inter-cytotype mating[124]. Selfing is also expected to increase the likelihood of establishment for homoploid hybrids according to a modelling study[125], and the higher probability of selfing may contribute to the higher frequency of hybrid species in plants. Fungal hybridization may result in asexual hybrid species, as Epichloe fungi where hybrids species are asexual while nonhybrids include both asexual and sexual species[126]. Hybridization between strongly divergent animal taxa may also generate asexual hybrid species, as shown e.g. in the European spined loaches, Cobitis[127], and most if not all asexual vertebrate species are of hybrid origin[128]. Interestingly, Arctic floras harbour an unusually high proportion of allopolyploid plants[129], suggesting that these hybrid taxa could have an advantage in extreme environments, potentially through reducing the negative effects of inbreeding. Hence, both genomic and ecological properties may affect the probability of hybrid species formation.
For introgressed taxa, the strength of selection on introgressed variants decides whether introgressed sections will spread in the population and stable introgressed genomes will be formed. Strong selection for insecticide resistance has been shown to increase introgression of an *Anopheles gambiae* resistance allele into *A. coluzzi* malaria mosquitoes[130]. In *Heliconius* butterflies, strong selection on having the locally abundant wing colour patterns repeatedly led to fixation of alleles that introgressed from locally adapted butterflies into newly colonizing species or subspecies[34]. Chances of fixation of beneficial introgressed variants depend on the type and strength of selection on the introgressed variant and linkage with other introgressed variants that are selected against.

**What genes or genomic regions are affected by hybridization?**

Genetic exchange can occur between populations or incipient species diverging in geographical proximity or between divergent taxa that come into secondary contact. Hybridization between more diverged lineages is expected to have a greater potential to contribute beneficial alleles or generate novelty than hybridization between less diverged populations because more divergent alleles are combined, and are thus more likely to have a large fitness effect, to generate transgressive phenotypes[131]. Hybridization between more diverged lineages is also more likely to generate incompatible allele combinations, reducing initial hybrid fitness[132] but potentially also contributing to hybrid speciation if they are sorted reciprocally as described above[131]. An intermediate genetic distance may thus be most conducive to hybrid speciation[131]. Experimental lab crosses support this hypothesis[65].

The proportion of the genome that is inherited from the recipient of introgressed material varies strongly among and within species. After the initial hybridization event the representation is 50% in many polyploid taxa, although parental gene copies are successively lost and might bias the contribution to one majority parent genome[133]. Relatively equal parental contributions are also found in some homoploid hybrid species[48] but in other cases they are highly unequal such as in some *Heliconius* species[134]. The majority ancestray may even be that from the donor of introgressed material, as was shown for *Anopheles gambiae* mosquitoes. [135] Interestingly there may also be variation in parental contribution within a hybrid species. In both swordtail fish and Italian sparrows there are populations which differ strongly in what proportions of the parent genomes they have inherited[43][44].

Patterns of introgression can vary strongly across the genome, even over short chromosomal distances. Examples of adaptive introgression of well defined regions, include an inverted region containing genes involved in insecticide resistance[21] and introgression of a divergent, inverted chromosomal segment has resulted in a “super gene” that encodes mimicry polymorphism in the butterfly *Heliconius numata*[136]. These findings are consistent with models suggesting that genomic rearrangements are important for the coupling of locally adaptive loci[137]. Genes and genomic regions that are adaptive may be readily introgressed between species e.g. in hybrid zones if they are not linked to incompatibility loci. This often referred to semi-permeable species boundaries[19][138][139], and examples include e.g. genes involved in olfaction that are introgressed across a *Mus musculus* and *M. domesticus* hybrid zone[140]. In hybrid zones with mainly permeable species boundaries, patterns of introgressed regions enable deducing what genomic regions are involved in incompatibilities and reproductive isolation [141].

**Conclusions and future directions**

Hybridization is a common phenomenon with a wide range of consequences. These include both the formation of novel hybrid species, which are reproductively isolated from their parent species and where the admixed genomes undergo independent evolution, and introgression of
adaptive variants across species boundaries in species that remain distinct in spite of occasional gene flow. The divergent genetic material in admixed genomes of hybrid taxa enables adaptation to novel environments and niches. When the divergent genomes of two species come together, incompatible combinations may reduce fitness. As hybrid genomes are frequently observed, the advantage of novel adaptive trait combinations can sometimes override potential negative effects from incompatibilities and enable hybrid lineages to purge these incompatibilities during the process of genome stabilization.

While the last decades have provided ample evidence for that hybrid genome formation is common and contributes novel species and enables adaptation, many questions remain. How long does it take for a hybrid genome to stabilize and why is there variation in time to genome stabilization[45][73]? To what extent are hybrid genomes shaped by selection for compatibility? Is there a tendency for reversal towards one parent species during genome stabilization in homoploid hybrids? Does donor ancestry typically remain primarily in high recombination tracts [43] or are there generally stable solutions with high contributions from both parent species across the genome [49]? What are the relative effects of hybridization vs. polyploidization in generating new phenotypes during allopolyploid speciation? Does time to stabilization differ between homoploid and allopolyploid hybrid taxa? Are most orthologous genes lost over time in allopolyploid hybrids leaving only the ones where it is advantageous to have both as double copies [99][133]? Does genome size in allopolyploids vary predictably with taxon age or does this vary as in Nicotiana[100]? Hybrid genomes are important components of biodiversity and hybrid origin may spur adaptation. Future investigations into the properties of hybrid genomes will improve our understanding of the potential of hybridization to produce novel adaptive variation.

Supporting information

S1 Text. Version history of the text file.
(XML)

S2 Text. Peer reviews and response to reviews.
(XML)

References

1. Abbott R, Albach D, Ansell S, Arntzen J, Baird S, Bierne N, et al. (2013), "Hybridization and speciation", Journal of Evolutionary Biology 26 (2): 229–246, https://doi.org/10.1111/j.1420-9101.2012.02599.x PMID: 23323997

2. Fisher R (1930), The genetical theory of natural selection., Oxford: Clarendon Press, https://doi.org/10.5962/bhl.title.27468

3. Mayr E (1963), Animal Species and Evolution., Cambridge, MA and London, England: Harvard University Press, https://doi.org/10.4159/harvard.9780674865327

4. Stebbins G (1959), "The Role of Hybridization in Evolution", Proceedings of the American Philosophical Society 103 (2): 231–251, ISSN 0003-049X, https://www.jstor.org/stable/985151

5. Anderson E, Stebbins G. (1954), "Hybridization as an evolutionary stimulus", Evolution 8 (4): 378–388, https://doi.org/10.1111/j.1558-5646.1954.tb01504.x ISSN 0014-3820, http://dx.doi.org/10.1111/j.1558-5646.1954.tb01504.x

6. Arnold M (1997), Natural Hybridization and Evolution., Cary: Oxford University Press, ISBN 9780195356687, OCLC 960164734, https://www.worldcat.org/oclc/960164734

7. Mallet J, Besansky N, Hahn M. (2016), "How reticulated are species?", BioEssays 38 (2): 140–149, https://doi.org/10.1002/bies.201500149 PMC PMC4813508, PMID: 26709636, http://doi.wiley.com/10.1002/bies.201500149
8. Lamichhaney S, Han F, Webster M, Andersson L, Grant R, Grant P. (2018), “Rapid hybrid speciation in Darwin’s finches”, Science 359 (6372): 224–228, https://doi.org/10.1126/science.aao4593 ISSN 0036-8075, http://www.sciencemag.org/lookup/doi/10.1126/science.aao4593 PMID: 29170277

9. Meier J, Marques D, Mwaiko S, Wagner C, Excoffier L, Seehausen O (2017), “Ancient hybridization fuels rapid cichlid fish adaptive radiations”, Nature Communications 8 (1), https://doi.org/10.1038/ncomms14363 ISSN 2041-1723, PMC PMC5309898, PMID: 28186104, http://www.nature.com/articles/ncomms14363

10. Mavarez J, Salazar C, Bermingham E, Salcedo C, Jiggins C, Linares M (2006), “Speciation by hybridization in Heliconius butterflies”, Nature 441 (7095): 868–871, https://doi.org/10.1038/nature04738 ISSN 0028-0836, http://www.nature.com/articles/nature04738 PMID: 16778888

11. Salazar C, Baxter S, Pardo-Diaz C, Wu G, Surridge A, Linares M, et al. (2010), “Genetic Evidence for Hybrid Trait Speciation in Heliconius Butterflies”, PLoS Genetics 6 (4): e1000930, https://doi.org/10.1371/journal.pgen.1000930 ISSN 1553-7404, PMC PMC2861694, PMID: 20428262, https://dx.plos.org/10.1371/journal.pgen.1000930

12. Melo M, Salazar C, Jiggins C, Linares M (2009), “Assortative mating preferences among hybrids offers a route to hybrid speciation”, Evolution 63 (6): 1660–1665, https://doi.org/10.1111/j.1558-5646.2009.00633.x http://www.wiley.com/10.1111/j.1558-5646.2009.00633.x PMID: 19492995

13. Tarweeds & silverswords: evolution of the Madininae (Asteraceae), Cartquist, S, Baldwin, B, Carr, G, St. Louis: Missouri Botanical Garden Press, 2003, ISBN 1930723202, OCLC 52892451, https://www.worldcat.org/oclc/52892451

14. Wolf D, Takebayashi N, Rieseberg L. (2001), “Predicting the Risk of Extinction through Hybridization”, Conservation Biology 15 (4): 1039–1053, https://doi.org/10.1046/j.1523-1739.2001.0150041039.x ISSN 0888-8892, http://www.wiley.com/10.1046/j.1523-1739.2001.0150041039.x

15. Prentis P, White E, Chang A, Shott C, Houston P, Schmidt H, et al. (2018), “The fate of genes that cross species boundaries after a major hybridization event in a natural mosquito population”, Molecular Ecology 27 (24): 4978–4990, https://doi.org/10.1111/mec.14947 http://doi.wiley.com/10.1111/mec.14947 PMID: 30447117

16. Servedio V, Noor M. (2003), "The Role of Reinforcement in Speciation: Theory and Data", Annual Review of Ecology, Evolution, and Systematics 34 (1): 339–364, https://doi.org/10.1146/annurev.ecolsys.34.011802.132412 ISSN 1543-592X, http://www.annualreviews.org/doi/10.1146/annurev.ecolsys.34.011802.132412

17. Rhymer J, Simberloff D (1996), "EXTINCTION BY HYBRIDIZATION AND INTRACROSSSPECIES DIFFUSION", Annual Review of Ecology and Systematics 27 (1): 83–109, https://doi.org/10.1146/annurev.ecolsys.27.1.83

18. Seehausen O (2006), “Conservation: Losing Biodiversity by Reverse Speciation”, Current Biology 16 (9): R334–R337, https://doi.org/10.1016/j.cub.2006.03.080 http://www.cell.com/retrieve/pii/S0096889206014138 PMID: 16682344

19. Thompson J. (1994), "Harrison R. G. (ed.). Hybrid Zones and the Evolutionary Process. Oxford University Press. Oxford. 364 pp. Price f45.00. ISBN: 0-19-506917-X.", Journal of Evolutionary Biology 7 (5): 631–634, https://doi.org/10.1046/j.1420-9101.1994.7050631.x ISSN 1010-061X, http://dx.doi.org/10.1046/j.1420-9101.1994.7050631.x

20. The Heliconius Genome Consortium (2012), “Butterfly genome reveals promiscuous exchange of mimicry adaptations among species”, Nature 487(7450): 94–98, https://doi.org/10.1038/nature11041 ISSN 0028-0836, PMC PMC3398145, PMID: 22722851, http://www.nature.com/articles/nature11041

21. Hanemaaier J, Collier T, Chang A, Shott C, Houston P, Schmidt H, et al. (2018), “The fate of genes that cross species boundaries after a major hybridization event in a natural mosquito population”, Molecular Ecology 27 (24): 4978–4990, https://doi.org/10.1111/mec.14947 http://dx.doi.org/10.1111/mec.14947 PMID: 30447117

22. Coyne J, Orr A (2004), Speciation, Sunderland: Sinauer Associates, ISBN 0878930914, OCLC 55078441, https://www.worldcat.org/oclc/55078441

23. Price T, Bouvier M. (2002), [2083:teofplj2.0.co,2 "The evolution of F1 postzygotic incompatibilities in birds"], Evolution 56 (10): 2083, https://doi.org/10.1554/0014-3820(2002)056[2083:teofplj2.0.co,2 ISSN 0014-3820, http://dx.doi.org/10.1554/0014-3820(2002)056[2083:teofplj2.0.co,2 PMID: 12449494

24. Steinkens R, Young K, Seehausen O (2010), “The accumulation of reproductive incompatibilities in African cichlid fish”, Evolution 64 (3): 617–633, https://doi.org/10.1111/j.1558-5646.2009.00849.x http://dx.doi.org/10.1111/j.1558-5646.2009.00849.x PMID: 19796149

25. Rebermig C, Lafon-Placette C, Hatorangan M, Slotte T, Kühler C (2015), “Non-reciprocal Interspecies Hybridization Barriers in the Capsella Genus Are Established in the Endosperm”, PLOS Genetics 11
58. Selz O, Thommen R, Maan M, Seehausen O. (2014), "Behavioural isolation may facilitate homoploid hybrid speciation in cichlid fish", *Evolution* 68 (2): 266–275, https://doi.org/10.1111/j.1558-5646.2007.00267.x ISSN 0014-3820, PMC PMCID: 18039323, PMID: 29674434, http://www.sciencemag.org/lookup/doi/10.1126/science.aaa3684

44. Runemark A, Trier C, Eroukhmanoff F, Hermansen J, Matschner M, Ravinet M et al. (2018), "Variation and constraints in hybrid genome formation", *Nature Ecology & Evolution* 2 (3): 549–556, https://doi.org/10.1038/s41559-017-0437-7 ISSN 2375-2548, PMC PMCID: 28630911, PMID: 29335572

45. Buerkle A, Rieseberg L. (2008), "The rate of genome stabilization in homoploid hybrid species", *Evolution* 62 (2): 266–275, https://doi.org/10.1111/j.1558-5646.2007.00267.x ISSN 0014-3820, PMC PMCID: 18039323, PMID: 18039323, http://wiley.com/10.1111/j.1558-5646.2007.00267.x

46. Ungerer M, Baird S, Pan J, Rieseberg L. (1998), "Rapid hybrid speciation in wild sunflowers", *Evolutionary Biology* 27 (2): 275–289, https://doi.org/10.1111/j.1558-5646.1999.tb00267.x ISSN 0014-3820, PMC PMCID: 24372872, PMID: 9751738, http://www.pnas.org/cgi/doi/10.1073/pnas.98.20.11757

47. Elgvin T, Trier C, Trier C, Terresen O, Hagen I, Lien S, Nederbragt A, et al. (2017), "The genomic mosaicism of hybrid speciation", *Science Advances* 3 (6): e1602996, https://doi.org/10.1126/sciadv.1602996 ISSN 2375-2548, PMC PMCID: 28630911, PMID: 29335572

48. Runemark A, Trier C, Eroukhmanoff F, Hermansen J, Matschner M, Ravinet M et al. (2018), "Variation and constraints in hybrid genome formation", *Nature Ecology & Evolution* 2 (3): 549–556, https://doi.org/10.1038/s41559-017-0437-7 ISSN 2375-2548, PMC PMCID: 28630911, PMID: 29335572

49. Otto S, Whitton J (2000), "Polyploid Incidence and Evolution", *Annual Review of Genetics* 34 (1): 401–437, https://doi.org/10.1146/annurev.genet.34.1.401 ISSN 0066-4197, http://www.anualreviews.org/doi/10.1146/annurev.genet.34.1.401 PMID: 11092833

50. Abbott, R, Rieseberg, L (2012), John Wiley & Sons, Ltd, ed., "Hybrid Speciation", Annual Review of Genetics 34 (1): 401–437, https://doi.org/10.1146/annurev.genet.34.1.401 ISSN 0066-4197, http://www.annualreviews.org/doi/10.1146/annurev.genet.34.1.401 PMID: 11092833

51. Abbott, R, Rieseberg, L (2012), John Wiley & Sons, Ltd, ed., "Hybrid Speciation", eLS (John Wiley & Sons, Ltd), https://doi.org/10.1002/9780470016176, PMC PMCID: 28565509, PMID: 2553645

52. Coyne J (1989), "Mutation rates in hybrids between sibling species of Drosophila", *Hereditas* 63 (2): 155–162, https://doi.org/10.1038/hdy.1989.87 ISSN 0018-067X, PMID: 2553645

53. Chase M, Paun O, Fay M (2010), "Hybridization and speciation in angiosperms: a role for pollinator shifts?", *Journal of Biology* 9 (3): 21, https://doi.org/10.1186/jbiol231 ISSN 1475-4924, http://jbiol.biomedcentral.com/articles/10.1186/jbiol231

54. Grant V (1949), "Pollination systems as isolating mechanisms in angiosperms", *Evolution* 3 (1): 82–97, https://doi.org/10.1111/j.1558-5646.1949.tb00007.x http://dx.doi.org/10.1111/j.1558-5646.1949.tb00007.x PMID: 18115119

55. Segraves K, Thompson J (1999), "Plant polyploidy and pollination: floral traits and insect visits to diploid and tetraploid Heuchera grossulariifolia", *Evolution* 53 (4): 1114–1127, https://doi.org/10.1111/j.1558-5646.1999.tb04526.x http://dx.doi.org/10.1111/j.1558-5646.1999.tb04526.x PMID: 28565509

56. Moe A, Weiblen G. (2012), "Pollinator-mediated reproductive isolation among dioecious fig species (Ficus, Moraceae)", *Evolution* 66 (12): 3710–3721, https://doi.org/10.1111/j.1558-5646.2012.01727.x http://dx.doi.org/10.1111/j.1558-5646.2012.01727.x PMID: 23206130

57. Lowe A, Abbott R (2004), "Reproductive isolation of a new hybrid species, Senecio ebrocensis Abbott & Lowe (Asteraceae)", *Hereditas* 92 (5): 386–395, https://doi.org/10.1038/sj.hdy.6800432 ISSN 0018-067X, http://www.nature.com/articles/6800432 PMID: 1501442

58. Selz O, Thommen R, Maan M, Seehausen O. (2014), "Behavioural isolation may facilitate homoploid hybrid speciation in cichlid fish", *Journal of Evolutionary Biology* 27 (2): 275–289, https://doi.org/10.1111/jeb.12287 http://doi.wiley.com/10.1111/jeb.12287 PMID: 24372872

59. Schwarzbach A, Donovan L, Rieseberg L. (2001), "Transgressive character expression in a hybrid sunflower species", *American Journal of Botany* 88 (2): 270–277, https://doi.org/10.2307/2657018 ISSN 0002-9122, http://dx.doi.org/10.2307/2657018 PMID: 11222249

60. Marneli G, López-Alvarado J, Farris E, Alfonso S, Filigheddu R, García-Jacas N (2014), "The role of parental and hybrid species in multiple introgression events: evidence of homoploid hybrid speciation
in Centaurea (Carcueae, Asteraceae): Introgression in Centaurea”, *Botanical Journal of the Linnean Society* 175 (3): 453–467, https://doi.org/10.1111/boj.12177 https://academic.oup.com/botlinnean/article-lookup/doi/10.1111/boj.12177

61. Xie X, Michel A, Schwarz D, Rull J, Velez S, Forbes, et al. (2008), “Radiation and divergence in the Rhoageletis Pomenella species complex: inferences from DNA sequence data”, *Journal of Evolutionary Biology* 21 (3): 900–913, https://doi.org/10.1111/j.1420-9101.2008.01507.x ISSN 1010-061X, http://doi.wiley.com/10.1111/j.1420-9101.2008.01507.x PMID: 18312319

62. Feder J, Xie X, Rull J, Velez S, Forbes A, Leung B, et al. (2005), “Mayr, Dobzhansky, and Bush and the complexities of sympatric speciation in Rhoageletis”, *Proceedings of the National Academy of Sciences*102 (Supplement 1): 6573–6580, https://doi.org/10.1073/pnas.0502099102 ISSN 0027-8424, PMC PMC1131876, PMID: 15851672, http://www.pnas.org/cgi/doi/10.1073/pnas.0502099102

63. Schumer, Molly, Powell, Daniel L, Delciòs, Pablo J, Squire, Mattie, Cui, Rongfeng, Andolfatto, Peter, Rosenthal, Gil G. (2017), 'Assortative mating and persistent reproductive isolation in hybrids’, *Proceedings of the National Academy of Sciences* 114 (41): 10936–10941, https://doi.org/10.1073/pnas.1711238114 ISSN 0027-8424, PMC PMCM642718, PMID: 28973863, http://www.pnas.org/lookup/doi/10.1073/pnas.1711238114

64. Rieseberg L, Linder C, Seiler G. (1995), “Chromosomal and genic barriers to introgression in Helianthus”, *Genetics* 141 (3): 1163–1171, ISSN 0006-6731, PMC 1206838, PMID: 8582621, https://www.ncbi.nlm.nih.gov/pmed/8582621

65. Comeault A, Matute D. (2018), “Hybrid floral scent novelty drives pollinator shift in sexually deceptive orchids”, *Molecular Ecology* 27 (8): 1540–1552, https://doi.org/10.1111/mec.14698, PMID: 29806154, http://doi.wiley.com/10.1111/mec.14698

66. Blancaart A, Bank C (2018), “In search of the Goldilocks zone for hybrid speciation”, *Journal of Evolutionary Biology* 31 (6): 1371–1380, https://doi.org/10.1111/jeb.13509

67. Schmer M, Cui R, Rosenthal G, Andolfatto P (2015), “Reproductive Isolation of Hybrid Populations Driven by Genetic Incompatibilities”, *PLOS Genetics* 11 (3): e1005041, https://doi.org/10.1371/journal.pgen.1005041 ISSN 1553-7404, PMC PMCM615587, PMID: 25768654, http://dx.plos.org/10.1371/journal.pgen.1005041

68. Vereeken N, Cozzolino S, Schiestl F (2010), “Hybrid floral scent novelty drives pollinator shift in sexually deceptive orchids”, *BMC Evolutionary Biology* 10 (1): 103, https://doi.org/10.1186/1471-2148-10-103 ISSN 1471-2148, PMC PMCM2875231, PMID: 20409296, http://bmcevolbiol.biomedcentral.com/articles/10.1186/1471-2148-10-103

69. Gaeta R, Chris P. (2010), “Homoeologous recombination in allopolyploids: the polyploid ratchet: Research review”, *New Phytologist* 186 (1): 18–28, https://doi.org/10.1111/j.1469-8137.2009.03089.x http://doi.wiley.com/10.1111/j.1469-8137.2009.03089.x PMID: 20002315

70. Hvala J, Frayer M, Payseur B. (2018), “Signatures of hybridization and speciation in genomic patterns of ancestry”, *Evolution* 72 (8): 1540–1552, https://doi.org/10.1111/evo.13509 PMC PMCM6261709, PMID: 29806154, http://doi.wiley.com/10.1111/evo.13509

71. Rieseberg L, Sinervo B, Linder C, Ungerer M, Arias D. (1996), “Role of Gene Interactions in Hybrid Speciation: Evidence from Ancient and Experimental Hybrids”, *Science* 272 (5262): 741–745, https://doi.org/10.1126/science.272.5262.741 ISSN 0036-8075, http://dx.doi.org/10.1126/science.272.5262.741 PMID: 8662570

72. Stukkenbrock E, Christensen F, Hansen T, Dutheil J, Schierup M. (2012), “Fusion of two divergent fungal individuals led to the recent emergence of a unique widespread pathogen species”, *Proceedings of the National Academy of Sciences* 109 (27): 10954–10959, https://doi.org/10.1073/pnas.1201403109 ISSN 0027-8424, PMC PMCM390827, PMID: 22711811, http://www.pnas.org/cgi/doi/10.1073/pnas.1201403109

73. Schmer M, Cui R, Powell D, Rosenthal G, Andolfatto P. (2016), “Ancient hybridization and genomic stabilization in a swordtail fish”, *Molecular Ecology* 25 (11): 2577–2591, https://doi.org/10.1111/mec.13602

74. Sankararaman S, Mallick S, Dannemann M, Prüfer K, Kelso J, Pääbo S, et al. (2014), “The genomic landscape of Neanderthal ancestry in present-day humans”, *Nature* 507 (7492): 354–357, https://doi.org/10.1038/nature12961 ISSN 0028-0886, PMC PMCM0723735, PMID: 24476815, http://www.nature.com/articles/nature12961

75. Eroukhmanoff F, Bailey R, Elgvin T, Hermansen J, Runemark A, Trier C, et al. (2017), “Resolution of conflict between parental genomes in a hybrid species”, *BioRxiv*, https://doi.org/10.1101/102970 http://biorxiv.org/lookup/doi/10.1101/102970
76. Ohta T (1971), "Associative overdominance caused by linked detrimental mutations", *Genetical Research* 18 (3): 277–286, https://doi.org/10.1017/s0016672300001268, ISSN 0016-6723, http://dx.doi.org/10.1017/s0016672300001268 PMID: 5158298

77. Zhao L, Charlesworth B (2016), "Resolving the Conflict Between Associative Overdominance and Background Selection", *Genetics* 203 (3): 1315–1334, https://doi.org/10.1534/genetics.116.188912 ISSN 0016-6731, PMC PMC4937488, PMID: 27182952, http://www.genetics.org/lookup/doi/10.1534/genetics.116.188912

78. Faria R, Johannesson K, Butlin R, Westram A. (2019), "Evolving Inversions", *Trends in Ecology & Evolution* 34 (3): 239–248, https://doi.org/10.1016/j.tree.2018.12.005 https://linkinghub.elsevier.com/retrieve/pii/S0169534718302866 PMID: 30691998

79. Barton N. (2018), "The consequences of an introgression event", *Molecular Ecology* 27 (24): 4973–4975, https://doi.org/10.1111/mec.14950 http://doi.wiley.com/10.1111/mec.14950 PMID: 30599087

80. Martin S, Davey J, Salazar C, Jiggins C. (2019), "Recombination rate variation shapes barriers to introgression across butterfly genomes", *PLOS Biology* 17 (2): e2006288, https://doi.org/10.1371/journal.pbio.2006288 ISSN 1545-7885, PMC PMC6366726, PMID: 30730876, http://dx.plos.org/10.1371/journal.pbio.2006288

81. Brandvain Y, Kenney A, Flagel L, Coop G, Sweigart A. (2014), "Speciation and Introgression between Mimulus nasutus and Mimulus guttatus", *PloS Genetics* 10 (6): e1004110, https://doi.org/10.1371/journal.pgen.1004410 ISSN 1553-7404, PMC PMC4072524, PMID: 24967630, http://dx.plos.org/10.1371/journal.pgen.1004410

82. Janoušek V, Munclinger P, Wang L, Teeter K, Tucker P. (2015), "Functionality Organization of the Genome May Shape the Species Boundary in the House Mouse", *Molecular Biology and Evolution* 32 (5): 1206–1220, https://doi.org/10.1093/molbev/msv011 ISSN 1537-1719, PMC PMC4408407, PMID: 25631927, https://academic.oup.com/mbe/article-lookup/doi/10.1093/molbev/msv011

83. Schumer M, Cui R, Powell D, Dresner R, Rosenthal G, Andolfatto P (2014), "High-resolution mapping reveals hundreds of genetic incompatibilities in hybridizing fish species", *eLife* 3, https://doi.org/10.7554/eLife.02535, ISSN 2050-084X, PMC PMC497343, PMID: 24898754, https://elifesciences.org/articles/02535

84. Liu S, Luo J, Chai J, Ren L, Zhou Y, Huang F. et al. (2016), "Genomic incompatibilities in the diploid and tetraploid offspring of the goldfish × common carp cross", *Proceedings of the National Academy of Sciences* 113 (5): 1327–1332, https://doi.org/10.1073/pnas.1512955113 ISSN 0027-8424, PMC PMC4747765, PMID: 26768847, http://www.pnas.org/lookup/doi/10.1073/pnas.1512955113

85. Trier C, Hermansen J, Saetre G-P, Bailey R. (2014), "Evidence for Mitot-Nuclear and Sex-Linked Reproductive Barriers between the Hybrid Italian Sparrow and Its Parent Species", *PloS Genetics* 10 (1): e1004075, https://doi.org/10.1371/journal.pgen.1004075 ISSN 1553-7404, PMC PMC3886922, PMID: 24415954, https://dx.plos.org/10.1371/journal.pgen.1004075

86. Giordano L, Sillo F, Garbelotto M, Gonthier P (2018), "Mitonuclear interactions may contribute to fitness of fungal hybrids", *Scientific Reports* 8 (1), https://doi.org/10.1038/s41598-018-19922-w ISSN 2045-2322, PMC PMC5786003, PMID: 29374209, http://www.nature.com/articles/s41598-018-19922-w

87. Case A, Finseth F, Barr C, Fishman L (2016), "Selfish evolution of cytonuclear hybrid incompatibility in Mimulus", *Proceedings of the Royal Society B: Biological Sciences* 283 (1838): 20161493, https://doi.org/10.1098/rspb.2016.1493 ISSN 0962-8452, PMC PMC5031664, PMID: 27629037, https://royalsocietypublishing.org/doi/10.1098/rspb.2016.1493

88. David W, Mitchell D, Walter R. (2004), "DNA repair in hybrid fish of the genus Xiphophorus", *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology* 138 (3): 301–309, https://doi.org/10.1016/j.cca.2004.07.006 https://linkinghub.elsevier.com/retrieve/pii/S1090860604001322 PMID: 15533788

89. Ávila V, Chavarrias D, Sánchez E, Manrique A, López-Fanjul C, García-Dorado A (2006), "Increase of the Spontaneous Mutation Rate in a Long-Term Experiment With Drosophila melanogaster", *Genetics* 173 (1): 267–277, https://doi.org/10.1534/genetics.106.056200 ISSN 0016-6731, PMC PMC1461422, PMID: 16557099, http://www.genetics.org/lookup/doi/10.1534/genetics.106.056200

90. Bashir T, Sailer C, Gerber F, Loganathan N, Bhoopalin H, Eichenberger C, et al. (2014), "Hybridization Alters Spontaneous Mutation Rates in a Parent-of-Origin-Dependent Fashion in Arabidopsis", *Plant Physiology* 165 (1): 424–437, https://doi.org/10.1104/pp.114.238451 ISSN 0032-0889, PMC PMC4012600, PMID: 24664208, http://www.plantphysiol.org/lookup/doi/10.1104/pp.114.238451

91. Dennenmoser S, Sedlazeck F, Iwaszkiewicz E, Li X-Y, Altmüller, J, Nolte, A. (2017), "Copy number increases of transposable elements and protein-coding genes in an invasive fish hybrid origin", *Molecular Ecology* 26 (18): 4712–4724, https://doi.org/10.1111/mec.14134 PMC PMC5638112, PMID: 28390096, http://doi.wiley.com/10.1111/mec.14134
92. Dion-Côté A-M, Renault S, Normandreau E, Bernatchez L (2014), "RNA-seq Reveals Transcriptomic Shock Involving Transposable Elements Reactivation in Hybrids of Young Lake Whitefish Species", *Molecular Biology and Evolution* 31 (5): 1188–1199, https://doi.org/10.1093/molbev/msu069 ISSN 1537-1719, https://academic.oup.com/mbe/article-lookup/doi/10.1093/molbev/msu069 PMID: 24505119

93. Senerchia N, Felber F, Parisod C (2015), "Genome reorganization in F1 hybrids uncovers the role of retrotransposons in reproductive isolation", *Proceedings of the Royal Society B: Biological Sciences* 282 (1804): 20142874, https://doi.org/10.1098/rspb.2014.2874 ISSN 0962-8452, PMC PMC4375867, PMID: 25716787, https://royalsocietypublishing.org/doi/10.1098/rspb.2014.2874

94. Ostberg C, Hauser L, Pritchard V, Garza J, Naish K (2013), "Chromosome rearrangements, recombination suppression, and limited segregation distortion in hybrids between Yellowstone cutthroat trout (Oncorhynchus clarkii bouvieri) and rainbow trout (O. mykiss)", *BMC Genomics* 14 (1): 570, https://doi.org/10.1186/1471-2164-14-570 ISSN 1471-2164, PMC PMC3765842, PMID: 23968234, http://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-14-570

95. Hirai H, Hirai Y, Morimoto M, Kaneko A, Kamanaka Y, Koga A (2017), "Night Monkey Hybrids Exhibit De Novo Genomic and Karyotypic Alterations: The First Such Case in Primates", *Genome Biology and Evolution* 9 (4): 945–955, https://doi.org/10.1093/gbe/evx058 ISSN 1759-6653, PMC PMC5388293, PMID: 28369492, https://academic.oup.com/gbe/article/9/4/945/3078090

96. Barkan A, Martienssen R. (1991), "Inactivation of maize transposon Mu suppresses a mutant phenotype by activating an outward-reading promoter near the end of Mu1.", *Proceedings of the National Academy of Sciences* 88 (8): 3502–3506, https://doi.org/10.1073/pnas.88.8.3502 ISSN 0027-8424, http://www.pnas.org/cgi/doi/10.1073/pnas.88.8.3502 PMID: 1849660

97. Raizada M, Benito M-I, Walbot V(2008), "The MuDR transposon terminal inverted repeat contains a complex plant promoter directing distinct somatic and germlinal programs: Transposon promoter expression pattern", *The Plant Journal* 25 (1): 79–91, https://doi.org/10.1111/j.1365-313X.2001.00939.x http://doi.wiley.com/10.1111/j.1365-313X.2001.00939.x

98. Lim K, Matyasek R, Kovarik A, Leitch A. (2004), "Genome evolution in allotetraploid Nicotiana", *Biological Journal of the Linnean Society* 82 (4): 599–606, https://doi.org/10.1111/j.1095-8312.2004.00344.x https://academic.oup.com/bioline/lookup/doi/10.1111/j.1095-8312.2004.00344.x

99. Baack E, Whitney K, Rieseberg L. (2005), "Hybridization and genome size evolution: timing and magnitude of nuclear DNA content increases in Helianthus homoploid hybrid species", *New Phytologist* 167 (2): 623–630, https://doi.org/10.1111/j.1469-8137.2005.01433 http://doi.wiley.com/10.1111/j.1469-8137.2005.01433 PMID: 15998412

100. Leitch I, Hanson L, Lim K, Kovarik A, Chase M, Clarkson J et al. (2008), "The Ups and Downs of Genome Size Evolution in Polyploid Species of Nicotiana (Solanaceae)", *Annals of Botany* 101 (6): 805–814, https://doi.org/10.1093/aob/mcm326 ISSN 0305-7364, PMC PMC2710205, PMID: 18222910, https://academic.copub.org/lookup/doi/10.1093/aob/mcm326

101. Wolfe K. (2001), "Yesterday's polyploids and the mystery of diploidization", *Proceedings of the National Academy of Sciences* 98 (11): 623–630, https://doi.org/10.1073/pnas.88.11.623 ISSN 0027-8424, http://www.pnas.org/cgi/doi/10.1073/pnas.88.11.623 PMID: 11004114

102. Freeling M, Scanlon M, Fowler J (2015), "Fractionation and subfunctionalization following genome duplications: mechanisms that drive gene content and their consequences", *Current Opinion in Genetics & Development* 35: 110–118, https://doi.org/10.1016/j.gde.2015.11.002 https://linkinghub.elsevier.com/retrieve/pii/S0959437X15001173 PMID: 26685781

103. Sankoff D, Zheng C, Zhu Q (2010), "The collapse of gene complement following whole genome duplication", *BMC Genomics* 11 (1): 313, https://doi.org/10.1186/1471-2164-11-313 ISSN 1471-2164, PMC PMC2896955, PMID: 20482863, http://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-11-313

104. Edger P, Poorten T, VanBuren R, Hardigan M, Colle M, McKain M, et al. (2019), "Origin and evolution of the octoploid strawberry genome", *Nature Genetics* 51(3): 541–547, https://doi.org/10.1038/s41588-019-0356-4 PMID: 30804557

105. Edger P, Smith R, McKain M, Cooley A, Vallejo-Marín M, Yuan Y, et al. (2017), "Subgenome Domination in an Interspecific Hybrid, Synthetic Allopolyploid, and a 140-Year-Old Naturally Established Neo-Allopolyploid Monkeyflower", *The Plant Cell* 29 (9): 2150–2167, https://doi.org/10.1105/tpc.17.00010 ISSN 1040-4651, PMC PMC635986, PMID: 28814644, http://www.plantcell.org/lookup/doi/10.1105/tpc.17.00010

106. Xu C, Bai Y, Lin X, Zhao N, Hu L, Gong Z, et al. (2014), "Genome-Wide Disruption of Gene Expression in Allopolyploids but Not Hybrids of Rice Subspecies", *Molecular Biology and Evolution* 31 (5): 1066–1076, https://doi.org/10.1093/molbev/msu085 ISSN 1537-1719, PMC PMC3995341, PMID: 24577842, https://academic.oup.com/mbe/article-lookup/doi/10.1093/molbev/msu085
128. Neaves W, Baumann P (2011), "Unisexual reproduction among vertebrates", *Trends in Genetics* 27 (3): 81–88, https://doi.org/10.1016/j.tig.2010.12.002, https://linkinghub.elsevier.com/retrieve/pii/S0168952510002295 PMID: 21334090

129. Charlton N, Craven K, Afkhami M, Hall B, Ghimire S, Young C. (2014), "Interspecific hybridization and speciation in a model plant as a primary postzygotic barrier between nascent species: On the interconnection between asexuality, hybridization and speciation", *Molecular Ecology* 23 (1): 248–263, https://doi.org/10.1111/mec.14377 PMID: 28987005

130. Janko K, Pačes J, Wilkinson-Herbots H, Costa R, Roslein J, Drozd P, et al. (2018), "Hybrid asexuality as a mechanism for speciation", *Trends in Genetics* 34 (6): 531–544, https://doi.org/10.1016/j.tree.2019.02.008 ISSN 0169-5347, http://dx.doi.org/10.1016/j.tree.2019.02.008 PMID: 30885412

131. Brochmann C, Brysting A, Alsos I, Borgen L, Grundt H, Scheen A-C, et al. (2004), "Polyploidy in arctic plants", *Biological Journal of the Linnean Society* 82 (4): 521–536, https://doi.org/10.1111/j.1095-8312.2004.00337.x https://academic.oup.com/biolinnean/article-lookup/doi/10.1111/j.1095-8312.2004.00337.x

132. Jiggins C, Salazar C, Linares M, Mavarez J (2008), "Hybrid trait speciation and Heliconius butterflies", *Current Biology* 18 (1): 67–76, https://doi.org/10.1010/j.cub.2018.04.072 https://linkinghub.elsevier.com/retrieve/pii/S096098221830544X PMID: 29804810

133. Hacking C, Wilkinson-Herbots H, Costa R, Roslein J, Drozd P, et al. (2018), "Hybrid asexuality as a mechanism for speciation", *Trends in Genetics* 34 (6): 531–544, https://doi.org/10.1016/j.tree.2019.02.008 ISSN 0169-5347, http://dx.doi.org/10.1016/j.tree.2019.02.008 PMID: 30885412

134. Maheshwari S, Barbash D (2011), "The Genetics of Hybrid Incompatibilities", *Annual Review of Genetics* 45 (1): 331–355, 10.1146/annurev-genet-110410-132514, ISSN 0066-4197, http://www.annualreviews.org/doi/10.1146/annurev-genet-110410-132514

135. Norris L, Main B, Lee Y, Collier T, Fofana A, Cornel A et al. (2015), "Adaptive introgression in an African malaria mosquito coincident with the increased usage of insecticide-treated bed nets", *Proceedings of the National Academy of Sciences* 112 (3): 815–820, https://doi.org/10.1073/pnas.1418892112 ISSN 0027-8424, PMC PMC4311837, PMID: 25561525, http://www.pnas.org/lookup/doi/10.1073/pnas.1418892112

136. Maheshwari S, Barbash D (2011), "The Genetics of Hybrid Incompatibilities", *Annual Review of Genetics* 45 (1): 331–355, 10.1146/annurev-genet-110410-132514, ISSN 0066-4197, http://www.annualreviews.org/doi/10.1146/annurev-genet-110410-132514

137. Buggs R, Doust A, Tate J, Koh J, Soltis K, Felts F, et al. (2009), "Gene loss and silencing in Tragopogon miscellus (Asteraceae): comparison of natural and synthetic allotetraploids", *Heredity* 103 (1): 73–81, https://doi.org/10.1038/hdy.2009.24 ISSN 0018-067X, http://www.nature.com/articles/hdy200924 PMID: 19277058

138. Jiggins C, Salazar C, Linares M, Mavarez J (2008), "Hybrid trait speciation and Heliconius butterflies", *Philosophical Transactions of the Royal Society B: Biological Sciences* 363 (1506): 3047–3054, https://doi.org/10.1098/rstb.2008.0065 ISSN 0962-8436, PMC PMC2607310, PMID: 18579480, https://royalsocietypublishing.org/doi/10.1098/rstb.2008.0065

139. Fontaine M, Pease J, Steele A, Waterhouse R, Neafsey D, Sharakhov I, et al. (2015), "Extensive introgression in a malaria vector species complex revealed by phylogenomics", *Science* 347 (6217): 1258524, https://doi.org/10.1126/science.1258524 ISSN 0036-8075, PMC PMC4380269, PMID: 25431491, http://www.sciencemag.orglookup/doi/10.1126/science.1258524

140. Harrison R, Larson E. (2014), "Hybridization, Introgression, and the Nature of Species Boundaries", *Journal of Heredity* 105 (S1): 795–809, https://doi.org/10.1093/jhered/esu033 ISSN 0022-1503, https://academic.oup.com/jhered/article/2961884/Hybridization, PMID: 25149255

141. Yeaman S. (2013), "Genomic rearrangements and the evolution of clusters of locally adaptive loci", *Proceedings of the National Academy of Sciences* 110 (19): E1743–E1751, https://doi.org/10.1073/pnas.1219381110 ISSN 0027-8424, PMC PMC3651494, PMID: 23610436, http://www.pnas.org/cgi/doi/10.1073/pnas.1219381110

142. Wu C-I (2001), "The genic view of the process of speciation: Genic view of the process of speciation", *Journal of Evolutionary Biology* 14 (6): 851–865, https://doi.org/10.1046/j.1420-9110.2001.00335.x, http://dx.doi.org/10.1046/j.1420-9110.2001.00335.x

143. Harrison R, Larson E. (2014), "Hybridization, Introgression, and the Nature of Species Boundaries", *Journal of Heredity* 105 (S1): 795–809, https://doi.org/10.1093/jhered/esu033 ISSN 0022-1503, https://academic.oup.com/jhered/article/2961884/Hybridization, PMID: 25149255

144. Teeter K, Payseur B, Harris L, Bakewell M, Thibodeau L, O'Brien J, et al. (2007), "Genome-wide patterns of gene flow across a house mouse hybrid zone", *Genome Research* 18 (1): 67–76, https://doi.org/10.1101/gr.6757907 ISSN 1088-8011, PMC PMC2134771, PMID: 18025268, http://www.genome.org/cgi/doi/10.1101/gr.6757907
157. Yu Y, Barnett M, Nakhleh L (2013), "Parsimonious Inference of Hybridization in the Presence of Incomplete Lineage Sorting", Systematic Biology 62 (5): 738–751, https://doi.org/10.1093/sysbio/syt037 ISSN 1076-836X, PMC PMC3793885, PMID: 23736104, https://academic.oup.com/sysbio/article/62/5/738/1686537

158. Wen D, Yu Y, Nakhleh L (2016), "Bayesian Inference of Reticulate Phylogenies under the Multispecies Network Coalescent", PLOS Genetics 12 (5): e1006006, https://doi.org/10.1371/journal.pgen.1006006 ISSN 1553-7404, PMC PMC4856265, PMID: 27144273, https://doi.org/10.1371/journal.pgen.1006006

159. Moorjani P, Patterson N, Hirschhorn J, Keinan A, Hao L, Atzmon G, et al. (2011), "The History of African Gene Flow into Southern Europeans, Levantines, and Jews", PLoS Genetics 7(4): e1001373, https://doi.org/10.1371/journal.pgen.1001373 ISSN 1553-7404, PMC PMC3080861, PMID: 21533020, http://dx.plos.org/10.1371/journal.pgen.1001373

160. Moorjani P, Sankararaman S, Fu Q, Przeworski M, Patterson N, Reich D (2016). "A genetic method for dating ancient genomes provides a direct estimate of human generation interval in the last 45,000 years", Proceedings of the National Academy of Sciences 113 (20): 5652–5657, https://doi.org/10.1073/pnas.1514696113 ISSN 0027-8424, PMC PMC4878468, PMID: 27140627, http://www.pnas.org/lookup/doi/10.1073/pnas.1514696113

161. Loh P-R, Lipson M, Patterson N, Moorjani P, Pickrell J, Reich D, Berger B(2013), "Inferring Admixture Histories of Human Populations Using Linkage Disequilibrium", Genetics 193 (4): 1233–1254, https://doi.org/10.1534/genetics.112.147330 ISSN 0016-6731, http://www.genetics.org/lookup/doi/10.1534/genetics.112.147330

162. Sankararaman S, Patterson N, Li H, Pääbo S, Reich D (2012), "The Date of Interbreeding between Neandertals and Modern Humans", PLoS Genetics 8 (10): e1002947, https://doi.org/10.1371/journal.pgen.1002947 ISSN 1553-7404, PMC PMC3464203, PMID: 23055938, https://dx.plos.org/10.1371/journal.pgen.1002947

163. Pinho C, Hey J (2010), "Divergence with Gene Flow: Models and Data", Annual Review of Ecology, Evolution, and Systematics 41 (1): 215–230, https://doi.org/10.1146/annurev-ecolsys-102209-144644 ISSN 1543-592X, http://www.annualreviews.org/doi/10.1146/annurev-ecolsys-102209-144644

164. Excoffier L, Dupanloup I, Huerta-Sánchez E, Sousa V, Foll M (2013), "Robust Demographic Inference from Genomic and SNP Data", PLoS Genetics 9 (10): e1003905, https://doi.org/10.1371/journal.pgen.1003905 ISSN 1553-7404, PMC PMC3812088, PMID: 24204310, https://dx.plos.org/10.1371/journal.pgen.1003905

165. Gutenkunst R, Hernandez R, Williamson S, Bustamante C. (2009), "Inferring the Joint Demographic History of Multiple Populations from Multidimensional SNP Frequency Data", PLoS Genetics 5(10): e1000695, https://doi.org/10.1371/journal.pgen.1000695 ISSN 1553-7404, PMC PMC2760211, PMID: 19851460, https://dx.plos.org/10.1371/journal.pgen.1000695

166. Beaumont M A. (2010), "Approximate Bayesian Computation in Evolution and Ecology", Annual Review of Ecology, Evolution, and Systematics 41 (1): 379–406, https://doi.org/10.1146/annurev-ecolsys-102209-144621 https://doi.org/10.1146/annurev-ecolsys-102209-144621

167. Theunert C, Slatkin M (2017), "Distinguishing Recent Admixture from Ancestral Population Structure", Genome Biology and Evolution 9 (3): 427–437, https://doi.org/10.1093/gbe/evx018 ISSN 1759-6653, PMC PMC5381645, PMID: 28186554, https://academic.oup.com/gbe/article/2982377/Distinguishing