Review

A Combinatorial View on Speciation and Adaptive Radiation

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Speciation is often thought of as a slow process due to the waiting times for mutations that cause incompatibilities, and permit ecological differentiation or assortative mating. Cases of rapid speciation and particularly cases of rapid adaptive radiation into multiple sympatric species have remained somewhat mysterious. We review recent findings from speciation genomics that reveal an emerging commonality among such cases: reassembly of old genetic variation into new combinations facilitating rapid speciation and adaptive radiation. The polymorphisms in old variants frequently originated from hybridization at some point in the past. We discuss why old variants are particularly good fuel for rapid speciation, and hypothesize that variation in access to such old variants might contribute to the large variation in speciation rates observed in nature.

Speciation Genomics Reveals an Important Role of Old Genetic Variants

The population genomics of speciation, 'speciation genomics', is a flourishing area of enquiry with much potential to address some of the big questions in speciation biology. The first generation of speciation genomics studies generated several new insights, but it is becoming clear that we are only beginning to understand the genomic basis of speciation. With the exception of a much improved understanding of the nature of genomic islands of differentiation and their link to speciation [1,2], genomics studies have so far neither fundamentally changed nor challenged our understanding of the process of speciation. However, one aspect shines through that we believe deserves recognition and synthesis at this point, and that may yet turn out to challenge how we think of speciation: the age of genetic variants underlying speciation often pre-dates the species splitting time, sometimes by orders of magnitude. We believe that this calls for critical rethinking of the genetic mechanisms underlying rapid speciation and adaptive radiation, and perhaps speciation more broadly. We review here the evidence that old variation, often derived from hybridization, facilitates rapid speciation and adaptive radiation into many distinct new species. We argue that the reassembly of such old variants into new combinations often underlies mysteriously rapid species radiations, and we hypothesize that variation in access to old gene variants might contribute to variation in speciation rates within and between lineages.

The Problem: Rapid Speciation, but Slow Mutation

Many lineages accumulate species diversity at the relatively slow pace of a few new species every few million years [3]. However, some lineages appear inherently prone to rapid speciation and species radiations [4–7]. This leads to dramatic variation in speciation rates among lineages, and thus to highly imbalanced phylogenetic patterns of species richness [8]. Some cichlid fishes (Cichlidae) [9], some postglacial freshwater fishes (e.g., Salmonidae [10,11]), Darwin's finches [12], capuchino seedeaters (genus *Sporophila*) [13], Hawaiian honeycreepers (tribe Drepanidini) [14], and Hawaiian silversword alliance (family Asteraceae) [15], among others (Figure 1), radiated quickly into many species with high levels of sympatry and ecological

Highlights

Recent studies show that cases of rapid speciation and rapid species radiations often involve old genetic variants that arose long before the speciation events.

Old genetic variation, previously tested by selection and occurring at higher allele frequency than new mutations, is a good substrate for speciation.

Admixture variation from divergent lineages may be particularly important, potentially causing intrinsic and extrinsic incompatibilities, transgressive traits, or novel trait combinations in hybrid populations.

We review the evidence for rapid speciation involving a 'combinatorial mechanism' – the reassembly of old genetic variants into novel combinations.

This genetic mechanism might not only facilitate rapid speciation but also adaptive radiation and sympatric speciation, and it might contribute to variation in speciation rates among lineages.

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and mating trait differentiation. By contrast, other lineages, often closely related, remain species-poor and do not form adaptive radiations despite ecological opportunity [5,6,14,16].

Several lineage-specific traits and properties have been shown to contribute to high speciation rates [4–6]. Examples include a prominent role of sexual selection [3,5,17] and its interaction with ecological opportunity [5], the acquisition of key innovations [4,18], large ecological versatility [19], high evolvability [8,20], the presence of discrete intraspecific morphs [21], or the ability of sister species to rapidly return to sympatry after speciation [4,22].

However, most of these properties are constrained by the genetic variation that is available to a single population, and waiting times for relevant *de novo* mutations are expected to be long [23]. If the relevant genetic variation depended on *de novo* mutations, it would thus be difficult to explain rapid speciation and adaptive radiations by any of the above lineage properties or their interaction with ecological opportunity alone. Similarly, many of the standard models of speciation (Box 1) assume that reproductive barriers accumulate by divergent fixation of new mutations, predicting that speciation is usually either a slow process or a process with long waiting times. The accumulating evidence for rapid speciation and adaptive radiation without waiting times in some lineages is thus difficult to reconcile with classical models of speciation.

The Data: Ancient Genetic Variation Fuels Much More Recent Speciation Events

A key to understanding rapid speciation might lie in asking which loci best reflect the speciation process and in reconstructing the source of variation in these genes. Inherent to the idea of 'speciation genes' was a close link between the evolutionary history of alleles causing reproductive isolation [2], namely their mutational origin, and the speciation process, in other words the evolution of reproductive isolation between populations. That evolutionary history differs markedly among loci in the genome has been known for some time [3], but only recently has it become possible to directly contrast the age of allelic variants that are causally involved in a speciation event with the time-frame over which reproductive isolation evolved.

Evidence is accumulating that alleles contributing to reproductive isolation are often much older than the actual speciation events, in other words when populations started to develop reproductive isolation, particularly in cases of rapid speciation and rapid species radiations (Table 1). For example, inversions containing multiple genes affecting diapause introgressed from Mexican Altiplano highland fruit flies into the ancestor of the apple maggot *Rhagoletis pomonella* species complex in the north-eastern USA and facilitated radiation into a variety of sibling species, host races adapted to recently introduced plants with different fruiting times [24,25]. Despite the very recent emergence of new species (e.g., the apple maggot in ~200 years; Figure 1), much of the genomic variation underlying the host switches and associated reproductive isolation evolved ~1.6 million years earlier in different populations in a different ecological context [24,25]. Similarly, genetic variation underlying beak shape (*ALX1*) and beak size (*HMGA2*) variation, that is associated with adaptation to different food resources and song-mediated reproductive isolation in the adaptive radiation of Darwin's finches [12], by far pre-dates the origin of the major species groups in this radiation [26–28]. Recent speciation events in the cichlid fish radiation in Lake Victoria involved divergent selection on *LWS* opsin haplotypes that affect both adaptation to light conditions at different water depths and female mate choice [29]. The *LWS* haplotype polymorphism, however, was generated about

Glossary

Adaptive radiation from a hybrid swarm: several ecologically differentiated species evolve from a single hybrid population, wherein admixture variation not only facilitates adaptation to a variety of new niches but importantly also reproductive isolation among the emerging species.

Balancing selection: a selective process by which two or more alleles are maintained in the gene pool of a population at frequencies larger than expected under neutrality. Mechanisms include negative frequency-dependent selection, spatial or temporal heterogeneity in the direction of selection, or global heterozygote advantage.

Bateson–Dobzhansky–Muller incompatibilities (BDMIs): alleles at different loci that are incompatible with each other when present in the same genome.

Founder-effect speciation: speciation following a founder effect, in which reproductive isolation arises because strong drift-induced allele-frequency changes alter selection pressures on epistatically interacting genes.

Hybrid speciation: two species through hybridization generate a third stable lineage, isolated from both parental species, either with a mosaic of parental chromosome blocks (i.e., homoploid hybrid speciation) or combining both parental chromosome sets (i.e., allopolyploid hybrid speciation). Deeply divergent haplotypes are immediately available throughout the genome, thereby facilitating response of the hybrid population to divergent selection between parental species, as well as associated ecological differentiation within the hybrid lineage. The hybrid species might become reproductively isolated from both parental species through sorting of incompatibilities additional to mating trait divergence and divergent adaptation.

Hybrid trait speciation: introgression from a distant relative of a 'magic trait', namely a trait conferring both ecological divergence and reproductive isolation, triggers speciation in the introgressed lineage.

100 000–200 000 years ago by hybridization between two cichlid lineages that were ~1.5 million years divergent by the time they hybridized [30]. Threespine stickleback (*Gasterosteus aculeatus* species complex) diverged into many parapatric pairs of freshwater and anadromous incipient species within the past 12 000 years, but the genomic variation that fueled divergent adaptation and indirectly reproductive isolation pre-dates the origins of these populations by orders of magnitude [31]. Combining in several different ways divergent haplotypes through selection on hybrid populations between the same two parental species has led to multiple new species adapted to extreme habitats in *Helianthus* sunflowers [32]. There is also evidence that hybridization between divergent ancestral lineages was important in most major adaptive radiations of cichlid fishes [30,33–37], the radiation of clownfish on coral reefs [38], and in the radiation of the silversword alliance on Hawaii [15,39] (Figure 1). Very few examples also exist for recent, rapid speciation with a known important role of *de novo* mutations. For instance, the monkeyflower *Mimulus guttatus* speciated in the past 150 years as a consequence of a pre-existing hybrid lethality mutation hitchhiking to high frequency in a copper mine population by physical linkage to a novel copper-tolerance allele [40]. In two clades of wild tomato, introgression between early branching lineages, adaptive sorting of standing genetic variation, and evolution of genes through selection on *de novo* mutations all contributed to their adaptive radiation [41,42]. For many examples of recent speciation and rapid adaptive radiation, either the reproductive isolation loci have not yet been identified or the timing of their evolution has not yet been reconstructed. Although it might thus be too early to quantify the relative importance of different sources of genetic variation for rapid speciation and adaptive radiation, the many recent studies showing involvement of old genetic variation make a reassessment of its role timely.

A Combinatorial View on the Genetics of Speciation

The recent speciation genomic findings exemplified by case studies in Table 1 conflict with standard speciation models (Box 1) in many of which the origin of alleles involved in speciation marks the beginning of the speciation process. In the studies we highlight, new species evolved through new combinations of old alleles (Table 1 and Table S1 in the supplemental information online). Such a pattern is expected under an alternative set of speciation models, including **recombinational speciation** (see Glossary) [43] or **hybrid speciation** [44], **hybrid trait speciation** [45], **adaptive radiation from a hybrid swarm** [46,47], **transporter hypothesis** [48], and some other mechanisms of speciation by selection on standing variation [49] that results in linkage disequilibrium among old but previously unlinked variants (Figure 2). Each model is defined by a restrictive set of conditions with variable overlap among models. However, all of these models can be unified by a common genetic mechanism: speciation through reassembly of old genetic variants into new combinations which we refer to in the following as 'combinatorial mechanism' (Figure 2C–E). That recombining pre-existing variation is a powerful way of generating new species quickly was recognized early on [43,50,51], and adopting a 'combinatorial view' of the genetics of speciation might contribute to a better understanding of phenomena left unexplained by individual models or by the mutation-driven view (Box 1 and Figure 1).

From a combinatorial view, it is not the origin but the reassembly of several old variants into novel combinations that constitutes the beginning of a speciation event. Old genetic variants that have never before been together in one population can be brought together through introgressive hybridization (Figure 2C,D). Gene flow between weakly differentiated or undifferentiated populations is often thought to oppose their speciation because it homogenizes allele frequencies between them [3,52], but this should not be confused with hybridization between divergent lineages which can sometimes facilitate the origin of one or many new species additional to the two that hybridized [46,47,52–54]. Alternatively, old genetic variants can also

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Glossary

Large-effect haplotypes: haplotypes that strongly influence the phenotype, its ecological function, its mating function, and/or fitness.
Recombinational speciation: a special form of hybrid speciation involving karyotype evolution (e.g., chromosome arm translocations) between the hybrid species and its parental lineages.
Transgressive trait values: extreme trait values in hybrids that lie outside the range of the values of both parental species combined.
Transporter hypothesis: a mechanism by which the standing genetic variation of a population or species is replenished by recurrent gene flow from a population or species adapted to an alternative habitat, and thereby facilitates repeated adaptation to the alternative habitat in additional locations, including possible parallel speciation.

Trends in Ecology & Evolution

Figure 1. Examples of Species That Arose from New Combinations of Ancient Alleles. From left to right, top to bottom: Darwin finch (*Geospiza conirostris*, photo by David Marques), freshwater stickleback (*Gasterosteus aculeatus*, David Marques), Lake Victoria cichlid (*Pundamilia nyererei*, Ole Seehausen), Hawaiian silversword (*Argyroxiphium sandwicense*, Ole Seehausen), scale-eater pupfish (*Cyprinodon desquamator*, Anthony Terceira), *Heliconius* butterfly (*Heliconius timareta*, Thomas Horton), capuchino seedeater (*Sporophila hypoxantha*, Hector Bottai), short-winged *Pogonus* beetle (*Pogonus chalceus*, Roy Anderson), red monkeyflower (*Mimulus aurantiacus* ssp. *puniceus*, Sean Stankowski), munia (*Lounchura castaneothorax*, Graham Winterflood), clownfish (*Amphiprion akallopisos*, Ole Seehausen), *Helianthus* sunflower (*Helianthus deserticola*, Jason Rick), and apple fly (*Rhagoletis pomonella*, Andrew Forbes).

accumulate as standing genetic variation through long persistence in a single large population or in a metapopulation (Figure 2E), although the conditions under which recombining such variation will result in new species might be more restrictive (see below).

Old Genetic Variation in Standing or Admixture Variation

Old genetic variation – divergent haplotypes combined into the same gene pool by hybridization or that are present as standing variation – might be a particularly good substrate for speciation compared with haplotypes that are gradually building from new mutations (Box 2). Standing genetic variation and admixture variation can represent two ends of a continuum, particularly if admixture took place in the more distant past. Similarly, in a metapopulation context, it is arbitrary whether populations exchanging genes are considered to share the same standing variation or to be admixing. Important for the combinatorial mechanism is that, within the range where hybrids are viable and fertile, the more divergent two lineages are, the greater we predict the potential will be for hybridization between them to generate polymorphisms that facilitate one or several new speciation events [52,55–58]. In line with this expectation, a recent experiment using *Drosophila* species hybrids showed that intermediate

Box 1. History of Speciation Models

Ernst Mayr defined speciation as the process that generates 'groups of interbreeding natural populations that are reproductively isolated from other such groups' [74]. In the view of Mayr and Dobzhansky [51], reproductive isolation evolves between populations in allopatry as they accumulate incompatible mutations at interacting genes, so-called BDMIs [3] (Figure 2A). Gene flow between populations was thought to hinder speciation because it opposes the formation of independent sets of compatible genes that are incompatible when combined [51,74]. Even though Dobzhansky recognized that "by hybridization a species can 'discover' new evolutionary possibilities" [51], hybridization was not considered important in the eyes of modern synthesis and post-modern synthesis zoologists. Nonallopatric speciation was deemed unlikely [3,88,106,107]. In the 1980s and 1990s, empirical evidence for nonallopatric speciation began to accumulate but the genetics remained unresolved [3].

The proposal by Wu [108] of the 'genic view' of speciation (Figure 2B) suggested a solution by emphasizing that speciation with gene flow might start with reproductive isolation at single genes where strong divergent selection overcomes homogenizing gene flow. The proportion of the genome diverging might then increase gradually until reproductive isolation is complete [108]. Loci that initiate speciation in this view of speciation include genes involved in ecological divergence, assortative mating, or intrinsic incompatibilities.

Both allopatric and nonallopatric speciation depend on the accumulation and divergent fixation of variants at genes relevant to speciation. If the source is *de novo* mutation, speciation is expected to be a slow process with long waiting times. However, some theoretical studies of sympatric speciation have suggested that speciation by disruptive selection on standing variation for quantitative traits can be immediate and rapid [109,110]. Mayr also proposed immediate and rapid speciation following a founder event (**founder-effect speciation**) [111]. In this model, reproductive isolation arises as a result of drift-induced allele-frequency changes which alter selection pressures on epistatically interacting genes [111], albeit evidence from nature is rare [112]. However, while speciation can be immediate and rapid in such models, they leave unexplained the accumulation and maintenance of the large amounts of standing variation that is required for rapid radiations into many species [59,60].

Table 1. Study Systems with Evidence for Ancient Genetic Variation Involved in Recent Rapid Speciation or in Recent Radiations with Several Speciation Events in Short Succession[a]

System[a]	Start of speciation	Age of alleles	Source(s) of alleles	Refs
Darwin's finch radiation (genera *Geospiza*, *Camarhynchus*, *Platyspiza*, *Certhidea*, *Pinaroloxias*)	~10 years, ~100–300 ka, <1 Ma	~1 Ma	Hybridization	[26–28,92]
Marine/freshwater threespine stickleback (*Gasterosteus aculeatus*)	34–50 years, <12 ka	1–14 Ma	Standing variation and hybridization	[31,63,64]
Tragopogon goatsbeard flowers	~90 years	~2 Ma	Hybridization	[89,101]
Rhagoletis pomonella species complex	~200 years	~1.6 Ma	Hybridization	[24,25]
Lake Ejagham *Coptodon* cichlid radiation	1–2 ka	~10 ka	Hybridization	[34]
Bahamas *Cyprinodon* pupfish radiation	~10 ka	>>10 ka	Hybridization	[93]
Italian sparrow (*Passer italiae*)	~10 ka	~800 ka	Hybridization	[76,90]
Lake Victoria Region superflock (tribe Haplochromini) encompassing multiple cichlid radiations in different lakes including the Lake Victoria radiation	~150 ka, ~15 ka (Victoria)	>2 Ma	Hybridization	[30]
Helianthus sunflowers	60–200 ka	>1 Ma	Hybridization	[32]
Mimulus aurantiacus monkeyflower species complex	Recent	Old	Hybridization	[91]
Sporophila capuchino seedeater radiation	44 k generations	>>44 k generations	Standing variation or hybridization	[13,102]
Australo-Papuan munia radiation (genus *Lonchura*)	<500 ka	>>500 ka	Standing variation or hybridization	[103]
Heliconius butterflies	<2 Ma, <1.5 Ma	~4 Ma, >2 Ma	Hybridization	[104,105]
Hawaiian silversword alliance (genera *Argyroxiphium*, *Dubautia*, *Wilkesia*)	~5 Ma	~15 Ma	Hybridization	[15,39]

[a]In all cases, the origin of relevant genetic variation clearly pre-dates the onset of speciation, in other words the beginning of the build-up of reproductive isolation. Taxa are only included if they are sufficiently reproductively isolated from each other to coexist in sympatry or where reproductive isolation has been shown experimentally (Table S1 for more details).
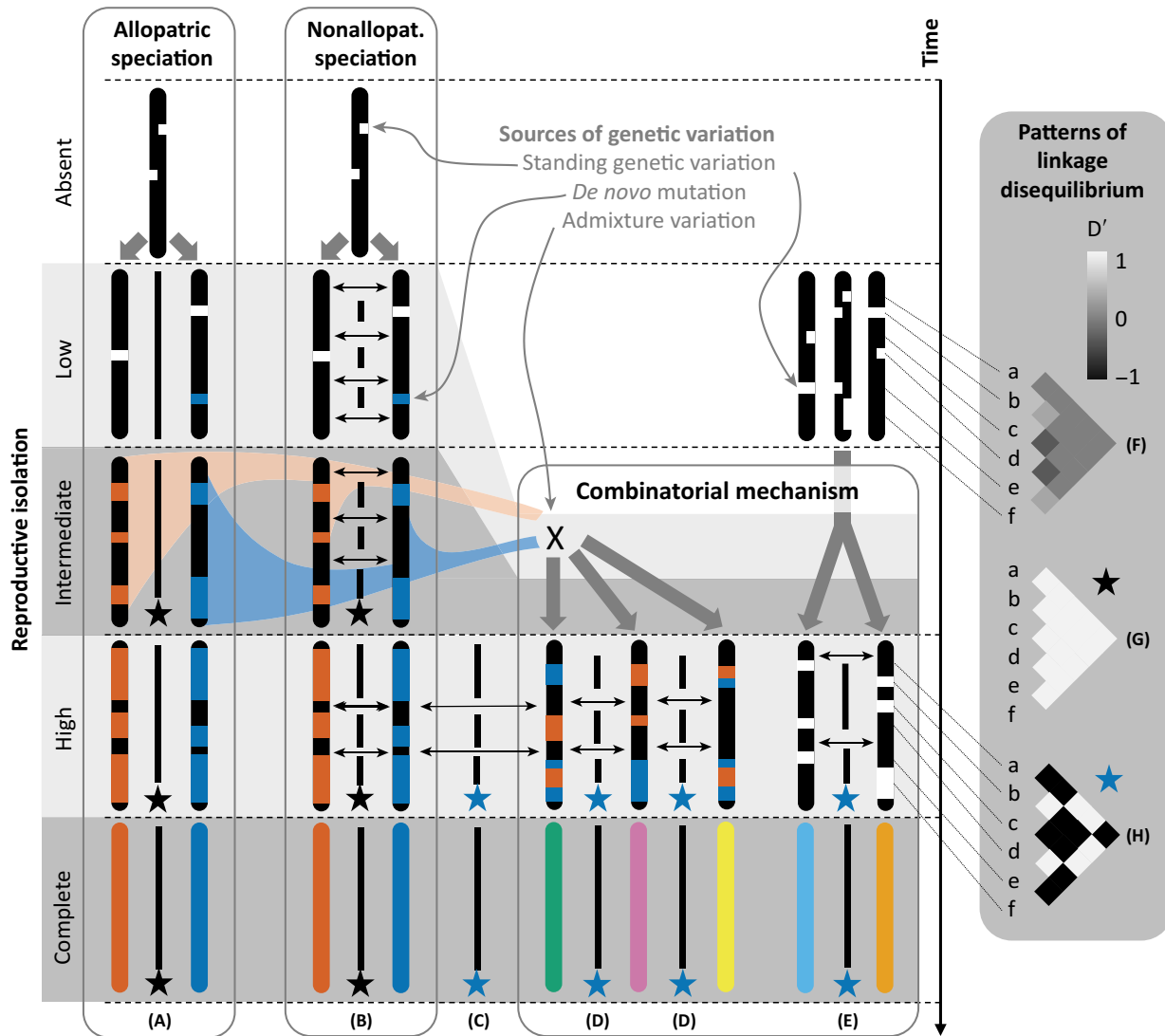
Figure 2. A Combinatorial View of the Genetics of Speciation. In models of allopatric speciation (A), or nonallopatric speciation (B), reproductive isolation usually evolves by the accumulation of barriers as a consequence of selection and drift that act on new mutations, and is thus coupled to time by mutation rate (Box 1). In speciation by a combinatorial mechanism, the reassembly of old genetic variation into new combinations (witnessed by novel patterns of linkage disequilibrium, H) marks a speciation event, thereby decoupling the evolution of reproductive isolation from mutation rate and thus time. Speciation by a combinatorial mechanism can start from admixture variation, such as during hybrid speciation (C) or adaptive radiation from a hybrid swarm (D), or from standing genetic variation in large populations or metapopulations (E) maintained for example by balancing selection. Speciation through selection on admixture variation generated by hybridization between two lineages will lead to sorting and thus to linkage disequilibrium (H) between some alleles from either parental lineage (G). From standing genetic variation, combinatorial reassembly should lead to strong linkage disequilibrium among sets of loci (H) that were previously in linkage equilibrium (F). Horizontal arrows indicate gene flow between diverging genomes, black vertical bars represent barriers to gene flow. Stars indicate predicted linkage disequilibrium patterns (right-hand box) between the populations on either side of a star.

> **Box 2. Old Genetic Variation Is a Good Substrate for Speciation**
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> We predict that old genetic variation is a better substrate for speciation than are haplotypes that gradually build up through new mutations, for multiple reasons. Most new mutations are expected to be neutral or deleterious [113], especially those that affect genes. Old variation, by contrast, has already been filtered by selection and old haplotypes have been shaped by selection in their native genomic and ecological context [52]. Strongly deleterious mutations will have been purged and old haplotypes are thus enriched for potentially (i.e., context-dependent) beneficial mutations. Variants that have passed the 'intrinsic fitness filter' are thus more likely to allow ecological and mating trait adaptation, and more rapidly, than *de novo* mutations [49].
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> In addition, alleles introduced by hybridization, or having been present as standing variation, occur at a much higher frequency than new mutations. They are thus less likely to be lost through drift and are more easily seen by selection even if recessive [49]. Old genetic variation might also be enriched for large-effect haplotypes, and are thus more likely to promote a fitness peak shift and the crossing of fitness valleys too wide to be crossed by most *de novo* mutations. In populations or species diverging with gene flow, evolution under migration–selection balance is expected to promote the clustering of many small-effect mutations into single large-effect haplotypes [86,114–116]. This is because adaptations underlain by such a clustered genomic architecture, possibly protected by locally reduced recombination (as in an inversion), persist better in the face of gene flow than do adaptations that rely on long-distance linkage disequilibrium between variants dispersed across the genome. Old haplotypes that have evolved under selection–migration balance might thus often confer large context-dependent fitness effects. Introgression of such large-effect haplotypes into a population experiencing ecological opportunity might facilitate jumps across fitness valleys which are otherwise difficult to cross under mutation-limited evolution [82,117].

levels of parental divergence and hybridization between more than two species are most conductive to generating hybrid species reproductively isolated from their parental lineages and from each other [55].

If several underutilized ecological niches are available, divergent and disruptive selection on variation resulting from mixing between distant lineages can facilitate the evolution of several new species through the many different ways in which old alleles from the same admixture event can be combined to generate completely novel phenotypes [46,47]. The large frequency of functionally relevant haplotype polymorphisms in admixed populations can facilitate simultaneous adaptation of different subpopulations to several distinct niches each of which requires adjustments of multiple traits [32], which is extremely difficult to achieve from *de novo* mutations or from standing genetic variation under migration–selection and mutation–selection balance [59,60]. Empirical examples are rapid adaptive radiations where admixture variation derived from a hybrid swarm ancestry or from secondary introgression is known to have played key roles, such as in the Hawaiian silversword alliance [39], cichlid fishes of Lake Victoria, Lake Malawi, and Lake Tanganyika [30,33,35–37,61], and Darwin's finches [26–28].

We suggest that intraspecific standing variation or variation arising from admixture between only weakly divergent young taxa is less likely to facilitate the rapid origin of many different species, but it can facilitate the recurrent evolution of similar species, in other words parallel speciation [62]. For example, upon colonization of a new habitat, reassortment of old alleles by selection can lead to the evolution of combinations beneficial in the new habitat that simultaneously also evolve upon colonization of a similar habitat elsewhere, or have also evolved previously in such habitats. Parallel speciation would thus increase the speciation rate but does not increase sympatric species richness. This is illustrated by parallel speciation in threespine stickleback [31,63,64], and by *Pogonus chalceus* beetles [65], whereby similar species or ecotypes evolved repeatedly in different sites from reassortment of standing variation, but novel ecologies rarely evolved and very little or no sympatric species richness emerged. In both cases, gene flow from populations already adapted to the alternative habitat enriched the standing variation in the large generalist population and facilitated parallel evolution of new habitat specialists [48,65].

Admixture Variation Is a Particularly Good Substrate for Speciation

We predict that old genetic variation derived from recent hybridization ('admixture variation') will be more powerful than standing genetic variation in facilitating rapid speciation and species radiations. We summarize the major reasons below. All apply to speciation in general, but for rapid speciation and rapid species radiations they are likely to be particularly important.

Large Amounts of Genetic Variation Increase the Potential for Phenotypic Evolution and Extrinsic Reproductive Isolation

Drift as well as purifying and directional selection limit the amount of standing genetic variation that can build and be maintained within a population through time [66]. By contrast, hybridization will immediately generate polymorphisms at a multitude of genes, including often strongly divergent haplotypes [52], and the number and likely effect-size of the polymorphisms depend on the divergence between hybridizing lineages [55]. A larger amount of genetic polymorphisms affecting phenotypes increases the potential for rapid adaptation to new environments and range expansion via adaptive introgression [23,67], rapid ecological differentiation, and phenotype-based reproductive isolation in emerging species. Admixture-derived allelic variation can also break up covariance between traits and thus relax genetic constraints and increase evolvability in situations where the ancestral line of least resistance in the covariance matrix was not aligned with the direction of selection in a new environment [20,68]. In addition, hybridization can indirectly augment genetic variation beyond reassembly by increasing mutation rates, for instance through activating transposable elements, inducing chromosomal rearrangements, or altering genome sizes (reviewed in [52]).

Recombining and Sorting of Intrinsic Incompatibilities Might Cause Leaps in Reproductive Isolation

Bateson–Dobzhansky–Muller incompatibilities (BDMIs) [51,69–72] are unlikely to arise or segregate as standing variation within a single population because selection purges mutations that are deleterious in their native background [51,73,74]. In admixed lineages, however, incompatible alleles initially segregate and their sorting into new compatible combinations can lead to reproductive isolation from the parental species [71,75–78], and potentially among multiple new species arising from the same hybrid ancestry [46]. Initially, the fitness of hybrids can be reduced if many partial incompatibilities are still segregating, but, unless individual incompatibilities are very strong, variation among hybrids will lead to the emergence of some hybrid combinations that are at least as fit as the parents, including combinations that are different from both parental combinations [51,79].

Transgressive Segregation Can Facilitate Crossing Fitness Valleys

Interactions among genes from different ancestries can lead to **transgressive trait values** [80]. Extreme trait values can facilitate adaptation to novel ecological niches in hybrid species [44,81] and in adaptive radiations [82]. Similarly, transgressive phenotypes or novel phenotype combinations can cause behavioral reproductive isolation if new allele combinations produce novel mating cues and novel preferences [55,58,83].

Hybridization Might Lead to Enrichment of Large-Effect Haplotypes

Haplotypes of large phenotypic, ecological, and context-dependent fitness effect increase the propensity of a population to respond to novel selection pressures and the propensity for ecological speciation given new ecological opportunity [84]. Empirical evidence shows that rapid ecological speciation often involves admixture-derived **large-effect haplotypes**, for example in *Rhagoletis* [25], cichlids [37], and Darwin's finches [28]. Parental haplotypes are

likely to contain multiple coadapted alleles which might together have a large effect on phenotype and function. The expected breakdown of such haplotypes by recombination in admixed populations might be impeded by sorting into emerging species that fix alternative haplotypes, and/or through restricted recombination, for example due to inversions such as in *Rhagoletis* [24]. We propose that selection in hybrid populations might further enrich admixture variation for large-effect haplotypes. First, theory suggests that large-effect haplotypes with ecological context-dependent fitness-effects are more likely to overcome purging selection on linked incompatibilities [85]. Second, in a situation of ongoing gene flow between species emerging from the hybrid population, divergent selection is more efficient in maintaining and strengthening differentiation if it is based on large-effect haplotypes than when based on dispersed small-effect variants [86].

Admixture Variation Might Facilitate Rapid Genome-Wide Reproductive Isolation

When an admixed population experiences ecological opportunity, new species might emerge through sorting of different genetic variants that contribute to ecological differentiation, assortative mating, and prevalent incompatibilities, all at the same time [52]. In principle, selection might favor linkage disequilibrium between loci involved in adaptation to different niches and those involved in assortative mating and perhaps also intrinsic incompatibilities [47]. We hypothesize that multiplicative effects of selection against recombination at many loci might lead to a nearly immediate reduction in gene flow, similar to the last phase in models of 'genome-wide congealing' [87]. This might also facilitate the emergence of multiple species with different combinations of genes from the same hybrid population. We expect that this becomes more likely with a larger number of differentiated loci, and a greater difference between the alleles, among the parental lineages.

Implications

Speciation via a combinatorial mechanism has many implications. One consequence is the decoupling of the speciation process from the slow rate of accumulation of mutations relevant to phenotypic differentiation and reproductive isolation (Figure 2 and Box 1). A second consequence is the facilitation of the evolution of linkage disequilibrium between genes even in the face of gene flow, and with it the partial alleviation of constraints to speciation imposed by sympatry [88]. Thereby, a combinatorial mechanism offers one possible explanation for how reproductive isolation can evolve extremely rapidly, for how multiple species can arise in short succession from the same ancestral population, and how such speciation can take place without geographical isolation.

A combinatorial mechanism allows early and rapid speciation at the time ecological opportunity arises, even when geographical isolation is lacking, because there is no waiting time for relevant mutations, and because some deviation from linkage equilibria is there from the onset. Sorting and recombining of pre-existing alleles with effects on gene flow can lead to leaps in reproductive isolation (Figure 2), for example as seen in the rapid genomic stabilization of *Tragopogon* [89] and sparrow hybrid species [76,90]. The mass of polymorphisms in ecologically relevant genes, with linkage disequilibrium between some alleles, facilitates crossing otherwise constraining fitness valleys by large peak shifts, and thereby facilitates ecological novelty and differentiation. Examples include *Mimulus* monkeyflowers [91] adapting to different pollinator syndromes, *Helianthus* sunflowers adapting to xeric habitats [32], a hybrid species of Darwin's finches with extreme body and beak size that arose within two generations [92], and pupfish that acquired a completely new feeding adaptation in the presence of the ancestral feeding type [93]. To the extent that adaptive radiation on islands and in lakes requires that the evolution of new species outpaces the arrival of existing species from the mainland, this effect of

jumpstarting adaptive radiations may not only affect the rate at which an adaptive radiation unfolds but it may also be decisive about whether a radiation occurs at all.

Variation in access to old genetic variation for combinatorial mechanisms might be one factor contributing to variation in speciation rates, and to variation in the propensity of adaptive radiation among lineages. Predictors might be the amount of standing genetic variation in a metapopulation, or whether divergent lineages with somewhat leaky reproductive isolation exist in geographic proximity. In addition, the longer that lineages retain the potential for hybridization after extended periods of isolation, the more likely they are to receive old genetic variation and to generate such variation in other lineages. Phylogenetically strongly isolated species (including 'living fossils') cannot receive gene flow from other species, and we hypothesize that this limits their potential for rapid speciation. Differences among lineages in the rates of evolution of complete intrinsic genetic incompatibility [94–96] might thus contribute to variation in lineage-specific speciation rates in a way contrary to predictions from classical speciation theory [97]: if the combinatorial mechanism is widespread and important in rapid speciation, we expect that high speciation rates should be associated with taxa showing slow completion of intrinsic incompatibility.

If speciation and hybridization occur repeatedly within the evolutionary history of a lineage, such as in 'fission–fusion–fission radiations', the genetic variation in the lineage is expected to

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Box 3. Roadmap for Studying Combinatorial Mechanisms in Speciation

A diagnosis of speciation with an important role of combinatorial mechanisms should include comparison of species splitting times with coalescent ages of haplotypes involved in speciation, as well as with linkage disequilibrium patterns at such loci between new species and ancestral species, to assess whether new species are characterized by new combinations of old variants.

If speciation took place through reassortment of old haplotypes, their coalescent time should considerably exceed the distribution of genome-wide coalescent times marking the start of speciation [118]. Underestimating species splitting times, for example as a result of gene flow in secondary contact or owing to incomplete isolation during early-stage speciation, can also lead to higher than expected coalescent ages of reproductive isolation loci even when the latter evolved from *de novo* mutation [119]. However, if the haplotypes form paraphyletic or polyphyletic gene trees when outgroup taxa are included or show clear signs of introgression, they are unlikely to represent new mutations. Detecting this will require studies of speciation in a strongly phylogenetic context. Many early speciation genetics studies overlooked the combinatorial process because they were confined to the diverging sister species.

Novel combinations of old alleles can be identified from patterns of linkage disequilibrium between reproductive isolation loci among the new species and between them and the ancestral species (Figure 2F–H). Combinatorial mechanisms from standing genetic variation should lead to the evolution of strong linkage disequilibrium between such loci from initial linkage equilibrium in the ancestral population (Figure 2F,H). Combinatorial mechanisms from admixture variation predicts, in the new species, the evolution of linkage disequilibria with reversed sign, as compared with other and with parental species, between some of the loci originating from different parental species (Figure 2G,H).

Empirical distributions of effect sizes of admixture-derived and other variants will be necessary to confirm the predicted shift to large effect sizes, for example via quantitative trait locus (QTL) mapping or genome-wide association studies (GWAS) [120,121]. Comparisons of variation in phenotypes, fitness (e.g., [32]), and mating behavior (e.g., [55,58]) between experimental hybrids and their parental lineages can elucidate the potential of hybrid populations to become new species or to initiate a new radiation. Evolution experiments with synthetic hybrid lineages and multiple ecological niches (e.g., [122]) might help to assess how the sorting of admixture-derived large-effect haplotypes contributes to adaptive radiation.

Comparing rapidly speciating lineages with close relatives that do not speciate could reveal to what extent combinatorial mechanisms contribute to heterogeneity in speciation rates and species richness. Such lineages should be investigated for differences in genetic variation, distributions of effect sizes, and admixture history or admixture potential, in particular where they co-occur with adaptive radiations on islands or lakes.

increase [98]. Whereas small-effect haplotypes and variants might become lost through drift, large-effect haplotype polymorphisms generated by hybridization and favored in different niches are likely to persist at high frequencies in a fission–fusion–fission radiation, a process akin to **balancing selection** in a metapopulation. Such enrichment might contribute to the persistent high propensity of speciation in lineages with a history of repeated hybridization and adaptive radiation, such as some lineages of African cichlid fish [22,30,33–37] and Darwin's finches [12,28,92]. Introgression might thereby also protect functionally relevant variation from extinction in single species or populations, and thus promote the long-term persistence of biodiversity at the gene-level. Future research will be necessary to subject these hypotheses to critical scrutiny (Box 3).

As indicated above, a combinatorial mechanism might also help to explain sympatric speciation. An important role of introgression from divergent lineages has been demonstrated for some of the better examples of sympatric speciation and sympatric adaptive radiation [34,37], raising a conflict with the most narrow-sense definitions of sympatric speciation that exclude cases where alleles did not evolve in the sympatric context [99]. Sympatric speciation from *de novo* mutation and panmixia (with complete linkage equilibrium) is expected to be very difficult [59,60,88,99]. However, old haplotypes with several coadapted SNPs might substantially increase the likelihood of sympatric speciation.

Finally, evolutionary diversification through combinatorial mechanisms of speciation generates a network-like evolutionary history of species rather than the tree-like evolution with dichotomous splitting of lineages that dominates evolutionary thinking. This might affect the suitability of tree-based comparative methods for research on rapid speciation and adaptive radiation, and perhaps more generally [100].

Concluding Remarks

Speciation through combinatorial mechanisms, by which new combinations of old gene variants quickly generate reproductively isolated species, offers a perspective on speciation that contrasts with the gradual growth of reproductive isolation through accumulation of differences generated by *de novo* mutations. Such a mechanism has the potential to explain how speciation can sometimes be very fast, and how multiple new species can arise nearly simultaneously and can persist in sympatry very soon after their origins. We propose that explicitly considering this class of mechanisms might help in understanding the often tremendous variation in speciation rates – something to be tested in future comparative work on speciation rates. Ongoing research in speciation genomics will soon allow more conclusive answers regarding the importance of combinatorial mechanisms relative to others in facilitating speciation and species radiations, and hence their contributions to patterns of biodiversity (see Outstanding Questions).

Supplemental Information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.tree.2019.02.008.

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Outstanding Questions

How often and how much does assembly of old genetic variation into new combinations contribute to speciation? In other words, what proportion of speciation events are characterized by the combinatorial process?

Does variation in the history of and/or the opportunity for hybridization contribute to variation in speciation rates among lineages?

Do distributions of phenotypic, ecological, and fitness effect-sizes differ in a consistent manner for loci derived from admixture variation, standing variation, or new mutations?

Are there systematic differences between admixture-derived variation and other standing variation in their effects on speciation?

Is speciation based on combinatorial mechanisms more robust to gene flow and does it more readily permit sympatric persistence and perhaps sympatric origins of sibling species than speciation relying on *de novo* mutations?

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