NON-GENETIC INHERITANCE
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The role of transgenerational epigenetic inheritance in diversification and speciation

Abstract
Inheritance is crucial to the evolutionary process. Although most evolutionary biologists assume that inheritance occurs exclusively through changes in DNA base sequence, it has long been known that inheritance can also occur through epigenetic mechanisms, such as chromatin marking, maternal effects, parasite transmission, or learning. In recent years, the possibility that such transgenerational epigenetic inheritance mechanisms can mediate long-term evolutionary change has received increased attention. Here, we consider the potential contribution of transgenerational epigenetic inheritance in driving diversification and speciation. As we describe, a growing body of theoretical and empirical studies suggests that epigenetic inheritance can accelerate the likelihood that genetic change will occur and thereby facilitate speciation. Additionally, evolution and diversification can potentially unfold based solely upon inherited environmental or learned effects, completely independent of any changes in DNA base sequence. Generally, clarifying whether (and how) epigenetic inheritance promotes—or impedes—diversification and speciation remains a key frontier of evolutionary biology.

Keywords
Genetic assimilation • Learning • Maternal effects • Reproductive isolation

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Glossary

Epigenetic effects - Broadly defined, any phenotypic variations that arise through processes other than those involving alterations in the base-pair nucleotide sequence of DNA.

Inheritance – The process by which phenotypic characters (including behaviors) are transmitted from parent to offspring.

Isolating mechanism – Any behavioral, morphological, physiological, genetic, or biochemical features of organisms that prevent gene exchange between populations (*sensu* Dobzhansky [1]).

Phenotypic diversification – As used here, the evolution of different traits in different populations.

Phenotypic plasticity – The capacity of a single genotype to produce different phenotypes in direct response to varying environmental conditions.

Speciation – The process by which barriers to gene flow evolve between populations within an ancestral species, resulting in two or more descendent species.

Species – Groups of interbreeding natural populations that are reproductively isolated from other such groups (*sensu* Mayr [2,3]).

Transgenerational epigenetic inheritance – The inheritance of phenotypic characters through processes other than those involving changes in DNA sequence, such as chromatin marking, maternal effects, parasite transmission, and learning (*sensu* Jablonka and Lamb [4]).

Section 1

Transgenerational epigenetic inheritance: a challenge for evolutionary biology

1.1 The importance of inheritance for evolution

A central goal of biology is to explain the diversity of life. Namely, why are there so many different kinds of living things, and why do they tend to differ from each other phenotypically? One hundred and fifty years ago, Darwin provided an answer, which he summarized in the last paragraph of *On the Origin of Species* [5]:

"It is interesting to contemplate an entangled bank, clothed with many plants of many kinds, with birds singing on the bushes, with various insects flitting about, and with worms crawling through the damp earth, and to reflect that these elaborately constructed forms, so different from each other, and dependent on each other in so complex a manner, have all been produced by laws acting around us. These laws, taken in the largest sense,

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being Growth with *Reproduction*; *inheritance* which is almost implied by reproduction; *Variability* from the indirect and direct action of the external conditions of life, and from use and disuse; a Ratio of Increase so high as to lead to a *Struggle for Life*, and as a consequence to Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms. Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved."

We have added italics to emphasize the "laws" that Darwin regarded as necessary for generating biodiversity: reproduction, inheritance, variability, and a struggle for life (i.e., competition).

From this quotation, two important points emerge. First, *inheritance is a prerequisite* for evolution to occur. Without inheritance, there would be no evolution and no diversity of life. Second, Darwin's theory says nothing about the *mechanism* of inheritance. Indeed, as Maynard Smith [6] noted, any population will evolve by natural selection if it exhibits reproduction, variability, competition, and as long as "like begets like"—however that occurs.

Not surprisingly, evolutionists have long sought to identify the mechanism(s) of inheritance. Although scientific inquiry into heredity traces back hundreds of years [7], two schools of thought coalesced by the late 19th century and have remained with us ever since [8]. Advocates of "soft inheritance" (e.g., Lamarck) proposed that individual organisms changed adaptively in direct response to their environment, and that these *acquired changes were then inherited by the individual's offspring* [4]. By contrast, advocates of "hard inheritance" (e.g., Weismann) maintained that parents transmitted their distinctive traits to their offspring via a chemical "blueprint" that was *impervious to environmental influences* [4]. With the discovery of Mendelian genetics in the early 20th century [9], and the subsequent deciphering of a chemical blueprint—DNA—the latter school eventually won out. Presently, most evolutionary biologists assume that inheritance occurs exclusively through alterations in DNA base sequence and that phenotypic changes induced directly by the environment are incapable of being inherited and therefore play no role in mediating evolutionary change [10]. Indeed, as discussed below, evolution is frequently defined in terms of *genetic* change.

Recently, an increasing number of researchers have begun to question these assumptions [4,8,11-15]. They point to a growing body of evidence suggesting that various extra- (or epi-) genetic factors that affect phenotype production—and that were initially induced directly by changes in the organism's abiotic or biotic environment (i.e., "epigenetic" changes [16])—can be propagated across generations, thereby constituting a form of soft inheritance known as "transgenerational epigenetic inheritance" [4,8,17-19]. The challenge has been to determine whether and how such mechanisms mediate long-term evolutionary change and the degree to which these mechanisms contribute to life's rich diversity [11,20-25].

Here, we consider the possible contribution of transgenerational epigenetic inheritance toward diversification and speciation. As we highlight below, epigenetic inheritance can be a key driver of diversification and new species, a possibility only now being recognized.

Before we begin, a few words about terminology. We define terms such as "evolution", "inheritance", and "epigenetic" more broadly than many previous authors [8] (but see [4]), for two reasons. First, semantic battles have paralyzed earlier discussions, and we wish to sidestep these debates by defining our terms as inclusively as possible. Second, we take a broad perspective on these phenomena in the hopes that doing so will allow readers to make new connections. For example, although evolution is often defined in terms of *genetic* change (e.g., "changes in allele frequencies over time" [26] or "change over time in the proportions of individual organisms differing genetically in one or more traits" [27]), defining it in this way misses an important point: that mechanisms of inheritance other than those based on changes in allele or genotype frequencies can mediate change that persists across many generations, including that which may have contributed to the diversity of life. Indeed, ignoring this possibility partly explains why epigenetic mechanisms were overlooked for so long [13]. Moreover, this broader perspective can help elucidate certain phenomena (e.g., the rapid evolution of behavior [28]) that cannot be explained otherwise. We therefore define evolution broadly as any *inherited* change in the characteristics of a group of organisms over generations, thereby encompassing the possibility that inheritance of phenotypic characters can occur through processes other than those involving changes in DNA sequence.

Finally, we do not use the term "non-genetic" inheritance because its meaning is ambiguous. Indeed, *all* inheritance mechanisms—whether they are based on changes in DNA sequence or not—likely entail some sort of *genetic* changes. For instance, mechanisms of inheritance that do not involve changes in DNA sequence, such as maternal effects, parasite transmission, and learning, are nevertheless frequently associated with changes in gene *expression* [16,29,30], and therefore have a genetic basis at some level.

With this background in mind, we begin by reviewing the common forms of transgenerational epigenetic inheritance.

1.2 Forms of transgenerational epigenetic inheritance

Epigenetic inheritance has been studied extensively in the context of cellular inheritance. However, similar mechanisms can promote inheritance *between* organisms. The best understood such mechanism involves chromatin marking [4], which occurs when small chemical groups (e.g., methyl groups) are covalently bound to DNA, or when proteins (e.g., histones) are non-covalently bound to DNA. The addition of these "marks" to DNA can modify the activity of certain genes.

For instance, for a gene to be activated (i.e., for RNA polymerase to attach to a gene's promoter and begin transcription), the DNA has to be unwound and untangled from proteins that surround it. The addition of a methyl group (CH_3) condenses the DNA/protein complex more tightly [16]. This prevents RNA polymerase from finding the promoter, thereby inactivating the gene (although methylation often leads to *reduced* activity of affected genes, in plants, methylation can increase gene activity [31]). Furthermore, once a gene has been inactivated by the addition of a methyl group (e.g., as a direct result of changes to the organism's environment), the gene's inactivated state can be inherited. During DNA replication, DNA methyltransferases can recognize a methylated sequence on the parent strand and then methylate the corresponding region on the newly synthesized daughter strand [16]. The inactivated state of a gene (as well as any changes to the phenotype) can thereby be *propagated in the absence of any changes in DNA sequence*.

Chromatin marking can potentially mediate cross-generational transmission of pronounced phenotypic variation [32]. For example, strikingly different floral morphologies in the toadflax plant, *Linaria vulgaris*, are transmitted from parent to offspring via different methylation patterns [33]. Thus, if DNA in germline cells (or in somatic cells of plants that reproduce clonally) undergoes chromatin marking, soft inheritance becomes possible.

In addition to chromatin marking, soma-to-soma transmission of epigenetically based variations is also potentially important in mediating evolutionary change [4]. Soma-to-soma transmission encompasses diverse processes, many (but not all) of which involve reconstructing the parental phenotype during somatic development in successive generations, without the direct involvement of the germline [4]. Here, we concentrate on three, main (non-mutually exclusive) processes.

First, soma-to-soma transmission can occur through "maternal effects," which arise when a female's phenotype influences its offspring's phenotype, independent of the direct effects of the female's coding sequences on its offspring's phenotype. For instance, in many animals, larger females produce larger young, simply because they produce larger eggs, more milk, and/or have larger wombs. Subsequently, the large daughters of these large females may perpetuate the trend of large offspring [4]. Likewise, females of many species differentially endow their seeds, eggs, or offspring with acquired information or materials (e.g., RNA transcripts, cytoplasm, hormones) that can influence their offspring's phenotype [34,35]. In some cases, maternal effects may self-perpetuate and endure for many generations, creating an "evolutionary momentum" that persists long after the original environmental stimulus that created the maternal effect in the first place disappears [36]. Such maternal effects can generate a response that is potentially indistinguishable from a phenotypic shift stemming from a change in DNA sequence. For example, gravid female fall field crickets, *Gryllus pennsylvanicus*, that experience cues associated with predators learn to be more fearful and subsequently give birth to more fearful offspring [37]. In this case, the "warning" is transmitted via a transgenerational maternal effect. We provide another example of a maternal effect below.

Second, soma-to-soma transmission can occur through parasite transmission. Many parasites can alter their host's phenotype [38]. Moreover, certain parasites are transmitted primarily or even exclusively from parent to offspring, thereby constituting soft inheritance. For example, in many arthropods and nematodes, an intracellular rickettsia-like bacterium (genus *Wolbachia*) is passed from infected females to their offspring via egg cytoplasm. This bacterium exerts a profound influence on its host's phenotype, including causing infected males to develop into females or infertile pseudo-females [39].

Finally, soma-to-soma transmission can occur through learning. In animals, feeding [40,41], mating [42-44], and habitat [41,45,46] preferences can be transmitted from parent to offspring via learning. Individuals may learn such preferences directly from their parents by observing them. Alternatively, they may learn these preferences indirectly by imprinting on cues that are associated with their parents (e.g., odors associated with a shared nest [47]). Indeed, imprinting has been recognized since the time of Lorenz to affect filial behavior and mate choice in ducks and geese [48]. Although this phenomenon is often associated with the artifact of the birds imprinting on an inappropriate model (e.g., Lorenz himself, or rather, his boots), in nature, the models for these learned preferences are generally mothers [49-51] or fathers [43,52,53]. Thus, the preferences are inherited. Sexual imprinting of mating preferences is widespread in birds [54] and has increasingly been noted in other taxa [43,51,55,56]. Birds are also known for learning their song [57]. While this learning often occurs non-specifically from nearby singing males, song learning from fathers also occurs, and has been found to be of particular importance in the evolution of certain species of Darwin's finches [58].

Having reviewed the common forms of transgenerational epigenetic inheritance, we now examine how this process may drive diversification and speciation.

Section 2

The possible role of epigenetic inheritance in diversification and speciation

2.1 Causes of diversification and speciation

Populations may diversify because of non-selective processes, such as when random genetic drift operates differentially in different populations [59]. However, diversification is often thought to occur when different populations experience divergent selection pressures [3]. In some cases, populations may diverge to such a degree that they become reproductively isolated from each other. In such cases, speciation may ultimately result.

Populations are considered to be reproductively isolated if they do not interbreed regularly when they occur together, or if they fail to produce fertile offspring if they do interbreed. Such populations are said to have evolved "isolating mechanisms"

that prevent gene exchange [2]. Isolating mechanisms can be grouped into two broad categories that differ depending on whether or not mixed-population (hybrid) zygotes are formed. Prezygotic isolating mechanisms are features that prevent gametes from different populations from uniting and creating a zygote; e.g., traits that preclude mating [60]. Postzygotic isolating mechanisms, by contrast, prevent hybrid offspring from surviving to adulthood or, if they do survive, prevent them (or their offspring) from reproducing. Essentially, they are features that cause hybrids to have low fitness.

The evolution of such isolating mechanisms, and ultimately, speciation, may proceed differently depending upon whether or not divergence occurs in the face of gene flow [61]. When populations do not exchange genes, both adaptive and neutral differences that accumulate in each population may foster the evolution of isolating mechanisms. In contrast, in the presence of ongoing gene flow, the evolution of reproductive isolation becomes difficult, except in cases in which isolation itself is favored. As discussed below, epigenetic factors may play different roles in these two types of situations.

2.2 How epigenetic inheritance may facilitate diversification and speciation

Transgenerational epigenetic inheritance may contribute to diversification and speciation in two general ways. The first occurs *indirectly* through an interaction between an epigenetic inheritance system and a *genetic* inheritance system. To see how such an interaction may come about, consider that when populations do not exchange genes, both prezygotic and postzygotic isolating mechanisms can accumulate as a byproduct of the different evolutionary pathways taken in each population [60,62]. Thus any process that accelerates change in each such population may enhance the likelihood of speciation.

Epigenetic factors may be especially likely to promote these changes. When confronted with a novel, stressful environment, epigenetic mechanisms enable organisms to generate new phenotypic variants *rapidly* through phenotypic plasticity [63]; this process increases the likelihood that at least some individuals will survive the stressful situation [64-66]. If these epigenetic variations are then capable of being transmitted to the next generation, such epigenetic inheritance should enhance population persistence even further. Populations that persist longer should, in turn, be more likely to accumulate *genetic* change, including those changes that lead to diversification and speciation. Thus, by increasing the chances that a population will endure until more permanent genetic changes accumulate, epigenetic factors (including those that can be inherited epigenetically) may fuel diversification and speciation *indirectly* [22].

Epigenetic inheritance mechanisms may also facilitate evolution by increasing the likelihood that genetic changes will occur in the first place. This can happen in two ways. First, epigenetically based variation can facilitate adaptive evolution by promoting accumulation of initially cryptic genetic variation in the genome. Specifically, epigenetically based variation can act as a capacitor of cryptic genetic variation by shielding it from selection until it is expressed phenotypically, such as when a population experiences a novel, stressful environment [67-69]. Second, epigenetically based variation can facilitate adaptive evolution by promoting a process known as “genetic accommodation” [63]. Genetic accommodation is any adaptive genetic change in the regulation and form of a novel phenotype. To see how this process unfolds, consider that if individuals in a population begin to express an environmentally induced phenotype that enables them to deal with a stressful event, and if there is underlying genetic variation in the magnitude and direction of the plastic response, then selection should favor those alleles or gene combinations that best stabilize, refine, and extend this induced phenotype’s expression [63]. Following strong and persistent divergent selection, alternative alleles may thereby become fixed in different populations, thereby potentially fueling diversification and, ultimately, speciation [63,70]. Although genetic accommodation does not require epigenetic *inheritance*, such an inheritance mechanism ensures that an originally environmentally induced trait will be reliably transmitted to offspring and thereby exposed to selection again in the next generation. This recurrence facilitates genetic accommodation [63].

A situation in which genetic accommodation is particularly likely to lead to reproductive isolation is when different populations have arrived at alternative “adaptive peaks”; i.e., areas of phenotypic space surrounded by phenotype combinations with lower fitness [71]. Phenotypic plasticity generally, and learning especially, increase the chances that a population will traverse low-fitness phenotype combinations to reach the vicinity of a new adaptive peak (via the “Baldwin effect” [72-75]). This process can occur rapidly, as when individuals learn novel adaptive food or habitat preferences from others [28]. Selection can then promote the evolution of genetic changes (through genetic accommodation) that propel the population closer to the peak. Because a population at this novel peak would be separated from one at the ancestral peak by a fitness valley, the two populations would exhibit postzygotic reproductive isolation. To the extent that epigenetic inheritance promotes genetic accommodation (see above), it could facilitate this route to speciation.

A second (and more controversial) way in which transgenerational epigenetic inheritance may *directly* contribute to diversification and speciation is when it forms the basis of *an alternative inheritance system on which evolution can unfold* (i.e., an inheritance system that does not involve changes in DNA sequence) [24]. Recall that any collection of entities will evolve by natural selection if they exhibit reproduction, variability, competition, and as long as “like begets like”—however this inheritance occurs. Essentially, transgenerational epigenetic inheritance, *by itself*, may drive evolution, diversification, and speciation.

Maternal effects, differential parasite transmission, and learning can all play this role. For example, both mating incompatibilities and postzygotic isolation can arise when

individuals are differentially infected with certain parasites, such as *Wolbachia* [76-79]. Moreover, maternal effects have been shown to mediate adaptive population divergence between populations [80-82], which could ultimately lead to the evolution of reproductive isolation.

For instance, a detailed study of spadefoot toads has revealed how a maternal effect can mediate adaptive phenotypic divergence between populations and species (specifically, character displacement [80]) and may even be facilitating the evolution of reproductive isolation [83,84]. In the southwestern U.S., two species (*Spea multiplicata* and *S. bombifrons*) occur in different parts of their range in both allopatry and sympatry (Figure 1a). In allopatric populations (Figure 1b), each species produces alternative resource-use phenotypes (ecomorphs): an omnivore ecomorph, and a larger, carnivore ecomorph, which is environmentally induced by shrimp ingestion [85]. Experiments have demonstrated that when these species first encountered each other, phenotypic plasticity likely enabled them to diverge in ecomorph production, such that *S. multiplicata* began to produce mostly omnivores, and *S. bombifrons* began to produce mostly carnivores [86] (Figure 1b).

However, these environmentally induced differences in morph production between species actually appear to be inherited via a maternal effect, at least in *S. multiplicata* [87]. Specifically, because *S. multiplicata* produce both morphs in allopatry, but only the smaller omnivore morph in sympatry (*S. multiplicata* are the poorer competitor for shrimp), *S. multiplicata* females from sympatry mature smaller and in poorer condition than *S. multiplicata* females from allopatry (Figure 1c). By contrast, because they produce both morphs in allopatry, but only the larger carnivore morph in sympatry, *S. bombifrons* females from sympatry mature larger and in better condition than *S. bombifrons* females from allopatry (the carnivore morph is larger, because it is able to monopolize the more nutritious

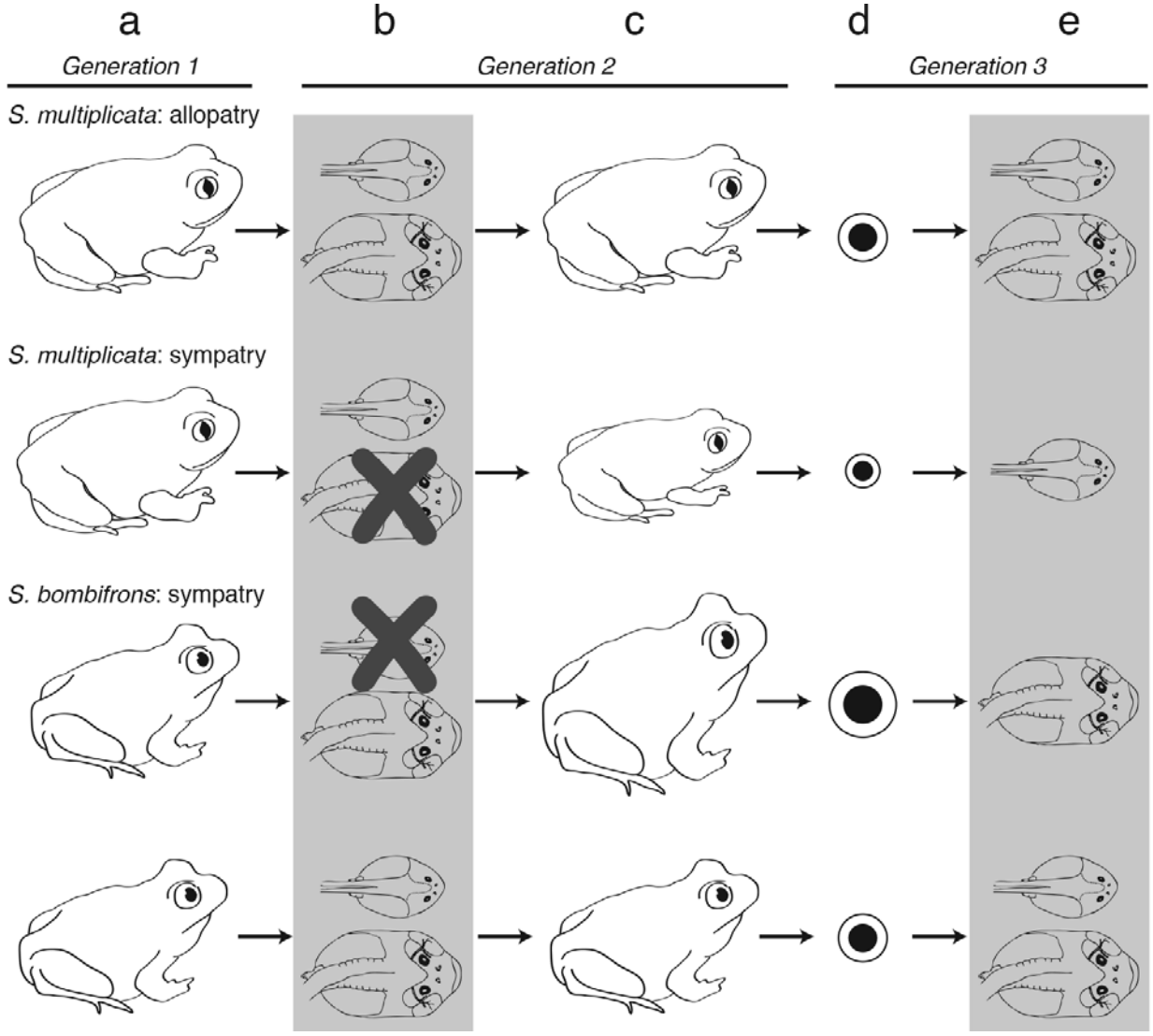

Figure 1. A diagram summarizing how a maternal effect has fostered phenotypic divergence (specifically, character displacement) between two species of spadefoot toads, and within species, between sympatric and allopatric populations. See text for details. Reproduced, with permission, from [80].

shrimp resource; Figure 1c). Consequently, in sympatry (Figure 1d), the two species diverge in maternal investment, such that *S. multiplicata* females invest less into offspring by producing smaller eggs, whereas *S. bombifrons* females invest more into offspring by producing larger eggs. Smaller eggs hatch into smaller tadpoles, which tend to become omnivores. By contrast, larger eggs hatch into larger tadpoles, which tend to become carnivores [88].

In other words, variation in egg size, tadpole size, and (ultimately) ecomorph production (Figure 1e) are all transmitted via a maternal effect across generations, thereby mediating divergence in these characters between as well as within each species (i.e., between allopatric and sympatric populations). Moreover, because sympatric and allopatric populations of *S. multiplicata* experience reduced gene flow [83,84], this maternal effect may also be contributing to the evolution of reproductive isolation. Maternal effects can therefore theoretically lead to reproductive isolation, as this example makes clear.

Another epigenetic mechanism that may be particularly important in promoting the evolution of reproductive isolation is learning [89]. Above we noted that when populations experience gene flow, the conditions for speciation are severely restricted [60]. One mechanism that can be particularly favorable for speciation in the face of gene flow, however, is when individuals prefer mates that match their own phenotype [90]. Perhaps the most common way a matching mechanism can occur is when animals sexually imprint upon the phenotype of their parents [43,56]. For example, speciation in brood-parasitic *Vidua* finches may have been caused by an isolating mechanism that was inherited entirely through learning. In this case, the young learn the distinctive songs of their foster parents, and then tend to chose foster parents of that species for their own broods [91].

Theoretical models have found that sexual imprinting on parental phenotypes facilitates speciation, even in the presence of gene flow [92,93]. Moreover, cross-fostering experiments have demonstrated that, in certain species, young females can learn sexual preferences, across species, for males from their foster parent (Figure 2), suggesting that learning creates conditions favorable for reproductive isolation to evolve.

Thus, speciation does not require *genetically based* reproductive isolation (as is generally assumed [60,81]). As with the evolution of any trait, traits involved in an isolating mechanism must merely be capable of being *inherited* in order to evolve, and (as we have seen) inheritance may occur through the transmission of epigenetically based variations.

Section 3. Conclusions

A growing body of theoretical and empirical studies suggests that epigenetic inheritance can accelerate the likelihood that populations will diverge in a way that contributes to reproductive isolation such that speciation may occur. Additionally, such diversification can unfold based solely upon inherited environmental effects, completely independent of any changes in DNA base sequence. A number of issues remain unresolved, however. Perhaps foremost among these is how frequently and how permanently epigenetic variations are transmitted across generations. In a recent review, Jablonka and Raz [19] reported over a hundred well-documented cases of epigenetic inheritance in 42 species. However, because most examples come from lab-based studies of model organisms, we still do not know how important these mechanisms are in natural populations. Moreover, the long-term stability of epigenetically based variations remains uncertain. Unlike with

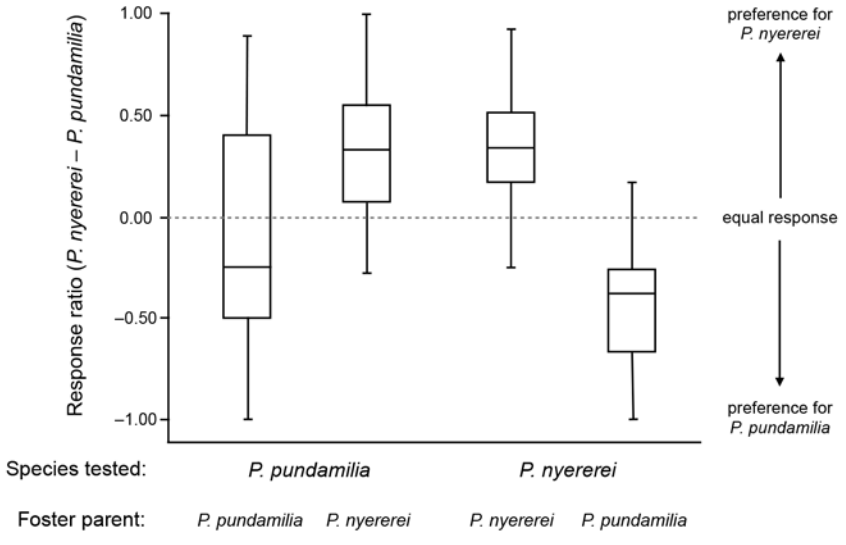

Figure 2. An experimental demonstration of how the learning of mate preferences from a parent may promote reproductive isolation. This particular example is based on a study of two closely related, sympatric species of cichlids from Lake Victoria, Pundamilia pundamilia and P. nyererei [56]. The two species are similar morphologically and ecologically, but they differ in male nuptial coloration. To evaluate whether learning plays a role in mate preferences, the researchers cross-fostered females between the two species and then tested their preference for males. They found that females preferred males of the same species as their foster mother. For example, as indicated by the last bar on the right, P. nyererei females cross-fostered by a P. pundamilia mother later preferred P. pundamilia males as mates.

DNA replication—where accuracy is largely insensitive to the environment—the stability of epigenetic changes depend on an organism's current environmental conditions; these changes can be reversed if environmental circumstances change [4]. Yet, even if most epigenetic variants last only a few generations, epigenetic inheritance mechanisms (and epigenetic mechanisms more broadly) may still be important if they decrease the chances of extinction and/or increase the likelihood of genetic change. Further research is needed to clarify this issue. We list some additional suggestions for future research in Box 1.

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Box 1. Suggestions for future research

- Most evolutionary biologists regard epigenetic inheritance as transient. Therefore, it is crucial *to compare directly*—in the same organism—the efficacy by which variation in traits can be transmitted via changes in DNA base sequence versus via epigenetically based changes.
- In contrast to the situation with soma-to-soma transmission, very little is known of the effects of chromatin marking on diversification and speciation. For example, it has been suggested that divergence between populations in epigenetic marks could *alone* generate incompatibilities [94] and reduced fitness of hybrids [13], thereby constituting postzygotic isolation. Empirical studies of *natural* populations are needed to shed light on this issue.
- Generally, little is known about whether trait variation mediated by maternal effects or learning is inherited in a particulate or blending fashion, and whether either mode of inheritance is more effective at mediating evolution. Traditionally, it was thought that with blending inheritance, variation would be depleted, causing evolution to eventually grind to a halt [95]. However, a recent model suggests that blending inheritance may be as effective as particulate inheritance in promoting adaptive evolution [96].
- Other than bird song, little is known about whether behaviors that are targets of mate choice by the opposite sex are learned. Cross-fostering or isolation experiments across a range of taxa are needed to address this issue.
- Theoretical models predict that learning may have different effects on speciation depending on whether offspring learn from their parents (mimicking genetic inheritance) or from unrelated individuals in the population. Empirical studies are needed to determine which type of learning is more common. Comparative studies are then needed to evaluate whether the former type of learning enhances diversification and speciation.
- Additional theoretical studies and empirical studies are needed to address to what extent epigenetic inheritance promotes diversification and speciation *indirectly* (i.e., by increasing population persistence) versus *directly* (by forming the basis of an alternative inheritance system on which evolution unfolds).
- Empirical studies are needed to evaluate whether "epigenetic assimilation" [97] typically precedes and even facilitates genetic assimilation [98].
- Epigenetic inheritance can contribute to adaptive divergence between populations (as occurs with adaptive plasticity) or, alternatively, to the accumulation of chance differences between populations (i.e., "*epigenetic drift*"). Future studies are needed to determine which route is more important in fostering stable divergence (and ultimately speciation) between populations.

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