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Invited Review

Haldane's Rule: Genetic Bases and Their Empirical Support

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Abstract

There are few patterns in evolution that are as rigidly held as Haldane's rule (HR), which states, "When in the first generation between hybrids between 2 species, 1 sex is absent, rare, or sterile, that sex is always the heterogametic sex." Yet despite considerable attention for almost a century, questions persist as to how many independent examples exist and what is (are) the underlying genetic cause(s). Here, we review recent evidence extending HR to plants, where previously it has only been documented in animals. We also discuss recent comparative analyses that show much more variation in sex–chromosome composition than previously recognized, thus increasing the number of potential independent origins of HR dramatically. Finally, we review the standing of genetic theories proposed to explain HR in light of the new examples and new molecular understanding.

Subject areas: Reproductive strategies and kinship analysis
Key words: dominance theory, faster-male evolution, faster-X, hybrid sterility, meiotic drive, sex chromosomes.

Haldane's rule (HR), whereby the heterogametic sex suffers the most in terms of sterility, rarity, or absence following hybridization (Haldane 1922), is an empirical phenomenon observed in organisms with sex chromosomes. Haldane found that in animals with XY systems, hybrid males were rare or absent and exhibited lower fitness than hybrid females; in ZW systems the reverse was true. This pattern suggested that even though sex chromosomes vary in many ways across different taxa, general similarities of sex chromosomes are in some way involved in intrinsic post-zygotic reproductive isolation between species. This potential generality, and its implications for speciation, has generated interest in understanding the applicability and genetic basis for HR among evolutionary biologists.

Here, we address 2 questions. First, we ask whether Haldane's rule is a general phenomenon. As previous reviews have thoroughly addressed this question, we focus on large taxonomic groupings rather than on individual studies of specific species pairs (Table 1). We take into account new studies of interspecific hybrids since the last tabulation of HR, and bring into the conversation recent challenges to the notion of sex-chromosome stability. We follow this by asking what the main underlying genetic mechanisms are thought to be that lead to the phenomenon. We explain in detail the workings of each of the various theories and evaluate evidence for and against each hypothesis.

Does the Rule Hold Across Diverse Taxa?

As early as 1991, Read and Nee (1991) argued that the apparent association between sex-chromosome heterogamety and hybrid fitness was based on a small number of independent origins of heterogamety (4, according to their calculations) and that Haldane's Rule might not enjoy truly significant support from existing data. Shortly thereafter, Laurie (1997) in a review of 75 years of studies on HR stated that "additional hybridization data from diverse groups" was needed, and she further suggested that comparisons be made between groups that differ in their levels of sex-chromosome heteromorphism (see also Howard et al. 2002; Servedio and Noor 2003). Since that time taxa from more diverse groups have been tested, leading Coyne and Orr (2004) and then Schilthuizen et al. (2011) to tabulate a combined 213 and 381 cases of hybrid sterility or inviability, respectively,

Table 1. Groups in which Haldane's rule has been tested for hybrid rarity and/or hybrid sterility. Whether the rule held [Yes or No] is indicated along with the relative number of cases in each category. M = males are the heterogametic sex (XY), F = females are the heterogametic sex (ZW), M* = males are XO. Information taken from Wade and Johnson (1994), Laurie (1997), Coyne and Orr (2004), Demuth and Wade (2007), Brothers and Delph (2010), Schilthuizen et al. (2011), Kozlowska et al. (2012), and Watson and Demuth (2012)

	Rarity	Sterility
Vertebrates		
Mammalia (M)	Yes >> no	Yes >> no
Aves (birds) (F)	Yes > no	Yes > no
Amphibia (M and F)	Yes > no	No
Reptilia (F)	—	Yes
Teleostei (fish) (M and F)	No > yes	Yes
Insects		
Diptera (M)	Yes > no	Yes
Hemiptera (M)	Yes = no	Yes
Orthoptera (M*)	Yes	Yes
Heteroptera (M*)	No	Yes
Coleoptera (M)	Yes = no	Yes
Lepidoptera (F)	Yes > No	Yes > no
Crustaceans (M)	—	No
Gastropods (F)	Yes	No
Nematodes (M*)	Yes	Yes
Plants		
Angiosperms (M)	Yes	Yes

that obey HR, but only 10 and 71 that do not conform. Although the number of species pairs conforming to HR is large, previous authors suggested these represent only 9 independent origins of the association between heterogametic sex chromosomes and HR (Lepidoptera, all other insects, birds, mammals, salamanders, lizards, nematodes, fish, and gastropods). Additionally, HR has now been shown among hybrids of 3 pairs of dioecious flowering plant species in the genus *Silene* (Table 1), thereby extending HR beyond the animal kingdom (Brothers and Delph 2010) and more than doubling the number of clearly independent origins since Read and Nee's estimate, from 4 to 10.

To understand why the number of origins still seems relatively low in the face of so many species pairs that obey the rule, one must understand that Read and Nee were arguing that HR might be a mirage; that there may in fact be no association between heterogamety and the sex of less fit hybrids. They proposed that "evidence relevant to Haldane's Rule is to be found only where independent changes in heterogametic sex have occurred." Thus, the 191 insect species pairs known to conform to HR at the time represented "just two pieces of information" given that male heterogamety is the ancestral state for insects, and the transition to female heterogamety in Lepidotera occurred once. The importance of requiring additional observations of transitions between XY and ZW systems lies in distinguishing the effects of heterogamety from the host of other factors that may also make Lepidoptera different from other insects. From this perspective, independent transitions that do not change the heterogametic sex do not add information because, e.g., all XY insects may share many underlying traits that make males more sensitive to hybridization, only one of which is heterogamety. Hence, under a strict interpretation of Read and Nee, the number of independent transitions currently known is 10.

However, Read and Nee (1991) also noted that, "a *theory* about any mechanism underlying Haldane's Rule may make predictions that can be tested experimentally or with novel comparative predictions." Orr (1997) also highlighted that a causal connection can be made if the underlying genetic basis to the phenomenon is known: "The notion that Haldane's rule is due to heterogamety can be tested by direct genetic analysis." Put more generally, if rather than asking whether HR is real, one asks what mechanism(s) are responsible for sex-specific hybrid sterility and inviability, the number of relevant comparisons that can be brought to bear on HR grows. If one argues that different independent variables can be assessed from transitions between heterogamety, non-homologous XY switches, and sex reversal, this allows for a broader interpretation of Read and Nee.

Recent evidence about sex-chromosome turnovers (i.e., which chromosome acts to determine sex) that do not involve changing the heterogamety (i.e., an X–Y chromosome pair switching to a different X–Y chromosome pair), together with knowledge of the genetic basis of HR, have provided us with additional evidence about the mechanistic underpinnings of HR. Sex-chromosome transitions occur much more frequently than previously thought. For instance, although Diptera and Coleoptera are both predominantly XY, the sex chromosomes of *Drosophila* and *Tribolium* are not homologous (Pease and Hahn 2012). Furthermore, although chromosomal elements (Muller A–F) are highly conserved within the order Diptera, parts or all of the 6 elements are used as sex chromosomes across the order, with transitions—wherein sex determination transitioned from one element to another—occurring even within taxonomic families (Vicoso and Bachtrog 2015; Blackmon and Demuth 2015a). Most Diptera studied to date exhibit male heterogamety (XY or XO), however there are lineages that exhibit female heterogamety (ZW) or even homomorphic sex chromosomes. HR has not yet been studied using crosses between species within these latter lineages.

These sex-chromosome transitions within Diptera expand the number of independent cases of the evolution of male heterogamety over 250 million years. Vicoso and Bachtrog (2015) revealed that although *Anopheles gambiae* (mosquitoes) uses Muller element A as its X chromosome, it is independently derived from the X of *Drosophila*. Although Muller element A is contained within the X of all *Drosophila*, this configuration was derived from an ancestral state in the higher flies in which Muller element F (known as the dot chromosome) was the X. Multiple independent derivations of the X have occurred within the genus *Drosphila*, as combinations of Muller element A (the likely ancestral X of this group), C, D, and F exist. Moreover, the X of stalk-eyed flies (Diopsidae), where interspecific hybrids also exhibit HR, is derived from Muller element B (Baker and Wilkinson 2010), while tsetse flies (Glossinidae) have a large X from the incorporation of Muller elements A and D to the ancestral F (Vicoso and Bachtrog 2015).

Sex-chromosome turnover is not limited to Diptera. For instance, HR is known in several Coleoptera hybridizations (Brouat et al. 2006; Demuth and Wade 2007; Bracewell et al. 2011), which are unlikely to share homologous XY systems (Blackmon and Demuth 2014, 2015b, unpublished data). In addition, sex-chromosome transitions have been shown between 3-spine stickleback fish (*Gasterosteus aculeatus*) and 9-spine stickleback (*Pungitius pungitius*) (Ross et al. 2009), both of which have been shown to exhibit HR (Takahashi et al. 2005; Kitano et al. 2009). In fact, in general, teleost fish frequently undergo sex-chromosome turnovers (Mank et al. 2006).

Transitions among non-homologous sex chromosomes where the heterogametic sex does not change may provide valuable insight about HR mechanisms, and in so doing provide indirect evidence for the overall significance of HR. With the exception of the faster-male theory, all theories for the mechanistic basis of HR involve

interaction with the sex chromosomes. Hence, comparison among taxa with nonhomologous XY sex chromosomes could reasonably be considered independent origins of heterogamety to the extent that it is relevant to mechanistic origins of HR. In experimental terms, comparison among nonhomologous XY systems explores one independent variable (sex-chromosome heterogamety) while holding sex constant. The complementary experimental test, where sex chromosomes are held constant while sex is reversed, has also been studied in at least one system that we are aware of (*Xenopus*; Malone and Michalak 2008). If investigation of multiple independent ZW origins and multiple independent XY origins support the same mechanistic basis of HR, it simultaneously rules out the thousands of other features that potentially differ between lineages and indicates that HR is not an illusory artifact of small sample size. Thus, in our view each of these lines of comparison—XY->ZW, XY->XY, ZW->ZW, sex reversal—provides valuable insight about the significance and mechanistic basis of HR. Given the new studies discussed, a broader sense interpretation of Read and Nee indicates that the number of independent transitions has nearly quadrupled since 1991. In summary, these include mosquitoes, stalk-eyed flies, tsetse flies, and *Drosophila*, giving 4 total independent origins in Diptera to date. Add to this *Silene*, *Tribolium*, 2 genera of stickleback fish, and the rest of the previously mentioned examples (Lepidoptera, birds, mammals, salamanders, lizards, nematodes, gastropods) and the total comes to 15. Note however, that we hesitate to even state this number as it depends on the extent to which transitions among non- (or only partially) homologous XY systems are included as independent origins of HR, which in turn depends on the underlying genetic bases of HR in the various systems. Lastly, the total will almost certainly increase as more studies of HR and clade-level sex-chromosome studies are completed.

The Genetic Mechanisms: Theoretical and Empirical Perspectives

Several hypotheses have been put forth to explain HR, some of which have been falsified (Wu et al. 1996; Coyne and Orr 2004). For example, Haldane himself rejected the idea that maleness (or sex) *per se* was the cause, because in butterflies and birds the ZW hybrid *females* are sterile (Haldane 1922). For simplicity, examples will be given here using XY, but are equally applicable to ZW systems unless otherwise explained. Of the nonrejected hypotheses, evidence appears to support some more than others, but nevertheless most need to be evaluated in more taxa for both rarity and sterility before they can be eliminated or accepted as general contributors to the rule.

Here, we describe 6 hypotheses for HR (Table 2) still considered to be credible based on theory and empirical data. Keep in mind that different genetic bases and/or combinations of hypotheses could all contribute to the phenotypes collectively recognized as HR (Slotman et al. 2005), especially in taxa with heterogametic males (Orr 1993; Wu and Davis 1993; Orr and Turelli 1996). The first, known as the dominance theory, is applicable to species with diploid expression of loci (more on this below), so is applicable to many but not all taxa. The second involves interactions with the sex specific chromosomes themselves, either Y or W. The third, known as faster-heterogametic sex theory, is a group of hypotheses that all propose genetic mechanisms unique to being heterogametic. The final 3 theories (faster-X, faster-males, and meiotic drive) all involve the basic premise that the rate of divergence varies among loci, and that loci whose rate of divergence is high are involved in the negative interspecific epistasis that leads to HR. Two suggest, for different reasons, that loci on the sex chromosomes should be diverging faster than loci on the autosomes, and one specifies which genes are likely to be evolving faster than others. While all 3 could be considered special cases of the faster-heterogametic sex theory, we treat them separately for historical reasons. Before explaining each hypothesis and evidence for or against it, we explain the Dobzhansky–Muller model of incompatibility upon which all of the hypotheses are based.

Dobzhansky–Muller (D–M) Model

The D–M model of hybrid incompatibility (Dobzhansky 1936; Muller 1939) can be described as follows. Start with an ancestral population with the genotype AABB at 2 loci. Split this population into 2 geographically isolated populations and allow mutations to build up over time via a process of selection and/or drift [or gene duplication followed by subfunctionalization (Lynch and Force 2000)]. Assume that as a consequence of this evolution one of the populations is now composed of individuals with the genotype A'A'BB and the other population is AAB'B' (and replicate this at numerous loci throughout the genome). Furthermore, assume for this example that the A'and B' alleles are incompatible with each other, causing either sterility or inviability when in combination. This does not present a problem for the 2 populations in allopatry, as the A' allele does not occur in combination with the B' allele.

However, when the 2 populations are brought together and allowed to hybridize, F1 hybrids will be A'AB'B and thus suffer a reduction in fitness relative to within-population crosses. Note that if the loci involved in D–M incompatibilities are all on the autosomes, then the sexes will be

Table 2. List of genetic hypotheses proposed to explain Haldane's rule (HR)

Theory	Theoretically applicable to HR in all systems?	Genetic explanation for why the heterogametic sex suffers	Sources
Dominance	No (requires diploid expression)	Hemizygosity of X- or Z-linked, partially recessive loci in the heterogametic sex	Muller (1942)
Sex-chromosome interactions	Yes	Interactions unique to sex chromosomes including: X–Y (Z–W) meiotic segregation difficulty[1], translocations[2], and epistasis[3]	Haldane (1922)[1]; Haldane (1932)[2]; Turelli and Orr (2000)[3]
Faster-heterogametic sex	Yes	Genome conflict involving sex chromosomes	Tao and Hartl (2003)
Faster-X (-Z)[a]	Yes	Faster divergence of X- or Z-linked loci	Charlesworth et al. (1987)
Faster male[a]	No (goes against HR in ZW systems)	Faster divergence and/or larger number of male reproductive genes	Wu and Davis (1993)
Meiotic drive[a]	Yes	Mismatch of drivers on sex chromosomes and restorers involved in sex-ratio distortion	Frank (1991a); Hurst and Pomiankowski (1991)

[a]Faster-X, faster-male and meiotic-drive theories can be framed as special cases of faster-heterogametic sex theory.

affected equally and HR will not be evident unless genes affecting only males or only females evolve at different rates (see below). Furthermore, even if F1 hybrid fitness is comparable to nonhybrid progeny, fitness reductions may occur in F2 hybrids as a result of genotypic combinations involving loci that are homozygous for derived alleles. Studies of HR typically ignore later generation hybrid breakdown because the rule is defined as an F1 phenomenon. However, sex differences in later generation hybrid phenotypes have been demonstrated in both animals and plants that contribute fruitful insight about the genetic basis of HR (Demuth and Wade 2007; Demuth et al. 2014).

All theories regarding the genetics underlying HR are based upon D–M incompatibilities as described above. In particular, these theories rely on the assumption that incompatibilities are more extreme in the sex with heterogametic sex chromosomes.

The Dominance Theory

The dominance theory is currently the predominant explanation for HR and is applicable to both hybrid sterility and rarity (Orr and Turelli 1996; Zeng 1996). It is based on the D–M model of incompatibility and is a derivation of the "X-autosome interaction theory" conceived by Muller (1942). For this hypothesis, at least one of the incompatible loci must be located on the sex chromosomes such that the heterogametic sex is hemizygous for the incompatibility (e.g., A'_B'B), while the homogametic sex is heterozygous (A'AB'B) in the F1 hybrids. If the sex-chromosome locus involved in the incompatibility is on the X chromosome, whether the locus acts in a dominant or recessive manner in hybrids will affect whether it counters or contributes to HR, which is why the theory is called the "dominance theory" (Turelli and Orr 1995, 2000). The logic behind this effect of dominance is as follows. Any X-linked gene that acts in a dominant fashion in the hybrids will be expressed in both sexes and hence, even if it is involved in a D–M incompatibility, it will not contribute to HR (e.g., the A'B' incompatibility will be expressed in both sexes in the F1 generation). In fact, such loci are likely to affect the homogametic sex more because they contain twice as many X chromosomes, each of which are likely to contain incompatible loci (Orr 1993). However, if an X-linked allele involved in the incompatibility is partially or fully recessive then it will disproportionately affect the heterogametic sex and will contribute to HR (e.g., incompatibilities involving a recessive A' may be masked by a dominant A in the heterozygous sex, A'AB'B, but not the hemizygous sex, A'_B'B). Hence, HR will hold when the X-linked loci involved in incompatibilities with the autosomes are, on average, partially recessive, and/or recessive incompatibilities have greater hemi/homozygous effects (Turelli and Orr 1995; Orr and Turelli 1996).

Given that much of the early empirical work on HR was dominated by *Drosophila* (with highly degenerate Y chromosomes), it is perhaps not surprising that explanatory descriptions of the theory often revolve around X chromosome-autosome incompatibilities and ignore the Y (e.g., Laurie 1997; Coyne and Orr 2004; Demuth and Wade 2005), when in fact the hemizygosity component of the theory is also applicable to Y-autosome and X–Y incompatibilities (Zeng 1996; Turelli and Orr 2000). Indeed, a*ny* Y-linked allele involved in a D–M incompatibility that is either not present or not expressed when it is on the X chromosome will be effectively hemizygous and contribute to HR, regardless of dominance.

There are several lines of evidence supporting the role of dominance in the manifestation of HR. First, dominance theory predicts that if incompatible loci located on autosomes could be made hemizygous, or homozygous on a foreign background, then HR should occur. Both deficiency screening (wherein a small autosomal region is deleted in 1 parent which is hybridized to produce progeny that are hemizygous for that region) and backcross introgressions have demonstrated that most autosomal loci contributing to isolation among *Drosophila* species are at least partially recessive (Muller and Pontecorvo 1942; Hollocher and Wu 1996; True et al 1996; Tao et al 2003; Presgraves 2003; Slotman et al. 2004). Second, dominance theory predicts that all else being equal, species with greater hemizygosity should evolve HR more rapidly. Turelli and Begun (1997) confirmed this prediction by comparing *Drosophila* species pairs with different proportions of their genome on the X. They found that species with relatively larger X chromosomes do evolve HR faster. Third, numerous studies have shown that sex-linked (X or Z) loci introgress less readily than autosomal loci across hybrid zones (Hagen and Scribner 1989; Saetre et al 2003; Payseur et al. 2004; Storchová et al. 2010; see also Harrison and Larson 2014) and that X-linked introgressions have a proportionally higher effect on hybrid progeny compared to autosomal introgressions (Orr 1987; Coyne and Orr 1989). Lastly, evidence consistent with the dominance theory for HR comes from coalescent-based models showing that autosomes have historically been more permeable to gene flow than sex-linked loci in birds (Carling et al. 2010; Manthey and Spellman 2014), flies (Garrigan et al. 2012), mice (Geraldes et al. 2008), and even our own species' hybridization with Neanderthals (Sankararaman et al. 2014). Based on these results we agree with Payseur (2009), who noted "multilocus surveys of population differentiation have a bright future in speciation research." It should be cautioned however, that although the patterns of sex-linked versus autosomal introgression and coalescence are expected under dominance theory, other factors may explain this "large X effect". Furthermore, observing an inequity between X and autosomal gene flow or discordance in the coalescence, may not necessarily indicate that HR is obeyed in the absence of evidence for sterility or inviability (Maroja et al. 2015).

In *Silene*, the sole plant genus investigated for HR so far, hybrids between *Silene latifolia* and *S. diclinus* showed significantly reduced pollen viability in F1 and second-generation hybrids (Brothers and Delph 2010; Demuth et al. 2014; Blackmon and Demuth 2016). Line-cross analysis revealed that the variation in pollen viability among generations was best explained by a combination of X-autosome epistasis and autosomal additive-by-dominance epistasis. In contrast, female ovule number, a measure of female fertility, was purely additive (i.e., hybrids show no reduction relative to the expected average value between parents). This pattern of X–A interaction in males but not females is the expected/necessary condition for dominance theory to hold (Demuth and Wade 2005).

Finding dominance theory as the underlying genetic basis to hybrid male sterility in *Silene* was not entirely expected. Heteromorphic sex chromosomes evolved independently more than once in the genus, coincident with dioecy (Mrackova et al. 2008), and they are relatively young in comparison to case studies in insects. Moreover, the differences in gene expression between the male gametes of animals (sperm) and the male gametophytes of plants (pollen) had been hypothesized to slow the rate of evolution of sex-chromosome heteromorphism, by slowing degeneration of Y-linked genes. Specifically, in contrast to spermatozoa, pollen grains express a large fraction of their genes (Haldane 1932), which permits purging of deleterious recessives during the haploid stage of pollen tube growth. The existence of these deleterious recessives is an important feature driving Y-degeneration in theory (Bull 1983; Charlesworth 2008; Chibalina and Filatov 2011). Early work on *Silene latifolia* supported the premise of relatively little degeneration (Bergero and Charlesworth

2011; Chilbalina and Filatov 2011). However, more recent results from a whole-genome sequencing study revealed extensive degeneration of Y-linked genes in this species on par with the level and rate of degeneration in animals (Papadopulos et al. 2015; see also Hough et al. 2014). This recent knowledge of relatively rapid degeneration is congruent with hemizygosity as the underlying genetic basis for the male sterility in hybrid dioecious *Silene*.

While abundant evidence now exists for this genetic basis to HR, the dominance theory cannot be applied to all organisms with heteromorphic sex chromosomes. What is not always appreciated is that the theory is based upon diploid expression of X-linked loci in the homogametic sex. This underlying assumption works for *Drosophila* (and all Diptera; Vicoso and Bachtrog 2015) and any other group that compensates for the presence of only one X in males by upregulating their X-linked genes rather than inactivating one of them in females—i.e. in cases in which hybrid females are heterozygous whereas hybrid males are hemizygous. It may also work in groups such as placental mammals that inactivate either the maternal X_m or the paternal X_p chromosome in a mosaic pattern among cells. However, in marsupials, where X_p is consistently silenced in all cells (Cooper et al. 1971; Richardson 1971), both females and males are functionally $X_mX_mA_mA_p$ and suffer the same potential suite of HR causing incompatibilities. As a consequence, the dominance theory cannot be applied to this group, and notably it contains the only examples where mammal hybrids do not conform to HR (see Watson and Demuth 2012). Nevertheless, the fact that many marsupial hybrids do exhibit HR, indicates that an additional mechanism(s) must contribute to the phenomenon (see below).

The roles of other mechanisms besides dominance theory also were previously indicated by *Drosophila* experiments where females inherit both X chromosomes from the same parent (Coyne 1985), and *Aedes* hybrids that lack hemizygous males (Presgraves and Orr 1998). In both cases, despite both sexes having the same potential complement of X-autosome incompatibilities, hybrid offspring tend to obey HR for sterility but not viability (i.e. depending on the species pair, F1 males but not females are sterile, or neither sex is viable). If the dominance theory explained HR, then all hybrids with the same X:A ratio should suffer the same sterility and viability consequences, independent of their sex.

Sex-Chromosome Interactions

Given that X–Y or Z–W interactions are specific to the heterogametic sex, it is reasonable to hypothesize that such interactions would be a factor contributing to Haldane's Rule. Such interactions have been shown to be involved in some (see Turelli and Orr 1995) but not all (Orr 1989; Johnson et al. 1992) studies of interspecific crosses between several *Drosophila* species. In addition, recent evidence from mice (Cocquet et al. 2012) are consistent with X and Y interactions in HR. In mice the X and Y-linked multicopy genes (*Slx*/*Slxl1* and *Sly*, respectively) seem to be involved in antagonistic coevolution wherein their relative expression but not their absolute expression is important for male fertility and sex ratio (Cocquet et al. 2012). Because these genes are present in different copy number across the *Mus* genus, hybrids that result in *Sly* deficient males are expected to be sterile.

However, it is worth noting that male sterility in the best-studied mouse hybrid system, *M. m. musculus* × *M. m. domesticus*, does not depend strongly on the Y-chromosome's origin (Campbell et al. 2012), and insect species with XO sex determination have been shown to follow HR (see Table 1). These results suggest that sex-chromosome incompatibilities are not a general explanation for HR. Nevertheless, they are implicated in at least some cases and therefore remain a credible mechanism.

Faster-Heterogametic Sex Theory

There are 3 ways that simply being heterogametic may foster the evolution of HR. The first, originally favored by Haldane (1922), is that non-coevolved X and Y (or Z and W) may have difficulty with proper segregation during meiosis. Haldane later suggested that this explanation was "inadequate" and evidence from *Drosophila* mutants with Y to X chromosome translocations caused him to favor a second, more generic, suggestion that the rule is a consequence of "interspecific differences in the sex chromosomes" Haldane (1932). Since translocations from the Y to the X (or W to Z) in 1 species will result in heterogametic hybrids that are missing part of their genome, the heterogametic sex potentially evolves postzygotic isolation faster than the homogametic sex. Although the original chromosomal mechanism *per se* (i.e. mispairing of XY or ZW in hybrids) largely fell out of favor, recent work has argued for its importance on theoretical grounds (Forsdyke 2000) and it is the best explanation for male rarity in some *Silene* hybrids noted above (Demuth et al. 2014).

The third way heterogamety may foster HR is faster evolution of individual loci that are either linked to the sex chromosomes or are autosomal but differentially expressed between sexes. The remaining 3 theories below each rely on this rapid evolution of loci that would ultimately affect heterogametic hybrids disproportionately and can therefore be framed as special cases of the faster-heterogametic sex theory. Furthermore, meiotic drive may also be viewed under the umbrella of conflict-driven evolution (Rice 2013). By definition, heterogametic sex chromosomes have asymmetric inheritance between males and females, which sets up the inevitability of genomic conflict because different parts of the genome have different optimal sex ratios. The consequences of genomic conflict are particularly acute for the heterogametic sex since the constant battle between X and Y (or Z and W) chromosomes for control of sex ratio within species is expected to result in interspecific heterogametic hybrids that bear maladapted, mismatched genome combinations (Tao and Hartl 2003).

Faster-X Theory

In *Drosophila*, X-chromosome substitutions have a larger impact than autosomal substitutions on hybrid sterility and inviability but not morphology (Coyne and Orr 1989). It has been suggested that both this "large-X effect" and HR may be explained by faster-X chromosome evolution (Charlesworth et al. 1987). This "faster-X" theory is based on the fact that under positive natural selection, X-linked substitutions occur at a faster rate than autosomal substitutions whenever new adaptive mutations are recessive on average. The main difficulty with the faster-X theory is that it cannot explain HR by itself since both sexes should be affected equally. Faster-X evolution may give rise to HR if X-linked substitutions also act recessively in hybrids (as in the dominance theory) and/or many genes involved in hybrid dysfunction are sex specific. The later will be true if adaptive substitutions in male-specific genes occur more rapidly than those of female genes when mutations are typically recessive and located on the X-chromosome.

Since faster-X evolution primarily explains the large-X effect and not HR *per se*, few studies unambiguously support the faster-X theory versus alternative hypotheses. For example, mapping studies that

demonstrate an overrepresentation of hybrid male-sterility genes on the X compared to the autosomes (Tao et al. 2003) or that show limited introgression of X-linked genes across hybrid zones (e.g., in mice, see Payseur et al. 2004; Macholan et al. 2007; Teeter et al. 2008) are demonstrations of the large-X effect that do not unambiguously implicate faster-X evolution. The most convincing evidence in support of faster-X would be accelerated molecular evolution of X-linked genes compared to autosomal genes.

In XY systems, the evidence for faster-X evolution was originally mixed, but recent studies mostly support faster-X evolution. Studies in *Drosophila* vary from early findings that showed no difference between X and autosome rates (Betancourt et al. 2002; Thornton et al. 2006), to limited (Counterman et al. 2004; Musters et al. 2006), or more recent strong support (Begun et al. 2007; Hu et al. 2013) for accelerated evolution on the X. In mammals, divergence consistent with the faster-X has been shown for comparisons between human and chimp (Lu and Wu 2005; Hvilsom et al. 2012), human and mouse (Torgerson and Singh 2003), mouse and rat (Baines and Harr 2007; Kousathanas et al. 2014), particularly for genes that are expressed more highly in males. The growing support for faster-X as a general explanation for the large-X effect is in part because of more powerful comparative approaches that incorporate within-species polymorphism data to calibrate divergence among species (reviewed in Meisel and Connallon 2013), and its role in driving substitution of sex-specific adaptations, such as sperm proteins (Torgerson and Singh 2003), may be particularly important for the evolution of HR.

Faster evolution of the Z relative to autosomes has also been detected in several birds (Mank et al. 2007, 2010; Corl and Ellegren 2012; Hogner et al. 2012; Wang et al. 2014; Oyler-McCance et al. 2015), snakes (Vicoso et al. 2013), and Lepidopterans (Sackton et al. 2014). However, unlike faster-X evolution, which appears to primarily be driven by selection, faster-Z evolution has mainly been attributed to random genetic drift (Wright et al. 2015). This may be because sexual selection on ZZ males will disproportionately decrease the effective population size of the Z more than similar selection on XY males. Moreover, results from flycatchers (Hogner et al. 2012) and ducks (Lavretsky et al. 2015) suggest selection is important for driving faster Z sequence divergence among species.

Faster-Male Theory

An alternative explanation for HR that also relies on rapid evolution of male specific genes is the "faster-male" hypothesis (Wu and Davis 1993). One distinction between the faster-X and faster-male hypotheses is that male reproductive genes *per se*, rather than genes on the X (i.e., these male reproductive genes can be anywhere), evolve more rapidly than female reproductive genes. The faster-male hypothesis also suggests that genes involved in spermatogenesis may be unusually susceptible to disruption in hybrids so that even if male and female genes evolve at the same molecular rate, the fitness consequences are greater for hybrid males (Wu and Davis 1993). For example, hybrid male *Xenopus* frogs appear to be sterile because spermatogenesis is "easily" disrupted and sensitive because of the relatively large number of genes involved (Malone and Michalak 2008).

The faster-male theory is not a universal explanation for HR. Indeed, a key insight of faster-males is that genes affecting fertility are likely to be sex specific, whereas genes affecting viability are not. Faster-male theory also cannot explain HR in species where females are the heterogametic sex; however, it does help explain cases of HR that cannot be reconciled with dominance theory. For example, the faster-male theory provides an explanation for the attached-X *Drosophila* (Coyne 1985), *Aedes* (Presgraves and Orr 1998), and marsupial (Watson and Demuth 2012) studies noted above where, in each case, hybrids more frequently obey HR for sterility than for inviability even when X:A ratios do not functionally differ between sexes. The evidence for faster mammal sperm-protein evolution (Torgerson and Singh 2003) is also consistent with the faster-male hypothesis, as are *Drosophila* introgression studies that find many more regions causing male sterility than female sterility (True et al 1996; Hollocher and Wu 1996; Tao and Hartl 2003). Finally, microarray studies show that male-specific genes are more likely to be misexpressed in *Drosophila* hybrids (e.g., Michalak and Noor 2003).

A difficulty with the faster-male theory is that it should actually work against development of HR in species with ZW sex determination systems (as in the *Xenopus* example above). The fact that birds and lepidopterans follow HR in so many instances suggests that even if the faster-male hypothesis is widely true, other mechanisms are also important in the evolution of HR.

Meiotic-Drive Theory

If a gene causing meiotic drive occurs on one sex chromosome and its suppressor(s) occurs on the other sex chromosome and/or an autosome, this could lead to biased sex ratios and sterility following hybridization (Frank 1991a; Hurst and Pomiankowski 1991). Moreover, new drivers can arise when fixed suppressors mask older drivers within populations (Hall 2004; Wilkinson et al. 2014). Basically, the theory assumes that a rapid arms race set up by drivers and suppressors leads to hybrid sterility because increasing divergence gives rise to incompatibilities; thus in addition to rarity of the heterogametic sex, gamete failure (sterility) can occur when there is a mismatch between the drivers and suppressors. Unlike faster-male evolution, this mechanism can work in both XY and ZW systems, and thereby apply to diverse taxa. In one type of meiotic drive, sperm/pollen are killed because the driving locus 'attacks' its counterpart on homologous chromosomes in male gametes (Wilkinson and Fry 2001; Taylor and Ingvarsson 2003). In the other, there is variation in centromeric sequences that determines which centromere makes it into the egg (Henikoff et al. 2001).

This explanation for HR was initially discounted, in part because F1 hybrids capable of reproducing (i.e., non-sterile) produced non-biased sex ratios (Coyne and Orr 1993), and because limiting assumptions regarding drivers on both the X and Y were made (Charlesworth et al. 1993). However since then, additional empirical work has heightened interest in, support for, and extensions to this theory (McDermoot and Noor 2010; Bundus et al. 2015). For example, a type of sex-chromosome drive has recently been shown to contribute to male rarity in crosses between nematode species in the genus *Caenorhabditis*: X-bearing sperm were shown to be superior competitors to Y-bearing sperm, as first-to-be-fertilized eggs produced more female-biased sex ratios than later fertilized eggs (Bundus et al. 2015). In addition, driver/suppressor systems have been shown to evolve rapidly (Pregraves et al. 2009; Bastide et al. 2011, 2013). Lastly, additional evidence showing either pleiotropy or tight linkage of X-linked suppressors and genes causing hybrid male sterility has been found in *Drosophila* (Tao et al. 2001; Orr 2005; Tao et al. 2007a, 2007b), as well as stalk-eyed flies (Wilkinson et al. 2014). This includes the X-linked gene *Overdrive*, which has been shown to affect both sex ratio and sterility in *Drosophila* (Phadnis and Orr 2009), and which interacts with other X-linked and autosomal loci to determine the extent of sex-ratio distortion

and sterility (Phadnis 2011). Hence, an important formerly missing piece of evidence—a direct connection between a driving gene and rarity/sterility (see Frank 1991b)—has been found.

Summary

The universality of Haldane's rule is now well established, emerging as one of the most robust generalizations in evolution. Indeed, what was once a phenomenon unique to animal speciation has now been demonstrated in plants as well. Furthermore, evidence from comparative genomics demonstrates that sex-chromosome turnover may be much more frequent that previously appreciated. Consequently, the number of independent associations between heterogamety and HR may be much larger than previously thought. Comparative genomic data, combined with additional species sampling, has lent support to mechanisms once discarded as unimportant (meiotic drive, Johnson et al. 1992; Coyne and Orr 1993) and the bevy of genetic mechanisms proposed to explain HR is as rich now as ever. Perhaps this should not come as a surprise, as multiple explanations for the same phenomenon is true for many patterns seen in nature.

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