

Haldane's Rule in Marsupials: What Happens When Both Sexes Are Functionally Hemizygous?

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During the process of speciation, diverging taxa often hybridize and produce offspring wherein the heterogametic sex (i.e., XY or ZW) is unfit (Haldane's rule). Dominance theory seeks to explain Haldane's rule in terms of the difference in X-linked dominance regimes experienced by the sexes. However, X inactivation in female mammals extends the effects of hemizyosity to both sexes. Here, we highlight where the assumptions of dominance theory are particularly problematic in marsupials, where X inactivation uniformly results in silencing the paternal X. We then present evidence of Haldane's rule for sterility but not for viability in marsupials, as well as the first violations of Haldane's rule for these traits among all mammals. Marsupials represent a large taxonomic group possessing heteromorphic sex chromosomes, where the dominance theory cannot explain Haldane's rule. In this light, we evaluate alternative explanations for the preponderance of male sterility in interspecific hybrids, including faster male evolution, X–Y interactions, and genomic conflict hypotheses.

Key words: *hybrid sterility, metatheria, reproductive isolation, speciation, X inactivation*

Haldane's Rule Is a Pattern Based on Sex Chromosomes, Not Sex

Of the few major patterns recognized in speciation, perhaps none has enjoyed as much attention as Haldane's rule. First noted by Haldane (1922), Haldane's rule describes the phenomenon that whenever divergent taxa produce hybrid offspring, the heterogametic (XY or ZW) sex suffers a reduction in fitness more often than the homogametic (XX or WW) sex. Several studies now demonstrate that Haldane's rule is a preliminary, though perhaps not requisite, stage of speciation (Coyne and Orr 1989a; Sasa et al. 1998; Presgraves 2002; Demuth and Wade 2007; Malone and

Fontenot 2008) and has come to be known as one of the "rules of speciation" (Coyne and Orr 2004; Demuth and Wade 2007; Turelli and Moyle 2007).

The study of Haldane's rule has shaped our understanding of speciation by providing a broad pattern in which to study the mechanisms of population divergence and fixation of reproductive isolating barriers. Importantly, this pattern holds across the majority of taxa studied, with examples of male and female heterogamety both conforming to Haldane's rule (Haldane 1922, 1932; Gray 1954, 1958; Hillis and Green 1990; Schilthuizen et al. 2011). For this reason, it is often noted that Haldane's rule cannot simply be explained by the general sensitivity of one sex over the other (Coyne and Orr 1989b). Instead, Haldane's rule is thought to be the result of genetic incompatibilities that are exaggerated in the genome of the heterogametic sex.

Dominance Theory and the Role of X Chromosomes in the Expression of Haldane's Rule

Among the early genetic explanations for Haldane's rule, Muller (1940, 1942) put forth the X-autosome interaction hypothesis noting that, owing to hemizyosity, hybrid males suffer from both dominant and recessive X-linked incompatibilities, whereas females only suffer from dominant incompatibilities (for convenience, we use male for the heterogametic sex and female for the homogametic sex). Orr (1993a) formalized Muller's theory mathematically and added that hemizyosity is a "double-edged sword": although males express every X-linked incompatibility, on average females contain twice as many because they possess 2 X chromosomes. If dominant and recessive incompatibilities are equally likely, these 2 factors cancel each other and cannot explain the consistently lower fitness of males (Orr 1993a). However, if recessive alleles are more likely to produce severe incompatibilities, Haldane's rule will result (Muller and Pontecarvo 1942). Thus, somewhat ironically, the "dominance theory" relies on genetic incompatibilities being recessive on average. To further complicate matters,

“dominance,” in the context of Haldane’s rule, refers only to the X-chromosome component of what is more precisely an epistatic interaction between X-linked and other (perhaps multiple) loci (Demuth and Wade 2007).

Beginning in the 1980s, studies extending the dynamics of hemizyosity to females began to suggest forces in addition to dominance might contribute to Haldane’s rule. For instance, when females carrying both X chromosomes from one parent in an otherwise hybrid genome (unbalanced females) were made from *Drosophila* species pairs that normally obey Haldane’s rule for sterility, the unbalanced female hybrids remained fertile. However, if the species pair normally obey Haldane’s rule for viability, unbalanced females became inviable (Coyne 1985; Orr 1993b). Later observations exploring *Aedes* mosquitoes that lack hemizygous sex chromosomes found related results. Hybrids follow Haldane’s rule for sterility, but not viability (Presgraves and Orr 1998). Although the mechanisms by which dominance effects in females are made equivalent to males is different in the unbalance female and *Aedes* studies, the conclusions are the same; when both sexes have the same dominance effects, fertility conforms to Haldane’s rule, but viability does not.

The unbalanced female and *Aedes* studies are instructive to the situation in mammals because female X-chromosome inactivation (XCI) results in only one X chromosome being expressed. Genetic explanations invoking dominance assume that chromosomal hemizyosity is equivalent to functional hemizyosity in terms of gene expression (Turelli and Orr 1995). Although this assumption is valid for *Drosophila*, where X-chromosome dosage compensation is achieved by the hypertranscription of the hemizygous X in males to equal the dosage expected of diploid autosomes and/or female Xs (Lucchesi 1973), it is clear that dosage compensation is not similarly achieved in other taxa (e.g., *Caenorhabditis elegans* and therian mammals—Xiong et al. 2010; *Anopheles*—Hahn and Lanzaro 2005; birds—Itoh et al. 2010; Lepidoptera—Zha et al. 2009; stickleback—Leder et al. 2010; platypus—Deakin et al. 2009; *Tribolium*—Prince et al. 2010; reviewed in Mank et al. 2011). Indeed, in their original formulation of dominance theory, Turelli and Orr (1995) asked, “Does the dominance theory work given mammalian dosage compensation?” Dosage compensation in mammals is particularly problematic for dominance theory because it involves XCI in females wherein one X chromosome is transcriptionally silenced (i.e., females are functionally hemizygous). Consequently, the average transcript ratio from XX:AA females is approximately 0.5—equal to the ratio in X:AA males (Gupta et al. 2006; but see Nguyen and Disteché 2006; Xiong et al. 2010). Following, we revisit Turelli and Orr’s question highlighting data from marsupial hybrids that have not previously been appreciated for what they may tell us about the genetic mechanisms underlying Haldane’s rule.

Dosage Compensation, X Inactivation, and the Role of Dominance in Haldane’s Rule

XCI is achieved by different means in metatherian (marsupial) and eutherian (placental) mammals. In placental

mammals, one copy of the X is randomly inactivated, forming a mosaic of maternal and paternal X-chromosome expression (Lyon 1961). In marsupial cells, males and females, both experience functional hemizyosity of the same set of alleles because it is always the paternal X chromosome that is inactivated (Cooper et al. 1971; Richardson et al. 1971; Al Nadaf et al. 2010). The consequences of mosaic XCI for dominance theory and Haldane’s rule in placentals depend on the degree of autonomy among cells, which is largely unknown in mammals. However, the consistent hemizygous expression of only the maternal X chromosome in marsupials has clear implications, providing a situation where, if Haldane’s rule is observed, dominance theory cannot be the explanation.

First, and perhaps more importantly, dominance theory assumes that all loci have diploid expression in F₁ females, as is the case in *Drosophila* (Turelli and Orr 1995; Orr and Turelli 1996; Turelli and Orr 2000). Because hemizygous expression of the maternal X chromosome is shared in both sexes in marsupials (Figure 1), dominance effects are the same in males and females. Hence, under dominance theory, hybrid males and females are expected to suffer the same expected reduction of fitness due to X-linked incompatibilities, and Haldane’s rule is not expected to consistently result. Additionally, the idea that females should suffer twice the average number of X-linked incompatibilities of males (Orr 1993a) is moot, if both sexes express the same X-chromosome complement. In sum, because X-linked alleles with strict paternal XCI are never functionally heterozygous, there is no X-linked dominance in either sex, and dominance theory predicts that Haldane’s rule should not hold in marsupial hybrids.

Haldane’s Rule for Sterility and Inviability in Hybrid Marsupials

Despite the prediction from dominance theory, published accounts show that Kangaroos (*Macropus*), Rock Wallabies (*Petrogale*), and Pademelons (*Thyogale*) obey Haldane’s rule for fertility in most cases (Close and Lowry 1990 and references therein; Sharman et al. 1990; Eldridge and Close 1993). In 10 of 11 species pairs, males are sterile while females are fertile. However, in the remaining species pair, females are sterile while males remain fertile, representing the only reported exception to Haldane’s rule for fertility among mammals (Table 1). When corrected for nonindependence among species pairs, the number obeying Haldane’s rule becomes 6 of 7 for sterility. Incomplete data for an additional 12 species pairs also suggest that fertility is more frequently disturbed in males than in females (Supplementary Table 1).

Despite the paucity of the female viability data reported, it remains possible to draw conclusions about Haldane’s rule for inviability. The probability of having exactly k offspring of a particular sex is $\binom{n}{k} p^k$, where n is the total number of offspring observed and $p = 0.5$. Two species pairs exhibit a >95% chance that one sex is rare or absent (*Petrogale assimilis* × *P. penicillata*, and *P. i. mareeba* × *P. assimilis*). The first species pair produced 9 females and 1 male,

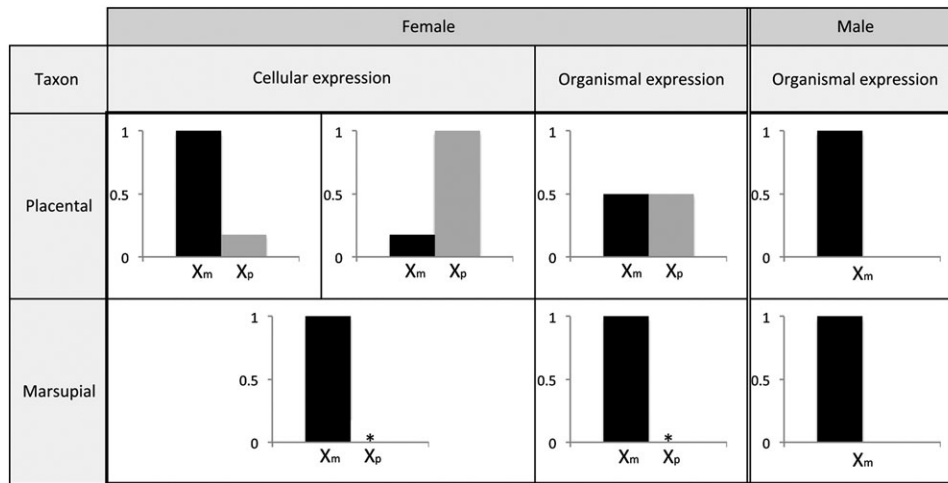


Figure 1. Expression of X-linked genes in therian mammals. Dosage inequality between the sexes is compensated in mammals by the inactivation of one X chromosome in females. Placental mammals inactivate either the maternal or paternal X chromosome at random, forming a mosaic of X-linked expression. Marsupial mammals inactivate only the paternal X chromosome, so that males and females only express the maternal X chromosome. Asterisk (*) indicates leaky expression.

conforming to Haldane's rule for inviability, whereas the second species pair produced 8 males and no females—a violation of Haldane's rule for inviability (Sharman et al. 1990). Interestingly, the reciprocal to this cross produced 6 females and 1 male, following Haldane's rule, although the result is nonsignificant ($p = 0.05469$). The majority of other interspecific crosses do not show significant asymmetry in viability between sexes ($0.5 \leq p \leq 0.05469$).

In placental mammals, Haldane's rule is obeyed in all 34 species pairs that produce sterile hybrids and in all 5 species pairs that produce only viable female hybrids (Laurie 1997; Schilthuizen et al. 2011). Marsupial crosses (reviewed in Close and Lowry 1990; Sharman et al. 1990; Eldridge and Close 1993) bring the overall therian mammal total for hybrid sterility to 40 of 41 species pairs and potentially add support for an additional 12 species pairs where data are limited (Supplementary Table 1). Although marsupials contain the only exceptions to Haldane's rule for both sterility and inviability among mammals, 52 of 53 hybridizations obeying the rule is still overwhelming support. If, as

we propose, dominance theory cannot explain Haldane's rule in marsupials, why does the pattern still hold so regularly?

Alternative Hypotheses for Haldane's Rule in Marsupials

A key insight following the unbalanced female experiments pointed out that the genetic basis for viability is likely to involve the same set of loci in both sexes, whereas the loci governing fertility are probably different in males and females (Wu and Davis 1993). Since then, many evolutionary biologists have viewed Haldane's rule as a composite phenomenon (Coyne 1992; Johnson et al. 1992; Orr 1993b; Wu and Davis 1993). This recognition, along with the observation that male sterility evolves faster than female sterility and faster than inviability in both sexes despite male fertility being less sensitive than viability to mutagenic disruption, led Wu and colleagues to propose that either sexual selection may drive rapid evolution of genes that contribute to male sterility or spermatogenesis may be inherently more sensitive than oogenesis to perturbation (Wu and Davis 1993, Wu et al. 1996). This so called “faster male” hypothesis has since been supported by diverse lines of evidence in plants and animals (Brothers and Delph 2010; Schilthuizen et al. 2011), including rapid evolution of male reproductive proteins by positive selection in placental mammals (Torgerson et al. 2002; Swanson et al. 2003; Clark and Swanson 2005; Good and Nachman 2005; Khaitovich et al. 2005). The data for marsupials is thus far consistent with the composite view of Haldane's rule. Evidence for Haldane's rule for viability is lacking, as expected under dominance theory with strict paternal XCI. Evidence for Haldane's rule for sterility is abundant, which is consistent with faster male evolution. Future studies of marsupial reproductive protein evolution may provide additional support for faster male evolution.

Table 1 Summary of studies of Haldane's rule in mammals

Group	Asymmetric phenotype	Crosses with asymmetric effects	Crosses obeying Haldane's rule	Percentage of obeying
Eutheria	Sterility	34	34	100.0
	Inviability	5	5	100.0
Metatheria	Sterility	7	6	85.7
	Inviability	2	1	50.0
Combined	Sterility	41	40	97.6
	Inviability	7	6	85.7

Data for eutherian mammals are from Schilthuizen et al. (2011). For a full list, see Supplementary Table 1.

Importantly, dominance and faster male theories need not be mutually exclusive. Indeed, Turelli and Orr (2000) discuss their relative roles under the same mathematical framework, where the influence of dominance scales with the proportion of the genome that is X linked, and the role of faster male evolution scales as the relative number and severity of male versus female incompatibilities. In marsupials, this interplay between dominance and faster male theories may remain, depending on the degree to which paternal X inactivation is leaky. Unfortunately, detailed mechanistic understanding of paternal XCI is still poorly understood. The most detailed study to date shows that paternal alleles escape XCI in 5–65% of cell lines (Al Nadaf et al. 2010). However, it remains unclear what proportion of transcripts at the surveyed loci belonged to the paternal X (i.e., it is unknown whether paternal alleles ever attain full expression) and furthermore, escape from inactivation may be stochastic (Al Nadaf et al. 2010).

An additional source of incompatibilities that may explain Haldane's rule in marsupials includes X–Y interactions, which have been suggested as a possible cause of male sterility in marsupials (Graves 1996; Graves and O'Neill 1997). In placental mammals, proper meiotic pairing of the X and Y is facilitated by pseudoautosomal regions (PARs). Disruption of pairing in the PAR blocks meiosis and results in male infertility due to abnormal sperm development (Burgoyne et al. 1992) and is a suggested explanation for Haldane's rule in placental mammals (Graves 1996). However, because marsupials do not possess a PAR region (X and Y pair at the tips in the absence of homology), X–Y interactions are suggested to be genic (Sharp 1982; Graves and O'Neill 1997). In hybrid males, the X and Y chromosomes are derived from different species, and heterospecific interactions or loss of gene complement may contribute to Haldane's rule for fertility in marsupials.

Additionally, genomic conflict, in the form of competition among oötidis for inclusion into the pronucleus, potentially plays a role in Haldane's rule in marsupials (reviewed in McDermott and Noor 2010). Centromeric sequences involved in spindle fiber attachment have been shown to be involved in such competition in mammals (Henikoff et al. 2001; Pardo-Manuel de Villena and Sapienza 2001). Separated by 1–2 My (Gifford et al. 2005), 2 wallaby sister species, *Macropus rufogriseus* and *M. eugenii*, differ greatly in the repeat content of their centromeric sequences (O'Neill et al. 1998; Metcalfe et al. 2007). Interspecific crosses between these species produce infertile male and female hybrids that display extensive chromosomal remodeling and genomic instability, for example, changes in chromatin structure and the amplification of satellite repeats and transposable elements (Metcalfe et al. 2007). The effects of genomic instability may contribute to Haldane's rule in marsupials if centromeric misalignment of the X and Y chromosomes during metaphase in hybrids leads to the failure of spermatogenesis (McKee 1997; Zwick et al. 1999; Henikoff et al. 2001). Furthermore, meiotic inactivation of sex chromosomes in male hybrids, a process crucial for male fertility in mammals (Royo et al. 2010), could be delayed or

derailed by the decondensation or amplification of centromeric regions. In marsupials, meiotic sex chromosome inactivation occurs before the X–Y associations that lead to the formation of the sex chromatin beginning at mid-pachytene (Namekawa et al. 2007). A delay in the formation of the sex chromatin may trigger the late-pachytene meiotic checkpoint and lead to spermatocyte apoptosis and reduced fertility, a phenomenon attributable to chromosomal asynapsis in placental mammals (Luan et al. 2001). If true, this mechanism would be consistent with more general “faster heterogametic sex” hypotheses that propose the XY sex evolves faster because of the conflicting pressures that the X and Y chromosomes experience to distort the sex ratio (Frank 1991; Hurst and Pomiankowski 1991; Tao and Hartl 2003).

Prospects for Future Research

In marsupial mammals, nature provides us with a system analogous to the unbalanced female experiments in *Drosophila* (Coyne 1985; Orr 1993b) and *Aedes* mosquito lacking hemizygous sex chromosomes (Presgraves and Orr 1998). In each case, the X-chromosome contribution to reproductive isolation is the same in males and females. In most species, dominance theory and faster male theory cannot be disentangled to reveal the cause of hybrid male sterility where they act simultaneously (Wu et al. 1996; Coyne and Orr 2004). However, because dominance theory cannot explain Haldane's rule in marsupials, understanding the genetics of hybrid male sterility and the evolutionary dynamics of sex chromosomes in this large group of diverse organisms will provide useful insight into one of the most sweeping empirical observations in evolutionary biology.

A major current limitation is that no records exist for hybridizations in non-macropodid marsupials such as opossums and possums (Didelphidae and Caenolestidae), gliders (Petauridae), bandicoots (Peramelemorphidae), and marsupial moles (Notoryctidae). While macropods, such as kangaroos, typically produce one offspring per season, many species in these families are highly fecund and produce anywhere from 4 to 10 offspring in a litter making them highly amenable to studying biases in sex ratio. Future research involving marsupials with high fecundity will potentially provide excellent candidates for studying the evolution of hybrid male sterility in nonplacental mammals.

Supplementary Material

Supplementary material can be found at <http://www.jhered.oxfordjournals.org/>.

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