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Haldane's Rule in Taxa Lacking a Hemizygous X

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Haldane's rule states that species hybrids of the XY sex are preferentially sterile or inviable. In all taxa known to obey this rule, the Y is inert and X-linked genes show full expression in XY individuals. Until recently, all theories of Haldane's rule depended on this hemizygosity. A test of Haldane's rule in animals lacking a hemizygous sex—mosquitoes having two functional sex chromosomes in both sexes—reveals that these species show Haldane's rule for sterility but not inviability. A related group having a "normal" hemizygous X obeys Haldane's rule for both sterility and inviability. These results support the faster male and dominance theories of Haldane's rule.

Mosquitoes of the genus *Aedes* have single-locus sex determination: Although females are XX and males are XY, both X and Y chromosomes carry complete homologous sets of genes and differ only at a single locus (or small chromosome region) specifying sex. Cytological work reveals that the X and Y, which recombine throughout their lengths, are morphologically indistinguishable (1). Genetic analysis of more than 60 sex-linked, visible, electrophoretic and DNA markers confirms that the Y carries homologous alleles at all loci studied (1, 2). Y gene activity has been confirmed in at least nine species of *Aedes* (1–3). Mosquitoes of the genus *Anopheles*, on the other hand, possess degenerate Y chromosomes and X-linked genes that show normal hemizygous expression and sex-linked patterns of inheritance (4).

The fact that *Aedes* lacks a hemizygous X, whereas *Anopheles* possesses one, allows several novel tests of the leading theories explaining Haldane's rule (5–7). Recent work suggests that Haldane's rule has two causes. The first, the so-called dominance theory, posits that the genes causing hybrid problems are mostly recessive (8–10). If so, XY individuals will suffer the full effects of all X-linked alleles causing hybrid problems, whereas XX individuals will partly mask such alleles in the heterozygous state. Consequently, the XY sex will suffer more severe hybrid problems than will the XX sex, and Haldane's rule results (8–10). Experiments with *Drosophila* suggest that dominance ex-

plains Haldane's rule for hybrid inviability (11–13). Dominance may also contribute to Haldane's rule for sterility, although the evidence here is less direct (12–14).

A second force, faster male evolution, may also cause Haldane's rule for sterility (6). Because male and female fertility typi-

cally involve different loci, Haldane's rule might simply reflect a faster rate of divergence of genes involved in male than in female reproduction. If so, hybrid male sterility would tend to arise before hybrid female sterility, yielding Haldane's rule in taxa with XY males. Several causes of faster male evolution have been suggested (6), the most popular positing that sexual selection drives especially rapid evolution of male-expressed genes (6, 15). Recent experiments suggest that faster male evolution may give rise to Haldane's rule for sterility, at least in *Drosophila* (12, 16). The faster male theory cannot, however, be extended to hybrid inviability, because genes affecting viability almost always affect both sexes (lethal mutations within species almost invariably kill both sexes) (6, 12, 16). The faster male theory also cannot be extended to explain hybrid sterility in taxa such as birds and butterflies, in which heterogametic females are preferentially sterile (6, 10).

The consensus view of Haldane's rule is, therefore, simple: Haldane's rule for inviability appears to be caused by dominance alone, whereas in taxa with heterogametic males, Haldane's rule for sterility appears to be caused by both dominance and faster male evolution (7, 12, 16, 17).

The contrast between *Aedes* and *Anopheles* provides nearly ideal material for testing this view. These theories predict that: (i) If the faster male theory is correct, *Aedes* should

Table 1. *Aedes* hybridizations. B, both sexes affected; M, males affected; F, females affected; N, neither sex affected. Dashes indicate no data or that data did not match criteria (18). Some hybridizations are reviewed in (23); a full list of references is available from the authors.

Species pair		Cross	
A	B	A × B	B × A
Hybrid sterility			
<i>Ae. zoosophas</i>	<i>Ae. hendersoni</i>	B	B
<i>Ae. zoosophas</i>	<i>Ae. brelandi</i>	—	B
<i>Ae. zoosophas</i>	<i>Ae. triseriatus</i>	M	M
<i>Ae. triseriatus</i>	<i>Ae. brelandi</i>	M	N
<i>Ae. triseriatus</i>	<i>Ae. hendersoni</i>	M	N
<i>Ae. sollicitans</i>	<i>Ae. taeniorhynchus</i>	B	B
<i>Ae. taeniorhynchus</i>	<i>Ae. nigromaculatus</i>	B	B
<i>Ae. s. malayensis</i>	<i>Ae. s. polynesiensis</i>	M	—
<i>Ae. cooki</i>	<i>Ae. pseudoscutellaris</i>	M	—
<i>Ae. cooki</i>	<i>Ae. p. Niuafo'o</i>	M	N
<i>Ae. s. malayensis</i>	<i>Ae. s. katharensis</i>	M	—
<i>Ae. mariae</i>	<i>Ae. zammitii</i>	M	M
<i>Ae. mariae</i>	<i>Ae. phoeniciae</i>	M	B
<i>Ae. zammitii</i>	<i>Ae. phoeniciae</i>	B	B
Hybrid inviability			
<i>Ae. albopictus</i>	<i>Ae. aegypti</i>	B	B
<i>Ae. albopictus</i>	<i>Ae. seatoi</i>	B	B
<i>Ae. albopictus</i>	<i>Ae. pseudoalbopictus</i>	B	B
<i>Ae. seatoi</i>	<i>Ae. pseudoalbopictus</i>	B	B
<i>Ae. pernotatus</i>	<i>Ae. hebrideus</i>	—	M
<i>Ae. communis</i>	<i>Ae. churchillensis</i>	B	—
<i>Ae. zoosophas</i>	<i>Ae. brelandi</i>	B	—
<i>Ae. aegypti</i>	<i>Ae. simpsoni</i>	—	B
<i>Ae. kesseli</i>	<i>Ae. alcasidi</i>	F	—

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obey Haldane's rule for sterility despite the fact that it lacks a hemizygous X. Because the faster male theory depends on sexual selection, it (unlike all other theories explaining Haldane's rule) can act in taxa lacking a hemizygous X. (ii) If dominance also causes Haldane's rule for sterility, then, all else being equal, a greater fraction of *Anopheles* than *Aedes* hybridizations should obey Haldane's rule for sterility. The reason is that two forces (faster male evolution and dominance) cause Haldane's rule in taxa having a hemizygous sex, whereas only one force (faster male evolution) causes Haldane's rule in taxa lacking a hemizygous sex. (iii) Considering Haldane's rule for inviability, *Anopheles* should show sex-limited inviability (with males preferentially affected), whereas *Aedes* should show little or no sex-limited inviability. Dominance, after all, is irrelevant to taxa lacking hemizygosity.

We collected data from the literature on species crosses in *Aedes* and *Anopheles*. Considering only species crosses showing some reproductive isolation, and tabulating hybrid sterility and inviability separately, we classified the outcome of each species cross as "male-affected" hybrid problems, "female-affected" problems, or "both-sexes-affected" problems (18) (Tables 1 and 2).

We consider our predictions in turn. First, *Aedes* obeys Haldane's rule for hybrid sterility (Table 3). Haldane's rule thus appears to extend beyond taxa having a hemizygous sex chromosome. Although we cannot be certain that all of the hybridizations in Table 3 are phylogenetically independent, the fact that male-only hybrid sterility is routinely seen in *Aedes* (11 out of 11 cases), whereas female-only sterility is never seen, provides strong support for faster male evolution. This pattern of conformity to Haldane's rule for sterility is as strong as that seen in mammals and Lepidoptera (5-7). These results also show that faster male evolution cannot be due to a higher rate of substitution of recessive male-beneficial mutations on the X chromosome (12, 17, 19), a process that depends on hemizygous selection of male-expressed genes and so cannot act in *Aedes*. Thus, at least one of the forces causing Haldane's rule for sterility must act when the X is not hemizygous. Sexual selection, which clearly operates in the genus *Aedes* (20), seems a likely candidate (6).

Second, the fraction of hybridizations showing Haldane's rule for sterility relative to those showing both-sex sterility is lower in *Aedes* than in *Anopheles*: About one-half of *Aedes* versus three-quarters of *Anopheles* crosses show male-affected problems. Although alternative explanations of this trend are certainly possible (21), it is at least consistent with the trend expected if both faster male evolution and dominance cause Hal-

Table 2. *Anopheles* hybridizations. B, both sexes affected; M, males affected; F, females affected; N, neither sex affected. Dashes indicate no data or that data did not match criteria (18). *Anopheles* hybridizations are reviewed in (23, 24); a full list of references is available from the authors.

Species pair		Cross	
A	B	A × B	B × A
Hybrid sterility			
<i>An. gambiae</i> A	<i>An. gambiae</i> B	M	M
<i>An. gambiae</i> A	<i>An. gambiae</i> C	M	M
<i>An. gambiae</i> A	<i>An. merus</i>	M	M
<i>An. gambiae</i> A	<i>An. melas</i>	M	M
<i>An. gambiae</i> B	<i>An. gambiae</i> C	M	M
<i>An. gambiae</i> B	<i>An. merus</i>	M	M
<i>An. gambiae</i> B	<i>An. melas</i>	M	M
<i>An. gambiae</i> C	<i>An. merus</i>	M	M
<i>An. gambiae</i> C	<i>An. melas</i>	M	M
<i>An. merus</i>	<i>An. melas</i>	M	M
<i>An. leucosphyrus</i> (Sum)	<i>An. leucosphyrus</i> (Thai)	M	—
<i>An. malanoon</i>	<i>An. atroparvus</i>	M	—
<i>An. labranchiae</i>	<i>An. atroparvus</i>	M	—
<i>An. subalpinus</i>	<i>An. atroparvus</i>	M	—
<i>An. maculipennis</i>	<i>An. atroparvus</i>	B	—
<i>An. labranchiae</i>	<i>An. subalpinus</i>	B	—
<i>An. labranchiae</i>	<i>An. maculipennis</i>	B	—
<i>An. freeborni</i>	<i>An. occidentalis</i>	M	M
<i>An. freeborni</i>	<i>An. atroparvus</i>	M	—
<i>An. freeborni</i>	<i>An. hermsi</i>	M	M
<i>An. faraulti</i> 1	<i>An. faraulti</i> 2	B	B
<i>An. faraulti</i> 1	<i>An. koliensis</i>	B	B
<i>An. faraulti</i> 2	<i>An. koliensis</i>	B	B
<i>An. koliensis</i>	<i>An. punctulatus</i>	—	B
<i>An. faraulti</i> 1	<i>An. faraulti</i> 3	M	B
<i>An. faraulti</i> 2	<i>An. faraulti</i> 3	B	B
<i>An. litoralis</i>	<i>An. subpictus</i>	M	—
<i>An. pseudopunct-Mex</i>	<i>An. pseudopunct-S. Am.</i>	B	N
<i>An. sudaicus</i>	<i>An. litoralis</i>	M	M
<i>An. dirus</i> A	<i>An. dirus</i> B	N	M
<i>An. dirus</i> A	<i>An. balabacensis</i>	M	M
<i>An. dirus</i> B	<i>An. balabacensis</i>	N	M
<i>An. dirus</i> A	<i>An. dirus</i> C	M	N
<i>An. dirus</i> E	<i>An. dirus</i> A	M	M
<i>An. dirus</i> E	<i>An. dirus</i> B	B	B
<i>An. dirus</i> E	<i>An. dirus</i> C	M	B
<i>An. dirus</i> E	<i>An. dirus</i> D	B	B
<i>An. albitarsus</i>	<i>An. daeneorum</i>	M	B
<i>An. crucians</i>	<i>An. bradleyi</i>	M	M
<i>An. quadrimaculatus</i> A	<i>An. quadrimaculatus</i> B	M	M
<i>An. culicifacies</i> A	<i>An. culicifacies</i> B	M	M
<i>An. culicifacies</i> A	<i>An. culicifacies</i> C	M	—
<i>An. sinensis</i>	<i>An. sp. Engaru</i>	M	M
<i>An. maculatus</i>	<i>An. willmori</i>	—	M
<i>An. minimus</i> Y	<i>An. minimus</i> G	M	M
<i>An. balabacensis</i> -TKK	<i>An. balabacensis</i> -KKT	M	M

dane's rule for sterility in taxa with a hemizygous sex.

Third, although *Anopheles* routinely shows sex-limited hybrid inviability, *Aedes* does not (Table 3). This observation supports the dominance theory: In *Anopheles*, recessive X-linked alleles might kill hybrid males but not females (as observed); in *Aedes*, on the other hand, any allele dominant enough to kill one hybrid sex should be dominant enough to kill the other as well, and thus most hybridizations should fall into the both-sexes-affected class (as observed) (22). It should be emphasized that the dominance theory would have been disproved if *Aedes* routinely showed sex-limited inviability or if *Anophe-*

les did not. Instead both groups behave as predicted by the dominance theory.

Taken together, these findings provide support for the recent suggestion that Haldane's rule is caused by at least two evolutionary forces—dominance and faster male evolution.

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Table 2 (continued).

Species pair		Cross	
A	B	A × B	B × A
Hybrid inviability			
<i>An. dirus B</i>	<i>An. dirus C</i>	B	—
<i>An. dirus B</i>	<i>An. dirus A</i>	B	B
<i>An. dirus D</i>	<i>An. dirus A</i>	M	—
<i>An. dirus D</i>	<i>An. dirus B</i>	B	—
<i>An. dirus D</i>	<i>An. dirus C</i>	B	—
<i>An. messeae</i>	<i>An. atroparvus</i>	B	—
<i>An. farauti 1</i>	<i>An. punctulatus</i>	B	B
<i>An. farauti 2</i>	<i>An. punctulatus</i>	B	M
<i>An. punctulatus</i>	<i>An. koliensis</i>	B	—
<i>An. sinensis</i>	<i>An. sineroides</i>	B	—
<i>An. sinensis</i>	<i>An. lesteri</i>	B	B
<i>An. philippinensis</i>	<i>An. nivipes</i>	M	M
<i>An. punctipennis</i>	<i>An. perplexens</i>	M	B
<i>An. quadrimaculatus D</i>	<i>An. quadrimaculatus A</i>	B	—
<i>An. minimus</i>	<i>An. aconitus</i>	B	B
<i>An. maculatus</i>	<i>An. willmori</i>	M	—
<i>An. freeborni</i>	<i>An. occidentalis</i>	M	M
<i>An. freeborni</i>	<i>An. quadrimaculatus</i>	B	B
<i>An. freeborni</i>	<i>An. aztecus</i>	M	M
<i>An. freeborni</i>	<i>An. punctipennis</i>	M	—
<i>An. freeborni</i>	<i>An. earli</i>	B	—
<i>An. freeborni</i>	<i>An. atroparvus</i>	M	—
<i>An. earli</i>	<i>An. occidentalis</i>	B	—
<i>An. quadrimaculatus</i>	<i>An. aztecus</i>	B	B
<i>An. punctipennis</i>	<i>An. aztecus</i>	B	B
<i>An. sacharovi</i>	<i>An. atroparvus</i>	F	—
<i>An. quadrimaculatus</i>	<i>An. atroparvus</i>	M	M
<i>An. labranchiae</i>	<i>An. maculipennis</i>	M	—
<i>An. labranchiae</i>	<i>An. messeae</i>	B	—
<i>An. maculipennis</i>	<i>An. messeae</i>	B	—
<i>An. quadrimaculatus</i>	<i>An. punctipennis</i>	B	B
<i>An. atropos</i>	<i>An. bradleyi</i>	B	—
<i>An. freeborni</i>	<i>An. bradleyi</i>	B	—
<i>An. quadrimaculatus</i>	<i>An. quadrimaculatus</i>	B	B
<i>An. crucians</i>	<i>An. freeborni</i>	B	—
<i>An. crucians</i>	<i>An. quadrimaculatus</i>	B	—
<i>An. stephensi</i>	<i>An. superpictus</i>	B	B
<i>An. stephensi</i>	<i>An. tesellatus</i>	B	—
<i>An. stephensi</i>	<i>An. maculatus</i>	M	B
<i>An. quadrimaculatus A</i>	<i>An. quadrimaculatus B</i>	M	—
<i>An. farauti 2</i>	<i>An. farauti 3</i>	M	—
<i>An. farauti 1</i>	<i>An. farauti 3</i>	M	—
<i>An. litoralis</i>	<i>An. subpictus</i>	M	—
<i>An. quadrimaculatus A</i>	<i>An. quadrimaculatus C</i>	F	F
<i>An. culicifacies A</i>	<i>An. culicifacies C</i>	M	B

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Table 3. Summary of hybridizations.

		Females affected	Males affected	Both sexes affected
<i>Aedes</i>	Sterility	0	11	10
	Inviability	1	1	11
<i>Anopheles</i>	Sterility	0	56	20
	Inviability	3	21	40

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18. We included only hybridizations showing clear evidence of postzygotic isolation. Isolation was classified by the following criteria. Hybrid sterility: Male-affected cases included hybridizations in which (i) F_1 hybrid males were completely sterile, whereas F_1 hybrid females were fertile, or (ii) F_1 male fertility was much lower than F_1 female fertility (as seen in crossing tests). The reverse held for female-affected sterility. Both-sexes-affected sterility included cases in which both hybrid males and females (i) were completely sterile; (ii) suffered similar and significant reductions in fertility relative to intraspecific controls; or (iii) had degenerate testes or sperm (or both) and ovaries that precluded crossing tests of fertility (nondegenerate gonads were never used as evidence of fertility, though fully atrophied gonads were assumed to be sterile). Hybrid inviability: Analogous rules were used to classify inviability. To prevent the confounding of hybrid inviability with postmating, prezygotic barriers to fertilization, we only included hybridizations in which eggs were embryonated. Reciprocal species crosses (where available) were scored separately.

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21. The average *Aedes* hybridization might, by chance, be older than the average *Anopheles* one. It is difficult to distinguish this possibility from the dominance theory, because the latter also predicts that *Aedes* will take longer than *Anopheles* to evolve postzygotic isolation (73).

22. *Aedes* routinely shows single-sex effects for hybrid sterility but not for hybrid inviability. This within-genus contrast cannot be explained by the notion that species pairs in one genus are older than those in the other.

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