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POPULATION DIFFERENTIATION IN THE BEETLE *TRIBOLIUM CASTANEUM*. II. HALDANE'S RULE AND INCIPIENT SPECIATION

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The heterogametic sex tends to be rare, absent, sterile, or deformed in F1 hybrid crosses between species, a pattern called Haldane's rule (HR). The introgression of single genes or chromosomal regions from one drosophilid species into the genetic background of another have shown that HR is most often associated with fixed genetic differences in inter-specific crosses. However, because such introgression studies have involved species diverged several hundred thousand generations from a common ancestor, it is not clear whether HR attends the speciation process or results from the accumulation of epistatically acting genes postspeciation. We report the first evidence for HR prior to speciation in crosses between two populations of the red flour beetle, *Tribolium castaneum*, collected 931 km apart in Colombia and Ecuador. In this cross, HR is manifested as an increase in the proportion of deformed males compared to females and the expression of HR is temperature dependent. Neither population, when crossed to a geographically distant population from Japan, exhibits HR at any rearing temperature. Using joint-scaling analysis and additional data from backcrosses and F2's, we find that the hybrid incompatibilities and the emergence of HR are concurrent processes involving interactions between X-linked and autosomal genes. However, we also find many examples of incompatibilities manifest by F2 and backcross hybrids but not by F1 hybrids and most incompatibilities are not sex different in their effects, even when they involve both X-autosomal interactions and genotype-by-environment interactions. We infer that incipient speciation in flour beetles can occur with or without HR and that significant hybrid incompatibilities result from the accumulation of epistatically acting gene differences between populations without differentially affecting the heterogametic sex in F1 hybrids. The temperature dependence of the incompatibilities supports the inference that genotype-by-environment interactions and adaptation to different environments contribute to the genetic divergence important to postzygotic reproductive isolation.

KEY WORDS: Dominance, epistasis, genotype-by-environment interaction, hybrid breakdown, joint-scaling, X-autosome interaction.

"When in the offspring of two different animal races one sex is absent, rare, or sterile, that sex is the heterozygous [hetergametic] sex." —J.B.S. Haldane (1922)

Haldane's rule's (HR) is the best supported empirical generalization about postzygotic isolation (Laurie 1997; Coyne and Orr 2004). The ubiquity of HR and the observation that, in inter-specific crosses, it tends to precede reproductive incompatibilities affecting both sexes (Coyne and Orr 1989, 1997; Presgraves 2002; Price and Bouvier 2002), suggest that it may be an obligatory first step in the origin of intrinsic reproductive isolation. Thus, understanding the origins and genetic basis of HR is critical to

understanding the origin of biological species (Mayr 1942, 1970; Coyne 1992).

Interactions between autosomal and recessive X-linked genes are the primary cause of HR (Muller 1940, 1942; Orr 1993; Turelli and Orr 1995, 2000; Demuth and Wade 2005). In taxa where males are the heterogametic sex, "faster–male evolution" also contributes to HR for hybrid male sterility (Wu and Davis 1993; Wu et al. 1996). Two other mechanisms, "faster-X" and "meiotic drive" may also contribute in some taxa, although the evidence is somewhat weaker (Frank 1991; Pomiankowski and Hurst 1993; Naveira 2003; Coyne and Orr 2004). Genetic studies of HR from *Drosophila* hybridizations implicate many genes (>120) of small effect (Palopoli and Wu 1994; True et al. 1996; Presgraves 2003; Tao and Hartl 2003; Taoet al. 2003a, 2003b). However, these estimates may be inflated by data from older species pairs because fewer genes appear to be involved in HR in crosses between subspecies of *Drosophila pseudoobscura* (Orr and Irving 2001).

In many taxa, prezygotic isolating mechanisms may eliminate gene flow prior to hybrid incompatibility (Grant and Grant 1997; Price and Bouvier 2002) with the result that post-zygotic isolating mechanisms, such as HR, maintain species boundaries but are not causative of speciation (Butlin and Tregenza 1997; Saetre et al. 1997; Mallet et al. 1998; Rundle and Schluter 1998; Nosil et al. 2003; Ortiz-Barrientos and Noor 2005). Under the standard interpretation of the Bateson–Dobzhansky–Muller speciation model, HR is generally attributed to adaptation to different local environments (e.g., Charlesworth et al. 1987). However, the role of environment in the expression of HR has not been extensively explored except in a handful of cases (Wade et al. 1999; Bordenstein and Drapeau 2001; Willett and Burton 2003) and "The relative importance of GEI [genotype-by-environment interaction] in the speciation process is not currently known (Bordenstein and Drapeau 2001, p. 499)." Furthermore, introgression studies are conducted under environmental conditions designed to give the strongest phenotypic signal, such as the absence of F1 males or maximum F1 male sterility, to better detect genetic causes of HR. Thus, fundamental questions about HR remain, including, "How much genetic divergence is necessary between populations before HR

Table 1. Effects of temperature, generation (parental crosses versus F1 and rF1 crosses) and temperature × cross interaction on differences in offspring numbers and proportion of developmental defects between sexes. Values represent *F*-statistics based on analysis of variance with associated *P*-values in parentheses. Degrees of freedom for each test are temperature = 1; cross and temp × cross = 3. Asterisk indicates not significant after sequential Bonferroni correction for 36 tests (Rice 1989). Bold values indicate $P < 0.05$.

Cross	Total males–females			Proportion deformed males–proportion deformed females		
	Temp.	Generation	G×E	Temp.	Generation	G×E
Croatia × Portugal	0.184 (0.67)	1.627 (0.208)	0.000 (1.0)	3.424 (0.067)	0.115 (0.736)	1.005 (0.321)
Colombia × Ecuador	1.358 (0.249)	0.260 (0.612)	0.802 (0.375)	**11.977** **(0.001)**	**8.586** **(0.005)**	**6.842** **(0.012)***
Nigeria × Croatia	0.002 (0.967)	0.503 (0.481)	0.000 (0.988)	**7.471** **(0.009)***	0.441 (0.51)	0.323 (0.572)
Tanzania × India	0.898 (0.348)	0.108 (0.744)	0.279 (0.6)	0.000 (0.988)	0.363 (0.549)	2.199 (0.145)
Peru × Mexico	0.008 (0.927)	0.839 (0.364)	1.048 (0.311)	0.059 (0.808)	0.497 (0.484)	0.078 (0.781)
Ecuador × Portugal	7.776 (0.007)	0.192 (0.663)	3.299 (0.075)	0.292 (0.591)	1.27 (0.264)	0.142 (0.707)
Peru × Portugal	3.915 (0.054)	0.528 (0.471)	0.236 (0.629)	0.384 (0.539)	0.113 (0.739)	**6.699** **(0.013)***
Malaysia × Croatia	1.04 (0.313)	1.556 (0.218)	0.434 (0.513)	0.373 (0.544)	0.132 (0.718)	0.004 (0.949)
Nigeria × Malaysia	0.211 (0.648)	0.088 (0.768)	0.088 (0.768)	0.01 (0.919)	0.049 (0.825)	0.521 (0.474)
Japan × Colombia	2.844 (0.098)	1.907 (0.173)	3.959 (0.052)	2.039 (0.16)	0.402 (0.529)	0.241 (0.626)
Ecuador × Japan	2.291 (0.136)	0.375 (0.543)	0.209 (0.65)	0.4 (0.53)	1.132 (0.293)	0.4 (0.53)
USA (IN) × Malaysia	0.946 (0.336)	1.023 (0.317)	1.483 (0.229)	0.325 (0.572)	0.136 (0.714)	2.546 (0.118)

is detectable?" and "What role does the environment play in the genetic divergence leading to HR?"

We established reciprocal crosses using males and females from 12 widely dispersed geographic populations of the red flour beetle, *Tribolium castaneum*, at two temperatures (29 and 34°C) and measured sex differences in offspring numbers (i.e., viability) and in the distal deformities of the exoskeleton. We report our observation of HR, measured as a male-biased incidence of deformities in the F1 and reciprocal F1 relative to parental crosses, occurring in hybridizations between two populations collected 931 km apart from Colombia and Ecuador. In this cross, the expression of Haldane's rule is temperature dependent and neither population, when crossed to a geographically distant population from Japan, exhibits Haldane's rule at any rearing temperature. We also find many examples of incompatibilities manifest by F2 and backcross hybrids but not by F1 hybrids and most observed incompatibilities are not sex different in their effects.

Methods

The red flour beetle, *Tribolium castaneum*, is a cosmopolitan human commensal and major pest of stored cereal crops. As part of a larger investigation of the genetic architecture of divergence among *T. castaneum* populations (Demuth and Wade 2007), we categorized interpopulation hybrid offspring by sex and by presence or absence of developmental abnormalities, including missing or fused antennal and limb segments and failure to properly eclose from the pupal stage. The experimental populations and protocols used here are the same as those of Demuth and Wade (2007), except that the Ecuador × Mexico, India × Mexico, and Tanzania × Mexico crosses are excluded because we did not score the sex of the hybrid offspring. *T. castaneum* has nine autosomes and X/Y sex determination. Thus, HR suggests males will suffer the negative consequences of hybridization to a greater extent than females.

To identify potential cases of HR, we first tested whether there was a sex difference in the numbers and/or proportion of deformed offspring of pure parent crosses versus F1 and reciprocal (rF1) hybrids. Specifically, we use generation (i.e., Parent or F1), and rearing temperature, as fixed effects in two-way analyses of variances (ANOVAs) on two composite variables, (total females–total males), and (proportion of deformed males–proportion of deformed females). When positive, both of these composite variables indicate a female biased sex difference in viability or development and, when either is significantly greater in F1 than in the Parental crosses, it is evidence of HR. Both variables have been shown to characterize inter-specific hybrids in crosses between males of *T. castaneum* and females of *T. freemani* and both types of HR exhibit significant G × E (Wade et al. 1999).

Quantitative genetic theory (Demuth and Wade 2005) predicts that HR will hold when the following condition is met:

$$\frac{\delta_x + J_{\delta\delta_x}}{x + K_{\delta x}} < 1, \tag{1}$$

where x is the additive effect of hemizygous males, δ_x is the dominance effect of X-linked heterozygosity, $K_{\delta x}$ is the X-autosome dominance-by-additive epistasis, and $J_{\delta\delta}$ is the X-autosome dominance-by-dominance epistasis. To test this prediction, we performed joint-scaling analyses separately on males
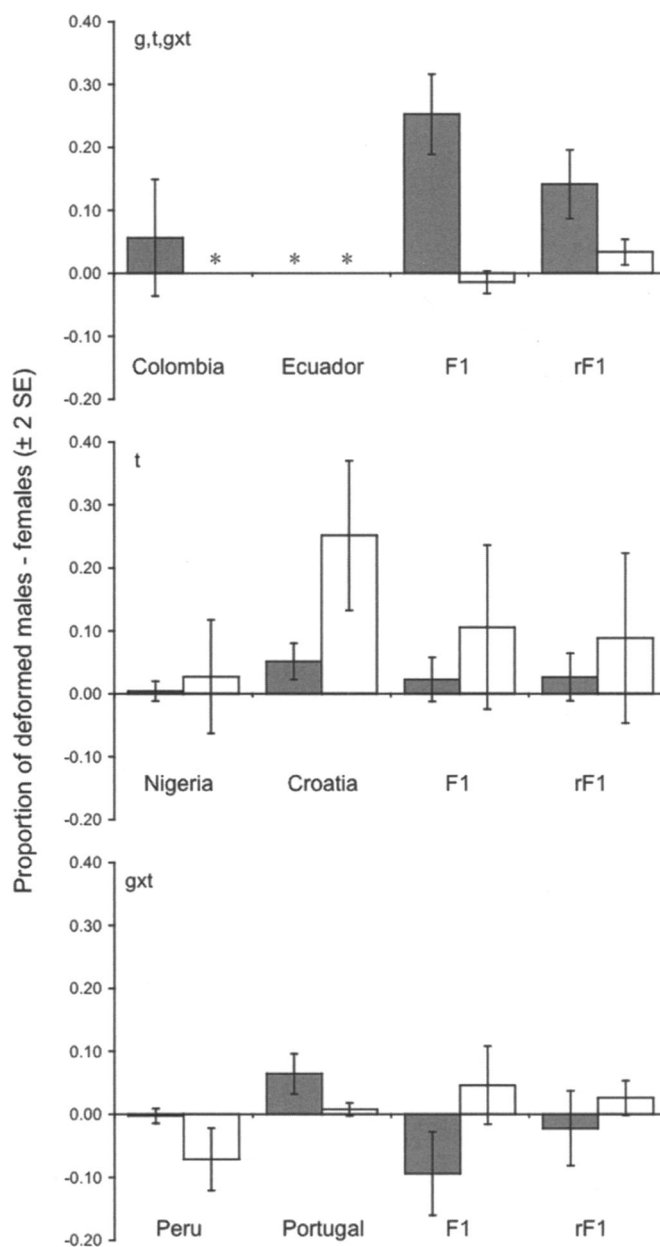

Figure 1. Sex difference in the proportion of deformed offspring from Columbia × Ecuador Nigeria × Croatia, and Peru × Portugal crosses. F1 and rF1 indicate reciprocal crosses. Positive deviations from zero indicate a larger proportion of deformed males than females. g, t, and g × t indicate where generation, temperature, and/or the generation × temperature interaction have *P* < 0.05 in two-way analysis of variance. Asterisks indicate no deformed individuals.

and females for the population pairs where ANOVA indicated a significant difference between pure Parent and F1 hybrid traits. In our sex specific joint-scaling model, we examined only X-linked additive (x), X-linked dominance (x_δ), X-autosome additive $\times$ X-linked additive ($I_{\alpha x}$), autosomal additive $\times$ X-linked dominance ($K_{\alpha\delta_x}$), autosomal dominance $\times$ X-linked additive (δx), and dominance $\times$ X-linked dominance epistasis ($J_{\delta\delta_x}$) parameters because they were purely autosomal, maternal effect, and cytoplasmic contributions to the phenotype are not expected to differ between males and females of the same cross type (see Demuth and Wade accompanying article for analysis of other joint-scaling models). Because Parental and F1 crosses are insufficient to simultaneously estimate a six parameter joint-scaling model, we incorporated additional F2 and backcross data on each sex to estimate the composite genetic effects.

Results

In total we assayed sex and deformities in 109,418 beetles, of which 53% were male. At least one deformity was present in 16,499 ($\sim$15%) of the individuals. Overall, males were deformed 19.7% of the time (9,605/48,871) whereas females were deformed 15.6% of the time (6,894/44,048). Among 12 population pairs studied, the Colombia $\times$ Ecuador cross, the second most geographically proximate populations studied, manifested HR as a sex difference in the proportion of deformed offspring (Table 1): the F1 and reciprocal F1 males suffer developmental defects sig-

nificantly more often than their hybrid sisters (Fig. 1). We found no evidence of HR expressed as a viability difference between sexes. There was a main effect of temperature but no interactions in the sex difference in deformities in the Nigeria $\times$ Croatia cross (Fig. 1) and the Peru $\times$ Portugal cross demonstrated G $\times$ E (Fig. 1); however, the pattern of sex-different effects is not consistent with HR in either case.

Joint-scaling results for Colombia $\times$ Ecuador are reported in Table 2 for males and females reared at both temperatures. The composite genetic effects underlying viability and deformities in each sex do not conform to the quantitative genetic prediction of equation (1) because of the relatively large contribution of the X-autosome dominance-by-dominance ($J_{\delta\delta_x}$) component.

Discussion

We report the first evidence for HR prior to speciation in crosses between two populations of *T. castaneum*, collected from Colombia and Ecuador. These populations are the second most geographically proximate pair of populations crossed and have a genetic distance of only 0.004 substitutions per site estimated from mitochondrial sequence variation (see table 1 of Demuth and Wade 2007). In this cross, the expression of Haldane's rule is temperature dependent and neither population, when crossed to a geographically distant population from Japan, exhibits Haldane's rule at either rearing temperature.

Our observation of HR is one of the earliest with respect to degree of genetic divergence among well surveyed animals (Fig. 2)
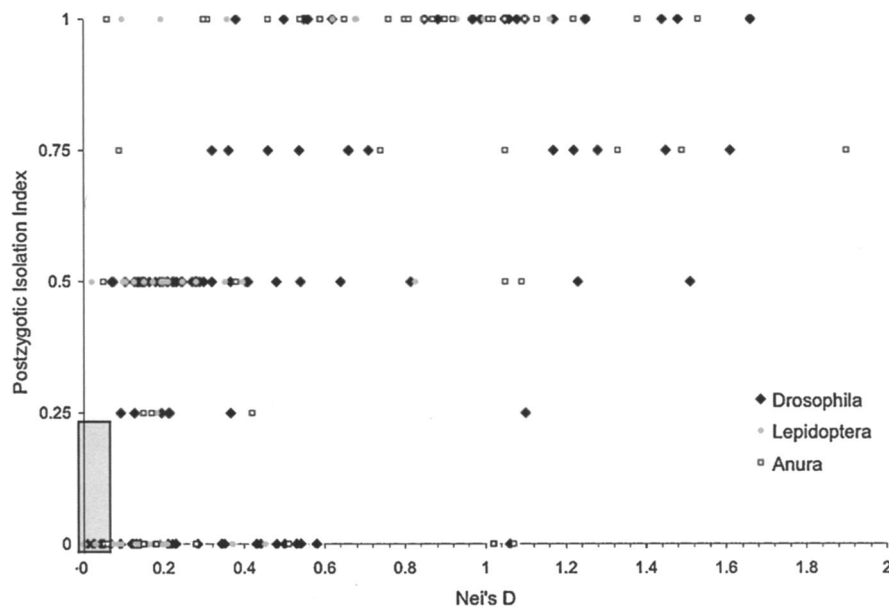

Figure 2. Postzygotic isolation as a function of molecular divergence. Data for postzygotic isolation are from *Drosophila* (Coyne and Orr 1989, 1997), Lepidoptera (Presgraves 2002), and Anura (Sasa et al. 1998). Postzygotic isolation index is the number of sexes in both reciprocal crosses that are sterile or inviable, divided by 4. Thus, an index of 1 is complete isolation. The maximum Nei's D among *Tribolium* populations is 0.125 (Demuth and Wade 2007). The grey box encompasses the range of genetic divergence and reproductive isolation found in this study.

Table 2. Composite genetic contributions to sex differences in viability. Parameter estimates are followed by their *t*-value and significance level after sequential Bonferroni (ns = not significant, *P < 0.05, **P < 0.01, ***P < 0.001). Note P < 0.05 for the χ^2 test indicates significant lack of fit to the whole model. See text for parameter descriptions.

Cross	Sex	Whole model χ^2 (df)	μ	X-linked additive, dominance x	δ_x	X-autosome digenic epistasis $I_{\alpha x}$	$K_{\alpha\delta x}$	$K_{\delta x}$	$J_{\delta\delta x}$
Colombia× Ecuador (29°C)	M	112.91 (12)*	0.5 (26.89)***	−0.04 (−1.95)ns		−0.55 (−16.09)***		0.12 (1.60)ns	
	F	71.5 (9)*	0.72 (10.55)***	0.09 (3.5)**	0.32 (2.7)*	−0.62 (−8.14)***	−0.03 (−0.49)ns	−0.41 (−4.26)***	−0.96 (−12.15)***
Colombia× Ecuador (35°C)	M	114.35 (12)*	0.02 (4.03)***	−0.01 (−3.30)**		−0.03 (−3.58)**		0.04 (0.97)ns	
	F	32.24 (9)*	0.09 (2.83)*	0 (0)ns	0.03 (0.49)ns	−0.09 (−2.83)*	−0.07 (−1.64)ns	0.04 (1.06)ns	−0.11 (−2.28)*

and to our knowledge is the first observation of intra-specific temperature-mediated HR. In *Drosophila*, where it has been most extensively surveyed, Haldane's rule has been reported in crosses between subspecies with Nei's $D = 0.194$ (Orr and Irving 2001), which is greater than the maximal divergence among *T. castaneum* populations in our study (table 1 in Demuth and Wade 2007). Our observation of significant genotype-by-environment interaction (G × E) for the expression of Haldane's rule supports the inference that G × E accelerates the development of HR (Wade et al. 1999), and consequently the process of speciation (Bordenstein and Drapeau 2001).

Using joint-scaling analysis and additional data from backcrosses and F2's, we found that interactions between X-linked and autosomal genes contribute to hybrid incompatibilities as well as to HR as predicted by theory. However, we could not test the specific quantitative predictions of the theory (see eq. [1]) because some of the composite genetic parameters could not be bounded away from zero. In the majority of cases, incompatibilities were manifested by F2 and backcross hybrids but not by F1 hybrids, indicating that HR, a characteristic of F1 incompatibilities, is not the leading genetic difference in the development of reproductive isolation between genetically diverging populations. Indeed, the population pair where we do find Haldane's rule does not show reduced offspring numbers in any of the hybrid generations (Demuth and Wade 2007) whereas some populations that have significant F2 breakdown for offspring numbers show no evidence of Haldane's rule. Furthermore, most hybrid incompatibilities were not sex different in their effects, even though they involved X-autosomal interactions expected on theoretical grounds to differ between homogametic female and heterogametic male hybrids.

In most crosses, the genetic architecture of the hybrid incompatibilities differed between the two rearing temperatures, both of which are well within the natural range of environments experienced by this species in nature and in the laboratory. This indicates that there is significant G × E interaction involved in the origins of reproductive isolation. G × E can act as a genetic constraint to local adaptation within populations when there is migration between heterogeneous environments (Wade et al. 1999; Wade 2000). However, when migration is halted, G × E becomes an accelerant of genetic diversification between populations (Wade et al. 1999; Wade 2000; Bordenstein and Drapeau 2001). Our observation of G × E affecting reproductive incompatibilities is consistent with this theoretical expectation.

We conclude that (1) HR is not a strictly a postspeciation phenomenon, it can occur between populations with a low level of genetic divergence and in the early stages of the evolution of reproductive isolation; (2) HR can occur prior to the origin of other forms of reproductive isolation, because significant hybrid incompatibilities can result from the accumulation of epistatically acting gene differences between populations without differentially

affecting the heterogametic sex in F1 hybrids; and (3) G × E is frequently involved in the expression of hybrid incompatibilities.

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