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FITNESS VARIATION DUE TO SEXUAL ANTAGONISM AND LINKAGE DISEQUILIBRIUM

Manus M. Patten,[1,2] David Haig,[1,3] and Francisco Úbeda[4,5]

[1]*Department of Organismic and Evolutionary Biology, Harvard University, 26 Oxford Street, Cambridge Massachusetts 02138*

[2]*E-mail: mpatten@oeb.harvard.edu*

[3]*E-mail: dhaig@oeb.harvard.edu*

[4]*Department of Ecology and Evolutionary Biology, 569 Dabney Hall, University of Tennessee, Knoxville, Tennessee 37996*

[5]*E-mail: fubeda@utk.edu*

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Extensive fitness variation for sexually antagonistic characters has been detected in nature. However, current population genetic theory suggests that sexual antagonism is unlikely to play a major role in the maintenance of variation. We present a two-locus model of sexual antagonism that is capable of explaining greater fitness variance at equilibrium than previous single-locus models. The second genetic locus provides additional fitness variance in two complementary ways. First, linked loci can maintain gene variants that are lost in single-locus models of evolution, expanding the opportunity for polymorphism. Second, linkage disequilibrium results between any two sexually antagonistic genes, producing an excess of high- and low-fitness haplotypes. Our results uncover a unique contribution of conflicting selection pressures to the maintenance of variation, which simpler models that neglect genetic architecture overlook.

Most multicellular organisms have separate sexes that can be morphologically, physiologically, and ecologically distinct (Fairbairn et al. 2007). Consequently, selection often runs in opposing directions for the two sexes (Cox and Calsbeek 2009), a situation termed sexual antagonism (Bonduriansky and Chenoweth 2009; van Doorn 2009). This mode of selection has attracted a sizeable body of theoretical attention, mostly in the form of single-locus population genetic models with two alleles (Haldane 1926; Owen 1953; Kidwell et al. 1977; Rice 1984). These models define three possible equilibria: either the male-beneficial allele or the female-beneficial allele becomes fixed in the population; or neither allele comes to dominate the population, with both settling at an intermediate frequency. This last scenario has been used to explain the high levels of sexually antagonistic fitness variation in natural and laboratory populations (Chippindale et al. 2001; Gibson et al. 2002; Pischedda and Chippindale 2006; Brommer et al. 2007; Foerster et al. 2007; Prasad et al. 2007; Delcourt et al. 2009). However, with reasonable assumptions about strength of selection and dominance, the conditions for a polymorphic equilibrium are restrictive (Prout 2000; Patten and Haig 2009). Although some notable exceptions exist (e.g., Rice 1984; Fry 2010), we question whether current population genetic theory can adequately explain the standing levels of sexually antagonistic fitness variance in natural populations. Here, we examine whether this shortfall is due to the overly simplistic nature of single-locus models, offering instead an analysis of the evolution of two genetic loci.

Model

Consider two diallelic autosomal loci, A and B, with recombination rate, r, between them. Let x_i and y_j be the frequencies of the ith and jth haplotypes in eggs and sperm, respectively, such that: x_1, y_1 are the frequencies of the A_1B_1 haplotype; x_2, y_2 are the frequencies of the A_1B_2 haplotype; x_3, y_3 are the frequencies of the A_2B_1 haplotype; and x_4, y_4 are the frequencies of the A_2B_2 haplotype. We assemble these into vectors: $\mathbf{x} = [x_1, x_2, x_3, x_4]$ and $\mathbf{y} = [y_1, y_2, y_3, y_4]$. Let p_x and p_y be the frequency of the A_1 allele in eggs and sperm and q_x and q_y be the frequency of the B_1 allele in eggs and sperm, respectively: $p_\xi = \xi_1 + \xi_2$ and $q_\xi = \xi_1 + \xi_3$, where $\xi \in \{x, y\}$.

We can express the haplotype frequencies in eggs and sperm as functions of allele frequencies and the linkage disequilibrium in eggs, D_x, and in sperm, D_y. This gives

$$\begin{aligned} x_1 &= p_x q_x + D_x & y_1 &= p_y q_y + D_y \\ x_2 &= p_x(1-q_x) - D_x & y_2 &= p_y(1-q_y) - D_y \\ x_3 &= (1-p_x)q_x - D_x & y_3 &= (1-p_y)q_y - D_y \\ x_4 &= (1-p_x)(1-q_x) + D_x & y_4 &= (1-p_y)(1-q_y) + D_y \end{aligned} \tag{1}$$

with

$$\begin{aligned} D_x &= x_1x_4 - x_2x_3 \\ D_x &= y_1y_4 - y_2y_3 \end{aligned} \tag{2}$$

(Lewontin and Kojima 1960; Karlin 1975).

The total linkage disequilibrium in a diploid population, D_t, is calculated as half of the difference in the frequencies of coupling and repulsion double heterozygotes (Crow and Kimura 1970). In our model this is

$$D_t = \frac{(x_1y_4 + x_4y_1) - (x_2y_3 + x_3y_2)}{2}. \tag{3}$$

Substituting (1) into (3) and simplifying gives

$$D_t = \frac{D_x + D_y}{2} + 2\mathrm{cov}(p, q). \tag{4}$$

Imposing different selection pressure on the two sexes produces stable linkage disequilibrium in polymorphic populations even when there is no epistasis between the loci considered (Úbeda et al. 2010).

Let w_{ijf} and w_{ijm} be the fitness of female and male zygotes that develop from the union of the ith egg haplotype and the jth sperm haplotype. We arrange these fitness values in a matrix

$$\mathbf{W}_\chi = \begin{bmatrix} w_{11\chi} & w_{12\chi} & w_{13\chi} & w_{14\chi} \\ w_{21\chi} & w_{22\chi} & w_{23\chi} & w_{24\chi} \\ w_{31\chi} & w_{32\chi} & w_{33\chi} & w_{34\chi} \\ w_{41\chi} & w_{42\chi} & w_{43\chi} & w_{44\chi} \end{bmatrix}, \tag{5}$$

where $\chi \in \{m, f\}$.

The $w_{ij\chi}$ are determined by combining fitness at each locus to produce an individual's overall fitness. Genotypes A_1A_1, A_1A_2, and A_2A_2 have fitnesses $1 - s_f$, $1 - h_f s_f$, and 1 in females and 1, $1 - h_m s_m$, and $1 - s_m$ in males, respectively. Fitness at the B locus is parameterized in the same way. We constrain the selection parameter to $0 < s_\chi \leq 1$, and we assume that allelic effects are additive at both loci ($h_\chi = {}^1/_2$), which guarantees opposing directional selection in the two sexes. Throughout, we take the fitness of a zygote, $w_{ij\chi}$, to be exactly the product of the fitnesses at each locus (Table 1). Therefore, there is no multiplicative epistasis within sexes.

The recursion equations for the frequencies of haplotypes in the next generation are:

$$\bar{w}_f x_i' = \frac{1}{2}\left[x_i(\mathbf{W_f y})_i + y_i\left(\mathbf{W_f^T x}\right)_i\right] - \varepsilon_i r a_f D_t \tag{6a}$$

$$\bar{w}_m y_i' = \frac{1}{2}\left[x_i(\mathbf{W_m y})_i + y_i\left(\mathbf{W_m^T x}\right)_i\right] - \varepsilon_i r a_m D_t \tag{6b}$$

with $\bar{w}_\chi$, the mean fitness of females or males, defined as $\bar{w}_\chi = \mathbf{x^T W}_\chi \mathbf{y}$, $\varepsilon_i = 1$ for $i = 1, 4$ and $\varepsilon_i = -1$ for $i = 2, 3$, and $a_\chi = (1 - {}^1/_2 \bullet s_\chi)^2$ is the fitness of double heterozygotes (Table 1).

The complexity of this model makes solving for polymorphic equilibria challenging. We use a code written in Matlab (2009) to calculate the equilibrium (denoted by "^") allele and haplotype frequencies, as well as equilibrium values of linkage disequilibrium. The equilibrium population attained is called the "E" population.

We also construct an artificial metapopulation from these equilibrium allele frequencies that has the following haplotype frequencies:

Table 1. Two-locus fitness parameterization for females. This is equivalent to W_f from equation (5) of the main text. Row and column reflect the haplotype inherited from the female and male parent, respectively.

	A_1B_1	A_1B_2	A_2B_1	A_2B_2
A_1B_1	$(1-s_f)^2$	$(1-s_f)\,(1-{}^1/_2 s_f)$	$(1-s_f)\,(1-{}^1/_2 s_f)$	$(1-{}^1/_2 s_f)^2$
A_1B_2	$(1-s_f)\,(1-{}^1/_2 s_f)$	$(1-s_f)$	$(1-{}^1/_2 s_f)^2$	$(1-{}^1/_2 s_f)$
A_2B_1	$(1-s_f)\,(1-{}^1/_2 s_f)$	$(1-{}^1/_2 s_f)^2$	$(1-s_f)$	$(1-{}^1/_2 s_f)$
A_2B_2	$(1-{}^1/_2 s_f)^2$	$(1-{}^1/_2 s_f)$	$(1-{}^1/_2 s_f)$	1

$$\begin{aligned} x_{1L} &= \hat{p}_x\hat{q}_x & y_{1L} &= \hat{p}_y\hat{q}_y \\ x_{2L} &= \hat{p}_x(1-\hat{q}_x) & y_{2L} &= \hat{p}_y(1-\hat{q}_y) \\ x_{3L} &= (1-\hat{p}_x)\hat{q}_x & y_{3L} &= (1-\hat{p}_y)\hat{q}_y \\ x_{4L} &= (1-\hat{p}_x)(1-\hat{q}_x) & y_{4L} &= (1-\hat{p}_y)(1-\hat{q}_y). \end{aligned} \quad (7)$$

We call this the "L" population. Although the L population has exactly the same allele frequencies as the E population, it has no linkage disequilibrium in gametes, which is achieved by combining alleles at random between loci within each sex.

For the E population, the fitness variance of females is given by

$$V_E = \sum_{ij} \hat{x}_i \hat{y}_j (w_{ijf} - \bar{w}_{fE})^2. \quad (8a)$$

For the L population, the fitness variance of females is given by

$$V_L = \sum_{ij} x_{iL} y_{jL} (w_{ijf} - \bar{w}_{fL})^2. \quad (8b)$$

Their difference, $V_E - V_L$, is given by

$$\Delta V = \frac{1}{4} s_f^2 \left\lfloor c_x \hat{D}_x + c_y \hat{D}_y - \frac{1}{4} s_f^2 (\hat{D}_x - \hat{D}_y)^2 \right\rfloor, \quad (9)$$

where $c_x = 2 - (2 + \hat{p}_y + \hat{q}_y - \hat{p}_x - \hat{q}_x)s_f + \lfloor \frac{1}{4} + \frac{1}{2}(\hat{p}_y(1-\hat{q}_x) + \hat{q}_y(1-\hat{p}_x) + \hat{p}_y\hat{q}_y - \hat{p}_x\hat{q}_x) \rfloor s_f^2$ and $c_y = 2 - (2 + \hat{p}_x + \hat{q}_x - \hat{p}_y - \hat{q}_y)s_f + \lfloor \frac{1}{4} + \frac{1}{2}(\hat{p}_x(1-\hat{q}_y) + \hat{q}_x(1-\hat{p}_y) + \hat{p}_x\hat{q}_x - \hat{p}_y\hat{q}_y) \rfloor s_f^2$. Extending this to male fitness variance is straightforward.

Results

We discover two sources of additional fitness variance in our model of two genetic loci. First, there is an increased opportunity for polymorphism as the recombination rate decreases. This means that the parameter space contains more area that permits polymorphism (Fig. 1). In a one-locus model of sexual antagonism, this area is bounded by

$$\frac{s_m}{1+s_m} < s_f < \frac{s_m}{1-s_m}. \quad (10)$$

(Kidwell et al. 1977). The results from our numerical analyses show that the opportunity for polymorphism when $r = 0.5$ approximates this condition (Fig. 1).

When $r = 0$, the population behaves virtually like a single locus with four alleles (the four haplotypes), which allows for an analytical statement of the opportunity for polymorphism. At polymorphic equilibrium, only two haplotypes persist, and their invasion conditions bound the parameter space that allows maintained polymorphism

$$1 + \frac{1}{1-\sqrt{8-(s_m-2)^2}} < s_f < 2 - \sqrt{\frac{(2-3s_m)^2 - 2s_m^2}{(1-s_m)^2}}. \quad (11)$$

As shown in Figure 1, the area described by (11) subsumes and expands upon that of (10). For $0 < r < 0.5$, statements of the opportunity for polymorphism are too complex to calculate analytically, but the spaces they bound are intermediate in size between the extremes described by (10) and (11).

Further comparison of these extremes helps define the limits of how much additional fitness variance linkage might provide. By integrating, we find that (10) blankets ~39% of the total parameter space, whereas (11) covers ~49%, representing a ~26% increase in the area that permits polymorphism. The percent increase in area that perfect linkage provides increases as we narrow consideration to smaller selection coefficients. If we constrain parameter space to $0 < s_\chi < 0.1$, equivalent to assuming that all mutations have smaller fitness effects, linkage accounts for a ~45% increase in the opportunity for polymorphism. Considering weaker selection still, with $0 < s_\chi < 0.01$, linkage accounts for a ~49% increase in the opportunity for polymorphism. Note that the total opportunity for polymorphism shrinks as selection strength declines for both linked and unlinked loci (Fig. 1). However, the relative amount of additional opportunity that linkage provides increases with decreasing selection strength.

Second, linkage disequilibrium exists at any polymorphic equilibrium in a two-locus model of sexual antagonism (Úbeda et al. 2010). The additional variance caused by the linkage disequilibrium in gametes is given in equation (9). This comparison is shown graphically in Figure 1C, D across a range of selection coefficients and recombination rates. For all fitness parameterizations, provided $r < 0.5$, the linkage disequilibrium in gametes that evolves under sexual antagonism is responsible for excess fitness variance at equilibrium, ranging from 50% to a negligible amount. Generally speaking, the excess fitness variance provided by linkage disequilibrium in the gametes increases with increasing selection and decreasing recombination. At the extreme, in the absence of recombination, the excess variance due to linkage disequilibrium is almost as great as the variance caused by allelic variation alone (Figs. 1C, D). As recombination grows, selection strength needs to grow accordingly for the contribution of linkage disequilibrium to be significant (Figs. 1C, D). For example, for two tightly linked genes: if $r = 0.001$ and $s_m = s_f = 0.1$, the variance excess is ~33%; if $r = 0.01$ and $s_m = s_f = 0.1$, the variance excess is ~6%.

Discussion

Our model provides greater fitness variance at equilibrium than is predicted by one-locus theory in two ways. First, linkage increases the likelihood that a locus retains allelic—and therefore

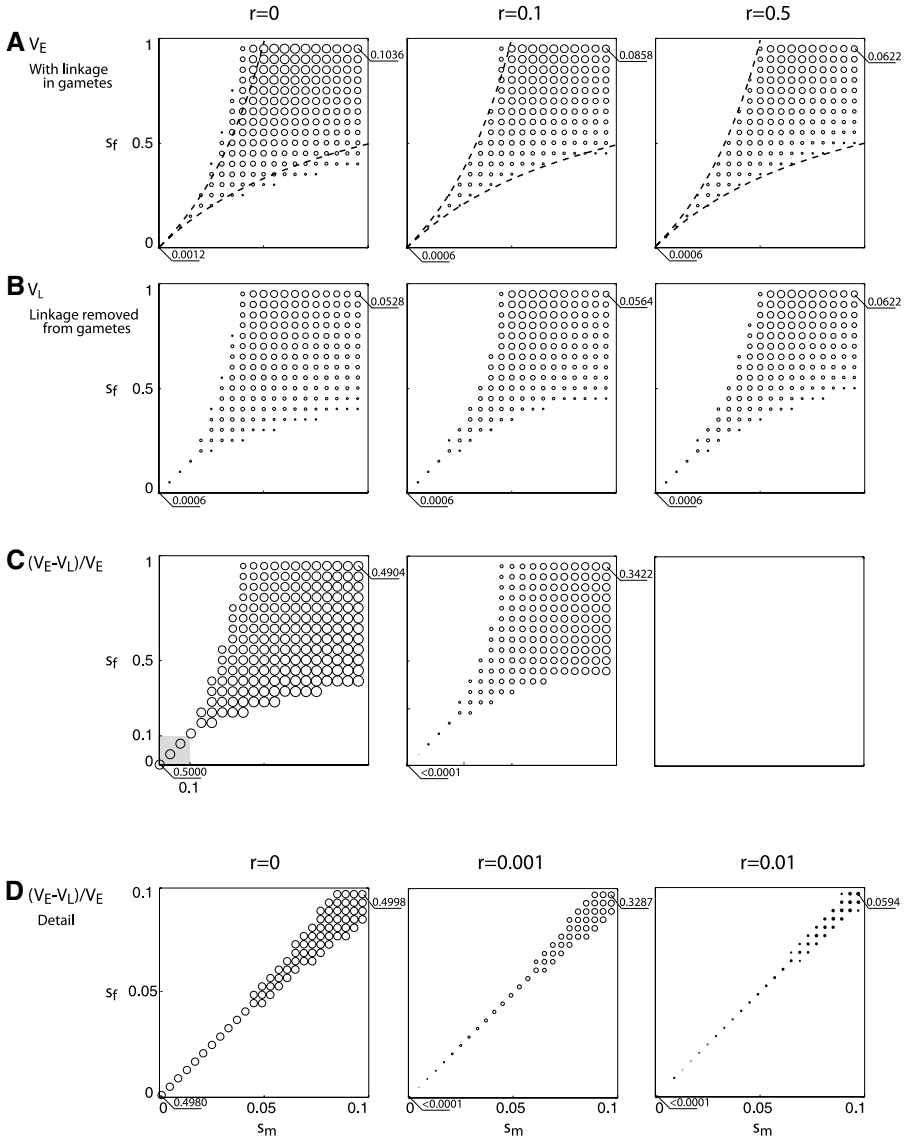

Figure 1. **Equilibrium fitness variance of females. Fitness variance of females is depicted by the area of the circles in each plot. In general, fitness variance increases with increasing selection strength and lowerrecombination. (A) The fitness variance of the equilibrium population, V_E (eq. 8a). Additionally, the boundary of the opportunity for polymorphism in a one-locus model is shown as a dashed line (eq. 10). (B) The fitness variance of a metapopulation without any linkage disequilibrium in its gametes, V_L (eq. 8.b). (C) The proportion of fitness variance, $\frac{V_E - V_L}{V_E}$, that linkage disequilibrium in the gametes provides. In (A–C), the range of parameter values *s* explored is [0.05, 0.95] with increments of 0.05. (D) Detail of previous figure with a low recombination rate and weak selection. In D, the range of parameter values *s* explored is [0.001, 0.097] (shaded box in C) with increments of 0.004.**

fitness—variation. When two sexually antagonistic genes are linked ($r < 0.5$), each can remain polymorphic under selection coefficients that result in fixation of one or the other allele in a single-locus model. The higher incidence of polymorphism in the two-locus model provides a boost to fitness variance because when fixation occurs, fitness variance is erased. The tighter the linkage, the greater is the expansion of parameter space to support polymorphism; for weak selection and loose linkage, this additional opportunity for polymorphism is vanishingly small. Thus, the population is more likely to retain fitness variance when loci are more tightly linked (Fig. 1). In one-locus models of sexual antagonism (Prout 2000; Patten and Haig 2009), strong selection is more conducive to a polymorphic equilibrium than weak selection. Intuitively, linkage favors polymorphism in our two-locus model by effectively increasing the strength of selection at each locus. The relative increase in the area of parameter space that permits polymorphism is greater for weak selection.

Second, sexual antagonism generates stable linkage disequilibrium (Úbeda et al. 2010), which alters fitness variance by its

impact on genotype frequencies in the population. In our model, the association that results is the coupling of male-beneficial with male-beneficial (A_1B_1) alleles and female-beneficial with female-beneficial (A_2B_2) alleles. The magnitude of this linkage disequilibrium is sensitive to selection strength and recombination rate, with greater correlations between loci reached for stronger selection and tighter linkage (Úbeda et al. 2010). Like the first effect, this theoretical contribution to fitness variance becomes small with weak selection and loose linkage.

Similar to our two-locus formulation, a one-locus model of sexual antagonism can achieve polymorphism, which has been used as the theoretical explanation for sexually antagonistic fitness variance up to this point. In the two-locus model; however, we show that a second linked locus expands the opportunity for such polymorphism, increasing the likelihood that allelic variation, and therefore fitness variation, is maintained. Further, the linkage disequilibrium that evolves in a two-locus model of sexual antagonism contributes excess fitness variance that, for certain parameterizations, can be almost as great as the fitness variance due to allelic variation alone. Theoretically, these can both be substantial contributions to fitness variance and they emerge in the model without reliance on any wishful assumptions.

The extent to which these contributions actually come into play in natural populations depends on two factors, as Figure 1 demonstrates: the recombination rate between sexually antagonistic loci and the strength of selection on such loci. Innocenti and Morrow (2010) find that ~8% of genes in the genome are sexually antagonistic. Based on our results, we predict that these genes are more clustered in the genome than they would be by chance because linkage facilitates polymorphism. Also, the strength of sexually antagonistic selection revealed in a recent metaanalysis (Cox and Calsbeek 2009) suggests that sexual antagonism can be quite strong for some traits, but it is not clear how strong selection is on any given locus. Future empirical tests of our theory may show that X-linkage is not the only feature of genetic architecture that facilitates the maintenance of sexually antagonistic genetic and fitness variance (Rice 1984; Patten and Haig 2009).

Our results enhance the ability to account theoretically for sexually antagonistic genetic and fitness variance in populations (Chippindale et al. 2001; Gibson et al. 2002; Pischedda and Chippindale 2006; Brommer et al. 2007; Foerster et al. 2007; Prasad et al. 2007; Delcourt et al. 2009), complementing our understanding from earlier one-locus theory. Some—or perhaps much—of the sexually antagonistic fitness variance in nature may owe its existence to the features of the two-locus model that we demonstrate here, a possibility that awaits empirical testing.

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