Evidence for an Association between Nonadditive Genetic Variation and Extreme Expression of a Trait

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NOTES AND COMMENTS

EVIDENCE FOR AN ASSOCIATION BETWEEN NONADDITIVE GENETIC VARIATION AND EXTREME EXPRESSION OF A TRAIT

Epistatic interactions among loci can have important effects on the evolution of quantitative characters, particularly those related to fitness (Barker 1979). Such interactions are important components of Wright's shifting balance theory of evolution (Wade and Goodnight 1991), as well as models of speciation (Templeton 1981) and the effects of outbreeding depression in captive populations (Shields 1982). However, attempts to detect epistatic interactions in populations have met with mixed success (Hedrick et al. 1978; Barker 1979; Cohan et al. 1989).

One reason that attempts to detect epistasis may have provided inconsistent results is that epistasis may be more evident under some conditions than others. At least two mechanisms may account for such a phenomenon. First, following Mather (1973), levels of epistasis may change as a consequence of the history of selection in a population. If a trait is under directional selection, epistatic interactions that increase the expression of a trait in the direction of selection could be favored, while stabilizing selection may select for weak epistasis (Mather 1973). Second, genetic interactions may depend on the way the environment influences the expression of genetic variation. This concept can be illustrated with respect to changes in the dominance component of genetic variance. Metabolic considerations suggest that alleles with a high fitness will often be dominant when flux through a metabolic pathway approaches a steady state (Kacser and Burns 1981), but this condition may change as environmental effects cause departures from steady state (Hartl et al. 1985; Hoffmann and Parsons 1991). It is not clear whether the level of epistasis should also vary with the environment, although the degree of F_2 breakdown that occurs in crosses between populations may depend on experimental conditions (Tantawy and El-Helw 1970), and significant levels of additive $\times$ additive epistasis appeared under more stressful conditions in some traits in *Nicotiana rustica* (Jinks et al. 1973).

If epistatic interactions are influenced consistently by a history of selection or environmental factors, the degree of epistasis may change predictably with conditions that influence the expression of a trait. Recently, researchers found that the level of nonadditive genetic variation for development time in laboratory populations of *Drosophila melanogaster* depended on the expression of this trait (Blows and Sokolowski 1995). They used the biometric genetic approach of

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Mather and Jinks (1982) to show that the expression of dominance [*h*], additive × additive epistasis [*i*], and dominance × dominance epistasis [*l*] progressively increased toward a longer or shorter development time. This relationship agreed with the earlier qualitative observation that in *N. rustica,* the expression of *i* increased with one or both extremes of several traits (Jinks et al. 1973).

To test whether the level of epistatic effects generally changes with the level of expression of a trait, we have further analyzed earlier data (Blows 1993) involving crosses among lines of *Drosophila serrata*. This data set provided an opportunity to quantify possible relationships between the expression of nonadditive genetic variation and trait levels as a consequence of the unusually large number of crosses conducted within a single experimental design. We consider data for three fitness-related traits (development time, viability, and fecundity) in crosses among lines with and without a history of selection for desiccation resistance.

METHODS

The populations of *Drosophila serrata,* method of selection for desiccation resistance, and crosses between populations are described elsewhere (Blows 1993; Blows and Hoffmann 1993). Briefly, four natural populations of *D. serrata* were sampled from areas ranging from the center to near the periphery of its distribution (denoted here as F, C, B, and T). Six replicate lines were created from each population, three of which underwent selection for desiccation resistance and three of which were maintained as controls. Selection was continued for 14 generations. After selection, selected lines from the four populations were crossed to each other, and control lines from each population were also intercrossed to determine the effect of selection for desiccation resistance on the level of epistatic genetic variation in three fitness components: development time, viability, and fecundity (Blows 1993).

The six possible combinations of crosses between the four natural populations are denoted as FC, FB, FT, CB, CT, and BT. To illustrate the crosses that were carried out, consider the case of the FC combination. For the selected lines, the S1 line from population F was crossed to the S1 line from population C, and F_1's were intercrossed and backcrossed to produce F_1, F_2, and backcross generations for estimating the effects of epistasis. In two separate experiments, similar crosses were carried out between the S2 and S3 lines from these two populations. By undertaking the same sets of crosses for the other combinations of populations, we generated 18 estimates of the parameters in the digenic model of Mather and Jinks (1982) for the selected lines. The same number of estimates was produced for the control lines.

RESULTS AND DISCUSSION

We estimated genetic effects under a model incorporating digenic epistasis outlined in Mather and Jinks (1982) as given in table 1. An alternative way of defining parameters for these effects has been used by other authors (Cockerham 1954; Kempthorne 1954; Falconer 1981), where additive × additive, additive ×

TABLE 1

ESTIMATION OF GENETIC EFFECTS UNDER THE DIGENIC MODEL FROM GENERATION MEANS

Genetic Effect	Estimation from Generation Means
Mean m	$\frac{1}{2}P_1 + \frac{1}{2}P_2 + 4F_2 - 2B_1 - 2B_2$
Additive [d]	$\frac{1}{2}P_1 - \frac{1}{2}P_2$
Dominance [h]	$6B_1 + 6B_2 - 8F_2 - F_1 - 1\frac{1}{2}P_1 - 1\frac{1}{2}P_2$
Additive × additive [i]	$2B_1 + 2B_2 - 4F_2$
Additive × dominance [j]	$2B_1 - P_1 - 2B_2 + P_2$
Dominance × dominance [l]	$P_1 + P_2 + 2F_1 + 4F_2 - 4B_1 - 4B_2$

NOTE.—Table follows Mather and Jinks (1982).

dominance, and dominance × dominance interaction effects are defined as AA, AD, and DD, respectively. These effects approximate the i, j, and l terms in table 1, and Hill (1982) concludes that the practical interpretation of the genetic effects are not affected by the choice of approaches for defining parameters. Estimates of the genetic effects for the three fitness components are given in tables 2–4. Deviations from the expectations of the additive-dominance model for these data have been dealt with elsewhere (Blows 1993).

In the absence of information on the degree of association between genes in the parental lines, the classification of epistatic interactions relies on the magnitude and sign of h and l (Mather and Jinks 1982). In almost all of the 36 crosses for the three traits, h and l have opposite signs (tables 2–4); this pattern was found for development time (35/36), viability (32/36), and fecundity (34/36), and it is significant ($P < .001$) for all three traits using a χ^2 test with one degree of freedom. The epistatic interactions are predominately of a duplicate type. This type of interaction is associated with traits that have a history of directional selection for extreme expression since it reduces the number of genotypes of lower fitness in the segregating generations (Mather 1967, 1973) and may indicate components of fitness (Jinks 1979). Duplicate type interactions have also resulted in minimal levels of heterosis as levels of h and l are of a similar magnitude with opposite sign, and their effects on the F_1 mean will therefore balance.

To determine whether the level of each genetic effect was associated with the expression of a trait, we followed the procedure described by Mather and Jinks (1982) for testing genotype × environment interactions in an arbitrary set of environments. This procedure calculates the magnitude of the interaction between each genetic effect and the level of the trait's expression. The parameters e, g_d, g_h, g_i, g_j, and g_l representing the interaction between the trait's expression and the parameters m, d, h, i, j, and l, respectively, were calculated from the values given in tables 2–4. For each of the three traits, this process involved subtracting the mean of each parameter, calculated over the six values for each cross, from each individual value contributing to that mean (following Blows and Sokolowski 1995). In this fashion, the environmental value e represents the difference between the mean phenotype of each of the six crosses from the overall mean of those six crosses, g_d represents the interaction of d effects with e for that cross, and so forth. The interpretation of the environmental value in this

TABLE 2

GENETIC EFFECTS ESTIMATED UNDER THE DIGENIC MODEL FOR DEVELOPMENT TIME

	GENETIC EFFECT					
CROSS	*m*	[*d*]	[*h*]	[*i*]	[*j*]	[*l*]
FC:						
C1	3.7	.3	−2.6	−.6	.1	1.9
C2	3.8	.1	−.9	−.8	−2.1	.3
C3	3.9	.4	−1.3	−.6	1.9	.3
S1	2.5	.1	2.5	.6	−.3	−2.3
S2	6.2	.6	−5.6	−2.0	−.3	2.9
S3	5.0	.0	−5.8	−1.8	1.4	3.5
FB:						
C1	4.2	.1	−2.8	−.8	−.5	1.4
C2	3.3	.5	1.5	.2	−.7	−1.2
C3	1.8	.1	3.5	1.2	−.5	−2.3
S1	3.5	.1	−1.2	−.4	.7	.6
S2	5.7	.3	−5.0	−1.8	1.2	2.7
S3	.9	.1	3.9	2.4	−.2	−2.1
FT:						
C1	4.3	.4	−3.1	−.6	1.4	1.8
C2	3.5	.3	−2.0	−.2	−1.6	2.4
C3	2.4	.3	−.6	.8	.2	1.2
S1	4.8	.1	−4.5	−1.8	.9	2.7
S2	4.4	.2	−1.2	−.6	1.0	.3
S3	3.5	.2	−.2	−.4	.9	−.2
CB:						
C1	3.3	.3	−1.6	−.2	.8	1.5
C2	5.2	.5	−3.5	−1.8	−.4	1.7
C3	4.7	.3	−2.7	−1.4	−.4	1.0
S1	4.7	.0	−3.1	−1.6	.0	1.4
S2	6.1	.3	−5.6	−1.6	−.5	3.4
S3	5.3	.1	−5.6	−2.0	1.4	3.1
CT:						
C1	4.4	.7	−2.9	−1.0	−2.3	1.6
C2	2.5	.3	1.9	.8	−.3	−.3
C3	3.4	.1	.1	.2	.5	−.4
S1	4.4	.1	−3.0	−1.4	−.8	1.5
S2	4.0	.3	1.4	.4	−.7	−1.4
S3	5.7	.2	−4.8	−2.6	.3	2.2
BT:						
C1	2.9	.3	.7	.8	−.7	−.8
C2	6.2	.2	−5.9	−2.4	−.7	3.2
C3	.7	.3	7.2	2.6	−2.7	−4.9
S1	4.4	.1	−2.6	−1.4	.4	1.1
S2	2.9	.1	1.9	1.2	−1.4	−1.0
S3	2.4	.3	2.1	.8	−.9	−1.5

NOTE.—Development time was scored in 12-h intervals from the beginning to the end of pupation (Blows 1993). See Material and Methods for an explanation of the cross notation.

TABLE 3

GENETIC EFFECTS ESTIMATED FROM THE DIGENIC MODEL FOR VIABILITY

CROSS	GENETIC EFFECT					
	m	$[d]$	$[h]$	$[i]$	$[j]$	$[l]$
FC:						
C1	6.5	.1	−4.7	−1.6	−2.0	2.4
C2	6.5	.1	−4.0	−2.2	1.5	2.0
C3	4.1	.3	.5	.1	−.5	.2
S1	4.6	.1	1.0	1.9	.3	−1.0
S2	6.4	.1	−4.0	−1.8	−.6	2.4
S3	5.8	.3	−2.0	−1.6	.1	.4
FB:						
C1	3.3	.1	3.1	1.6	.7	−1.8
C2	6.3	.2	−3.6	−1.8	.6	1.9
C3	5.6	.3	−1.9	−1.4	−.7	.6
S1	3.5	.1	2.9	1.1	.5	−1.7
S2	3.3	.0	3.2	1.4	.9	−1.8
S3	5.7	.4	−1.7	−1.3	.5	.7
FT:						
C1	4.2	.2	1.2	.3	.1	−1.1
C2	4.8	.2	.2	−.3	.1	−.3
C3	5.4	.4	−1.4	−1.1	−1.0	.9
S1	2.6	.1	2.4	1.9	2.1	−.2
S2	4.8	.3	.8	−.4	−.7	−1.1
S3	2.1	.4	4.8	2.2	.0	−2.4
CB:						
C1	7.2	.0	−6.6	−2.2	−1.3	3.9
C2	4.8	.3	.3	−.4	−1.0	−.3
C3	5.4	.1	−.6	−.9	.3	−.2
S1	5.1	.0	−.1	−.4	.0	−.3
S2	6.0	.1	−2.8	−1.3	.8	1.7
S3	5.3	.2	−1.5	−.7	.8	.9
CT:						
C1	8.2	.3	−9.4	−3.6	1.1	5.5
C2	6.4	.3	−3.6	−2.0	−1.3	1.7
C3	6.3	.1	−4.1	−1.8	−1.1	2.3
S1	4.1	.1	.3	.5	.7	.4
S2	3.8	.3	3.3	.4	.3	−3.2
S3	5.7	.2	−1.5	−1.1	−.1	.2
BT:						
C1	8.1	.3	−8.8	−3.3	2.2	5.6
C2	2.4	.0	4.9	2.2	.0	−2.7
C3	3.6	.1	2.4	1.1	1.0	−1.6
S1	4.3	.1	.2	.2	.5	.1
S2	5.0	.3	.0	−.7	−.4	−.5
S3	5.0	.0	−1.0	−.2	.2	.8

NOTE.—Viability was scored as the number of flies eclosing in a vial of a possible five individuals (Blows 1993). See Material and Methods for an explanation of the cross notation.

TABLE 4

GENETIC EFFECTS ESTIMATED FROM THE DIGENIC MODEL FOR FECUNDITY

CROSS	GENETIC EFFECT					
	m	[*d*]	[*h*]	[*i*]	[*j*]	[*l*]
FC:						
C1	131	8.5	−162	−67	−15	106
C2	13	5.0	132	44	−34	−97
C3	77	9.4	−51	−27	4	43
S1	43	10.0	30	26	−19	2
S2	93	8.0	−62	−45	−9	30
S3	52	1.0	17	2	−12	−13
FB:						
C1	123	4.7	−177	−55	14	121
C2	62	3.9	−50	−4	44	52
C3	58	5.0	−7	−4	−21	2
S1	102	17.0	−84	−40	−10	57
S2	11	1.0	93	46	−2	−44
S3	35	4.0	38	22	−42	−16
FT:						
C1	−71	9.0	305	135	−3	−156
C2	−9	2.0	187	69	−21	−116
C3	103	1.0	−100	−43	−25	59
S1	45	14.0	83	20	−80	−50
S2	89	5.0	−76	−38	−15	32
S3	−12	6.0	133	59	5	−65
CB:						
C1	75	4.0	−45	−16	24	25
C2	25	.0	75	29	19	−46
C3	−14	5.5	150	60	−21	−89
S1	12	7.0	136	40	−24	−95
S2	24	9.0	60	24	16	−30
S3	28	2.0	56	26	36	−17
CT:						
C1	68	1.0	−23	−13	−43	21
C2	51	2.0	18	6	18	1
C3	28	10.0	74	23	26	−54
S1	45	3.0	70	11	−19	−34
S2	22	4.0	56	21	−24	−16
S3	−15	3.0	136	65	1	−59
BT:						
C1	76	4.0	−30	−17	−2	26
C2	84	2.0	−31	−28	−37	9
C3	107	6.0	−154	−52	−17	108
S1	−5	4.0	221	53	−15	−146
S2	20	5.0	59	32	−5	−25
S3	75	5.0	−35	−28	−16	24

NOTE.—Fecundity was measured as the total number of eggs laid by a female over a 4-d period (Blows 1993). See Material and Methods for an explanation of the cross notation.

instance, however, does not consist solely of environmental influences. Sources of variation in the environmental value (e) consist of (1) environmental differences between the three replicate experiments that had been run sequentially, (2) possible genotype × environment interactions between the population crosses and the environment, (3) possible genotype × environment interactions between replicate lines and the environment as a result of genetic drift between replicate lines (note that sources 1 and 3 are confounded in the present design since each replicate line was measured in a different experiment), and (4) genotype × environment interactions with undefined microenvironmental factors. The range of environmental values around the mean (i.e., $e = 0$) displayed in figure 1 is quite large for the three traits, spanning -31.2 h $< e <$ 34.8 h in development, $-46\% < e < 68\%$ in viability, and $-95 < e < 79$ eggs in fecundity.

Two-way ANOVAs without replication (six in total) were used to test whether the possible sources of variation in e, identified in the experimental design (i.e., not including source 4), had a significant effect on e. No evidence suggested that the experiment/replicate (the confounded sources 1 and 3) or population cross (source 2) affected the environmental value in any of the three traits, in either the selected or control lines (for the population combination term, $P > .60$; for the experiment/replicate term, $P > .15$ for all six ANOVAs). It appears, therefore, that the range of environmental values is a consequence of the undefined microenvironmental factors (source 4). Microenvironmental factors can extensively affect the expression of genotypes even when, as is the case in this study, they are placed in complete randomized blocks (e.g., Pooni et al. 1978).

The absolute values of g_h, g_i, and g_l were plotted against the corresponding environmental value (e), separately for crosses between selected and control lines, for development time, viability, and fecundity (figs. 1, 2, and 3, respectively). Parabolic relationships between the environmental value and a number of the genetic effects are apparent. To test for a significant increase in the multiple coefficient of determination of the linear and quadratic powers (represented below as r^2) over that of the determination of the linear component alone, we used the multiple-regression approach given in Sokal and Rohlf (1981, p. 635). In the crosses between the control lines, significant quadratic relationships were detected between e and g_h and g_l for development time ($r^2 = 0.86$, $P < .001$; $r^2 = 0.72$, $P < .001$) (fig. 1), viability ($r^2 = 0.86$, $P < .001$; $r^2 = 0.85$, $P < .001$) (fig. 2), and fecundity ($r^2 = 0.85$, $P < .001$; $r^2 = 0.67$, $P < .001$) (fig. 3). Similar relationships are also evident between e and g_i in the control lines for development time ($r^2 = 0.92$, $P < .001$) and fecundity ($r^2 = 0.93$, $P < .001$), but viability displays no association between these two parameters. In the crosses between selected lines, similar relationships to the control lines occur between e and g_h, g_i, and g_l for development time, viability, and fecundity; all three of the quadratic terms are significant at the $P < .001$ level ($r^2 = 0.88$, 0.86, and 0.70, respectively). However, weaker relationships between g_h, g_i, and g_l and trait expression are indicated in the crosses between the selected lines for development time ($r^2 = 0.63$, $P < .001$; $r^2 = 0.55$, $.001 < P < .01$; $r^2 = 0.40$, $.01 < P < .05$) and viability ($r^2 = 0.71$, $.001 < P < .01$; $r^2 = 0.54$, $.05 < P < .10$; $r^2 = 0.45$, $.05 < P < .10$).

Significant, although weak, linear relationships were found between the environmental value e and g_j for viability in the control lines ($b = 0.20$, $r^2 = 0.25$,

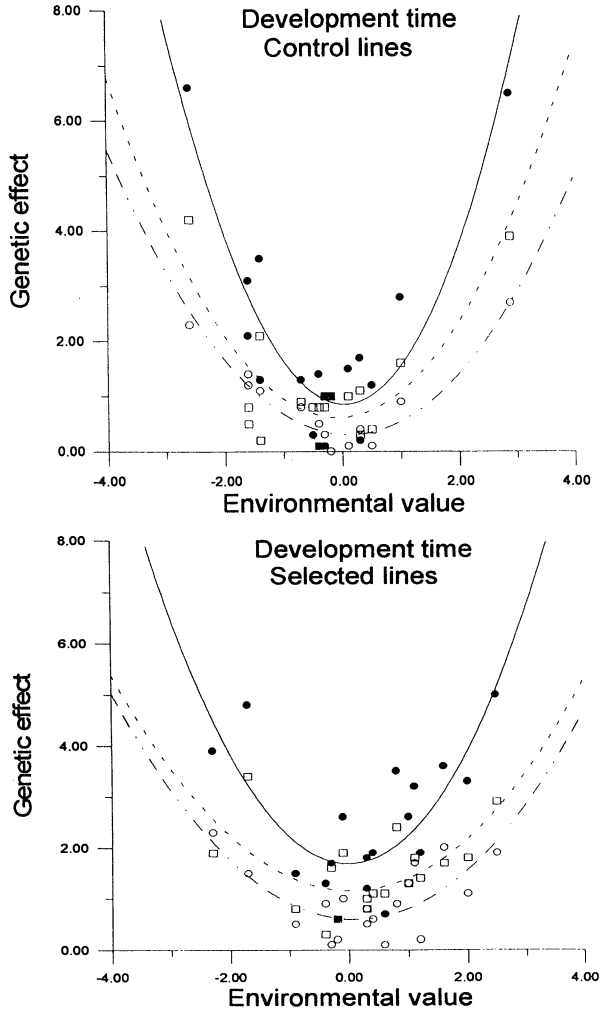

FIG. 1.—Values of g_h (*solid circles, solid line*), g_i (*open circles, dashed/dotted line*), and g_l (*open squares, dashed line*) plotted against the environmental value e for the selected and control lines for development time. Each point represents an individual cross from table 2. Significance values of the relationships are given in the text. Units are as indicated in the legend of table 2.

$.01 < P < .05$) and development time in the selected lines ($b = 0.20$, $r^2 = 0.32$, $.01 < P < .05$). The expression of additive × dominance epistasis increased with slower development and higher viability. No association was found between e and the additive effects (g_d) for any trait.

To test directly for an effect of selection on the relationship between g_h, g_i, and g_l and a trait's expression, an ANCOVA was conducted across each of the parameters for each trait (i.e., e was used as the covariate). The raw scores rather than the absolute values presented in figures 1–3 were used for this analysis since they exhibited linearity. There was no evidence for a significant effect of selection

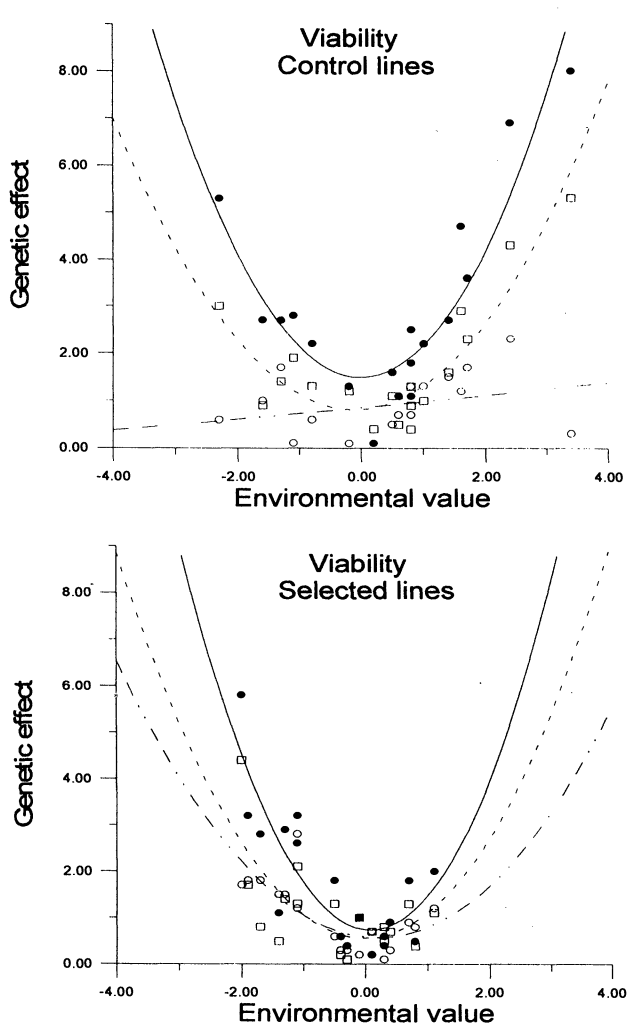

FIG. 2.—Values of g_h (*solid circles, solid line*), g_i (*open circles, dashed/dotted line*), and g_l (*open squares, dashed line*) plotted against the environmental value e for the selected and control lines for viability. Each point represents an individual cross from table 3. Significance values of the relationships are given in the text. Units are as indicated in the legend of table 3.

on the association between nonadditive genetic variation and the expression of the traits (i.e., the selection by environmental value interaction terms in the ANCOVAs was not significant).

In summary, the degree of nonadditive genetic variation in three fitness-related traits was associated with the expression of these traits. The contribution of dominance and dominance × dominance epistasis to the phenotype of all three traits and the contribution of additive × additive epistasis to development time and fecundity increased as the expression of traits deviated from the mean value. Previous work with *Drosophila melanogaster* found similar relationships between

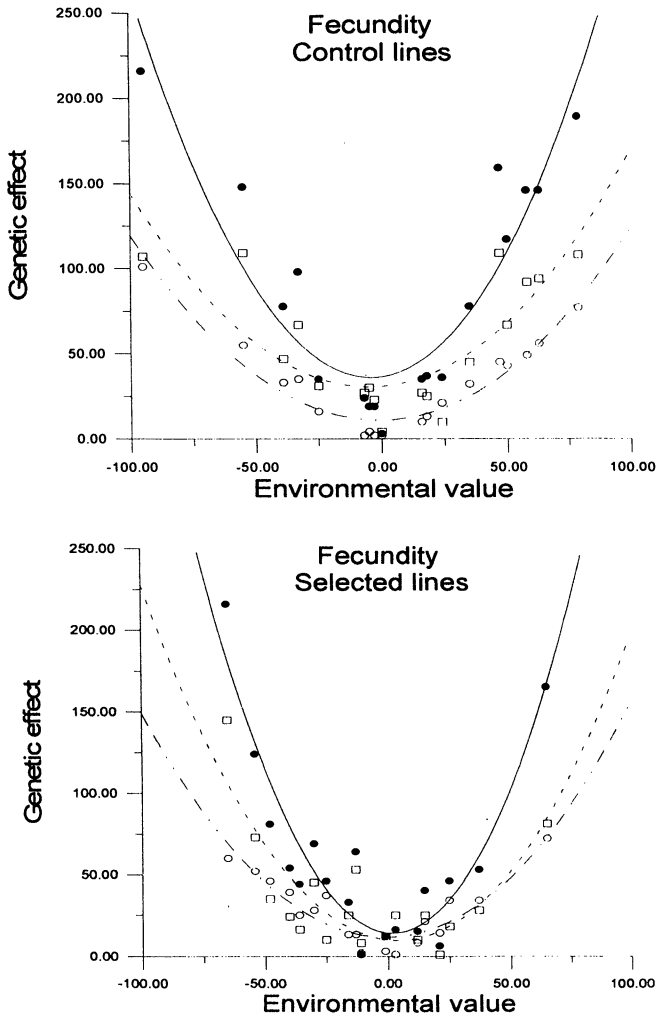

FIG. 3.—Values of g_h (*solid circles, solid line*), g_i (*open circles, dashed/dotted line*), and g_l (*open squares, dashed line*) plotted against the environmental value e for the selected and control lines for fecundity. Each point represents an individual cross from table 4. Significance values of the relationships are given in the text. Units are as indicated in the legend of table 4.

trait values and g_h, g_i, and g_l in development time but not in viability (Blows and Sokolowski 1995). In both data sets, the expression of additive effects (g_d) was not associated with trait values. Experiments designed to test for epistasis, at least of a duplicate type, may therefore need to focus on conditions resulting in either high or low expression levels of fitness components. However, since a series of environments, differing in a controlled environmental variable, was not used to generate the range of expression levels in this study, an association between the expression of nonadditive genetic variation and environmental stress can only be inferred indirectly.

At least two explanations are possible for an association between trait values and nonadditive genetic variation that relate to the selection history of a trait. Jinks et al. (1973) suggested that an increase in epistasis at extremes may result from the types of selection that operate in normal and extreme environments. Under normal conditions, stabilizing selection may predominate and favor a reduction in the expression of dominance and epistasis in the genes that contribute to the trait (Mather 1973). Under extreme conditions, however, directional selection would predominate, favoring the expression of dominance and epistasis in the direction of selection. This argument may not apply to the traits we considered here because development time, viability, and fecundity are expected to be under directional selection, although intermediate levels of these traits might be favored if there are trade-offs among life-history traits.

Another explanation is that, under the conditions normally experienced by the organism, stabilizing selection reduces the expression of dominance and epistasis. When placed in more extreme environments, genes other than those normally controlling the trait may contribute to the phenotype (i.e., the genetic correlation between the same trait in two environments is less than one). Since these genes may not have been under stabilizing selection, levels of dominance and epistasis may not have been reduced. As the environment becomes extreme, genes demonstrating dominance and epistatic interactions will more likely contribute to a trait. The increase in dominance and epistasis as traits deviate from a mean value may therefore not be a response to directional selection. This argument requires that the undefined microenvironmental factors responsible for the variation in the environmental value are sufficient to reduce genetic correlations between environments.

More work is required to distinguish between these and other explanations. In particular, crosses involving the same set of genotypes need to be carried out across a wide range of defined environments.

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