Epistasis and Its Contribution to Genetic Variance Components

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Manuscript received July 6, 1994
Accepted for publication December 12, 1994

ABSTRACT

We present a new parameterization of physiological epistasis that allows the measurement of epistasis separate from its effects on the interaction (epistatic) genetic variance component. Epistasis is the deviation of two-locus genotypic values from the sum of the contributing single-locus genotypic values. This parameterization leads to statistical tests for epistasis given estimates of two-locus genotypic values such as can be obtained from quantitative trait locus studies. The contributions of epistasis to the additive, dominance and interaction genetic variances are specified. Epistasis can make substantial contributions to each of these variance components. This parameterization of epistasis allows general consideration of the role of epistasis in evolution by defining its contribution to the additive genetic variance.

EPISTASIS is the phenotypic effect of interaction among alleles at multiple loci. Our knowledge of biochemistry and physiological genetics strongly suggests that interaction among gene products is ubiquitous (WRIGHT 1980). A belief in the importance of genic interaction lies at the core of WRIGHT's ideas concerning the genetic basis of evolution (WRIGHT 1932, 1980; PROVINE 1986; WADE 1992) and plays a central role in founder effect models of speciation (TEMPLETON 1979, 1980; CARSON and TEMPLETON 1984). Furthermore, theoretical models indicate that with epistasis, population bottlenecks and subdivision expose hidden additive genetic variance to selection (CARSON and TEMPLETON 1984; BRYANT *et al.* 1986; GOODNIGHT 1987, 1988; TACHIDA and COCKERHAM 1989; BRYANT and MEFFERT 1992; WADE 1992) allowing rapid adaptation to new environments.

However, reviews of experimental results suggest that the effects of epistasis on viability may be weak (SIMMONS and CROW 1977; HEDRICK *et al.* 1978; BARKER 1979; CROW 1979, 1987). The quantitative effects of epistasis have been difficult to discern by traditional techniques because they are difficult to estimate (FALCONER 1989). Epistatic terms contribute relatively little to the covariance among relatives, except when clones are available (FALCONER 1989). For these reasons, despite elegant models of selection in special two-locus systems (LEWONTIN and KOJIMA 1960; KARLIN and FELDMAN 1970; KARLIN 1975; HASTINGS 1982, 1985) and the contribution of epistatic variance to the covariance among relatives (COCKERHAM 1954, 1963; HAYMAN and MATHER 1955), the contribution of epistasis to genetic variance components and, hence, to evolutionary processes remains obscure.

To improve our understanding of the role of epistasis, it is necessary to differentiate between physiological and statistical genetic definitions of the phenomenon. In physiological genetics, epistasis occurs when the phenotypic differences among individuals with various genotypes at one locus depends on their genotypes at other loci. In statistical genetics, the epistatic (or interaction) deviation is the deviation of multilocus genotypic values from the additive combination of their single-locus components (FALCONER 1989). There are two important distinctions inherent in these definitions. First, statistical epistasis is a population phenomenon depending on allele frequencies present in a specific population whereas physiological epistasis is a genotypic phenomenon, independent of allele frequencies at the loci in question. Previous models of the effects of epistasis have dealt mainly with its statistical effects (CROW and KIMURA 1970; GOODNIGHT 1987, 1988; WADE 1992). Second, epistatic interaction deviations are, by definition, associated only with the interaction genetic variance component, whereas physiological epistasis can also contribute to additive and dominance genetic variance components (CROW and KIMURA 1970).

We present a quantitative description of physiological epistasis so that epistasis can be considered as a genotypic phenomenon, independently from its difficult-to-detect contribution to interaction genetic variance (also referred to as epistatic genetic variance). We will then specify the contribution of physiological epistasis to the various genetic values and variance components of quantitative genetics. This allows us to specify the role of physiological epistasis in general evolutionary models through its effects on additive genetic variance.

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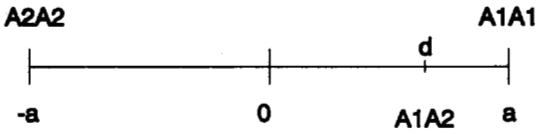

FIGURE 1.—Physiological dominance (d) is the deviation of the heterozygote genotypic value from the midpoint of the homozygote genotypic values. The term "a" is the additive genotypic value given by the deviation of the larger homozygote from the midpoint of the homozygote genotypic values.

DOMINANCE

The distinction between statistical and physiological epistasis is similar to that made between statistical and physiological dominance. Physiological dominance occurs when the phenotypic value of the heterozygote is not midway between the phenotypic values of the two homozygotes (Figure 1). Statistical-dominance deviations are deviations of single-locus genotypic values from the additive combination of the alleles contributing to the genotype (CROW and KIMURA 1970). In the single-locus case the additive (a) and dominance (d) genotypic values do not depend on allele frequencies at the locus in question. The value d reflects physiological dominance because deviations of d from 0 reflect the phenotypic effects of intralocus allelic interaction (see Figure 1). In contrast, the additive effects of alleles and dominance deviations depend critically on allele frequencies.

Additive (a) and dominance (d) genotypic values are least squares solutions for the coefficients of an unweighted regression of genotypic value on the number of "1" alleles (a) and whether the genotype is heterozygous (d). In this unweighted regression, genotypic values are not weighted according to their population frequencies. In contrast, average effects of alleles and dominance deviations are the least-squares coefficients and residuals, respectively, of a weighted regression of genotypic values on the number of 1 alleles (CROW and KIMURA 1970). We will treat physiological epistasis in a similar fashion with a two-allele, two-locus unweighted regression model.

It is well known that physiological dominance contributes to both the additive genetic and dominance values and variances (CROW and KIMURA 1970; FALCONER 1989). Likewise, physiological epistasis contributes to additive genetic, dominance and interaction genetic values and variances. We will derive the contributions of epistasis to the various genetic variance components.

EPISTASIS

Defining physiological epistasis: Epistasis occurs when differences in genotypic values at one locus vary depending on the genotype present at a second locus. Two-locus genotypic values (G_{ijkl}) are simply the average phenotype for individuals carrying the ij genotype at the first locus and the kl genotype at the second locus. The loci will be referred to as A and B each with two alleles, 1 and 2. Allele frequencies are p_1 and p_2 at locus A and q_1 and q_2 at locus B. By definition, the two-locus genotypic values are independent of the allele frequencies at the two loci in question. For present purposes, they will also be considered as independent of allele frequencies at all other loci, implying no three-way or higher level epistasis. If higher levels of epistasis occur, the epistasis values defined here will depend on allele frequencies at other loci.

The single-locus genotypic values (SLV) are defined as the unweighted average of the three genotypic values tallied across the other locus,

$$G_{ij..} = (G_{ij11} + G_{ij12} + G_{ij22})/3 \qquad (1)$$

at locus A and

$$G_{..kl} = (G_{11kl} + G_{12kl} + G_{22kl})/3 \qquad (2)$$

at locus B.

The single locus additive (a) and dominance (d) genotypic values can then be defined in the usual way as,

$$a_A = G_{11..} - [(G_{11..} + G_{22..})/2] \qquad (3)$$

and

$$d_A = G_{12..} - ((G_{11..} + G_{22..})/2]. \qquad (4)$$

Similar equations hold at locus B. These genotypic values are the unweighted averages of the a and d values across the three genotypes at the alternate locus,

$$a_A = (a_{A,B1B1} + a_{A,B1B2} + a_{A,B2B2})/3 \qquad (5)$$

and

$$d_A = (d_{A,B1B1} + d_{A,B1B2} + d_{A,B2B2})/3, \qquad (6)$$

where the subscripts denote the alternate locus genotypes. Similar equations hold at locus B.

As in the single locus case, the additive and dominance values are the least-squares coefficients of an unweighted regression of genotypic values on the number of 1 alleles at locus A (a_A), whether the locus A genotype is heterozygous (d_A), the number of 1 alleles at locus B (a_B) and whether the B locus genotype is heterozygous (d_B). They are not the same as the single-locus a and d values if there is epistasis, because these single-locus values change as allele frequencies change at the alternate locus whereas the values in Equations 3 and 4 are invariant relative to allele frequencies at the two loci in question. The marginal single locus genotypic values (Equations 1 and 2 can be summed to provide two-locus genotypic values without epistasis or nonepistatic genotypic values (ne_{ijkl})

$$ne_{ijkl} = G_{ij..} + G_{..kl} - G_{....} \qquad (7)$$

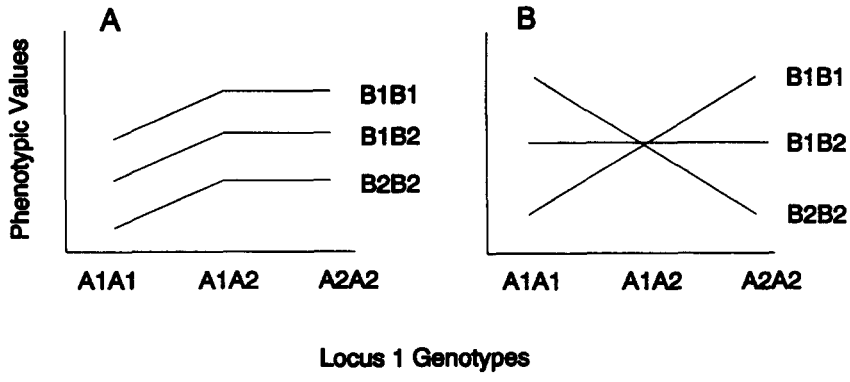

FIGURE 2.—(A) No epistasis, the two-locus genotypic values are parallel to one another across both loci. (B) Epistasis is measured as the deviation of the two-locus genotypes from a parallel arrangement.

where $G_{\ldots}$ is the unweighted average of the nine genotypic values. These nonepistatic genotypic values are the predicted values given by the unweighted least-squares regression of two-locus genotypic values onto the single-locus components. Differences among nonepistatic genotypic values at one locus are independent of alternate locus genotypes (see Figure 2).

The epistasis values (e_{ijkl}) are the deviation of the two-locus genotypic values from the nonepistatic values,

$$e_{ijlk} = G_{ijkl} - ne_{ijkl}, \quad (8)$$

and are therefore the residuals of the unweighted regression of genotypic values onto single-locus components. The row and column sums of epistasis values across single-locus genotypic classes at both loci are 0 by definition.

With this definition of epistasis, it is possible to measure and test for epistasis independent of its effect on the various genetic variance components. Individual epistasis values can be statistically compared with 0. The error variance for an individual epistasis value [$V(e_{ijkl})$] can be given in terms of the error variances of the observed genotypic values assuming that genotypic value estimates are independent of one another. For example,

$$V(e_{1111}) = [16V(G_{1111}) + 4V(G_{1112}) + 4V(G_{1122}) + 4V(G_{1211}) + 4V(G_{2211}) + V(G_{1212}) + V(G_{1222}) + V(G_{2212}) + V(G_{2222})]/81. \quad (9)$$

In general, a coefficient of 16 is associated with the genotypic value error variance of the target two-locus genotype, coefficients of 4 are applied to genotypic value variances with the same genotype as the target at one locus but a different genotype at the other locus and coefficients of 1 are applied to genotypic value variances when genotypes at both loci are different from the two-locus target genotype.

The overall level of epistasis (E^2) can be measured by the sum of the squared epistasis values because their sum is 0 by definition,

$$E^2 = (e^2_{1111} + e^2_{1112} + e^2_{1122} + e^2_{1211} + e^2_{1212} + e^2_{1222} + e^2_{2211} + e^2_{2212} + e^2_{2222}). \quad (10)$$

The overall level of epistasis can be tested for statistical significance with a F-test

$$F = EMS/RMS, \quad (11)$$

with $4, N - 9$ degrees of freedom where N is the total sample size. The residual mean square (RMS) is the pooled within-genotype variance and can be obtained from the residual variance of a two-way ANOVA with single-locus genotypes and their interaction as the factors. The epistasis mean square (EMS) is

$$EMS = [(N_{1111}e^2_{1111} + N_{1112}e^2_{1112} + N_{1122}e^2_{1122} + N_{1211}e^2_{1211} + N_{1212}e^2_{1212} + N_{1222}e^2_{1222} + N_{2211}e^2_{2211} + N_{2212}e^2_{2212} + N_{2222}e^2_{2222}) - (SUM^2/N)]/4, \quad (12)$$

where N_{ijkl} is the sample size for each genotype and SUM is the sum of the phenotypes across the entire population (SOKAL and ROHLF 1981). This provides an empirical means of demonstrating epistasis when measured genotype data is available. The residual mean square for the weighted and unweighted regressions are the same but the division of variance among the genotypic components varies, the results being genotype-specific with the unweighted regression and population-specific with the weighted regressions. We will now describe the relationship between our genotype-specific values and the population-specific values of quantitative genetics. These relationships depend on allele frequencies at the epistatically interacting loci.

Contributions of epistasis to genetic values and variance components: Given the definition of epistasis provided above, it is possible to specify its contribution to the various population-level quantitative genetic values and variance components. First, the population mean value is

$$\mu = a_A(p_1 - p_2) + 2p_1p_2d_A + a_B(q_1 - q_2) + 2q_1q_2d_B + e_{\ldots}, \quad (13)$$

where $e_{\ldots}$ is the population average epistasis value,

$$e_{....} = p_1^2q_1^2e_{1111} + 2p_1^2q_1q_2e_{1112} + p_1^2q_2^2e_{1122} + 2p_1p_2q_1^2e_{1211} + 4p_1p_2q_1q_2e_{1212} + 2p_1p_2q_2^2e_{1222} + p_2^2q_1^2e_{2211} + 2p_2^2q_1q_2e_{2212} + p_2^2q_2^2e_{2222}, \quad (14)$$

assuming Hardy-Weinberg and linkage equilibrium. Note that the mean in Equation 13 is the same as that given for single loci in FALCONER (1989, Equation 7.2) summed over two loci with an additional term due to epistasis. Unlike the definition of physiological epistasis, the population mean epistasis naturally depends on the allele frequencies at the two loci in question.

With random mating and linkage equilibrium, the average effect of an allele (α_i) is the mean deviation from the population mean of individuals that received that allele from one parent, the allele received from the other parent having come at random from the population (FALCONER 1989),

$$\alpha_{A1} = p_2[a_A + d_A(p_2 - p_1)] + p_1p_2(e_{11..} - e_{12..}) + p_2^2(e_{12..} - e_{22..})$$

and

$$\alpha_{A2} = (-p_1)[a_A + d_A(p_2 - p_1)] + p_1p_2(e_{22..} - e_{12..}) + p_1^2(e_{12..} - e_{11..}). \quad (15)$$

Similar equations are available for locus B. The epistasis terms ($e_{ij..}$) are the population means across the specified genotype (ij). For example, $e_{11..}$ is the population average epistasis value for A_1A_1 homozygotes,

$$e_{11..} = q_1^2e_{1111} + 2q_1q_2e_{1112} + q_2^2e_{1122}. \quad (16)$$

Note that Equations 15 are the same as FALCONER's (1989) Equation 7.4 for the average effects of alleles with the addition of the epistasis terms. The average effect of an allele substitution (α) at locus A is

$$\alpha_A = a_A + d_A(p_2 - p_1) + p_1(e_{11..} - e_{12..}) + p_2(e_{12..} - e_{22..}), \quad (17)$$

with a similar equation for locus B.

The population-specific single locus additive (a') and dominance (d') values can also be redefined to include the potential effects of epistasis,

$$a'_A = a_A + (e_{11..} - e_{22..})/2 \quad (18)$$

and

$$d'_A = d_A + (-e_{11..} + 2e_{12..} - e_{22..})/2. \quad (19)$$

Similar equations hold for locus B. These equations specify how additive and dominance genotypic values at one locus depend on epistasis values and alternate locus allele frequencies. Note that the epistasis terms in Equations 18 and 19 are the population additive and dominance genotypic values, respectively, for the epistasis genotypic values (see Equations 3 and 4).

The average effects of alleles are used to define breeding values (A_{ijkl}) for particular genotypes, the breeding values being the sum of the contributing genic values,

$$A_{ijkl} = \alpha_{Ai} + \alpha_{Aj} + \alpha_{Bk} + \alpha_{Bl}. \quad (20)$$

Because these genic values contain epistasis terms, it can be seen that epistasis contributes to the average effects of alleles and to the breeding value of genotypes. In doing so, epistasis contributes to the additive genetic, or breeding value, variance and thus to evolutionary response to selection. It has long been recognized that epistasis contributes to additive genetic variance (CROW and KIMURA 1970) but this effect can now be quantified by comparing additive genetic variances for nonepistasis values with variances obtained with total genotypic values.

Epistasis also contributes to the dominance deviations at each locus. It can be shown that

$$\delta_{A11} = -2p_2^2d_A + p_2^2(e_{11..} - 2e_{12..} + e_{22..})$$
$$\delta_{A12} = 2p_1p_2d_A - p_1p_2(e_{11..} - 2e_{12..} + e_{22..})$$
$$\delta_{A22} = -2p_1^2d_A + p_1^2(e_{11..} - 2e_{12..} + e_{22..}). \quad (21)$$

Similar equations hold for locus B. Note that these equations correspond to those given in FALCONER's (1989) table 7.3 with the addition of the terms due to epistasis. The dominance variance due to locus A is given by

$$V_{dA} = [2p_1p_2d_A - p_1p_2(e_{11..} - 2e_{12..} + e_{22..})]^2, \quad (22)$$

with a similar equation for locus B.

The interaction deviations (I) can also be derived in this two-locus system. Interaction deviations are sometimes referred to as epistatic deviations but it is important to distinguish between them and the epistasis values described here. For genotype *ijkl* the interaction deviation is

$$I_{ijkl} = e_{ijkl} - e_{ij..} - e_{..kl} + e_{....} \quad (23)$$

The interaction variance is the variance of these interaction deviations and, because interaction deviations average 0 by definition, the interaction variance is the sum of the squared interaction deviations weighted by the corresponding genotype frequencies.

It is important to note that additivity (a), dominance (d) and epistasis (e) all contribute to the average effects of alleles and additive genetic variance (Equations 15), whereas only dominance and epistasis contribute to the dominance deviations and variance (Equations 21 and 22), and epistasis alone contributes to interaction deviations and variance (Equation 23). Epistasis can make important contributions to the additive and dominance variances, only the remainder of its effects contributing to the interaction variance. The importance of epistasis

in evolution is not confined to its influence on the interaction variance but is crucially related to its influence on additive genetic, or heritable, variance.

NUMERICAL EXAMPLE

We provide a numerical example based on genotypic effects on 10-wk body weight measured at two short sequence repeat (SSR) loci, *D1Mit7* and *D7Mit17*, in a population of 534 F_2 mice produced by intercrossing two inbred mouse strains, Small (SM/J) and Large (LG/J; ROUTMAN and CHEVERUD 1994). *D7Mit17* will be referred to as locus *A* and *D1Mit7* as locus *B*. The *1* allele comes from the Large (LG/J) strain ($p_1 = 0.495$; $q_1 = 0.537$) and the *2* allele from the Small (SM/J) strain. The genotypic, nonepistatic and epistatic values are given in Table 1, as are the standard errors and associated *t*-values for individual epistatic values.

Figure 3 compares the total (Figure 3A), nonepistatic (Figure 3B) and epistatic (Figure 3C) genotypic values. Note that because the edges connecting the total genotypic values are not parallel, epistasis is indicated. The edges connecting the nonepistatic values are parallel, indicating that the differences between genotypic values at one locus are independent of the genotype at the other locus. Finally, the edges connecting the epistatic genotypic values are nonparallel, illustrating the dependence of genotypic value differences at one locus on genotypes at the second locus.

The single-locus genotypic values indicate that the *LG* allele produces a positive effect and is dominant to the *SM* allele at both loci. Note that for the nonepistatic values, differences among genotypic values at one locus are constant over the genotypes at the alternate locus. The epistasis values indicate that epistasis at this pair of loci is due to relative underdominance within the heterozygous genotypes at each locus ($A_1A_2B_1B_2$ genotype is significantly smaller than 0 at the 5% level) contrasted with relative overdominance within the *SM* homozygous genotypes at the *D7Mit17* locus ($A_2A_2B_1B_2$ genotype is significantly larger than 0 at the 5% level) and within the *LG* homozygous genotypes at the *D1Mit7* locus ($A_1A_2B_1B_1$ genotype is significantly larger than 0 at the 6% level). The sum of the squared epistasis values (E^2, Equation 10) is 2.126 with a significant associated F-ratio (4,496 df) of 2.550 ($P = 0.038$).

Given these genotypic values and allele frequencies and, using Equations 15–23, the genotypic variance components are given in Table 2. These are the same values as are obtained from standard quantitative genetic equations (FALCONER 1989). The contribution of physiological epistasis to the genetic variance components can be considered by removing epistasis from the genotypic values and recalculating the components using only the nonepistatic values (Table 2).

The additive genetic variance at locus *A* is suppressed by locus *B* at intermediate allele frequencies in that the total genotypic values display 12% less additive genetic variance at locus *A* than observed with the nonepistatic genotypic values. In contrast, additive genetic variance at locus *B* is enhanced by epistatic interaction with locus *A* at intermediate allele frequencies, the total genotypic values displaying 9% more variance at locus *B* than the nonepistatic values. In this example, epistasis severely suppresses dominance variance at both loci at intermediate allele frequencies.

The interaction variance at this locus is not statistically significant at the 0.05 level despite the observation

TABLE 1

Genotypic, nonepistatic and epistatic values

	A_1A_1	A_1A_2	A_2A_2	SLV*
		Genotypic values		
B_1B_1	36.839	37.951	34.118	36.302
B_1B_2	36.527	35.898	34.894	35.773
B_2B_2	33.824	34.125	31.234	33.061
SLV*	35.730	35.991	33.415	
		Nonepistatic values		
B_1B_1	36.987	37.248	34.672	36.302
B_1B_2	36.458	36.719	34.143	35.773
B_2B_2	33.746	34.007	31.431	33.061
SLV*	35.730	35.991	33.415	
		Epistasis values		
B_1B_1	−0.148	0.703	−0.555	
B_1B_2	0.069	−0.821	0.752	
B_2B_2	0.079	0.118	−0.197	
		Standard errors of individual epistasis values		
B_1B_1	0.409	0.370	0.456	
B_1B_2	0.345	0.311	0.375	
B_2B_2	0.416	0.367	0.464	
		t-values (ratio of epistasis value to standard error)		
B_1B_1	−0.361	1.898	−1.217	
B_1B_2	0.201	−2.642	2.005	
B_2B_2	0.189	0.322	−0.424	
		Single-locus genotypic values		
	$a_A = 1.157$		$d_A = 1.419$	
	$a_B = 1.621$		$d_B = 1.092$	

Values for 10-wk body weight (in grams) at marker loci *D7Mit17* (locus *A*) and *D1Mit7* (locus *B*) in a F_2 intercross of Large (LG/J; allele *1*) and Small (SM/J; allele *2*) inbred mouse strains. Also included are the standard errors and *t*-values for individual epistatic values. *t*-values with an absolute value greater than 1.96 are statistically significant at the 5% level.

[a] SLV, single-locus marginal genotypic values (see Equations 1 and 2).

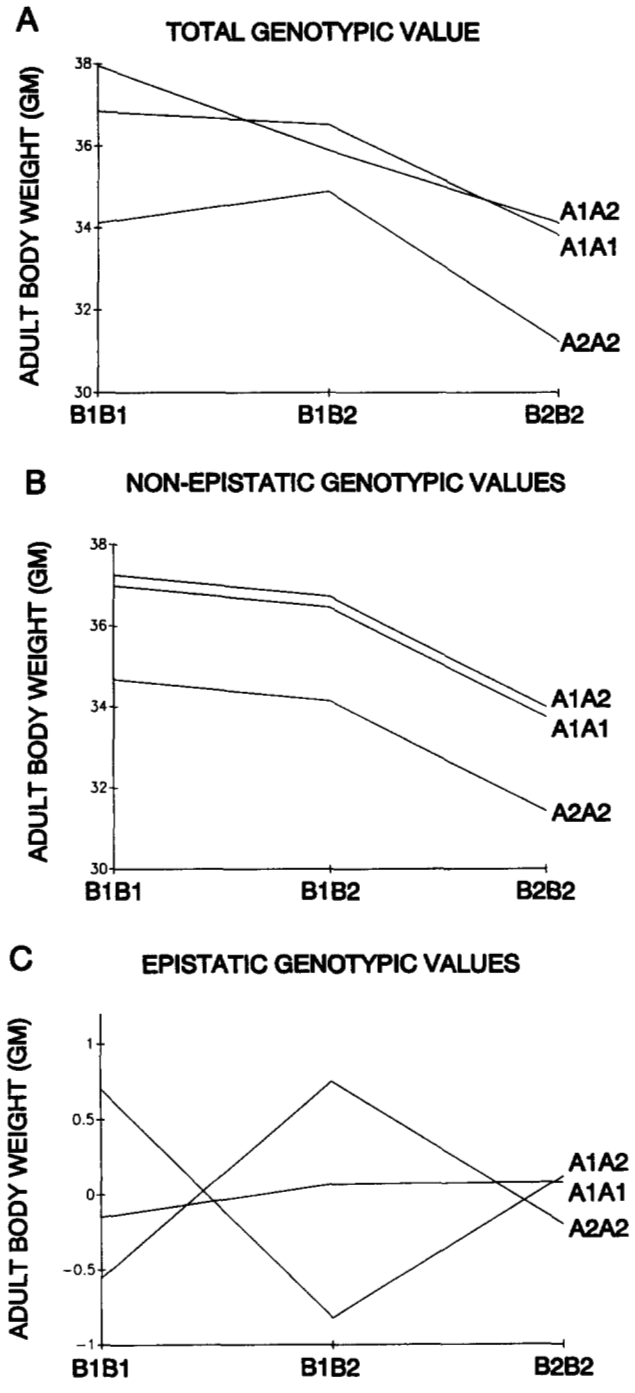

FIGURE 3.—Total (A), nonepistatic (B) and epistatic (C) genotypic values at microsatellite marker loci *D7Mit17* (locus *A*) and *D1Mit7* (locus *B*) for adult murine body weight in F_2 animals from an intercross of LG/J and SM/J inbred strains. Deviations from a parallel arrangement of the lines indicate epistasis.

of considerable epistasis (E. J. ROUTMAN and J. M. CHEVERUD, unpublished data), demonstrating the point that testing for interaction variance is a relatively ineffective means of detecting epistasis. In a study of adult murine body weight, 15% of 120 two-locus combinations tested displayed statistically significant epistasis although only 5% of the combinations had significant interaction variances (E. J. ROUTMAN and J. M. CHEVERUD, unpublished data).

TABLE 2

Additive (a), dominance (d), interactive (i) and total (g) genetic variance components

Variance components	Total genotypic values	Nonepistatic values	Epistatic ratio
V_{aA}	0.487	0.551	0.883
V_{aB}	1.449	1.330	1.090
V_a	1.936	1.881	1.029
V_{dA}	0.303	0.497	0.610
V_{dB}	0.141	0.298	0.473
V_d	0.444	0.795	0.558
V_i	0.250	0.000	N/A
V_g	2.630	2.677	0.982

Variance components for 10-wk body weight at marker loci *D7Mit17* (locus *A*) and *D1Mit7* (locus *B*) in the F_2 intercross of Large (LG/J) and Small (SM/J) strains of mice. Variance components for total genotypic values are contrasted with those for nonepistatic values alone. The ratio of variances based on total and nonepistatic genotypic values represents the effects of epistasis on these variance components. Ratios <1 indicate variance suppression due to epistasis whereas ratios >1 indicate variance enhancement.

CONCLUSION

Our parameterization of epistasis allows for the detection and quantification of the interaction among genes at multiple loci. With the growing frequency of measured genotype studies (in which known genotypes are related to phenotypic values; *e.g.*, EDWARDS *et al.* 1987; SING *et al.* 1988; PEDERSEN and BERG 1989; DOEBLY and STEC 1991; ANDERSSON *et al.* 1994), access to the two-locus genotypic values necessary for performing this analysis is increasingly available. Epistasis can be quantified in measured genotype studies so that the prevalence and patterns of interlocus interaction can be empirically addressed. Previous studies (*e.g.*, EDWARDS *et al.* 1987; DOEBLEY and STEC 1991) have relied on detecting significant interaction variance as a means of detecting epistasis. As we have shown, this is a relatively inefficient method of doing so because interaction deviations are only a portion of their corresponding epistatic values (see Equation 23). The recent proliferation of quantitative trait locus studies provides the data for direct measurements of epistasis.

By defining the contribution of epistasis to the genetic variance components of quantitative and population genetic theory, we provide a general means for considering the role of epistasis in evolution. Most previous theoretical papers were restricted to special cases

of epistasis (HAYMAN and MATHER 1955; HASTINGS 1985; GOODNIGHT 1987, 1988; TACHIDA and COCKERHAM 1989). Disputes have arisen in the past about the potential role of interlocus genetic interaction systems in evolution and speciation (*e.g.*, BARTON and CHARLESWORTH 1984 *vs.* CARSON and TEMPLETON 1984). Now epistasis can be measured and its contribution to heritable variance specified, allowing more general theoretical and empirical approaches to this question.

We thank ALAN TEMPLETON and GUNTER WAGNER for helpful discussions of the ideas presented here, and SHIMELIS BEYENE, MARGUERITE BUTLER, EIRIK CHEVERUD, KILINYAA COTHERAN, FRANCISCO DUARTE, DUNCAN IRSHICK, CHRISTY PEREL, BRUNO VON SWINDEREN and NATALIA VASEY for laboratory help. This work was supported by National Science Foundation grant BSR-9106565 to J.M.C.

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Communicating editor: P. D. KEIGHTLEY