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Dominance Alone Is Not Enough

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It has often been noted that the correlation between dizygotic (DZ) twins is smaller than predicted from the monozygotic (MZ) correlation under a simple additive genetic model. Possible genetic explanations of this finding are considered. It is shown that duplicate gene interactions between pairs of moderately frequent alleles at polygenic loci are sufficient to produce surprisingly small (approximately 0.12) genetic correlations between siblings.

KEY WORDS: dominance; epistasis; emergenesis; extroversion; twins; genetic correlation.

INTRODUCTION

Given random mating, the classical model of additive gene action is expected to yield a genetic correlation between dizygotic (DZ) twins or siblings which is exactly half that of monozygotic (MZ) twins. It has been a cause of some puzzlement among investigators that the correlation between DZ twins often appears to be much less than expected. How is the discrepancy to be explained? One school (e.g., Eaves and Eysenck, 1975) has adopted a conservative position which has claimed that, although the DZ correlation *looks* too small, the discrepancy is not larger than might be expected by chance alone and so should not be used as a foundation for theories of unwarranted complexity. Although it is true that many studies are still too small to justify any other position, there is now replication of the small DZ correlation for extraversion (perhaps sociability rather than impulsivity), in samples which are so large as to render the

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discrepancy from classical additivity far greater than might be expected by chance alone (see Eaves *et al.*, 1987).

Thus, in this case at least, the failure of the usual additive genetic model has to be taken seriously. Two kinds of explanation can be offered. The first is genetic, in terms of nonadditive genetic effects. The second seeks an explanation in social terms, for example, competitive social interactions between twins based on their genetic differences. The purpose of this paper is to examine the value of purely genetic explanations of the phenomenon.

Among genetic explanations, there have been two major contenders. The relatively conservative position, from a scientific point of view, exemplified by Eaves *et al.*, has parameterized the extra difference between MZ and DZ correlations in terms of genetic dominance. Such a model fits the data for extroversion by purely statistical criteria but usually leads to a (nonsignificant) negative estimate of the component due to additive gene action. Such estimates can arise quite often by chance because of the high correlation between estimates of additive and estimates of dominance effects derived from twin data alone. However, the large numerical values of the dominance parameters obtained in such analyses are consistent only with a heterozygous advantage or very extreme gene frequencies and dominance effects. Even when the allele frequencies are so extreme as to all but eliminate the contribution of homozygous effects to variation, the limiting value of the sibling genetic correlation is one-fourth of the MZ correlation. This value is greater than that sometimes observed in practice.

An alternative genetic explanation for the low DZ correlation is advanced by Lykken (e.g., 1982), who invokes very high-order interactions ("emergenesis") between large numbers of relatively infrequent alleles at different loci.

The problem with the "dominance" and "emergenesis" models is that they are not consistent with what is known about the mechanisms of gene action inferred from experimental studies in other organisms (see, e.g., Mather and Jinks, 1982). Careful experimental analysis in species such as *Nicotiana rustica* suggests that virtually all cases of apparent "overdominance" at polygenic loci can be resolved in terms of epistatic effects. There is little evidence in experimental organisms that heterozygous effects exceed the additive genetic deviations. On the other hand, although higher-order interactions (e.g., trigenic interactions) can be detected in careful breeding studies, their effects are far outweighed by interactions between pairs of loci ("digenic interactions"). Thus, we would tend to reject any model which requires extreme amounts of dominance, on the one hand, or large contributions of high-order interactions,

on the other. However, it may be shown that a model which invokes only digenic interactions could, under certain reasonable and theoretically important conditions, yield quite large correlations between MZ twins but very low (of the order of 0.12) genetic correlations for siblings and DZ twins.

THE MODEL

The model for nonallelic interactions between pairs of loci has been well-known among biometrical geneticists for a long time (see, e.g., Mather and Jinks, 1982, Chap. 5) and has been applied quite straightforwardly to behavioral traits in infrahuman species to account for the pattern of generation means derived by controlled matings between inbred lines and their F_1's. Few have considered its practical application to man for a number of reasons. First, the expectations for covariances between relatives (see, e.g., Mather, 1974) involve far more parameters, even for the simple case of random mating without cultural inheritance, than any data set is ever likely to resolve. In Mather's (1974) notation, the parameters include the usual terms for additive and dominance variation (D_R and H_R, respectively) but also three components of variance to allow for epistatic interactions between loci: I_R to reflect the contribution of additive $\times$ additive interactions, J_R for additive $\times$ dominance interactions, and L_R for heterozygote $\times$ heterozygote interactions. Second, another reason for the lack of appeal of epistatic models in man arises because, even if a constellation of relatives could be identified which would allow all these parameters to be estimated in theory, the correlations between the estimates of the genetic parameters would be so high that their reliable resolution would be virtually impossible. Third, all the problems which attend the interpretation of additive and dominance variance components when allele frequencies are unequal apply a fortiori to the expectations in the presence of epistatic interactions. That is, when the frequencies of increasing and decreasing alleles are not equal at each and every locus, the additive genetic parameter, D_R, contains heterozygous effects (when there is dominance) and a contribution from all three types of epistatic interaction when these are also present. Indeed, when there are digenic interactions, all the variance components, with the exception of L_R, are such complex functions of gene frequencies, additive and dominance effects, and the various types of epistatic interactions that no simple interpretation is possible (Mather, 1974).

These basic problems vitiate any attempt at the detailed analysis of nonallelic interaction in man and have resulted in a climate in which, when the additive genetic model fails, we add a dominance parameter

(H_R or V_D) to absorb genetic nonadditivity and make sure that its interpretation is sufficiently circumscribed to reflect the fact that other nonadditive genetic effects might also be confounded with the additive and dominance components and remain unresolved.

However, a sibling correlation which is "too low for dominance" can be interpreted in terms of a model involving digenic interactions between polygenic loci which has major biological significance without recourse to the more extreme (and less plausible) hypothesis of invoking higher-order epistatic interactions. Mather (1974) undertook the tedious task of deriving the expected values of the five components of variance defined above in terms of the frequencies and effects of individual loci and pairs of interacting loci. These expectations are reproduced by Mather and Jinks (1982, pp. 221–223). They each involve the frequencies, u_a and v_a, of increasing and decreasing alleles; the additive deviation (d_a) of the homozygote from the midpoint, m, of the two homozygotes; the dominance deviation (h_a) at each locus; and the three epistatic effects, i_{ab}, between homozygotes at locus A and those at locus B, j_{ab}, between homozygotes at locus A and heterozygotes at locus B, and l_{ab}, between heterozygotes at locus A and those at locus B. The important point is that only when $u_a = v_a$ at every locus are the variance components D_R, H_R, I_R, J_R, and L_R pure functions of d, h, i, j, and l, respectively. By applying certain constraints to the gene effects, the classical forms of epistasis which yield the familiar segregation ratios in an F_2 from a dihybrid cross can be derived. Thus, the 15:1 segregation of the classical "duplicate gene" case is obtained when $d_a = h_a$ at two loci, and all the epistatic effects are negative but equal in absolute value to the additive effect. The same segregation occurs when $d_a = -h_a = i_{ab} = -j_{ab} = -j_{ba} = l_{ab}$. Other special cases are given by Mather and Jinks (1982, p. 84). The case of duplicate genes achieves some importance theoretically because such duplicate interactions are sometimes components in the genetic architecture of fitness traits (Mather, 1967). That is, when traits have been monotonically related to fitness for a long time it is expected that gene expression may be modified to buffer the phenotype. Duplicate gene effects are one mechanism by which this may be achieved. The possibility that a given trait may show epistatic interaction of the duplicate gene type, therefore, is of great importance to behavior geneticists because it provides a heuristic for identifying traits which have been fundamental to evolutionary change.

The total genetic variance in a randomly mating population is:

$$V_G = \tfrac{1}{2}D_R + \tfrac{1}{4}H_R + \tfrac{1}{4}I_R + \tfrac{1}{8}J_R + \tfrac{1}{16}L_R$$

and the sibling (DZ twin) genetic covariance is

$$C_{SIB} = \tfrac{1}{4}D_R + \tfrac{1}{16}H_R + \tfrac{1}{16}I_R + \tfrac{1}{64}J_R + \tfrac{1}{256}L_R,$$

so the ratio of the two is the genetic correlation between siblings, ρ_{SIB}, which is expected to be one-half in the absence of nonadditive effects and to approach a limit of one-quarter under a purely additive-dominance model when extreme gene frequencies remove all traces of additive genetic effects. The crucial question remains: What happens to the sibling correlation when there are epistatic interactions?

METHOD

The complexity of the expectations for the variance makes it difficult to see, simply by inspection of the expectations, what values are likely for the additive, dominance, and epistatic components under different conditions. To circumvent this difficulty we performed series of numerical substitutions in the expressions for the components, the total genetic variance, and the genetic correlation between siblings using a program written in BASIC. Various allele frequencies were assumed. The additive genetic deviation was fixed at unity, the dominance deviation at -1, -0.5, 0, 0.5, and 1 and a parameter, θ, introduced to provide a scale factor for the epistatic effects. Gene frequencies and effects were assumed to be identical at all loci and pairs of interacting loci. The expectations were evaluated for the case of $k = 2$ and $k = 5$ loci. The epistatic effects were parameterized as follows: $i = d^2\theta$, $j = dh\theta$, $l = h^2\theta$. Thus, for the two-locus case, when $d = h = 1$ and $\theta = -1$ we have the classical duplicate gene interaction. The other case of duplicate gene action is given by $d = 1$, $h = -1$, $\theta = 1$ for the two-locus case.

RESULTS

Selected but typical results are given in Table I. For the case of two loci and equal gene frequencies, the classical duplicate gene model yields the smallest genetic correlation (approximately 0.27). However, in striking contrast to the effect of unequal gene frequencies in the presence of dominance, only a modest inequality of gene frequencies ($u = 0.8$) is required before the sibling correlation is reduced to almost one-eighth (0.128) of the genetic correlation between MZ twins. Such small correlations are achieved only, over the parameter range studied here, for the case of duplicate genes. Furthermore, they occur only for the specific case of duplicate gene interaction consistent with the effects of directional selection, i.e., when the direction of dominance (h) is in the same direction as the effect of the most frequent allele. Thus, for $u = 0.8$ we obtain only

Table I. Genetic Variance and Sibling Genetic Correlation in the Presence of Digenic Interactions Between Two and Five Loci[a]

	$k = 2$					$k = 5$				
		$u = 0.5$		$u = 0.8$			$u = 0.5$		$u = 0.8$	
h	θ	V_G	ρ_{SIB}	V_G	ρ_{SIB}	θ	V_G	ρ_{SIB}	V_G	ρ_{SIB}
−1.0	−1.0	3.94	0.382	1.80	0.355	−0.50	16.40	0.396	3.02	0.297
	−0.5	2.48	0.403	1.58	0.438	−0.25	8.79	0.407	2.92	0.427
	0.	1.5	0.417	1.84	0.472	0.	3.75	0.417	4.61	0.472
	0.5	0.98	0.382	2.61	0.451	0.25	1.29	0.350	8.08	0.456
	1.0	0.94	0.271	3.87	0.418	0.50	1.41	0.174	13.34	0.433
−0.5	−1.0	2.07	0.434	0.68	0.370	−0.50	7.12	0.445	0.84	0.251
	−0.5	1.50	0.459	0.77	0.463	−0.25	4.59	0.461	1.09	0.443
	0.	1.12	0.472	1.13	0.489	0.	2.81	0.472	2.83	0.489
	0.5	0.94	0.451	1.77	0.477	0.25	1.78	0.444	6.07	0.480
	1.0	0.95	0.389	2.67	0.459	0.50	1.49	0.340	10.81	0.470
0.	−1.0	1.25	0.450	0.20	0.375	−0.50	3.13	0.450	0.32	0.300
	−0.5	1.06	0.485	0.34	0.481	−0.25	2.66	0.485	0.32	0.450
	0.	1.00	0.500	0.64	0.500	0.	2.50	0.500	1.60	0.500
	0.5	1.06	0.485	1.11	0.494	0.25	2.66	0.485	4.16	0.496
	1.0	1.25	0.450	1.74	0.485	0.50	3.13	0.450	8.00	0.492
0.5	−1.0	0.95	0.389	0.05	0.312	−0.50	1.49	0.340	0.33	0.402
	−0.5	0.94	0.451	0.15	0.451	−0.25	1.78	0.444	0.07	0.394
	0.	1.12	0.472	0.36	0.465	0.	2.81	0.472	0.91	0.465
	0.5	1.50	0.459	0.70	0.462	0.25	4.59	0.461	2.85	0.463
	1.0	2.07	0.434	1.16	0.458	0.50	7.12	0.445	5.87	0.461
1.0	−1.0	0.94	0.271	0.02	0.128	−0.50	1.41	0.174	0.60	0.312
	−0.5	0.98	0.382	0.10	0.320	−0.25	1.29	0.350	0.02	0.167
	0.	1.50	0.417	0.31	0.333	0.	3.75	0.417	0.77	0.333
	0.5	2.48	0.403	0.66	0.331	0.25	8.79	0.407	2.85	0.332
	1.0	3.94	0.382	1.16	0.329	0.50	16.41	0.396	6.25	0.331

[a] Parameters are defined in the text. All statistics are based on an additive genetic deviation $(d) = 1$.

a low sibling correlation when $h = 1$, $\theta = -1$ (Table I) and not when $h = -1$, $\theta = 1$. Therefore, an unexpected disparity between the correlation of MZ and that of DZ twins is entirely consistent with the expected genetic covariance of fitness traits. The findings are essentially the same for the case of five genes, each interacting pairwise with every other. Now a fairly narrow range of values for θ when $d = h = 1$ leads to a rapid reduction in the sibling genetic correlation down to an apparent minimum of 0.1 when $\theta = -0.27$. The smaller value of θ is offset by the much larger number of pairwise interactions between the larger number of loci.

CONCLUSION

Dominance alone is probably not enough to explain the very low correlation between DZ twins observed in very large samples for some traits relative to that for MZ twins. However, assuming that the explanation is to be sought in genetic rather than social terms, neither is it necessary to invoke extreme gene frequencies or high-order nonallelic interactions. Digenic interactions of the duplicate type, allied to only moderate inequality of allele frequencies, can produce the surprisingly low genetic correlations between siblings inferred from some twin studies. Such interactions are commonly asserted to occur when the trait in question has been monotonically related to fitness over a long period.

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