EVIDENCE FOR POLYGENIC EPISTATIC INTERACTIONS IN MAN?

A. C. HEATH,¹ N. G. MARTIN,² L. J. EAVES¹ AND D. LOESCH³

Department of Human Genetics, Medical College of Virginia, Richmond, Virginia 23298

Manuscript received October 18, 1983
Revised copy accepted December 13, 1983

ABSTRACT

Studies of multifactorial inheritance in man have ignored nonadditive gene action or attributed it entirely to dominance. Reanalyses of dermatoglyphic data on monozygotic and dizygotic twins, siblings and parents and offspring suggest that a substantial proportion of variation in total finger pattern intensity is due to epistatic interactions between additive genetic deviations, not dominance. Bootstrapping and power simulations support this interpretation of the data. We believe this is the strongest evidence so far for polygenic epistasis in man.

STUDIES of the transmission of multifactorial traits in man have assumed that all gene effects combine additively (MORTON 1974; RAO, MORTON and YEE 1976; RAO, MORTON and CLONINGER 1979; CLONINGER, RICE and REICH 1979) or else that any genetical nonadditivity is purely the result of dominance (JINKS and FULKER 1970; JINKS and EAVES 1974; RAO et al. 1982). Nonallelic interaction (epistasis) has simply been ignored. Dermatoglyphic variables have long been used to illustrate the principles of polygenic inheritance in man (HOLT 1968). These variables are particularly suitable for testing assumptions about gene action. Their broad heritability is very high. They appear to be immune from the effects of the shared family environment. They are not affected, directly or indirectly, by assortative mating. They do not vary with age (HOLT 1968). Under these circumstances, our ability to resolve additive and nonadditive gene action will be at its greatest.

It has usually been supposed that, apart from environmental effects unique to the individual, variation in dermatoglyphic characters simply reflects the cumulative and additive effects of multiple loci (HOLT 1968). Most of the support for an additive model comes from extensive studies of sibling and parent-offspring correlations. Under the simple additive model, both of these correlations are expected to be equal to one-half of the total genetic variance. Any dominance deviations would inflate the sibling correlation but not that between parent and offspring (FALCONER 1960). Since these two correlations

² Former address: Department of Population Biology, Research School of Biological Sciences, Australian National University, Canberra, Australia.
³ Permanent address: Department of Human Genetics, Psychoneurological Institute, Warsaw, Poland.

have been found to be virtually identical in large family studies, this has been taken as evidence supporting the additive model. Nonallelic interactions between the additive deviations at different loci will, however, inflate the sibling and the parent-offspring correlations by an identical amount (Cockerham 1954; Kempthorne 1954).

Twin studies of total finger ridge count (Lamy et al. 1957; Holt 1968) are consistent with a purely additive model. In twin studies of total finger pattern intensity (TFPI, the total number of triradii on all ten digits), however, the correlation between monozygotic (MZ) twins has been found to be substantially greater than twice the value of the correlation between dizygotic (DZ) twins (Loesch 1974, 1979). This would be consistent with an effect of dominance on variation in TFPI. Parent-offspring and sibling correlations for this variable are very similar in magnitude (Loesch 1974, 1979); therefore, it has been suggested that the twin and family correlations are inconsistent (Loesch 1979). When twin data alone are used, dominance and additive × additive epistasis are completely confounded (Cockerham 1954; Kempthorne 1954). Both sets of correlations are consistent with a model that allows for additive gene action and additive × additive epistasis but no dominance. By combining both sets of data, we can resolve the contributions of additive gene action, dominance and additive × additive epistasis to variation in TFPI. We have, therefore, reanalyzed the previously published data of Loesch to test for epistasis.

DATA ANALYSES

The correlations between relatives for TFPI obtained by Loesch are reproduced in Table 1. The twin correlations are intraclass; all others are product-moment correlations. The original papers by Loesch should be consulted for further details of data collection and summary statistics. Alongside each correlation, the expected contributions of the main components of gene action are given below:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>N</th>
<th>r</th>
<th>VA</th>
<th>VD</th>
<th>VAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ male twins</td>
<td>60</td>
<td>0.91</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MZ female twins</td>
<td>50</td>
<td>0.90</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>DZ male twins</td>
<td>62</td>
<td>0.24</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>DZ female twins</td>
<td>49</td>
<td>0.36</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Male siblings</td>
<td>461</td>
<td>0.40</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Female siblings</td>
<td>309</td>
<td>0.33</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Opposite-sex siblings</td>
<td>857</td>
<td>0.33</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Father-son</td>
<td>469</td>
<td>0.33</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Father-daughter</td>
<td>547</td>
<td>0.40</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Mother-son</td>
<td>460</td>
<td>0.41</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Mother-daughter</td>
<td>540</td>
<td>0.31</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Spouses</td>
<td>281</td>
<td>0.04</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations used are: VA, additive genetic variance; VD, dominance variance; VAA, epistatic variance arising from interactions of additive effects of genes.
POLYGENIC EPISTASIS IN MAN 721

relation we tabulate the proportional contribution to the expected untransformed correlation of additive genetic (VA), dominance (VD) and additive × additive epistatic (VAA) components of variance. Definitions of these components of variance in terms of gene effects at one or more pairs of loci have been given by MATHER (1974). We have not allowed for sex-dependent effects, since preliminary analyses showed no evidence for sex linkage or sex limitation (HEATH 1983). We have also assumed that there is no special effect of the environment shared by twins. Since we have neither pooled correlations across sexes nor pooled twin and sibling correlations, violation of these two assumptions should lead to the rejection of our simple models. Random mating is assumed because the spousal correlation is effectively zero, but this assumption also will be tested by model fitting.

Four genetic models were fitted to these correlations. These allow for (1) additive gene action only; (2) additive gene action plus dominance; (3) additive gene action plus additive × additive epistasis; and (4) additive gene action, dominance and epistasis. Models were fitted by the method of weighted least squares (EAVES 1975; RAO et al. 1977). Since the sampling distribution of an untransformed correlation is non-normal and has a variance that varies inversely with the magnitude of the correlation, the raw correlations given in Table 1 were converted to z values using Fisher's transformation

\[ z = \frac{1}{2}[\log(1 + r) - \log(1 - r)]. \]

Such z-transformed correlations are approximately normally distributed with sampling variance \(1/n_i\), where for a product-moment correlation based on \(N\) pairs of observations, \(n_i = N - 3\), and for an intraclass correlation, \(n_i = N - 1.5\). The expected correlations under any set of parameter values were also converted to z values. For a given model, parameter values were found that minimized the sum of the weighted square deviations of the expected z values from the corresponding observed z values, each square deviation being weighted by the reciprocal of the sampling variance of the expected z value; i.e.,

\[ C = \sum_i n_i (z_i - \bar{z}_i)^2, \]

where \(z_i\) is the z transform of the \(i\)th observed correlation, \(\bar{z}_i\) is the corresponding z-transformed expected correlation and \(n_i\) is the reciprocal of the variance of the z-transformed expected correlation.

Function (1) was minimized using a commercially available optimization subroutine, E04JBF (NUMERICAL ALGORITHMS GROUP 1978). If the observed statistics are independent and the sampling distribution of the z-transformed correlations is multivariate normal, minimization of this function yields maximum-likelihood estimates of the parameters of a model (RAO et al. 1977), which have the usual desirable properties of maximum-likelihood estimators (consistency, sufficiency and minimum variance; see KENDALL and STUART 1973). The minimum value of \(C\) obtained is distributed in large samples as chi-square with number of degrees of freedom equal to the number of observed correlations.
minus the number of model parameters estimated. This chi-square value not only provides a test of the goodness-of-fit of the model, but also allows the comparison of its fit with other models by likelihood-ratio test (JÖRESKOG 1978): if $C_1$ is the chi-square value obtained after fitting a complex model, and $C_2$ the value obtained after fitting a simpler model in which $k$ parameters have been deleted from the complex model, the difference, $C_1 - C_2$, is a likelihood ratio that is approximately distributed as chi-square with $k$ degrees of freedom. In this application, some of our observed correlations are not independent, data on the same individual being used to calculate both parent-offspring and sibling correlations, for example. Nevertheless, when the effect of ignoring the correlation between correlations has been examined (e.g., RAO et al. 1977), it has been found to be slight.

Results of model fitting: The results of model fitting are summarized in Table 2. The classical additive genetic model (VA) is rejected at a high level of significance. Models that allow for additive gene action plus dominance (VA VD) or additive gene action plus additive $\times$ additive epistasis (VA VAA) both give adequate fits, but, of the two models, it would seem that the hypothesis of epistasis is to be preferred to dominance. The results for the last model support this conclusion still more convincingly. A model that allows for additive gene action, dominance and epistasis (VA VD VAA) gives a significantly better fit than the VA VD model ($\chi^2 = 6.79, P < 0.01$) but does not give any significant improvement in fit over the VA VAA model ($\chi^2 = 0.30, P < 0.50$). Furthermore, a small but negative and, therefore, unacceptable estimate of the dominance component of variance is obtained when the full three-parameter model is fitted. We are, therefore, forced to conclude that a two-parameter model that allows for additive gene action and additive $\times$ additive epistasis gives the best fit to these data.

Power simulations: Even if variation in TFPI is determined by additive gene action plus dominance, i.e., the VA VD model is the correct model, there is a chance that sampling variation would lead us to infer a significant effect of additive $\times$ additive epistasis from the results of model fitting. We have, therefore, conducted two series of simulations to determine the probability of finding apparent evidence for dominance when the VA VAA model is the true model and the probability of incorrectly inferring an effect of epistasis when the VA VD model is the true model. In each case, we use as population values the z-transformed expected correlations obtained by fitting the true model to

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter estimates ($\times 100$)</th>
<th>Goodness-of-fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>VA: 80</td>
<td>VD: 11</td>
</tr>
<tr>
<td>VA VD</td>
<td>68</td>
<td>21</td>
</tr>
<tr>
<td>VA VAA</td>
<td>52</td>
<td>39</td>
</tr>
<tr>
<td>VA VD VAA</td>
<td>48</td>
<td>-06</td>
</tr>
</tbody>
</table>
our observed correlations and simulate 1000 new sets of correlations. Since
the sampling distribution of the ith z-transformed correlation is approximately
normal with variance 1/n_i, z-transformed correlations corresponding to the ith
population value are simulated by sampling random numbers from a normal
distribution with mean equal to the population value and variance 1/n_i. A
commercially available Fortran subroutine for random number generation
G05DDF (NUMERICAL ALGORITHMS GROUP 1978) was used for this simulation
work.

Four genetic models were fitted to each set of simulated correlations, exactly
as in our analyses of the observed correlations. The critical outcomes of these
analyses are summarized in Table 3. If we consider only the results based on
the overall chi-square test of goodness-of-fit, our ability to discriminate between
VA VD and VA VAA models is poor: in approximately 80% of samples we
would be unable to reject the VA VD model when the true model is the VA
VAA model, and vice versa. This is not surprising, since comparing competing
models by chi-square test of goodness-of-fit only is a much less powerful pro-
cedure than combining likelihood-ratio comparisons with the overall test of
goodness-of-fit. By goodness-of-fit test alone we could not have distinguished
between the VA VD and VA VAA models in our analysis of the observed
correlations. Using the combined criteria for assessing the fit of a model, we
would expect to infer incorrectly the presence of dominance when the true
model is VA VAA or to infer incorrectly the presence of additive × additive
epistasis when the true model is VA VD, in less than one of 40 samples. These
results, therefore, give grounds for considerable confidence that our earlier
analyses have not mistaken dominance for epistasis. Unfortunately, they also

<table>
<thead>
<tr>
<th>Outcome of model fitting</th>
<th>Statistics used as population values for simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected z values for best fitting VA VAA model</td>
</tr>
<tr>
<td></td>
<td>Expected z values for best fitting VA VD model</td>
</tr>
<tr>
<td>VA model rejected by χ² test of fit</td>
<td>97.5</td>
</tr>
<tr>
<td></td>
<td>90.9</td>
</tr>
<tr>
<td>VA VD model rejected by χ² test of fit</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>5.9</td>
</tr>
<tr>
<td>VA VAA model rejected by χ² test of fit</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>19.0</td>
</tr>
<tr>
<td>VA VA VAA model rejected by χ² test of fit</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
</tr>
<tr>
<td>VA VD model fits, VA VD VAA ≫ VA VAA*</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>42.8</td>
</tr>
<tr>
<td>VA VAA model fits, VA VA VAA ≫ VA VD*</td>
<td>53.2</td>
</tr>
<tr>
<td></td>
<td>2.3</td>
</tr>
</tbody>
</table>

*VA VD VAA ≫ VA VAA: VA VD VAA model gives significantly better fit than VA VAA
model, so that evidence for dominance is inferred.

*VA VD VAA ≫ VA VD: VA VD VAA model gives significantly better fit than VA VD model,
so that evidence for additive × additive epistasis is inferred.
indicate that attempts to replicate our findings need to be based on sample sizes considerably larger than those reported here. Even when correlations were simulated using expected statistics for the VA VAA model, fitting models to the simulated correlations detected epistasis in little more than 50% of data sets. With larger sample sizes the sampling variances of our expected correlations will be smaller, and our ability to detect epistasis and to reject dominance will be correspondingly greater.

**Bootstrap analyses:** The validity of our simulation studies depends critically upon the assumption that the sampling distribution of the z-transformed correlations is normal. This assumption was used in the simulation of new sets of data and in all model-fitting analyses. As the sample sizes on which the correlations are based are, in some cases, rather small and as the distribution of pattern intensity is far from normal (see Figure 1 for the distribution of TFPI

![Distribution of TFPI](image)

**Figure 1.**—Distribution of TFPI in a sample of Polish male and female twins.
in the twins in this sample), the validity of this assumption could be questioned. To provide a test of its validity, the method of bootstrapping (Efron 1982) was used to approximate the sampling distribution for the first of the observed correlations, the MZ male twin correlation.

The original 60 data points (pairs of observations) from which the intraclass correlation had been calculated were sampled at random, and with replacement, to generate 1000 new sets of 60 data points, and an intraclass correlation was calculated for each set and $z$ transformed. If the sampling distribution of the $z$-transformed correlation is normal, then we would also expect the distribution of the bootstrapped $z$ values to be normal (Efron 1982). The goodness-of-fit of a normal distribution to the bootstrapped distribution was calculated using both the theoretically expected variance of the distribution ($1/58.5$) and an estimate of the variance obtained from the bootstrapped data. In each case, the mean of the distribution was estimated from the empirical distribution. The bootstrapped $z$ values were divided into ten frequency classes. When the theoretical variance was used, a highly significant chi-square value was obtained ($\chi^2 = 35.14, P < 0.001$). The standard deviation of the bootstrapped $z$ values was found to be 0.1470, somewhat higher than the expected value of 0.1307. When the empirical standard deviation was used to assess the goodness-of-fit of a normal distribution, no evidence was found for a significant deviation from normality ($\chi^2 = 9.38, P = 0.23$). An additional four sets of $z$ values were bootstrapped, and, in all cases, it was found that the bootstrapped distribution did not deviate significantly from normal but had a larger variance than the theoretically expected value. A mean value of 0.1425 was estimated for the standard deviation of the bootstrapped distribution, a value that would be expected for a $z$-transformed correlation based upon 50.75, rather than 60, pairs of observations.

The findings from our bootstrap analyses suggest that we have underestimated the variance of the sampling distribution of our $z$ values both in model fitting and in simulation but not by a great amount. In view of the highly significant value of the likelihood ratio obtained when the fit of the VA VD and VA VD VAA models is compared with the observed correlations, we have not repeated the model-fitting analyses. Had the discrepancy between the theoretically expected and empirical variances of $z$ been much greater, it would have been desirable to repeat the weighted least-squares analysis using the standard deviations of the bootstrapped distributions of our $z$ values to replace $n_i$ in function (1). The bootstrap analyses give no reason to doubt our conclusion that we would be unlikely to mistake dominance for additive $\times$ additive epistasis, or vice versa, but do suggest that we may have overestimated the proportion of data sets with sample sizes comparable to the present sample in which we would detect epistasis when it is present.

**DISCUSSION**

Until now it has been assumed that the resolution of dominance and additive $\times$ additive epistasis for polygenic characters would not be feasible in man. The results of our analyses of TFPI data are, however, consistent with a major
effect of additive × additive epistasis and cannot be explained by assuming additive gene action plus dominance. Other explanations of these data seem unlikely. The fact that data on siblings and DZ twins can be integrated in the same analysis without significant residual effects supports the assumption that environmental factors of relevance of TFPI are comparable in both twins and singletons. Small differences in correlations of monochorionic and dichorionic MZ twins for digital dermatoglyphic characters (Reed et al. 1978) do not suggest that the high MZ correlation can be explained by features of the uterine environment. Analyses of simulated data have confirmed that the resolution of large amounts of dominance and epistasis in man for highly heritable characters such as TFPI is feasible, although the probability of detecting and identifying epistasis, even with sample sizes as large as in the present study, is disappointingly small. Applications of bootstrapping have confirmed the validity of the distributional assumptions used in model fitting and data simulations. We are, therefore, confident that we have found evidence of epistatic interaction for a polygenic character in man.

This is paper 220 from the Department of Human Genetics, Medical College of Virginia. Work reported in this paper was partly supported by a United Kingdom Medical Research Council postgraduate studentship to A. C. H., an Australian-European award to D. L. from the Australian Department of Education, and National Institutes of Health grants GM30250 and HL28922.

LITERATURE CITED


Corresponding editor: B. S. WEIR