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CORRESPONDENCE

A cautionary note regarding the interpretation of heritabilities

To the Editor:

In a population-based study of panic disorder (PD) in female twins, Kendler *et al.* (1993) report heritability estimates of 30–40%, along with moderate concordance rates for MZ twins. While the authors themselves do not make this argument, the relatively low estimates of heritability might be taken by some to suggest that PD is not a good candidate for linkage analysis. This would be a mistake. Comparison of the twin-study results with the results of a segregation analysis illustrates the point.

In a recent segregation analysis of 30 PD probands and 189 of their first-degree relatives (Vieland *et al.* 1993), we obtained the following parameter estimates under a single major gene model assuming dominant inheritance: p = frequency of the disease allele = 0·01; f = P(individual with the disease allele will eventually become affected) = 0·50; g = P(individual without the disease allele will eventually become affected) = 0·01. (We were unable to *test* the fit of this model in our sample; these estimates are obtained *assuming* dominant inheritance).

These parameter estimates allow us to *predict* the proband-wise twin concordance rates (Smith, 1974) that we would expect to find in a population-based sample such as Kendler *et al.* examined. Let x = P(an individual is a genetic case | the individual is affected); then $(1-x)$ = P(individual is a phenocopy | the individual is affected). Note that our parameter estimates predict that 49% of all cases of PD will be phenocopies. For MZ twins, the P(concordant twin pair) can be calculated as $x*f+(1-x)*g$. The concordance rate for DZ twins is $\frac{1}{2}$ this quantity. (Since p = 0·01, we can safely ignore the possibility of more than one disease allele segregating in a single twin pair.) Then the proband-wise concordance rate predicted by our results can be compared with the concordance rate actually measured by Kendler *et al.*

When we do this, we obtain strikingly similar results (see Table 1). Thus, the concordance rates predicted by our segregation analysis are virtually identical to those measured by Kendler *et al.*

These calculations are crude: for example, we have ignored the age of onset distribution of PD and the age structures of the two samples, sex differences in rates and in the sample structures, as well as potential differences in the base rates of PD in the populations being considered, all of which will influence twin concordance rates. And, since the segregation analysis is based on the assumption of dominant inheritance, we cannot conclude that this model is correct. (When we assume a recessive mode of inheritance, which provides an equally good fit to our data as the dominant model, we obtain a predicted MZ concordance rate of 0·52.) However, these calculations do illustrate an important point regarding linkage analysis.

In spite of the relatively low heritability estimates, PD may still be an excellent candidate for linkage studies. If a dominant gene with 50% penetrance is responsible for even a small proportion of PD cases, and if families are sampled in such a way as to maximize the probability that this gene is segregating in them (for instance, by following the common practice of using only families with multiple affected individuals for linkage studies), then the gene may very well be localized using linkage methods. Even if this gene accounts for a small proportion of cases, characterization of the mutation leading to PD in these cases might

Table 1. *Comparison of predicted with measured twin concordance rates*

	Predicted twin concordance rates	Measured twin concordance rates
MZ twins	0·26	0·24
DZ twins	0·13	0·11

Rates reported using Kendler *et al.*'s 'clinician narrow' diagnosis, which corresponds most closely to the best-estimate diagnosis of definite or probable DSM-III-R PD used in our study.

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illuminate the mechanisms of non-genetic cases as well, and is surely of scientific interest. Such reasoning has motivated successful genome searches for disorders such as breast cancer (Hall *et al.* 1990) and melanoma (Cannon-Albright *et al.* 1992), which are presumed to be highly heterogeneous in the population.

Estimates of heritability which depend, among other things, on gene frequencies and on types and levels of heterogeneity, are not directly useful as predictors of the potential of linkage studies. A purely polygenic trait has a heritability of 1, yet provides virtually no linkage information whatsoever. On the other hand, if a single gene accounts for a small proportion of cases in the population, then heritability may be quite low. Nonetheless, selective sampling of families may produce a very high power to find the gene using linkage methods.

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