Gene x Gene Interaction in Shared Etiology of Autism and Specific Language Impairment

Supplemental Information

The Variance Component Model

A vector of quantitative trait values for a pedigree of n number of subjects is defined as $Y = (y_{1.} \ldots y_n)$, has an assumed multivariate normal mean μ and variance-covariance matrix **Ω.** To allow for covariates, μ is replaced with $\mu + \beta$ **X**, where **X** is the vector of covariates and β is the vector of coefficients for the covariates. The phenotypic covariance between relatives is the sum of the individual covariances between relatives:

$$\Omega = 2\mathbf{\Phi}\sigma_g^2 + \mathbf{I}\sigma_e^2$$

Where **Φ** is the genetic kinship matrix, σ_g^2 is the additive genetic variance, **I** is the identity matrix, σ_e^2 is the environmental variance. Additional genetics effects may be modeled by adding terms to this equation with the appropriate matrix to define the genetic effects (such as dominance, gene-gene interactions) and the likewise variance component.

Analysis Procedures

Since variance components analysis has a documented sensitivity to violations of multivariate normality, we have applied robust estimation by assuming a multivariate t-distribution as suggested for scores with kurtosis > 1.5 (1, 2). The multivariate t-distribution down-weights extreme values relative to the multivariate normal distribution. Note that the robust estimator is not required for parameter estimation, but is necessary for statistically valid hypothesis testing (3).

Significance of parameters estimates are determined by comparing the likelihood of the model with heritability estimates constrained between zero and one, versus the likelihood of the model with the heritability constrained to zero. This is a likelihood ratio test with a test statistic distributed as a mixture of a chi-square and a point mass of zero (4). Standard errors were derived by inversion of Fisher's information matrix.

Supplemental References

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