

Studio Biostatistics seminar:

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Methodological issues in the detection of associations between genetic markers and complex (psychiatric) traits

Genetic factors explain a large proportion of the variation in psychiatric traits (e.g., the heritability of schizophrenia is about 64-80%). Nevertheless, despite the very large sample sizes available to date, the identification of the specific genetic variants which play a role has proven to be difficult. I will discuss three explanations (and ignore many others) for the disappointing findings of the last couple of years.

First, there is large phenotypic heterogeneity in psychiatric traits; patients with the same psychiatric diagnosis may show very different symptom profiles. Sample sizes are increased by combining data from different studies even though this may further increase phenotypic heterogeneity. Second, until recently, genetic studies have mainly focused on the detection of common genetic variants while at least part of the variation may be explained by rare variants. The role of common vs rare genetic variants in complex disorders is hotly debated and I will discuss the arguments made by both groups. Third, genetic studies usually test for the association between 500,000-1,000,000 genetic markers and a single phenotype. The common approach is to perform many single marker tests instead of combining all variables in a combined model. In addition to the problem of multiple testing (which decreases the statistical power) single marker tests may severely underestimate effect sizes if a dichotomous trait is influenced by multiple (e.g., 100) genetic variants. This problem has not yet been described in the literature and can not be solved by increasing sample sizes.

I will conclude with evaluating the role of genetic factors in psychiatric traits in the context of findings for other complex disorders (e.g., height) and make future recommendations.

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