Is Schizophrenia Linked to Chromosome 1q?

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Levinson *et al.* (1) reported the results of a meta-analysis of families showing no major schizophrenia locus on chromosome 1q. These results, based on a multicenter study of affected sibling pairs (ASPs), are in striking contrast to findings of several recent papers reporting susceptibility loci on 1q in extended families. Significant linkage (LOD = 6.5) at 1q21-22 was detected in Canadian families (2) and replicated in European origin families (3, 4). At 1q42, Blackwood *et al.* (5) obtained a LOD of 7.1 in a single Scottish family, while Ekelund *et al.* (6) obtained a LOD of 3.2 in Finnish pedigrees. How can these apparently conflicting results be reconciled? We suggest that locus heterogeneity adequately explains the failure of an ASP study with any reasonable sample size to replicate results from large extended families, and we have strong reservations about the limited interpretation of the results in (1).

We considered the effect of heterogeneity in two ways. First, we evaluated the power of the ASP mean test under heterogeneity. The number of sib pairs required to detect linkage is inversely proportional to the square of the proportion of linked families (7). Fig. 1 shows the effect of heterogeneity on the power to detect linkage given the effect of an allele segregating in the linked families, which increases risk to sibs by a given factor. Three effect sizes—small (factor 1.35), moderate (factor 3), and large (factor 7)—were considered. As

shown, a sample of less than 1000 ASPs, as studied in (1), has little power to replicate linkage of schizophrenia to a locus that contributes to risk of illness in less than 20% of families. Note that Levinson *et al.* used the relative risk to siblings of affected individuals across the whole sample [λ_{sibs} in (1)] to determine power. Our interest is in showing how large a part heterogeneity plays in determining power. In the case of breast cancer, for example, the BRCA1 and BRCA2 genes have a large effect on risk (10- to 20-fold) in mutation carriers (8) but, because they are very rare in most populations, they are not readily detectable in large heterogeneous samples.

We also considered the power of nuclear families using SLINK software (9). Sixty families (each with 6 individuals in the sibship, equivalent to 15 ASPs) were simulated under a partially penetrant model and analyzed allowing for heterogeneity (10). The power to detect a LOD of 3 decreased rapidly; power for 75%, 50%, and 33% of families with mutations segregating at the gene of interest was 80%, 40%, and 5%, respectively.

In concluding that there is no locus of major effect on chromosome 1q, Levinson *et al.* have not appropriately considered locus heterogeneity. The logistic regression used in (1) ignores within-sample heterogeneity. Parametric linkage analysis incorporating heterogeneity is used but only with a recessive model. To ensure good power one must also fit a dominant model (11).

Though the results in initial genome scans are likely to be overestimates of effect size, the effects found in the studies reporting linkage to chromosome 1q21-22 and 1q42 are unlikely to be small in magnitude. Such effects will account for a sizable proportion of the variance in liability in particular families. The distribution of risk to schizophrenia can be well described by a model that incorporates genes of major effect and substantial locus heterogeneity. Under heterogeneity, ASP studies will require extremely large samples. Linkage analyses with large families and identification of cytogenetic variants associated with schizophrenia are appropriate strategies when heterogeneity is expected.

References and Notes

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Fig. 1.

Power of the ASP mean test at different heterogeneity levels. The power to detect linkage ($\text{LOD} = 3$) and replication of linkage ($\text{LOD} = 1.2$) were determined for three effect sizes: small (factor 1.35), moderate (factor 3), and large (factor 7).