Homing in on Depression Genes

This issue of the *Journal* contains two articles (Holmans et al. and Levinson et al.) that report the results of the final stage of a whole genome linkage scan of 656 families, the Genetics of Recurrent Early-Onset Major Depression (GenRED) Study, as well as the results of fine mapping a linkage region on chromosome 15q. The 15q region was shown to have genomewide significance in the first wave of the study (1). Two other regions on chromosomes 8p and 17p also showed suggestive evidence for linkage in the final-stage whole genome scan, but what made the chromosome 15q region the principal focus for fine mapping was that two other independent large-scale studies provide support for linkage here: the European-U.S. Depression Network (DeNt) study (2) and a study from Utah (3).

All three studies used DSM-IV criteria and had similar phenotypic definitions of major depressive disorder in other respects. For example, the GenRED study and the Utah study focused on recurrent early-onset depression. The DeNt study required only recurrence for inclusion of affected subjects, but the average age of onset was the early 20s. The findings are clearly promising, providing what may be the first example of a positional cloning approach, giving real clues into the etiology of unipolar depression. However, they also raise a number of interesting issues. The first is, given that much time and effort has been expended in other familial psychiatric disorders, why is it only now that we are beginning to have results in unipolar depression? The second is, given the large sample sizes involved, why are the findings only "promising" and not definitive? The third is how do we interpret the chromosome 15q findings (and the other "suggestive linkages"), and where do we go from here?

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The probable reason why genetic linkage studies in depression have lagged behind those in other adult psychiatric disorders, such as bipolar disorder and schizophrenia, is that there is a widespread perception that depression may be only moderately genetically influenced in comparison to these other disorders (4). This is probably because most modern twin studies of depression have been community based and have suggested only modest heritability of around 30% (5). On the other hand, the one twin study with a clinically ascertained sample large enough to perform model fitting provided an estimate of heritability on the order of 70% (6). This disparity between the community-based and clinically-based heritability estimates is large enough to be worthy of brief consideration. It may be partly due to the fact that a lifetime diagnosis of unipolar depression is difficult to make in general population samples and is often unreliable and "unstable." For example, in one study where subjects were interviewed twice, only 75% of those who received a lifetime diagnosis of major depression in the first wave of interviews retained this diagnosis in the second wave (7). Much greater reliability or stability (around 96%) was obtained when the diagnosis was narrowed to include only those who had sought treatment or had eight or more symptoms of depression. Incorporating a similar index of severity, having data at two time points, and incorporating measurement error in their model, Kendler and colleagues (8) estimated that the heritability of major depression increased to about 70% in their community-based study of female twins. Therefore, we can conclude that if the focus is on clinical samples or more severe or clear-cut cases in the community, then the heritability of ma-

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jor depression is only slightly less than the 80% figure usually quoted for schizophrenia or bipolar disorder. There is also reasonable evidence that focusing on recurrent depression increases the genetic effect even further (5, 6).

Another feature that all three disorders share is that Mendelian forms are exceedingly rare or perhaps nonexistent. Instead, it is likely that genetic liability to these common familial disorders is contributed to by multiple genes, each having a small effect. This makes genetic linkage studies aiming to pinpoint the location of susceptibility genes difficult and explains why it is only comparatively recently that some consistent patterns are emerging in bipolar disorder and schizophrenia, despite many whole genome linkage scans having been performed. In addition, the majority of linkage studies of psychiatric disorders have begun with an overoptimistic estimate of the effect size of the susceptibility loci to be detected and consequently have underestimated the required sample sizes. The designers of the more recently published whole genome linkage searches in unipolar depression have learned from these mistakes and have sought to collect much larger samples with adequate power to detect genes of modest effect. They have also placed an emphasis on affected sibling pairs, which are more straightforward for the statistical analysis of linkage and arguably more representative of depression as a whole than multigenerational families containing many affected subjects.

Why, then, are the findings of the GenRED Study not more conclusive? The most likely answer is that despite its high heritability overall, each of the genes that contribute to depression has close to the lower limit of an effect size that can be detected by linkage studies, and so findings yield suggestive rather then definitive results. Levinson and colleagues estimate that the locus-specific increase in relative risk for siblings of affected subjects compared with the population risk, attributable to the 15q locus, is at most 1.38 and may be as low as 1.21. That means a person who carries the markers associated with genetic risk at 15q has only a 21% to 38% increase in risk for depression over individuals in the general population; if the general risk for depression is 5%, then the risk in someone who carries the markers is only 6%. This may seem surprisingly small to readers unfamiliar with complex genetics. However, we need to bear in mind that the total relative risk to siblings of depressed probands is around three to four; that means the chance of having depression if your sibling has depression is three to four times the general population risk, so that if the general risk is 5%, then the chance of a sibling of a depressed person having depression is 15% to 20% (9). Because relative risks across susceptibility loci are multiplicative, it will only take six or seven genes each with a locus-specific risk of 1.2 to confer such a risk. Furthermore, it may not be the same genes in every family, and this could explain why the support for the 15q locus is less strong in the other two comparable studies (2, 3).

The next stage, as Levinson and colleagues conclude, should involve a meta-analysis or, preferably, a combined analysis of the raw data from all available sources. Discussions are in progress about how to effect this. If such studies can provide more confidence in the 15q or other regions, this should lead to association studies using even denser marker maps focused on such regions. Meanwhile whole genome association studies are about to begin in unipolar depression. Such studies effectively treat whole populations as families of very many generations and therefore require very dense marker maps capable of detecting linkage disequilibrium. In this technique, many thousands of markers are studied simultaneously so that the chance of a marker being close to actual DNA change that conveys risk for the illness or of actually being that change itself is increased. The markers may be so close to those disease-causing changes that they stay together through many generations. Whole genome association studies will be able to locate disease susceptibility loci either through linkage disequilibrium or because the genotyped markers themselves have functional effects. The disadvantage of this approach is that whole genome association studies require hundreds of thousands of markers, and it is only recently that such studies have become techni-

cally feasible. The great advantage is that association can detect genes of very small effect that will be overlooked by linkage studies (10). Therefore, the future looks bright, and it seems likely that a combination of linkage disequilibrium searches across linkage regions and whole genome association studies of unipolar depression will soon yield solid findings.

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