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Genetics of psychiatric disorders

It's hard to please two masters, as most scientists who do interdisciplinary work eventually discover. This problem is particularly acute for researchers who study the neural mechanisms by which genetic variation influences the risk of psychiatric disorders. A paper in this issue[1] illustrates the promise of this approach—along with the biological complexity and scientific uncertainties that make the problem so hard.

Although vulnerability to mental illness tends to run in families, there are no genes for psychiatric disorders in the sense that there are genes for eye color. No known gene is either necessary or sufficient to produce disease. Instead there are many susceptibility genes with small effects, each increasing the risk of illness by 5% or less in an individual. It remains unclear how these genes interact with each other or with the environment, which could increase the system's complexity enormously[2].

There are two basic approaches to finding susceptibility genes for complex disorders. Linkage studies are a hypothesis-neutral search for markers that statistically segregate with a disease, followed by fine mapping to identify the actual gene or genes. Association studies, on the other hand, ask whether particular variants of a candidate gene are more prevalent in patients than would be expected by chance. The definition of chance levels is controversial, and depends—implicitly or explicitly—on the prior probability that the gene is involved in the disease[3]. This approach may identify effects that are too small to be detected in linkage studies, but it also has considerable potential for false-positive results, so geneticists tend to mistrust these studies.

Many proposed susceptibility genes for psychiatric disorders do not replicate consistently, showing statistically significant effects in some studies but not others. To some extent, this may simply reflect the difficulty of measuring small effects, which can require thousands of subjects to reach significance. However, geneticists attribute some of the variability to population stratification, a confound that may be unfamiliar to many neuroscientists. Differences in the genetic background of experimental and control groups can lead to false-negative or false-positive results. Avoiding such artifacts requires matching groups not only for race, but also for more subtle aspects of ethnicity, such as the proportion of genetic background from northern versus southern Europe. Though the magnitude of the problem is unclear, this is potentially an important source of error for studies with small sample sizes, like most neuroscience studies. Researchers can increase sample size by sharing genotype and phenotype data across groups, but this approach is relatively uncommon.

Ultimately, of course, we want to know not only whether a gene is linked to disease vulnerability, but how it exerts its influence. One promising approach is to study intermediate phenotypes, such as a well-defined cognitive symptom or diagnostic subgroup. Genetic polymorphisms may be more strongly linked to a particular cognitive function than to the heterogeneous set of symptoms that make up a diagnostic category, as suggested by evidence that some candidate genes are linked to more than one disorder. Exploring specific symptoms may be easier in animal models as well. It is difficult to imagine plausible mouse models of a complete psychiatric disorder, but mutants with hypomorphic alleles that model particular symptoms may be a very useful tool. The hope is that multiple genes involved in a particular disease will be found to converge onto the same biochemical pathway, preferably one that can be manipulated to influence the disease symptoms.

One intriguing possibility is that certain life events may interact with brain vulnerabilities created by particular genes to produce behavioral symptoms. For example, in one prospective study, people homozygous for the short allele of the serotonin transporter gene were more likely to experience depression after stressful life experiences than were heterozygotes or long allele homozygotes[4]. This finding—and others like it—have been controversial because the genetic association of this polymorphism with depression and anxiety is statistically weak and could be artifactual. However, other scientists feel that convergent evidence from biology increases the likelihood that this polymorphism may mediate vulnerability to mood disorders.

In this issue[1], Pezawas *et al.* report neural correlates of these serotonin transporter alleles in people without psychiatric diagnosis. Examining normal subjects allows larger sample sizes, and it avoids potential complications from diagnostic heterogeneity and medication history in patients. Relative to long allele homozygotes, the homozygous and heterozygous carriers of the short allele had reduced amygdala and perigenual anterior cingulate cortex volumes and less correlated activity between these regions during exposure to fearful faces. The authors propose that the short allele affects the development of these brain regions, which may increase vulnerability to depression and anxiety.

Which genetic associations are worthy of such intensive follow-up? That depends on our goals. Successful identification of susceptibility genes seems unlikely to lead to gene therapy for psychiatric illnesses. If the ability to identify people at risk is critical, then we should restrict our efforts to genes with strong evidence for linkage. On the other hand, if our main goal is to develop effective treatments, then it may be more important to determine the biochemical pathways involved in producing particular symptoms, which could be downstream of a group of genes with individually weak effects—and may also have the advantage of affecting a larger proportion of patients than any individual gene variant. Thus it may be worthwhile to pursue some genes with weak linkage data if functional evidence strengthens the case for them. Genes provide a good starting point for the neuroscience of psychiatric disorders—and neuroscientists must take into account the lessons learned from genetics about potential sampling artifacts—but they cannot be an end in themselves.

1. Pezawas, L. *et al. Nat. Neurosci.* **8**, 828–834 (2005).
2. Weaver, I.C. *et al. Nat. Neurosci.* **7**, 847–854 (2004).
3. Freimer, N. & Sabatti, C. *Nat. Genet.* **36**, 1045–1051 (2004).
4. Caspi, A. *et al. Science* **301**, 386–389 (2003).