Can Single Genes Matter in a Polygenic World?

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Like dogs chasing a car down the street, investigators in psychiatric genetics sometimes appear uncertain about what we will do once we actually catch up with our prey. As putative risk genes begin to appear more consistently in large-scale disease-association studies, the need for clarity about how they can be followed up becomes more acute. Two articles in this issue frame the challenge well. The first, by Terracciano et al. (1), describes a meta-analysis of two genome-wide association studies (GWAS) of trait depression, a subscale derived from the Revised NEO Personality Inventory. Using eight items from that scale in population-based cohorts not screened for psychiatric illness, the authors seek to identify common variation associated with trait depression—really a predisposition that may indicate risk for mood or anxiety disorders or current symptoms of such disorders. The study builds on a tradition within psychiatric genetics emphasizing the phenotype, one that long predated the preoccupation with endophenotypes or intermediate phenotypes. The notion is simply that using a more refined understanding of diseases or traits will facilitate identification of risk markers. Although intuitively appealing, it bears noting that even single-gene deletions may exhibit remarkably pleiotropy (2).

In results that will be familiar to any consumer of the GWAS literature, the authors identify numerous intriguing results, some in or near genes that would seem to be strong priori candidates for psychiatric disorders. “A steroid receptor,” the reader cries, “why of course! It had to be . . . .” That is unless one is inclined to glutamergic hypotheses, in which case there is something to celebrate here, too. Other associations are in or near genes that are essentially uncharacterized. None, however, achieve what has become the de facto standard for genome-wide statistical significance. So we may be nipping at the car’s bumper, but this particular car has not yet been caught, at least in a manner convincing to reviewers and journal editors.

In the face of an onslaught of suggestive findings, the application of meta-analysis to examine ever-larger samples is one well-trodden path that has yielded success. Indeed, meta-analysis has now provided abundant support for CACNA1C, the gene that codes for a subunit of L-type calcium channels, in conferring risk for bipolar disorder. This gene is the subject of the article by Dao et al. (3) in this issue. Initially associated with bipolar disorder liability (4) in GWAS, subsequent studies suggest variants in this gene may also confer risk for other serious mental illness, including recurrent major depressive disorder and schizophrenia (5). Ever-larger collaborations under the aegis of the Psychiatric GWAS Consortium (6) should help to refine confidence in associations and further clarify their disease specificity, or lack thereof.

But, the relatively slow progress in understanding single-gene disorders such as Huntington disease, even after initial identification of genes of large effect, argues that the hard work really begins after the gene has been “caught.” A frequent criticism of recent meta-analyses is that the genes identified are likely to be of such small effect as to be of modest utility at best (7). If there are 1000 genes in which common variation confers small incremental risk for bipolar disorder, does knowing any one of these matter?

If the goal is an immediate diagnostic tool for bipolar disorder, the answer is probably not (8). However, the diagnostic criteria for many psychiatric disorders in adults are in fact excellent, at least in terms of reliability and predictive validity, so refinement of diagnosis may not be so critical as a first step. Instead, substantial opportunities may arise from knowing even one of the risk genes: the capacity to investigate the pathophysiology of neuropsychiatric disorders in model systems. The question would be, is it realistic to anticipate that individual genes will have phenotypes detectable in these model systems? The work of Dao et al. (3) provides an important proof-of-concept that indeed such genes might.

The authors show that haploinsufficiency of CACNA1C is associated with multiple behavioral changes in mouse models—for example, with an apparent antidepressant-like effect in the tail suspension test. Some of these effects appear to be sex-specific, perhaps most notably a decrease in learned helplessness. Taken together these behaviors appear most consistent with depression resistance—that is, with protection against developing depression-like behaviors.

The work also underscores some of the limitations of animal models of bipolar disorder. First, as the authors recognize, some of the sex differences are difficult to interpret in light of the observed difference in locomotion among females. In general, a key question in these models is whether the effects might be explained by a more basic motor (or sensory) deficit. Second, the models themselves are not necessarily satisfactory proxies for disease states. Models that rely on acute or chronic amphetamine administration to examine mania-like phenotypes are a case in point: drugs such as lamotrigine that lack acute antimanic efficacy in humans have lithium-like effects in some models (9), whereas amphetamines are not necessarily precipitants of mania in many bipolar patients (10).

Still, although the correspondence between mouse and human phenotypes remains unclear, the description of multiple phenotypic differences among CACNA1C haploinsufficient mice is difficult to ignore. It provides an important complement to human studies, which have suggested that phenotypic differences may be detected in individuals with risk alleles (11) in this gene, even among healthy individuals (12). In this light, even complex polygenic disorders such as bipolar disorder may be approachable from the single-gene perspective, as such risk loci begin to be identified with confidence.

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