Open Peer Commentary

Praise for a critical perspective

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Abstract: The target article skillfully evaluates data on mental disorders in relation to predictions from evolutionary genetic theories of neutral evolution, balancing selection, and polygenic mutation-selection balance, resulting in a negative outlook for the likelihood of success finding genes for mental disorders. Nevertheless, new conceptualizations, methods, and continued interactions across disciplines provide hope.

The insightful and balanced treatment in the target article takes a pessimistic view of the likelihood of finding genes for mental disorders. In the view of the authors, if polygenic mutation-selection balance truthfully characterizes the complex genetics of mental disorders, our task may be more difficult than we had hoped, barring new approaches. Nevertheless, several points in the article resonated with us, including (1) an appreciation for evolutionary genetics, (2) the watershed analogy, (3) the concepts of endophenotype and of genetic correlation, (4) the implied necessity of animal models, and (5) the need for cross-fertilization among disciplines. We touch on each of these aspects in our commentary.

The authors' analogy of the neurogenetic watershed is simplistic but useful. One of us (Shelton) has created and used a genetic reference population of cultured human fibroblasts to investigate intracellular signal transduction cascade differences in patients with mood disorders. Using this system, it was discovered that patients with the melancholic subtype of major depression have reductions in the activity of protein kinases A and C (critical to the synthesis of, for example, brain-derived neurotrophic factor and the glucocorticoid receptor), and altered serotonin receptor 2A–mediated phosphoinositide signaling (Akin et al. 2004; 2005). These findings have been demonstrated in human postmortem brain tissue, as well. This research illustrates the ex vivo study of endophenotypes very proximal to genes implicated in depression (kinases, HTR2A), that is, very upstream in the watershed model. Another approach, still in humans, uses "imaging genetics" to study endophenotypes more downstream at the level of neural systems. For example, genetic variation in important serotonin genes (TPH2, the gene for tryptophan hydroxylase, and SLC6A4, the serotonin transporter) has been associated with activation of the amygdala by fearful stimuli (Brown et al. 2005; Pezawas et al. 2005). Notably, in both approaches, relatively smaller samples were required to detect differences, implying genetic simplification followed the phenotypic simplification.

While the authors point out that heritability refers only to the role of genetic variation in differences between individuals, and not the similarities, they also highlight the usefulness of the genetic correlation. A genetic correlation between two measured traits implies shared allelic variants or genes in linkage disequilibrium. From an evolutionary standpoint, it is usually the former that is more interesting (Airey et al. 2000) as common developmental programs are implicated. The genetic correlation is a heavily used concept and tool in mouse genetics (Crabbe 1999). We look forward to the further development of this concept in psychiatric genetics coupled with measured endophenotypes.

The explicit emphasis on endophenotypes as measured (continuous) traits, and the arguments against expectations of distributional bimodality in affected (diagnosed) and unaffected (undiagnosed) individuals, were welcome. Although perhaps not the usual medical model, continuous variation opens the door to a more complete understanding of mechanisms underlying individual differences, broadly defined. To be fair, psychiatric genetics has made significant inroads, showing that genetic variation in psychiatric candidate genes like DAT, COMT, TPH2, and SLC6A4 is associated with cognitive and emotional dimensions in the normal human range (Bertolino et al. 2006; Brown et al. 2005; Mattay et al. 2003; Pezawas et al. 2005).

We would like to point out that researchers focusing on other complex genetic illnesses have successfully used population-based sampling schemes to support the common disease rare variant hypothesis. Cohen et al. (2005) found enrichment of rare nonsynonymous variants of large effect size in candidate genes for plasma levels of high-density-lipoprotein (HDL) cholesterol from the lower 5% tail of a large population-based sample. More recently, and in line with the target article's predictions, Cohen et al. (2006) have found enrichment of rare variants of a gene involved in cholesterol absorption, but where the effect sizes of the variants were more moderate. Certainly, this leaves open the possibility of effect sizes that are smaller still, as the target article predicts. These works represent reasonable models for the study of the genetics of mental disorders. A downside to this approach is that it is candidate gene based. Because the approach relies on sequencing and polymorphism discovery, rather than on typing known markers, the approach is not feasible for genome scans. In other words, the onus is on the investigator to understand enough about the biology of their disease to nominate candidate genes for rare variant discovery.

The study of endophenotypes is presented as integral to progress despite the implications of polygenic mutation-selection balance. However, it cannot be avoided that the study of endophenotypes in humans is limiting. Most neural endophenotypes remain inaccessible. Therefore, genetic model organisms can be used to widen the scope of understanding universal (translatable) brain mechanisms and to nominate candidate genes for the aforementioned nonsynonymous rare variant methods.

The target article skillfully evaluates data on mental disorders in relation to predictions from evolutionary genetic theories of neutral evolution, balancing selection, and polygenic mutation-selection balance. Although the arguments for the latter theory are persuasive, we think it best, as Keller & Miller (K&M) have done, to continually and critically evaluate theories that are borrowed into secondary fields.

Genes for susceptibility to mental disorder are not mental disorder: Clarifying the target of evolutionary analysis and the role of the environment

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Abstract: In this commentary, we critique the appropriate behavioural features for evolutionary genetic analysis, the role of the environment, and the viability of a general evolutionary genetic model for all common mental disorders. In light of these issues, we suggest that the authors may have prematurely discounted the role of some of the mechanisms they review, particularly balancing selection.

Keller & Miller's (K&M's) integration of quantitative evolutionary genetics with evolutionary approaches to psychiatric disorder is timely and important. Their article convincingly argues that the role of polygenetic mutation-selection balance has not been

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