Genetic Boundary Violations: Phobic Disorders and Personality

In many ways, establishing a valid nosology has been the most fundamental and the most challenging project facing modern psychiatry. The definition and classification of mental disorders are essential prerequisites to diagnosis, treatment, and etiologic research. Two reports in this month's *Journal* advance this project by using genetic methods to uncover important connections between categorical anxiety disorders and dimensional personality traits.

With DSM-V on the horizon, there is a renewed imperative to examine the structure of psychiatric disorders. The modern conceptualization of anxiety disorders was formalized less than 30 years ago with the publication of DSM-III, and the common comorbidity among the anxiety disorders has raised suspicion that some of the distinctions between them are artificial. In addition, the essences of these disorders—anxiety and fear—are universal and evolutionarily conserved responses to threat, and the threshold between "normal" and pathologic anxiety states can be difficult to define. Indeed, the studies of Bienvenu et al. and Reichborn-Kjennerud et al. in this issue suggest that a full account of anxiety syndromes may need to reconcile both categorical and dimensional approaches.

"Genetic and neuroscience research provide support for the incorporation of dimensional phenotypes into the definition of pathologic anxiety syndromes."

Phobic disorders are common disorders that typically have their onset in childhood or adolescence. They are unique among psychiatric disorders in that the main categories of phobias are distinguished by the nature of an external stimulus rather than by differences in symptoms or course. Thus, individuals who have an irrational fear of animals are diagnosed with specific phobia, whereas those whose fear is triggered by people are diagnosed with social phobia. However, the quality of each disorder is distinctive. For example, generalized social phobia is often a chronic condition whose effects can be so pervasive and enduring that they seem to merge inextricably with underlying personality.

Genetic studies can be useful in defining the structure and relationships among disorders and traits. The extent to which genetic influences on two phenotypes are shared or unique can help clarify nosologic boundaries between the phenotypes. In this issue, Bienvenu et al. and Reichborn-Kjennerud et al. apply twin study methodology to examine the genetic relationship between anxiety disorders and personality. An important strength of both studies is the inclusion of large, population-based twin samples that reduce biases and spurious comorbidity that can occur in clinically ascertained samples. The intriguing results suggest that from a genetic standpoint, certain categorical anxiety disorders and dimensional personality traits may be two sides of the same coin.

Bienvenu and colleagues examine two heritable personality dimensions, neuroticism and introversion (low extraversion), that have been implicated in both axis I anxiety/depressive disorders and axis II disorders. They asked to what extent the genetic and environmental influences on neuroticism and introversion overlap with those underlying three phobias: social phobia, agoraphobia, and animal phobia (a specific phobia). Consistent with previous studies, they found that social phobia and agoraphobia were associated with elevations in both neuroticism and introversion. Using model-fitting analy-

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ses, they further found that the genetic determinants of these personality traits entirely accounted for the genetic influences on social phobia and agoraphobia. Put another way, there were no genetic risk factors for these phobias over and above those underlying the personality traits. In contrast, the genes influencing animal phobia appeared to be largely distinct from those influencing the personality traits. Environmental determinants of the traits and phobias were essentially unrelated, suggesting that nongenetic factors contribute little to the relationship between personality and phobic disorder.

These findings have several implications for our understanding of the structure of phobic disorders. First, they help validate the nosologic hypothesis that all phobias are not alike: the etiology of specific phobias (or, at least, animal phobia) is distinct from that of social phobia and agoraphobia. Second, they highlight the importance of introversion, a trait that has received far less attention than neuroticism in genetic studies and clinical research on anxiety. Studies aimed at identifying susceptibility genes for anxiety disorders have often used neuroticism as an intermediate phenotype. These results suggest that a parallel effort is warranted to identify the specific genes underlying introversion. A third and related implication is that personality traits are an appropriate target for researchers interested in the genetic basis of social phobia and agoraphobia since the underlying genes may be identical. From a methodological standpoint, quantitative phenotypes may be preferred because they provide more power and reduce the risk of misclassification that can arise in the analysis of binary categories.

The study of Bienvenu and colleagues also raises questions for future research. Their models do not explicitly address the question of whether there is a causal pathway from genes to personality to disorder. It should also be noted that their findings do not mean that phobias and personality traits are simply alternate descriptions of the same phenotypes. First, as this study shows, the phobic diagnoses also reflect environmental determinants that are distinct from those influencing personality, and a full account of the etiology of phobias must identify these determinants. Second, by definition, a clinical diagnosis of phobia requires significant distress or impairment, features not captured by measures of personality.

The second study, by Reichborn-Kjennerud and colleagues, provides further insights into the relationship between social phobia and personality. These investigators studied a large population-based female twin sample to estimate the common and disorder-specific influences on social phobia and avoidant personality disorder with a dimensional measure of avoidant personality disorder criteria. Although these disorders fall on different DSM axes, they share core phenotypic features of social inhibition and fear of negative evaluation. The estimated heritability of avoidant personality disorder (37%) closely matched that of social phobia (39%). Moreover, genetic influences on these disorders were entirely overlapping, whereas the environmental influences were uncorrelated. These data suggest that the set of genes influencing social phobia and avoidant personality disorder are essentially the same, and whether an individual carrying these genes develops one or the other disorder depends on environmental factors. These findings are reminiscent of prior studies demonstrating that depression and generalized anxiety disorder are also the result of the "same genes, different environments" (1). The intriguing implication of the current study is that this phenomenon can operate even across the boundary between axis I and axis II. Given the phenotypic similarity of social phobia and avoidant personality disorder, one might worry that the genetic overlap occurs "by definition," i.e., because of overlapping diagnostic criteria. This does not appear to be the case because only a minority of individuals with one disorder met criteria for the other.

Again, these data cannot resolve whether genes act on phobia risk through the intermediate of personality or whether they have pleiotropic effects that result in distinct entities (in this case, avoidant personality disorder and social phobia). Research by other groups, however, suggests a developmental trajectory by which genes influencing social

anxiety are first expressed as childhood inhibited temperament, a precursor of anxious personality traits and a risk factor for social phobia (2). Twin studies also cannot tell us about the detailed genetic architecture of anxiety-related traits and disorders: the number, effect size, and identity of the genes involved. The evidence to date strongly suggests that these phenotypes are the result of many genes of small effect interacting with environmental factors. Indeed, a whole genome association study was unable to find any loci accounting for more than 1% of the variance in neuroticism (3).

The studies published in this issue complement previous research suggesting that genetic influences transcend the boundaries of DSM-IV anxiety disorders (4). Do such findings mean that a redefinition of anxiety disorder nosology is needed? Perhaps, although not necessarily. As Kendler pointed out in these pages (5), the fact that two disorders share genetic determinants need not imply that the boundaries between them are artificial. Many genes are known to have pleiotropic effects, and the definition of a disease entity does not rest on its risk factors being unique to that entity. For example, recent genomewide association analyses have shown that the same specific genetic variant confers susceptibility to both rheumatoid arthritis and type I diabetes (6), but no one would claim that this undermines the distinction between these disorders. At a minimum, however, such studies may reveal underlying pathogenetic mechanisms that cross diagnostic boundaries. In the case of anxiety, evidence that genetic influences span disorder categories is complemented by neuroimaging studies suggesting that hyperactive fear circuitry (involving the amygdala and insula) is a brain phenotype underlying several different anxiety disorders (7). Taken together, then, genetic and neuroscience research provide support for the incorporation of dimensional phenotypes into the definition of pathologic anxiety syndromes. Ultimately, such insights should bring us closer to a nosology based on pathogenesis rather than descriptive categories (8).

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