Deconstructing Psychiatric Disorders, Part 1
Genotypes, Symptom Phenotypes, and Endophenotypes

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**Issue:** DSM-IV psychiatric disorders are collections of phenotypic symptoms. These descriptive phenotypes are increasingly associated with traits—or endophenotypes—such as malfunctioning neurocircuits that can be correlated with genotypes of neurotransmitter receptors and enzymes.

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**A NEW BIOLOGICAL PARADIGM IN PSYCHIATRY**

Two key advances are changing the modern conceptualization of psychiatric disorders: molecular genetics and functional neuroimaging. Molecular genetics is pointing away from the model that a few important genes cause major psychiatric disorders. Now it appears that many genes regulate the neurophysiology of the specific brain circuits that may be associated with the symptoms of major psychiatric disorders. Abnormalities in these circuits can increasingly be detected with functional neuroimaging techniques. Although behavioral symptoms can result from these neuropsychologic abnormalities, they do not always appear, since compensation may occur in otherwise healthy individuals. By correlating genetic abnormalities with specific neuroimaging abnormalities, it has been possible to demonstrate the effects of genes not only in symptomatic patients with psychiatric disorders but also in asymptomatic normal controls and unaffected siblings of patients with psychiatric disorders. Apparently, genes regulate neurobiology, but whether neurobiology results in overt psychiatric symptoms may depend on many other factors, including the presence of additional genetic abnormalities as well as environmental stressors.

**5-HT Transporter Genotypes**
The 5-HT transporter (5-HTT) is famous for being the site of action for many antidepressants, notably the selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and others. There are 2 allelic forms of the gene for the 5-HTT: a short (s) form and a long (l) form. The more copies an individual has of the s allele, the fewer 5-HTTs are made, the less 5-HT gets transported, and presumably the higher the synaptic concentrations of 5-HT. Although there have been attempts to correlate the s genotype with anxiety disorders and depression, the predictive value of this genotype for these symptomatic phenotypes has been inconsistent. On the other hand, the s allele is more robustly associated with greater neuronal activation of the fear circuit in the amygdala of normal humans in response to fearful stimuli than is the l allele. Thus, the s allele genotype of the 5-HTT has a more obvious impact on the endophenotypic physiologic response of the amygdala during processing of fearful stimuli than on the phenotypic subjective experience of emotional symptoms.

The increased anxiety and fear associated with the s allele of the 5-HTT may reflect hyperresponsiveness of the amygdala to environmental stimuli. This factor may be important in disorders of fear, including many anxiety disorders, and in mediating psychological reactions to stressful experiences. Although evidence for an association between the s allele of the 5-HTT and depression is inconsistent, individuals with more copies of the s allele, rather than the l allele, do exhibit far more depressive symptoms, diagnosable depression, and suicidality when they experience stressful life events. This association is consistent with a stress-diathesis model of depression, where sensitivity to stressful events depends on genotype, and development of a psychiatric disorder is the product when a vulnerable
Genes may not cause psychiatric disorders per se, but may contribute to them by independently regulating the neurobiological substrates that underlie each key psychiatric symptom.

Genotypes of the serotonin transporter and of the enzyme catechol O-methyltransferase correlate better with the endophenotypes of functional neuroimaging abnormalities than they do with the traditional phenotypes of psychiatric disorders or psychiatric symptoms.

Various genotypes are now known to comprise risk factors for psychiatric symptoms and psychiatric disorders, but overt manifestations of psychiatric illnesses may require the presence of multiple simultaneous genetic and environmental risk factors.

geneotype meets stressful events. The s allele of the 5-HTT is apparently one genotype that endows vulnerability to depression, but perhaps only if that individual experiences stressful life events.

COMT Genotypes

Another potentially important genotype is the Val amino acid form of the enzyme catechol O-methyltransferase (COMT), which is 4 times more active than the Met form.2-4 Enzyme activity has an important impact on the availability of dopamine in frontal cortex, since COMT is the major enzyme that inactivates dopamine there. Thus, individuals with the more active Val form of the enzyme have less dopamine available for neurotransmission.

One consequence of this Val COMT genotype with high enzyme activity and low frontal dopamine levels is a small increase in the risk for the phenotype of schizophrenia, particularly for people of European ancestry.2,4,8 A more robust finding is the correlation of the Val COMT genotype with the phenotype of poor performance on cognitive testing, whether observed in normal controls or schizophrenic patients or their siblings.2-5 Furthermore, the Val COMT genotype also correlates with the endophenotype of greater activation in the dorsolateral prefrontal cortex during functional neuroimaging tests, consistent with greater inefficiency of this neuronal circuit for executive functioning.2 Other functional neuroimaging experiments confirm that cognitively intact siblings of patients with schizophrenia have this same inefficiency in the dorsolateral prefrontal cortex even though it does not result in phenotypic expression as cognitive dysfunction or schizophrenia.5 These data suggest that the endophenotype of inefficient information processing in prefrontal cortex could be associated with increased risk for schizophrenia and might be a more sensitive indicator than whether or not overt phenotypic symptoms of cognitive dysfunction are present.

REFERENCES