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NON-MENDELIAN ETIOLOGIC FACTORS IN NEUROPSYCHIATRIC ILLNESS: PLEIOTROPY, EPIGENETICS, AND CONVERGENCE

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Abstract

The target article by Charney on behavior genetics/genomics discusses how numerous molecular factors can inform heritability estimations and genetic association studies. These factors find application in the search for genes for behavioral phenotypes, including neuropsychiatric disorders. We elaborate upon how single causal factors can generate multiple phenotypes, and discuss how multiple causal factors may converge on common neurodevelopmental mechanisms.

Behavior genetics takes into account several sources of complexity in estimating heritability, including genetic and environmental factors, their interaction, and covariance. Dr Charney argues that a fully realized model would ideally take into account not only these sources of variance but also numerous molecular features. Charney's discussion is wide-ranging, with an emphasis on the inclusion of both mendelian and non-mendelian factors in heritability estimations, and how these issues impact genetic association studies.

These molecular genetic and genomic factors are central to gene discovery for behavioral phenotypes. This is keenly felt in medical behavior genetics, notably in the search for genetic factors underlying neuropsychiatric illness. Gene discovery has been frustrated by difficulties in the modeling of genetic architecture of complex disorders (Psychiatric GWAS Consortium, 2009; Yeo, 2011). Further, the confounding of heterogeneous etiologies and phenotypes for a disorder can undermine the statistical power to identify genes (Deutsch et al, 2008).

In this discussion, we expand upon the role played by some of these factors. We consider the role of pleiotropy in gene identification for brain-based disorders; a shorthand for this source of complexity is *one gene, multiple phenotypes*. We also discuss the converse association: *one phenotype, multiple genetic factors*, adding a consideration of epigenetic factors, as well. Finally, we examine how multiple, heterogeneous effects may disrupt common underlying molecular pathways for brain-based disorders.

Pleiotropy

This signifies multiple manifestations stemming from a single causal factor. Take, for example, the effects of the Phosophatase and Tensin Homolog (PTEN) gene, located at 10q23.31. It encodes a tumor suppressor phosphatase that antagonizes the PI3K signaling pathway, which contributes to a variety of conditions. These include specific clinical genetic syndromes (e.g., Bannayan-Riley-Ruvalcaba), macrocephaly, autism, and malignant

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melanoma (Nadeau and Topol, 2006). These multiple manifestations are conceptually unified when the underlying mechanism is revealed.

A single etiologic factor can have multiple phenotypes, present in some but not all gene carriers. This genetic heterogeneity, combined with reduced penetrance for a diagnosis, may increase the risk of false negatives in gene discovery; the power to detect linkage on the basis of the disease phenotype alone is limited. Thus, there is a potential boon in studying not only the psychiatric illness but also alternative phenotypes that provide a more complete picture of pleiotropic manifestations.

There can be marked statistical power benefits to this pleiotropic approach (Sunga et al, 2009). For example in schizophrenia, common underlying causal factor(s) may generate not only the clinical diagnosis but also eye movement disorders, which are present in the majority of schizophrenia patients. Matthysse and his colleagues (2006) modeled the co-transmission of both phenotypes, schizophrenia and eye movement disorders, among probands and their relatives, yielding a linkage analysis that identified a locus on Chromosome 6.

Copy number variants (CNVs)

Recent genetic studies have heralded the importance of genetic CNVs in brain-based disorders, as Charney describes. Pleiotropy is increasingly discussed with respect to CNVs (e.g., Poot et al, 2011), and single microdeletions and microduplications have been found to have a variety of manifestations. For example, a cluster of rare disorder-associated CNVs on Chromosome 9 (containing the microdeletion 9q33.1 which includes neurodevelopmental genes astrotactin 2 [ASTN2] and tripartite motif-containing 32 [TRIM32]) has been associated with a variety of conditions: bipolar disorder, schizophrenia, and Autism Spectrum Disorder (ASD; Lionel et al, 2011). A similar phenomenon exists for the microdeletion of 16p11.2, observed in ASD (McCarthy et al, 2009); the same CNV is also seen among individuals with intellectual disability in the absence of ASD (Bijlsma et al, 2009). The association of *both* intellectual disability and psychiatric illness with a single CNV is seen for a number of other novel recurrent copy-number changes, including 1q21.1 deletion and duplication, 3q29 deletion, 15q11.2 deletion, 15q13.3 deletion, 15q24 deletion, 16p13.11 deletion and duplication, and 17q12 deletion (Mefford et al, 2012).

Single genes

A limitation to gene discovery in CNVs is the sheer magnitude of genetic material within many deleted or duplicated regions; yet the chief pathogenic genes may isolated to a small subset of this region. Without a comprehensive genetic dissection of the region, strong inference about associations with phenotypes is impossible. A more direct approach is to delineate genotype-phenotype relationships for a single gene.

Many genes are associated with the diagnosis of autism. This is best illustrated by the long list of *de novo* single nucleotide variants (SNVs) now emerging in autism within the Simons Simplex Collection of families (Neale et al, 2012Neale et al, in press; O'Roak et al, 2012 in press; Sanders et al, 2012 in press). These SNVs may be found to have broad pleiotropic manifestations beyong ASD *per se*. An example of classical pleiotropy for psychiatric diagnosis can be found for the gene diacylglycerol kinase eta (DGKH). It has been implicated in not only bipolar disorder but also unipolar depression and ADHD (Weber et al, 2011). Also, the gene synaptosomal-associated protein 25 (SNAP25) has been associated with ADHD and antisocial disorders, and may be associated with lower reward dependence and higher novelty seeking (Basoglu et al, 2011).

Epigenesis

Dysregulation of DNA methylation and histone modification are likely to play a major role in the pathophysiology of ASD and other neuropsychiatric illness (Shulha et al, 2011). Studies of post-mortem prefrontal brain tissue have revealed epigenetic profile alteration for literally hundreds of loci, notably, ones implicated in neurodevelopment. These epigenetic effects may converge on common developmental pathways in autism.

Convergent neurodevelopmental pathogenesis

There is also strong evidence from postmortem brain studies that multiple genes may disrupt common neurodevelopmental pathways in autism. Voineagu et al (2011) found that gene expression influencing cortical patterning is markedly altered in ASD. Their findings, taken as a whole, indicate that heterogeneous gene splicing and transcriptional dysregulation may underlie neurodevelopmental pathogenesis in autism.

Summary

The enterprise of gene discovery for neuropsychiatric disorders is revealing how multiple etiologies can contribute to one phenotype and multiple phenotypes can be manifested for one etiology. Once causal factors for brain-based disorders are identified, a new challenge emerges: determining how multiple pathogenetic factors conspire to disrupt common underlying neurodevelopmental mechanisms.

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