The Omnigenic Model: Implications for Psychiatric Genetics

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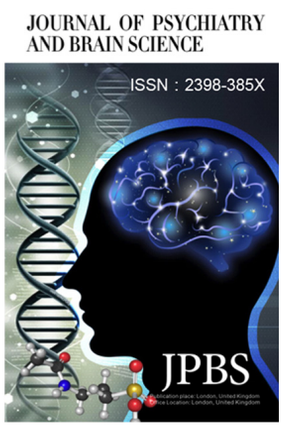
Boyle *et al.*'s [1] omnigenic model posits "core genes" that have "biologically interpretable roles in disease" and many more "peripheral genes" that regulate the activity of the core genes. Because there are many more peripheral genes, they account for a greater proportion of the variability in heritability than do the core genes. Their work is an important milestone for the field inasmuch as it brings into focus many key issues.

The concept of peripheral genes is intriguing, especially because, as a group, they account for more heritability than core genes. It builds upon other work showing that the lion's share of heritability is explained by SNPs in regulatory regions rather than coding regions, especially DNaseI hypersensitivity sites (DHSs) [2]. Among the many functions of regulatory regions is how they use signals from the environment to modify cellular activity. Boyle *et al.* do not discuss how their omnigenic model interfaces with the environment. A better accounting of this could raise the relative importance of "core genes" vs. "peripheral genes" given that, at least for psychiatric disorders, a substantial fraction of heritability is likely explained by interactions between genes and familial environment. This is seen in current estimates of SNP heritability, which are well below the heritability computed by twin studies. A further complication is that the environment likely contributes to pleiotropy. For psychiatric disorders we know of many shared environmental risks (e.g., anoxic episodes, exposures to toxins, low birth weight) each of which have small effects on disease risk.

Boyle *et al.*'s assessment of the relative importance of peripheral and core genes is based on a compelling analysis of the proportion of heritability accounted for by each set (their Fig. 3). Readers should be aware that the importance of a locus for drug discovery many not be a simple monotonic function of the amount of heritability accounted for by that locus. Gene by environment interaction is one reason. But, perhaps more importantly, GWAS data provide no indication about how the proteins coded by core genes will respond to pharmacologic manipulation and how that manipulation will affect disease. We can find a useful analogy in the study of rare diseases. When there are rare and common genetic forms of a disease, the rare forms typically account for a small amount of population heritability. Yet, there are empirical examples of how a biological pathway and drug target implicated by a rare variant is relevant to the common form. Rare variants of PCSK9 cause a rare autosomal dominant familial



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hypercholesterolemia. Drugs that inhibit PCSK9 protein lower cholesterol and are a viable treatment for common forms of hypercholesterolemia and atherosclerosis[3, 4]. Canakinumab is a human monoclonal antibody that was developed and approved to treat cryopyrin-associated periodic syndrome, a rare autoinflammatory syndrome caused by mutations in NLRP3, the gene encoding cryopyrin [5]. Subsequently, canakinumab was approved for use in gout [6, 7], a common inflammatory syndrome; it is also effective in treating common rheumatoid arthritis [8]. So, just as rare variants with a low impact on heritability have implications for the pharmacotherapy of common diseases, it may also be the case that core genes will be key players in drug discovery. Indeed, as Boyle *et al.* point out, the core genes that might have the most druggable targets.

I'll end with a bit of speculation about the omnigenics and the pathophysiology of psychiatric disorders, which show pervasive pleiotropy, a substantial contribution of regulatory variants and a substantial contribution from the environment. For many of these disorders have data suggesting that the initial pathophysiology occurs early in neurodevelopment due to genetic effects or early toxic exposures. Let's posit this sequence of events: 1) in utero, the developing brain is assaulted by a toxic environment or aberrant core genetic variants that pose a risk to survival. 2) As a reaction to this assault, the regulatory mechanisms governed by peripheral genes make adjustments that decrease the risk of death but increase the risk for psychiatric illness. 3) The initial assault may leave a widespread signature in the brain such as reduced brain volumes (as we see for many psychiatric disorders) and 4) The regulatory responses (#2) up- or down-regulate proteins that directly cause psychiatric symptoms. In this model, the core genes are, paradoxically, not directly relevant to the end state pathophysiology. This is consistent with the fact that most candidate genes for psychiatric disorders have not been confirmed by GWAS. It also provides an explanation for why diseases might share so many regulatory variants because, in this model, regulatory variants that promote survival under assault are more likely to be observed among psychiatric patients than those without a disorder. For example, we tested the hypothesis that that selective neuronal vulnerability explains variable brain volumetric losses in ADHD [9]. Our results suggested that normal variability in pathways mediating apoptosis, autophagy, and oxidative stress may regulate sensitivity to the genetic and environmental events that lead to the disorder.

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