Biological Psychiatry: Celebrating 50 Years

Commentary

Leveraging Human Induced Pluripotent Stem Cell–Based Models Provides Biological Context to Genome-wide Association Study Findings

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As genetic studies of increasing scope identify a growing list of variants associated with risk for neurodegenerative and psychiatric disease, a critical challenge is understanding the complex interplay between genetic risk loci to facilitate improved diagnosis and better prediction of prognosis and treatment response.

Although there is a clear overlap among the genetic risk factors underlying psychiatric disorders, neurological disorders are increasingly recognized as more distinct from one another and from the psychiatric disorders (1). Psychiatric risk variants differ in penetrance and prevalence; rare variants of large effect often mutate the coding sequences of one or more proteins, whereas common variants of small effect frequently occur in noncoding putative regulatory sequences. Both types are increasingly thought to impact genes expressed during fetal cortical development and to converge on synaptic function and epigenetic processes (2). Postmortem brain transcriptomic profiling supports a shared molecular neuropathology of the major psychiatric disorders (3). Integration with single cell expression datasets adds further insights, such as in schizophrenia, where risk loci map predominantly to genes expressed in pyramidal excitatory neurons and a subset of gamma-aminobutyric acidergic interneurons (4). Overall, schizophrenia-associated risk genes show strong evidence of genetic and developmental regulation, particularly related to synaptic processes (5).

To provide new biological context to the growing list of common variants linked to neuropsychiatric disease, Ori *et al.* (6) queried longitudinal gene expression of human induced pluripotent stem cell (hiPSC)–derived neurons across neuronal differentiation. Such an approach is similar to one recently applied by Rajarajan *et al.* (7) to infer pathway and epigenetic relationships between schizophrenia genome-wide association study genes by monitoring developmentally regulated changes in chromosomal conformations during the course of neuronal and glial differentiation. These isogenic experimental designs, which study the impact of neuronal specification and maturation across donor-matched cells, minimize experimental variability arising from genetic and epigenetic differences between individuals and so increase the power of the associated analyses.

Ori *et al.* (6) demonstrated that the cumulative impact of risk loci of psychiatric disorders is significantly associated with genes that are differentially expressed during neuronal differentiation. Consistent with the established literature, they found that genes associated with schizophrenia risk were upregulated during neuronal differentiation, and that coexpression of these genes was linked to synaptic function (6). Intriguingly, these findings seem to be specific to schizophrenia risk and were not also observed for the other neuropsychiatric disorders queried. Given that the risk of Alzheimer's disease is heavily enriched for microglia genes (8), a cell type not generated by the in vitro differentiation protocol used, it is perhaps unsurprising that no signal was detected here. But why did longitudinal transcriptomic evaluation of hiPSC neuron differentiation capture schizophrenia but not autism spectrum disorder risk? While this may indicate differences in the genetic and/or cellular origins of autism spectrum disorder, it could instead reflect aspects of experimental design, such as the cell type composition or maturity of the hiPSC-derived neurons studied. Consequently, these longitudinal analyses are worth revisiting using subtype-specific transcriptomic profiles generated from more advanced neuronal and glial differentiation/induction protocols, as well as through the incorporation of more complex "circuit-like" populations of interacting neural cell types. It will also be interesting to repeat these studies across a larger population of donors, including hiPSCs derived from individuals with high polygenic risk and individuals with low polygenic risk for neuropsychiatric disease. Overall, this work successfully demonstrated that isogenic longitudinal in vitro transcriptomic signatures could serve as a cellular readout for the application to the genetics of complex traits.

Others have also demonstrated that the molecular dynamics underlying in vitro human neuronal differentiation can inform polygenic psychiatric disorder susceptibility. hiPSC neurons are widely accepted to most resemble those of the fetal brain, and so are thought to be well-suited for modeling genetic risk of disease. The evaluation of cell type–specific open chromatin regions highlighted disease-relevant noncoding sequences, identifying putative causal schizophrenia risk variants, one of which was subsequently validated by clustered regularly interspaced short palindromic repeats (CRISPR)–mediated genome editing (9). Mapping of neuronal expression quantitative trait loci through hiPSC-based analyses have confirmed in vivo postmortem findings, while also discovering novel expression quantitative trait loci missed by tissue-level analyses. Nonetheless, directed neuronal differentiation from hiPSCs remains a variable process, resulting in variation within and between differentiations, even from the same individual (10). Importantly, genes that are significantly upregulated after neuronal differentiation from hiPSCs, including those critical to neuronal function,

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seem to be the most variable (10), reinforcing the need to validate hiPSC-based findings across multiple donors.

Toward the ultimate goal of using genotype information to accurately diagnose patients and predict treatment response, genetic risk for neuropsychiatric disease should be interpreted through a variety of perspectives. Given that risk arises through the interplay of hundreds of risk variants across a multitude of cell types, important insights lie in the points of convergence (and divergence) between disorders. Mapping polygenic risk to biologically relevant pathways is an important step toward translating genetic risk into clinically actionable information, as querying the relationships between the many risk-associated genes through developmental, brain region, and cell type–specific coexpression patterns will facilitate improved understanding of the impact of risk variants on cellular function. Nonetheless, as genetic studies continue to identify loci associated with disease risk, causality must ultimately be empirically validated and not just inferred. The integration of CRISPR genome engineering and in vitro hiPSC-based models seem to be the most likely strategy by which to systematically demonstrate the cell type–specific impacts of neuropsychiatric disease–associated variants.

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Article Information

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