

Pathways to the Future: The promise of stem-cell biology in diagnosing, treating, and preventing schizophrenia

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The complex genetic mechanisms underlying schizophrenia remain unclear. We employ a functional genomics approach that integrates stem cell models and genome engineering, resolving the combinatorial impact of patient-specific variants across cell types, donor genetic backgrounds, and environmental contexts. Individually small risk effects combine to yield much larger impacts in aggregate, but the interactions between the myriad variants remain undetermined. First, we evaluated the impact of patient-specific *NRXN1*^{+/-} deletions in hiPSC-neurons, observing greater than two-fold reduction of half of the wildtype *NRXN1* α isoforms and detecting dozens of novel isoforms expressed from the mutant allele; reduced neuronal activity in patient hiPSC-neurons was ameliorated by overexpression of individual control isoforms in a genotype-dependent manner, whereas individual mutant isoforms decreased neuronal activity levels in control hiPSC-neurons. Second, we integrated CRISPR-mediated gene editing, activation and repression technologies to study putative causal common variants and their associated target genes, alone and in combination. This allowed us to uncover an unexpected synergistic effect between schizophrenia risk genes that converges on synaptic function and links the rare and common variant genes implicated in psychiatric disease risk, one which may represent a generalizable phenomenon occurring more widely in complex genetic disorders. We demonstrate a systematic and scalable strategy to interpret and evaluate the additive impact of a growing number of schizophrenia-associated variants and genes within and across pathways, neural cell types and treatments. We seek to decode highly complex genetic insights into medically actionable information, better connecting the expanding list of genetic loci associated with human disease to pathophysiology. Our goal is to improve diagnostics, predict clinical trajectories, and identify pre-symptomatic points of therapeutic intervention.

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