A new molecular map of psychiatric disease mechanisms

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Genetic analyses of patients with schizophrenia, bipolar disorder, major depression, and other psychiatric disorders are advancing rapidly and yielding the first well-validated insights into the neurobiology of these diseases. The emerging genetic risk architectures of these severe illnesses are, however, proving highly complex. They are extremely polygenic, involving thousands of DNA sequence variants linked to many hundreds of genes. Risk associated DNA variants have also proven pleiotropic, meaning that they are shared across multiple psychiatric disorders and normal cognitive and behavioral phenotypes. Given such complexities, neurobiology faces significant challenges in the quest to exploit genetic findings in the service of understanding disease mechanisms and discovering much needed biomarkers and therapeutic interventions. I will discuss computational and experimental strategies that have already been applied to schizophrenia (and that should prove generally applicable to other disorders), which have begun to identify cell types and biological pathways involved in pathogenesis. I will also describe investigations of human phenotypes and human neurobiology that are advancing understandings of disease mechanisms and that promise to deliver biomarkers and nominate therapeutic targets.