In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Special Issue: The New Psychiatric Genetics: Toward Next Generation Diagnosis and Treatment

Advances in Psychiatric Genetics

This review by **Lehner *et al.*** (pages 6–14) traces the convergence of historical and current developments in disparate areas of science and policy that have led to unprecedented progress in psychiatric genetics. In particular, they focus on the team science approach, bio and data repositories, policies for broad data sharing, and scientific advances in our understanding of the structure and function of the human genome.

In this review, **Donaldson and Hen** (pages 15–21) discuss the progress to date and the future efforts to enhance translation between human and animal studies in order to advance our study and understanding of psychiatric illness. Of particular importance is the identification of psychiatrically-relevant intermediate phenotypes that can be studied across species, as well as the need to refine modeling of human disease-associated genetic variation in mice and other animal models.

Horváth and Mirnics (pages 22–28) review the molecular underpinnings of neuropsychiatric disease by evaluating the relationship between transcript disturbances, genetic susceptibility, and environmental influences. They suggest that most environmental influences could be viewed as common predisposers/protectors across various brain diseases, and that disease specificity appears to be defined by genetic predisposition. The authors argue that research should be focused on understanding the function of genes and integration of data from many different sources.

This selective review highlights investigations into the genetic factors influencing drug response in psychiatric disorders. **Hamilton** (pages 29–35) discusses current methodological challenges, set in the context of the distinctions between gene finding studies for psychiatric disorders and genetic analyses of medication treatment phenotypes. He also presents the state of the literature with antidepressants and antipsychotics, along with the barriers to implementation and possible approaches to successfully using genetic information to guide psychiatric drug treatment.

Virtually all psychiatric traits are genetically complex. In this review, **Gelernter** (pages 36–42) discusses the genetics of complex traits, which is accounted for by numerous factors, including multiple risk alleles, epistasis, and epigenetic effects such as methylation. Recent developments, including new analytic methods and the emergence of large meta-analysis and mega-analysis consortia, are vital to advance the psychiatric genetics field and promise productive gains in the years to come as they are applied more widely.

Potential Targets for Pharmacotherapy

Here, **Karch and Goate** (pages 43–51) review recent advances in our understanding of the genes that can influence an individual's risk of developing Alzheimer's disease. Using modern methods for surveying the entire human genome in tens of thousands of samples, scientists have now identified more than twenty genes associated with disease risk. These genes seem to fall in common pathways implicating a small number of molecular processes, which may be targets for future drug treatments to prevent Alzheimer's disease.

Schizophrenia is highly heritable and the identification of genetic variants associated with the disorder offers one major route to advance our understanding of this disorder. This review by **Hall *et al.*** (pages 52–58) focuses on recent studies of rare but deleterious mutations in patients with schizophrenia and highlights evidence that these converge on particular molecular pathways at the synapses between nerve cells. These findings may have implications for the development of novel treatments for schizophrenia and related conditions.

Novel Approaches in the Study of Psychiatric Genetics

Here, **Kohane** (pages 59–65) describes the use of a systematic approach to large-scale data to make strides towards a "precision medicine" of neuropsychiatric disease, highlighting the contributions of large-scale data sets from the published literature, electronic health records, and high-throughput genomic studies. Using autism spectrum disorders (ASD) as an exemplar, he illustrates how this approach reveals two productive but largely separate avenues of research in ASD defined by apparently distinct mechanistic hypotheses: ASD as a disorder of neural connectivity and synaptic function and ASD as a disorder of immunological signaling.

Here, **Kim and Leventhal** (pages 66–74) use ASD as a paradigmatic neurodevelopmental disorder (NDD) to review the complexities of identifying specific pathophysiologic processes. While there has been considerable progress in exploring genetic substrates of NDD/ASD, the next steps require examination of the roles of environmental factors and gene-environment interactions, which pose new challenges. They detail genetic epidemiologic strategies, which offer new opportunities to not only understand the pathobiology of these NDDs but also create the possibilities for novel approaches to treatment and prevention.

Glahn *et al.* (pages 75–83) present an analytic approach for discovering and empirically validating endophenotypes, i.e., traits related to the genetic risk for an illness, in extended pedigrees with very few affected individuals. Applying this method to neurocognitive and cortical surface area traits, they identified three neurocognitive tasks and six medial temporal and prefrontal cortical surfaces associated with liability for schizophrenia, despite having sampled just 6 individuals with schizophrenia in randomly ascertained pedigrees.

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