

## Introduction: The Use of Endophenotypes to Deconstruct and Understand the Genetic Architecture, Neurobiology, and Guide Future Treatments of The Group of Schizophrenias

This issue of *Schizophrenia Bulletin* includes a series of articles on the “endophenotype strategy” to explore and understand the genetics of “schizophrenia.” Initially, an atheoretical search for associations between the qualitative diagnostic disorder schizophrenia and regions of the genome was a useful first step in the high-risk voyage of discovery seeking genes conveying vulnerability to schizophrenia. However, with a huge ocean of 3 000 000 000 base pairs harboring 25 000 or so structural genes in *Homo sapiens*, alternative strategies for schizophrenia vulnerability gene identification were and are needed.

In this issue, “Endophenotyping Schizophrenia” is an article that describes this alternative and rational endophenotype approach to gene discovery in schizophrenia. In 1972, Gottesman and Shields introduced the concept of the “endophenotype” into the schizophrenia literature to signify quantitative measures that were “intermediate,” functionally important links in the pathways between genetic variation and clinical expression of the disorder. Invisible to the naked eye and based on instrument or laboratory measurements, these heritable endophenotypes accounted, in principle, for genetic risk factors that interacted with nongenetic factors to create the brain-based neurobiological soil from which schizophrenia is more likely to spring forth. Gur et al and Turetsky et al describe some of these neurocognitive and neurophysiological endophenotypes that act as genetically mediated neurobiological components of the risk for developing schizophrenia. Schork et al show how advances in statistical genetics enable psychiatric geneticists and neuroscientists to use this endophenotypic information in the service of interrogating the genome and identifying specific genes and SNPs that create risk for developing schizophrenia.

The advantages of the endophenotype strategy are that endophenotypes are quantitative and functionally relevant reflections of genetic risk, and they are amenable to advanced statistical analysis. Further, they increase the power of any subsequent analyses because more relatives will have the candidate endophenotype than will have the full-blown clinical phenotype of schizophrenia. A classical example in medicine is the

role of an abnormal glucose tolerance test in the relatives of diabetes patients in furthering our understanding of the genetic architecture of diabetes itself. But exactly how can we get endophenotype information about families? Using endophenotype selection described by Braff et al and illustrated by Gur et al and Turetsky et al, this issue describes a model National Institute of Mental Health-funded project that uses a family-based, multisite endophenotype strategy to ascertain and gather information to unlock the genetic complexities of schizophrenia. In “The Consortium on the Genetics of Endophenotypes in Schizophrenia (COGS): Model Recruitment, Assessment, and Endophenotyping Methods for a Multi-Site Collaboration” by Calkins et al, the major issues and strategies for setting up the Consortium on the Genetics of Schizophrenia (COGS) are described. From training research assistants to reliably diagnosing schizophrenia to testing for quantitative endophenotypes, this article is an excellent guide to setting up and running a multisite consortium that explores the intricate genetic architecture of a complex multifactorial disorder such as schizophrenia. It should serve as a useful reference for others who are facing similar consortium-building challenges.

The genesis and progress of the endophenotype strategy and its implementation in the COGS is well described in these articles. By starting with heritable and quantitative measures, cutting-edge statistical genetic analyses can be employed in order to unravel the complex genetic mysteries of schizophrenia. Certainly, as we utilize the genetic mantra of “DNA to RNA to Protein,” we must better understand genetic variation in the context of quantitative functional shifts in behavior, neurophysiology, metabolism, and neurodevelopment, which is complicated even further by epistasis (gene by gene interaction), gene by environment interaction, and by still unspecified epigenetic factors. The endophenotype strategy, although still in its infancy and open to challenge for some of its assumptions, potentially provides a very potent platform from which we can position ourselves to understand the genetics of schizophrenia and, ultimately, to select strong-inference-based compounds to treat or

## Editorial

even prevent this cruel and devastating “no fault” clinical brain disorder. In addition, we could not have a series of articles on the endophenotype strategy without thanking Dr Gottesman for his ongoing, stimulating, and lively intellectual leadership in this field of psychiatric genetics and neuroscience. Speaking for all the COGS investiga-

tors, I hope that the reader gains knowledge, direction, and insight from these carefully crafted articles.

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