TRANSLATIONAL GENETICS AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

M. Egan
Clinical Neuroscience, Merck, North Wales, PA, USA

Purpose: Genetic studies have implicated specific molecular mechanisms in cognitive impairment associated with schizophrenia. Several of these appear to be tractable targets for drug development.

Method: Genetic studies have found that single nucleotide polymorphisms (SNPs) in a variety of genes impact risk for schizophrenia and/or performance on cognitive tests. Follow up studies using brain imaging and molecular techniques have provided convergent evidence implicating these genes and related molecular mechanisms.

Results: Evidence for a role in schizophrenia and/or cognition is strongest for NRGI, dysbindin, COMT, and DISC1. Additional studies to confirm these and clarify risk alleles and transcripts are needed.

Nevertheless, these findings implicate several molecular pathways and targets for drug development. Perhaps the most straightforward is COMT, which appears to modulate cognition via its effects on prefrontal dopamine. Of available COMT inhibitors, tolcapone does cross the blood brain barrier and has been reported to improve cognition. Toxicity and uncertain degree of central COMT inhibition suggest new COMT inhibitors are needed.

The discovery of a highly penetrant gene, DISC1, in patients with schizophrenia provides a new path forward for developing novel therapeutic agents to enhance cognition in schizophrenia. While additional molecular studies are needed to validate these mechanisms, they suggest a new model for schizophrenia drug discovery based on specific molecular and cellular phenotypes. The remaining challenge, inherent to all complex genetic disorders, is to understand in greater detail how genes and disordered pathways work together to impair cognition and what mechanisms are most tractable for normalizing them.

RELATIONSHIP BETWEEN NEUROLOGICAL SOFT SIGNS AND COGNITION IN FIRST EPISODE PSYCHOSIS

Institute of Psychiatry, Kings College London, London, United Kingdom

Neurological Soft Signs (NSS) are minor neurological abnormalities present in excess in psychosis. NSS have been suggested to predict poor cognitive performance, specifically executive function, mostly in patients with chronic psychosis. Unfortunately, it remains unclear whether this is already true for patients at the first illness episode. We examined an epidemiological sample of 248 first episode psychosis patients from the AESOP study (mean age 30 SD 10.81; 146 males; 48% Schizophrenia, 33% Affective Psychosis, 19% Other Psychosis. Mean current IQ 90.79 SD 17). Data relating to NSS were obtained using the Neurological Evaluation Scale (NES). IQ was obtained from the WAIS-R, executive function was measured using Trail Making Tests A and B and a Verbal Fluency task. NSS scores were divided into four groups on the basis of performance. Multinomial logistic regression analysis revealed that individuals with more NSS were more likely to have a low IQ (p=0.005), while individuals with less NSS were more likely to have a high IQ (p=0.014). Similarly, individuals with more NSS were more likely to perform worse on Trails A (p=0.004) and B (p=0.001) and the Verbal Fluency Task (p=0.001). Likewise, individuals with less NSS were more likely to perform well on the Verbal Fluency Task (p=0.007). These results suggest that neurological impairment predicts a worse general cognitive performance. Further investigation is needed from tests evaluating specific cognitive domains, such as short term and working memory, to clarify this issue. This study is funded by the UK Medical Research Council. We would like to thank the Stanley Medical Research Foundation and The Wellcome Trust for their support.