

VISN 5 MIRECC Research Abstract

Familial Schizophrenia Spectrum Personality Disorders Gunvant Thaker, MD

Identifying disease-related genetic effects is a major focus in schizophrenia research. Efforts have been multifaceted with the ultimate goal to describe a causal path from specific genetic variants to changes in neuronal functioning to behavioral and functional impairments. The schizophrenia diagnosis likely reflects a heterogeneous combination of several such causal paths, and is therefore characterized by a varying collection of phenotypes each associated with specific neurocognitive deficits reflecting the effects of a small subset of genes. Thus genetic findings based on the clinical phenotype are likely to vary, which may explain repeated failures to replicate identified disease loci. Defining who is affected based on the clinical diagnosis also ignores the likelihood that some relatives, although clinically unaffected, also carry aspects of disease risk. Environmental factors are also implicated, adding to the etiologic complexity of the disease. In light of these complexities there is a critical need for phenotypes that reflect specific aspects of disease risk. The identification, validation, and application of endophenotypes that mark specific aspects of disease risk has important implications for future genetic studies, studies examining the interaction of genes and environment, studies of pathophysiology, and prevention research.

We propose to conduct a family case-control study to confirm the association(s) between putative neurophysiological and cognitive phenotypes and schizophrenia liability and to determine if these deficits are associated with the presence of schizophrenia spectrum personality (SSP) symptoms among case relatives ruling out the effects of SSP symptoms per se. We propose to examine the relationships among neurophysiological/cognitive measures to determine which deficits reflect a common underlying phenotype and which represent independent aspects of disease risk. We will determine the differential risk of single and composite deficits among case relatives based on the presence/absence of deficits in case probands. Within family correlations for implicated measures will be examined to derive estimates of heritability and to examine the relative contributions of genetic and shared environmental effects. We also propose to examine the relationships between neurophysiological phenotypes and schizophrenia-related symptom domains. We plan to recruit 120 patients and all available first-degree relatives (300, 60 with SSP). For each case proband, we will identify an age (+ 3 yrs), sex, race, county matched control proband using targeted telephone calling (TTC) procedures. We will recruit all available and eligible control relatives (300). We will also recruit a separate group of persons from the community who exhibit SSP in the absence of a family history of psychotic disorders in order to examine the effects of SSP symptoms per se. Clinical information, electrophysiological and cognitive measures will be collected and compared among the groups using standard family case control analytic procedures. Blood samples will be collected for future genetic analyses.