Schizophrenia-Associated SNPs Proximal to Neurotransmission Genes Impact Cognitive Functions in Patients and Controls.

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Keywords: Biology & Life Sciences

Abstract

Schizophrenia is a psychiatric disorder with symptoms that include cognitive deficits. Due to the high degree of heritability of the disorder, large population genome wide studies have been performed to identify genetic regions associated with schizophrenia. The most recent genome wide study discovered 83 new regions of interest, encompassing over 350 genes. In this study, selected single-nucleotide polymorphisms located near genes involved in neurotransmission have been selected for analysis. The effect of these polymorphisms on neurotransmission, which is disrupted in schizophrenia, have been characterized in terms of their effects on IQ, memory, attention, and social cognition as measured by a neuropsychological test battery. Significant effects of multiple genes were found across cognitive domains.

1. Introduction

Schizophrenia (SZ) is characterized by positive, negative, affective and cognitive symptoms. SZ is known to be highly heritable, with 83 new genomic regions of interest (over 350 genes) associated with SZ in a recent genome wide scan [1]. The associations with these loci include both single-nucleotide polymorphisms (SNPs) and copy number variants. The mechanism by which these variants increase SZ risk is currently unknown. To take these results forward, these functions need to be identified, be that at the level of protein, neural pathway or phenotype.

2. Methods

To characterize the effect of these identified single-nucleotide polymorphisms (SNPs) on cognitive function, first a selection was carried out based on the following classifications 1) SNP located within or less than 50kb from gene of interest, 2) unique association of this gene to SNP, and 3) gene involvement in neurotransmission, which is disrupted in SZ. This resulted in a selection of SNPs in close proximity to four genes involved in glutamatergic neurotransmission (GRM3, GRIN2A, SRR, and CLCN3), four signaling (CACNB2, HCN1, RIMS1, two associations with CACNA1C) and two receptor genes (DRD2, CHRN). To assess the impact of each SNP on cognitive function, neuropsychological measures of IQ, memory (subtests from the Wechsler Adult Intelligence Scale-III, Wechsler Memory Scale-III and the Cambridge Neuropsychological Test Automated Battery), attention (Continuous Performance Test and Sustained Attention to Response Task), and social cognition (Reading the Mind in the Eyes, the Hinting Task, and the Internal, Personal and Situational Attributions Questionnaire) were analyzed. Linear regressions of the whole sample population, controls only (n=190), patients with SZ and schizoaffective disorder (n=454) and patients with a broader psychosis diagnosis (n=148) were carried out, with age and gender as variables of no interest.

3. Results

Analyses indicate a significant effect on measures of cognition in patients and controls. Initial analyses showed that SNPs within regions of eight genes (CACNA1C, CHRN, CLCN3, CACNB2, GRIN2A, GRM3, HCN1 and RIMS1) show a significant effect on multiple measures of IQ, memory, attention and social cognition. After a multiple testing correction, the SNPs proximal to the following genes findings remained significant: CACNA1C (SART) GRIN2A (CANTAB PAL), GRM3 (WMS-III: Faces 2), HCN1 (WAIS-III: LM2), and RIMS1 (Reading the Mind in the Eyes); $p<0.01$ for all.

4. Discussion

SZ risk variants located within or proximal to genes involved in neurotransmission have significant effects on cognitive functions as measured by the neuropsychological test battery. Future work will aim to further elucidate this in conjunction with impact on fMRI and DTI measures, in addition to investigating other functional groups of SZ-associated genes. Outcomes put into context from such investigations may point towards specific neurotransmission pathways contributing to the disorder.

5. References

[1] Schizophrenia Working Group of the Psychiatric Genomics Consortium. "Biological insights from 108 schizophrenia-associated genetic loci." *Nature* 511.7510 (2014): 421-427.