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Association of common and rare genetic variants with cognition in schizophrenia

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Abstract

Cognitive dysfunction is one of the core features in schizophrenia (SZ), which is a common neuro-psychiatric disorder affecting ~1% of the population globally. Cognitive impairment is related to social deficits with severity and breadth of these impairments varying across patients. Further, different cognitive domains seem to be dysfunctional in different patients. Severity of cognitive decline depends on the age of onset of SZ, with higher severity in early onset cases and generally manifests before the actual onset of psychosis. Though estimated heritability of cognition is ~50-70% little is known about its genetic basis. Of note, contemporary antipsychotic medication is also not effective in addressing this endophenotype. In this study we recruited SZ patients (n=158) from Dr. RML hospital, New Delhi and assessment of cognition was performed using Hindi version of University of Pennsylvania Computerized Neurocognitive Battery (Penn CNB). Eight selected cognitive domains namely abstraction and mental flexibility, attention, face memory, spatial memory, working memory, spatial ability, sensorimotor and emotional processing known to be impaired among patients with SZ were measured. Whole exome sequencing of the study cohort was performed and data were processed using standard tools and software. To identify variants/genes associated with cognitive domains, we performed two different levels of association testing: 1) linear regression analysis using the common variants (MAF>0.01) and eight different domains of cognition; and 2) gene-level tests for rare variant (MAF<0.01) association using burden tests (CMC, CMC-Wald & Zeggini). We identified 11 common variants associated ($P<10^{-7}$) with different cognitive domains, which withstood Bonferroni corrections and rare variant burden analysis identified four genes associated ($P<10^{-7}$). Genes identified by these two approaches and their implications for cognitive deficits will be presented.