M41. PLEIOTROPIC EFFECTS OF SCHIZOPHRENIA AND COGNITIVE LOCI: A META-ANALYTIC APPROACH

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Background Cognitive deficits are a key feature of schizophrenia. The genetic architecture underlying cognition is investigated. A novel method of using cross-phenotype meta-analysis to elucidate overlapping genetic substrates between established schizophrenia loci and cognitive loci was conducted.
Methods 895 healthy controls and 648 schizophrenia subjects with intact cognitive data were included in the discovery dataset after standard genome-wide QC procedures. The markers were imputed via Minimac (MACH) to the 1000 genomes phase 1 reference panel. Strict post-imputation filtering of rsq > .9 was carried out. Publicly available leave-one-out summary statistics from the PGC2 schizophrenia working group were employed for meta-analysis. Meta-Analysis for cognition and schizophrenia was conducted in METAL.
Results 51 markers were found to be enriched for the cognition-schizophrenia cross-phenotype meta-analysis (33.6%; $p < 3.66 \times 10\text{-}24$). 22 loci were found on the 128 PGC loci, 21 loci were in LD with the 128 PGC Loci, and eight loci were novel. DAVID pathway analysis revealed voltage-gated ion channel, calcium channel activity and metal ion transportation activity (FDR p-values: $2.58 \times 10\text{-}6$; $6.6 \times 10\text{-}5$; $7.14 \times 10\text{-}6$) to be enriched. Further hierarchical bi-clustering analysis revealed significant expression of genes like PLCH1, FURIN, CUL3, CACNB2, GPM6A, TCF4, DGKZ, CSMD1, KCDT13, GRIN2A, CACNA1C, DGKI in frontal-temporal and hippocampal regions of the brain.
Discussion Cross-phenotype meta-analysis revealed voltage-gated ion channels, calcium channels, and metal-ion transport pathways to be implicated in both schizophrenia and cognition. Areas of the brain with which these candidate genes are involved are also known regions that have been reported to be associated with cognitive deficits in schizophrenia. Results from the current analysis support evidence that has previously been reported in both schizophrenia and cognitive literature. The results provide potential biological insights to the understanding of cognitive impairments found in schizophrenia. Further research is necessary to replicate the current findings and to understand if there might be potential approaches to modify cognition via targeting the above mentioned biological pathways.
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