M61. SHARED GENETIC VARIANTS BETWEEN SCHIZOPHRENIA AND GENERAL COGNITIVE FUNCTION INDICATE COMMON MOLECULAR GENETIC MECHANISMS

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Background Schizophrenia (SCZ) is a severe mental disorder characterized by widespread cognitive impairments including deficits in learning, memory, processing speed, attention and executive functioning. Although cognitive deficits are a strong predictor of functional outcome in SCZ, current treatment strategies largely fail to ameliorate these impairments. Thus, in order to develop more efficient treatment strategies in SCZ, a better understanding of the pathogenesis of these cognitive deficits is needed. Given that both SCZ and cognitive ability are substantially heritable, we here aimed to determine whether SCZ share genetic influences with general cognitive function (COG), a phenotype that captures the shared variation in performance across several cognitive domains.

Methods We analyzed GWAS results in the form of summary statistics (p-values and z-scores) from SCZ (the Psychiatric Genomics Consortium; n=82 315) and COG (CHARGE Consortium; n=53 949). We applied a conditional false discovery rate (FDR) framework. By leveraging SNP-associations in a secondary trait (SCZ or COG), the conditional FDR approach increases power to detect loci in the primary trait (COG or SCZ), regardless of the directions of allelic effects of the risk loci. We then applied the conjunction FDR to identify shared loci between the phenotypes. The conjunction FDR is defined as the maximum of the conditional FDRs for both directions, and we used an overall FDR threshold of 0.05.

Results To visualize pleiotropic enrichment, we constructed conditional Q-Q plots which indicate substantial polygenetic overlap between SCZ and COG. For progressively stringent p-value thresholds for SCZ SNPs, we found approximately 150-fold enrichment for COG. For progressively stringent p-value thresholds for COG SNPs, we found approximately 100-fold enrichment for SCZ. We then used the conjunction FDR and identified fourteen independent loci shared between SCZ and
COG. The majority of the shared loci show inverse associations in SCZ and COG, in line with the observed cognitive dysfunction in SCZ.

**Discussion** Our preliminary findings indicate shared molecular genetic mechanisms between SCZ and COG, which may provide important new insights into the pathogenesis of cognitive dysfunction in SCZ.

**Disclosure:** Nothing to Disclose.