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GWAS of Cognitive Abilities and Risk for Substance Abuse

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COGENT has led or collaborated on a series of recent large-scale genome-wide association studies (GWAS) of general cognitive function, intelligence, and educational attainment. In samples ranging in size from 35,298[1] to 107,207[2] to 269,867[3] to 300,486[4] to 1,131,881[5], we have identified hundreds of new independent loci, genes, functional pathways, neurodevelopmental processes, and genetic correlations associated with human cognitive abilities. Functional biological annotation methods have revealed GWAS hits for cognitive function are significantly associated with Mendelian intellectual disability disorders, neurogenesis, neuron differentiation, synaptic structure, and potential nootropic pharmacologic agents. Gene expression analyses have shown genes associated with cognitive function are strongly expressed in the brain relative to other tissue types, specifically in striatal medium spiny neurons and cortical and hippocampal pyramidal neurons. Transcriptome-wide analyses have revealed cognitive loci are strongly expressed in neurons (not glia) and are associated with fetal brain expression. We have found enrichment of genetic effects in conserved and coding regions, and identified ~150 nonsynonymous exonic variants linked to intelligence. Mendelian randomization has shown protective effects of intelligence for Alzheimer's and ADHD, and bidirectional causation with strong pleiotropy for schizophrenia. In independent samples, polygenic risk scores for cognition and educational attainment account for 7-10% of the variance in cognitive performance and 11-13% of the variance in years of schooling. Genome-wide pleiotropy has proven ubiquitous, including significant genetic correlations between cognitive function and cigarette smoking behavior, alcohol dependence, and drug use. Relevance of these findings to the genetics of substance abuse risk will be discussed.