Large-scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets

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Background: Neurocognitive deficits represent a critical component of many neuropsychiatric disorders and disease states that can affect health outcomes across the lifespan. Recently, a large (N~78,000) genomewide association study (GWAS) reported 18 genomewide significant loci for cognitive performance as measured primarily by brief assessment (Sniekers et al. 2017, *Nature Genetics*, PMID: 28530673). At the same time, the Cognitive Genomics Consortium (COGENT), utilizing a PCA-derived measure of general cognitive ability, has reported two loci from its own collection of >35,000 subjects in 24 cohorts (Trampush et al. 2017, *Molecular Psychiatry*, PMID: 28093568). In the present report, we meta-analyze results of these two studies to perform the largest cognitive GWAS to date. To further boost power to detect loci associated with cognitive ability, we utilized a novel approach, Multi-Trait Analysis of GWAS (MTAG; Turley et al. 2017, *Nature Genetics in press*) to combine our results with related data from a large GWAS on educational attainment (Okbay et al. 2016, *Nature*, PMID: 27225129).

Methods: After accounting for overlapping cohorts, the combined dataset for cognitive ability included N=107,207 unique individuals. All subjects were of European ancestry and were drawn from the general population. Genotype data across all cohorts was imputed using the 1000 Genomes v3 reference panel, resulting in ~8M high-quality SNPs. GWAS summary statistics were combined for meta-analysis using the sample-size weighted method in METAL, with gene-wise and pathway results examined using MAGMA. MTAG was applied to summary statistics from this dataset, combined with data from ~300,000 individuals of European ancestry assessed for educational attainment (years of schooling). Genetic overlap with other GWAS phenotypes was examined using the LD score regression (LDSC) method.

Results: Meta-analysis of the cognitive performance samples (N=107K) yielded 28 genomewide significant independent loci, 10 of which were novel. Inclusion of the educational attainment in MTAG analysis boosted the signal of our cognitive GWAS by ~75% and resulted in 70 genomewide significant loci, of which 34 are novel to either phenotype. Results showed significant enrichment for genes causing Mendelian disorders with an intellectual disability phenotype. Competitive pathway analysis implicated the biological processes of neurogenesis and synaptic regulation, as well as the gene targets of two pharmacologic agents: cinnarizine, a T-type calcium channel blocker; and LY97241, a potassium channel inhibitor. Transcriptome-wide and epigenome-wide analysis revealed that the implicated loci were enriched for genes expressed across all brain regions (most strongly in the cerebellum); enrichment was exclusive to genes expressed in neurons, but not oligodendrocytes or astrocytes. LDSC analyses of the meta-analytic and MTAG results revealed several novel genetic correlations, including a surprising strong correlation with parental age at death (r_g~.4-.5), possibly mediated by correlation of both with smoking behavior.

Discussion: Sample sizes for GWAS of cognitive ability have finally attained critical mass to uncover increasing numbers of significant loci associated with brain function. Genetic overlap analysis reveals very strong correlations with psychiatric disorders, as well as with many health-relevant phenotypes. Based on the GWAS power curves that have been observed for other complex phenotypes, further increases in sample size will demonstrate substantially enhanced yield.