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Polygenic Risk Score, Genome-wide Association, and Gene Set Analyses of Cognitive Domain Deficits in Schizophrenia

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Abstract

This study assessed genetic contributions to six cognitive domains, identified by the MATRICS Cognitive Consensus Battery as relevant for schizophrenia, cognition-enhancing, clinical trials. Psychiatric Genomics Consortium Schizophrenia polygenic risk scores showed significant negative correlations with each cognitive domain. Genome-wide association analyses identified loci associated with attention/vigilance (rs830786 within *HNF4G*), verbal memory (rs67017972 near *NDUFS4*), and reasoning/problem solving (rs76872642 within *HDAC9*). Gene set analysis identified unique and shared genes across cognitive domains. These findings suggest involvement of common and unique mechanisms across cognitive domains and may contribute to the discovery of new therapeutic targets to treat cognitive deficits in schizophrenia.

Keywords

schizophrenia; PRS; GWAS; neuropsychology; MCCB

1. Introduction

Schizophrenia is highly heritable (h^2=0.8) (McGuffin et al., 1984). Moreover, cognitive impairments are core heritable features of schizophrenia (h^2=0.20–0.80) (Blokland et al., 2017), yet contributing genes remain to be determined.

Psychiatric Genomics Consortium (PGC) case-control genome-wide association (GWA) studies have found 108 schizophrenia risk loci, including several in *ZNF804A*, *NRGN*, *TCF4*, *MIR137*, and major histocompatibility complex regions (Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

PGC schizophrenia polygenic risk scores (PRS) have been associated with lower general cognitive ability (Lencz et al., 2014; McIntosh et al., 2013), speed of emotion identification and verbal reasoning (Germine et al., 2016), as well as verbal-numerical reasoning, reaction time, and memory (Hagenaars et al., 2016). Additionally, several control (Davies et al., 2015; Need et al., 2009) and schizophrenia GWAS using cognitive traits have been reported on (Hashimoto et al., 2013; Ohi et al., 2015; Ren et al., 2015; Sanchez-Roige et al., 2018; Smeland et al., 2017; Trampush et al., 2017). However, no PRS or GWA studies have assessed cognitive domains identified by the MATRICS Cognitive Consensus Battery (MCCB), developed for clinical trials of cognition-enhancing treatments for schizophrenia (Kern et al., 2008; Nuechterlein et al., 2008).

Here we report PRS, GWA, and gene set findings from genetic analyses with six MCCB cognitive domain scores (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, and reasoning/problem solving) previously shown impaired in schizophrenia (Cohen's d=−0.67 to d=−1.14) (van Erp et al., 2015).

2. Materials and Methods

2.1 Participants

This study includes data from 127 clinically stable individuals with schizophrenia (DSM-IV-TR, no medication changes within the last two months, no tardive dyskinesia) and 136 healthy volunteers (Table 1). Individuals with a history of major medical illness, drug dependence in the last 5 years (except nicotine), or current substance abuse disorder were excluded. Healthy volunteers with a history of major neurological or psychiatric illness or with a first-degree relative with an Axis-I psychotic disorder were also excluded. Participants' cognitive domain scores, based on the Computerized Multiphasic Interactive Neurocognitive System (CMINDS®) neuropsychological test battery (O'Halloran et al., 2008), were published in a prior report (van Erp et al., 2015). Genotyping of blood samples from unrelated and mixed ethnicity subjects was performed using the Illumina MEGA +Psych chip (Illumina, SD, USA). All subjects signed written informed consent approved by institutional review boards.

2.3 Polygenic Risk Score, Genome-wide Association, and Gene Set Analysis

Genotyping data were filtered to remove single-nucleotide polymorphisms (SNPs) with low minor allele frequency (MAF<0.01), deviations from Hardy-Weinberg Equilibrium ($p<1\times10^{-6}$), or poor genotyping call rate (<95%) using PLINK (Purcell et al., 2007). Filtered data were imputed to the 1000 Genomes Project reference panel (1000 Genomes Project Consortium et al., 2015) (phase 1, version 3) using the Michigan Imputation Server (Das et al., 2016). For each individual, a PRS was generated using the GWAS summary of

Psychiatric Genomics Consortium (PGC)-schizophrenia meta-analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), with linkage disequilibrium pruning parameters of R^2=0.5 over 250 kb windows using 1000 Genomes Project reference panel (ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502). The current sample was not part of the PGC analysis on which the PRS was based. PRS was used to test for association with cognitive domain scores using Pearson's correlations (two-tailed), statistically controlling for age, sex, and 4 multidimensional-scaling components (MDS). Genomewide linear regression analyses predicted each neuropsychological domain with each SNP, statistically controlling for diagnosis, age, sex, site, and four MDS. Fast and flexible gene- or set-based association tests, using GWAS summary data from the neuropsychological domain scores, were performed using Genome-wide Complex Trait Analysis (GCTA) (Bakshi et al., 2016; Yang et al., 2011). This method overcomes the limitations of the resampling-based methods by calculating the p-value for a set of SNPs (±50 Kb of a gene) from an approximated distribution of the sum of χ2-statistics over the SNPs using GWAS summary data and linkage disequilibrium correlations between SNPs from 1000 Genomes Project samples as a reference. We listed the top 40 identified genes and their p-values.

3. Results

The positive study results are that: 1) PGC-schizophrenia PRS showed significant negative correlations with each cognitive domain; 2) GWA identified significant associations for 3 out of 6 cognitive domains; and 3) gene-set analyses found unique and common contributing genes across the cognitive domains.

3.1 Polygenic Risk Score Analyses

PRS showed significant negative correlations with speed of processing (r_{260}=−0.20, p=0.001), attention/vigilance (r_{258}=−0.15, p=0.015), working memory (r_{261}=−0.19, p=0.0018), verbal learning (r_{261}=−0.19, p=0.0018), visual learning (r_{258}=−0.28, $p=2.8\times10^{-6}$), reasoning/problem solving (r_{260}=−0.21, p=0.0005), and the CMINDS composite (r_{256}=−0.29, $p=1.6\times10^{-6}$).

3.2 Genome-wide Association Analyses

GWA analyses identified significant associations for attention/vigilance (rs830786 within *HNF4G*), verbal memory (rs67017972 100bp upstream of *NDUFS4*), and reasoning/problem solving (rs114499642, rs74412765 within LOC102724945, and rs76872642 within *HDAC9*) domain scores ($p<5\times10^{-8}$; Figure 1; Table 2).

3.3 Gene Set Analyses

Gene set analyses identified unique and shared genes associated with cognitive domain scores (Table 3).

4. Discussion

All correlations between the PGC schizophrenia PRS and the cognitive domains scores were negative, consistent with the interpretation that higher schizophrenia genetic risk is associated with worse cognitive performance, corroborating prior findings (Germine et al., 2016; Hagenaars et al., 2016; Lencz et al., 2014; McIntosh et al., 2013).

With regard to the GWAS locus associated with attention/vigilance, *HNF4G* is expressed in the brain (http://www.brain-map.org). *HNF4G* is regulated by miR-194, which is dysregulated in individuals with 22q11.2 deletion syndrome who have a 20–30 fold increased risk for psychosis (Sellier et al., 2014). Additionally, mouse Hnf4g was found to be upregulated after toxoplasma gondii infection (He et al., 2016) which is a putative risk factor for schizophrenia (Webster et al., 2013). With regard to reasoning/problem solving, little is known about the *LOC102724945* and rs114499642 loci. However, *HDAC9*, histone deacetylase 9, is expressed in brain and has previously been associated with schizophrenia (Kebir et al., 2014; Tam et al., 2010). *HDAC9* is involved in transcriptional regulation, cell cycle progression, and neuronal development and transmission. Rs67017972, associated with verbal memory, is located 100bp upstream of *NDUFS4*. Lower prefrontal cortex and hippocampal NDUFS4 expression has been found in schizophrenia (Altar et al., 2005; Arion et al., 2015), and *Ndufs4* cKO mice show impaired cognitive function and increased anxiety-like behavior (Choi et al., 2017).

Gene set analyses, based on the GWAS results, found that several genes contribute to multiple cognitive domains. For example, *PPM1B* is associated with working memory, visual memory, and CMINDS composite. PPM1B is a member of the PP2C family of Ser/Thr protein phosphatases, and is expressed in brain. PP2C family members are known negative regulators of cell stress response pathways, and are involved in neuroprotection and neurodegeneration (Klumpp et al., 2006, 2002). Protein interactions between PPM1B, NRG1, and DTNBP1, putative schizophrenia susceptibility genes, have also been reported (Tsuang, 2000). *HSPA8*, associated with attention/vigilance and speed of processing, was previously identified as a schizophrenia risk locus (Bozidis et al., 2014). HSPA8, Heat shock 70 kDa protein 8, is known to contribute to many biological processes, including signal transduction, apoptosis, autophagy, protein homeostasis, and cell growth and differentiation. PLCB3-PARD3-PARD6A complex, associated with the CMINDS composite and working memory, was found to be associated with schizophrenia in BA22 RNA-Seq study (Huang et al., 2014). *PARD6A*, partitioning defective 6 homolog alpha, is involved in asymmetrical cell division and cell polarization processes. *ALOX12*, associated with CMINDS composite and visual learning, had been identified in a Korean schizophrenia study (Kim et al., 2010). *MIR497*, related to the CMINDS composite and visual learning, was differentially expressed in the prefrontal cortex exosome in schizophrenia and bipolar disorder (Delgado-Morales, 2017). Finally, *MIR195*, associated with visual memory and CMINDS composite, was found to be upregulated in the superior temporal gyrus of individuals with schizophrenia (Beveridge et al., 2010, 2008). *MIR195* regulates numerous schizophrenia-related genes, such as *BDNF*, *RELN*, Visinin-like 1, 5-hydroxytryptamine (serotonin) receptor 2a, and glutamate receptor, ionotropic, *N*-methyl-d-aspartate 3A. Each of the cognitive domains, especially the CMINDS composite, shares several genes with another cognitive domain.

Given that the CMINDS composite is an average across all 6 cognitive domains, overlap in genes with the CMINDS composite is expected.

Study strengths are the use of cognitive domain scores that are considered important targets for cognition-enhancing treatments for schizophrenia. Study limitations include sample size and lack of a replication sample, though the observed negative correlations between the schizophrenia PRS and the cognitive domain scores strengthen the confidence in our GWA and gene set findings. Nevertheless, replication of the findings in larger cohorts is warranted.

In conclusion, we found that the PGC-based schizophrenia PRS was significantly negatively correlated with CMINDS cognitive domain performance. In addition, we identified novel loci associated with cognitive domain performance. Finally, gene-based analysis revealed that cognitive domains share contributing genes. These findings suggest involvement of novel unique and common biological mechanisms in cognitive domain deficits in schizophrenia and may contribute to the discovery of new therapeutic targets to treat cognitive deficits in schizophrenia, which do not respond well to traditional antipsychotic treatments (Kahn and Keefe, 2013).

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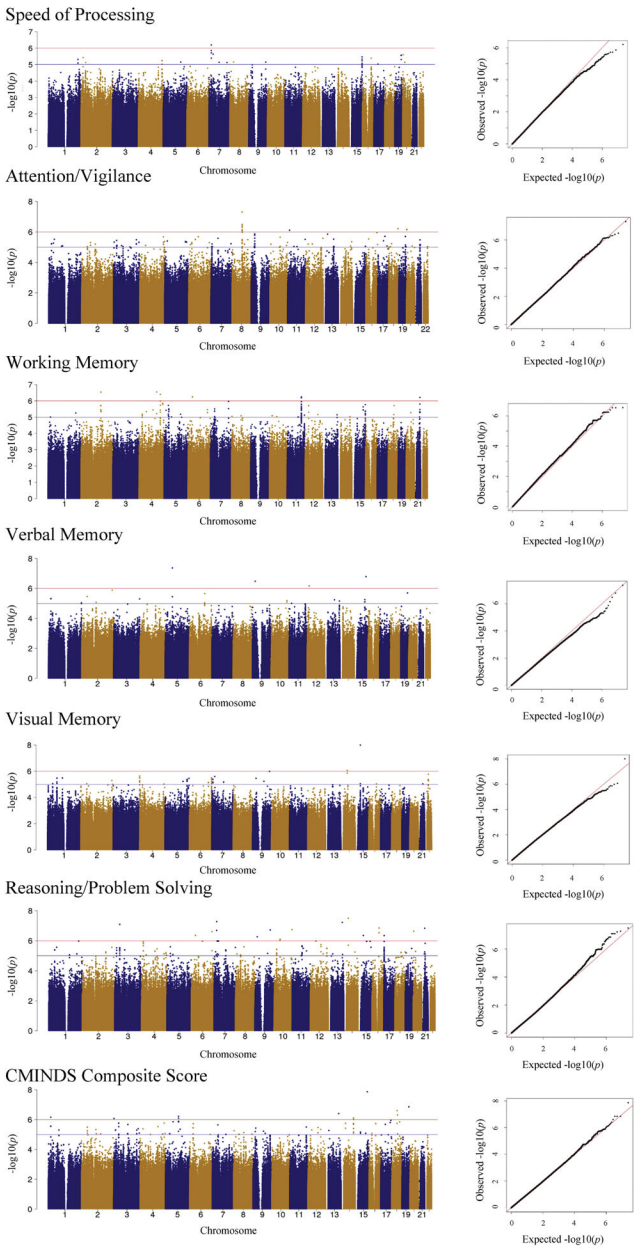

Figure 1

Figure 1.

GWAS Manhattan and QQ Plots for each Cognitive Domain. The Manhattan plots display the association p-value for each SNP in the genome (displayed as −log10 of the p-value). Red and blue lines display $p=1\times10^{-6}$ line and $p=1\times10^{-5}$ respectively. Quantile-quantile plot for the empirical and theoretical distributions are shown as black and red lines, respectively.

Table 1

Sample Demographics and Clinical Characteristics

	Schizophrenia Patients (n=127)	Healthy Volunteers (n=136)	Statistic	p-value
Mean Age (SD)	39.1 (11.2)	38.6 (11.4)	t_{261}=0.35	0.73
Sex (Male/Female)	106/21	98/38	χ^2_1=4.91	0.03
Handedness[a] (bilateral/left/right)	3/10/114	2/6/128	FET	0.46
Subject Education[b] (SD)	4.6 (1.0)	5.8 (0.9)	t_{261}=11.46	<0.0001
Parental Education[b] (SD)	5.7 (1.8)	5.8 (1.5)	t_{261}=0.20	0.66
Race			FET	0.31
American Indian or Alaskan Native	2	2		
Asian	18	10		
Black or African American	20	17		
Native Hawaiian or Pacific Islander	1	1		
White	86	106		
NAART	29.3 (12.8)	40.7 (11.4)	t_{258}= −7.55	<0.0001
Age at Onset	21.5 (6.6)			
Duration of Illness	17.7 (11.2)			
PANSS positive	15.4 (5.0)			
PANSS negative	14.6 (5.5)			
PANSS general	28.5 (7.5)			
PANSS composite	0.8 (6.4)			

FET=Fisher's Exact Test; NAART=North American Adult Reading Test; PANSS=Positive and Negative Syndrome Scale;

[a]Based on the Edinburgh Handedness Inventory;

[b]Based on the Hollingstead Socioeconomic Status Scale.

Table 2

Genetic variants associated with cognitive domains.

	rsID	CHR	BP	A1	BETA	STAT	p-value	Gene
Speed of Processing	rs1149530	7	16848375	T	0.77	5.1	6.4×10^{-7}	
	rs818800	7	16846521	G	0.73	4.9	1.4×10^{-6}	
	rs11763030	7	16887616	A	0.62	4.9	1.9×10^{-6}	
Attention/Vigilance	rs830786	8	76355875	T	−1.5	−5.6	4.9×10^{-8}	*HNF4G*
	rs75131442	8	76831979	T	−1.8	−5.3	3.3×10^{-7}	
	rs79963003	8	76874205	A	−1.6	−5.2	4.0×10^{-7}	
Working Memory	rs17511050	4	133842651	T	−1.4	−5.3	2.8×10^{-7}	
	rs148396385	2	151173721	G	−1.0	−5.3	2.9×10^{-7}	
	rs17396139	4	162285366	C	−0.42	−5.2	4.0×10^{-7}	
Verbal Memory	rs67017972	5	53071288	A	0.60	5.7	4.3×10^{-8}	*NDUFS4*
	rs7164861	15	89125815	T	−1.3	−5.4	1.6×10^{-7}	
	rs78096325	9	20207963	A	−1.2	−5.2	3.3×10^{-7}	
Visual Memory	rs776010265	9	126073408	G	−0.49	−5.0	1.0×10^{-6}	
	rs2900031	14	48879362	T	0.59	5.0	1.4×10^{-6}	
	rs7156750	14	48885146	T	0.48	4.9	1.7×10^{-6}	
Reasoning/Problem Solving	rs74412765	14	34522904	T	−1.7	−5.7	3.2×10^{-8}	*LOC102724945*
	rs76872642	7	18669403	A	−3.4	−5.6	5.3×10^{-8}	*HDAC9*
	rs114499642	13	104628385	G	−2.6	−5.6	6.0×10^{-8}	
CMINDS Composite Score	rs150466277	19	50957600	C	−2.8	−5.4	1.4×10^{-7}	
	rs80284955	18	41042547	G	−1.1	−5.3	2.5×10^{-7}	
	rs185342442	13	98503979	G	−3.1	−5.2	3.9×10^{-7}	

rsID=SNP ID; CHR=chromosome; BP=base pair position; A1=minor allele; BETA=regression coefficient; STAT=t-statistic; Gene=lists a known gene near SNPs that are significant at about $p<5.0\times10^{-8}$.

Table 3

Gene set analysis based on GWAS results identified unique (non-shaded) and shared genes (shaded) associated with cognitive domain scores

Speed of Processing	p-value	Attention/Vigilance	p-value	Working Memory	p-value	Verbal Memory	p-value	Visual Memory	p-value	Reasoning/Problem Solving	p-value	CMINDS Composite Score	p-value
AGR2	0.0002	ACD	0.00077	ACD	0.00017	C10orf25	0.00095	ADH1A	0.00115	APIP	0.00044	ACD	0.00041
AGR3	0.0004	ABCB1	0.00076	BRF2	0.00010	DTYMK	0.00057	AGAP11	0.00109	BAG4	0.00068	ABCA11P	0.00069
ANGEL1	0.0009	ACTR3	0.00092	C5orf22	2.31E-005	FAM200B	0.00092	ALOX12	0.00011	CATSPER2	0.00052	ALOX12	0.00032
ANGEL2	0.0010	C16orf86	0.00077	C16orf86	0.00017	GCSAML	0.00097	ARL6	0.00064	CHN1	0.00048	C16orf86	0.00041
ATF1	0.0016	C19orf48	0.00014	CCDC42B	0.00029	GTF2H1	0.00011	C17orf49	0.00058	CKMT1B	0.00048	C17orf49	0.00078
BTD	0.0010	CBWD6	0.00074	CTCF	0.00033	HOXD-AS1	0.00035	CAMK2N2	0.00064	CLTA	0.00082	BLVRA	0.00105
CDH1	0.0002	CEBPA	0.00084	DDX54	0.00045	HOXD-AS2	0.00048	COL28A1	0.00039	CYP2A13	0.00033	BRINP2	0.00061
CDH3	0.0002	CEBPA-AS1	0.00065	E2F2	0.00029	HOXD1	0.00080	DACT2	5.89E-005	CYP2F1	0.00058	ATP6V1B1	0.00110
DIO3	0.0017	ENKD1	0.00077	ENKD1	0.00017	HOXD3	0.00017	DDOST	0.00100	DDHD2	0.00031	ENKD1	0.00041
DIO3OS	0.0007	EVPLL	0.00063	FAM102A	0.00048	HOXD4	0.00010	DNALI1	9.88E-005	FGFR1	0.00011	CCDC116	0.00033
FLJ43681	0.0017	FKBP9	0.00086	GPR124	0.00016	HOXD8	0.00094	ECE2	0.00061	FKBP9	0.00015	DCLK3	0.00034
HIF1AN	0.0011	FOXD4L6	0.00075	GFOD2	0.00025	HSPA13	0.00044	FAM25A	0.00044	HIC1	0.00065	GFOD2	0.00083
HSPA8	0.0016	HSPA8	0.00029	IQCD	0.00039	ING5	0.00034	GLUD1	0.00123	KLRG2	0.00069	EIF4E3	0.00093
HYAL1	0.0015	HAX1	0.00059	IRF4	0.00048	LDHA	0.00039	GNL2	0.00043	LETM2	0.00012	C9orf92	8.59E-005
LINC00687	0.0012	KLK1	4.38E-006	KLK1	0.00040	LDHC	0.00075	LOC101927780	0.00060	MEPCE	0.00057	FARP2	0.00053
LOC101927881	0.0014	KLK15	3.01E-006	KLK15	0.00030	LOC101928869	0.00052	LINC00656	0.00061	MIR132	0.00074	GSTM2P1	0.00071
NDUFB8	0.0007	KLK3	1.66E-006	KLK3	0.00014	LOC102800310	0.00033	LOC101928035	0.00105	MIR1343	0.00067	LOC100289361	0.00068
LOC442497	0.0013	KLK2	3.07E-006	LOC100506178	0.00045	MATR3	0.00025	LINC00458	4.16E-005	MIR212	0.00075	LINC00458	0.00068
LRRC74	0.0014	KLKP1	6.88E-006	LOC401320	0.00039	MIR10B	0.00017	LOC100506713	0.00011	MIR6840	0.00057	LOC100506713	0.00039
LOC341056	0.0012	LOC341056	0.00082	MIR6762	0.00048	MIR1228	0.00093	LOC101929420	4.04E-006	OR5A1	0.00083	LOC101927750	0.00068
MIR4311	0.0011	LARS2-AS1	0.00100	MIR7106	0.00039	MIR4781	0.00062	MIR1470	0.00024	OR5A2	0.00036	MIR130B	0.00067
MIR6872	0.0012	LINC01210	0.00066	MPZ	0.00045	MZB1	0.00088	MIR195	0.00071	OR5AN1	0.00069	MIR195	0.00094
MYF6	0.0012	LOC100499194	0.00031	NEUROD6	3.34E-005	NDUFA4L2	0.00044	MIR497	0.00071	PILRB	0.00050	MIR497	0.00094
MCEMP1	0.0012	LAMA4	0.00056	R3HCC1L	0.00035	NOMO3	0.00049	MIR497HG	0.00071	PMS2P1	0.00035	MIR497HG	0.00094
NHEG1	0.0004	LOC440896	0.00075	PPM1B	0.00011	NXPH4	0.00073	PPM1B	0.00024	PPAPDC1B	0.00029	PPM1B	0.00012
NPBWR2	0.0010	MGC45922	8.75E-006	PTN	0.00013	OR10S1	0.00030	PAQR9	0.00073	PPP1R35	0.00081	PAQR9	0.00074
OPRL1	0.0017	PARD6A	0.00077	PARD6A	0.00017	OR2G2	0.00030	MN1	9.86E-005	PVRIG2P	0.00069	PARD6A	0.00041
PCP2	0.0017	OR5AR1	0.00052	RASAL1	0.00026	OR4D5	0.00014	PPIL2	0.00013	RP9P	0.00028	PPIL2	0.00018

Speed of Processing	p-value	Attention/Vigilance	p-value	Working Memory	p-value	Verbal Memory	p-value	Visual Memory	p-value	Reasoning/Problem Solving	p-value	CMINDS Composite Score	p-value
RETN	0.0010	OR5M11	0.00080	RNU6-83P	0.00018	OR6T1	9.57E-005	PINK1-AS	0.00114	RNU6-83P	0.00012	MIR301B	0.00067
RPS6KC1	0.0006	OR5M3	0.00061	RLTPR	0.00044	OR8D4	0.00026	MIR5581	0.00116	SERF2	0.00078	RLTPR	0.00069
SEC31B	0.0009	RUNDC3B	0.00057	RUNDC3B	0.00011	PAIP2	0.00095	PROK2	0.00047	SLC4A4	0.00063	RNASE10	0.00071
SEMA3B-AS1	0.0015	OR5M9	0.00082	SDHC	0.00038	RPF2	0.00021	RNASEK	0.00046	SMG6	0.00018	RNASEK	0.00066
SLC35D3	0.0011	OR9G1	0.00084	SLC25A40	0.00033	SHMT2	0.00062	RNASEK-C17orf49	0.00056	SPDYE3	0.00021	RNASEK-C17orf49	0.00074
STXBP2	0.0014	OR9G9	0.00084	SPRR2B	0.00047	SLC23A1	0.00077	SNIP1	0.00023	SRSF10	0.00030	SDF2L1	0.00038
TFDP2	0.0007	MIR6778	0.00097	SPRR2E	0.00036	SNHG4	0.00032	TFAMP1	0.00105	STAG3L5P	0.00043	STK25	0.00089
TMEM225	0.0015	PGM5P2	0.00075	SPRR2F	0.00032	TMEM225	0.00055	TFAP2B	0.00071	STAG3L5P-PVRIG2P-PILRB	0.00040	TMEM225	0.00044
WNT8B	0.0011	OR5M8	0.00035	THAP11	0.00049	SPRN	0.00088	UBE2L3	0.00087	STRC	0.00072	UBE2L3	0.00099
TUSC2	0.0016	SNORD88C	0.00030	TPCN1	0.00048	STAC3	0.00036	YPEL1	0.00033	TBX21	0.00090	YPEL1	0.00033
TSNAXIP1	0.0012	SOX14	0.00086	TSNAXIP1	0.00045	SNORA74A	0.00036	WIZ	0.00039	WHSC1L1	0.00011	YDJC	0.00058
ZNF596	0.0017	TOP3A	0.00084	ZNF596	0.00032	TMEM59	0.00082	ZNF121	0.00105	ZCWPW1	0.00069	VAX2	0.00012

The shaded genes are associated with two or more cognitive domains presented on the same row.