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Association study of MiRSNPs with schizophrenia, tardive dyskinesia and cognition

Jibin John[a], **Triptish Bhatia**[b], **Prachi Kukshal**[a], **Puneet Chandna**[c], **Vishwajit L. Nimgaonkar**[d], **Smita N. Deshpande**[b], and **B.K. Thelma**[a,*]

[a]Department of Genetics, University of Delhi South Campus, Benito Juarez Road, New Delhi 110 021, India

[b]Department of Psychiatry, PGIMER-Dr. RML Hospital, New Delhi 110 001, India

[c]AceProbe Technologies (India) Pvt. Ltd., New Delhi, India

[d]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA

Abstract

MicroRNAs (miRNAs) bind to 3′UTRs of genes and negatively regulate their expression. With ~50% of miRNAs expressing in the brain, they play an important role in neuronal development, plasticity, cognition and neurological disorders. Conserved miRNA targets are present in > 60% genes in humans and are under evolutionary pressure to maintain pairing with miRNA. However, such binding may be affected by genetic variant(s) in the target sites (MiRSNPs), thereby altering gene expression. Differential expression of a large number of genes in postmortem brains of schizophrenia (SZ) patients compared to controls has been documented. Thus studying the role of MiRSNPs which are underinvestigated in SZ becomes attractive. We systematically selected 35 MiRSNPs with predicted functional relevance in 3′UTRs of genes shown previously to be associated with SZ, genotyped and tested their association with disease, using independent discovery and replication samples (total $n = 1017$ cases; $n = 1073$ controls). We also explored genetic associations with two sets of quantitative traits, namely tardive dyskinesia (TD) and cognitive functions disrupted in SZ in subsets of the study cohort. In the primary analysis, a significant association of MiRSNP rs7430 at *PPP3CC* was observed with SZ in the discovery and the replication samples [discovery: $P = 0.01$; OR (95%CI) 1.24 (1.04–1.48); replication: $P = 0.03$; OR (95%CI) 1.20 (1.02–1.43)]. In the exploratory analyses, five SNPs were nominally associated with TD (P values 0.04–0.004). Separately, 12 SNPs were associated with one or more of the eight

*Corresponding author. thelmabk@gmail.com (B.K. Thelma).

Contributors

Prof. B.K. Thelma, Prof. S. N. Deshpande and Prof. V. L. Nimgaonkar designed the study and wrote the protocol. Mr Jibin John prioritized and genotyped the SNPs in the replication phase, performed statistical analysis and wrote the first draft of the manuscript. Dr Puneet Chandna contributed to the genotyping. Prof. S. N. Deshpande and her team provided the research samples and Dr. T. Bhatia did the cognitive analysis and Dr. Prachi Kukshal contributed to the statistical analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest in relation to the subject of this study.

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cognitive domains (*P* values 0.05–0.003). These associations, particularly the SNP at *PPP3CC* merit further investigations.

Keywords

MiRSNP; Schizophrenia; Tardive dyskinesia; Cognition; Association study; 3′-Untranslated region (3′-UTR)

1. Introduction

Genetic heterogeneity combined with variable phenotypic expressivity in schizophrenia (SZ) has made it difficult to dissect the pathogenesis of this common, complex neuropsychiatric disorder. Of the 60 to 83% heritability estimated for this disorder (Cannon et al., 1998; Lichtenstein et al., 2009), a major proportion remains to be explained (Lee et al., 2012). Recent genome wide association studies (GWAS) have identified several common SNPs as risk factors, supporting the polygenic inheritance of SZ (Purcell et al., 2009). However, ~90% of the associated variants from GWAS are localized to non-coding regions of the genome – a situation similar to other genetically complex disorders. Though the functional significance of these associated variants remains obscure, some may influence gene expression (Richards et al., 2012). Differential expression of a number of genes involved in neurodevelopment, neurotransmitter mediated signaling pathways, immune response and other signaling pathways has been observed in both blood/lymphoblastoid cell lines and postmortem brain samples of SZ patients compared with suitable controls (Harrison, 1999; Harrison and Weinberger, 2005; Michel et al., 2012; Schmitt et al., 2011). Variation in gene expression is controlled by both *cis* and *trans* acting loci. Further, polymorphisms at these loci can also influence gene expression (Kim et al., 2012b). The majority, ~69–80% of these variants act in a cell type dependent manner (Dimas et al., 2009), but the mechanism by which they affect gene expression in health and disease is largely unknown.

Approximately half of all protein coding genes in mammals are thought to be under the regulation of microRNAs (miRNAs) (Krol et al., 2010), which are ~22 nucleotide long single stranded non coding RNA molecules, that negatively regulate gene expression (Schanen and Li, 2010). Most of the cellular processes are directly or indirectly influenced by miRNAs by base pairing to 3′UTR regions of target mRNA genes and lead to either mRNA cleavage or translation repression based on miRNA-target mRNA complementarity (Nilsen, 2007). miRNA-mRNA base pairing mediated regulation of gene expression can be influenced by several factors, including chromosomal abnormalities encompassing miRNA genes (Calin and Croce, 2006), their epigenetic modifications (Fabbri et al., 2013), genetic variants in the miRNA and their targets and proteins involved in miRNA processing (Ryan et al., 2010). Roughly 50% of all known miRNAs are expressed in mammalian brains (O'Carroll and Schaefer, 2013). Spatio-temporal and sex related expression patterns of miRNAs in brains of humans are observed and the target genes of these miRNAs are mainly associated with various neurodevelopmental processes/disorders and transcriptional regulation (Ziats and Rennert, 2013). Conserved miRNA targets are present in >60% of protein coding genes in humans and are also under evolutionary pressure to maintain pairing

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with miRNA (Friedman et al., 2009). Such binding may be affected by ins/del variations or SNPs located in the target site of the miRNAs (MiRSNPs), which could create a new binding site or abolish an existing one or may modulate the strength of binding. Thus, MiRSNPs can affect gene expression and may have influence on phenotypic variability and risk of various diseases (Chen et al., 2008).

Regulatory functions of miRNAs in nervous system range from all stages of neuronal development to plasticity, cognitive functions and several neurological disorders and disease (Fiore et al., 2011). miRNAs are differentially expressed in brains of SZ patients compared to controls (Beveridge and Cairns, 2011). Similarly, differential expression of genes involved in miRNA processing among cases and controls has also been reported (Zhou et al., 2012).

Furthermore, association of SNPs in miRNAs with SZ have been reported (Beveridge and Cairns, 2011). On the other hand, MiRSNPs have also been identified among SNPs reported in Chinese SZ GWAS and brain eQTLs (Liu et al., 2012). Association of MiRSNPs has also been reported in an independent candidate gene based association study in a Chinese population (Gong et al., 2013). This association though modest, reiterates the likely role of MiRSNPs in SZ pathogenesis. With this background, we primarily aimed at investigating the association of MiRSNPs in well investigated candidate genes with SZ in genetically distinct north Indian cohorts. Several of these genes are also reported to be associated with tardive dyskinesia (TD), an iatrogenic disorder observed in a subset of SZ patients and to a lesser extent in cognition. Further, the role of MiRSNPs in TD or in cognition has not been reported. Therefore, we also explored the association of the selected SNPs with these two quantitative traits in the study cohort.

2. Materials and methods

2.1. Sample recruitment and diagnostic assessment

Recruitment of the participants with SZ and controls (adult/cord blood) and inclusion criteria have been previously described (Kukshal et al., 2013; Tiwari et al., 2007, 2005a). Briefly, patients diagnosed with SZ or schizoaffective disorder conforming to DSM IV criteria were consented and were recruited from PGIMER-Dr. RML Hospital, New Delhi. All participants were assessed using the Hindi version of the Diagnostic Interview for Genetic Studies (DIGS) and the Family Interview for Genetic Studies (FIGS) (Deshpande et al., 1998; Nurnberger et al., 1994). Controls in the study comprised of adults and cord blood samples. Written informed consent was obtained from all the adult participants. Cord blood controls were collected from anonymous discarded placenta, with institutional ethical committee clearance and approval from the participating hospitals. The study was approved by the institutional ethical committees of all participating institutions.

The participants were divided into two groups: a discovery sample composed of 496 patients and 522 controls and a replicative sample composed of 521 patients and 551 controls (457 were cord blood controls). Two different subsets of the discovery cohort were used for association with TD and cognition.

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2.2. Assessment of tardive dyskinesia

A subset of SZ patients assessed for TD at the time of recruitment of the participants for genetic analysis, were included in this study (Tiwari et al., 2005b). Briefly, TD was assessed using the Abnormal Involuntary Movement Scale (AIMS). A total of 91 SZ patients were diagnosed with TD (denoted as TD-Y Mean AIMS score 6.19 ± 3.38) and 161 were without TD (TD-N). 26 of the 91 TD-Y cases received first generation antipsychotic medications (duration of schizophrenia 11.8 ± 8.67 years; mean AIMS score 6.54 ± 3.6), 23 received atypical antipsychotic drugs (duration of schizophrenia 6.86 ± 5.08 years; mean AIMS score 5.69 ± 3.17) and 42 were treated with both sets of antipsychotic drugs at different times during their illness (duration of schizophrenia 10.40 ± 8.40 years; mean AIMS score 6.24 ± 3.31). Although the data on the class of drugs that was received by the patients was available, no reliable information on drug dosage could be documented as detailed in our previous published papers on TD (Tiwari et al., 2005a, 2005b). Research diagnostic criteria (a total of two mild or at least one moderate or higher rating in any of the symptoms) was used for classifying SZ patients as tardive dyskinesia positive or tardive dyskinesia negative and only this status was used for association analysis.

2.3. Neurocognitive assessment

Cognitive assessment was performed using the Hindi version of University of Pennsylvania Computerized Neurocognitive Battery (Penn CNB) as described in our previous studies (Bhatia et al., 2012; Kukshal et al., 2013). The Penn CNB estimates variation in eight selected cognitive domains known to be impaired among patients with SZ, namely abstraction and mental flexibility, attention, face memory, spatial memory, working memory, spatial ability, sensorimotor and emotional processing. It was administered to a subset of SZ cases ($n = 152$; 96 males and 56 females; mean age 31 ± 9.54 years) and adult controls ($n = 292$; 181 male and 111 female; mean age 38 ± 14.17 years) at the time of recruitment. The Penn CNB estimates accuracy and speed for each cognitive domain. As they are correlated, only the accuracy indices were used for the genetic analyses. The Penn CNB data of participants is automatically stored at CNB site at University of Pennsylvania. Normalized Z scores retrieved from the repository at Penn CNB for the eight selected cognitive domains namely abstraction and mental flexibility, attention, face memory, spatial memory, working memory, spatial ability, sensorimotor and emotional processing were used for association testing.

2.4. Selection of MiRSNPs

As mentioned earlier, this study was aimed at investigating the association of MiRSNPs in known SZ candidate genes with SZ, TD and cognition using case-control approach. MiRSNPs to be included in the study were prioritised as detailed below.

- 100 top ranked candidate genes from schizophrenia gene resource (Jia et al., 2010) (http://bioinfo.mc.vanderbilt.edu/SZGR) were selected. In addition, since a considerable number of candidate gene based association studies in SZ as well as TD and to some extent cognition, are from the dopaminergic pathway, genes from this pathways were also included.

- 611 3′UTR SNPs from dbSNP (http://www.ncbi.nlm.nih.gov/snp) with minor allele frequency (MAF) >0.01 (since the focus of the study is to investigate the role of common variants) which were distributed over 92 of the selected genes mentioned above were selected. In the remaining genes, the MAF of 3′UTR SNPs was <0.01 and therefore not included for further analysis.
- 254 MiRSNPs from among the 611 SNPs listed above were identified (Barenboim et al., 2010) (http://cbdb.nimh.nih.gov/microsniper).
- The binding strength of miRNA to its target mRNA is usually measured by minimal Gibbs free energy (MFE) (Rusinov et al., 2005). In general, the greater the MFE, the higher the strength of miRNA-mRNA pairing, with a related negative impact on gene expression. The MFE difference between variant and wild type alleles were calculated using RNA Hybrid software (Rehmsmeier et al., 2004) (http://bibiserv.techfak.uni-bielefeld.de/rnahybrid) and MiRSNPs showing E difference 1.5 KCal/mol between the alleles, were prioritized.
- Co-expression of target gene and miRNA(s) in brain tissues is an essential requirement for pairing between miRNA and its target site in 3′UTR. Accordingly, expression of miRNA in brain tissue was checked using microRNA.org (http://www.microrna.org/microrna/home.do) and 59 SNPs from 46 genes that bind to at least one miRNA expressed in the brain were selected.
- Of these, a total of 35 MiRSNPs that could be genotyped reliably by MassARRAY® System by Agena Bioscience™ were finally included in the study (Supplementary Table 1). Of note, miRNA 137 was reported to be significantly associated with SZ based on a genome-wide association study (Ripke et al., 2011). However, this miRNA does not have any binding site in the 3′UTR of the gene that we prioritised for the study.

2.5. Genotyping

All participants provided 5 ml each of venous blood for genetic analysis. Genomic DNA was extracted using conventional phenol chloroform method, routinely used in the laboratory. All the MiRSNPs (N=35) were assayed using MassARRAY® System at a commercial facility (Aceprobe Technologies, India). SNP(s) associated with SZ in discovery cohort were genotyped in the replication cohort using PCR-RFLP. Briefly, forward and reverse primers were designed using Primer3 software and used for PCR amplification. Amplified products were genotyped by RFLP, using Tail restriction enzyme (Supplementary Table 2) and resolved on 2% agarose gel.

2.6. Statistical analysis

Hardy Weinberg equilibrium (HWE) for each SNP genotyped was checked using PLINK. All SNPs in HWE ($p > 0.001$) were included in the association analyses. Associations of MiRSNPs with SZ or TD were evaluated using Trend test in PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/). The power of the combined study sample was calculated using Quanto software (Gauderman, 2006). Linear regression analysis to

determine the association between the SNPs and different cognitive domains, using the normalized accuracy scores was performed separately by SPSS ver. 14.

3. Results

Demographic details of the study cohort are provided in Table 1.

3.1. Genotyping quality control

All the 35 SNPs were in HWE ($p > 0.001$).rs17036056 and rs7124665 were monomorphic and were excluded from the study. Individuals with genotype failure of 3SNPs were discarded from the study. Thus, a total of 490 cases and 518 controls and 33 SNPs were included for association analysis. Each MassARRAY® assay plate included a CEPH sample as a known positive control, one negative control and a duplicate sample as plate control. All these samples produced concordant results.

3.2. Tests of genetic associations

3.2.1. Primary analyses: associations with SZ—Of the 33 SNPs tested, only one MiRSNP namely rs7430 from *PPP3CC* showed significant association with SZ [$\chi^2 = 5.85$; $P = 0.01$; OR (95% CI) 1.24 (1.042–1.48)] in the discovery cohort. The association was also detected in the replication sample [$\chi^2 = 4.54$; $P = 0.03$; OR (95% CI) 1.20 (1.02–1.43)] and in combined analysis of two cohorts [$\chi^2 = 10.38$; $P = 0.001$; OR (95% CI) 1.22 (1.08–1.38)] with >80% power.

3.2.2. Exploratory analyses with tardive dyskinesia—Five MiRSNPs one each from *MTHFR, SCN1A, PIP4K2A, CLDN5* and *GCLM* showed allelic association with TD (Table 2). The power of the analyses ranged from 36 to 96%.

3.2.3. Exploratory analyses with cognitive domains—Nominal association of MiRSNPs from 12 candidate genes was observed with one or more measures of the cognitive domains assessed in this study (Table 3). There was no overlap between the miRNAs which were binding to each of these target genes (Table 3).

4. Discussion

A few studies have reported on the association of regulatory SNPs at miRNA binding sites with risk for SZ but none have been reported in relation to quantitative traits such as TD and cognition. Of the 33 MiRSNPs from 32 candidate genes tested in this study rs7430 from *PPP3CC* was associated with SZ in two independent samples. *PPP3CC* codes for calcineurin catalytic γ subunit (CNA), which is a calcium-dependent serine/threonine protein phosphatase involved in the downstream regulation of dopaminergic signal transduction (Greengard, 2001), Long Term Depression (LTD) (Mulkey et al., 1994) and bidirectional plasticity (Mulkey et al., 1994; Zeng et al., 2001). Decreased hippocampal expression of this gene in SZ has been reported (Eastwood et al., 2005). Furthermore, this gene is located at chromosome 8p21.3, one of the chromosomal regions linked to SZ in early family based studies (Gerber et al., 2003). SNPs at this gene have also been reported to be associated with SZ in different populations (Horiuchi et al., 2007; Liu et al., 2007). Further, rs7430, the

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associated SNP is localized to the putative binding sites of two miRNAs, namely hsa-miR-662 and hsa-miR-657. The SNP is predicted to have functional impact, as *in silico* analysis indicates differential binding affinity of its wild type and variant alleles (Supplementary Table 1).

The five MiRSNPs associated with TD were localized to different genes. The strongest association was observed with the MiRSNP in *SCN1A*, that encodes the alpha subunit of voltage gated sodium channel NaV1.1 and it is essential for generation and propagation of action potential in nerve cells. However, the exact role of this gene in the pathogenesis of TD is uncertain. On the other hand, *GCLM* codes for the first rate-limiting enzyme in glutathione synthesis and its decreased expression in SZ patient fibroblasts (Tosic et al., 2006) and in peripheral blood of SZ patients (Che et al., 2009) has been reported. A number of studies have reported that oxidative stress is involved in the pathophysiology of TD (Thelma et al., 2007), providing a testable mechanism underpinning the genetic association. *MTHFR*, a commonly investigated candidate gene in SZ is essential for the conversion of homocysteine to methionine. In TD positive cases a higher homocysteine level is reported (Lerner et al., 2005), thus the nominal association of MiRSNP rs4846049 in *MTHFR* in our study may also have a functional basis. The observed association of MiRSNP rs10734041 in *PIP4K2A* is consistent with a prior reported association with TD in a Caucasian ancestry sample (Fedorenko et al., 2014). Further, *PIP4K2A* is involved in G-protein coupled receptor mediated signaling and may provide protection against apoptosis and the stress response (van den Bout and Divecha, 2009).

A total of 12 MiRSNPs associated with one or more of cognitive domains (Table 3) are from strong SZ candidate genes, which are directly or indirectly involved in neurotransmitter signaling processes and these are individually discussed below. Of these, MiRSNPs from *MTHFR*, *PIP4K2A and SCN1A* associated with TD and described in the preceding section were also seen to be associated with one or more cognitive domains. Of the associated genes, *CACNA1B* encodes the pore-forming subunit of an N-type voltage-dependent calcium channel, which facilitates Ca^{2+} entry, thus promoting neurotransmitter release and synaptic transmission (Catterall, 2000). *CACNA1A* a paralog of this gene has been implicated for various cognitive functions (Alonso et al., 2008). *IL1RN* codes for Interleukin-1 receptor antagonist (IL-1RA) which inhibits the activities of interleukin 1, alpha (IL1A) and interleukin 1, beta (IL1B), and modulates a variety of IL-1 related immune and inflammatory responses. Low levels of IL-1RA expression in the prefrontal cortex of SZ patients has been reported (Toyooka et al., 2003) and elevated serum levels of IL-1RA in bipolar disorder patients were associated with impaired cognitive function (Lotrich et al., 2014). It is also known that post-operative cognitive declines can be prevented by intracisternal administration of il-1ra in aged rats (Barrientos et al., 2012).

PIP4K2A, another gene found to be associated with cognition is involved in phosphoinositide signal transduction pathway and consequently modulates AKT activity. AKT signaling pathway is known to be associated with cognitive impairments (Shu et al., 2013). Expression of *PIP4K2A* mRNA was also reported to be significantly increased in lymphocyte cell lines derived from schizophrenia patients (Saggers-Gray et al., 2011). Early Growth Response3 *(EGR3)* is an early gene transcription factor, expressed throughout the

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brain (Beckmann and Wilce, 1997), playing an important role in neuronal development, synaptic plasticity, learning and memory processes (O'Donovan et al., 1999) It is also involved in the regulation of NMDA receptor levels in cortical neurons (Kim et al., 2012a) and various cognitive processes like learning and memory (Poirier et al., 2008). EGR3 transcript is known to be down regulated in the prefrontal cortex of SZ patients (Yamada et al., 2007). Notably different laminar patterns of COMT mRNA expression in pyramidal neurons has been observed in SZ cases compared to controls (Matsumoto et al., 2003). Association of *COMT* with various cognitive functions has been reported (Simpson et al., 2014). *DISC1* is a major risk gene in SZ with an important role in neuronal maturation, proliferation, migration, positioning, differentiation, dendritic growth, axonal outgrowth, and synaptic plasticity through its direct or indirect interactions with various signaling pathways in brain including AKT, GABA, GSK3β, WNT, and NMDA-R (Wu et al., 2013). Its role in cognition has been documented (Burdick et al., 2005; Thomson et al., 2013). Differential expression of *NRG1* transcripts was observed in postmortem brains of SZ patients compared to controls (Hashimoto et al., 2004). This gene is also reported to be associated with cognition (Alfimova et al., 2011; Kukshal et al., 2013). Various studies in mice have shown that *NRG1* is associated with various cognitive functions and social behavior (Kato et al., 2010; O'Tuathaigh et al., 2007). *SCN1A* has been discussed in the preceding section on TD. Knock down of this gene in basal forebrain region in rats induces cognitive impairments without seizure (Bender et al., 2013). As for *MAOB*, an important gene from the dopaminergic pathway, animal studies have reported its role in various cognitive functions (Singh et al., 2013). *SYN2* codes for neuronal phosphoproteins associated with the cytoplasmic surface of synaptic vesicles, and are implicated in synaptogenesis and the modulation of neurotransmitter release, suggesting a potential role in several neuropsychiatric diseases (Lee et al., 2005). Decreased expression of *SYN2* is reported in brains of SZ patients (Mirnics et al., 2000) *SYN2* knockout mice demonstrate deficits in cognition and neuronal loss and gliosis during senescence (Corradi et al., 2008). *CHGB* encodes a tyrosine-sulfated secretory protein abundant in peptidergic endocrine cells and neurons and may serve as a precursor for regulatory peptides. Differential expression of this gene is reported in SZ postmortem brain samples compared to controls (Chu and Liu, 2010). *MTHFR* is associated with TD and has been discussed in TD section. This gene is also known to be associated with cognition (Ford et al., 2012) and higher homocysteine levels are reported with cognitive dysfunction (Lerner et al., 2005).

In summary, we report on plausible associations between MiRSNPs associated with SZ and TD. Other associations with cognitive domains were also noted. All the associations merit further investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2016.03.031.

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Table 1

Demographic details of the sample.

Study cohort	Discovery		Replication	
Samples (total)	**Cases (496)**	**Controls (522)**	**Cases (521)**	**Controls (551)[a]**
Males	279	319	291	273
Females	217	203	230	278
Mean age (range in years)	30.47 ± 9.97 (14 to 66)	39.34 ± 9.97 (15 to 60)	30.14 ± 8.76 (15 to 60)	33.13±10.51 (19 to 71)

[a]457 cord blood controls; mean age calculated for adult controls only

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Table 2

MiRSNPs associated with tardive dyskinesia among SZ patients.

Gene	SNP	χ^2	P	OR (95% CI)	Binding MiRNAs
SCN1A	rs10497275	8.50	0.004	0.42 (0.23–0.77)	hsa-miR-1286
GCLM	rs17881908	5.53	0.02	5.56 (1.11–27.89)	hsa-miR-582-3p
MTHFR	rs4846049	5.19	0.02	1.54 (1.06–2.24)	hsa-miR-555
PIP4K2A	rs10734041	4.70	0.03	0.26 (0.08–0.92)	hsa-miR-602
CLDN5	rs756654	3.90	0.04	1.53 (1.0–2.41)	hsa-miR-486-3p

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Table 3

MiRSNPs associated with accuracy index of cognitive domains.

GENE	SNP-id	Face memory	Emotion	Working memory	Spatial memory	Sensory motor and emotional processing	Attention	Abstraction and mental flexibility	Spatial ability	Binding MiRNAs
PIP4K2A	rs10734041	0.009	0.03	–	–	–	–	–	–	hsa-miR-602
EGR3	rs11136094	–	0.04	0.001	–	–	–	–	–	hsa-miR-940
COMT	rs165728	–	0.05	–	0.05	–	–	–	–	hsa-mir-654-5P
DISC1	rs16856322	–	–	–	–	0.03	0.03	–	–	hsa-miR-409-3p
NRG1	rs17731664	–	–	–	–	–	–	0.04	–	hsa-miR-641
										hsa-miR-3617-5p
										hsa-miR-199a-3p
										hsa-miR-208a
										hsa-miR-936
										hsa-miR-199b-3p
										hsa-miR-128
SCN1A	rs1813502	–	–	–	–	–	–	–	0.03	hsa-miR-1286
MAOB	rs2072745	–	–	–	–	–	–	–	0.02	hsa-mir-635
SYN2	rs2289708	–	0.005	–	–	–	–	–	–	hsa-miR-1908
CHGB	rs2821	–	–	0.003	–	–	–	–	–	hsa-miR-577
MTHFR	rs4846049	–	–	–	–	–	–	–	0.01	hsa-miR-555
IL1RN	rs9005	–	–	0.02	0.03	–	0.003	0.05	–	hsa-miR-1538
										hsa-miR-138-5p
CACNAIB	rs9414688	–	0.02	0.002		–	–	0.001	0.003	hsa-miR-760
										hsa-miR-627
										hsa-miR-760