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A novel risk variant block across introns 36–45 of *CACNA1C* for schizophrenia: a cohort-wise replication and cerebral region-wide validation study

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Abstract

Objectives: Numerous genome-wide association studies (GWASs) have identified *CACNA1C* as one of the top risk genes for schizophrenia. As a necessary *post*-GWAS follow-up, here, we focused on this risk gene, carefully investigated its novel risk variants for schizophrenia, and explored their potential functions.

Methods: We analyzed four independent samples (including three European and one African-American) comprising 5,648 cases and 6,936 healthy subjects to identify replicable SNP-schizophrenia associations. The potential regulatory effects of schizophrenia-risk alleles on *CACNA1C* mRNA expression in 16 brain regions (n=348), gray matter volumes (GMVs) of five subcortical structures (n=34,431), and surface areas (SA) and thickness (TH) of 34 cortical regions (n=36,936) were also examined.

Results: A novel 17-variant block across introns 36–45 of *CACNA1C* was significantly associated with schizophrenia in the same effect direction across at least two independent samples (1.8×10^{-4} p 0.049). Most risk variants within this block showed significant associations with *CACNA1C* mRNA expression (1.6×10^{-3} p 0.050), GMVs of subcortical structures (0.016 p 0.048), cortical SA (0.010 p 0.050) and TH (0.004 p 0.050) in multiple brain regions.

Conclusion: We have identified a novel and functional risk variant block at *CACNA1C* for schizophrenia, providing further evidence for the important role of this gene in the pathogenesis of schizophrenia.

Keywords

CACNA1C; schizophrenia; eQTL; gray matter volume; cortical surface area; cortical thickness

1. Introduction

Numerous genome-wide association studies (GWASs) have reported the α -1C subunit of the L-type voltage-gated calcium channel gene (*CACNA1C*, 12p13.3, Chr12:1948979–2677376 (b36), between *CACNA2D4* and *ITFG2-AS1*) as one of the top risk genes for schizophrenia. Many risk variants at *CACNA1C* have been associated with schizophrenia, some of which were replicated across multiple independent studies^{1–12}. However, this gene remains to be comprehensively investigated; in particular, the functional roles of most risk variants have yet to be thoroughly explored.

To build on GWAS findings, it is necessary to continue focusing on this risk gene. Recently, we examined 847 SNPs at *CACNA1C*, and identified a 20-SNP block at intron 3 that was consistently associated with schizophrenia across seven independent cohorts

(2.5×10^{-17} p 0.049). This block was also significantly associated with *CACNA1C* mRNA expression in the brain across three independent European cohorts (5.1×10^{-12} p 8.3×10^{-3}), and could be tagged by the most significant risk SNP, rs1006737 (meta-analysis of 17 studies: $p=1.62 \times 10^{-42}$)¹³. Moreover, rs1006737 was found to be significantly negatively associated with the gray matter volume (GMV) of thalamus ($p=0.010$), the surface area (SA) of isthmus cingulate cortex ($p=0.013$), and the thickness (TH) of transverse temporal and superior temporal sulcus cortexes (0.005 p 0.043)¹³. These pieces of evidence supported the most promising role of this variant block in schizophrenia risk.

However, *CACNA1C* is a large gene that is 730kb-long with 58 exons, and might harbor other missing risk variant blocks for schizophrenia. Therefore, in the present study, we aimed to identify those missing risk blocks independent of the previously-reported one, and explore their potential, and maybe distinct, regulatory effects on *CACNA1C* mRNA expression in the brain, subcortical GMVs, as well as cortical SA and TH, in order to complete the map of all risk variant blocks for schizophrenia across entire *CACNA1C*.

Usually, a GWAS examines variants across genome unbiasedly, and thus is subject to an overly-conservative Bonferroni correction ($\alpha=5 \times 10^{-8}$) to control for false positives, which may lead to the loss of some important information, e.g., missing critical findings with $5 \times 10^{-8} < p < 10^{-5}$, because, for most common diseases such as schizophrenia that involves many common variants with small effect sizes, most risk effects of individual variants are difficult to reach this significance level. The present study, as a *post*-GWAS follow-up, aimed to preserve the information as loosely as possible ($\alpha=0.05$), but control for false positives as strictly as possible using an alternative strategy, i.e., a series of replication and functional validation steps (detailed below). We examined replicable SNP-schizophrenia associations across multiple cohorts to ensure their robustness, and then demonstrated them to be biological, but not only statistical, associations by examining a series of potential regulatory effects on *CACNA1C* mRNA expression and brain structure.

2. Materials and Methods

2.1. Subjects

Four independent samples, comprising three European and one African-American population, were used for SNP-schizophrenia association analysis. Sample #1 was sourced from the GAIN dataset (dbGaP access number: phs000021.v3.p2), consisting of 1,350 European patients with schizophrenia and 1,378 healthy European controls. Sample #2 was obtained from the Ashkenazi Jewish dataset (phs000448.v1.p1), comprising 1,044 Jewish patients with schizophrenia and 2,052 healthy Jewish controls. Sample #3 was sourced from the Bulgarian Schizophrenia Trio Sequencing Study (phs000687.v1.p1), consisting of a total of 1826 European parent-offspring trio subjects, of which 621 were offspring with schizophrenia. Sample #4 was sourced from the GAIN dataset (phs000021.v3.p2), comprising 1,195 African-American patients with schizophrenia and 954 healthy African-American controls. Samples #1 and #2 were also examined in the previous study¹³.

All subjects included in the study were 18 years or older. Affected subjects met DSM-IV criteria for schizophrenia¹⁴. Subjects with neurological disorders, substance use disorders,

or mental retardation were excluded. Controls were free of schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, and psychotic symptoms such as auditory hallucination and persecutory delusion. Informed written consents were obtained from all subjects before participating in the study, which was reviewed and approved by the Human Investigation Committee of Yale University. Detailed demographic data for these samples have been published in previous studies^{15–18}.

2.2. SNP-disease association analysis

Genotyping, imputation (using IMPUTE2¹⁹), and data cleaning has been described in details earlier¹³. The allele frequencies of SNPs were compared between individuals with schizophrenia and controls using the Fisher exact test as implemented in the program PLINK²⁰, to examine the SNP-disease associations.

Although the Bonferroni correction is a commonly used method to correct for multiple comparisons, it may miss some weak but valuable SNP-disease associations. To avoid overly-conservative correction and preserve the information of modest SNP-disease associations, we used a replication and functional validation design. This approach allowed us to control for false positives by requiring the associations to be replicable in the same effect direction across at least two independent cohorts and the risk SNPs to be functionally validated. Only then, we considered them as statistically significant associations if the p-values for associations were close to 0.05.

2.3. *cis*-acting expression quantitative trait locus (*cis*-eQTL) analysis

To investigate the potential regulatory effects of schizophrenia-risk variants on the *CACNA1C* mRNA expression in human postmortem brains, we conducted *cis*-eQTL analysis on two independent cohorts: a UK European cohort (n=138) (BRAINEAC dataset)²¹ and a European-American cohort (n=210) (GTEx dataset)²². All subjects were free of significant neurodegenerative and neuropsychiatric disorders.

In the UK European cohort, we analyzed a total of 10 brain regions, including the cerebellar cortex, prefrontal cortex, hippocampus, medulla, occipital cortex, putamen, substantia nigra, temporal cortex, thalamus, and intralobular white matter. In the European-American cohort, we analyzed a total of 11 brain regions, including the basal ganglia (putamen, caudate, nucleus accumbens, and substantia nigra), limbic system [anterior cingulate cortex (BA24), amygdala, hippocampus, and hypothalamus], prefrontal cortex (Brodmann Area or BA9), cerebellum, and cerebellar hemisphere. To compare the normalized mRNA expression levels between different alleles of each variant, we used t-tests.

2.4. Regulatory effect of risk variants on the GMVs of subcortical structures

The potential regulatory effects of schizophrenia-risk variants on the GMVs of several brain regions were analyzed in a European sample (n=34,431; ENIGMA2 dataset)²³ using multiple linear regression analysis. Specifically, we focused on the nucleus accumbens, amygdala, brainstem, caudate, and thalamus. All subjects were free of neurodegenerative and neuropsychiatric disorders.

2.5. Regulatory effect of risk variants on cortical surface area and thickness

A total of 36,936 subjects, including 33,992 European (23,909 from 49 ENIGMA cohorts and 10,083 from the UK Biobank) and 2,944 non-European participants (eight cohorts)²⁴, were analyzed. Measures of cortical SA and TH were derived from *in vivo* whole brain T1-weighted MRI scans using FreeSurfer²⁵. The potential regulatory effects of schizophrenia-risk variants on 70 traits (total SA, average TH, and the SA and TH of 34 cortical regions averaged across right and left hemispheres) were analyzed using multiple linear regression. The analysis adjusted for the effects of sex, linear and nonlinear age effects, interactions between age and sex, ancestry (the first four MDS components), diagnostic status (when the cohort followed a case-control design), MRI acquisition orientation, scanner (when multiple scanners were used at the same site), and global measure (total SA or average TH).

3. Results

3.1. A variant block across introns 36–45 of *CACNA1C* was significantly associated with schizophrenia across multiple samples

Independent of the previously-reported risk variant block at intron 3 mentioned earlier¹³, we identified a novel 17-variant block (within block: $D' > 0.85$)¹³ spanning introns 36–45 of *CACNA1C* (Supplementary Figure S1). This new variant block was significantly associated with schizophrenia in at least two of the five independent samples we studied (1.8×10^{-4} p 0.049; Table 1). The risk allele of each variant had a significantly higher frequency in the cases (or “transmitted” group) than in the controls (or “untransmitted” group), and this was consistent across the samples. When further defining a block with $R^2 > 0.85$, this 17-variant block could be classified into three sub-blocks, i.e., classes #1, #2 and #3 harboring one, twelve and four SNPs, respectively (Figure S1; Table 1). Based on the three identified classes of alleles, we were able to distinguish between different functional patterns, as described below.

3.2. The schizophrenia-risk alleles were significantly associated with the *CACNA1C* mRNA expression in the brain

All seventeen risk variants within the variant block showed significant associations with *CACNA1C* mRNA expression in different brain regions, including the cerebellar, frontal (including anterior cingulate (ACC)), occipital, temporal cortices, and amygdala (1.6×10^{-3} p 0.050). Specifically, the schizophrenia-risk allele of class #1 (including rs2238096) showed significant positive associations with *CACNA1C* mRNA expression in the frontal, occipital, and temporal cortices (1.6×10^{-3} p 0.050); the schizophrenia-risk alleles of class #2 showed a significant positive association with *CACNA1C* mRNA expression in the cerebellar cortex, but a negative association with expression in amygdala (0.020 p 0.050); and the schizophrenia-risk alleles of class #3 showed a significant positive association with *CACNA1C* mRNA expression in ACC (0.012 p 0.042). (Table 1).

3.3. The schizophrenia-risk alleles were significantly associated with subcortical GMVs

Seven of the seventeen risk variants within the variant block (41%) showed significant association with the GMVs of subcortical structures, including the nucleus accumbens,

brainstem, and caudate (0.016 p 0.048). Specifically, the schizophrenia-risk allele of class #1 was positively associated with the GMVs of the caudate and brainstem (0.017 p 0.040); the schizophrenia-risk alleles of class #2 were negatively associated with the GMVs of the nucleus accumbens (0.034 p 0.048); and the schizophrenia-risk alleles of class #3 were positively associated with the GMVs of the nucleus accumbens and brainstem (0.016 p 0.028). (Table 2).

3.4. The schizophrenia-risk alleles were significantly associated with the cortical SA

All seventeen risk variants were significantly associated with the cortical SA of various brain regions, including frontal (pole, superior, and rostral middle), parietal (precuneus), temporal (pole), occipital (lateral, pericalcarine, lingual, and fusiform), and limbic [anterior (ACC) and posterior cingulate (PCC)] cortices (0.010 p 0.050). Specifically, the schizophrenia-risk allele of class #1 was positively ($\beta > 0$) associated with the SA of ACC ($p = 0.043$), but negatively ($\beta < 0$) with the SA of parietal (precuneus) and temporal (pole) cortices, and PCC (0.015 p 0.037); the schizophrenia-risk alleles of class #2 were positively ($\beta > 0$) associated with the SA of parietal (precuneus) cortex and PCC (0.010 p 0.050), but negatively ($\beta < 0$) with the SA of occipital (pericalcarine and fusiform) cortices (0.020 p 0.050); and the schizophrenia-risk alleles of class #3 were positively ($\beta > 0$) associated with the SA of occipital (lateral, pericalcarine, and lingual) cortices (0.017 p 0.047), but negatively ($\beta < 0$) with the SA of frontal (pole, superior, and rostral middle) cortices (0.025 p 0.048). (Table 3).

3.5. The schizophrenia-risk alleles were significantly associated with the cortical TH

Sixteen of the seventeen risk variants were significantly associated with the cortical TH, which includes the frontal (pars opercularis), occipital (lateral, pericalcarine, and fusiform), temporal (middle and inferior), and limbic (entorhinal) cortices (0.004 p 0.050). Specifically, the schizophrenia-risk allele of class #1 was positively ($\beta > 0$) associated with the TH of entorhinal cortex ($p = 0.039$), but negatively ($\beta < 0$) with the TH of frontal (pars opercularis) cortex ($p = 0.032$); the schizophrenia-risk alleles of class #2 were positively ($\beta > 0$) associated with the TH of occipital (fusiform), and temporal (middle and inferior) cortices (0.015 p 0.049); and the schizophrenia-risk alleles of class #3 were positively ($\beta > 0$) associated with the TH of occipital (pericalcarine) cortex (0.004 p 0.009), but negatively ($\beta < 0$) with the TH of occipital (lateral), and temporal (inferior) cortices (0.013 p 0.050). (Table 4).

Discussion

We comprehensively examined a large set ($n = 847$) of *CACNA1C* SNPs and identified two independent risk variant blocks associated with schizophrenia. The first block ($n = 20$), located in intron 3, has been reported before¹³, and was significantly associated with schizophrenia across four Psychiatric Genomics Consortium cohorts (PGC) cohorts^{3,11,12,26} and the GMV of thalamus¹³. The second block ($n = 17$), located in introns 36–45, is a novel finding and has distinct features from the first one, including that it was not associated with schizophrenia in those four PGC cohorts at all (data not shown), and was associated with the GMVs of multiple regions (see below) other than thalamus. These two blocks were

associated with mRNA expression, cortical SA and TH in different brain regions too (see below)¹³.

We observed significant associations between the seventeen variants within the second risk block and schizophrenia in our samples, with one of the schizophrenia-risk alleles being a major allele (class #1) and all of the others being minor alleles (classes #2 and #3) with distinct functional effects. All risk alleles in three classes were positively associated with *CACNA1C* mRNA expression in the cerebellar, frontal (including ACC), occipital, and/or temporal cortices, but risk alleles in class #2 were negatively associated with it in amygdala. Risk alleles in classes #1 and #3 were positively associated with the GMVs of nucleus accumbens, brainstem, and/or caudate, but risk alleles in class #2 were negatively associated with the GMVs of nucleus accumbens. Additionally, risk alleles were significantly associated with the SA or TH in multiple regions. These findings suggest that *CACNA1C* might play a critical role in the pathogenesis of schizophrenia.

Most of the published studies reported reduction of cortical GMVs²⁷⁻³⁰ and enlargement of basal ganglia GMVs^{27,31-34} in schizophrenia. Our study found that the schizophrenia-risk alleles of classes #1 and #3 potentially increased the GMVs of caudate and nucleus accumbens, respectively, while potentially decreasing the SA of frontal (pole, superior, and rostral middle), parietal (precuneus), temporal (pole) cortices, and posterior cingulate cortex (PCC), as well as the TH of frontal (pars opercularis), occipital (lateral), and temporal (inferior) cortices. On the other hand, the schizophrenia-risk alleles of class #2 potentially decreased the SA of occipital (pericalcarine and fusiform) cortices. These findings are consistent with literatures, suggesting that *CACNA1C* might be implicated in schizophrenia via regulating these regional morphometrics.

The caudate is a critical component of the cognitive/associative pathways and one of the main input nuclei of the basal ganglia in the cortico-basal ganglia-thalamic loop. It receives inputs from various cortical structures³⁵. The dorsolateral caudate receives projections from the dorsolateral prefrontal cortex, including the rostral middle frontal gyrus, and projects to the lateral dorsomedial globus pallidus (GPi) and rostral substantia nigra (SNr) where signals are relayed to the lateral ventral anterior nucleus pars magnocellularis (VAmc) and medial pars magnocellularis of the thalamus. This circuit is involved in executive functioning, emotion regulation, and working memory, which is known to be compromised in schizophrenic patients³⁶. The ventromedial caudate, on the other hand, receives inputs from the lateral orbitofrontal cortex, the temporal gyrus, and ACC, and projects to the lateromedial GPi and rostromedial SNr before looping into the cortex via the medial VAmc and medial magnocellularis. This circuit is central to decision-making and goal-directed action³⁶; the ACC in particular is involved to behavioral adjustment to meet changing environmental challenges³⁷. Dysfunction of this pathway may relate to the symptoms of schizophrenia, similar to those that result from damage to the prefrontal cortex³⁸.

The pars opercularis of the inferior frontal cortex (Brodmann area 44) is part of Broca's area and is associated with language processing³⁹. The inferior temporal cortex is involved in complex visual processing, face perception, recognition of numbers and objects, social cognition, and memory⁴⁰. The precuneus is involved in mental imagery concerning the

self⁴¹, episodic memory⁴², and visuospatial imagery⁴³, as well as mental effort^{44,45} and social cognition⁴⁶. Along with the precuneus, the PCC has been implicated in awareness, arousal⁴⁷, and episodic memory⁴⁸. The occipital (pericalcarine and fusiform) cortices are involved with visual and sensory information-processing⁴⁹. The entorhinal cortex plays an important role in declarative (autobiographical/episodic/semantic) memory formation and consolidation, and memory optimization in sleep⁵⁰. Alteration of these regions might be also related to the symptoms, including hallucination, delusion, cognitive including memory impairment, and motivational dysfunction, as commonly observed in schizophrenia patients.

We observed that schizophrenia-risk alleles belonging to class #3 were positively correlated with the SA of the lateral occipital cortex but negatively correlated with its cortical TH. Similarly, risk alleles of class #2 were positively correlated with the TH of the fusiform but negatively correlated with its SA. While these findings may seem contradictory, they could potentially be explained by the radial unit hypothesis⁵¹, which proposes that distinct developmental mechanisms promote the expansion of SA and increases in TH. Nevertheless, further research is necessary to fully understand these associations.

Finally, in the current study, the genetic regulatory effects of risk alleles were examined only in individuals of European ancestry, which is a limitation. These effects should be examined in other major populations, such as Africans, when available in the future.

Overall, we have identified a novel risk variant block at *CACNA1C* for schizophrenia. These variants are biologically functional and robustly associated with schizophrenia, suggesting that they may play significant roles in the pathogenesis of this disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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Availability of data and materials:

The datasets used for the analyses described in this manuscript were obtained from dbGaP at <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gap>. The dbGaP accession numbers include phs000021.v3.p2, phs000448.v1.p1, phs000167.v1.p1 and phs000687.v1.p1.

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Table 1.

p values for SNP-schizophrenia and SNP-mRNA expression associations

Class	SNP	Genomic position (b36)	Risk allele	“CACNA1C-SNP - Schizophrenia” associations.				“SNP - CACNA1C mRNA” associations										Effect direction of risk or effect alleles			
				Europeans		Africans		Europeans					Europeans								
				Sample #1	#2	#3	Risk allele	1195	Effect	CRBL	FCTX	OCTX	TCTX	Effect	AMYL	ACC	210		210		
				Case=1351	1044	621 (offspring)	1205 (parents)	954	allele	138	138	138	138	allele	210	210	210				
#1	rs2238096	2620174	<i>a</i>	-	>0.05	0.021	A	0.047	A	>0.05	1.6×10 ⁻³	0.022	0.050	0.050	-	-	-	-	-	-	↑↑
#2	rs10848680	2635439	G	0.005	-	0.020	G	-	G	0.020	>0.05	>0.05	>0.05	>0.05	A	0.050	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs216047	2636121	T	1.8×10 ⁻⁴	-	0.013	T	-	T	0.024	>0.05	>0.05	>0.05	>0.05	C	0.035	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs1894979	2637260	G	2.3×10 ⁻⁴	-	0.004	G	-	G	0.023	>0.05	>0.05	>0.05	>0.05	A	0.050	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs3794291	2639926	C	0.048	-	0.007	C	-	C	0.026	>0.05	>0.05	>0.05	>0.05	T	0.035	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs10161181	2640991	A	-	>0.05	0.001	A	0.011	<i>a</i>	0.025	>0.05	>0.05	>0.05	>0.05	-	-	-	-	-	-	↑↑
#2	rs10161275	2641279	T	0.046	>0.05	0.009	T	-	T	0.026	>0.05	>0.05	>0.05	>0.05	-	-	-	-	-	-	↑↑
#2	rs11062298	2641970	A	0.039	-	0.001	A	0.015	<i>a</i>	0.029	>0.05	>0.05	>0.05	>0.05	C	0.050	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs11062299	2641999	T	>0.05	0.011	0.002	T	>0.05	T	0.029	>0.05	>0.05	>0.05	>0.05	C	0.050	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs10848682	2642017	C	>0.05	0.011	0.002	C	-	C	0.029	>0.05	>0.05	>0.05	>0.05	G	0.050	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs10774052	2642432	C	0.039	-	0.002	C	>0.05	C	0.036	>0.05	>0.05	>0.05	>0.05	-	-	-	-	-	-	↑↑
#2	rs7315556	2644116	G	>0.05	0.009	0.002	G	-	G	0.037	>0.05	>0.05	>0.05	>0.05	A	0.037	>0.05	>0.05	>0.05	>0.05	↑↑
#2	rs7310079	2645738	T	>0.05	0.027	0.044	T	-	T	0.034	>0.05	>0.05	>0.05	>0.05	-	-	-	-	-	-	↑↑
#3	rs7306298	2647572	A	-	0.030	0.011	A	-	-	-	-	-	-	-	A	>0.05	0.042	>0.05	>0.05	>0.05	↑↑
#3	rs10744567	2651077	G	>0.05	0.034	0.015	G	-	-	-	-	-	-	-	G	>0.05	0.020	>0.05	>0.05	>0.05	↑↑
#3	rs7136355	2653737	C	-	0.019	0.004	C	-	-	-	-	-	-	-	C	>0.05	0.020	>0.05	>0.05	>0.05	↑↑
#3	rs2302729	2654233	C	-	0.028	0.020	C	>0.05	-	-	-	-	-	-	C	>0.05	0.012	>0.05	>0.05	>0.05	↑↑

Abbreviations: cerebellar cortex (CRBL), frontal cortex (FCTX), occipital cortex (OCTX), temporal cortex (TCTX), amygdale (AMYL), and anterior cingulate cortex (ACC). The italic bold lowercase risk allele is a major allele ($f > 0.5$). #1, #2 and #3 are classified based on $R^2 > 0.85$ within each class. ↑ and ↓, increase or decrease risk for disease, or mRNA expression level, referencing to the disease-risk alleles; “-”, missing.

Table 2.

p values for SNP-gray matter volumes (GMV) associations in Europeans

SNP	Schizophrenia -risk allele	"SNP - GMV" associations			Effect direction risk or effect alleles	
		Effect allele	Accumbens 28,697	Brainstem 28,809		Caudate 30,153
rs2238096	<i>a</i>	<i>a</i>	>0.05	0.017	0.040	↑↑
rs11062298	A	C	0.048	>0.05	>0.05	↑↓
rs11062299	T	C	0.045	>0.05	>0.05	↑↓
rs10848682	C	G	0.042	>0.05	>0.05	↑↓
rs10774052	C	T	0.034	>0.05	>0.05	↑↓
rs7315556	G	A	0.034	>0.05	>0.05	↑↓
rs2302729	C	C	0.028	0.018	>0.05	↑↑

The italic lowercase risk allele is a major allele ($f > 0.5$). ↑ and ↓, increase or decrease risk for disease or GMV, respectively, referencing to the disease-risk alleles.

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Table 3.

p values for SNP-cortical surface area (SA) associations

SNP	Disease-risk allele	Effect allele	"SNP-cortical SA" associations												Effect direction of risk or effect alleles	
			European			Mixed			Occipital			Limbic				
			pole	superior	middle	rostral	Frontal	Temporal	posterior	peri-calcarine	lingual	fusiform	anterior cingulate			
			n=32742	35198	35198	35198	35198	32742	35198	35198	35198	32742	35198	35198	35198	
rs2238096	<i>a</i>	C	>0.05	>0.05	>0.05	0.032	0.015	0.037	<i>a</i>	>0.05	>0.05	>0.05	>0.05	>0.05	0.043	↑↑
rs10848680	G	G	>0.05	>0.05	>0.05	0.018	>0.05	0.028	A	>0.05	>0.05	>0.05	>0.05	0.036	>0.05	↑↑
rs216047	T	T	>0.05	>0.05	>0.05	0.023	>0.05	0.028	C	>0.05	>0.05	>0.05	>0.05	0.037	>0.05	↑↑
rs1894979	G	G	>0.05	>0.05	>0.05	0.017	>0.05	0.029	A	>0.05	>0.05	>0.05	>0.05	0.033	>0.05	↑↑
rs3794291	C	C	>0.05	>0.05	>0.05	0.011	>0.05	0.038	T	>0.05	>0.05	>0.05	>0.05	0.020	>0.05	↑↑
rs10161181	A	A	>0.05	>0.05	>0.05	0.008	>0.05	0.050	C	>0.05	>0.05	>0.05	>0.05	0.022	>0.05	↑↑
rs10161275	T	T	>0.05	>0.05	>0.05	0.011	>0.05	0.039	C	>0.05	>0.05	>0.05	>0.05	0.023	>0.05	↑↑
rs11062298	A	A	>0.05	>0.05	>0.05	0.012	>0.05	0.048	C	>0.05	>0.05	>0.05	>0.05	0.032	>0.05	↑↑
rs11062299	T	T	>0.05	>0.05	>0.05	0.011	>0.05	0.048	C	>0.05	>0.05	>0.05	>0.05	0.036	>0.05	↑↑
rs10848682	C	C	>0.05	>0.05	>0.05	0.011	>0.05	>0.05	-	-	-	-	-	-	-	↑↑
rs10774052	C	C	>0.05	>0.05	>0.05	0.010	>0.05	>0.05	T	>0.05	>0.05	>0.05	>0.05	0.027	>0.05	↑↑
rs7315556	G	G	>0.05	>0.05	>0.05	0.013	>0.05	0.028	A	>0.05	>0.05	>0.05	>0.05	0.050	>0.05	↑↑
rs7310079	T	T	>0.05	>0.05	>0.05	0.011	>0.05	>0.05	C	>0.05	>0.05	>0.05	>0.05	0.024	>0.05	↑↑
rs7306298	A	G	>0.05	>0.05	0.045	>0.05	>0.05	>0.05	A	0.035	0.027	>0.05	>0.05	>0.05	>0.05	↑↑
rs10744567	G	A	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	G	0.026	0.026	>0.05	>0.05	>0.05	>0.05	↑↑
rs7136355	C	T	>0.05	0.048	>0.05	>0.05	>0.05	>0.05	C	0.034	0.017	0.038	>0.05	>0.05	>0.05	↑↑
rs2302729	C	T	0.041	0.025	>0.05	>0.05	>0.05	>0.05	C	0.030	0.037	0.047	>0.05	>0.05	>0.05	↑↑

The italic bold lowercase risk allele (class #1) is a major allele (≥ 0.5). ↑ and ↓, increase or decrease risk for disease, or effects on SA, respectively, referencing to the disease-risk alleles; "-", missing.

Table 4.

p values for SNP-cortical thickness (TH) associations

SNP	Disease	Effect	"SNP-cortical TH" associations in Europeans									Effect direction of risk or effect alleles	
			Frontal			Occipital			Temporal		Occipital		Limbic
			opercularis	lateral	pusiform	middle	inferior	inferior	Effect	calcarine	entorhinal		
	<i>-risk allele</i>	allele	n=9921	9921	23,909	23,909	23,909	9921	allele	23,909	9921		
rs2238096	<i>a</i>	C	0.032	>0.05	>0.05	>0.05	>0.05	>0.05	<i>a</i>	>0.05	0.039	↑↓	
rs10848680	G	G	>0.05	>0.05	0.024	0.025	0.019	>0.05	G	>0.05	>0.05	↑↑↑	
rs216047	T	T	>0.05	>0.05	0.031	0.029	0.019	>0.05	T	>0.05	>0.05	↑↑↑	
rs1894979	G	G	>0.05	>0.05	0.033	0.031	0.023	>0.05	G	>0.05	>0.05	↑↑↑	
rs3794291	C	C	>0.05	>0.05	0.050	0.044	0.018	>0.05	C	>0.05	>0.05	↑↑↑	
rs10161181	A	A	>0.05	>0.05	>0.05	0.049	0.015	>0.05	A	>0.05	>0.05	↑↑↑	
rs10161275	T	T	>0.05	>0.05	0.049	0.042	0.015	>0.05	T	>0.05	>0.05	↑↑↑	
rs11062298	A	A	>0.05	>0.05	0.038	0.037	0.030	>0.05	A	>0.05	>0.05	↑↑↑	
rs11062299	T	T	>0.05	>0.05	0.038	0.037	0.030	>0.05	T	>0.05	>0.05	↑↑↑	
rs10848682	C	C	>0.05	>0.05	0.040	0.042	0.032	>0.05	C	>0.05	>0.05	↑↑↑	
rs10774052	C	C	>0.05	>0.05	0.036	0.048	0.047	>0.05	C	>0.05	>0.05	↑↑↑	
rs7315556	G	G	>0.05	>0.05	0.037	>0.05	>0.05	>0.05	G	>0.05	>0.05	↑↑↑	
rs7306298	A	G	>0.05	>0.05	>0.05	>0.05	>0.05	0.038	A	0.005	>0.05	↑↓	
rs10744567	G	A	>0.05	>0.05	>0.05	>0.05	0.046	0.040	G	0.004	>0.05	↑↓	
rs7136355	C	T	>0.05	0.050	>0.05	>0.05	0.036	0.033	C	0.009	>0.05	↑↓	
rs2302729	C	T	>0.05	0.033	>0.05	>0.05	0.033	0.013	C	0.005	>0.05	↑↓	

The italic bold lowercase risk allele (class #1) is a major allele ($f > 0.5$). ↑ and ↓, increase or decrease risk for disease, or effects on TH, respectively, referencing to the disease-risk alleles; "-", missing.