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Genome-wide association analysis reveals substantial genetic overlap between schizophrenia and cortical brain measures

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Key Points

Question: To what extent is the genetic architecture of schizophrenia shared with cortical brain surface area and thickness?

Findings: The analysis of independent genome-wide association study datasets revealed that 95% of the genetic variants associated with total cortical surface area and all variants associated with average cortical thickness are also associated with the genetic risk of schizophrenia, despite non-significant genetic correlations.

Meaning: The amount of shared genetic variants between schizophrenia and cortical brain structure suggests overlapping molecular genetic mechanisms between cortical development and schizophrenia.

ABSTRACT

Importance Schizophrenia (SCZ) is a complex heritable disorder associated with many genetic variants, each with a small effect. While cortical differences between patients with SCZ and healthy controls are consistently reported, the underlying molecular mechanisms remain elusive.

Objective To investigate the extent of shared genetic architecture between SCZ and brain cortical surface area (SA) and thickness (TH), and to identify shared genomic loci.

Design, Setting, and Participants Independent genome-wide association study (GWAS) data on SCZ (PGC and CLOZUK, N=105,318), SA, and TH (UK Biobank, N=33,735) were obtained. We investigated the extent of polygenic overlap using MiXeR. The specific shared genomic loci were identified by conditional/conjunctional false discovery rate (cFDR) analysis, and were further examined in three independent cohorts.

Main Outcomes and Measures The primary outcomes were estimated fractions of polygenic overlap between SCZ, total SA, and average TH and a list of functionally characterized shared genomic loci.

Results MiXeR estimated SCZ to be more polygenic (9.7k causal SNPs) than total SA (2.1k causal SNPs) and average TH (1.3k causal SNPs). The vast majority of SNPs influencing total SA (2.0k out of 2.1k) and average TH (1.3k out of 1.3k) contribute to the development of SCZ. Subsequent cFDR analysis identified 44 and 23 SCZ risk loci shared with total SA and average TH, respectively. The SNP associations of shared loci between SCZ and total SA revealed en masse concordant effect between the discovery and independent cohorts. After removing high linkage disequilibrium regions, such as MHC region, the shared loci were enriched in immunologic signature gene-sets. We also identified polygenic overlap and shared loci between SCZ and SCZ-associated regions of interest for SA (superior frontal and middle temporal gyri) and for TH (superior temporal, inferior temporal, and superior frontal gyri).

Conclusions and Relevance This study demonstrated shared genetic loci between cortical morphometry and SCZ, among which a subset are related to immunity. These findings provide an insight into the complex genetic architecture and etiology of SCZ.

INTRODUCTION

Schizophrenia (SCZ) is a severe brain disorder with an estimated heritability up to 80%[1] in twin studies, indicating a prominent genetic component in its etiology. Genetic risk of SCZ has been suggested to influence early brain development,[2] and patients with SCZ exhibit many brain structural abnormalities.[3,4] Recent structural magnetic resonance imaging (MRI) studies have reported a smaller total cortical surface area (SA) and thinner average cortical thickness (TH) in SCZ, with the largest effect sizes found in the frontal and temporal lobes.[3,5] Similar frontotemporal patterns in SA and TH were also reported in non-affected relatives of SCZ patients,[6] and in relation to polygenic risk for SCZ in healthy population.[7] As both SA and TH are highly heritable with common SNPs explaining 26~34% of the phenotypic variation,[8] the above findings proposed that the genetic mechanisms contributing to the risk of SCZ may also influence brain anatomy. This hypothesis is further supported by evidence that polygenic risk scores of SCZ is associated with global TH in healthy individuals[9,10] and that genetic variance of SCZ is shared with SA (0.5%) and TH (6.3%) in twins.[11]

While previous studies have indicated an overlapping genetic basis between SCZ and brain anatomy, [12,13] the polygenic overlap of SCZ and cortical brain structure remains elusive. A recent GWAS of SA and TH found no significant genetic correlation with SCZ using linkage disequilibrium (LD) score regression.[8] However, LD score regression[14] is not able to capture genetic overlap with mixed effect directions, which is often the case between complex phenotypes.[15,16] To address that, Frei et al developed MiXeR which evaluates genetic overlap regardless of effect directions and estimates the overall shared polygenic architecture.[16] Moreover, identifying specific shared genetic loci offers biological insights into the polygenic overlap between two traits. As both SCZ and brain anatomy are associated with many small-effect genetic variants, applying statistical tools, such as conditional or conjunctional false discovery rate (cFDR)[15,17,18], to improve the yield of existing GWAS provides a cost-efficient approach to boost power for discovery. The cFDR was built on an empirical Bayesian statistical framework, and it improves power of SNP detection by leveraging the combined power of

two GWAS studies.[19-25] For example, while conventional statistical tools reported no evidence of genetic overlap between SCZ and subcortical volumes,[26] cFDR identified shared genomic loci between SCZ and subcortical volumes utilizing cross-trait SNP enrichment.[27]

Here we applied MiXeR[16] to investigate whether SCZ share a genetic basis with cortical SA and TH and the conjFDR approach[15,17,18] to identify specific shared loci using GWAS summary statistics. By exploring the shared genetic architecture of SCZ and brain structure, we ultimately aim to provide key insights into the pathophysiology underlying SCZ.

METHODS

Details of datasets and methods are provided in **Supplementary Method** and corresponding publications.[8,16-18,28,29]

Genome-Wide Association Studies (GWAS) Datasets

All GWAS datasets included in this study were approved by the relevant ethics committees, and informed consent was obtained from all participants. The Regional Committee for Medical and Health Research Ethics of South-East Norway approved the inclusion of data from UK biobank.

For the discovery analyses, the GWAS summary statistics for SCZ (40,675 cases and 64,643 controls) were generated by meta-analyzing the SCZ cases from UK (CLOZUK) and an independent Psychiatric Genomics Consortium (PGC) datasets.[28,29] The summary statistics of total SA and average TH were generated from UK Biobank (N=33,735).[30] For validation of findings, we included summary statistics of independent cohorts, including SCZ from a Norwegian cohort (961 cases and 5000 controls) and total SA and average TH from the ENIGMA cohort of European ancestry (N=23,909).[7] We also

included summary statistics for SCZ in East Asian cohorts (22,778 cases and 35,362 healthy controls).[31]

Summary statistics for regional SA and TH were acquired from UK Biobank with 33,735 volunteers.[30] We selected regions which have been reported as significantly different with the largest effect sizes between SCZ cases and healthy controls in a previous large-scale study,[3] including fusiform, inferior temporal (ITG), middle temporal (MTG), precentral, and superior frontal gyri (SFG) for SA and fusiform, ITG, MTG, SFG and superior temporal gyri (STG), insula and pars opercularis for TH.

As height showed phenotypic association,[32] limited shared genomic regions,[33] and non-significant genetic correlation[34] with SCZ, we included a height GWAS dataset as a heritable, polygenic, non-brain-related comparator.[35]

Statistical Analysis

We constructed conditional QQ plots to visualize polygenic enrichment, after excluding SNPs within four regions with complex LD pattern (MHC region: chr6:25119106–33854733; 8p23.1: chr8:7200000–12500000; MAPT region: chr17:40000000–47000000; APOE region: chr19:44909039–45912650).[36] Each QQ plot reveals the distribution of *P*-values for the primary phenotype conditioning on the significance of association with the secondary trait at the level of $P<0.1$, $P<0.01$, and $P<0.001$.

Polygenic overlap irrespective of genetic correlation between selected phenotypes was evaluated by MiXeR (https://github.com/precimed/mixer).[16] Univariate analysis estimated polygenicity (estimated number of causal variants) and discoverability (the average magnitude of additive genetic effects across causal variants) of each phenotype. Causal variants represent variants with nonzero additive

genetic effect on a trait. Bivariate analysis modeled additive genetic effects on two traits as a mixture of four bivariate Gaussian components, representing variants influencing only one trait, variants affecting both traits, and variants have no effect on either trait. The unique and shared polygenic components with the estimated number of causal variants are presented in a Venn diagram. MiXeR calculated a Dice coefficient (DC), a ratio of shared causal variants to the total number of causal variants, to evaluate the polygenic overlap. Based on Akaike information criterion (AIC), MiXeR evaluated model fitting based on current power of input summary statistics. A comparison between MiXeR and LD Score regression is provided in **Supplementary Method.**

The cFDR method (https://github.com/precimed/pleiofdr), including condFDR and conjFDR analysis, was applied to identify specific shared loci.[15,17,18] The condFDR analysis, as an extension of standard FDR, utilizes the associations between variants and the secondary phenotype to re-rank test statistics and to re-calculate the associations between these variants and the primary phenotype. Thus, we applied conFDR to boost the power of SNP discovery for each individual trait. The conjFDR analysis is a conservative estimate of the posterior probability that an SNP has no association with either trait, given that the *P*-values for that SNP in both the primary and secondary traits are lower than the observed *P*-values. After repeating conFDR for both traits, we applied conjFDR analysis to identify shared genetic loci. The FDR significance cutoffs were 0.05 for conjFDR and 0.01 for condFDR in line with prior studies.[15,17] We also included shared loci with conjFDR<0.01 in **Supplementary Result**.

For identified loci, we examined significance and directionality of allelic effect in independent cohorts using lead SNPs. For genomic loci with a primary lead SNP missing in an independent dataset with European ancestry, we assigned a secondary lead SNP if available. SNP sign test[26,29] verified directionality of allelic effect between the discovery and independent cohorts with the null

hypothesis of randomly oriented effects. Sign concordancy for shared lead SNPs was defined only when SNP associations of both phenotypes showed congruent effects in independent cohorts.

Identify Genomic Loci, Functional Annotation, and Novelty

Independent genomic loci were defined using FUMA protocol.[37] A locus, which was not physically overlapping with findings from the original GWASs, NHGRI-EBI GWAS Catalog,[38] or previous cFDR studies,[16-18] was considered as 'novel'. The Z-scores from original GWASs reflected the directionality of allelic effect. FUMA[37] annotated Combined Annotation Dependent Depletion (CADD),[39] RegulomeDB scores,[40] and chromatin states[41,42] for candidate SNPs with FDR ≤ 0.1. We performed three gene-mapping strategies to candidate SNPs, including: 1) positional mapping by physical position using a 10kb window; 2) expression quantitative trait locus (eQTL) association; 3) chromatin interaction mapping.[37] Genes mapped by all three mapping strategies were considered as 'credible' genes. After excluding mapped genes in the regions with complex LD pattern (MHC, 8p23.1, MAPT, APOE regions), we applied the rest in gene-set analysis.[37] The Molecular Signatures Database (MSigDB) evaluated enrichment in immunological signature gene-sets.[43] GTEx portal (v8) obtained eQTL associations in brain tissues for lead SNPs and expression trajectories for genes.[44]

RESULTS

Genetic Overlap Between SCZ and Global Cortical Structural Measures

The stratified conditional QQ plots showed SNP enrichment for SCZ as a function of their associations with total SA and average TH, and *vice versa* (**eFigure1 in the Supplement**), suggesting the existence of polygenic overlap. While the corresponding genetic correlations are non-significant (SCZ and total SA: r_g= -0.01; SCZ and average TH: r_g= 0.01), 95% of causal variants influencing total SA (2.0k out of 2.1k, DC=0.33) and all variants influencing average TH (1.3k, DC=0.24) contribute to the

risk of SCZ (**Figure1; eTable1-2 and eFigure2 in the Supplement**). Specifically, 51% of shared variants between SCZ and total SA and 50% shared variants between SCZ and average TH showed concordant effects on both traits. MiXeR also revealed a higher polygenicity in SCZ than in total SA and average TH with 7.7K and 8.4K variants influencing SCZ but not affecting SA and TH respectively. As a somatic control, height shared a smaller proportion of causal variants (25%, 1.0K out of 4.0k, DC=0.15, **eTable1-2 and eFigure2 in the Supplement**) with SCZ, with a non-significant genetic correlation.

Shared and Novel Loci Between SCZ and Global Cortical Structural Measures

The conjFDR analysis identified 44 genomic loci shared between SCZ and total SA (**Figure 2**), with 19 and 37 novel loci for SCZ and total SA, respectively. SCZ and average TH shared 23 genomic loci (**Figure 2**), with eight and 19 loci novel for SCZ and average TH. Four loci were jointly associated with SCZ, total SA, and average TH. The shared loci showed mixed directions of allelic effects, with 17 of 44 loci (39%) showing concordant effects on SCZ and total SA, and eight out of 23 loci (35%) had concordant effects on SCZ and average TH. The shared genomic loci, candidate SNPs, allelic effects and novelty for each trait are summarized in **eTables 3-6 in the Supplement**.

Among those shared loci, CADD scores indicated three lead SNPs (SCZ|SA: rs7146019; SCZ|TH: rs13107325 and rs11975) as pathogenic (CADD > 12.37, **eTables 3 in the Supplement**). A subset of lead SNPs had a minimum chromatin state < 8, indicating a location within regulatory regions (**eTables 3 in the Supplement**). We found 92 significant eQTLs for lead SNPs shared between SCZ and total SA, and 61 significant eQTLs for lead SNPs shared between SCZ and average TH, implying shared loci alter gene expressions in brain tissues (**eTables 7 in the Supplement**). After excluding high LD regions, mapped genes for SCZ and total SA were enriched in 26 GO terms, including "GO_COMMITMENT_OF_NEURONAL_CELL_TO_SPECIFIC_NEURON_TYPE_IN_FOREBRAIN" and "GO_POSITIVE_REGULATION_OF_TYPE_I_INTERFERON_PRODUCTION", and 27 immunologic

signature gene-sets. Mapped genes for SCZ and average TH showed significant enrichments in two GO terms and ten immunologic signature gene-sets. Mapped genes and gene-sets are listed in **eTables 8-11 in the Supplement**.

Besides, condFDR analysis identified 214 SCZ-associated genomic loci, in which 33 were novel for SCZ, conditional on their associations with SA (**eTable 12 in the Supplement**). Conditioning on SNP associations with TH, we found 201 genomic loci associated with SCZ, including 28 novel loci. Conditioning on SNP associations with SCZ, condFDR analysis reported 76 genomic loci for total SA and 57 loci for average TH, with 52 and 35 novel for total SA and average TH, respectively (**eTable 13 in the Supplement**)**.**

Concordancy and Significance of Identified Genomic Loci in Independent Samples

Of 43 lead SNPs that were shared between SCZ and total SA and available in the independent Norwegian and ENIGMA datasets, 67% (29/43) showed a consistent direction of effect between the discovery and independent cohorts (Binomial P=.02), suggesting corresponding SNP associations replicated *en masse* in independent cohorts. As for SCZ and average TH, 13 out of 23 shared lead SNPs showed the same direction of effect (Binomial P=.3) in independent cohorts. Examining the effect of those 23 loci on each phenotype separately showed significant sign concordancy in average TH (concordant sign: 19 out of 23 lead SNPs; Binomial P=.001) but not in SCZ (concordant sign: 15 out of 23 lead SNPs; Binomial P=.1). Further, the genetic effect of shared lead SNPs on SCZ replicated *en masse* in East Asian samples[31] (SCZ and total SA: Binomial $P=1.56\times10^{-4}$; SCZ and average TH: Binomial $P=3.64\times10^{-4}$). Lead SNPs identified in condFDR analysis revealed *en masse* concordant effect in independent cohorts as well as in East Asian samples (**Supplementary Result**).

A group of shared loci (SCZ and total SA: 23 out of 43; SCZ and average TH: 12 out of 23) showed nominal significance between lead SNPs with at least one phenotype (P<.05, **Table 1-2**).[45,46] For those shared loci, five credible mapped genes, including *INA*, *ATP5G1*, *SREBF2*, *MAPT*, and *DNPH1*, showed a high expression in the brain cortex (TPM>40,[47] Figure 3). More details are included in **Supplementary Result and eTable 14-17 in Supplements**.

Shared Genetic Mechanisms between SCZ and SCZ-Related Regional Cortical Measurements

We observed SNP enrichment in QQ plots for two regions of interest for SA (SFG and MTG) and three for TH (STG, ITG, and SFG) with SCZ, and *vice versa* (**eFigure 5-6 in Supplement**). The largest overlap as measured with DC was observed in MTG among SA and SCZ (DC=0.32), and in STG among TH and SCZ (DC=0.40, **eFigure 7-8 and eTable 1 in the Supplement**). For the conjFDR analysis, SCZ shared 9, 16, 9, 11, and 10 genomic loci with regional SA (SFG and MTG) and regional TH (STG, ITG, and SFG), respectively (**eTable 18 in the Supplement**).

Discussion

In the present study, we identified a shared genetic basis between SCZ and SA and TH of cerebral cortex using MiXeR and cFDR. Specifically, we 1) showed that a substantial proportion of SNPs associated with total SA and average TH contribute to the risk of SCZ; 2) identified shared genomic loci between SCZ and total SA and average TH; 3) revealed polygenic overlap between SCZ and relevant regions of interest for SA (SFG and MTG) and for TH (STG, ITG, and SFG); and 4) suggested immune functions participate in cortical development and the pathology of SCZ.

Individual differences in cortical brain structure have been linked to cognition, mood, and behavior.[48,49] Previous studies have suggested cortical brain structure as an endophenotype of SCZ,[50] mainly supported by phenotypic associations.[3,4] Here we identified genetic overlap between SCZ and

cortical structure, suggesting that previously reported group differences in these brain MRI features between patients with SCZ and healthy controls are partly genetically determined, in line with the reported association between polygenic risk score of SCZ and cortical TH.[7,9,10] Specifically, MiXeR revealed many variants shared between SCZ and cortical morphology with a distinct pattern of effect distributions that approximately 50% of shared variants demonstrated concordant effects on SCZ and cortical structure. The mixed effect directions across the shared genetic variants[15,16] help explain the polygenic overlap despite non-significant genetic correlation.[8] Meanwhile, MiXeR reported a higher polygenicity for SCZ compared to cortical SA and TH, which is likely due to the biological complexity and clinical heterogeneity of SCZ.[16,51,52] These findings indicate a "polygenic pleiotropy"[15] model for the brain in which polygenic phenotypes related to brain may have overlapping genetic determinants along with comparatively distinct genetic characteristics, including different polygenicities and phenotype-specific effect distributions. Regional TH measures showed a bigger genetic overlap with SCZ than global measures, while SA did not show this pattern. While the brain MRI associations with SCZ show substantial between-subject heterogeneity,[7,10,53] this pattern generally complies with the anatomical distribution of effects observed for TH in SCZ while the association with SA appears to be global.[3]

Notably, after excluding the regions with complex LD patterns, genes implicated by the shared loci were significantly enriched in biological processes related to inflammation. Previous studies have suggested that the activity of neuroinflammatory receptors affects cortical development,[54] along with significant associations between inflammation makers with cortical SA[55] and TH.[56] Immune dysfunction has been proposed as an important factor in the pathogenesis of SCZ[57] as evidenced by the involvement of immune-related genes[29] and altered various inflammatory makers in SCZ.[58] Immune-related synapse pruning, which decreases cortical TH,[59] has been reported in SCZ.[60] Our results suggest immune processes may be involved in the shared genetic component between SCZ and cortical structure, providing an insight into the above observations. Although most prior reports

highlighted the MHC region, the enrichment in inflammation-related gene-sets without MHC implies that genetic factors linking to the immune system to cerebral cortex and SCZ are not only driven by the strong and complex association at the MHC region. Further experimental studies are needed to understand the roles of immunity in cortical structure and in SCZ.

Our study found five credible mapped genes, including *INA, ATP5G1, SREBF2, MAPT,* and *DNPH1*, have a high expression in the brain cortex. *INA* encodes neurofilaments, which are involved in the morphogenesis of neurons and work as biomarkers in neurological disorders.[61] Previous studies have suggested ATP5G1, encoding a subunit of mitochondrial ATP synthase, is associated with major depression disorder and Alzheimer's disease.[62,63] The *SREBP2* has been indicated as a genetic susceptibility factor in SCZ and an antipsychotic-activated transcription factor. *MAPT* encodes microtubule-associated protein tau, which participates in axonal transport and neurite outgrowth.[64] Mutations within *MAPT* are associated with neurodegenerative disorders,[65] learning disability, [66] and alterations in cortical TH, gray matter volume and white matter integrity.[67,68] *DNPH1* encodes a hydrolase and a GWAS study has reported *DNPH1* is associated with risk-taking behavior.[69]

However, some limitations should be noted. Firstly, the sample size of the independent Norwegian GWAS dataset for SCZ was small with a limited power. Given the shared loci between SCZ and average TH failed to show concordancy in the Norwegian cohort, a future examination with a large cohort is necessary. Secondly, although gene-set analysis provided potential insights, whether the overlapping genetic components reflect shared biological pathways or more unspecific effects of brain expressed genes warrants further research.

In summary, our study uncovers shared polygenicity between SCZ and cortical brain structure. Mapped genes of shared loci along with previous reports suggest potential connections of immunity

to the development of cortical brain structure and to the pathology of SCZ. These findings provide molecular genetic insights into the phenotypic correlations between SCZ and brain structure.

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Conflict of Interest Disclosures:

O.A.A. has received speaker's honorarium from Lundbeck and is a consultant for Healthlytix. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. Remaining authors have no conflicts of interest to declare.

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Author Contributions:

Dr. Cheng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Cheng, Andreassen, Frei, Dale.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Cheng, Smeland, Andreassen, Hindley, Westlye.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Cheng, Frei, van der Meer, Wang, O'Connell, Chu, Andreassen.
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Figure Legends

Figure 1. Polygenic overlap between schizophrenia and global cortical measures in discovery study.
Venn diagrams shows the unique and shared polygenic components which contribute to corresponding traits. The numbers with standard deviation in bracket reflect the estimated unique (in color) and shared (gray) causal variants (in thousands). The size of each circle is in proportion to the corresponding polygenicity. The r_g reflects the genetic correlation for each two traits.

Figure 2. Shared genetic loci between schizophrenia and global cortical measures in discovery study.
The y-axis represents $-\log_{10}$ transformed conjFDR values for each SNP and the x-axis reflects the chromosomal position. The dotted horizontal line is the cutoff for significance. Details for genomic loci and candidate SNPs are provided in eTable 2,5-6 in the Supplement. SCZ, schizophrenia; SA, surface area; TH, thickness.

Figure 3. Expression of credible genes of shared loci in brain tissue
Among the shared loci which were significantly associated with at least one phenotype in the independent cohorts, 31 credible genes were mapped by all three strategies: positional mapping, expression quantitative trait locus (eQTL) mapping; chromatin interaction mapping. Corresponding expression patterns in brain tissue were extracted from GTEx. The expression pattern for *has-mir-8072* was not found. The *KMT5A* is also named as *SETD8*. Transcripts per Million (TPM) is used to measure gene expression levels.

Table 1. Twenty-three shared genomic loci between schizophrenia and total surface area which showed conjunctional FDR<0.05 and significance in independent cohorts.

Genomic Loci				Discovery study						Independent GWAS datasets				Novelty
#	CHR	MinBP	MaxBP	Primary lead SNP	conjFDR	A1	A2	Credible Mapped Gene	Cor _Eff	Lead SNP	SCZ GWAS PVAL	Total SA GWAS PVAL	Rep _Dir	
3	1	243639859	244014490	rs1058304	4.74×10^{-4}	T	C	-	-	rs1058304	.675	2.35×10^{-4}	0	total SA
4	2	48177487	48707841	rs72872724	7.34×10^{-4}	G	A	FOXN2	+	rs72872724	.972	1.17×10^{-4}	+	SCZ, total SA
8	3	71481192	71611630	rs7610856	.010	A	C	-	-	rs7610856	.058	.005	+	total SA
12	4	103112470	103387161	rs34316881	.001	T	C	-	+	rs34316881	.407	.001	+	total SA
13	4	139927828	140130524	rs28565133	.021	T	C	-	-	rs28565133	.069	5.01×10^{-5}	+	SCZ, total SA
14	5	5426431	5533414	rs3111175	.030	G	T	-	-	rs2578558	.532	.030	+	SCZ, total SA
15	5	38922826	39094257	rs12233987	.038	C	T	-	-	rs12233987	.220	.002	+	SCZ, total SA
19	5	170776747	170848124	rs7715167	.047	T	C	-	-	rs7715167	.031	1.37×10^{-5}	+	SCZ, total SA
21	6	108868422	109035704	rs9398172	.002	G	A	FOXO3	-	rs9398172	.272	4.69×10^{-4}	+	
23	7	1860728	2167939	rs11764960	.035	A	G	-	-	rs11764960	.472	.013	+	total SA
24	7	28454580	28482115	rs2391665	.029	G	A	-	-	rs2391665	.383	.008	0	SCZ, total SA
25	7	104587323	105063372	rs3779210	.017	T	C	-	+	rs3779210	.101	8.44×10^{-6}	+	total SA
26	8	40712159	40771375	rs1004412	.017	T	C	-	-	rs1004412	.036	.664	0	SCZ, total SA
28	10	104965551	105176914	rs7082288	9.11×10^{-4}	T	C	INA;PDCD11	-	rs7082288	.013	3.35×10^{-8}	+	
29	11	46257757	47242761	rs6485671	7.75×10^{-5}	A	G	-	+	rs6485671	.106	.030	+	total SA
31	12	66277698	66384362	rs61921611	.001	C	T	-	-	rs61921611	.632	6.94×10^{-8}	+	SCZ
32	12	79760388	79891269	rs2895728	.041	C	T	-	-	rs2895728	.327	4.01×10^{-4}	0	SCZ, total SA
35	12	123447928	123891209	rs61955214	.021	T	C	OGFOD2;PITPNM2;MPHOSPH9;RP11-282O18.3;hsa-mir-8072;SETD8	+	rs61955214	.665	.018	0	total SA
37	14	99733954	99751588	rs7146019	6.16×10^{-4}	A	G	-	+	rs7146019	.700	.004	0	total SA
39	17	43463493	44865603	rs2532392	.008	A	G	MAPT-AS1;MAPT;STH;KANSL1-AS1;RP11-259G18.1;WNT3	+	rs199504	.301	1.99×10^{-22}	+	SCZ
40	17	46835629	47047868	rs35929648	.007	A	G	TTLL6;SUMO2P17;ATP5G1;UBE2Z	-	rs35929648	.774	.001	0	total SA
43	22	29360297	29399244	rs2213645	.046	A	G	-	-	rs2213645	.976	5.50×10^{-5}	+	SCZ, total SA
44	22	41437526	42308739	rs12170228	.004	T	C	POLR3H;CSDC2;DESI1;MEI1;SREBF2	-	rs12170228	.023	.899	+	total SA

This table provides 23 genomic loci which identified as shared between schizophrenia (SCZ) and total surface area (SA) in discovery study and showed a significant association with at least one phenotype in the independent Norwegian and ENIGMA cohorts. For each locus, we provide the following information. 1) The "Genomic Loci" section provides the identifier ("#") and physical location (MinBP: start position; MaxBP: end position) of each locus. 2) The "Discovery study"

section includes the primary lead SNP identified in discovery study and related information. The “Cor_Eff” shows the directionality of allelic effects on both phenotypes in discovery datasets using Z-scores ("+" stands for the same direction, and "-" for opposite direction). 3) The “Independent GWAS datasets” section reveals the P values of lead SNPs in independent cohorts. For genomic loci of which the primary lead SNP is not available in independent datasets, we assigned a secondary lead SNP. The “Rep_Dir” shows the concordancy of effect directions of lead SNPs between the discovery and independent samples using Z-scores (“+” for both phenotypes show the same direction between the discovery and independent cohorts, and “0” for at least one phenotype shows opposite direction). 4) The “Novelty” section demonstrates whether a locus was novel for two traits, according to the original GWAS, NHGRI-EBI GWAS Catalog, and previous condFDR/conjFDR publications. More information about all identified genomic loci are listed in eTable 3 and 14 in the Supplement, with details of defining genomic loci, lead SNP, credible mapped genes and novelty in Supplementary Method.

Table 2. Twelve shared genomic loci between schizophrenia and average thickness which showed conjunctional FDR<0.05 and significance in independent cohorts.

Genomic Loci				Discovery study						Independent GWAS datasets				Novelty
#	CHR	MinBP	MaxBP	Primary lead SNP	conjFDR	A1	A2	Credible Mapped Gene	Cor_Eff	LEAD_SNP	SCZ GWAS PVAL	Average TH GWAS PVAL	Rep_Dir	
1	1	98336823	98664991	rs10875133	.012	A	G	-	+	rs10875133	.632	.002	+	average TH
2	2	26961166	27351279	rs34472003	.007	C	T	SLC35F6;DPYSL5;KHK	-	rs7602823	.430	6.90×10^{-4}	0	average TH
4	2	97349315	98599499	rs78381888	.002	G	A	-	+	rs78381888	.636	.025	+	average TH
7	4	102702364	103387161	rs13107325	1.97×10^{-7}	T	C	-	-	rs13107325	.209	9.97×10^{-5}	+	average TH
9	6	26410800	33548090	rs2523548	.008	A	G	-	-	rs3130100	.225	.006	+	average TH
10	6	43160375	43212493	rs9462876	.024	G	A	CUL9;DNPH1	+	rs9462876	.026	.848	0	average TH
11	8	26119170	26279173	rs147506820	7.01×10^{-5}	A	G	SDAD1P1	+	rs147506820	.725	.012	0	average TH
15	10	123902771	123912298	rs7902292	.036	T	C	-	-	rs7902292	.681	.023	0	SCZ, average TH
17	15	58873555	59115995	rs4774310	.010	G	T	-	+	rs4774310	.354	.003	+	average TH
19	17	2532052	2586229	rs6502460	.002	G	T	-	+	rs6502460	.775	.022	+	SCZ, average TH
21	17	19897445	20384834	rs7209734	.011	C	A	-	-	rs7209734	.544	.004	+	average TH
22	17	43463493	44865603	rs2532392	.013	A	G	MAPT-AS1;MAPT;STH;KANSL1-AS1;RP11-259G18.1;WNT3	-	rs199504	.301	1.47E-04	+	SCZ, average TH

This table provides 12 genomic loci which identified as shared between schizophrenia (SCZ) and average thickness (TH) in discovery study and showed significant associations with at least one phenotype in the independent Norwegian and ENIGMA cohorts. For each locus, we provide the following information. 1) The "Genomic Loci" section provides the identifier ("#") and physical location (MinBP: start position; MaxBP: end position) of each locus. 2) The "Discovery study" section includes the primary lead SNP identified in discovery study and related information. The "Cor_Eff" shows the directionality of allelic effects on both phenotypes in discovery datasets using Z-scores ("+" stands for the same direction, and "-" for opposite direction). 3) The "Independent GWAS datasets" section reveals the P values of lead SNPs in independent cohorts. For genomic loci of which the primary lead SNP is not available in independent datasets, we assigned a secondary lead SNP. The "Rep_Dir" shows the concordancy of effect directions of lead SNPs between the discovery and independent samples using Z-scores ("+" for both phenotypes show the same direction between the discovery and independent cohorts, and "0" for at least one phenotype shows opposite direction). 4) The "Novelty" section demonstrates whether a locus was novel for two traits, according to the original GWAS, NHGRI-EBI GWAS Catalog, and previous condFDR/conjFDR publications. More information about all identified genomic loci are listed in eTable 3 and 14 in the Supplement, with details of defining genomic loci, lead SNP, credible mapped genes and novelty in Supplementary Method.