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The Role of 3' Regulatory Region Flanking Kinectin 1 Gene in Schizophrenia

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ABSTRACT

Objective: Schizophrenia is often associated with volumetric reductions in cortices and expansions in basal ganglia, particularly the putamen. Recent genome-wide association studies have highlighted the significance of variants in the 3' regulatory region adjacent to the kinectin 1 gene (*KTN1*) in regulating gray matter volume (GMV) of the putamen. This study aimed to comprehensively investigate the involvement of this region in schizophrenia.

Methods: We analyzed 1136 single-nucleotide polymorphisms (SNPs) covering the entire 3' regulatory region in 4 independent dbGaP samples (4604 schizophrenia patients vs. 4884 healthy subjects) and 3 independent Psychiatric Genomics Consortium samples (107 240 cases vs. 210 203 controls) to identify consistent associations. Additionally, we examined the regulatory effects of schizophrenia-associated alleles on *KTN1* mRNA expression in 16 brain areas among 348 subjects, as well as GMVs of 7 subcortical nuclei in 38 258 subjects, and surface areas (SA) and thickness (TH) of the entire cortex and 34 cortical areas in 36 936 subjects.

Results: The major alleles ($f > 0.5$) of 25 variants increased ($\beta > 0$) the risk of schizophrenia across 2 to 5 independent samples ($8.4 \times 10^{-4} \leq P \leq .049$). These schizophrenia-associated alleles significantly elevated ($\beta > 0$) GMVs of basal ganglia, including the putamen ($6.0 \times 10^{-11} \leq P \leq 1.1 \times 10^{-4}$), caudate ($8.7 \times 10^{-4} \leq P \leq 9.4 \times 10^{-3}$), pallidum ($P = 6.0 \times 10^{-4}$), and nucleus accumbens ($P = 2.7 \times 10^{-5}$). Moreover, they potentially augmented ($\beta > 0$) the SA of posterior cingulate and insular cortices, as well as the TH of frontal (pars triangularis and medial orbitofrontal), parietal (superior, precuneus, and inferior), and temporal (transverse) cortices, but potentially reduced ($\beta < 0$) the SA of the whole, frontal (medial orbitofrontal), and temporal (pole, superior, middle, and entorhinal) cortices, as well as the TH of rostral middle frontal and superior frontal cortices ($8.9 \times 10^{-4} \leq P \leq .050$).

Conclusion: Our findings identify significant and functionally relevant risk alleles in the 3' regulatory region adjacent to *KTN1*, implicating their crucial roles in the development of schizophrenia.

Keywords: *KTN1*, schizophrenia, cortex, subcortical structure, putamen, gray matter volume, surface areas, thickness

Introduction

Schizophrenia manifests as a debilitating behavioral syndrome characterized by profound emotional, cognitive, and social impairments. Neuroimaging studies consistently reveal alterations in various brain regions in individuals with schizophrenia, including widespread reductions in cortical volumes or thickness across frontal, occipital, parietal, temporal, insular, and limbic regions.[1-24] Surprisingly, contrary to these cortical changes, reports indicate increased gray matter volumes (GMVs) within the basal ganglia among schizophrenia patients,[25-33] with particular emphasis on the enlargement of the putamen as a prominent neural risk marker.[26,30,31,34-37]

Recent genome-wide scans investigating GMVs of subcortical nuclei, including the basal ganglia (putamen, pallidum, caudate, and nucleus accumbens), amygdala, hippocampus, and thalamus, have consistently pinpointed a robust association between putamen GMV and the kinectin 1 gene (*KTN1*), which encodes a receptor crucial for regulating neuronal cell shape and volume.[38-41] Notably, all known significant variants linked to putamen GMV, such as rs945270 ($P = 1.1 \times 10^{-33}$)[38] and rs8017172 ($P = 6.7 \times 10^{-34}$ in both discovery and replication samples),[42] are situated within the regulatory region flanking the 3′ end of *KTN1*.

Beyond schizophrenia, *KTN1* variants have been implicated in various neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (9 single-nucleotide polymorphisms (SNPs) in the 5′ flanking region and 18 SNPs in the 3′ flanking region, including rs945270),[43-47] Parkinson's disease (8 SNPs in 3′, including rs8017172 and rs945270),[48-51] heroin dependence (rs945270 in 3′),[52] marijuana dependence (3 SNPs in 3′),[53] alcohol and drug co-dependence (14 SNPs in the 5′ flanking region and 13 SNPs in the 3′ flanking region, including rs945270 and rs8017172),[54] and cognitive dysfunction in the elderly (rs12895072 in 3′).[55] Remarkably, all identified risk variants reside within the regulatory regions flanking either the 5′ end (33%) or the 3′ end (67%) of *KTN1*, with none located within the open reading frame (ORF).

While associations between *KTN1* variants and schizophrenia were previously unexplored until our recent investigation,[56] where we assessed SNPs across the entire 120 kb-wide regulatory region flanking the 5′ end, the entire ORF, and an 8 kb-wide portion of the regulatory region proximal to the 3′ end of *KTN1*. In our study, we identified 4, 20, and 2 risk SNPs for schizophrenia, respectively (see Supplementary Figure 1).[56] However, none of these risk alleles was linked to increased GMVs of the basal ganglia. This spurred our current study, aiming to explore the entire 4.3 Mbp-wide regulatory region flanking the 3′ end of *KTN1*, spanning from its proximal to distal ends (see Figure S1), to uncover novel and robust risk variants for schizophrenia, particularly those contributing to basal ganglia enlargement. Additionally, we investigated the associations of these risk variants with the expression of *KTN1* mRNA, GMVs of other subcortical nuclei, cortical surface areas, and cortical thicknesses across various brain areas.

Material and Methods

Subjects

We examined 4 independent samples for the SNP-schizophrenia association analysis, comprising 3 European cohorts and 1 African-American cohort. Sample #1 included 1351 European-American schizophrenia cases and 1378 healthy subjects sourced from the "GAIN: Genome-Wide Association Study of Schizophrenia" dataset (dbGaP#: phs000021), genotyped using the AFFY_6.0 platform, with data provided by Dr. Gejman from Northwestern University. Sample #2 consisted of 1437 European-American patients and 1347 healthy controls from the "MGS-nonGAIN: Molecular Genetics of Schizophrenia - nonGAIN Sample" (phs000167; AFFY_6.0 platform; and by Dr. Gejman). Sample #3 comprised 1826 European parent–offspring trio subjects, including 621 offspring diagnosed with schizophrenia, sourced from the "New_CMB-trios: Bulgarian Trio Sequencing Study to Identify de Novo Mutations in Schizophrenia" dataset (phs000687; SeqCap EZ Human Exome Library v2.0; by Dr. Owen from Cardiff University). Sample #4 included 1195 African-American patients and 954 healthy subjects from the "GAIN" dataset (phs000021).

Participants were all aged 18 years or older and met schizophrenia diagnosis (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition).[57] Exclusions were made for individuals with mental retardation, substance use disorders, or neurological diseases. Controls were devoid of depression, bipolar disorder, schizoaffective disorder, schizophrenia, and psychotic symptoms. Written informed consent was obtained from all participants, and the study was approved by the Institutional Review Board of Yale University (Approval No HIC# 1007007175, Date April 29, 2004). More details of demographics were previously published.[58-62]

Single-Nucleotide Polymorphism-Disease Association Analysis

We analyzed a total of 1136 imputed SNPs covering the entire 3′ regulatory region (4,337,443bp) from the transcription end site (Chr14:55,684,585) of *KTN1* to the transcription start site (Chr14:56,118,328) of the next protein-coding gene (*PELI2*). Genotyping, imputation, and data cleaning details were outlined previously.[56,63] Allele frequencies of SNPs were compared between untransmitted and transmitted alleles using the "--dfam" option or between schizophrenia patients and controls using the Fisher exact test in PLINK.[64] Replicable associations had a *P*-value < .05 across ≥ 2 cohorts with consistent association direction. These associations were verified using 3 large independent Psychiatric Genomics Consortium (PGC) datasets (107 240 cases vs. 210 203 controls).[65-67] Multiple comparisons were corrected using false discovery rate (FDR) adjustment, with *q*-values < 0.05 indicating statistical significance.

cis-acting Expression Quantitative Trait Locus Analysis

We investigated the regulatory effects of schizophrenia-associated variants on *KTN1* mRNA expression using *cis*-eQTL analysis in 16 brain areas from 2 cohorts: a UK cohort with 138 subjects sourced from the BRAINEAC dataset,[68] and a European-American cohort (n = 210) obtained from the GTEx dataset.[69] Normalized mRNA expression levels were compared between different alleles of each variant using *t*-tests.

Regulatory Effect of Risk Variants on the Gray Matter Volumes of Subcortical Nuclei

Gray matter volumess of basal ganglia and limbic system structures were measured in 38 258 European subjects from 14 CHARGE, 35 ENIGMA2 cohorts, and the UK Biobank,[38,42] using structural magnetic resonance imaging (MRI) with standardized protocols. Genetic homogeneity among subjects was analyzed by multi-dimensional scaling (MDS). Multiple linear regression analysis was conducted

MAIN POINTS

- *Recent genome-wide association studies have suggested that variants in the 3′ regulatory region flanking kinectin 1 gene (KTN1) most significantly regulate the gray matter volume (GMV) of the putamen.*
- *In total, 1136 single-nucleotide polymorphisms covering the entire 3′ regulatory region of KTN1 were analyzed in 111 844 patients with schizophrenia vs. 215 087 healthy subjects in this study.*
- *The major alleles of 25 KTN1 variants increased the risk of schizophrenia and the GMVs of basal ganglia, including the putamen.*
- *KTN1 variants might play crucial roles in the pathogenesis of schizophrenia.*

to examine the regulatory effects of schizophrenia-associated variants on GMVs, controlling for relevant covariates including age, sex, 4 MDS components, total intracranial volume, and diagnosis (when applicable, as most participants did not have neurodegenerative or neuropsychiatric disorders).

Regulatory Effect of Risk Variants on the Surface Area and Average Thickness of Cortices

A total of 36 936 subjects underwent analysis, comprising 33 992 individuals of European descent from the UKBB and 49 ENIGMA cohorts, along with 8 non-European cohorts with 2944 participants.[70] Cortical surface area (SA) and thickness (TH) measurements were obtained from in vivo whole brain T1-weighted MRI scans using FreeSurfer.[71] Surface area and TH were quantified for each subject across the entire cortex and within 34 distinct gyral-defined regions in each hemisphere, based on the Desikan–Killiany atlas.[72] Surface area and TH were measured.

We investigated the associations of schizophrenia-associated variants with a total of 70 traits, encompassing SA and TH of 34 cortical areas, average TH, and total SA. They were evaluated through multiple linear regression analyses, controlling for various factors such as diagnosis, ancestry proportions, age, gender, average TH, and total SA.

Results

Replicable Associations Between Risk Variants and Schizophrenia

A total of 25 risk SNPs spanning the entire 3′ regulatory region flanking *KTN1* demonstrated association with schizophrenia across ≥2 analyzed cohorts (Tables 1-3). Within these SNPs, 24 distal variants from *KTN1* were situated within the same variant block ($r^2 = 1$), while 1 proximal variant (rs10137995) remained independent of this block ($r^2 = 0.002$) (Supplementary Figure 1).

The major alleles (with a frequency, $f > 0.5$) of all 24 variants within the block exhibited a nominal increase in schizophrenia risk across 5 independent samples of European or mixed European and East Asian origin ($8.4 \times 10^{-4} \leq P \leq .049$; Table 1). Additionally, the major allele A of rs10137995 significantly increased schizophrenia risk in 1 European sample ($P = 8.0 \times 10^{-3}$; $q = 0.002$) and nominally in 1 African-American sample ($P = .012$; Table 3). Interestingly, none of these identified variants significantly regulated the expression of *KTN1* mRNA in the brain.

Table 1. Associations of *KTN1* Single-Nucleotide Polymorphisms Within a Block with Schizophrenia in 5 Samples

			P-Values for "SNP–Schizophrenia" Associations					P (β) for "SNP–GMV" Associations	
			dbGaP Data		PGC Data			ENIGMA2 Data	
			Sample 1	Sample 2	I	II	III		
			"phg000013"	"nonGAIN"	"daner"	"rall"	"scz.swe"		"ENIGMA2"
			Europeans	Europeans	Europeans + Asians	Europeans	Europeans		Europeans
	Genomic	Risk	Cases = 1351	1437	56418	36989	13833	Effective	Pallidum
SNP	position	allele	Controls = 1378	1347	78818	113075	18310	allele	n = 13688
rs34036456	55515657	A	1.8×10^{-3}	0.016	1.7×10^{-3}	2.9×10^{-3}	0.040	A	0.049 (6.148)
rs1542577	55516009	A	3.0×10^{-3}	0.046	1.7×10^{-3}	3.0×10^{-3}	0.040	A	0.047 (6.210)
rs34467825	55521079	G	0.011	0.019	1.7×10^{-3}	3.6×10^{-3}	0.034	G	0.038 (6.499)
rs35257549	55523610	G	1.9×10^{-3}	0.021	1.1×10^{-3}	1.8×10^{-3}	0.018	G	**0.016** (7.709)
rs35408298	55523626	T	1.9×10^{-3}	0.021	9.5×10^{-4}	1.6×10^{-3}	0.018	T	**0.017** (7.632)
rs34334073	55523811	C	1.9×10^{-3}	0.017	1.1×10^{-3}	1.8×10^{-3}	0.018	C	**0.015** (7.738)
rs35829669	55523849	G	1.9×10^{-3}	0.019	1.1×10^{-3}	1.8×10^{-3}	0.018	–	–
rs12880666	55524342	G	2.8×10^{-3}	0.015	1.3×10^{-3}	2.9×10^{-3}	0.019	G	**0.015** (7.734)
rs12880724	55524549	C	2.6×10^{-3}	0.019	1.1×10^{-3}	1.8×10^{-3}	0.018	–	–
rs12883824	55530038	C	3.0×10^{-3}	0.027	3.5×10^{-3}	5.4×10^{-3}	0.028	–	–
rs12884345	55530432	A	3.0×10^{-3}	0.027	4.0×10^{-3}	8.4×10^{-3}	0.028	A	**0.012** (8.627)
rs12880629	55532790	G	2.6×10^{-3}	0.027	0.701	–	–	–	–
rs12886405	55533851	G	3.0×10^{-3}	0.030	1.0×10^{-3}	1.8×10^{-3}	0.018	G	**0.015** (7.786)
rs12887940	55534128	T	3.0×10^{-3}	0.030	9.9×10^{-4}	1.8×10^{-3}	0.018	T	**0.015** (7.786)
rs12887272	55534572	A	3.9×10^{-3}	0.019	9.6×10^{-4}	1.8×10^{-3}	0.019	A	**0.015** (7.786)
rs12892142	55534928	C	3.1×10^{-3}	0.030	0.727	–	–	–	–
rs12883777	55537300	C	8.5×10^{-3}	0.025	8.5×10^{-4}	1.8×10^{-3}	0.021	C	**0.015** (7.807)
rs12889395	55538139	C	5.7×10^{-3}	0.016	8.5×10^{-4}	1.8×10^{-3}	0.022	C	**0.014** (7.866)
rs12889609	55538299	C	6.6×10^{-3}	0.026	9.2×10^{-4}	1.7×10^{-3}	0.021	C	**0.014** (7.873)
rs12890551	55538620	G	5.7×10^{-3}	0.023	8.4×10^{-4}	1.8×10^{-3}	0.022	G	**0.014** (7.821)
rs12896789	55541352	C	4.4×10^{-3}	0.016	1.4×10^{-3}	4.0×10^{-3}	0.040	C	0.018 (7.578)
rs2086424	55542460	C	4.3×10^{-3}	0.022	2.9×10^{-3}	8.4×10^{-3}	0.078	C	**0.014** (7.914)
rs2101072	55542648	C	9.0×10^{-3}	0.022	2.9×10^{-3}	8.5×10^{-3}	0.079	–	–
rs12893970	55544255	G	8.0×10^{-3}	0.014	3.2×10^{-3}	7.9×10^{-3}	0.074	G	**.015** (7.873)

Dash represents missing values. Risk alleles are major alleles ($f > 0.5$). The bold *P*-values survived false discovery rate adjustment ($q < 0.05$).
β, regression coefficient; GMV, gray matter volume; PGC, Psychiatric Genomics Consortium; SNP, single nucleotide polymorphism.

Table 2. Associations of *KTN1* Single-Nucleotide Polymorphisms Within a Block with Cortical Surface Area and Thickness in ENIGMA3 Cohorts

	P-values (β) for "SNP–SA" Associations					P-values (β) for "SNP–TH" Associations		
	Europeans		Mixed	Europeans		Europeans	UK Europeans	
	n = 33 992		36 936	33 992		23 909	10 083	
SNP	Effective Allele	Posterior Cingulate	Effective Allele	Medial Orbitofrontal	Entorhinal	Effective Allele	Pars Triangularis	Medial Orbitofrontal
rs34036456	A	0.025 (2.680)	G	0.016 (3.961)	0.041 (1.563)	A	9.9×10^{-4} (0.004)	0.053 (0.005)
rs1542577	A	0.025 (2.708)	G	0.018 (3.915)	0.042 (1.557)	A	9.7×10^{-4} (0.004)	0.053 (0.005)
rs34467825	G	0.023 (2.858)	T	0.021 (3.829)	0.027 (1.738)	G	8.9×10^{-4} (0.004)	0.044 (0.005)
rs35257549	G	0.031 (2.713)	A	0.037 (3.541)	0.034 (1.694)	G	7.1×10^{-3} (0.004)	0.042 (0.006)
rs35408298	T	0.034 (2.833)	C	0.048 (3.375)	0.033 (1.664)	T	5.2×10^{-3} (0.004)	0.037 (0.006)
rs34334073	C	0.028 (2.835)	A	0.041 (3.463)	0.030 (1.726)	C	8.9×10^{-3} (0.003)	0.045 (0.006)
rs35829669	G	0.029 (2.777)	C	0.040 (3.490)	0.030 (1.721)	G	8.9×10^{-3} (0.003)	0.044 (0.006)
rs12880666	G	0.029 (2.518)	A	0.064 (3.099)	0.022 (1.703)	G	9.9×10^{-3} (0.003)	0.054 (0.005)
rs12880724	C	0.031 (2.714)	G	0.038 (3.520)	0.030 (1.720)	C	9.3×10^{-3} (0.003)	0.045 (0.005)
rs12883824	C	0.011 (3.592)	G	0.073 (3.189)	0.020 (1.993)	C	0.021 (0.003)	0.089 (0.005)
rs12884345	A	0.011 (3.444)	C	0.103 (2.859)	0.014 (2.019)	A	0.028 (0.003)	0.098 (0.005)
rs12880629	G	0.030 (2.809)	A	0.047 (3.365)	0.030 (1.715)	G	9.5×10^{-3} (0.003)	0.047 (0.005)
rs12886405	G	0.030 (2.709)	A	0.043 (3.439)	0.031 (1.710)	G	0.011 (0.003)	0.047 (0.005)
rs12887940	T	0.030 (2.697)	C	0.042 (3.449)	0.031 (1.694)	T	0.011 (0.003)	0.048 (0.005)
rs12887272	A	0.030 (2.708)	G	0.043 (3.432)	0.032 (1.699)	A	0.011 (0.003)	0.048 (0.005)
rs12892142	C	0.030 (2.727)	A	0.042 (3.450)	0.031 (1.687)	C	0.011 (0.003)	0.047 (0.005)
rs12883777	C	0.030 (2.720)	T	0.043 (3.425)	0.033 (1.663)	C	0.011 (0.003)	0.048 (0.005)
rs12889395	C	0.030 (2.650)	T	0.050 (3.312)	0.038 (1.583)	C	8.9×10^{-3} (0.003)	0.044 (0.006)
rs12889609	C	0.029 (2.885)	T	0.054 (3.273)	0.042 (1.543)	C	7.4×10^{-3} (0.004)	0.036 (0.006)
rs12890551	G	0.029 (2.661)	A	0.056 (3.232)	0.039 (1.568)	G	8.3×10^{-3} (0.004)	0.037 (0.006)
rs12896789	C	0.050 (2.197)	T	0.053 (3.266)	0.039 (1.498)	C	5.9×10^{-3} (0.004)	0.029 (0.006)
rs2086424	C	0.042 (2.295)	A	0.081 (2.962)	0.037 (1.557)	C	5.8×10^{-3} (0.004)	0.019 (0.006)
rs2101072	C	0.042 (2.306)	G	0.083 (2.943)	0.038 (1.554)	C	5.9×10^{-3} (0.004)	0.019 (0.006)
rs12893970	G	0.043 (2.292)	A	0.085 (2.928)	0.042 (1.507)	G	5.8×10^{-3} (0.004)	0.019 (0.006)

β, regression coefficient; SA, surface areas; SNP, single nucleotide polymorphism; TH, thickness.

The Schizophrenia-Associated Alleles Significantly Increased the Gray Matter Volumes of Subcortical Nuclei

Most schizophrenia-associated alleles within the 24-variant block demonstrated an increase in pallidum GMV ($\beta > 0$; $0.012 \le P \le .049$), with 14 remaining significant after FDR adjustment ($0.040 \le q \le 0.049$; Table 1). The schizophrenia-associated allele of rs10137995 increased GMVs of basal ganglia, including putamen ($6.0 \times 10^{-11} \le P \le 1.1 \times 10^{-4}$; $4.2 \times 10^{-9} \le q \le 8.0 \times 10^{-4}$), caudate ($8.7 \times 10^{-4} \le P \le 9.4 \times 10^{-3}$; $0.049 \le q \le 0.203$), pallidum ($P = 6.0 \times 10^{-4}$; $q = 0.004$), and nucleus accumbens ($P = 2.7 \times 10^{-5}$; $q = 0.002$), with most remaining significant after FDR correction ($q < 0.05$; Table 3). Notably, among all subcortical nuclei, putamen was most significantly regulated across 2 independent samples. However, no regulatory effects on GMVs of amygdala, hippocampus, and thalamus were observed ($P > .05$).

The Schizophrenia-associated Alleles Regulated the Cortical Surface Area and Thickness

Most, if not all, schizophrenia-associated alleles within the block nominally increased ($\beta > 0$) SA of the posterior cingulate cortex ($.011 \le P \le .050$) and TH of the pars triangularis cortex ($8.9 \times 10^{-4} \le P \le .028$) and medial orbitofrontal cortex ($.019 \le P \le .048$). However, these alleles also decreased ($\beta < 0$) SA of the medial orbitofrontal cortex ($.016 \le P \le .050$) and entorhinal cortex ($.014 \le P \le .042$) (Table 2). The schizophrenia-associated allele of rs10137995 nominally increased ($\beta > 0$) SA of the insular cortex ($P = .017$) and TH of the parietal [superior ($P = .049$), precuneus ($P = 9.4 \times 10^{-3}$), and inferior ($P = .015$)] and transverse temporal cortices ($P = 5.5 \times 10^{-3}$). However, it also decreased ($\beta < 0$) SA of whole ($P = 5.2 \times 10^{-3}$) and temporal [pole ($P = 7.4 \times 10^{-3}$), superior ($P = .025$), and middle ($P = 2.2 \times 10^{-3}$)] cortices, as well as TH of the frontal [superior ($P = .016$) and rostral middle ($P = .023$)] cortices (Table 3). None of these regulations survived FDR correction.

Discussion

Across the entire 3′ regulatory region flanking *KTN1*, we identified 25 risk variants for schizophrenia. The major alleles of 24 variants, clustered in a distal block, along with 1 independent variant (rs10137995) proximal to *KTN1*, consistently increased schizophrenia risk in European, Asian, and/or African populations across 5 and 2 independent cohorts, respectively; the latter survived FDR correction. These schizophrenia-associated alleles significantly augmented the GMVs of basal ganglia, particularly the putamen, and nominally influenced the TH and SA of the frontal, parietal, temporal, insular, and posterior cingulate cortices. These findings underscore the functional significance of *KTN1* variants in schizophrenia pathogenesis.

Interestingly, the schizophrenia-associated alleles identified in the present study, referred to as "Block #2," exhibited distinct functional features compared to those in another *KTN1* variant block ("Block #1") reported in a previous study by Mao et al (summarized in Table 4),

Table 3. Associations of rs10137995 with Schizophrenia, Gray Matter Volumes of Basal Ganglia, and Cortical Surface Area and Thickness

***P* for "SNP–Schizophrenia" Associations**					***P*-values (Effect Sizes) for "SNP–GMV" Associations**											
dbGaP Data					**ENIGMA2 Data**											
Sample #3	**Sample #4**															
"CMB-trios"	**"phg000014"**															
Europeans	**Africans**															
Risk	**Cases = 621**	**Cases = 1195**		**Effective**	**"unretricted" Europeans Putamen**	**"ENIGMA2" Europeans putamen**	**"unretricted" Europeans caudate**	**"ENIGMA2" Europeans caudate**	**"unretricted" Europeans pallidum**	**"unretricted" Europeans accumbens**						
allele	**Total = 1826**	**Controls = 954**		**allele**	**29 451**	**13 688**	**29 451**	**13 688**	**29 451**	**29 451**						
A	**8.0×10^{-3}**	0.012		A	**6.0×10^{-11}**	**1.1×10^{-4}**	**8.7×10^{-4}**	9.4×10^{-3}	**6.0×10^{-4}**	**2.7×10^{-5}**						
					($Z = 6.543$)	($\beta = 35.018$)	($Z = 3.331$)	($\beta = 19.220$)	($Z = 3.430$)	($Z = 4.200$)						
***P*-values (β) for "SNPSA" Associations**									***P*-values (β) for "SNP-TH" Associations**							
ENIGMA3 data									ENIGMA3 data							
Effective Allele	Mixed 36936 Insula	Effective Allele	Mixed 36936 Whole	Mixed 36936 Temporal Pole	Europeans 33992 Superior Temporal	Mixed 36936 Middle Temporal	Effective Allele	Europeans 23909 Superior Parietal	Europeans 23909 Precuneus	Europeans 23909 Inferior Parietal	Europeans 23909 Transverse Temporal	Effective Allele	Europeans 23909 Superior Frontal	Europeans 23909 Rostral Middle Frontal		
A	0.017	G	5.2×10^{-3}	7.4×10^{-3}	0.025	2.2×10^{-3}	A	0.049	9.4×10^{-3}	0.015	5.5×10^{-3}	G	0.016	0.023		
	($\beta = 4.534$)		($\beta = 466.777$)	($\beta = 1.390$)	($\beta = 5.355$)	($\beta = 8.202$)		($\beta = 0.002$)	($\beta = 0.003$)	($\beta = 0.002$)	($\beta = 0.006$)		($\beta = 0.002$)	($\beta = 0.002$)		

The *P*-values surviving false discovery rate adjustment are bold.
β, regression coefficient; *Z*, meta z-score.

suggesting that they might play differential biological roles even in the same brain region. Block #1 encompasses the ORF, whereas block #2 spans the 3' flanking region. Notably, these 2 blocks exerted opposite effects across various brain areas. Block #2 was associated with basal ganglia volume enlargement, reduced SA of the whole and middle temporal cortices, reduced TH of the superior frontal and rostral middle frontal cortices, elevated SA of the insula, and elevated TH of the transverse temporal and precuneus cortices; while block #1 showed contrasting effects (see Table 4), which could be well interpreted by the hypothesis that these 2 variant blocks play dominant roles in different areas.

Basal ganglia, crucial for emotion and cognition, was significantly and reliably regulated by the schizophrenia-associated variants. Alleles within block #2 may upregulate kinectin expression in neurons, leading to cell size expansion,[38-41] thereby contributing to basal ganglia volume enlargement, in line with most previous findings of enlarged BG GMVs in schizophrenia patients. Among the basal ganglia nuclei, the putamen was most prominently affected, aligning with prior reports identifying *KTN1* as a key regulator of putamen GMV.[38] These findings support the notion that basal ganglia volumes, particularly the putamen, could serve as predictors of schizophrenia risk.[31]

Basal ganglia is integral to the cognitive/associative "cortico-basal ganglia-thalamo-cortical" loop. Enlargement of the basal ganglia may enhance neurotransmission within this loop. As a compensatory response to this enhancement, the volumes of certain cortices such as the whole, temporal (pole, superior, middle and entorhinal), and frontal (superior and rostral middle) cortices might diminish, thereby reducing the excitatory glutamatergic output from cortices to the basal ganglia, in order to restore neural transmission within this loop. This interpretation well explains the associations observed between block #2 alleles and cortical volume reduction in various areas, and is consistent with previous findings that most cortical volumes were reduced in schizophrenia patients. Volume reduction in these regions may relate to schizophrenia symptoms, such as auditory hallucinations (superior and middle temporal cortices),[73,74] self-awareness (superior frontal cortex),[75] and executive function (emotion regulation and working memory) (rostral middle frontal cortex).[76]

Our earlier study revealed that the schizophrenia-associated alleles within block #1 decreased the BG GMV. As another compensatory response to the BG GMV expansion by block #2, the expression of BG volume-controlling alleles, such as those in block #1, may be activated to restore the BG GMV. However, in the BG, block #2 may exert dominance over block #1, leading to an incomplete restoration of BG volumes. This hypothesis provides a plausible explanation for the opposing effects of the 2 variant blocks on BG expansion while the eventual BG GMV remains expanded in schizophrenia patients, consistent with existing literature.

On the other hand, we observed that the schizophrenia-associated alleles within block 2 were associated with the volume increase of other cortices, including the frontal (pars triangularis), parietal (superior, precuneus, and inferior), temporal (transverse), limbic system (posterior cingulate), and insular cortices. It is hypothesized that in some of these regions, such as the insular, transverse temporal, and precuneus cortices, block #1 may exert dominance over block #2. As per our earlier report, block #1 shrinks the volumes of these cortices (see Table 4). Consequently, as a compensatory response to this shrinkage,

Table 4. Distinct Functions of 2 *KTN1* Variant Blocks

	Previous Study (Mao et al., 2023)	Current Study
Schizophrenia-associated variants	Independent **block #1** (see Figure S1)	Independent **block #2** (including rs10137995; see Figure S1)
Locations of variant blocks	Open reading frame	3′ flanking region
Replicable associations with schizophrenia across dbGaP cohorts	2 European and 1 African cohorts	2 European cohorts
Replicable associations with schizophrenia across PGC cohorts	1 European cohort	3 European cohorts
Associations with KTN1 mRNA expression	14 brain regions	0 region
Associations with GMVs of the basal ganglia	**Reduction**	**Enlargement**
Associations with ICV	Yes	No
SA increased by schizophrenia-risk alleles	**Whole**, lingual, **middletemporal**	Posteriorcingulate, **insula**
SA decreased by schizophrenia-risk alleles	Precuneus, **insula**, frontalpole, superiortemporal	Medialorbitofrontal, entorhinal, **whole**, **temporal** [pole, superior, **middle**]
TH increased by schizophrenia-risk alleles	Frontalpole, **superiorfrontal, rostralmiddlefrontal**, fusiform, lateralorbitofrontal, inferiortemporal, parsopercularis, isthmuscingulate	Parstriangularis, medialorbitofrontal, parietal [superior, inferior, **precuneus**], **transversetemporal**
TH decreased by schizophrenia-risk alleles	Pericalcarine, **transversetemporal, precuneus**, paracentral′	**Superiorfrontal, rostralmiddlefrontal**

GMV, gray matter volumes; ICV, intracranial volume; PGC, Psychiatric Genomics Consortium; SA, surface area; TH, thickness. *The bold in the top 7 rows emphasizes the key difference between two blocks; the bold in the bottom 4 rows emphasizes the similar brain regions between two blocks and between increased and decreased SA or TH.*

the expression of cortical volume-expanding alleles, such as those in block #2, may be activated to restore the cortical volumes. However, this activation of block #2 did not fully restore the cortical volumes reduced by block #1, also because block #1 may exert dominance over block #2 in these regions. This hypothesis elucidates how the "recessive" associations between "block #2 alleles and cortical volume increase" coexist with the "dominant" associations between "schizophrenia and eventual cortical volume reduction" in these brain areas.

Notably, the schizophrenia-associated alleles in block #2 were associated with both the SA reduction and TH expansion of the same medial orbitofrontal cortex. This supports the radial unit hypothesis, which posits that SA and TH have differential origins in neurodevelopment.[77]

In summary, we have identified significant and functionally relevant risk variants for schizophrenia in the 3′ regulatory region flanking *KTN1* (referred to as "Block #2" here). This set of risk variants appears to be the major determinants of genetic factors dominantly regulating the volume expansion of the basal ganglia, particularly the putamen, in individuals with schizophrenia. Meanwhile, this set of risk variants might play a "recessive" role in the volumes of certain cortices, such as the insular, transverse temporal, and precuneus cortices.

Limitations and future work: We investigated the potential functions of the target alleles by analyzing their statistical correlations with schizophrenia risk, subcortical GMVs, and cortical SA and TH. However, it is crucial to recognize that these correlations only offer indirect evidence regarding the biological functions of the alleles. To gain a deeper understanding of their roles, direct evidence from gene knockout experiments is essential. For future research, direct knockout of blocks #1 and #2, respectively, would help elucidate their opposite functional roles in BG GMV. Furthermore, all the aforementioned correlations were studied in separate cohorts, limiting our ability to thoroughly explore interactions between these factors and their moderating effects. For future research, it would be advantageous to examine these functional studies within the same sample.

Data Availability Statement: *The datasets used for the analysis described in this manuscript were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gap, with the following accession numbers: phs000021.v3.p2, phs000687.v1.p1. and phs000167.v1.p1.*

Ethics Committee Approval: *This study was approved by the Ethics Committee of Yale University (approval number: 1007007175; date: April 29, 2004).*

Informed Consent: *Informed consent was obtained from the patient who agreed to take part in the study.*

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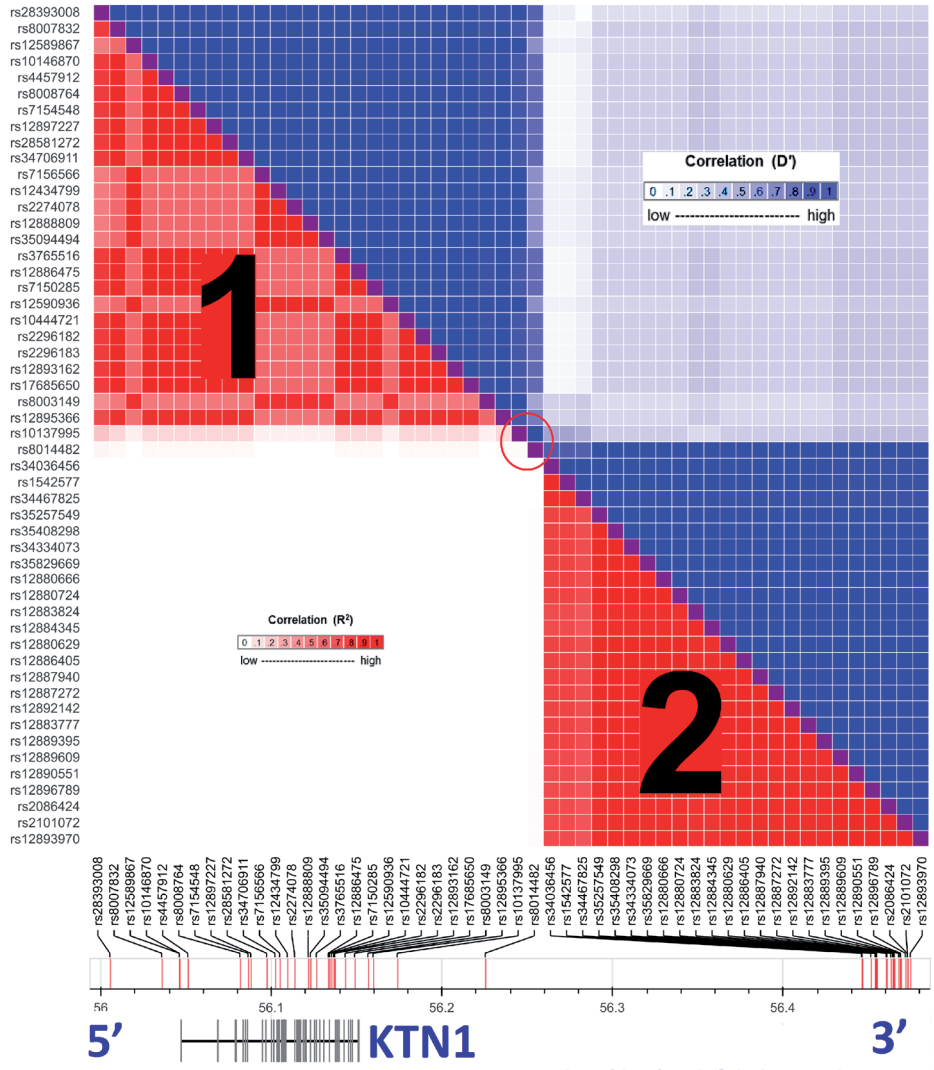

Supplementary Figure S1. LD map of risk *KTN1* variants for schizophrenia [Blocks #1 and #2 were reported by Mao et al. 2023 and the present study, respectively; rs10137995 and rs8014482 between two blocks were reported in the present study and omitted (due to opposite effects across samples), respectively. Red and blue squares indicate r^2 and D' values, respectively]

Supplementary Figure 1. LD map of risk *KTN1* Variants for schizophrenia [Blocks #1 and #2 were reported by Mao et al. 2023 and the present study, respectively; rs10137995 and rs8014482 between two blocks were reported in the present study and omitted (due to opposite effects across samples), respectively. Red and blue squares indicate r^2 and D' values, respectively].