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RESEARCH ARTICLE

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SERINC2 increases the risk of bipolar disorder in the Chinese population

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Abstract

Background: Although common variants in a large collection of patients are associated with increased risk for bipolar disorder (BD), studies have only been able to predict 25%-45% of risks, suggesting that lots of variants that contribute to the risk for BD haven't been identified. Our study aims to identify novel BD risk genes.

Methods: We performed whole-exome sequencing of 27 individuals from 6 BD multi-affected Chinese families to identify candidate variants. Targeted sequencing of one of the novel risk genes, *SERINC2*, in additional sporadic 717 BD patients and 312 healthy controls (HC) validated the association. Magnetic resonance imaging (MRI) were performed to evaluate the effect of the variant to brain structures from 213 subjects (4 BD subjects from a multi-affected family, 130 sporadic BD subjects and 79 HC control).

Results: BD pedigrees had an increased burden of uncommon variants in extracellular matrix (ECM) and calcium ion binding. By large-scale sequencing we identified a novel recessive BD risk gene, *SERINC2*, which plays a role in synthesis of sphingolipid and phosphatidylserine (PS). MRI image results show the homozygous nonsense variant in *SERINC2* affects the volume of white matter in cerebellum.

Conclusions: Our study identified *SERINC2* as a risk gene of BD in the Chinese population.

KEYWORDS
BD, bipolar disorder, exome sequencing, pedigree analysis, *SERINC2*

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Affiliated Brain Hospital of Guangzhou Medical University contributed majorly in this study.

1 | INTRODUCTION

Bipolar disorder (BD) is a complex mental disorder that principally manifests in mania (or mixed mood) episodes, or hypomania episodes plus an episode of major depression (Phillips & Kupfer, 2013). It affects approximately 1% of the global population and onset usually occurs in adolescence or early adulthood (Ferrari et al., 2016). BD is one of the main causes of disability worldwide and is among the top five leading causes of mental and substance use disorders due to its early onset, recurrence, and severity (Ferrari et al., 2016). Heritability contributes 58% to 85% of an individual's lifetime risk for BD (Baselmans et al., 2021; McGuffin et al., 2003; Song et al., 2015). Furthermore, genetic correlation between BD and other diseases were reported (Carmiol et al., 2014; Cross-Disorder Group of the Psychiatric Genomics C., 2013; Drange et al., 2019; Liu et al., 2020; Murphy et al., 2013; O'Connell et al., 2019), including schizophrenia (SZ), major depressive disorder recurrent (MDDR), substance abuse (SA), generalized anxiety disorder (GAD), attention-deficit/hyperactivity disorder, Alzheimer's disease, obsessive–compulsive disorder.

Despite an estimated lifetime prevalence of ~1% and a huge impact on individuals, families, and public health, little is known about the complex etiology of BD. Improved understanding of the genetic basis of BD has the potential to reduce its impact by improving our understanding of disease etiology, supporting the identification of novel drugs and therapies, enabling better targeting of preventive and therapeutic approaches, and providing more accurate risk prediction.

Recent large-scale genome-wide association studies (GWAS) have identified hundreds of risk variants. Variants in genes including calcium voltage-gated channel subunit (CACNA1C), Tetratricopeptide Repeat And Ankyrin Repeat Containing 1 (TRANK1), ankyrin 3 (ANK3), spectrin repeat-containing nuclear envelope protein 1 (SYNE1), and teneurin transmembrane protein 4 (TENM4) have shown significantly replicable, genome-wide associations with BD (Ferreira et al., 2008; Gordovez & McMahon, 2020; Hou et al., 2016; Psychiatric GCBDWG, 2011; Rathje et al., 2021; Sklar et al., 2008; Stahl et al., 2019; Xu et al., 2014). GWAS in Han Chinese population also revealed similar BD genetic architecture. Recently TMEM108 locus was identified a novel candidate locus contributing to the risk of BD for Chinese Han specially (M. T. Lee et al., 2011; Li et al., 2021).

Although common variants in a large collection of patients suggest an increased risk for BD, these studies have limited power to identify causal genes (Purcell et al., 2014) and were only able to predict approximately 25%–45% of the risk for BD (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Gordovez & McMahon, 2020; Hou et al., 2016; Stahl et al., 2019), suggesting that a vast number of rare variants that contribute to the risk for BD still haven't been discovered. It has been reported that possession of one or a few rare variants can dramatically increase disease risk in a given multi-affected family (Ament et al., 2015; Goes, 2016; Rao et al., 2017). Thus, our study aimed to identify risk genes from multi-affected families. Meanwhile, by investigating the alterations in the brain sub regions associated with risk variants using magnetic resonance imaging (MRI), we aimed to provide further clue of the pathophysiology of BD.

2 | METHODS AND MATERIALS

2.1 | Assessments and selection of families

All individuals were recruited from the inpatient and outpatient department at the Affiliated Brain Hospital of Guangzhou Medical University. Study procedures were approved by the Institutional Review Boards at the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital). Written informed consent of all participants was obtained in advance of enrollment in the study. Study subjects underwent blinded, independent psychiatric assessment using the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) employing the Structured Clinical Interview for DSM-IV Axis I Disorders. The information of individuals who could not attend the face-to-face assessment (such as the dead relatives), was collected from different provenances, including medical records, case history, and/or family informants. The disease history of all multi-affected Chinese families had been evaluated with the Family Interview for Genetic Studies. Inclusion criteria of multi-affected families include the following (Phillips & Kupfer, 2013): the proband had a diagnosis of BDI or BDII based on DSM-IV criteria, and at least one relative satisfied the requirements for diagnosis with Axis I or Axis II psychiatric disorders (Ferrari et al., 2016); all participants were Han Chinese and from southern China. The families were excluded if the proband had (Phillips & Kupfer, 2013): any current Axis I diagnosis besides BD (Ferrari et al., 2016), obvious somatic illnesses (McGuffin et al., 2003), neurological diseases, or (Song et al., 2015) a history of traumatic brain injury that caused a disturbance in consciousness. We collected a total of 27 multi-affected Chinese Han families. To identify risk genes, we further selected 6 of the multi-affected families in which the proband had a diagnosis of BD and mental diseases were transmitted over at least two generations. These families contained 111 individuals in total, of whom 22 were affected and 89 unaffected (Figure 1a). 52 of the core family members out of these 111 individuals participated in face-to-face assessment and offered blood samples for DNA extraction. Twenty-seven of these 52 participants, consisting of 6 probands and their nearest relatives, were selected for exome sequencing (3–6 subjects per family, 2–4 affected subjects per family). In total, 10 unaffected individuals and 17 affected individuals were selected with the following diagnoses: BDI ($n = 6$), BDII ($n = 5$), major depressive disorder ($n = 1$), SZ ($n = 3$), substance abuse ($n = 1$), and generalized anxiety disorder ($n = 1$).

Subjects for replication: we selected another 1029 Chinese subjects, including 717 sporadic patients with BD and 312 healthy controls (HC). HC consisted of individuals with no family or personal history of psychiatric illness, no obvious somatic illnesses, no neurological diseases, and no history of traumatic brain injury.

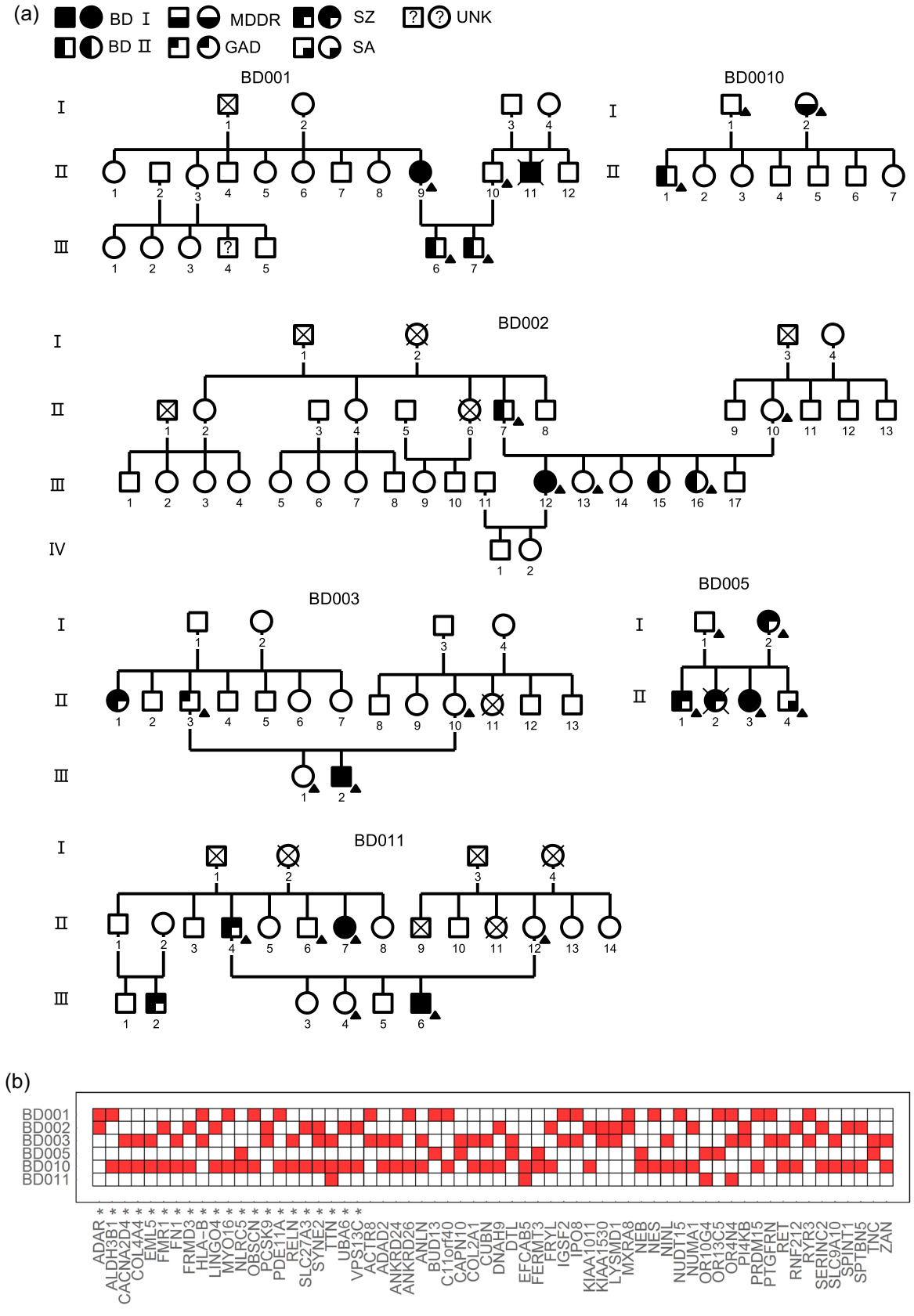

FIGURE 1 (See caption on next page)

TABLE 1 Subjects for brain structural imaging study (total 213 samples, age ≥ 18) (mean ± *SD*)

Variable	BD subjects (*n* = 134)			HC (*n* = 79)		BD vs HC	HO vs non-HO
	C/C (*n* = 103)	C/T (*n* = 23)	T/T (*n* = 8)	C/C (*n* = 66)	C/T (*n* = 13)	Statistic (*p* value)	Statistic (*p* value)
Sex (male/female)	48/55	11/12	4/4	35/31	6/7	0.474 (.491)	0.005 (.946)
Age (years)	26.11 ± 6.89	24.71 ± 4.51	32.375 ± 14.26	24.68 ± 4.61	23.92 ± 5.44	3.335 (.069)	9.360 (.003)
Education	12.48 ± 3.33	14.17 ± 2.31	12.38 ± 3.89	15.21 ± 1.82	15.08 ± 1.50	37.011 (<.001)	1.494 (.223)
HAM-D	3.44 ± 5.23	3.35 ± 3.59	6.00 ± 3.96	0.39 ± 0.84	0.15 ± 0.38	33.202 (<.001)	6.307 (.013)
YMRS	3.82 ± 6.88	3.80 ± 6.22	4.25 ± 5.31	0.16 ± 0.60	0.23 ± 0.83	23.083 (<.001)	0.881 (.349)

BD patients were identified as previously described. Ten milliliters of blood was collected from each participant for extracting the genomic DNA samples.

2.2 | Whole exome sequencing and primary identification of risk candidates

Due to the high genetic correlation between BD and its comorbidities (e.g., SZ, MDDR, GAD, SA) (Ament et al., 2015; et al., 2013), individuals suffering from BD or its comorbidities were considered affected during primary identification of risk candidates. Whole exome sequencing of 27 individuals (17 affected, 10 unaffected) from 6 multi-affected families (Figure 1a) was performed according to the Ion PI™ Hi-Q™ Sequencing 200 Kit, covering 95.31% of exomes with 123.94 × mean coverage. Variants that passed quality control were identified by the Ion Torrent Variant Caller 4.4. Rare or uncommon variants with read coverage ≥ 40 and minor allele frequency (MAF) ≤ 5% were filtered out for annotation of potential function-disrupting variants (frame-shift insertions and deletions (indels), nonsense single nucleotide variants (SNVs), and predicted damaging protein function SNVs) using Polyphen-2 (Adzhubei et al., 2010). Next, inheritance models (dominant and recessive) were applied to identify associated variants for each family respectively. To increase power, we only focused on variants with complete penetrance. Then, genes associated with BD in multiple families in pedigree analysis were identified as risk candidates. Last, exome-wide association analysis was performed with all the 27 individuals to identify potential risk candidates.

2.3 | Validation of risk candidates

One of the risk candidate variants in *SERINC2* identified from BD002 family was validated in additional 19 individuals from BD002 family (Figure 1a) and 1029 subjects for replication using Sanger targeted sequencing.

2.4 | MRI and statistical analysis

Two hundred and thirteen subjects participated in the brain structural imaging study, including 4 BD patients from the BD002 family, and 209 subjects (130 sporadic BD subjects and 79 HC) from the Chinese cohort (Table 1).

Imaging data were acquired within 3 days after clinical assessment, using a Philips Achieve X-series 3.0 Tesla scanner with an eight-channel SENSE head coil in the Guangzhou Huiai Hospital (Affiliated Brain Hospital of Guangzhou Medical University), China. We collected the High-resolution T1-weighted images using a sagittal T1-weighted 3D turbo field echo (T1W 3D TFE) sequence. The parameters were: repetition time = 8.2 ms, echo time= 3.8 ms, field of view = 256 × 256 mm^2, view matrix = 256 × 256, slices = 188, slice thickness = 1 mm.

All structural MRI images were inspected for gross artifacts. To measure the subcortical volume of the hippocampus and cerebellum, the FreeSurfer software v.6.0 was used followed by a series of standard procedures (Fischl et al., 2002; Fischl, 2012; Postelnicu et al., 2009). Six subcortical indexes were considered regions of interest (ROIs): right and left hippocampal volumes, right and left white matter cerebellar volumes, and right and left gray matter cerebellar volumes. Statistical analyses were performed using IBM SPSS Statistics (Version 22.0). Normality and homogeneity of the variables were verified, and the variables that fell short of normal distribution transformation or homogeneity were transformed. Comparisons of demographic and clinical data were performed using ANOVA and χ^2 tests.

The subjects were divided into five groups: *SERINC2* rs2275434 homozygous carriers with BD (T/T HO BD),

FIGURE 1 Genograms of six multi-affected families and their candidate risk genes. (a) Individuals labeled with black triangles underwent whole exome sequencing. (b) Heat map illustration of 62 common candidate risk genes existing in more than one family. Twenty-one genes (* labeled) had previously been reported to be associated with BD or SZ. Red indicates variant in a gene was identified as risk candidate from the pedigree analysis of a family. BDI, type I bipolar disorder; BDII, type II bipolar disorder; GAD, generalized anxiety disorder; MDDR, major depressive disorder, recurrent; SA, substance abuse; SZ, schizophrenia; UNK, unknown phenotype (not ascertained)

heterozygous carriers with BD (C/T HE BD), reference carriers with BD (C/C ref BD), healthy heterozygous carriers (C/T HE H), and healthy reference carriers (C/C ref H). As the volumetric measurements needed to be normalized by intracranial volume (ICV) (Buckner et al., 2004), comparisons of subcortical structure volumes among five subgroups were performed using ANCOVA with age, sex, and ICV as covariates, the brain ROIs as dependent variables, and the genotype as independent variables. Post hoc comparisons between subgroups were made using the Bonferroni correction.

3 | RESULTS

3.1 | Identification of BD and comorbidity-associated candidate variants through exome sequencing of multi-affected families

Whole exomes of 27 individuals (17 affected, 10 unaffected) from 6 multi-affected families were sequenced (Figure 1a). Rare or uncommon function-disrupting variants for each individual were identified. Pedigree analysis were then applied to identify the BD associated variants for each family (Table 2) (Section 2). To increase the power, we focused on 62 common risk genes existing in multiple families (Figure 1b). 33.87% (21/62) of these genes had a previously known association with BD or SZ.

To identify the BD risk variants under an additive model, function-disrupting variants from all the families were included in the exome-wide association study. The top disease-associated variants were in AGRN, CDK18, OR2T8, EVC2, LHPP, NID2, and CASS4 (Figure S1). Four of them (AGRN, EVC2, LHPP, and CASS4) had been previously identified to have associations with BD or SZ (Bodily et al., 2016; Ginns et al., 2015; Malhotra et al., 2011; Neff et al., 2009; Nurnberger et al., 2014). CDK18, OR2T8, and NID2 were identified in this study.

In total, 69 candidate genes (62 from the dominant or recessive models and 7 from the additive model) were identified in the first round.

3.2 | Dysfunction in the extracellular matrix (ECM) and calcium signaling increases the risk of BD

To reveal the functional impact of the 69 risk candidates, functional enrichment analysis was performed using DAVID (Huang da et al., 2009), based on functional annotation (Gene Ontology), pathway (KEGG, BBID, BIOCARTA), and protein structure (INTERPRO, SMART, PIR_SUPERFAMILY). The top significantly enriched cluster contained ECM-related functions: pathways and domains including ECM receptor interaction ($p = 1.5 \times 10^{-5}$), ECM organization ($p = 5.7 \times 10^{-5}$), and cell adhesion ($p = 7.0 \times 10^{-4}$) (Figure S2). 42% (29/69) of our candidate genes were related to the ECM, including 13 published genes and 16 novel genes. The second cluster involved calcium signaling, including calcium ion binding ($p = 7.5 \times 10^{-3}$) and calmodulin-binding ($p = 8.1 \times 10^{-2}$).

3.3 | A novel variant in *SERINC2* is significantly associated with BD

We next focused on one of the most interesting candidate risk genes, *SERINC2*. *SERINC2* encodes serine incorporator 2, which incorporates serine into membranes and promotes the synthesis of two important serine-derived membrane lipids: sphingolipids and phosphatidylserine (PS) (Inuzuka & Hayakawa, 2005). *SERINC2* has never been reported to be associated with BD, but was reported to be a significant and replicable risk gene for alcohol dependence (Zuo et al., 2014; Zuo et al., 2015; Zuo, Wang, Zhang, Krystal, et al., 2013; Zuo, Wang, Zhang, Li, et al., 2013) and a risk gene for autism spectrum disorder (Hnoonual et al., 2017), which shared a partial etiology with BD (Prisciandaro et al., 2017; Skokauskas & Frodl, 2015; Yasseen et al., 2010). We hypothesized that the variant in *SERINC2* might lead to structural abnormalities in a patient's brain, which increases the risk of BD.

To test this hypothesis, we focus on an uncommon nonsense variant rs2275434 on exon 4 of the *SERINC2* (uc009vtw.1). The homozygous variant was detected in 3 BD cases (II-7, III-12 and III-16), while heterozygous variant existed in two unaffected

TABLE 2 Total number of candidates variants identified for each family in the first round pedigree analysis

		DOMINANT				RECESSIVE			
Pedigree	No. of individuals	SNP	MNP	INS	DEL	SNP	MNP	INS	DEL
BD001	4	57	20	35	56	18	5	10	9
BD002	5	39	0	9	30	2	0	7	10
BD003	4	191	22	50	111	23	8	22	25
BD005	5	85	17	21	37	18	2	7	9
BD010	3	133	0	120	227	31	0	42	46
BD011	6	18	1	1	5	1	1	2	3
Total	27	523	60	236	466	93	16	90	102

individuals (II-10 and III-13) in BD002, which only suffered from BD (Figure 1a). To validate the risk association of this variant in large cohort, we performed targeted Sanger sequencing (Methods and materials) of another 14 relatives in this family. 13 unaffected members were identified as absent ($n = 9$) or heterozygote ($n = 4$), while 1 affected individual (III-15) who suffered from type II BD was identified as a homozygote (Figure 2a–c), which perfectly fits the recessive model. These results further confirmed a significant association between the nonsense *SERINC2* variant and BD ($p = 1.3 \times 10^{-5}$) in this family with more than 10 years follow-up. To further evaluate the impact of this variant on BD-affected patients in the Chinese population, we recruited and analyzed 717 sporadic BD patients and 312 unaffected HC using targeted sequencing and found that all the individuals ($n = 9$) carrying the homozygous *SERINC2* variant were BD-affected ($p = .04$, Fisher's exact test) (Figure 2d), while heterozygous carriers did not show an increased BD risk. Taken together, these results reveal a strong association between the early stop of *SERINC2* and BD in a recessive manner.

3.4 | *SERINC2* is significantly associated with increasing right cerebellum white matter volume in BD

SERINC2 is highly expressed in cerebellum and hippocampus and plays an important role in the synthesis of sphingolipid and phosphatidylserine (PS) (Inuzuka & Hayakawa, 2005), which are important structural lipids in brain. To further evaluate the impact of this variant, we analyzed structural abnormalities in the cerebellum and hippocampus in 213 subjects who participated in the brain structure imaging study. Demographic and clinical characteristics of these subjects were shown in Table 1. We observed a significant difference in white matter volume of right cerebellum among five groups of individuals (ANOVA, $F = 4.482$, $p = .012$). Further analysis showed that the white matter volume of right cerebellum in HO cases, all of whom were BD patients (T/T HO BD), was significantly larger than that of the other four groups (Figure 2e). C/T HE BD: $p = .015$, C/C ref BD: $p = .002$, C/T HE H: $p = .001$, C/C ref H: $p = .002$, post-hoc test). No significant differences in right cerebellum white matter volume were observed among these four groups in a pairwise comparison.

4 | DISCUSSION

BD is a complex mental disorder. Heritable factors comprise the majority of BD risk factors. However, common variants in a large collection of patients could only explain about 25%–45% of the risk for BD (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Gordovez & McMahon, 2020). Rare variants fitting the genetic inheritance model in multi-affected families could contribute additional risk for BD.

In our study, consistent with previous research, we detected an increased burden of uncommon variants in ECM and calcium ion binding in BD multi-affected pedigrees. The ECM comprises approximately 20% of the normal adult brain and wraps around all brain cells (Chvatal et al., 1999; Sykova & Nicholson, 2008; Thorne & Nicholson, 2006). It has been shown to play a key role in the regulation of multiple neurodevelopmental processes including neuronal genesis, neuronal differentiation, neuronal migration, and neuronal network formation, all of which are directly related to the pathophysiology of BD and SZ (Berretta, 2012; Eastwood & Harrison, 2003; Guidotti et al., 2000; Impagnatiello et al., 1998; Pantazopoulos et al., 2010; Takahashi et al., 2011; Zaharieva et al., 2008). Calcium signaling has been reported to be one of the most consistently affected functions in multiple psychiatric studies (Ament et al., 2015; Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Krumm et al., 2014; Purcell et al., 2014), leading to vast changes in physiological processes including abnormal neuronal excitability, synaptic transmission, and synaptic plasticity (Ghosh & Greenberg, 1995).

Secondly, we identified *SERINC2* as a novel risk gene for BD. *SERINC2* and its produces are key components for maintaining the structure and function of biological membranes. It is interesting that most of the top candidate genes in BD up to now (Orrù & Carta, 2018; Stahl et al., 2019), such as CACNA1C, ODZ4, SYNE1, also play vital roles in biological membranes activities. These previous findings fit with our current results, highlighting the cell membrane dysfunction involvement in the etiology of BD.

As the product of SERINC2, sphingolipids are abundant in the brain, particularly in the myelin sheaths that surround nerve cell axons as insulators (Olsen & Faergeman, 2017; Voet et al., 2008). Defects in the assembly of sphingolipids would lead defective myelin insulation, which is essential for the transmission of action potentials and the transduction of neuronal signal, and consequently is crucial for normal sensory function and cognition. This defect can be detected via MRI of brain white matter, which is mainly composed of myelinated axons. We identified a significant association between the nonsense variants in *SERINC2* and an increase in right cerebellum white matter volume, where the *SERINC2* is highly expressed (Inuzuka & Hayakawa, 2005), suggesting that the early stop of SERINC2 could result in abnormalities of serine incorporation into sphingomyelin. The resulting defective sphingomyelin may accumulate and increase the white matter volume in the right cerebellum, which has been reported to be significantly associated with SZ and autism (Courchesne et al., 1994; K. H. Lee et al., 2007; Levitt et al., 1999). White matter abnormalities, including white matter hyper intensities (Beyer et al., 2009; Kempton et al., 2008), decreased density (Bruno et al., 2004; McDonald et al., 2004; McIntosh et al., 2005; Stanfield et al., 2009), and reduced integrity of WM tracts (Sarrazin et al., 2014), have been reported in BD neuroimaging studies. Another study found that greater vermis white matter volume in patients with SZ significantly correlated with the severity of positive symptoms and impairment in cognitive function, such as impaired verbal logical memory (Levitt et al., 1999). Taken together,

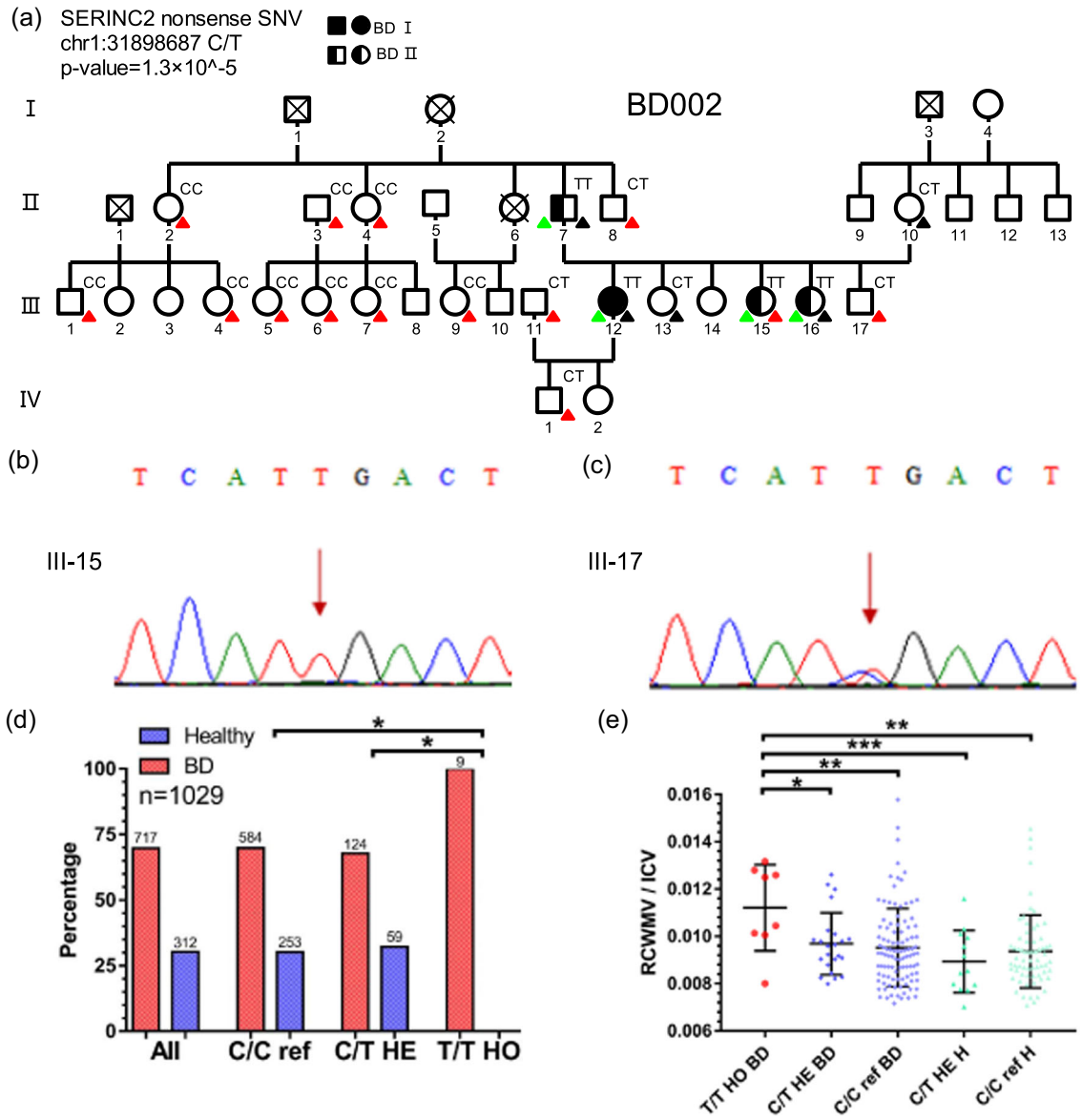

FIGURE 2 A*SERINC2* variant is significantly associated with BD. (a) Pedigree showing that a *SERINC2* variant fits the recessive inheritance pattern for BD in 19 individuals from the BD002 family ($p = 1.3 \times 10^{-5}$). Black triangles below an individual indicate whole exome sequencing. Red: *SERINC2* targeted sequencing. Green: magnetic resonanceimaging. (b, c) Partial electropherograms of *SERINC2* gene mutations in III-15 and III-17, respectively. Homozygous variation T/T in affected III-15 individual, heterozygous variation C/T in unaffected III-17 individual (red arrow) were detected. (d) All the individuals ($n = 9$) carrying the homozygous variation were affected by BD, out of 717 sporadic patients and 312 normal individuals. The number of subjects in each group is shown on top of each bar. T/T HO: *SERINC2* T/T homozygous carrier, C/T HE: *SERINC2* C/T heterozygous carrier, C/C ref: *SERINC2* reference C/C carrier, All: all the individuals tested by Sanger sequencing. (e) The volume of white matter in the right cerebellum of eight homozygous carriers was significantly higher than in other groups. Right cerebellum white matter volume (RCWMV) is normalized by intracranial volume (ICV). C/T HE BD: *SERINC2* C/T heterozygous carrier affected by BD. C/T HE H: *SERINC2* C/T heterozygous healthy carrier

the present results shed lights on a link between *SERINC2* and the abnormal phospholipid metabolism on central nervous system in BD.

Additionally, PS, another product of SERINC2, is the major anionic phospholipid class in cell membranes, with the highest concentrations in neural tissues (Kim et al., 2014). PS is critical for neuronal differentiation , survival, and synaptic neurotransmission (Kim et al., 2014). It facilitates the activation of Akt and protein kinase C signaling, which are considered to be involved in the pathology of BD and are also the therapeutic targets of mood stabilizers (Abrial et al., 2014; Campbell & Campbell, 2020; Huang et al., 2011; Machado-Vieira et al., 2015; Newton & Keranen, 1994). PS also restores the discharge of dopamine, and the dopamine reward system may act as a functional modulator of different mood states (Arjmand et al., 2017; Orłowski et al., 2012). Further evidence from clinical

trials has shown that PS supplementation has a positive influence on mood in elder patients with late-life depression, as well as in elder patients with dementia (Komori, 2015; More et al., 2014). This evidence from both basic and clinical research suggests that *SERINC2* may have an important effects on BD through PS. Thus, our study highlights the potential of PS to act as a precise treatment strategy in BD patients with *SERINC2* defects.

Last but not the least, according to our targeted sequencing results on *SERINC2* of 1029 subjects (Figure 2d), the estimated MAF of Southern Han Chinese is 0.098. Compared to the MAF from European (Italia: 0.02, Finland: 0.03, and Spain: 0.03), Chinese have a much higher chance to be homozygote, which could potentially increase the risk for BD.

This is the first report of an association between the abnormality of *SERINC2* and the occurrence of BD, as well as abnormal right cerebellum white matter volume. Considering the promising impact of this variant on the synthesis of PS, which has already been showed therapeutic potential for BD in previous studies (Arjmand et al., 2017; Orłowski et al., 2012). Further effort is needed to reveal functional mechanisms and develop new therapies.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

PEER REVIEW

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