Received: 24 November 2024 | Revised: 24 January 2025 | Accepted: 4 February 2025

DOI: 10.1002/pcn5.70071

PCN Reports
Psychiatry and Clinical Neurosciences
Open Access

ORIGINAL ARTICLE

Family study of bipolar disorder with comorbid anxiety disorder points to *THSD7A* with possible role of parent-of-origin effect

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Funding information
Japan Agency for Medical Research and Development, Grant/Award Number: 24tm0424224; Japan Society for the Promotion of Science, Grant/Award Number: 22H00468

Abstract

Aim: The aim of this study was to provide new insights into the genetics of bipolar disorder (BD) by analyzing BD comorbid with anxiety disorders.

Methods: Structured interviews were conducted with BD patients and their parents. Cases were classified into those with comorbid anxiety spectrum (AS) and those without. The family history of patients with BD with comorbid AS was assessed. Focusing on parent-of-origin effects and genomic imprinting from the results, imprinted genes and tested single nucleotide polymorphisms (SNPs) in the identified genes were investigated for an association with BD by transmission disequilibrium test (TDT) using published whole-exome sequencing data.

Results: The incidence of comorbid AS among all the patients with BD analyzed in this study was 39.6%. Patients with BD whose fathers had AS or mood disorders exhibited a significantly higher rate of AS. Among the known imprinted genes, two were associated with BD: *THSD7A* and *CACNA1C*. By pruning SNPs, six variants of the *THSD7A* exons and four variants of the *CACNA1C* exons were included in the analysis. Among these, one variant of *THSD7A*, rs2074603, showed over-transmission from parents to patients with BD. Furthermore, it was nominally significant only for fathers when TDT was performed separately for fathers and mothers.

Conclusion: *THSD7A* may play a role in BD with parent-of-origin effects. Further research is necessary to explore the mechanisms by which genomic imprinting is associated with BD.

Clinical Trial Registration: N/A.

KEYWORDS

anxiety disorders, bipolar disorder, comorbidity, genomic imprinting, single nucleotide polymorphism

INTRODUCTION

Bipolar disorder (BD) is a mental disorder characterized by recurrent manic and depressive episodes, affecting approximately 1% of the global population.[1] This disorder significantly affects the personal relationships and occupational life of affected patients, potentially causing severe social dysfunction.

Genetic factors are involved in the pathogenesis of BD. Furthermore, the analysis of genes associated with BD has evolved with advances in genomic technologies. Genome-wide association studies (GWASs) have identified many genomic loci associated with BD.[2,3] Some genes, such as *ANK3* and *CACNA1C*, are reproducible in subsequent larger-scale GWASs. In GWASs targeting the Japanese population,[4] *FADS1/2* has significant genome-wide associations replicated in Europe.[5] A GWAS conducted by the Psychiatric Genomics Consortium involving 41,917 BD cases identified 64 associated loci, including *ANK3*, *CACNA1C*, and *FADS2*.[6]

Large-scale whole-exome analyses have explored the association between BD and rare variants. The Bipolar Exome (BipEx) project, a study of 13,933 BD cases, found that protein truncating variants, which are extremely rare in the general population, are relatively common in patients with BD. When combined with the results of whole-exome analyses of schizophrenia, *AKAP11* was identified as a susceptibility gene for both disorders.[7]

Since BD is a highly heterogeneous disorder,[8] stratification based on clinical characteristics effectively generates genetically robust findings. Genetic analyses have been conducted based on BD Type I and Type II,[9] psychotic features,[10] symptom domains,[11] and suicide risk.[12]

The comorbidity of anxiety has been studied extensively through genetic analysis.[13,14] The present study aims to provide new insights into the genetics of BD by stratifying BD by comorbid anxiety disorders, using clinical information of patients with BD obtained through structured interviews.[15] Patients with BD are more susceptible to anxiety disorders than the general population.[16] BD cases with comorbid anxiety disorders are characterized by treatment resistance, such as lower responsiveness to mood stabilizers,[17] longer manic and depressive episodes,[18] and higher suicide risk.[19] Because the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) has added the specific term "with anxiety distress" to the criteria for BD,[20] the association between BD and anxiety disorders is expected to further attract research attention. From a genetic perspective, BD comorbid with anxiety disorders is possibly a distinct subgroup of BD, and family studies have been conducted to investigate this possibility.[21–23]

Our analysis of the clinical information of patients with BD and their parents indicates that parent-of-origin effects are potentially involved in the transmission of BD because inherited diseases vary in their effects on the comorbidities of BD depending on parent of origin. Family studies in the 20th century that explored parent-of-origin effects in BD have had conflicting results.[24–27] Combining clinical information and genetic analyses could provide more reproducible results.

The present study investigated the genetic variants that confer a risk of BD by stratifying BD by comorbid anxiety disorders. Because the initial analysis indicated the potential role of parent-of-origin effects, we searched an existing database for known genes subjected to genomic imprinting, which is the biochemical basis of parent-of-origin effects.[28] By filtering genes with susceptible genetic loci according to large-scale GWASs for BD,[6] we identified two imprinted genes, *THSD7A* and *CANA1C*. We further investigated whether the paternal expression of these genes is associated with the development of BD by a family-based association analysis using our whole-exome sequencing data of families with BD for which structured interviews were performed.

METHODS

Collection and Analysis of Clinical Information from Patient Trio With BD

Structured interviews with BD patients and their parents were conducted by senior psychiatrists, junior psychiatrists, and a psychologist using the Japanese version of the Mini International Neuropsychiatric Interview (MINI).[29] Of the 287 families that participated in the project, we excluded cases that lacked responses from both the patient and their parents. All diagnoses were made based on DSM-IV because it was used at the start of this project.[30] Senior psychiatrists made the diagnosis alone, while the diagnosis of junior psychiatrists and the psychologist were confirmed by a senior psychiatrist.

We also excluded cases in which the proband was not diagnosed with BD. Thus, a total of 225 cases (probands of trios) were included in the analysis: 144 BD Type I cases and 81 BD Type II cases. These cases were then classified into those with comorbid anxiety spectrum (AS) and those without. AS was defined according to DSM-IV as a condition involving the following disorders: panic disorder, including symptom-limited attacks; agoraphobia; social anxiety disorder; generalized anxiety disorder; obsessive–compulsive disorder; and post-traumatic stress disorder.

Statistical Analyses

The relationships between various clinical variables of BD—such as comorbidity with AS and BD subtype—are complex in the context of genetic factors. Therefore, we employed multiple logistic regression analysis to evaluate the effects of these interacting factors on AS comorbidity. The dependent variable was the presence or absence of AS comorbidity in the proband. Independent variables included BD subtype (Type I or II) of the proband, proband sex, presence of AS in either parent, and presence of mood disorders in either parent. All analyses were conducted using R statistical software (The R Foundation for Statistical Computing, Vienna, Austria, Version 4.1.1).[31]

Analysis of Common Variants of Imprinted Genes

Because we focused on parent-of-origin effects and genomic imprinting based on the results of the preceding analysis, we

explored imprinted genes and tested single nucleotide polymorphisms (SNPs) in the identified genes for an association with BD through the transmission disequilibrium test (TDT)[32] using the published whole-exome sequencing data of the families with BD based on the analysis of data from the structured interviews in these families.[15] Of the 225 families in which the proband was diagnosed with BD, genetic information for the proband and both parents were available for 192 families and their data were analyzed.

Parents were considered affected if they had BD or major depressive disorder. We selected SNPs by linkage disequilibrium (LD) pruning, a method of filtering SNPs based on LD and minor allele frequency (MAF).

We utilized the co-occurrence data of SNPs in the Japanese population from the Tohoku Medical Megabank Organization (ToMMo)[33] and data on exonic regions retrieved from the University of California-Santa Cruz Genome Browser[34] to construct a dataset containing LD for SNPs located within the exonic regions.

SNPs with MAF > 0.05 were selected. Then, for each pair of these SNPs in LD with $r^2 > 0.2$, we adopted the SNPs with higher MAF in the Japanese population. The SNPs selected as described were included in our analysis.

Ethical Considerations

This study was approved by the Juntendo University Certified Review Board, and all participants provided informed consent. All data were kept confidential and patient anonymity was maintained throughout this study.

RESULTS

Collection and Analysis of Clinical Information from Trio Families With BD

The comorbid rate of AS in all the patients with BD analyzed in this study was 39.6%, 37.5% for Type I, and 43.2% for Type II, with no significant differences among the three (Table 1 and S1).

Multiple logistic regression analysis revealed that the explanatory variables selected in the most appropriate model that were associated with AS comorbidity with BD were "being a female proband," "having a father with a history of AS," and "having a father with a history of mood disorders" (Table 2). The regression coefficients for these variables indicated non-significance except for "being a female proband," although they were significant on univariate analysis (Table S2). We conducted multiple logistic regression analysis on "presence of AS or mood disorders in the mother or father," which was selected in the most appropriate model, and its regression coefficients were significant (Table 2), implying that female patients with BD had a significantly higher comorbidity rate compared to male patients. Furthermore, patients with BD whose fathers had AS or mood disorders also had a significantly higher rate than those with fathers without either disorder. A multiple logistic regression analysis was conducted for the 192 families included in the genetic analysis, and the same explanatory variables were selected. "Presence of AS or mood disorders in the father" remained significantly associated with AS comorbidity with BD (Table S3).

TABLE 1 Clinical information of bipolar disorder probands and parents.

Characteristics	Probands	Mothers	Fathers
Age of BD onset (years)	24.2 ± 8.1	—	—
Male sex (%)	89 (39.6)	0 (0.0)	225 (100)
BD Type I (%)	144 (64.0)	1 (0.4)	3 (1.3)
BD Type II (%)	81 (36.0)	0 (0.0)	5 (2.2)
BD comorbid AS (%)			
Type I	54 (37.5)	—	—
Type II	35 (43.2)	—	—
Type I + II	89 (39.6)	—	—
Mood disorders (%)	—	25 (11.1)	25 (11.1)
AS (%)	—	2 (0.9)	6 (2.7)
High suicide risk[a] (%)	38 (16.9)	0 (0)	0 (0)
BD with AS	27 (30.3)	—	—
BD without AS	11 (8.1)	—	—

Note: Age of BD onset: Some values were missing for nine probands.
Abbreviations: AS, anxiety spectrum; BD, bipolar disorder.
[a]Probands with AS were significantly more likely to be at high risk for suicide than probands without AS ($p < 0.0001$).

Exploration of Imprinted Genes Associated With BD

These results indicate that parent-of-origin effects are potentially involved in the transmission of BD because only the paternal history of disease was associated with AS comorbidity with BD in the proband. Therefore, we focused on genes subject to genomic imprinting, which is the biochemical basis of parent-of-origin effects.

We searched for genes that have been associated with BD in the GWAS[6] from among the genes that undergo genomic imprinting. With a focus on the 64 loci indicated in the GWAS[6] with BD, we targeted 422 genes within ±50 kb of these loci that are in LD with $r^2 \geq 0.6$. We then used the list of known human genomic imprinted genes published in "*Genomic Imprinting and Physiological Processes in Mammals*,"[35] which includes 228 genes (152 paternally expressed, 48 maternally expressed, 24 unknown, three isoform-specific, and one tissue-specific). Of these, the 152 paternally expressed genes, including 84 genes experimentally confirmed in placental tissue, were considered as candidates. We then searched for overlapping genes between the 84 canonical paternally expressed genes and 422 BD-GWAS associated genes.

TABLE 2 Multiple logistic regression analysis of bipolar disorder with comorbid anxiety spectrum.

Variable	*B* (SE)	OR (95% CI)	*p*-value (Regression)[a]	*p*-value (χ^2)[b]
Proband's sex	0.78 (0.30)	2.00 (1.10–3.70)	0.025	0.022
Father with AS	2.18 (1.15)	8.27 (1.14–168.21)	0.067	0.037
Father with mood disorders	0.67 (0.46)	1.92 (0.78–4.83)	0.155	0.027
Father with AS or mood disorders	1.10 (0.43)	3.00 (1.29–6.98)	0.011	0.015

Note: Proband's sex: male, 0; female, 1. Father with AS/mood disorders: without the disease, 0; with the disease, 1.

Abbreviations: AS, anxiety spectrum; CI, confidence interval; SE, standard error.

[a]*p*-value for significance test of regression coefficients.

[b]*p*-value when performing a chi-square test to determine an association with comorbid AS in bipolar disorder.

As a result, two genes, *THSD7A* (thrombospondin type-1 domain containing 7A) and *CACNA1C* (calcium voltage-gated channel subunit alpha1 C), met the criteria. We searched the 48 maternally expressed genes for negative controls, but no gene satisfied the criteria. *THSD7A* and *CACNA1C* were also included in 365 genes in LD with 44 significant genome-wide loci identified by analysis of BD Type I conducted in the GWAS.[6] Although they were not significant in BD Type II, one significant gene was identified in the GWAS.

Analysis of Common Variants of Imprinted Genes

Among the single nucleotide variants on the *THSD7A* and *CACNA1C* exons, those that were pruned by LD were analyzed by TDT.[32]

Six variants on the *THSD7A* exons and four variants on the *CACNA1C* exons were included in the analysis. Figure 1 shows the positions of exonic SNPs with MAF > 0.05 on *THSD7A* (Figure 1a) and *CACNA1C* (Figure 1b); LD between these SNPs was calculated from 192 trios in this study. The variants included in the analysis are also shown in Figure 1.

Among these variants, one variant on *THSD7A*, rs2074603,[36] showed over-transmission from parents to patients with BD even after Bonferroni correction (corrected $p = 0.047$). Interestingly, the variant was nominally significant only for fathers when TDT was performed separately for fathers and mothers. (Table 3).

DISCUSSION

This study analyzed the clinical information on patients with BD and their parents. Paternal, but not maternal, history of AS or mood disorders is associated with the comorbidity of AS in the proband. This implies that BD comorbid with AS may be characterized by parent-of-origin effects.

The parent-of-origin effect is a phenomenon where the expression of a gene depends on maternal or paternal inheritance, and is caused by epigenetic mechanisms, mainly genetic imprinting.[28] Previous family studies on parent-of-origin effects of BD found that maternal inheritance was more prevalent than paternal inheritance[26]; however, another study showed that children were more likely to develop BD if their fathers suffered from BD.[24] Yet another study reported no significant difference between maternal and paternal inheritance; however, families with maternally and paternally inherited diseases have different genetic models.[27] Some linkage studies have identified paternally over-transmitted alleles at markers on chromosome 18.[37,38] Thus, no consensus has been reached.

We assumed that genetic analysis may provide stronger evidence for parent-of-origin effects in BD. Therefore, we explored variants on genes subject to genomic imprinting associated with BD. Database searches revealed that *THSD7A* and *CACNA1C* were paternally expressed and associated with BD in GWAS.

THSD7A is known to be one of the genes for which antibodies cause membranous nephropathy[39] and have functions in endothelial cell migration and vascularization in angiogenesis.[40] In the mouse brain, *Thsd7a* is highly expressed in the hippocampal dentate gyrus and the medial habenula.[41] In the hippocampal dentate gyrus, neural sprouting may be increased in BD patients,[42] and hyperactive action-potential firing has been observed in hippocampal-dentate-gyrus-like neurons derived from induced pluripotent stem cells of patients with BD.[43] Volume reduction in the hippocampus has been reported in patients with BD.[44] The habenula sends projections to dopaminergic and serotonergic neurons and regulates anti-reward behaviors, indicating its role in mood disorders.[45] Although controversial, the habenular volume was reported to be reduced in the postmortem brains of patients with BD,[46] and antidepressant treatment can increase the habenular volume, as measured on magnetic resonance imaging.[36] As for genomic imprinting, *THSD7A* exhibits paternal expression in the human placenta.[47]

In neuropsychiatry, rs6955807 on *THSD7A* is associated with plasma kynurenine and kynurenic acid concentrations,[48] which affect glutamatergic neurotransmission.[49] *THSD7A* expression levels are also associated with the response to antipsychotics in patients with schizophrenia.[50] GWASs found that rs3807866, located in the upstream region of *THSD7A* and between *THSD7A* and *TMEM106B*, was associated with anxiety disorder.[51,52] The BipEx project[7] found that damaging missense variants on the exons of *THSD7A* are significantly more prevalent in BD cases than in controls ($p = 0.000458$, Fisher's test). A GWAS of patients with BD showed that rs78835388 on *THSD7A* may be associated with a poor response to mood stabilizers.[53] The latest GWAS[54] found that *THSD7A* was included in the

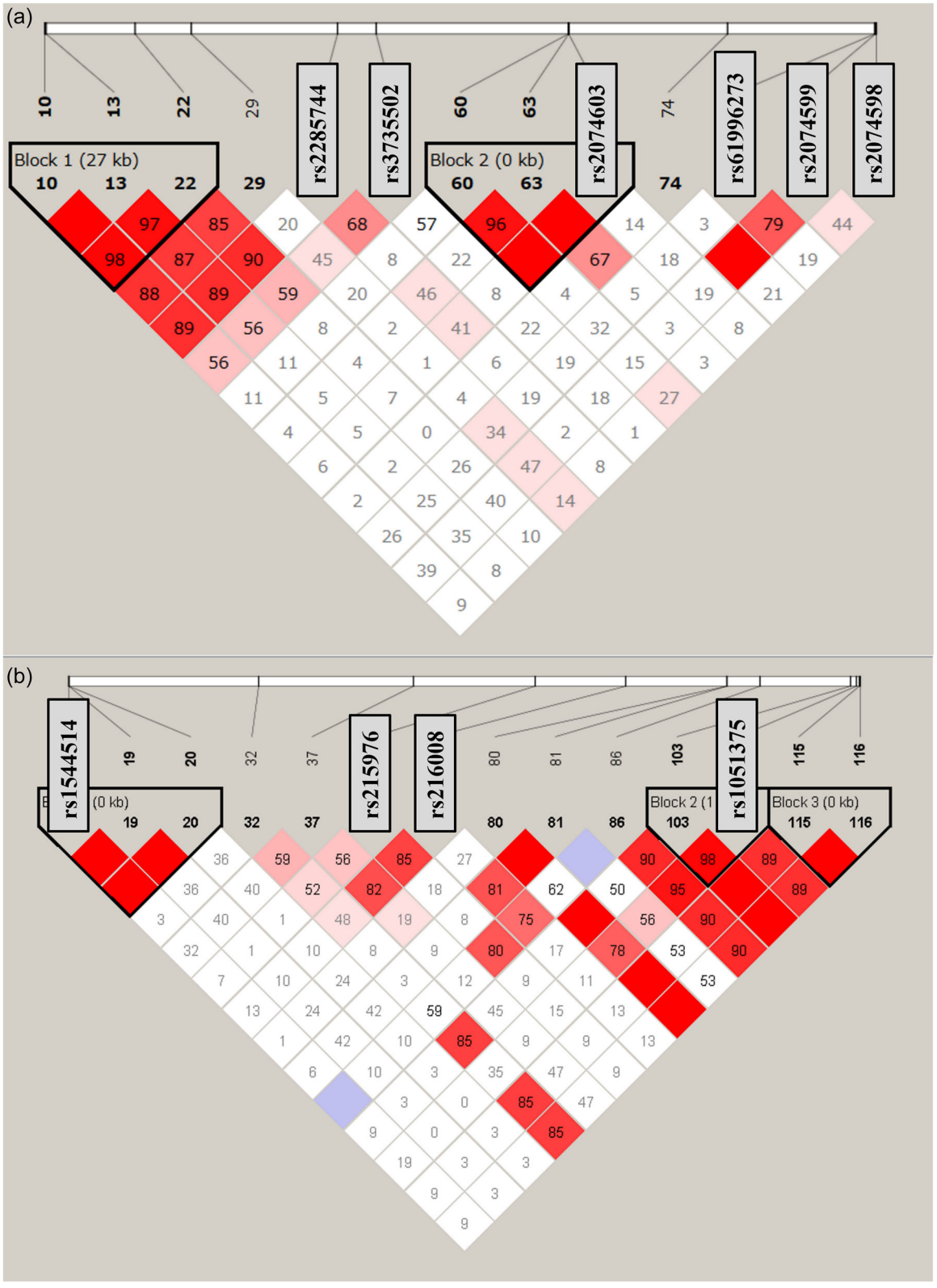

FIGURE 1 Exonic single nucleotide polymorphisms (SNPs) on *THSD7A* and *CACNA1C*. (a) SNPs with a minor allele frequency (MAF) > 0.05 on the exons of *THSD7A* and linkage disequilibrium (LD) between them. The positions of six variants in the analysis were indicated by their SNP IDs. (b) SNPs with MAF > 0.05 on the exons of *CACNA1C* and LD between them. The positions of four variants in the analysis were indicated by their SNP IDs. Figures were produced using Haploview Version 4.1. (https://www.broadinstitute.org/haploview/haploview).

TABLE 3 Data on the variants analyzed in this study on the exons of *THSD7A* and *CACNA1C*.

Gene	Variant position, dbSNP ID	Alleles, function	MAF[a]	MAF (ToMMo)[b]	T:U[c]	TDT *p*-values[d]		
						Parents	Mothers	Fathers
THSD7A	chr 7:11469934 rs2285744	C > G missense	G:0.225	G:0.223	62:61	0.928	1.000	0.900
	chr 7:11481915 rs3735502	T > C synonymous	C:0.119	C:0.112	35:38	0.726	1.000	0.622
	chr 7:11541507 rs2074603	T > C synonymous	C:0.471	C:0.479	104:67	0.0047*	0.064	0.032*
	chr 7:11636228 rs61996273	T > C synonymous	C:0.262	C:0.232	69:74	0.676	0.154	0.409
	chr 7:11636438 rs2074599	G > C missense	C:0.122	C:0.114	39:49	0.286	0.042*	0.662
	chr 7:11636750 rs2074598	G > A synonymous	A:0.397	A:0.399	94:85	0.501	0.518	0.756
CACNA1C	chr 12:2449020 rs1544514	G > A synonymous	A:0.068	A:0.074	24:22	0.768	0.835	0.532
	chr 12:2585472 rs215976	C > T synonymous	T:0.372	T:0.336	83:92	0.496	0.758	0.502
	chr 12:2611971 rs216008	C > T synonymous	T:0.439	T:0.407	94:95	0.942	0.922	1.000
	chr 12:2679713 rs1051375	A > G synonymous	G:0.428	G:0.444	74:101	0.041	0.122	0.182

Note: In the TDT conducted separately for fathers and mothers on rs2074603, the results obtained for fathers only were significant. It was also significant when the TDT was performed on rs2074599 for mothers only, but not those for the analysis of both parents.

Abbreviations: MAF, minor allele frequency; SNP, single nucleotide polymorphism; TDT, transmission disequilibrium test; ToMMo, Tohoku Medical Megabank Organization.

[a]The MAF of each variant in this study.

[b]The MAF in the Japanese population obtained from the ToMMo.

[c]The number of transmitted (T) and untransmitted (U) alleles.

[d]The *p*-values when the transmission disequilibrium test was performed for parents and for mothers and fathers separately.

*$p < 0.05$.

genes annotated to fine-mapped SNPs from the multi-ancestry meta-analysis excluding self-reported data.

Our genetic analysis revealed that rs2074603, a variant of the *THSD7A* exons, showed over-transmission from parents to patients with BD. This implies that genomic imprinting of *THSD7A* may contribute to the parent-of-origin effects of BD. Since this variant is a synonymous variant, variants of *THSD7A* associated with BD may not necessarily be rs2074603 itself. It is possible that other functional variants in LD with this variant, such as exonic missense variants or variants on regulatory regions, are also associated with BD. When we searched for variants in LD with $r^2 > 0.2$ with rs2074603 in the Japanese population by ToMMo[33]; one missense variant, rs47, was found on the exons of *THSD7A*. However, it was not significant on TDT ($P = 0.205$). Alternatively, rs2074603 may be associated with the regulation of *THSD7A* expression. Expression quantitative trait locus (eQTL) mapping showed that C/C carriers of rs2074603 exhibit a significantly high expression of *THSD7A* in the nucleus accumbens.[55]

The effect of the presence or absence of rs2074603 in the proband on AS comorbidity rate of the proband and AS or mood disorder rate of their father/mother were not conclusive (Tables S4–S6).

This study reports for the first time the comorbidity rate of anxiety disorders in Japan. The comorbidity rate of 39.6% found in this study is comparable to those previously reported in other countries also based on DSM-IV, such as 38.3% in the United States,[56] 55.8% in Canada,[16] and 24% in France.[17]

Though we started this study from focusing on BD with comorbid anxiety, we could not show any evidence on the relationship between genetic factors of BD and AS in this study. There is a significant genetic correlation between BD and lifetime anxiety disorder,[52] which suggests the common genetic factors between these two disorders. On the other hand, polygenic risk for anxiety is reportedly associated with comorbid anxiety disorder in BD, implicating that genetic factors of these two disorders are different.[57] Further studies will be necessary to understand the genetic relationship between these disorders.

One limitation of this study was the definition of AS used, which was based on DSM-IV and thus does not reflect the latest findings.

However, even after excluding obsessive–compulsive disorder and post-traumatic stress disorder from the AS definition based on DSM-5, the comorbidity rate was 37.8%, with no significant difference. A significant association was still found in probands with BD with AS comorbidity and paternal history of AS or mood disorders.

Although small sample size can be another limitation, we assume that a certain degree of the power of test has been obtained. If TDT is performed separately for fathers and mothers, informative families would be limited to those in which the parent is heterozygous of the wild-type allele and the variant allele. Using MAF of the variant, the theoretical number of such families is $192 \times 2 \times \mathrm{MAF} \times (1 - \mathrm{MAF})$. Since the test statistic for TDT follows a chi-square test with one degree of freedom, when the significance level $\alpha = 0.05$, the power of test $1 - \beta = 0.9$, and the effect size is 0.3, the required sample size of alleles is 117, hence the required number of families is 117/2 = 58.5. The theoretical number of informative families exceeds 58.5 when MAF > 0.13. Thus, we believe that the analysis for rs2074603 with MAF = 0.471 has sufficient power of test even with the sample size in this study.

Since our analysis targeted exonic SNPs, which were selected by LD pruning, we may not have completely analyzed each gene. Thus, the number of SNPs to be analyzed, including intronic SNPs, may be higher, and appropriate tag SNPs should be selected for future studies.

We focused on imprinted genes suggested in existing databases and did not confirm *in vivo* DNA methylation for these genes. Therefore, future studies are expected to conduct a more targeted, larger-scale analysis of *THSD7A*, and to analyze its actual DNA methylation in the brain.

In conclusion, this study found *THSD7A* may play a role in BD with parent-of-origin effects. Further research is necessary to explore the mechanisms by which genomic imprinting is associated with BD.

AUTHOR CONTRIBUTIONS

Hiroaki Maki and Tadafumi Kato conceived the study. Hiroaki Maki conducted all analyses and wrote the paper. Naomi Sakai, Muneko Kataoka, Kumiko Fujii, Yuki Kageyama, Takashi Hayama, Koji Matsuo, and Tadafumi Kato performed structured interviews. Masaki Nishioka and Tadafumi Kato supervised the project and revised the paper.

ACKNOWLEDGMENTS

This study was supported by AMED grant 24tm0424224 and Grants-in-Aid for Scientific Research (KAKENHI) 22H00468 for Tadafumi Kato.

CONFLICT OF INTEREST STATEMENT

Tadafumi Kato is an Associate Editor of *Psychiatry and Clinical Neurosciences Reports* and a co-author of this article. Tadafumi Kato was excluded from editorial decision-making related to the acceptance and publication of this article. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The whole-exome data with consent for database registration are available through the NBDC Human Database, Japan (JGAS000273/JGAD000379). The interview data are not publicly accessible due to ethical regulations.

ETHICS APPROVAL STATEMENT

This study was approved by the Juntendo University Certified Review Board. All data were kept confidential and patient anonymity was maintained throughout this study.

PATIENT CONSENT STATEMENT

All participants provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Maki H, Sakai N, Kataoka M, Fujii K, Kageyama Y, Hayama T, et al. Family study of bipolar disorder with comorbid anxiety disorder points to *THSD7A* with possible role of parent-of-origin effect. Psychiatry Clin Neurosci Rep. 2025;4:e70071. https://doi.org/10.1002/pcn5.70071