

# A single-nucleotide polymorphism influences brain morphology in drug-naïve patients with major depressive disorder

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**Objective:** Recently, a genome-wide association study successfully identified genetic variants associated with major depressive disorder (MDD). The study identified 17 independent single-nucleotide polymorphisms (SNPs) significantly associated with diagnosis of MDD. These SNPs were predicted to be enriched in genes that are expressed in the central nervous system and function in transcriptional regulation associated with neurodevelopment. The study aimed to investigate associations between 17 SNPs and brain morphometry using magnetic resonance imaging (MRI) in drug-naïve patients with MDD and healthy controls (HCs).

**Methods:** Forty-seven patients with MDD and 42 HCs were included. All participants underwent T1-weighted structural MRI and genotyping. The genotype–diagnosis interactions associated with regional cortical thicknesses were evaluated using voxel-based morphometry for the 17 SNPs.

**Results:** Regarding rs301806, an SNP in the *RERE* genomic regions, we found a significant difference in a genotype effect in the right-lateral orbitofrontal and postcentral lobes between diagnosis groups. After testing every possible diagnostic comparison, the genotype–diagnosis interaction in these areas revealed that the cortical thickness reductions in the MDD group relative to those in the HC group were significantly larger in T/T individuals than in C-carrier ones. For the other SNPs, no brain area was noted where a genotype effect significantly differed between the two groups.

**Conclusions:** We found that a *RERE* gene SNP was associated with cortical thickness reductions in the right-lateral orbitofrontal and postcentral lobes in drug-naïve patients with MDD. The effects of *RERE* gene polymorphism and gene–environment interactions may exist in brain structures of patients with MDD.

**Keywords:** single-nucleotide polymorphism, brain morphology, major depressive disorder, genome-wide association

## Introduction

Major depressive disorder (MDD) is chronic or recurrent disease accompanied with high morbidity and mortality.<sup>1</sup> Heritability of MDD is about 40% by twin study.<sup>2</sup> Lots of genetic loci are attribute to MDD. Each genetic locus influences small effect. Despite the evidence of heritability, the identification of the specific genetic variants involved in MDD remains challenging. Genome-wide association studies (GWASs) investigate the differences in allele frequencies between disease and control groups at millions of frequently occurring single-nucleotide polymorphisms (SNPs) throughout the genome. These differences are possibly functionally relevant

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to the disease or may represent loci that are transmitted in linkage disequilibrium with a causative polymorphism.

Recently, a GWAS successfully identified genetic variants associated with MDD. This study identified 17 SNPs associated with MDD because the study sample exhibited reduced heterogeneity and increased sample size relative to other studies. Hyde et al<sup>3</sup> identified 17 independent SNPs significantly associated with MDD diagnosis. These SNPs were predicted to be enriched in genes that are expressed in the central nervous system and function in transcriptional regulation associated with neurodevelopment.

The critical goal of GWAS is the identification of biological pathways underpinning depression; risk alleles with small effects can also yield enormous insights. Using these significant SNPs facilitates a strategy complementary to intensive phenotyping for identifying common variant associations with phenotypically heterogeneous neuropsychiatric diseases. This strategy may shed light on the massive worldwide impact of such disorders, and any approach that aids in clarifying the pathophysiology is worth considering.

Genetic and epigenetic factors regulating brain development and neurodegeneration may play roles in morphological brain abnormalities in patients with MDD. Regarding MDD, previous magnetic resonance imaging (MRI) studies using voxel-based morphometry (VBM) have reported evidence of a relationship between brain volume and genetic factors, including brain-derived neurotrophic factor, norepinephrine transporter gene (*SLC6A2*), FK506-binding protein 51, and ethylenetetrahydrofolate reductase/catechol-*O*-methyltransferase polymorphisms. In our previous report,<sup>4</sup> we found the SNP (rs2522833) of piccolo presynaptic cytomatrix protein (*PCLO*), playing an important role in monoaminergic neurotransmission in the brain is associated with a gray matter volume reduction in the left temporal pole in drug-naïve, first-episode patients with MDD carrying the C-allele. SNPs used in any previous studies were not included in the ones used in this study.<sup>4-11</sup> To our knowledge, this is the first study that investigates associations between those 17 SNPs and brain morphometry using MRI in patients with MDD and HCs. We identified several new brain regions associated with the recently reported 17 SNPs associated with MDD.

## Patients and methods

### Ethics statement

The study protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health

Japan. Written informed consent was obtained from all subjects who participated in this study. Informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

### Participants

The subjects in the present study were partially overlapped with our recent study.<sup>12-14</sup> Specifically, 12 MDD patients were additionally enrolled in the present study, and five healthy controls (HCs) were excluded because of the lack of their genome samples.

In the present study, MDD patients were recruited between March 2009 and January 2017. All patients were diagnosed by using a fully Structured Clinical Interview for *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text revision* Research Version. Severity of depressive state was evaluated using the 17-item Hamilton Rating Scale for Depression (HAM-D-17).

The psychiatrist included patients who met the following criteria: (a) diagnosed patients with MDD, (b) with a total HAM-D-17 score of  $\geq 14$ , and (c) drug-naïve patients. Patients who met the following criteria were excluded: (a) a history of neurological disease and the presence of psychiatric disorders on either Axis I (schizophrenia, other affective disorders, etc.) or Axis II (personality disorders, mental retardation, etc.), (b) presence of co-morbid substance use disorders, and (c) unwillingness to provide informed consent. Lastly, 47 right-handed drug-naïve patients with MDD were included in this study.

We described the inclusion and exclusion criteria of HCs. The inclusion criteria of HCs were (1) never been diagnosed with an axis I or II psychiatric disorder, as confirmed by the Structured Clinical Interview for the DSM-IV (SCID<sup>15</sup>), (2) no history of psychotropic medication use within the preceding 6 months, (3) no history of significant head injury, seizure, or neurologic condition. The subjects who met even one of those criteria were excluded in the present study. Fifty-two subjects were also recruited from nearby communities as HC.

### Genotyping

Eighty-nine subjects from the neuroimaging study provided a blood sample, from which DNA was extracted using standard laboratory protocols. DNA was isolated from peripheral blood mononuclear cells using the QIAamp DNA Mini-Kit (QIAGEN, Tokyo, Japan). Genotyping was carried out with a PCR SNP genotyping system using the BigDye Terminator v3.1 Cycle Sequencing Kit (Life Technologies Corporation,

Tokyo, Japan). The DNA was read using a BMG Applied Biosystem 3730xl DNA Analyzer (Life Technologies Corporation). The PCR products were purified enzymatically. Sequencing reactions were performed using the Big Dye Terminator v3.1 Cycle Sequencing Kit (Life Technologies Corporation). The sequencing primers used were the same as the PCR primers. The sequences were analyzed with the Applied Biosystems 3730xl DNA Analyzer (Life Technologies Corporation). The sequencing output data were then compared to a reference sequence (NC\_000007.13).

## MRI acquisition

MRI data were obtained based on the methods we have already reported using 3 T MRI system (Signa EXCITE 3T; GE Healthcare, Waukesha, WI, USA) with an eight-channel brain phased-array coil. Original T1 images were acquired by three-dimensional fast-spoiled gradient recalled acquisition with steady state.

All images were corrected for image distortion due to gradient non-linearity using the “Grad Warp” software program<sup>16</sup> and for intensity inhomogeneity with the “N3” function.<sup>17</sup> The regional cortical thickness was estimated using the FreeSurfer v. 5.3.0 software program (<http://surfer.nmr.mgh.harvard.edu>), which has been well documented and is freely available online. The technical details of the cortical thickness analysis have been described elsewhere.<sup>18</sup>

## Image processing

### Whole-brain analyses using SBM

The regional cortical thickness was estimated using the FreeSurfer software program (version 6.0, [www.freesurfer.net/fswiki/HippocampalSubfields](http://www.freesurfer.net/fswiki/HippocampalSubfields)), which has been well documented and which is freely available online. The technical details of the cortical thickness analysis have been described elsewhere.<sup>18</sup> The entire cortex of each participant was inspected visually; topological defects were corrected manually. Cortical thickness measurements were obtained by reconstructing representations of the gray matter–white matter boundary<sup>18,19</sup> and the pial surface. The distance between these surfaces at each point across the cortical mantle was then calculated. For each participant, the regional thickness value at each vertex was mapped to the surface of an average brain template. This allowed for the visualization of data across the entire cortical surface. The data were re-sampled for all participants onto a common spherical coordinate system.<sup>19</sup> The cortical map of each participant was smoothed with a

10-mm kernel in full width at half-maximum (FWHM) for the cortical analyses.

## Statistical analysis

Voxel-wise statistical analysis was used by a surface-based analysis and the Freesurfer statistical tool, QDEC, after 10-mm FWHM kernel smoothing. A general linear model was adopted at each vertex. We estimated the main effects, (a) diagnostic effect (MDD vs HC) and (b) genotype effect in total subjects (the T/T versus the C-carriers) and then (c) genotype–diagnosis interaction effect was estimated. Furthermore, the effects of genotypes in each group (controls carrying the T/T versus controls carrying the C-carrier and MDD carrying the T/T versus MDD carrying the C-carrier) were estimated within the ANCOVA design matrix.<sup>20</sup> Moreover, age and sex were set as inconsiderable factors to control for confounding variables. Controls and patients with MDD included in this study may show different cortical evolution rates. Therefore, we used different offsets and different slopes.

For the cluster analysis, a Monte Carlo simulation was used for correction regarding multiple comparisons; for the cluster-forming, threshold was set at  $P < 0.05$ . We tested clusters against an empirical null distribution of maximum cluster size built by synthesized Z-distributed data across 10,000 permutations, which produced clusters-wise  $P$ -values fully corrected for multiple comparisons.<sup>21,22</sup>

We used values of  $P < 0.05$  (two-tailed) as a statistically significant difference.

## Results

### Participants

The genotypes of the 89 subjects were 47 patients with MDD and 42 HCs. All participants including MDD patients and controls were Japanese. The allele frequencies of the 17 SNPs were within the Hardy–Weinberg equilibrium (Table 1). Rs4543289, rs11209948, and rs8025231 could not perform direct sequence reads because of insufficient volume. Thus, we could not obtain the information of genotyping. The distributions of genotypes are shown in Table 1.

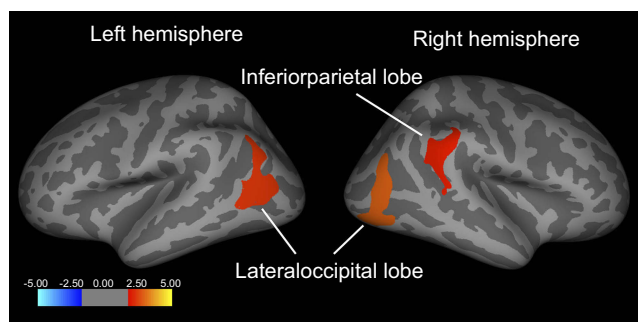
### Effect of diagnosis on cortical thickness

Irrespective of genotype, the cortical thickness showed significant differences between the MDD and HCs. We found that the cortical thicknesses in the left lateral occipital ( $p = 0.005$ , Monte Carlo simulation corrected), right lateral occipital ( $p = 0.001$ , Monte Carlo

**Table 1** Summary of polymorphisms identified across analyses

SNP	Chromosome	Minor allele	Genotype distribution (n=89)	HWE
rs10514299	5	T	CC/CT/TT: 74/13/2	0.145
rs1518395	2	A	GG/AG/AA: 37/45/7	0.184
rs2179744	22	A	GG/AG/AA: 47/40/2	0.05
rs11209948	1	G	NA	NA
rs454214	5	A	GG/AG/AA: 24/44/21	0.924
rs301806	1	C	TT/CT/CC: 56/30/3	0.674
rs1475120	6	C	TT/CT/CC: 47/36/6	0.8
rs10786831	10	A	GG/AG/AA: 36/49/7	0.054
rs12552	13	T	CC/CT/TT: 22/46/21	0.75
rs6476606	9	A	GG/AG/AA: 52/31/6	0.641
rs8025231	15	A	NA	NA
rs12065553	1	G	AA/AG/GG: 43/41/5	0.232
rs1656369	3	T	AA/AT/TT: 64/23/2	0.969
rs4543289	5	T	NA	NA
rs2125716	12	T	CC/CT: 77/12	0.495
rs2422321	1	G	AA/AG: 72/17	0.419
rs7044150	9	T	CC/CT: 82/7	0.699

**Abbreviations:** HWE, Hardy–Weinberg equilibrium; NA, not available.



**Figure 1** Comparison of the cortical thicknesses of patients with major depressive disorder (MDD) and healthy controls (HCs). Red and orange clusters representing significantly thinner cortical regions (bilateral lateral occipital and right inferior parietal lobes) in patients with MDD (FWE corrected  $P < 0.05$ ).

simulation corrected) and right inferior parietal lobes ( $p = 0.010$ , Monte Carlo simulation corrected) were significantly reduced in the patients with MDD than in the HCs. (Figure 1 and Table 2).

### Effect of genotype on cortical thickness

We did not find any effects of 14 SNPs on cortical thickness ( $P > 0.05$ , Monte Carlo simulation corrected).

### Genotype × diagnosis interaction on cortical thickness

For only rs301806, an SNP in the arginine–glutamic acid dipeptide (RE) repeats gene (*REPERE*) regions, we found a significant difference in a genotype effect in the right-

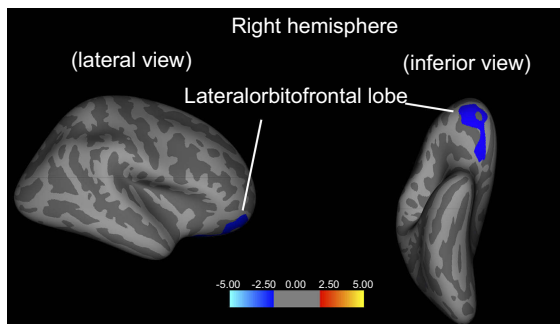
**Table 2** Results of the image analysis

Anatomical regions	cluster size	TalX	TalY	TalZ	CWP
Cortical thickness, between-group comparison (HS > MDD)					
Left lateraloccipital lobe	1,201	-41	-62	7	0.005
Right lateraloccipital lobe	1,393	48	-70	12	0.001
Right inferiorparietal lobe	1,078	52	-45	25	0.010
Genotype × diagnosis interaction on cortical thickness					
Right lateralorbitofrontal lobe	991	29	47	-11	0.016

**Abbreviations:** HS, healthy subjects; MDD, major depressive disorder; CWP, cluster-wise  $P$ -value.

lateral orbitofrontal lobes between the MDD and HC groups ( $p = 0.016$ , Monte Carlo simulation corrected). After testing every possible diagnostic comparison, the genotype–diagnosis interaction in these areas showed that the cortical thickness reductions in the MDD group relative to those in the HC group were significantly larger in T/T individuals than in C-carrier individuals ( $P < 0.05$ , FWE corrected; Figure 2 and Table 2). Table 3 shows the demographic and clinical characteristics of the participants with regard to rs301806.

For other SNPs, we identified no brain area in which a genotype effect differed significantly between diagnosis groups ( $P > 0.05$ , Monte Carlo simulation corrected).



**Figure 2** Genotype  $\times$  diagnosis interaction on cortical thickness. The blue cluster represents the genotype  $\times$  diagnosis interaction effect on the cortical thickness of the right-lateral orbitofrontal lobe (FWE corrected  $P < 0.05$ ).

## Discussion

The *RERE* gene contains SNP rs301806. The *RERE* gene, previously known as atrophin 2 because of similarities between *RERE* and atrophin 1, is termed after the dipeptide repeats present in the carboxyl terminal of *RERE*. To the best of our knowledge, the findings of this study provide the first evidence of a relationship between cortical thickness and polymorphisms in the *RERE* gene in patients with MDD. Specifically, significant *RERE* genotype–diagnosis interaction effects were noted in the right-lateral orbitofrontal and postcentral lobes, which suggested that the *RERE* genotype affects the cortical thickness in MDD. We recruited drug-naive patients with MDD, which is a strength of this study since antidepressant medication may increase heterogeneity and limit the interpretability and generalizability of the results, especially in the light of evidence that drugs may have important effects, such as upregulating neurotrophin expression,<sup>23</sup> altering neuronal remodeling,<sup>24</sup> and protecting against GM loss,<sup>25,26</sup> in both animal and human studies.<sup>27–29</sup> Differences in drug treatment may contribute to variability among MRI results in MDD. In view of this, we targeted our analysis to only drug-naive patients with MDD for eliminating interference by antidepressant treatment. The reduction of cortical thickness noted in this study may be associated with the acute state of MDD and not with the effects of pharmacotherapy and/or duration of the depressive state.

The role of the genetic variation of the *RERE* gene in brain pathology is yet to be elucidated. Jordan et al provided evidence that implicates *RERE* in various 1p36 chromosome-deletion phenotypes.<sup>30</sup> The major clinical features of 1p36 deletion syndrome demonstrate motor developmental delay, hypotonia, and craniofacial dysmorphisms including a large anterior fontanel, prominent forehead and chin, deep eyes, flat nasal bridge, maxillary hypoplasia, and ear asymmetry. Thus, *RERE* may play a pivotal role in normal brain development.<sup>31,32</sup> In addition, a recent report indicated that *RERE* and its *Drosophila* homolog were associated with histone methyltransferases in the regulation of gene expression.<sup>33</sup> Gene–environment interactions play an essential role in MDD pathogenesis, which is a polygenic and heterogeneous disease. A recent hypothesis indicates that certain environmental factors hijack the brain’s epigenetic machinery and, in combination with genetic predispositions, produce several of the behavioral manifestations of MDD.<sup>34,35</sup> Epigenetic modulation comprises three broad umbrella systems: DNA methylation, histone modification, and noncoding RNA-mediated mechanisms. These are meiotically and mitotically heritable changes that are not directly coded in the DNA sequence.<sup>36</sup> Thus, we speculate that *RERE* plays a pivotal role in the pathophysiology of MDD combined with epigenetic mechanisms associated with histone methyltransferases.

In the present study, the association of the SNP in the *RERE* gene (rs301806) with alterations in the reduction of the cortical thickness in the right-lateral orbitofrontal and postcentral lobes in MDD is unclear. A previous study also indicated that MDD was characterized by reduced brain volume in the frontal cortex, orbitofrontal cortex (OFC), cingulate cortex, hippocampus, and striatum.<sup>37</sup> Anterior cingulate cortex, OFC, and dorsolateral prefrontal cortex are all prefrontal regions involved in the automatic regulation of emotional behavior in MDD.<sup>38</sup> The OFC plays a crucial role in neuropsychological functioning including exteroceptive and interoceptive information coding, reward-guided behavior, impulse control, and mood regulation. The OFC

**Table 3** Demographic and clinical characteristics among 4 groups regarding the rs301806

	MDD patients		Healthy subjects	
	C/C and C/T (n=19)	T/T (n=28)	C/C and C/T (n=14)	T/T (n=28)
Male/female	10/9	9/19	10/4	22/6
Age (year)	50.8 $\pm$ 16.0	49.5 $\pm$ 18.7	39.5 $\pm$ 9.8	38.5 $\pm$ 10.1
HAMD-17 score	21.6 $\pm$ 6.8	22.2 $\pm$ 7.1		

**Abbreviations:** MDD, major depressive disorder; HAMD17, 17-item Hamilton Rating Scale for Depression.



may exhibit different involvement in the pathophysiology of MDD<sup>39</sup> and gray matter volume reduction of the OFC in MDD.<sup>40</sup> Reports also indicate decreases in cortical thickness, neuronal sizes, and neuronal and glial densities in cortical layers of the OFC in patients with MDD.<sup>41</sup> However, factors contributing to the alteration of OFC structure in MDD remain unclear. The lateral OFC is granular and considered to have evolved from a paleocortical moiety; it is associated with medial and dorsal parts of the basal nucleus of the amygdala as well as with sensory and premotor areas and the posterior cingulate. It is part of the frontostriatal system, which is an executive control system, and the lateral OFC has been related functionally to the formation of associations between emotions, especially positive ones, and cognitions.

In this study, the significant *RERE* genotype–diagnosis interaction demonstrated that the reductions in cortical thicknesses in patients with MDD relative to those in the HCs were significantly larger in the T/T homozygous individuals than in the C-carrier individuals. However, the mechanism underlying the alterations of neuronal functions and/or brain development caused by genetic variation of the *RERE* gene remains to be elucidated. Genetic polymorphisms that increase the risk for MDD are considered to be one of the contributors because these genetic variants are presumed to act on brain function and architecture.

One of the limitations of this study is the small sample size. However, recruiting and retaining drug-naïve patients with MDD presented a challenge because many were administered antidepressants before they underwent MRI. Second, the study<sup>3</sup> of Hyde et al was detected by Europeans. Since we evaluated the SNPs using Japanese, we should be cautious for interpretation of the results. Third, new additional genes associated with MDD<sup>42–49</sup> were not examined. Fourth, the result was a chance finding because, sample number was small. Therefore, we should perform a study considering above points in further study.

In conclusion, our findings suggest that an SNP in the *RERE* gene was associated with reductions of cortical thicknesses in the right-lateral orbitofrontal and postcentral lobes in drug-naïve patients with MDD. Furthermore, we suggest that the effects of *RERE* gene polymorphism and gene–environment interactions may exist in the brain structure of patients with MDD.

## Author contributions

Dr. Katsuki designed the study, collected the clinical data, performed the statistical analyses, and wrote the first draft managed the literature searches. Professor Yoshimura

revised the study protocol wrote the final manuscript. Dr. Korogi checked the final manuscript. Drs. Kakeda and Watanabe helped the statistical analyses. Dr. Igata collected the clinical data. Drs. Nguyen and Otsuka collected the clinical data. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

Dr. Katsuki has received speaker's honoraria from Dainippon Sumitomo. Dr. Kishi has received speaker's honoraria from Abbott, Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Yoshitomi, Otsuka, Meiji, Shionogi, Tanabe-Mitsubishi, Novartis and Pfizer. Professor Iwata has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer and has had research grants from GlaxoSmithKline, Meiji, and Otsuka. Professor Yoshimura has received speaker's honoraria from Eli Lilly, Janssen, Dainippon Sumitomo, Otsuka, Meiji, Pfizer and Shionogi. The authors report no other conflicts of interest in this work.

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