

# Genetic effects on white matter integrity in drug-naive patients with major depressive disorder: a diffusion tensor imaging study of 17 genetic loci associated with depressive symptoms

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**Background:** A genome-wide association study using megadata identified 17 single-nucleotide polymorphisms (SNPs) in candidate genes for major depressive disorder (MDD). These MDD susceptibility polymorphisms may affect white matter (WM) integrity. This study aimed to investigate the relationship between WM alterations and 17 SNPs in candidate genes for MDD in the first depressive episode of drug-naive MDD patients using a tract-based spatial statistics (TBSS) method.

**Methods:** Thirty-five drug-naive MDD patients with a first depressive episode and 47 age- and sex-matched healthy subjects underwent diffusion tensor imaging scans and genotyping. The genotype–diagnosis interactions related to WM integrity were evaluated using TBSS for the 17 SNPs.

**Results:** For the anterior thalamic radiation, cingulum, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, forceps major, and forceps minor, the genotype effect significantly differed between diagnosis groups ( $P < 0.05$ , family-wise error corrected) in only one SNP, rs301806, in the arginine–glutamic acid dipeptide (RE) repeats (*RERE*) gene.

**Conclusion:** The RERE polymorphism was associated with WM alterations in first-episode and drug-naive MDD patients, which may be at least partially related to the manifestation of MDD. Future studies are needed to explore the gene–environment interactions with regard to individual WM integrity.

**Keywords:** depressive disorder, single-nucleotide polymorphism, MRI, fractional anisotropy, tract-based spatial statistics, arginine–glutamic acid dipeptide repeats gene

## Introduction

White matter (WM) alterations constitute one element of the pathogenesis of major depressive disorder (MDD).<sup>1,2</sup> Quantitative measures using diffusion tensor imaging (DTI), including fractional anisotropy (FA) values, are useful markers for WM changes. Recently, tract-based spatial statistics (TBSS) was introduced; TBSS projects FA data on to an average FA tract skeleton before applying voxel-wise cross-subject statistics, which minimizes the effects of misalignment.<sup>3</sup> Previous DTI studies using TBSS methods have found alterations, such as reduced FA, in various WM fiber tracts in MDD patients, including the anterior thalamic radiation (ATR),<sup>4,5</sup> inferior fronto-occipital fasciculus (IFOF),<sup>4,5</sup> uncinate fasciculus (UF),<sup>4,6</sup> sagittal stratum,<sup>7,8</sup> cingulum,<sup>4,7,9</sup> longitudinal fasciculus (LF),<sup>4,6,10,11</sup> internal and external capsules,<sup>4,7,12</sup>

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corpus callosum,<sup>4,8,10,12</sup> and corona radiata.<sup>4,5,7,10–12</sup> These fiber tracts provide important anatomical connectivity or form circuits; therefore, they may be directly relevant to the pathophysiology of MDD.<sup>13</sup>

Although a meta-analysis of relevant data from primary studies of the genetic epidemiology of major depression has revealed that heritability of MDD is estimated to be 31%–42%,<sup>14</sup> extensive heterogeneity and a complex genetic architecture have complicated the efforts to detect associated genetic risk variants. More recently, a genome-wide association study (GWAS) using megadata identified 17 SNPs in candidate genes for MDD.<sup>15</sup> Hyde et al presented a complementary approach to collect large-scale genotypic data (75,607 MDD and 231,747 controls), and they identified 17 independent single-nucleotide polymorphisms (SNPs) significantly associated with diagnosis of MDD.<sup>15</sup> These SNPs were predicted to be enriched in genes that are expressed in the central nervous system and function in transcriptional regulation related to neurodevelopment.

Several previous magnetic resonance imaging (MRI) studies using TBSS reported a relationship between WM integrity and genetic factors, which included brain-derived neurotrophic factor,<sup>16</sup> the serotonin transporter gene *SLC6A4*,<sup>17</sup> the neuronal amino acid transporter gene *SLC6A15*,<sup>18</sup> and methylenetetrahydrofolate reductase/catechol-O-methyltransferase polymorphisms.<sup>19</sup> This suggests that WM alterations in MDD patients may be attributable to genetic factors regarding neurodegeneration and brain development. Thus, we hypothesized that these 17 polymorphisms of MDD susceptibility genes and genotype–diagnosis interactions may affect individual WM integrity. To the best of our knowledge, no previous MDD studies have examined neuroimaging changes associated with the 17 SNPs as candidate genes for MDD. Thus, in this study, using TBSS we investigated the relationship between WM alterations and the 17 SNPs as candidate genes for MDD in first depressive episode drug-naive MDD patients.

## Materials and methods

### Ethics statement

This study was approved by the local ethics committee of the University of Occupational Environmental Health and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant after they were given a detailed description of the study.

### Participants

Thirty-five right-handed, drug-naive MDD patients in their first depressive episode were recruited. A psychiatrist

(KH, with 7 years of experience in psychiatry), who did not know the serum cortisol level or imaging data for the patients, diagnosed them as having MDD using a structured clinical interview according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR) criteria. The severity of depression was evaluated using the 17-item Hamilton Rating Scale for Depression (HAM-D17). Only those with a HAM-D17 score  $\geq 14$  were eligible for the study. The exclusion criteria included any history of neurological diseases or other physical diseases, or the presence of other disorders (ie, the subjects had no evidence of schizoaffective disorder, bipolar disorder, axis II personality disorders, or mental retardation). The age of the MDD patients ranged from 20 to 67 (mean  $\pm$  SD 47.1 $\pm$ 15.2) years. Eighteen were male and 17 were female.

Thirty-five right-handed, healthy subjects (HS) were recruited via an interview using the structured clinical interview from the DSM-IV-TR. None had a serious medical or neuropsychiatric illness or a family history of major psychiatric illness, and all were matched with the patients in terms of age and sex. The age of the HS ranged from 20 to 65 (mean  $\pm$  SD 44.1 $\pm$ 11.2) years. Twenty-two of the HS were male and 13 were female.

### Genotyping

All 70 subjects provided a blood sample. DNA was isolated from peripheral blood mononuclear cells. Genotyping was evaluated by a PCR SNP genotyping system (Life Technologies Japan, Tokyo, Japan). The PCR products were purified enzymatically.

### MRI acquisition

All magnetic resonance (MR) examinations were performed using a 3 T MR system (Signa EXCITE 3T; GE Healthcare, Waukesha, WI, USA). Diffusion tensor images were acquired by a single-shot, spin-echo echo-planar sequence (TR/TE=12,000/83.3 ms; 4 mm slice thickness; no gap; field of view=26 cm; number of excitations=1). Diffusion gradients were applied for the three axes simultaneously around the 180-degree pulse ( $b$  value=1,000 s/mm<sup>2</sup>). The diffusion properties were measured in 25 non-collinear directions.

### Image processing

The structural distortion of the diffusion-weighted MR images was corrected based on each T2-weighted echo planar image ( $b=0$  s/mm<sup>2</sup>) using eddy current correction in the Functional MRI of the Brain (FMRIB) Diffusion Toolbox software program (part of the FMRIB Software Library; FSL v5.0.4). Non-brain tissue in each MR image was deleted

using the brain extraction tool. The voxel-wise statistical analysis of the DTI data was performed using the TBSS version 1.1 software program. The FA volumes were aligned to a target image as follows: 1) the nonlinear registration of each subject's FA was applied to the FMRIB58\_FA\_1 mm standard-space image as the target image; and 2) the target image was affine transformed to 1×1×1 mm MNI 152 (Montreal Neurological Institute, Montreal, Canada) space. A mean FA image was created by averaging the aligned individual FA images and was then thinned to create an FA skeleton representing WM tracts common to all subjects.<sup>3</sup> The FA skeleton was thresholded at 0.2 to exclude voxels with low FA values, which are likely to include gray matter or cerebrospinal fluid. Individual FA data were projected on to this FA skeleton. The mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were projected on to the mean FA skeleton and also compared between groups.

## Statistical analysis

The FA, AD, and RD values were compared between HS and MDD patients using a two-sample *t*-test. Age and sex were included as covariates of no interest to control for confounding variables. The number of permutations in all voxel-wise analyses was set at 10,000. Values of  $P < 0.05$  and  $> 50$  voxels indicate a significant difference, and for multiple comparisons at the cluster level, a correlation after family-wise error (FWE) correction was performed with threshold-free cluster enhancement option. The brain region of significant clusters was detected based on the

WM tractography atlas of Johns Hopkins University (JHU) and the white matter labels atlas based on International Consortium of Brain Mapping (ICBM)-DTI-81.

The FSL Randomise tool<sup>50</sup> was used to perform permutation-based non-parametric inference on the skeletonized FA data at a threshold of 0.2 (TBSS default). The significance level was set at  $P < 0.05$  after multiple comparisons correction using threshold-free cluster enhancement,<sup>51</sup> an approach that allows the significance of a target voxel to take into account not only the amplitude of the signal (in this case FA) but also the contributions of both the spatial extent and the magnitude of supporting voxels. Age and sex were included as covariates of no interest to control for confounding variables. To assess the main effect of genotype, of diagnostic group, and their interaction on FA, an ANOVA-style design matrix was built with genotype and diagnosis (MDD and HS) as the two independent variables. Mean FA in the largest cluster of each effect was graphically plotted for a visual overview.

The anatomical location of significant clusters was detected using the JHU WM tractography atlas and the ICBM-DTI-81 white matter labels atlas; only clusters with  $> 1\%$  probability were included in the cluster table.

## Results

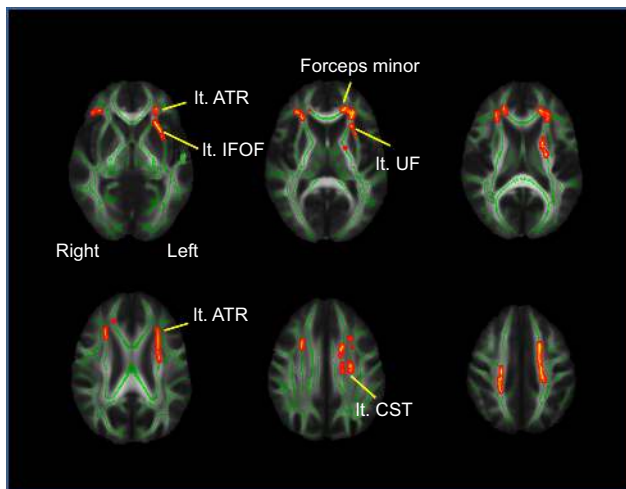
### Participants

For the genotyping of 70 subjects (35 MDD and 35 HS), the allele frequencies of 17 SNPs were within the Hardy-Weinberg equilibrium (Table 1). We could not perform direct

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

SNP	Chromosome	Minor allele	Genotype distribution (n=70)	HWE
rs10514299	5	T	CC/CT/TT: 57/11/2	0.01
rs1518395	2	A	GG/AG/AA: 30/36/4	0.106
rs2179744	22	A	GG/AG/AA: 36/30/4	0.484
rs11209948	1	G	NA	NA
rs454214	5	A	GG/AG/AA: 18/32/20	0.477
rs301806	1	C	TT/CT/CC: 44/23/3	0.998
rs1475120	6	C	TT/CT/CC: 35/27/8	0.432
rs10786831	10	A	GG/AG/AA: 27/35/8	0.506
rs12552	13	T	CC/CT/TT: 17/38/15	0.469
rs6476606	9	A	GG/AG/AA: 41/25/4	0.941
rs8025231	15	A	CC/AC/AA: 37/26/7	0.451
rs12065553	1	G	AA/AG/GG: 36/31/3	0.245
rs1656369	3	T	AA/AT/TT: 47/21/2	0.85
rs4543289	5	T	NA	NA
rs2125716	12	T	CC/CT: 62/8	0.612
rs2422321	1	G	AA/AG/GG: 53/16/1	0.867
rs7044150	9	T	CC/CT: 65/5	0.757

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



**Figure 1** A comparison of FA findings between MDD patients and HS.

**Note:** Axial slices of the cohort's mean FA skeleton (green) overlaid with red clusters depicting significantly lower FA values (left ATR, IFOF, CST, UF, and forceps minor) in the MDD patients compared to that in HS (FWE-corrected  $P < 0.05$ ).

**Abbreviations:** ATR, anterior thalamic radiation; CST, corticospinal tract; FA, fractional anisotropy; FWE, family-wise error; HS, healthy subjects; IFOF, inferior fronto-occipital fasciculus; It., left; MDD, major depressive disorder; UF, uncinate fasciculus.

sequence reads for rs11209948 and rs4543289 because of insufficient volume; therefore, we could not obtain their genotype information. The distributions of genotypes are shown in Table 1.

## Effect of diagnosis on FA

Irrespective of genotype, significant differences in FA were shown between the HS and MDD patients. Figure 1 demonstrates the spatial brain region distribution, indicating a reduction in FA in the MDD patients compared to the HS. The MDD patients showed significantly reduced FA values ( $P < 0.05$  with FWE correction) in the left ATR, IFOF, corticospinal tract (CST), UF, and the forceps minor (Figure 1 and Table 2). For MD, AD, and RD, no significant differences were found.

## Effect of genotype on FA

When we tested rs301806, an SNP in the arginine–glutamic acid dipeptide (RE) repeats gene (*RERE*), across the brains of MDD patients, the T/T individuals showed significantly reduced FA compared to the C-carrier individuals (C/C or C/T) in the bilateral IFOF, bilateral inferior longitudinal fasciculus (ILF), right superior longitudinal fasciculus (SLF), and forceps major (Figure 2 and Table 3). For analysis of the demographic and clinical characteristics of participants with regard to rs301806, an ANOVA was performed to compare the differences in age among four groups (T/T individuals and C-carrier individuals in HS, T/T individuals and C-carrier individuals with MDD). The chi-squared test was used to evaluate the sex differences among the four groups. An unpaired *t*-test was used to compare the total of the HAMD17 scores between the T/T individuals and C-carrier individuals with MDD and there were no significant differences in terms of age or sex (Table 4).

For other SNPs, we found no significant effect of genotype in MDD ( $P < 0.05$ , FWE-corrected). For all 16 SNPs with genotype information, we found no significant effect of genotype in HS ( $P < 0.05$ , FWE-corrected).

## Genotype–diagnosis interaction on FA

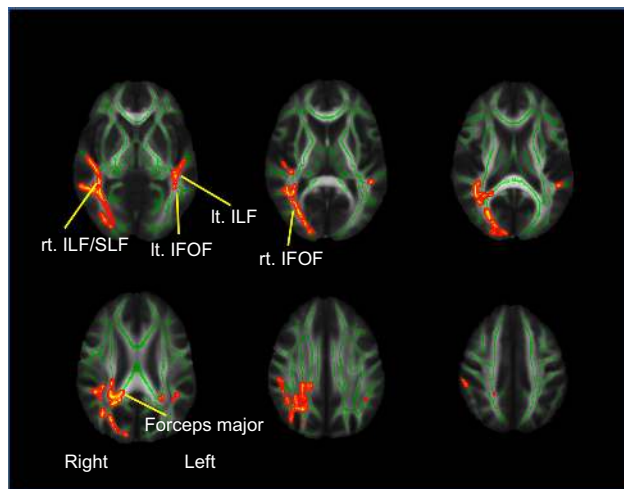
We tested every possible diagnosis-wise comparison, and only for rs301806, an SNP in the *RERE* gene, the genotype effect differed significantly between diagnosis groups ( $P < 0.05$ , FWE-corrected) for the left ATR and cingulum, bilateral CST, IFOF, ILF, SLF, UF, forceps major, and forceps minor. In these WM fiber tracts, the genotype–diagnosis interaction showed that the FA reduction in MDD compared to HS was significantly larger in T/T individuals than in C-carrier individuals ( $P < 0.05$ , FWE-corrected) (Figure 3 and Table 5). For other SNPs, we found no WM fiber tracts where a genotype effect (in any direction)

**Table 2** The effect of diagnosis on FA values (HS > MDD patients)

	P-value*	MNI coordinates (mm)			Voxel size	Tract(s) within clusters
		x	y	z		
Cluster 1	0.035	-24	29	8	868	Anterior thalamic radiation L Forceps minor Inferior fronto-occipital fasciculus L
Cluster 2	0.034	-19	-18	39	661	Corticospinal tract L
Cluster 3	0.042	27	32	16	403	
Cluster 4	0.036	-27	17	-2	270	Inferior fronto-occipital fasciculus L Uncinate fasciculus L
Cluster 5	0.042	23	-32	42	191	
Cluster 6	0.047	19	32	18	85	

**Note:** \*Family-wise error-corrected.

**Abbreviations:** FA, fractional anisotropy; HS, healthy subjects; L, left; MDD, major depressive disorder; MNI, Montreal Neurological Institute.



**Figure 2** A comparison of FA findings between T/T individuals (rs301806) and C-carrier individuals with MDD.

**Note:** Axial slices of the cohort's mean FA skeleton (green) overlaid with red clusters depicting significantly lower FA values (bilateral IFOF, bilateral ILF, right SLF, and forceps major) in T/T individuals with MDD compared to that in C-carrier individuals with MDD (FWE-corrected  $P < 0.05$ ).

**Abbreviations:** FA, fractional anisotropy; FWE, family-wise error; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; Lt., left; MDD, major depressive disorder; rt, right; SLF, inferior longitudinal fasciculus.

differed significantly between diagnosis groups ( $P < 0.05$ , FWE-corrected).

## Discussion

The SNP rs301806 is found in the *RERE* gene. The *RERE* gene is named after the dipeptide repeats found in the carboxyl terminal of RERE. RERE was previously known as Atrophin 2 (ATR2), based on the similarities between RERE and Atrophin 1 (ATR1). To our knowledge, this study provides the first evidence of a relationship between WM integrity and polymorphisms in the *RERE* gene in MDD patients.

Specifically, the significant *RERE* genotype–diagnosis interaction effects were found in the ATR and cingulum, CST, IFOF, ILF, SLF, UF, forceps major, and forceps minor, suggesting that the *RERE* genotype affects the FA values in these WM tracts in MDD. The strength of this study lies in the recruitment of the drug-naive MDD patients. Previous studies indicated that alterations in WM integrity may occur during the course of MDD and after treatment.<sup>20,21</sup> However, in this study, the WM alterations may be the acute state of MDD and not the effects due to treatment or chronic MDD. Furthermore, for the analyses of the effect of genotype on FA, we investigated the genotype–diagnosis interaction (the difference between MDD patients and HS with T/T vs C-carrier MDD patients and HS), because a genotype comparison in MDD patients and/or a simple genotype–diagnosis comparison may not be sufficient to identify an association between the polymorphism and brain changes in MDD patients.

The role of the RERE gene in brain pathology remains poorly understood. Jordan et al highlighted evidence implicating *RERE* in various 1p36 chromosome deletion phenotypes.<sup>22</sup> The major clinical features of 1p36 deletion syndrome include motor developmental delay, hypotonia, and craniofacial dysmorphisms, such as a large anterior fontanelle, prominent forehead and chin, deep eyes, a flat nasal bridge, maxillary hypoplasia, and ear asymmetry. Thus, RERE appears to be required for normal brain development.<sup>23,24</sup>

Furthermore, a recent report indicates that RERE and its *Drosophila* homolog associate with histone methyltransferases to regulate gene expression.<sup>25</sup> MDD is a polygenic and multifactorial disease, and gene–environment interactions play a pivotal role in its pathophysiology. Accordingly,

**Table 3** The effect of genotype (rs301806) on FA values in MDD (C-carrier individuals > T/T individuals)

	P-value*	MNI coordinates (mm)			Voxel size	Tract(s) within clusters
		x	y	z		
Cluster1	0.028	40	-41	-8	5,024	Forceps major Inferior fronto-occipital fasciculus R Inferior longitudinal fasciculus R Superior longitudinal fasciculus R Superior longitudinal fasciculus (temporal part) R
Cluster2	0.04	-41	-40	-7	385	Inferior fronto-occipital fasciculus L Inferior longitudinal fasciculus L
Cluster3	0.045	51	-31	45	355	
Cluster4	0.045	-40	-11	-18	194	Inferior longitudinal fasciculus L
Cluster5	0.047	-42	-43	26	122	
Cluster6	0.049	-45	-38	8	65	

**Note:** \*Family-wise error-corrected.

**Abbreviations:** FA, fractional anisotropy; HS, healthy subjects; L, left; MDD, major depressive disorder; MNI, Montreal Neurological Institute; R, right.

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

	MDD patients		Healthy subjects		P-value
	C/C and C/T (n=14)	T/T (n=21)	C/C and C/T (n=12)	T/T (n=23)	
Male/female	8/6	10/11	7/5	15/8	0.70
Age (years)	46.7±11.8	47.4±17.1	46.2±11.4	43.0±11.0	0.74
HAMD17	20.7±5.3	21.2±6.2			0.80

**Note:** Data are presented as mean ± SD.

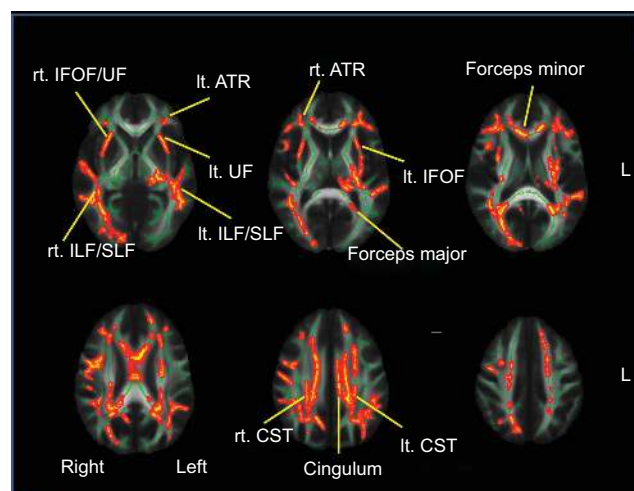
**Abbreviations:** HAMD17, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; SNP, single-nucleotide polymorphism.

a recent hypothesis is that certain environmental factors hijack the brain's epigenetic machinery and, in combination with genetic predispositions, produce many of the behavioral manifestations of MDD.<sup>26,27</sup> Epigenetic machinery comprises three broad umbrella systems: DNA methylation, histone modification, and non-coding RNA-mediated mechanisms. These are meiotically and mitotically heritable changes that are not directly coded in the DNA sequence.<sup>28</sup> Thus, RERE may play an important role in the pathophysiology of depression through epigenetic machinery related to histone methyltransferases.

In this study, it is unclear why the polymorphism in the *RERE* gene was associated with alterations in specific WM tracts in MDD, because RERE is a nuclear receptor coregulator that is widely expressed in the developing central nervous system.<sup>29,30</sup> However, our findings are supported by

the several studies using DTI in MDD that demonstrated the presence of WM alterations (ie, reduced FA) in the ATR,<sup>4,5</sup> IFOF,<sup>4,5,31</sup> UF,<sup>4-6,31</sup> cingulum,<sup>4,7,9</sup> longitudinal fasciculi,<sup>4,6,10,11</sup> and forceps major.<sup>32</sup> A previous study also suggested that lower FA values in the IFOF may partly contribute to the impairments in memory, executive functioning, and emotional regulation seen in patients with MDD.<sup>33</sup> Furthermore, because these fiber tracts form important anatomical connectivity or circuits, they may be directly relevant to the pathophysiology of MDD.<sup>13</sup> The IFOF, UF, and ATR may have key roles in frontal-subcortical circuits and frontal-limbic circuits.<sup>34</sup> Anatomically, the IFOF, UF, and ATR have a projection into the frontal cortex from the thalamus. The "disconnection" of the frontal-subcortical circuit was considered as one of the pathogenic elements associated with MDD.<sup>13</sup> Frontal-limbic circuits are "open" loops incorporated into the functional connectivity between frontal areas (anterior cingulate cortex and orbitofrontal cortex) and other cortex, thalamus, and limbic system areas (amygdala and hippocampus).<sup>35</sup> Anatomically, the UF has a projection into the anterior cingulate cortex and orbitofrontal cortex from limbic system areas.<sup>36</sup> An association between dysregulation of the frontal-limbic circuits and MDD has been postulated based on functional imaging studies.<sup>1,37,38</sup>

Reduced FA values are thought to reflect reduced organization of the WM, reduced axonal density, and/or reduced myelination.<sup>39,40</sup> In this study, the significant RERE genotype-diagnosis interaction showed that the FA reductions in MDD compared to those in HS were significantly larger in the T/T individuals than in the C-carrier individuals. However, the results from many GWASs imply that specific genetic variants individually make very small contributions to the etiology of MDD.<sup>41</sup> Therefore, further studies with large sample sizes are required to prove whether one single risk variant (genetic variation of *RERE*) has an effect on the pathophysiology of MDD, such as decreased WM integrity. To increase power substantially, it would be useful to conduct analyses using polygenic risk scores, which provide an



**Figure 3** Genotype-diagnosis interactions.

**Note:** Axial slices of the cohort's mean FA skeleton (green) overlaid with red clusters depicting a significant genotype-diagnosis interaction in which the lower FA values (left ATR and cingulum, bilateral CST, IFOF, ILF, SLF, UF, forceps major, and forceps minor) in MDD patients compared to that in HS are significantly larger in T/T individuals than in C-carrier individuals (FWE-corrected  $P < 0.05$ ).

**Abbreviations:** ATR, anterior thalamic radiation; CST, corticospinal tract; FA, fractional anisotropy; FWE, family-wise error; HS, healthy subjects; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; lt., left; MDD, major depressive disorder; rt., right; SLF, inferior longitudinal fasciculus; UF, uncinate fasciculus.

**Table 5** The genotype–diagnosis interaction on FA values (rs301806: C-carrier individuals > T/T individuals)

	P-value*	MNI coordinates (mm)			Voxel size	Tract(s) within clusters
		x	y	z		
Cluster1	0.012	-10	-9	29	19,599	Anterior thalamic radiation L Corticospinal tract L Corticospinal tract R Cingulum (cingulate gyrus) L Forceps major Forceps minor Inferior fronto-occipital fasciculus L Inferior fronto-occipital fasciculus R Inferior longitudinal fasciculus L Inferior longitudinal fasciculus R Superior longitudinal fasciculus L Superior longitudinal fasciculus R Uncinate fasciculus L Uncinate fasciculus R Superior longitudinal fasciculus (temporal part) L Superior longitudinal fasciculus (temporal part) R
Cluster2	0.031	42	-3	26	1,326	Superior longitudinal fasciculus R
Cluster3	0.042	33	33	22	970	Inferior fronto-occipital fasciculus R
Cluster4	0.036	-32	7	0	638	Inferior fronto-occipital fasciculus L Uncinate fasciculus L
Cluster5	0.047	-16	41	29	187	
Cluster6	0.05	17	33	12	117	Forceps minor
Cluster7	0.048	-17	44	23	70	
Cluster8	0.048	-15	16	47	57	

**Note:** \*Family-wise error-corrected.

**Abbreviations:** FA, fractional anisotropy; HS, healthy subjects; L, left; MDD, major depressive disorder; MNI, Montreal Neurological Institute; R, right.

estimate of the combined effect of a large number of SNPs associated with a trait, each with a very subtle individual effect.<sup>42</sup> In this study, the mechanism underlying how the genetic variation of *RERE* alters pathophysiological brain conditions has not been elucidated. Therefore, further fundamental studies are also required to determine which physiological systems the *RERE* genotype may particularly be related to in terms of myelination of the WM fiber tracts, to confirm the preliminary findings. Furthermore, in this study, we evaluated only the 17 SNPs as candidate genes for MDD. Many studies have reported new candidate genes for MDD,<sup>43–49</sup> in which bioinformatics may provide new channels for examining neuroimaging changes.

Our study had limitations. First, this study was limited by a small sample size, which may have prevented us from detecting other potentially relevant genotypes that influence WM integrity, and may have also led to some of the negative results. However, because many patients were administered antidepressants before the MRI, it may be difficult to recruit first-episode and drug-naive patients with MDD. Second, in this study, we evaluated only people of Japanese

background. There has been no GWAS regarding the genetic architecture of MDD in the Japanese population. Moreover, ethnic heterogeneity among the Japanese population has not been proved. Therefore, MDD genetic studies focusing on Japanese ethnicity by GWAS are required to generalize our findings to other ethnic groups.

## Conclusion

The *RERE* polymorphism was associated with WM alterations of the ATR, cingulum, CST, IFOF, ILF, SLF, UF, forceps major, and forceps minor in first-episode and drug-naive MDD patients, which may be at least partially related to the manifestation of MDD. Further studies are required to explain how the *RERE* genotype results in WM alterations. Furthermore, the effects of one gene may not explain the morphological changes seen in MDD patients and we suggest that, in addition to the effects of the *RERE* gene polymorphism, gene–environment interactions may exist with regard to the individual brain networks. Future studies are also needed to explore the effects of epigenetic contributions, with the goal of clarifying disease mechanisms.

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## Disclosure

The authors report no conflicts of interest in this work.

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