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Altered expression of long noncoding RNAs in patients with major depressive disorder

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ABSTRACT

Although major depressive disorder (MDD) is a leading cause of disability worldwide, its pathophysiology is poorly understood. Increasing evidence suggests that aberrant regulation of transcription plays a key role in the pathophysiology of MDD. Recently, long noncoding RNAs (lncRNAs) have been recognized for their important functions in chromatin structure, gene expression, and the subsequent manifestation of various biological processes in the central nervous system. However, it is unclear whether the aberrant expression and function of lncRNAs are associated with the pathophysiology of MDD. In this study, we sought to evaluate the expression of lncRNAs in peripheral blood leukocytes as potential biomarkers for MDD. We measured the expression levels of 83 lncRNAs in the peripheral blood leukocytes of 29 MDD patients and 29 age- and gender-matched healthy controls using quantitative reverse transcription PCR (RT-qPCR) analysis. We found that MDD patients exhibited distinct expression signatures. Specifically, the expression level of one lncRNA (RMRP) was lower while the levels of four (Y5, MER11C, PCAT1, and PCAT29) were higher in MDD patients compared to healthy controls. The expression level of RMRP was correlated with depression severity as measured by the Hamilton Depression Rating Scale (HAM-D). Moreover, RMRP expression was lower in a mouse model of depression, corroborating the observation from MDD patients. Taken together, our data suggest that lower RMRP levels may serve as a potential biomarker for MDD.

1. Introduction

The greatest problem in the diagnosis of depression stems from the fact that only an operational diagnostic method exists from which to judge a combination of symptoms such as those included in the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). The development of objective and predictive biomarkers has become a major focus of recent research. Among a variety of approaches, epigenetics may yield novel biomarkers for the diagnosis of depression. Epigenetics refers to modifications in chromatin structure that underlie changes in gene expression that are not associated with alterations in DNA sequence. Epigenetic mechanisms include various histone modifications as well as changes to the DNA itself, such as DNA methylation (Kouzarides, 2007; Suzuki and Bird, 2008). Several studies report altered gene expression involved in these epigenetic mechanisms in patients with MDD. For instance, MDD patients exhibited distinct expression signatures of histone deacetylases (Abe et al., 2011; Hobara et al., 2010; Iga et al., 2007; Luo and Zhang, 2016; Rey et al., 2019) and DNA methyltransferases (Higuchi et al., 2011; Numata et al., 2015) in peripheral blood leukocytes. Furthermore, altered expression of epigenetic machinery genes was also observed in the postmortem brain tissues of MDD patients, as well as in murine brain tissues of a mouse model of depression (Covington et al.,

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2009; Lepack et al., 2016). These findings suggest that abnormal gene expression of epigenetic regulators may be involved in the pathophysiology of MDD and could thereby serve as potential biomarkers for the disorder.

In addition to DNA methylation and histone modifications, the most recently discovered processes mediated by non-coding RNA (ncRNA) have been shown to play a significant role in epigenetic modification and the regulation of expression at both the genetic and chromosomal levels to control cell differentiation (Costa, 2008; Ghildiyal and Zamore, 2009; Peschansky and Wahlestedt, 2014). With regard to the central nervous system, several reports have demonstrated critical roles of ncRNAs in brain development, homeostasis, stress responses, and plasticity (Bian and Sun, 2011; Cui et al., 2016; Ng et al., 2013; Salta and De Strooper, 2017).

Generally, ncRNAs are divided into long ncRNAs (lncRNAs) greater than 200 nucleotides and small RNAs, including micro RNAs (miRNAs), that are less than 200 nucleotides (Bian and Sun, 2011). MiRNAs have been reported to serve as transcriptional regulators throughout epigenetic processes and are implicated in psychiatric diseases (Beveridge and Cairns, 2012; Fregeac et al., 2016; Kocerha et al., 2015; Uchida et al., 2018) including MDD (Belzeaux et al., 2012; Fries et al., 2019; Kocerha et al., 2015; Lopez et al., 2014; Roy et al., 2017; Torres-Berrio et al., 2017). Indeed, the expression level of miR-135a-5p was lower in the total blood of MDD patients and in the postmortem brains of suicide victims (Issler et al., 2014) compared to controls. Other studies report that the expression of miRNA-124–3p was altered in an animal model of depression (Higuchi et al., 2016) and in the peripheral blood mononuclear cells of MDD patients (He et al., 2016). These results suggest that ncRNAs could act as possible biomarkers for depression and are likely involved in the pathophysiology of MDD.

Although miRNAs have received much attention, the roles of lncRNA in psychiatric disease are largely unknown. It has been widely reported that lncRNAs participate in a variety of biological functions including regulation of chromatin and gene activation, mediation of epigenetic changes, chromosome imprinting, and apoptosis (Ma et al., 2013). However, unlike miRNAs, lncRNAs are specifically expressed in species arising in the later stages of evolution and are thus considered to be involved in higher-order functions such as mental activity (Barry, 2014). It is becoming clear that lncRNAs play a pivotal role in cellular maintenance governing epigenetic processes (Barry, 2014) and epigenetic control has been found to be abnormal in MDD (Tsankova et al., 2007).

Reports have indicated that lncRNAs could act as biomarkers for MDD. For example, the expression level of LINC01108 was reported to be significantly higher while LINC00998 was significantly lower in the peripheral blood cells of MDD patients when compared to healthy controls (Ye et al., 2017). Another study reported 1556 upregulated and 441 downregulated lncRNAs in MDD patients compared to healthy controls. Four of the upregulated genes were quantified by RT-qPCR and individual expression changes were verified (Liu et al., 2014). In addition, researchers reported six differentially expressed lncRNAs in the blood samples of 138 MDD patients compared to 63 healthy controls using microarray analysis with validation by RT-qPCR (Cui et al., 2016). However, given that neither the specific physiological functions of most lncRNAs nor how they are involved in the pathogenesis of depression have yet been studied, their causal involvement in MDD remains unknown. Therefore, it is necessary to search for lncRNA biomarkers for depression focusing on those whose physiological functions are already known. Several lncRNAs have been implicated in the pathophysiology of central nervous system-related diseases (Ng et al., 2013; Salta and De Strooper, 2017). For example, knockdown of an lncRNA known as Gomafu in the mPFC increased anxiety-like behaviors in mice, possibly precipitated by an interaction with BMI1 which regulates the expression of the schizophrenia-related crystalline gene (Spadaro et al., 2015). The expression of lncRNA MIAT was significantly downregulated in the brain parenchyma of Alzheimer transgenic mice, while knockdown of MIAT led to cerebral microvascular degeneration, progressive neurodegeneration, and behavioral deficits (He et al., 2016). We hypothesized that these lncRNAs associated with central nervous system-related diseases could be candidate biomarkers for MDD.

In this study, we selected 83 lncRNAs whose functions had been reported previously in other diseases and pathologies, particularly those related to the central nervous system. We compared the expression of these lncRNAs in the peripheral blood leukocytes of MDD patients and healthy participants. The analysis of focused targets allows us to build on insights from previous studies and gives a better opportunity to detect lncRNAs specific to the pathophysiology of depression.

2. Materials and methods

2.1. Experiment 1

2.1.1. Participants

Patients with MDD were recruited from Yamaguchi University Hospital from Feb 2012 to June 2015. All participants were assessed according to the MDD diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision by senior psychiatrists. Current mood states were assessed by psychiatrists using the Structured Interview Guide for the Hamilton Depression Rating Scale (HAM-D) and a depressed state was defined as scores greater than 18. Current anxiety was assessed with the State-Trait Anxiety Inventory (STAI). Patients were diagnosed by clinical interviews performed by senior skilled psychiatrists, case conferences with psychiatrists, and structured interviews using the Mini-International Neuropsychiatric Interview (M.I.N.I., Japanese version 5.0.0; Otsubo et al., 2005). Patients with current or a history of substance abuse/dependence or other psychotic illnesses were excluded from the study. Healthy controls were recruited from the local community and those with any psychiatric illness as evaluated via the M.I.N.I. and clinical interviews, or having any close family member with a psychiatric disorder, were excluded. Serum cortisol concentration was gathered from clinical data. This study was approved by the Institutional Review Board of Yamaguchi University Hospital and carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all participants after providing them with a complete description of the study.

2.1.2. Quantitative reverse transcription PCR with human samples

Total RNA isolation from peripheral blood leukocytes was performed according to methods reported previously (Yamagata et al., 2017). One microgram of total RNA was reverse transcribed to cDNA using a QuantiTect Reverse Transcription Kit (Qiagen, Hilden, Germany). Real-time PCR was performed an Applied Biosystems™ Step One Real-Time PCR System using SYBR® Green PCR Master Mix (Applied Biosystems/Thermo Fisher Scientific, Foster City, CA, USA) according to the manufacturer's protocol. PCR conditions were as follows: 2 min at 50 °C, 10 min at 95 °C, followed by 40 cycles of 15 s at 95 °C and 1 min at 60 °C. The Disease Related Human LncRNA profiler Cat. #RA920A-D-1 (System Biosciences, Palo Alto, CA, USA) was used as the primer plate. It included 83 lncRNAs and 11 internal controls with 8 housekeeping genes and 3 small RNA transcripts. The 83 lncRNAs were selected based on previous studies that implicated them in diseases ranging from neurodegeneration to cancer.

2.2. Experiment 2

2.2.1. Animals

Adult male BALB/c (BALB) mice were obtained from Charles River Laboratories (Wilmington, MA, USA) and maintained in an air-conditioned room at 24 ± 2 °C on a 12 h/12 h light/dark cycle with ad libitum access to mouse chow and water. Mice were 8 weeks old at the

start of the experiments. All experimental procedures were performed according to the Guidelines for Animal Care and Use of Yamaguchi University Graduate School of Medicine.

2.2.2. CORT administration

Corticosterone [CORT (250 μg/mL)] or vehicle (0.45% 2-hydroxypropyl-beta-cyclodextrin) was administered via drinking water for a total of 4 weeks. Light shielding bottles were used to avoid light-induced degradation of the compound.

2.2.3. Behavioral procedures

The forced swim test (FST) was performed during the light phase (9:00 a.m. to 3:00 p.m.) as described in previous reports (Uchida et al., 2011a, 2011b). Each mouse was placed in a water tank (20-cm in height and 14-cm in diameter filled with 23–24 °C water to a depth of 13 cm) for 5 min; the total duration of immobility (i.e., the time during which the mouse performed only small movements necessary to keep its head above water) was monitored.

2.2.4. Quantitative reverse transcription PCR with mice samples

Total RNA extraction was performed as follows: mice from both groups were anesthetized and sacrificed to obtain blood by cardiac puncture (500–1000 μL), which was collected into heparinized tubes. Total RNA was extracted using a GeneJET Whole Blood RNA Purification Mini Kit (Thermo Fisher Scientific) according to the manufacturer's instructions. RNA quantity and quality were determined using a NanoDrop™ ND-1000 spectrophotometer (Thermo Fisher Scientific). The OD 260/280 ratios were ≥1.5 for all RNA preparations. Real-time PCR was performed with the same equipment as Experiment 1. PCR conditions were as follows: 10 min at 95 °C followed by 50 cycles of 15 s at 95 °C and 30 s at 60 °C, 15 s at 95 °C, 1 min at 60 °C, and finally 15 s at 95 °C. The following primers were used for RT-qPCR: RMRP, forward (5′-CACTGTTAGCCCGCCAAGAA-3′) and reverse (5′-CACTGC CTGCGTCACTATGT-3′); GAPDH, forward (5′-TGCACCACCAACTGCT TAG-3′) and reverse (5′-GGATGCAGGGATGATGTTC-3′); actin, forward (5′-GACGGCCAGGTCATCACTAT-3′) and reverse (5′-CGGATGTCAACG TCACACTT-3′); U6, forward (5′-ATACAGAGAAGATTAGCATGGCC-3′) and reverse (5′-CGAATTTGCGTGTCATCCTTG-3′). Levels of GAPDH mRNA, β-actin mRNA, and U6 snRNA were used to normalize the relative expression levels of target mRNAs and RMRP, respectively. We confirmed that heparin did not affect PCR performance in comparison with EDTA (Supplemenatal Fig. 1).

2.3. Statistical analysis

SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for data analysis. The chi-square test and the independent samples *t*-test were used to compare the demographic variables between MDD patients and healthy subjects. Nonparametric outlier tests were performed using the interquartile ranges (IQRs) of the expression levels for each gene and outliers were excluded. Tukey's rule was used such that a data point was considered an outlier if it was more than 1.5 times the IQR above the third quartile or below the first quartile (Tukey, 1977). The amplification curves representing the expression levels of 83 lncRNAs and 11 internal controls were checked; those lncRNAs that did not amplify were excluded. Thereafter, those with an average Ct value of 35 or more for all samples were excluded according to the manufacturer's recommendation. We calculated the average Ct values of 11 genes (see Supplemenatal Table 1) as internal controls ($Ct^{AVG\ Internal\ Control}$). Next, the ΔCt for each lncRNA was calculated with the following equation: $\Delta Ct = Ct^{lncRNA} - Ct^{AVG\ Internal\ Control}$. ΔΔCT was calculated as follows: ΔΔCT = ΔCT (MDD sample) – ΔCT (HC sample). The fold-change from control to sample was obtained for each gene as $2^{-\Delta\Delta CT}$. The Mann-Whitney *U* test was used to compare the difference in the expression levels of lncRNAs between MDD patients and healthy subjects. Bonferroni's correction was performed for multiple-testing correction.

Table 1
Demographic data for participants in Experiment 1.

	Healthy controls	MDD patients
Number of subjects	29	29
Sex (Male/Female)	13/16	11/18
Age (years)	47.0 ± 16.3	48.5 ± 12.9
HAM-D score	0.6 ± 0.9	21.5 ± 2.9*
STAI score	39.7 ± 4.7	37.5 ± 5.6
Equivalent dose of imipramine (mg)	–	212 ± 140
Number medication		28
SSRI		14
SNRI		11
Tricyclic Antidepressants		7
tetracyclic antidepressant		4
NaSSA		8
SARI		7

Note: Data are shown as mean ± SD. *p < 0.001 compared to healthy controls.

Spearman correlation analysis was used to investigate the correlations between lncRNA expression levels and the ages of all participants, onset ages, disease durations, HAM-D score, state anxiety score (STAI-S score), and antidepressant dose for MDD patients. Two-factor univariate analysis of variance (ANOVA) was performed for the expression level of each lncRNA, in order to investigate the relationship by gender and diagnosis. For mouse data, the independent samples *t*-test was used for two-group comparisons. $P < 0.05$ was considered statistically significant. Data are presented as mean ± SEM.

3. Results

3.1. Experiment 1

The demographic and clinical data of the participants are shown in Table 1. There were no significant differences between MDD patients and healthy subjects in terms of age and sex distribution except for HAM-D scores (p = 1.8E−40, t = 36.1) (Table 1).

Among the 83 tested lncRNAs and 11 internal controls, the expression of 43 lncRNAs and all internal controls could be detected (Table 2, Supplemenatal Table 2). Five were found to be differentially expressed in MDD patients compared to healthy subjects (Fig. 1, Supplemenatal Table 3): MER11C, PCAT1, PCAT29, RMRP, and Y5. Whereas the expression level of RMRP in MDD patients was significantly lower than in healthy subjects (p = 0.000227, U = 175), the expression levels of MER11C, PCAT1, PCAT29, and Y5 were significantly higher in MDD patients than in healthy subjects (MER11C: p = 0.0215, U = 262; PCAT1: p = 0.0183, U = 199; PCAT29: p = 0.00693, U = 165; Y5: p = 0.00665, U = 226). Receiver operating characteristic (ROC) curves were created by calculating sensitivity-specificity of each gene (Supplemenatal Fig. 2). Areas under the ROC curves of each gene were as follows: MER11C 0.6773; PCAT1 0.6929; PCAT29 0.725; RMRP 0.7845; and Y5 0.7114. After Bonferroni's correction, the corrected p-values (q-values) were: RMRP q = 0.00972; MER11C q = 0.946; PCAT1 q = 0.787; and PCAT29 q = 0.298; Y5 q = 0.286. Gender effects and interactions between diagnosis and sex were not found (data not shown). Only the expression level of RMRP was correlated with HAM-D score in MDD patients (Table 3, Fig. 2). None of the lncRNA expression levels correlated with disease duration or STAI-S score (Table 3). The expression levels of PCAT1 and Y5 correlated with onset age in MDD patients (Table 3) and age in all participants (PCAT1: correlation coefficient = −0.484, p = 0.00032; Y5: correlation coefficient = −0.271, p = 0.043). In addition, MER11C, PCAT1, and Y5 expression levels were correlated with the imipramine equivalent doses, while RMRP and PCAT29 were not (Table 3). We investigated the correlation of the expression levels of MER11c, PCAT1, and Y5 with each of the following types of

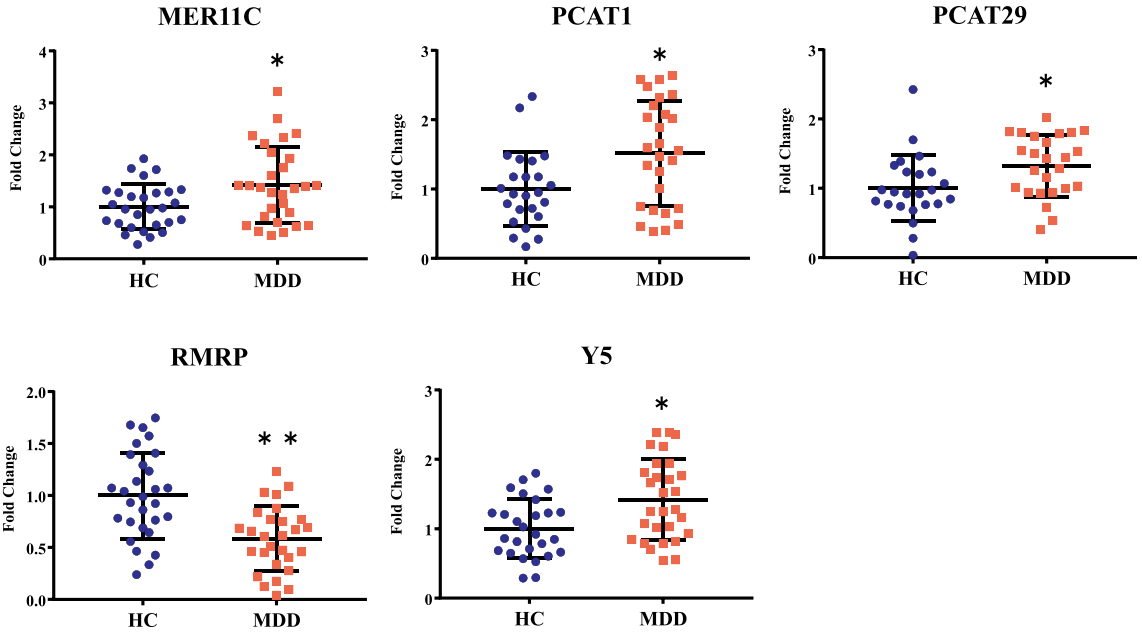

Fig. 1. Expression levels of 5 lncRNAs with significant differences in MDD patients compared to healthy controls. Expression levels are represented by dots ± SD. *p < 0.05 compared to healthy controls. **p < 0.001 compared to healthy controls.

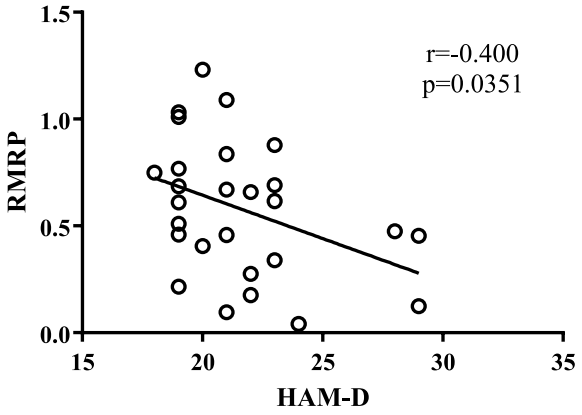

Fig. 2. Correlation between the expression levels of RMRP and HAM-D scores in MDD patients. Spearman correlation analysis was used; p = 0.0351, r = −0.400.

antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), the combined total of SSRIs and SNRIs, combined total of tricyclic and tetracyclic antidepressants, noradrenergic and specific serotonergic antidepressants (NaSSAs), and serotonin 2 antagonist and reuptake inhibitor (SARI). There was a correlation between the expression level of MER11c and the combined total of SSRIs and SNRIs (correlation coefficient = 0.384, p = 0.040), but the others were not correlated (date not shown).

The expression levels of RMRP did not correlate with cortisol concentration in MDD patients (correlation coefficient = 0.156, p = 0.428).

3.2. Experiment 2

Among five lncRNAs with expression levels that were altered in patients with MDD, RMRP is conserved in both humans and rodents. We therefore examined whether the altered expression of RMRP would also be observed in an animal model of depression. Increasing evidence indicates that chronic treatment with glucocorticoids induces depression- and anxiety-related states in rodents (David et al., 2009; Gourley et al., 2008; Murray et al., 2008). Indeed, we confirmed that mice receiving CORT for 1 month showed significantly prolonged immobility time in the FST (p = 0.000357, t = 4.25), indicating depressive-like states (Porsolt et al., 1977) (Fig. 3A).

We then measured the expression of RMRP via RT-qPCR and found that the level in blood was significantly decreased by CORT administration (p = 0.00315, t = 3.33). This significant decrease of RMRP expression in CORT-treated mice was confirmed with three different internal controls, including Gapdh (p = 0.0131, t = 2.71), β-actin (p = 0.00975, t = 2.84), and U6 (p = 0.00316, t = 3.33) (Fig. 3B).

4. Discussion

In Experiment 1, we identified changes in the expression levels of five lncRNAs in the peripheral leukocytes of MDD patients when compared to healthy subjects. Among them, the expression level of RMRP was lower while the expression levels of MER11C, PCAT1, PCAT29, and Y5 were higher in MDD patients. Furthermore, the expression level of RMRP was correlated with depression severity. In Experiment 2, the expression level of RMRP was reduced in the blood of a mouse model of depression, suggesting that RMRP expression changes depended on the depressed state. To the best of our knowledge, this is the first study to identify an lncRNA that exhibits altered expression both in patients with MDD and in a mouse model of depression. The consistency between the human and mouse data corroborates this evidence (Herve et al., 2017; Miyata et al., 2016; Pajer et al., 2012; Yamagata et al., 2017); the results together indicate the potential usefulness of these lncRNAs—RMRP in particular—as biomarkers of MDD.

The five lncRNAs described above have been partially implicated in psychiatric and physical conditions. RMRP is a nuclear DNA-encoded lncRNA that causes cartilage-hair hypoplasia (CHH)—an autosomal recessive chondrodysplasia characterized by shortened limbs, short stature, and sparse hair (Hermanns et al., 2006). Other ailments associated with CHH include immunodeficiency, anemia, gastrointestinal dysfunction, and increased risk of malignancy and cognitive deficiency (Makitie and Vakkilainen, 1993, [updated 2018 May 24]). RMRP plays at least four important roles in multiple cellular functions. First, RMRP is known as a component of the nuclear RNase MRP complex, which plays an important role in the processing of ribosomal RNA (Goldfarb and Cech, 2017; Schmitt and Clayton, 1993). Ribosomal dysfunction

Table 2
Forty-three lncRNAs detected in peripheral blood leukocytes of participants and eleven internal control genes in Experiment 1.

	LncRNA name							
Detected lncRNA	aHIF	AK023948	BACE1AS	BCMS	BIC	DD3	DISC2	DLG2AS
	EGO	GAS5	GOMAFU	HAR1B	HOTAIRM1	IPW	IGF2AS	LIT
	LUST	LincRNA-VLDLR	MALAT1	MER11C	NEAT1	NDM29	PANDA	PAR5
	PCAT1	PCAT29	PCAT43	PR-AT2	PTENP1	RMRP	Saf	SRA
	ST7OT1	TMEVPG1	TU_0017629	TUG	UCA1	Y1	Y3	Y4
	Y5	ZEB2NAT	7SK					
Internal control	7SL scRNA-5.1	5.8S rRNA-5.1	U6 smRNA-5.1	ACTB	B2M	PGK	GAPDH	HPRT
	RPL1A	RPL13A	U87 scaRNA-5.1					

Table 3
Correlation coefficients for the expression levels of 5 lncRNAs with onset age, disease duration, HAM-D score, STAI score, and antidepressant dose in MDD patients in Experiment 1.

	MER11C	PCAT1	PCAT29	RMRP	Y5
Onset age	−0.228	−0.537*[2]	−0.122	−0.070	−0.448*[5]
Disease duration	0.189	−0.097	0.210	0.126	0.079
HAM-D score	0.036	−0.165	−0.106	−0.400*[4]	−0.044
STAI score	0.034	0.325	−0.182	−0.180	0.014
Antidepressant dose	0.414*[1]	0.393*[3]	−0.064	−0.313	0.405*[6]

Note: *[1]p = 0.026, *[2]p = 0.004, *[3]p = 0.043,*[4]p = 0.035, *[5]p = 0.015, *[6]p = 0.029.

has been reported to cause neurodegenerative diseases including Alzheimer's and Parkinson's (Ding et al., 2005; Honda et al., 2005; Vilotti et al., 2012); moreover, the hypothalamus and hippocampus of a mouse model of depression showed abnormal ribosomal gene expression (Smagin et al., 2016). Second, RMRP performs important epigenetic functions. For example, RNase MRP, similar to RNase P, may be associated with chromatin remodeling (Jarrous, 2017), while small RNAs derived from RMRP regulate gene expression (Rogler et al., 2014). Third, RMRP interacts with the telomerase reverse transcriptase catalytic subunit (TERT) and forms the ribonucleoprotein complex (Maida et al., 2009). RMRP may play an important role in lymphocyte telomerase activity, as shorter telomere length was reported not only in patients with CHH but also in heterozygote RMRP carriers (Aubert et al., 2017). Interestingly, shorter telomere length in leukocytes has also been reported in MDD patients (Karabatsiakis et al., 2014). Additionally, Tert −/− mice exhibit depression-like behavior, which is normalized by the reactivation of Tert in the hippocampus (Zhou et al., 2016). From these findings the impaired functioning of RMRP in TERT may play a pivotal role in the pathophysiology of depression. Fourth, in the mitochondria, RMRP works as a mitochondrial RNase MRP complex, which participates in mitochondrial DNA replication, RNA processing, and mitochondrial respiration (Noh et al., 2016). Mitochondrial dysfunctions contribute to mood disorders (Czarny et al., 2018; Kasahara and Kato, 2018). For example, the dysfunction of Polg1, which encodes the catalytic subunit mitochondrial DNA polymerase in the forebrain, induces depression-like behavior in mice (Kasahara et al., 2016). In summary, based on its multiple functions described above, RMRP may serve as a hub that connects organelles including the nuclei, ribosomes, and mitochondria, contributing to stress and mood regulation. In corroboration with this critical role, our results showed that the expression level of RMRP was reduced in both MDD patients and in a mouse model of depression; furthermore, in MDD patients, the expression level of RMRP correlated with HAM-D scores. Further research is necessary to determine the specific mechanism of the involvement of RMRP in depression.

Next, Y5 is one of the YRNAs found in systemic lupus erythematosus (SLE) and Sjogren's syndrome as a complex of auto-antibody Ro 60

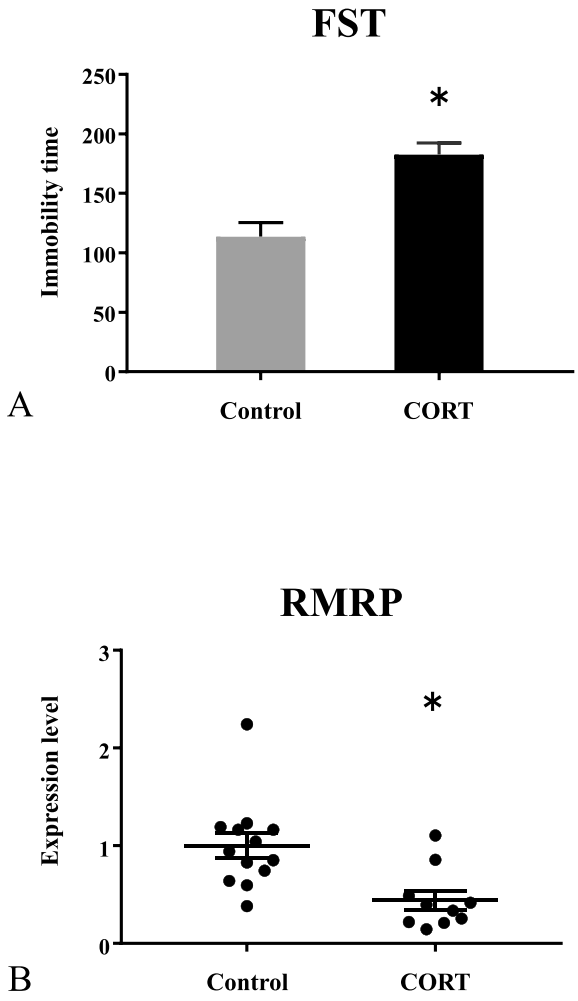

Fig. 3. Experiment 2 data from the mouse model of depression. A. Forced swim test. CORT-administered mice demonstrated longer immobility time in the forced swim test than control mice. Data indicate the mean ± SEM. *p < 0.001 compared to control mice. B. Expression level of RMRP. Expression level of RMRP in murine blood of CORT-administered mice (n = 10) was significantly lower than that of control mice (n = 13). *p < 0.05 compared to control mice.

protein and La protein (Hendrick et al., 1981). YRNAs have a stem-loop structure and are believed to contribute to the quality control of small RNAs, DNA replication, cell stress reaction, and proliferation (Kohn et al., 2013; Kowalski and Krude, 2015). Unlike other YRNAs, Y5 forms a complex with L5 ribosomal protein, a binding factor of 5S ribosomal RNA, as well as a complex with Ro protein and La protein. Moreover, since Y5 binds to the 5S RNA variant, Y5 may be involved in the biogenesis of 5S ribosomal RNA (Hogg and Collins, 2007). As mentioned above, it has been suggested that ribosome biosynthesis may affect

depression; Y5 may also be involved in depression via ribosome biosynthesis.

MER11C is one of the human polypyrimidine tract-binding protein-associated splicing factors (hPSFs) binding RNAs. The binding of RNA by hPSF promotes transformation and tumorigenesis by reversing suppression of proto-oncogene translation by PSF. Dysregulation of hPSF binding RNA expression plays a central role in the pathogenesis of human cancer (Li et al., 2009).

PCAT1 has been identified as an oncogenic lncRNA, especially in prostate cancer. It regulates cancer cell proliferation, apoptosis, migration, and invasion (Xiong et al., 2019). It was reported that PCAT1 levels increased with the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) (Prensner et al., 2011). SAHA was reported to improve depressive-like behaviors in mice (Covington et al., 2009). In this study, PCAT1 was correlated with the dose of antidepressants; its expression might be associated with antidepressant effect.

PCAT29 shows a cancer suppressive phenotype including inhibition of cell proliferation, migration, tumor growth, and metastasis and is suppressed by androgen signaling (Malik et al., 2014). When the expression of PCAT29 decreased, tumors increased/metastasized and clinical outcome worsened (Malik et al., 2014). As we observed increased expression of MER11C, PCAT1, and PCAT29, future studies should be conducted to investigate their specific functions in the pathophysiology of depression.

To date, research on lncRNAs in MDD is scarce—most of it involving comprehensive genome-wide analysis. Among the lncRNAs exhibiting significantly differential expression in this study, RMRP was reported to be significantly reduced in MDD patients compared with healthy controls based on the microarray data set published by Belzeaux et al. (2012). For the other four lncRNAs, none of the papers published previously report results consistent with our findings regarding lncRNAs that are significantly altered in MDD patients. By focusing on 83 targets in the present study, we identified new lncRNAs related to depression that have not been reported previously. However, MER11C, PCAT1, PCAT29, and Y5 might be considered false positives in that only RMRP showed significant changes in expression after Bonferroni's multiple comparison correction.

The strength of this research is that all participants were diagnosed by experienced psychiatrists, confirmed by M.I.N.I., and selected by strict exclusion criteria. However, our study had the following limitations. First, the number of human subjects is small. Future research with larger sample sizes is required to increase the statistical power and confirm our results. Second, we targeted 83 types of lncRNA using plated primers, including several lncRNAs reported previously by others. H19 (Han et al., 2018), Gas5 (Miao and Liang, 2019; Zhao et al., 2018), Gomafu (Barry et al., 2014; Spadaro et al., 2015), and MALAT1 (Wang et al., 2018) are reportedly involved in other diseases and in the pathophysiology of the central nervous system. Unfortunately, the expression level of H19 was too low in the blood samples of our study and the expression levels of Gas5, Gomafu, and Malat1 were similar between MDD patients and healthy controls. Notably, we analyzed the expression levels using peripheral blood samples; consequently, there was a possibility that genes potentially involved in depression in the central nervous system were excluded due to their low levels of expression in peripheral blood leukocytes. Third, we could not exclude the effects of smoking and drinking in that we did not collect detailed information regarding these habits. Fourth, we used only male mice in Experiment 2. However, there were no gender differences in the expression level of RMRP in human samples. Finally, it is impossible to exclude the potential influence of antidepressants on the expression levels of these genes, as all MDD participants except for one were taking antidepressant medications and MER11C, PCAT1, and Y5 correlated with the equivalent dose of imipramine. However, it should be noted that similar RMRP expression changes were observed in a mouse model of depression, suggesting RMRP's direct effect on the pathophysiology of depression.

Our results, combining data from both human and mouse subjects, suggest the usefulness of five lncRNAs—particularly RMRP—as biomarkers of depression. Future studies should clarify whether lncRNAs are functionally involved in MDD pathophysiology. Our encouraging findings may help develop a new approach to the identification of potential biomarkers for the clinical screening and diagnosis of MDD.

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Conflicts of interest

No conflict of Interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.07.004.

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