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Investigation of mitochondrial DNA copy number in patients with major depressive disorder

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ABSTRACT

Mitochondrial dysfunction is implicated in the pathophysiology of major depressive disorder (MDD). This dysfunction can be indirectly assessed using the mitochondrial DNA (mtDNA) copy number. A total of 118 patients with MDD and 116 age- and sex-matched control subjects were recruited for this study, and mtDNA copy numbers were measured in peripheral blood cells. This study also examined the potential variables that might impact mtDNA copy number in MDD, including age and clinical features. Additionally, epigenetic control of mtDNA copy number was examined by assessing DNA methylation ratios in the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) promoter in nuclear DNA and the displacement loop (D-loop) region of mtDNA. The present results showed that patients with MDD had a higher mtDNA copy number and a decreased DNA methylation status in the PGC1α promoter. mtDNA copy numbers were negatively associated with an age, psychomotor agitation, and somatic symptoms in MDD. These results suggest that the alterations in mitochondrial function and epigenetic change of PGC1α may be relevant to the pathophysiology of MDD.

1. Introduction

Major depressive disorder (MDD) is a very common psychiatric disorder (Disease et al., 2016). Because the pathophysiology of MDD is not yet clearly understood, it is necessary to explore the biological mechanisms associated with MDD. Beyond studies assessing the neurochemical factors associated with MDD, many studies have investigated neurotrophic factors, neuroplasticity, and mitochondrial dysfunction to propose biological hypotheses of MDD (Duman, 2002; Duman et al., 1997; Manji et al., 2012).

Mitochondria play a primary role in the brain as an energy-generating intracellular organelle that performs the oxidative phosphorylation of adenosine triphosphate (ATP), which is a major source of energy. It is also important for intracellular processes associated with signal transduction, neuronal survival, and neuronal plasticity (Frye and Rossignol, 2011). Mitochondrial dysfunction may affect key cellular processes due to impairments in cellular resilience and synaptic plasticity (Manji et al., 2012; Schloesser et al., 2009) and has also been associated with psychiatric illnesses such as bipolar disorder, MDD, schizophrenia, and anxiety disorder (Jou et al., 2009; Rezin et al., 2009; Schapira, 2012; Shao et al., 2008).

A variety of studies have proposed that there is a possible link between depression and mitochondrial dysfunction. Structured psychiatric evaluations of patients with mitochondrial disease have shown that approximately 50% of these patients have lifetime MDD prevalence (Anglin et al., 2012; Fattal et al., 2007; Inczedy-Farkas et al., 2012; Koene et al., 2009; Mancuso et al., 2013). Furthermore, it has been reported that the deletion of mitochondrial DNA (mtDNA) in pediatric patients with a mitochondrial disorder is associated with mild-to-moderate unipolar depression (Koene et al., 2009). On the other hand, there are decreases in the intracellular pH and phosphorylated creatine levels during the depressed phase of bipolar disorder. Conversely, brain

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pH levels increase in response to triacetyluridine, which is a precursor of uridine that improves mitochondrial function, when administered to patients with bipolar disorder during the depressive phase of bipolar disorder (Jensen et al., 2008; Kato and Kato, 2000; Moore et al., 1997). Taken together, these findings suggest that triacetyluridine improves the symptoms of depression by improving mitochondrial function. Muscle biopsies performed on patients with MDD revealed a decrease in the rate of mitochondrial ATP production compared to the control group (Gardner et al., 2003).

It is possible to indirectly assess mitochondrial function by measuring mtDNA copy numbers. Cells requiring high energy, such as heart cells, skeletal muscle cells, and neurons, require large amounts of ATP and maintain a high mtDNA copy number (Moyes et al., 1998). mtDNA copy number is considered to be a marker of mitochondrial energy function (Clay Montier et al., 2009; Lee and Wei, 2005; Moyes et al., 1998). Abnormal mtDNA copy numbers have been reported to be associated with several types of mental illness (Bersani et al., 2016; Li et al., 2015; Yoo et al., 2017). In particular, several studies have investigated the association between MDD and mtDNA copy number. Some studies found that the mtDNA copy number was higher in patients with MDD (Nicod et al., 2016; Tyrka et al., 2016). On the contrary, others reported a lower mtDNA copy number in peripheral blood leukocytes of patients with MDD (Chang et al., 2015) or no significant differences in mtDNA copy number between patients with MDD and healthy controls (He et al., 2014; Lindqvist et al., 2018). It has been reported that the leukocyte mtDNA copy number is reduced during a depressive episode of bipolar disorder compared to controls (Wang et al., 2018). Taken together, these findings suggest that mtDNA copy number studies using the peripheral blood of patients with MDD have produced inconsistent results.

Several types of mechanisms may regulate the contents of mtDNA. Epigenetic change is one of the mechanisms that control mtDNA copy number (Kelly et al., 2012). The nuclear genes associated with the regulation of mtDNA expression include mitochondrial transcription factor A, mitochondrial specific DNA polymerase γ, and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), and it is important to note that DNA methylation has been studied at these sites (Barres et al., 2009; Choi et al., 2004; Kelly et al., 2012). PGC1α is a nuclear gene that mediates the biogenesis of mitochondria (Lehman et al., 2000) and the PGC1α protein is a transcriptional coactivator that regulates genes involved in energy metabolism, including mitochondrial-associated proteins and transcriptional factors, by activating nuclear receptors, especially peroxisome proliferator-activated receptors (PPARs) (Jarvis and Lopez-Juez, 2013; Liu et al., 2007). Clinical trials have shown that PPAR agonists effectively improve symptoms in patients with MDD (Kashani et al., 2013; Lin et al., 2015) and PGC-1α has been shown to be associated with depression-like behavior in animal models (Agudelo et al., 2014; Glombik et al., 2015). PGC1α expression in skeletal muscle is protective against the induction of depressive symptoms in a mouse model of chronic mild stress (Agudelo et al., 2014). PGC1α mRNA levels are lower in patients with MDD than healthy controls (Ryan et al., 2018). Methylation in the PGC1α promoter leads to long-lasting changes in PGC1α transcription and decreases in PGC1α expression that reduces the expression of mitochondrial genes (Barres et al., 2009; Scarpulla, 2008). Thus, it can be hypothesized that changes in the amount of mtDNA may be related to methylation in the PGC1α promoter in MDD. mtDNA may also undergo epigenetic modulations associated with aging and the development of disease (Blanch et al., 2016; Mawlood et al., 2016; Zheng et al., 2016). Changes in mtDNA methylation have been investigated in the displacement loop (D-loop), NADH dehydrogenase subunit 6 (ND6), and cytochrome C oxidase (CO1) regions (Pirola et al., 2013; Sanyal et al., 2018; Tong et al., 2017), and the replication of mitochondria is known to occur in the D-loop region of mitochondria (Clayton, 2000). Although this has been analyzed in several studies to identify its biological characteristics, contradictory results have been reported regarding the role that methylation in the D-loop plays in disorders such as Alzheimer's disease. DNA methylation levels in the mtDNA D-loop region of patients with late-onset Alzheimer's disease are lower than those of control subjects (Stoccoro et al., 2017) but higher in patients with early-onset Alzheimer's disease (Blanch et al., 2016).

Several studies have suggested that aberrant epigenetic mechanisms associated with MDD pathogenesis may cause changes in gene expression and be related to disease (Byrne et al., 2013; Na et al., 2014; Numata et al., 2015). However, little is known about the epigenetic modifications associated with mitochondrial content in MDD. Thus, it was hypothesized in the present study that nuclear DNA, PGC1α, and the mtDNA, D-loop would regulate mitochondrial content via epigenetic regulations.

Here, peripheral blood samples were obtained to compare the mtDNA copy numbers of patients with MDD and control subjects to determine whether mitochondrial dysfunction contributes to the pathophysiology of patients with MDD. Additionally, DNA methylation ratios in the D-loop region and PGC1α promoter were examined to identify which factors might lead to changes in the mtDNA copy number.

2. Methods

2.1. Subjects

Subjects for the present study were gradually recruited from among patients who routinely visited the outpatient psychiatric clinic of Eulji General Hospital and several other psychiatric clinics in the Republic of Korea. Patients with MDD were diagnosed by at least two psychiatrists according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). For the final diagnosis of each patient, the psychiatrists reviewed medical records and reached a consensus via discussion. Additional information on the clinical features of each patient was obtained from psychiatric interview data conducted by research nurses. Patients with previous hypomanic/manic episodes, an intellectual disability, organic brain syndromes, current alcohol use disorder, dementia, and/or a psychiatric disorder due to another medical conditions were excluded; ultimately, 118 patients with MDD (46 males and 72 females, age range: 19–76 years) were enrolled in the present study. Additionally, 116 age- and sex-matched control subjects were selected through a matching process using a pool of control subjects previously developed by our research group. Written informed consent was obtained from all subjects prior to participating in this study, and the ethics committee of Eulji General Hospital approved the study protocol.

2.2. Clinical assessments

Data regarding age of onset, total duration of depressive episodes, number of depressive episodes, family history of mood disorder, and history of suicide attempts were collected. The clinical features of patients with MDD were qualitatively evaluated by the clinician in charge by assessing the presence of the following symptoms: psychotic features, psychomotor retardation, psychomotor agitation, weight gain, increased appetite, hypersomnia, somatic symptoms, and panic attacks.

2.3. Study sample and DNA extraction

Peripheral blood samples drawn from the 118 patients with MDD and the 116 control subjects were collected in cryotubes and stored at −70 °C. The genomic DNA of each sample was extracted using DNeasy Blood & Tissue kits (Qiagen; Hilden, Germany) at Eulji University, Korea according to the manufacturer's instructions. The quantity and purity of the DNA samples were quantified using a Nanodrop 2000 spectrophotometer (Thermo Scientific, Korea).

2.4. mtDNA copy number

mtDNA copy numbers were measured and analyzed as described previously (Yoo et al., 2017). The mtDNA copy number was determined by the ratio of mtDNA to the single-copy nuclear DNA (nDNA). The quantities of mtDNA and nDNA were represented by the threshold cycle (Ct) of a mitochondrial gene, Cytochrome b (CYTB), and a single-copy nuclear gene, pyruvate kinase (PK), respectively, using quantitative polymerase chain reaction (qPCR) analyses. The mixtures of qPCR for both CYTB and PK were identically composed of 20 ng of genomic DNA and the IQ SYBR Green Supermix (BioRad Laboratories, Korea) in 10 μl reaction samples, except for each primer set. Supplementary Table 1 lists the primer sets and qPCR conditions. Each sample was measured in duplicate (all standard deviations [SD] of the duplicate threshold cycle were < 0.7). The mtDNA copy number was calculated using the following formula: mtDNA/nDNA ratio = $2^{-\Delta Ct}$ ($\Delta Ct = Ct_{CYTB} - Ct_{PK}$).

2.5. metDNA/unmetDNA ratio measurements

Bisulfite conversion and methylation-specific PCR (MSP) processes were performed on MDD and control samples. For mtDNA linearization, genomic DNA was treated with BamHI before bisulfite conversion (Liu et al., 2016). The bisulfite conversion of purified DNA was carried out using the EpiJET Bisulfite conversion kit (Thermo Scientific, Korea) according to the manufacturer's protocol. In the bisulfite reaction, all unmethylated cytosines are converted to uracils while methylated cytosines remain unchanged. The MSP was performed using two special primer pairs, M primers for methylated DNA (metDNA) and U primers for unmethylated DNA (unmetDNA), in the PGC1α promoter and mitochondrial D-loop region (Sookoian et al., 2010; Zheng et al., 2015). 10 ng of bisulfite-converted DNA was used with IQ SYBR Green Supermix (Bio-Rad Laboratories). Supplementary Table 1 lists the primer sequences and PCR conditions. DNA methylation status was evaluated based on the metDNA/unmetDNA ratio ($2^{-\Delta Ct}$ [$\Delta Ct = Ct_{metDNA} - Ct_{unmetDNA}$]).

2.6. Statistical analysis

The demographic and clinical characteristics of each group were presented as a mean and SD for continuous variables and as number of cases or a proportion for categorical variables. The Shapiro-Wilk test was used for normality. T-tests were used to compare the mtDNA copy numbers and DNA methylation status of the MDD and control groups as well as mtDNA copy numbers according to the presence or absence of the clinical features of MDD; Mann-Whitney U-tests were performed when necessary. Correlations between mtDNA copy numbers and other variables (i.e., age, age at onset, number of episodes, duration of illness, and DNA methylation status) were calculated using Pearson's correlation analyses. A stepwise multiple linear regression analysis was conducted to determine which factors were predictive of mtDNA copy numbers in patients with MDD using mtDNA copy number as a dependent variable and demographic data, clinical features, and DNA methylation status as independent variables. All statistical analyses were performed with SPSS software (ver. 22.0; IBM Corp.; Armonk, NY, USA) and Prism 7, and p-values < 0.05 were considered to indicate statistical significance.

3. Results

3.1. Demographic and clinical characteristics (Table 1)

This study included 118 patients with MDD. Of them, 50 (42.4%) had a single episode of MDD and 68 (57.6%) had recurrent MDD. The mean age was 47.6 ± 16.7 years, the mean duration of disease was 7.0 ± 9.7 years, and 18 patients (15.3%) had a history of suicide attempts.

Table 1
Demographic and clinical characteristics of the major depressive disorder and control groups.

	MDD (n = 118)	Control (n = 116)
Age (years)*	47.6 (16.7)	47.7 (16.8)
Sex (n,%)		
Female	72 (61.0)	70 (60.3)
Male	46 (39.0)	46 (39.7)
Clinical diagnosis (n,%)		
MDD, single episode	50 (42.4)	
MDD, recurrent	68 (57.6)	
Age at onset (years)*	41.8 (16.5)	
Duration of illness (years)*	7.0 (9.7)	
Number of mood episode*	1.7 (0.9)	
Clinical features (n,%)		
Family history of mood disorder	38 (32.2)	
Psychotic feature	12 (10.2)	
Psychomotor retardation	30 (25.4)	
Agitation	102 (86.4)	
Weight gain	16 (13.6)	
Increased appetite	6 (5.1)	
Hypersomnia	6 (5.1)	
Somatic symptoms	78 (66.1)	
Panic attack	10 (8.5)	
History of suicide attempts	18 (15.3)	

* Mean (SD)
MDD: Major depressive disorder.

Table 2
Comparison of mtDNA copy numbers and metDNA/unmetDNA ratio between MDD and control groups.

	MDD Mean	SD	Control Mean	SD	p
mtDNA copy numbers					
MDD (n = 118)	141.95	57.28	102.17	29.13	< 0.001
MDD, single episode (n = 50)	141.56	57.61	96.93	24.89	< 0.001
MDD, recurrent (n = 68)	142.25	57.46	106.01	31.50	< 0.001
Methylation status of PGC1α promoter	0.69	0.34	0.89	0.35	< 0.001
Methylation status of D-loop region	0.38	0.15	0.39	0.16	0.640

MDD: Major depressive disorder.
PGC1α: peroxisome-proliferator-activated receptor γ co-activator-1α, D-loop: displacement loop.

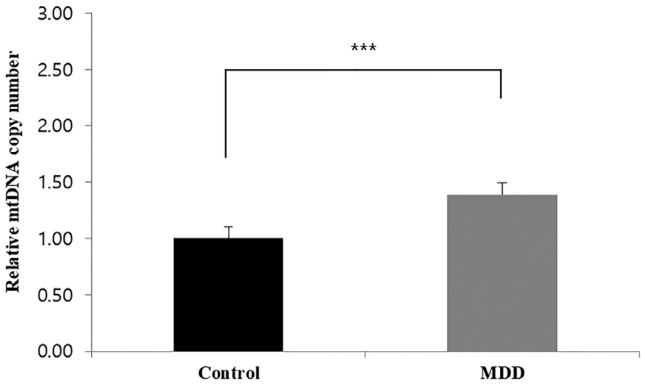

Fig. 1. Comparison of the average relative mtDNA copy number between control and major depressive disorder groups. The mtDNA copy number of the MDD group (n = 118) was significantly higher than that of the control group (n = 116). ***p < 0.001. Data is expressed as mean ± SD. MDD, major depressive disorder. mtDNA, mitochondrial DNA.

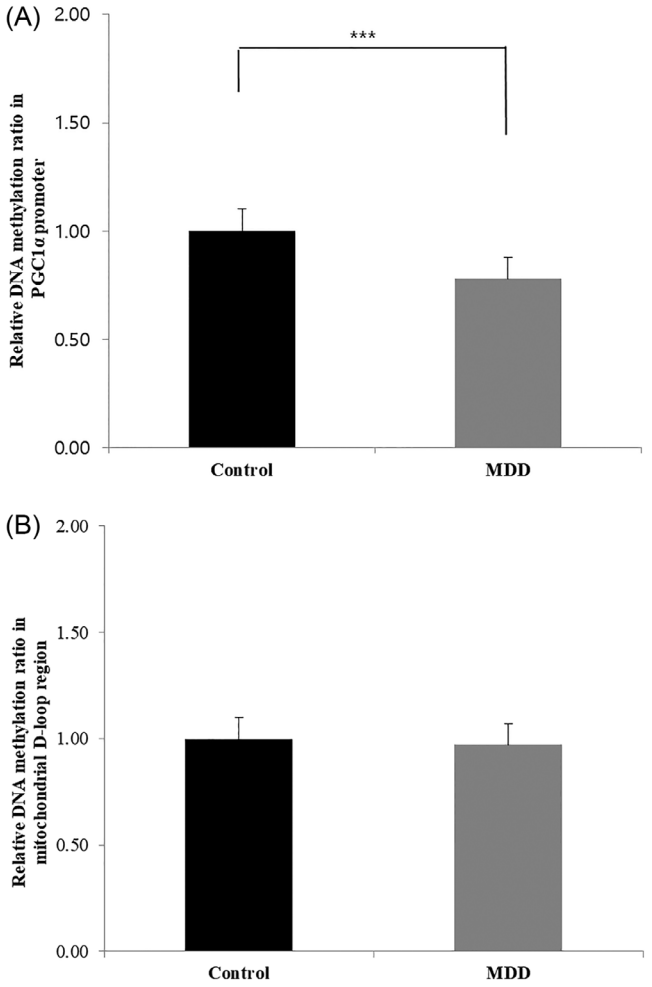

Fig. 2. Comparison of the average relative DNA methylation ratio in (A) PGC1α promoter and (B) mitochondrial D-loop region between control and major depressive disorder groups. (A) DNA methylation ratio in the PGC1α promoter was significantly lower in the MDD group ($n = 118$) than the control group ($n = 116$). ***$p < 0.001$. (B) The methylation status of the D-loop region did not differ significantly between the MDD ($n = 118$) and control ($n = 116$) groups. Data is expressed as mean ± SD. PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha. D-loop, displacement loop.

3.2. Comparisons of mtDNA copy numbers and metDNA/unmetDNA ratios between the MDD and control groups (Table 2)

The mtDNA copy number of the MDD group was significantly higher than that of the control group ($p < 0.001$; Fig. 1). Single-episode MDD ($p < 0.001$) and recurrent MDD ($p < 0.001$) patients differed significantly from the control group in terms of mtDNA copy number, while the mtDNA copy numbers of the two MDD groups did not significantly differ from each other ($p = 0.949$). The metDNA/unmetDNA ratio in the MDD group was significantly lower than that of the control group in the PGC1α promoter ($p < 0.0001$) but not the mitochondrial D-loop region (Fig. 2).

3.3. Comparisons of mtDNA copy numbers according to the presence or absence of clinical features in the MDD group (Table 3)

Patients with MDD that exhibited psychomotor agitation ($p < 0.001$) and somatic symptoms ($p < 0.001$) had significantly lower mtDNA copy numbers, whereas patients with clinical features of weight gain ($p = 0.001$) and increased appetite ($p = 0.019$) had significantly higher mtDNA copy numbers.

Table 3
Comparison of mtDNA copy numbers according to presence or absence of clinical features in major depressive disorder.

	mtDNA copy numbers				
	Presence		Absence		
	Mean	SD	Mean	SD	*p*
Family history of mood disorder	145.54	53.42	139.76	59.48	0.612
Psychotic feature	153.70	66.98	140.62	56.29	0.456
Psychomotor retardation	132.20	55.70	144.89	57.96	0.299
Psychomotor agitation	132.98	51.40	200.52	63.23	< 0.001
Weight gain	184.56	68.14	134.84	52.79	0.001
Increased appetite	194.98	79.29	138.75	55.02	0.019
Hypersomnia	182.42	88.26	139.43	55.02	0.074
Somatic symptoms	126.20	45.63	172.50	66.17	< 0.001
Panic attack	135.47	44.22	142.21	58.63	0.724
History of suicide attempts	148.98	67.89	140.30	55.60	0.558

Table 4
Correlations between mtDNA copy numbers and measured variables in major depressive disorder and control groups.

	MDD		Control	
	r	*p*	*r*	*p*
Age	−0.502	< 0.001	0.116	0.215
Age at onset	−0.460	< 0.001		
No. of episode	−0.058	0.538		
Duration of illness	−0.117	0.209		
Methylation status of PGC1α promoter	−0.048	0.603	−0.029	0.757
Methylation status of D-loop region	0.016	0.862	−0.096	0.307

r:Pearson correlation coefficient.
MDD: Major depressive disorder.
PGC1α: peroxisome-proliferator-activated receptor γ co-activator-1α, D-loop: displacement loop.

3.4. Associations between the measured variables and mtDNA copy numbers in the MDD and control groups (Table 4)

The mtDNA copy numbers were lower in patients with MDD who had an older age and a later age of disease onset. In both the MDD and control groups, there were no correlations between mtDNA copy number and the metDNA/unmetDNA ratios in the PGC1α promoter or mitochondrial D-loop regions (Fig. 3). However, when exploratory analyses were conducted in a mixed group that included all subjects from the patient and control groups, there was a negative correlation between mtDNA copy number and metDNA/unmetDNA ratio in the PGC1α promoter ($p = 0.026$; Fig. 3).

3.5. Stepwise multiple linear regression analysis of the measured variables and mtDNA copy numbers in the MDD group (Table 5)

A stepwise multiple linear regression analysis was conducted to assess whether the measured variables had significant associations with the mtDNA copy number in the MDD group. This analysis involved using an F-test of the model's overall significance ($F = 18.178$, $p \leq 0.001$), in which 39.4% of the variance was explained by the mtDNA copy number ($R^2 = 0.394$). Lower mtDNA copy numbers were significantly associated with an older age, psychomotor agitation, and somatic symptoms; whereas higher mtDNA copy numbers were significantly associated with weight gain. The other independent variables (i.e., sex, duration of illness, history of suicide attempts, number of episodes, family history of mood disorder, psychotic features, psychomotor retardation, increased appetite, hypersomnia, panic attacks, methylation status in the PGC1α promoter, and methylation status in the D-loop region) were not associated with mtDNA copy number. Although patients with increased appetite had a significantly higher mtDNA copy number, this symptom was excluded from the analyses as a non-significant predictive variable of mtDNA copy number by the

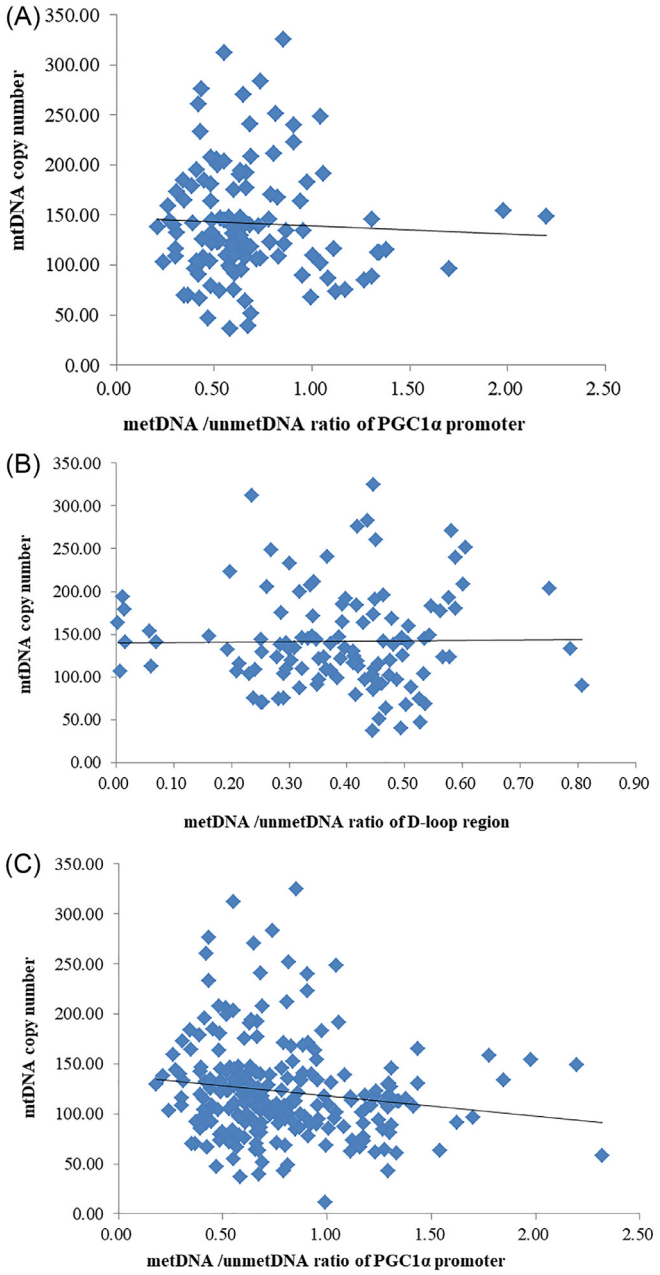

Fig. 3. Correlation between relative mtDNA copy number and DNA methylation statue of (A) PGC1α promoter and (B) mitochondrial D-loop region in patients with major depressive disorder (n = 118) and (C) PGC1α promoter in a mixed group of all participants (n = 334). (A) There was no correlation between mtDNA copy number and the DNA methylation ratio in the PGC1α promoter. p = 0.603. (B) There was no correlation between mtDNA copy number and the DNA methylation ratio in the mitochondrial D-loop region. p = 0.862. (C) There was a significant negative correlation between mtDNA copy number and DNA methylation ratio in the PGC1α promoter. p = 0.026. mtDNA, mitochondrial DNA. PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha. D-loop, displacement loop.

multiple linear regression analysis (p = 0.961).

4. Discussion

The present study demonstrated that the peripheral blood samples of patients with MDD had a higher mtDNA copy number than those of control subjects; these results were robust regardless of whether an individual had single-episode or recurrent MDD. Previous studies

Table 5
Stepwise multiple linear regression analysis of variables with mtDNA copy numbers in major depressive disorder.

Independent variables	*B*	ß	ΔR^2	*t*	*p*
Sex					0.160
Age	−1.17	−0.34	0.256	−4.253	< 0.001
Age at onset					0.766
No. of mood episode					0.579
Duration of illness					0.766
Family history of mood disorder					0.710
Psychotic feature					0.549
Psychomotor agitation	−31.48	−0.18	0.064	−2.275	0.025
Psychomotor retardation					0.119
Somatic symptoms	−29.17	−0.24	0.042	−3.061	0.003
Weight gain	31.12	0.19	0.031	2.401	0.018
Increased appetite					0.961
Hypersomnia					0.404
Panic attack					0.890
Methylation status of PGC1α promoter					0.433
Methylation status of D-loop region					0.676
	F value	18.178**			
	R^2	0.394			

** $p < 0.01$
B:regression coefficient, β:standardized regression coefficient
PGC1α: peroxisome-proliferator-activated receptor γ co-activator-1α, D-loop: displacement loop.

investigating mtDNA copy number in individuals diagnosed with MDD or showed depressive symptoms have yielded inconsistent results. Similar to the present findings, some studies have reported a higher mtDNA copy number in MDD cohorts (Cai et al., 2015; Nicod et al., 2016; Tyrka et al., 2016), whereas others have reported lower mtDNA copy numbers in individuals with depression (Chang et al., 2015; Kim et al., 2011) or no changes in mtDNA copy number (He et al., 2014; Lindqvist et al., 2018; Tymofiyeva et al., 2018; Verhoeven et al., 2018). The reasons underlying the inconsistencies in previous findings of mtDNA copy number in patients with depression remain unclear. The variations may be due to differences in the medication status of subjects, duration of illness, the age compositions of the study populations (youth vs. elderly), the phenotypes of various MDD diagnoses that are difficult to homogenize, and/or the comorbidities of somatic illnesses.

In particular, antipsychotics and mood stabilizers are known to affect mitochondrial function in bipolar disorder (Bachmann et al., 2009; Scaini et al., 2016), and antipsychotics have been shown to reduce mtDNA copy number in MDD (Chang et al., 2015). Furthermore, a study of the peripheral blood mononuclear cells of MDD patients who do not take psychotropic medications, including antidepressants, found no difference in mtDNA copy number compared to controls (Lindqvist et al., 2018). As such, mitochondrial function may have been influenced by the medication statuses of subjects. However, the patients in the present study were heterogeneous in terms of medication status and physical comorbidities. All of the patients were taking psychotropic medications as usual, with some taking several classes of psychotropic medications concurrently. Moreover, some of patients were prescribed medications to treat comorbidities of somatic illnesses such as hypertension or gastrointestinal disorders. Further studies are needed to assess changes in mtDNA copy number according to medication status in patients with MDD.

The present study also demonstrated that the mtDNA copy number decreased as age increased in the MDD group, but not in the control group. Previous investigations of the relationship between mtDNA copy number and age in patients with depression have yielded inconclusive results: some studies found no association between the mtDNA copy number and age in patients with MDD (Cai et al., 2015; Chang et al., 2015), whereas another study found that the mtDNA copy number

decreased with age in patients with depression (Verhoeven et al., 2014). Studies conducted in specific age groups, such as the elderly or adolescents, may help to approach this relationship. A study of community-dwelling older Korean women found that a low leukocyte mtDNA copy number is associated with depressive symptoms (Kim et al., 2011). In contrast, a study involving adolescents and young adults found no differences between the mtDNA copy numbers of MDD and healthy controls (He et al., 2014; Tymofiyeva et al., 2018). Moreover, studies have revealed that telomeres and mitochondria are functionally linked to the aging process. Shortening of telomere length has been found in MDD (Garcia-Rizo et al., 2013; Verhoeven et al., 2014), and more severe and longer-lasting MDD is also associated with shorter telomeres (Edwards et al., 2016; Tyrka et al., 2016; Verhoeven et al., 2014). Low mtDNA copy numbers are linked to various age-related health outcomes in terms of cognitive function, physical strength, and mortality (Mengel-From et al., 2014). The present results suggest that mtDNA copy number may have increased due to a depression-related effect, but the mtDNA copy number would have decreased due to aging. As a result, the mtDNA copy number of the MDD group was increased overall, due to the enhancing effects of disease rather than the reducing effects of aging.

The present study revealed that weight gain was significantly associated with a higher mtDNA copy number in patients with MDD after controlling for the influence of other variables. Patients with MDD also had a higher mtDNA copy number if they had increased appetite, but after controlling for the effects of other variables, increased appetite was not significantly associated with a higher mtDNA copy number. Mitochondria play a central role in energy metabolism, so mitochondrial impairments interfere with this process. Several types of abnormal energy metabolisms have been observed in the brains of patients with MDD (Harper et al., 2017; Iosifescu et al., 2008; Renshaw et al., 2001; Su et al., 2014; Videbech, 2000; Volz et al., 1998), suggesting that an increased mtDNA copy number may represent decreased energy metabolism and that there is an association between mitochondria and abnormal energy metabolism in patients with MDD. This interpretation is preliminary because the present data were obtained from qualitative measurements; quantitative data on the weights of individual patients were not collected. Therefore, it was not possible to analyze quantitative correlations between mtDNA copy number and the amount of weight gain. Moreover, only 16 patients, a small subset of 118 patients with MDD, showed weight gain, which limited our interpretation of the results. Further studies on these issues will be required.

In the present study, psychomotor agitation and somatic symptoms were significantly associated with a lower mtDNA copy number in patients with MDD after controlling for the influence of other variables. Psychomotor agitation is a symptom included in the diagnostic criteria for major depressive episode on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. MDD frequently co-occurs with somatic symptoms (Bekhuis et al., 2015). A high proportion of our patients had clinical characteristics of psychomotor agitation and somatic symptoms. Although the biological meanings of these associations cannot be speculated on at this point, the present study was the first to investigate the associations between mtDNA copy number and various clinical features of MDD. The present findings support the necessity of performing mitochondrial studies on the clinical phenotypes of MDD.

The present study also demonstrated that the DNA methylation ratio in the PGC1α promoter was significantly lower in the MDD group than the control group. There is a possibility that epigenetic change via methylation in the PGC1α promoter may explain the change in mitochondrial function in MDD. Transcriptional activity of PGC1α, termed 'regulator of mitochondrial biogenesis' (Fernandez-Marcos and Auwerx, 2011), can also be modulated by post-translational modifications, including methylation, acetylation or phosphorylation (Villena, 2015). The hypomethylation of PGC1α is concomitant with an increase in PGC1α expression and mitochondrial content in patients with type 2 diabetes (Barres et al., 2009), and PGC1α expression has been shown to increase as PGC1α promoter methylation decreased in Parkinson's disease (Su et al., 2015). As mentioned in the introduction, PGC1α has been implicated in depression. Therefore, hypomethylation of PGC1α promoter may have affected PGC1α expression in our MDD group. Epigenetic mechanisms that regulate the expression of nuclear genome have an effect on mitochondria, and mtDNA copy number can also influence the methylation pattern of nuclear genes (Manev and Dzitoyeva, 2013).

To date, no studies have investigated how methylation in the PGC1α promoter causes changes in mitochondrial content in those with psychiatric disorders, including MDD. The blood samples obtained from the present MDD cohort revealed decreased methylation levels in the PGC1α promoter and an increased mtDNA copy number, but the relationship between these variables was not statistically significant. Our exploratory analyses were conducted on a mixed group that included all subjects from the patient and control groups and revealed a significant negative correlation between mtDNA copy number and methylation status in the PGC1α promoter. It is likely that there are many types of control mechanisms for mtDNA and that DNA methylation is merely one type of epigenetic regulation. Moreover, the DNA methylation of a nuclear gene (e.g., PGC1α) could explain the regulation of mtDNA to a small degree. Future studies investigating a variety of mechanisms that influence the replication of mtDNA using additional populations will be helpful.

It was hypothesized in the present study that mitochondrial content might be regulated by the epigenetic modification of the mitochondrial D-loop region in patients with MDD. Contrary to expectations, the methylation status of the D-loop region did not differ significantly between the MDD and control groups, and mtDNA copy number and methylation status in the D-loop region were not correlated. However, the pattern of mtDNA methylation can be altered by various diseases, aging, or environmental toxicity (Blanch et al., 2016; Mawlood et al., 2016; Yang et al., 2016; Zheng et al., 2016), and mtDNA is subject to higher mutation rates than nDNA (Maynard et al., 2015). Thus, in addition to mood status, many factors could affect the methylation of the D-loop region. Furthermore, a wide variety of factors appears to play roles in the regulation of mtDNA.

In the present study, peripheral blood cells were used to study mtDNA because these cells can be collected using non-invasive methods without any significant inconvenience to the patient. Mood states are expressed in terms of brain function, so it would be helpful to have adequate samples of brain tissue to study mtDNA. However, mtDNA copy numbers in the peripheral blood are strongly related to mtDNA copy numbers in brain tissue (Feng et al., 2013; Kazachkova et al., 2013), so alterations in the mtDNA of peripheral blood cells might be relevant to brain function and pathology.

The present study has several limitations that should be discussed. First, the mood status of the patients was not quantitatively evaluated when the blood samples were collected. At the time of blood sampling, the mood status of the patients was judged to be euthymic because they were in the maintenance phase of treatment. However, their evaluation results could have been influenced by subclinical mood symptoms. Second, because the number of subjects used to determine clinical phenotype was relatively small, analyses of the relationships between mtDNA copy number and clinical phenotype lacked statistical power. Additionally, the clinical characteristics of the patients with MDD were qualitatively assessed, so there were limitations regarding confirmation of the severity and consequences of the clinical phenotypes seen in the patients with MDD. Third, various environmental and genetic factors act as potential confounding factors that can affect mtDNA copy numbers (Lopez et al., 2014; Wong et al., 2017), and the experimental design of the present study made it difficult to rule out these confounding influences.

In conclusion, the present study demonstrated that patients with MDD had a higher mtDNA copy number. These results suggest that the alterations in mitochondrial function may be relevant to the

pathophysiology of MDD. The exact epigenetic control for mitochondrial content measured by DNA methylation of the PGC1α promoter and D-loop has not been identified by the present findings. However, a variety of epigenetic controls and other mechanisms may regulate mitochondrial function through pathways other than PGC1α and the D-loop. Thus, future studies of these mechanisms will help to clarify the contribution of mitochondria to the development of MDD and the epigenetic control of mtDNA.

Declaration of Competing Interest

The authors report no conflicts of interest.

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Supplementary materials

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