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Major depressive disorder-associated *SIRT1* locus affects the risk for suicide in women after middle age

Takashi Hirata[a], Ikuo Otsuka[a], Satoshi Okazaki[a], Kentaro Mouri[a], Tadasu Horai[a], Shuken Boku[a], Motonori Takahashi[b], Yasuhiro Ueno[b], Ichiro Sora[a], Osamu Shirakawa[c], Akitoyo Hishimoto[a,*]

[a] Department of Psychiatry, Kobe University Graduate School of Medicine, Kobe, Japan
[b] Division of Legal Medicine, Department of Community Medicine and Social Health Science, Kobe University Graduate School of Medicine, Kobe, Japan
[c] Department of Neuropsychiatry, Kindai University Faculty of Medicine, Osaka, Japan

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ABSTRACT

A recent genome-wide association study (GWAS) for major depressive disorder (MDD) in Chinese women identified a single-nucleotide polymorphism (SNP), rs12415800, near the *Sirtuin1* (*SIRT1*) gene as one of the top candidate loci. However, no study has shown a genetic association between *SIRT1* and completed suicide, which is one of the most serious outcomes of MDD. In this study, 778 suicide completers and 760 controls in a Japanese population were genotyped for two SNPs in strong linkage disequilibrium (rs12415800 and rs4746720 in 3′UTR). We found significant associations between both SNPs and completed suicide among women aged ≥50 years. Additional analysis using postmortem brain tissues (10 suicide brains and 13 non-suicide brains) revealed the following: while *SIRT1* gene expression in the prefrontal cortex did not differ between suicide and non-suicide brains, *DNAJC12* gene expression, potentially implicated by the SNPs genotyped here, was significantly decreased in suicide brains ($p = 0.003$). In conclusion, regarding the genetic association of *SIRT1* with MDD that was previously identified in women by the Chinese GWAS, we successfully validated our results using a female suicidal cohort in the same Asian population with the same direction of allelic effect.

1. Introduction

Suicide is a significant public health problem that causes nearly 1 million deaths worldwide each year (WHO, 2014). Twin, family, and adoption studies have revealed evidence for genetic factors in suicidal behavior. However, due to the difficulty in obtaining samples from suicide completers, few genetic studies, such as genome-wide association studies (GWASs), have been conducted; therefore, genetic insights into suicide lag behind those of other mental problems (Mirkovic et al., 2016).

Among the various psychiatric disorders, major depressive disorder (MDD) is reported to be the one most related to suicidality (Sokero et al., 2005). Attempts to find genetic risk loci for MDD have failed because the clinical heterogeneity of MDD might reduce the power to detect genetic effects (Mullins and Lewis, 2017). However, a recent large-scale GWAS for MDD identified single nucleotide polymorphisms (SNPs) near the *Sirtuin1* (*SIRT1*) gene as the top associated variants contributing to risk of recurrent MDD in Chinese women (CONVERGE consortium, 2015). Animal studies have also revealed that depressive-like behavior is mediated by hippocampal SIRT1 signaling (Abe-Higuchi et al., 2016), and that antidepressant effects are promoted by treatment with resveratrol, a well-known SIRT1 activator (Hurley et al., 2014). Moreover, in humans, *SIRT1* gene expression in blood samples was significantly decreased in MDD patients relative to healthy subjects (Luo and Zhang, 2016). Several studies have also documented the involvement of *SIRT1* in other psychiatric disorders, such as schizophrenia (Wang et al., 2015) and bipolar disorder (Nivoli et al., 2016).

Based on these findings, SIRT1 dysregulation has attracted special attention because of its key role in the pathogenesis of MDD and other psychiatric disorders. However, no study has shown the involvement of *SIRT1* polymorphisms or expression in completed suicide, which is one of the most serious outcomes of psychiatric disorders, including MDD. Indeed, several lines of evidence have revealed both clinical and genetic

Abbreviations: DNAJC12, DnaJ Heat Shock Protein Family (Hsp40) Member C12; DLPFC, dorsolateral prefrontal cortex; EAF, effect allele frequency; GAPDH, Glyceraldehyde-3-Phosphate Dehydrogenase; GWAS, genome-wide association study; HWE, Hardy-Weinberg equilibrium; LD, linkage disequilibrium; MDD, major depressive disorder; qRT-PCR, quantitative real-time polymerase chain reaction; SIRT1, Sirtuin1; SNP, single-nucleotide polymorphism

* Corresponding author.
E-mail address: hishipon@med.kobe-u.ac.jp (A. Hishimoto).

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Table 1
Demographic and clinical details of suicide completers and healthy controls for *SIRT1* SNP association study.

	Suicide completers (n = 778)			Healthy controls (n = 760)	p
Average age in years (± s.d.)	50.0 (16.4)			50.5 (17.2)	0.538[a]
Sex (male/female)	530/248			364/396	<0.001[b]
Suicide methods	All n (%)	Men n (%)	Women n (%)		
Neck hanging	501 (64.3)	353 (66.6)	148 (59.7)	–	–
Jumping from heights	128 (16.4)	80 (15.1)	48 (19.3)	–	–
Gas suffocation	35 (4.4)	27 (5.1)	8 (3.0)	–	–
Drowning	21 (2.7)	10 (1.9)	11 (4.4)	–	–
Jumping in front of vehicles	11 (1.4)	8 (1.5)	3 (1.2)	–	–
Drug overdosing	8 (1.0)	5 (0.9)	3 (1.2)	–	–
Self-inflicted penetrating wounds	7 (0.9)	4 (0.8)	3 (1.2)	–	–
Self-burning	2 (0.3)	2 (0.4)	0 (−)	–	–
Taking poison	2 (0.3)	2 (0.4)	0 (−)	–	–
Others	12 (1.5)	7 (1.3)	5 (2.0)	–	–
Unknown	51 (6.6)	32 (6.0)	19 (7.7)	–	–
Presence of mood disorder history[c]	278 (−)	134 (−)	144 (−)	–	–

Abbreviation: s.d., standard deviation.
[a] p value was calculated by Mann–Whitney U test.
[b] p value was calculated by χ^2 test.
[c] Percentage in each group is not shown because our suicidal population included suicide completers with unknown medical history.

overlap between MDD and suicide (Chesney et al., 2014; Levey et al., 2019). Therefore, we first conducted a candidate SNP analysis of 778 suicide completers (one of the largest samples in the suicide genetics field), focusing on the top associated *SIRT1* SNP (rs12415800) previously identified by the Chinese GWAS for MDD in women. Second, we conducted postmortem brain analysis to investigate whether mRNA expression levels of the related genes were aberrantly changed in suicide brains.

2. Methods

2.1. Subjects

Our SNP association study consisted of 778 suicide completers and 760 unrelated healthy volunteers (Demographic and clinical data are shown in **Table 1**). For postmortem brain analysis, autopsied brains were obtained from 10 suicide completers and 13 non-suicide control subjects (Autopsy data are shown in **Supplementary Table 1**). All subjects were of Japanese descent. Autopsies of suicide completers were conducted, and their verdicts of suicide were determined, at the Division of Legal Medicine in the Department of Community Medicine and Social Health Science at the Kobe University and Examiner's Office of Hyogo Prefecture, as previously described (Otsuka et al., 2017). None of the unrelated healthy volunteers had psychiatric problems as determined from unstructured interviews conducted by two psychiatrists using DSM-IV or DSM-5. We excluded control subjects with a personal and/or familial history of psychiatric disorders and/or suicidal behavior. Informed consent was obtained from all of the participants and from the families of the subjects who were used for postmortem blood and brain samples. This study was performed in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee for Genetic Studies of the Kobe University Graduate School of Medicine.

2.2. SNP selection

We selected rs12415800, located upstream of *SIRT1*, which was previously identified as one of the top MDD-associated SNPs in a large-scale Chinese GWAS (CONVERGE Consortium, 2015). In addition, we selected rs4746720, located in the 3′UTR of *SIRT1*, as a potential functional SNP in strong linkage disequilibrium (LD) with rs12415800 (r^2 > 0.8) by using HaploReg (v4.1) (Ward and Kellis, 2012). Additionally, a recent study in a healthy Chinese cohort (Rao et al., 2018) revealed that the minor allele of rs4746720 contributed to higher grey matter density in the inferior frontal cortex, which led to increased functional connectivity; this was also reported in suicide attempters (Chase et al., 2017), thereby supporting our selection of this potential functional SNP. According to the database (HaploReg), these SNPs have perfect LD with rs2273772 in Asian populations, located in the 5′UTR of *DnaJ heat shock protein family (Hsp40) member C12* (*DNAJC12*) gene.

2.3. SNP genotyping

Peripheral blood samples were obtained from 778 suicide completers (530 men and 248 women) and 760 healthy volunteers (364 men and 396 women) and were stored at −80 °C before use. DNA was extracted using the QIAamp DNA Blood Midi Kit (Qiagen NV, Venlo, the Netherlands). Extracted DNA was quantified and subjected to quality control using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). rs12415800 and rs4746720 were genotyped using TaqMan assays (Applied Biosystems, Foster City, CA, USA) with a 7500 Real-Time PCR System (Applied Biosystems), in accordance with the manufacturer's protocol.

2.4. mRNA expression of SIRT1 and DNAJC12 in postmortem brain

Brain samples were stored at −80 °C before use. The dorsolateral prefrontal cortex (DLPFC) was dissected on dry ice for subsequent RNA extraction. Total RNA was isolated from collected brain samples by using RNeasy Plus Universal Mini Kit (Qiagen NV). The concentration and purity of the extracted RNA were estimated using a NanoDrop spectrophotometer (Thermo Fisher Scientific), which confirmed the RNA integrity number (RIN) of all samples to be >5, generally regarded as the quality threshold for subsequent use in quantitative real-time polymerase chain reaction (qRT-PCR) (Fleige and Pfaffl, 2006; van der Linden et al., 2014). Reverse transcription was performed to synthesize cDNA by using QuantiTect Reverse Transcription Kit (Qiagen NV). The relative mRNA expression of *SIRT1* and *DNAJC12* were evaluated using the qRT-PCR method, which was performed with TB Green Advantage qPCR premix (Takara Bio Inc, Japan) in a 7500 Real-Time PCR System (Applied Biosystems). The primer sequences and cycling conditions are shown in **Supplementary Table 2**. GAPDH served as the internal control. The mRNA data were quantified using the comparative threshold cycle ($2^{\Delta\Delta CT}$) method (Livak and Schmittgen, 2001).

2.5. Statistics

Statistical analysis was performed with R version 3.4.1 (R

Foundation for Statistical Computing, Vienna, Austria). As shown in Table 1, there was a significant difference in sex distribution between the suicidal group and healthy control group for the SNP association study ($p < 0.001$ by χ^2 test). Therefore, we conducted a sex-stratified analysis for the SNP association study. We used the Haploview version 4.2 software program to determine the Hardy–Weinberg equilibrium (HWE), LD, allelic frequencies, and genetic associations (Barrett et al., 2005). The allele-based association analysis and genotype-based association analysis were performed with the χ^2 test and the Cochran–Armitage trend test, respectively. Power analysis was performed with the PS version 3.0 program (Dupont and Plummer, 1998). The effects of age for female suicide completers for SNPs were calculated with a linear regression model. Mann-Whitney U test was implemented for assessments involving between-group comparisons of mRNA expression in postmortem brains. Dummy variables were used as necessary (phenotype, control = 0 and suicide = 1; sex, male = 0 and female = 1). Differences with $p < 0.05$ were deemed statistically significant.

3. Results

rs12415800 and rs4746720 showed strong LD to each other in our dataset using the Haploview software ($D' = 0.992$, $r^2 = 0.977$) (**Supplementary Figure 1**). The distributions of all SNPs did not deviate from the HWE in each dataset. Because the effect allele frequency (EAF) of the SNPs seemed to be affected by age at suicide in female subjects (rs4746720: $p = 0.024$, beta = 3.5 years) (**Supplementary Table 3**), we performed an age-stratified analysis by dividing our female suicide completer cohort into two groups based on age at suicide (aged < 50 years or ≥50 years). Consequently, we found that only female suicide completers aged ≥50 years had a significantly higher EAF of both SNPs than controls (rs4746720: genotype $p = 0.014$, allele-corrected $p = 0.016$, OR = 1.43); these results were in the same direction of the allelic effect of the two SNPs in women with MDD detected by the previous Chinese GWAS (CONVERGE Consortium, 2015) (Table 2). Conversely, neither female suicide completers aged <50 years nor male suicide completers showed a significant difference in the EAF of these SNPs, compared to healthy controls.

The sex, age, PMI and measured pH of the preservative solution for postmortem brains did not differ between suicide completers and control groups (**Supplementary Table 1**). While there was no significant difference in *SIRT1* mRNA expression between suicide brains and non-suicide brains, *DNAJC12* mRNA expression was significantly decreased in suicide brains compared to controls ($p = 0.003$, Fig. 1).

4. Discussion

The two SNPs (rs12415800 and rs4746720) were reported to be the top SNPs associated with female MDD in a large-scale Chinese GWAS (CONVERGE Consortium, 2015). That GWAS included only subjects with recurrent MDD, focusing on severe cases. Similarly, our results showed that the two SNPs contributed to suicide risk only in our female subjects after middle age. Previous work on female MDD has revealed an association between more severe depression and a greater number of episodes with high suicidality (Zhu et al., 2013). Regarding the genetic association of *SIRT1* SNPs with female MDD previously identified by the Chinese GWAS, we successfully validated these results using a female cohort of suicide completers (one of most severe phenotypes for MDD) with the same direction of the allelic effect in the same Asian population. Particularly, rs4746720 is a functional polymorphism located in the 3′UTR region of *SIRT1*, which contains a binding site for HuR, an RNA-binding protein reported to stabilize *SIRT1* mRNA and increase *SIRT1* expression levels (Abdelmohsen et al., 2007). Although our postmortem brain analysis did not reveal definitive aberrant gene expression of *SIRT1* in suicide brains, our analysis was limited to DLPFC specimens and excluded other brain regions that are involved in the pathophysiology of suicide, such as the orbitofrontal cortex, ventral prefrontal cortex, hippocampus, and amygdala (Oquendo et al., 2014). Therefore, gene expression of *SIRT1* in those brain regions correlated with suicidal vulnerability should be explored in future studies. In addition, rs4746720 was associated with increased grey matter density in the inferior frontal cortex (Rao et al., 2018); thus, this SNP might contribute to suicide risk through another mechanism, rather than direct changes in *SIRT1* expression. Meanwhile, we showed that *DNAJC12* mRNA expression was significantly decreased in suicide brains. rs2273772 in perfect LD with the SNPs genotyped here, is located in the 5′UTR of *DNAJC12*. The recent findings focusing on depletion of neurotransmitter metabolites in the cerebrospinal fluid of individuals with null mutations in *DNAJC12* suggest that this gene has

Table 2
Sex-stratified association analysis between *SIRT1* SNPs and suicide completers.

SNP ID[a] Position[a]	Sex	Phen	Genotype distribution			Effect allele (REF allele)	EAF	*p*			Power	OR (95% CI)	Previous GWAS for female MDD (CONVERGE Consortium., 2015)
			MM	Mm	mm			HWE	Genotype	Allele			
rs12415800	Female	SC	85	121	42	A (G)	0.413	1.000	0.093	0.091	0.393	1.22	
Chr10: 69624180		CON	161	180	55		0.366	0.740				(0.97–1.53)	
	Female	SC (Age < 50)	47	56	18		0.369	0.697	0.696	0.693	0.051	1.06	Effect allele: A
		CON	161	180	55		0.366	0.740				(0.79–1.42)	$p = 1.92 \times 10^{-8}$
	Female	SC (Age ≥ 50)	38	65	24		0.445	0.855	**0.026**	**0.025**	0.613	**1.38**	OR = 1.16
		CON	161	180	55		0.366	0.740		**(0.029)**[b]		**(1.04–1.85)**	
	Male	SC	221	233	76		0.363	0.284	0.615	0.571	0.087	0.95	
		CON	140	175	49		0.376	0.665				(0.78–1.12)	
rs4746720	Female	SC	86	121	41	C (T)	0.409	1.000	0.094	0.092	0.394	1.22	
Chr10: 69676830		CON	163	179	54		0.362	0.723				(0.97–1.53)	
	Female	SC (Age < 50)	48	57	16		0.368	1.000	0.879	0.879	0.054	1.02	Effect allele: C
		CON	163	179	54		0.362	0.723				(0.76–1.38)	$p = 3.32 \times 10^{-8}$
	Female	SC (Age ≥ 50)	38	64	25		0.449	1.000	**0.014**	**0.014**	0.696	**1.43**	OR = 1.16
		CON	163	179	54		0.362	0.723		**(0.016)**[b]		**(1.08–1.91)**	
	Male	SC	221	234	75		0.362	0.341	0.546	0.583	0.087	0.94	
		CON	145	182	56		0.384	1.000				(0.77–1.14)	

Statistical values that reached significance ($p < 0.05$) are shown in bold.
Abbreviations: SNP ID, single-nucleotide polymorphism identification; Phen, phenotype; M, major allele; m, minor allele; EAF, effect allele frequency; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; SC, suicide completers; CON, controls.
[a] SNP ID number and positions are based on Human Genome version 19 (hg19), build 37.
[b] Corrections for multiple comparisons are in parentheses (for 10,000 permutations).

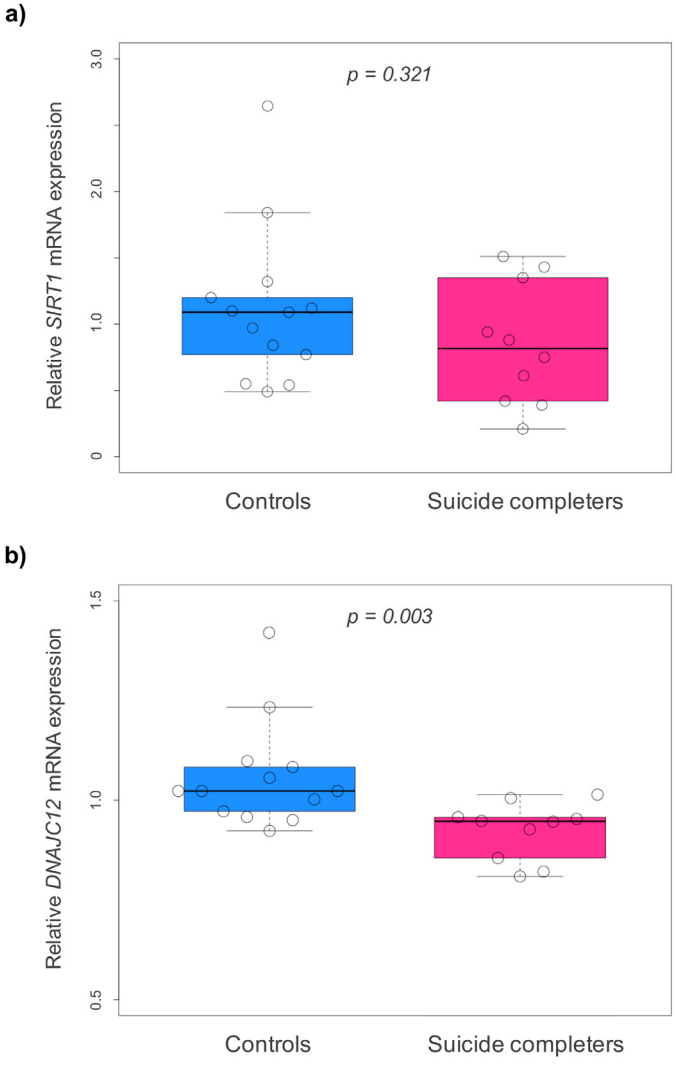

Fig. 1. mRNA expression of *SIRT1* and *DNAJC12* in postmortem brains of suicide completers and non-suicide controls.
Scatter dot plot including box and whiskers (with minimum to maximum) are shown. (a) The distribution of *SIRT1* mRNA expression in DLPFC. (b) The distribution of *DNAJC12* mRNA expression in DLPFC. *p* value were calculated using Mann–Whitney U test.

potential neuropsychiatric impact (Anikster et al., 2017).

There were several limitations to our present study. First, there were no controls for the confounding effects of comorbid psychiatric disorders, although many suicide completers had experienced various psychiatric disorders, including mood disorder. Second, although our sample size of suicide completers was one of the largest ever reported, the number of subjects in our SNP association study may not have been sufficiently large to avoid statistical errors. Third, since our SNP selection originated with the previous Chinese GWAS (CONVERGE Consortium, 2015), we should also have focused on *LHPP* gene (rs35936514) which was identified as another top MDD-associated SNP in that GWAS. Fourth, our postmortem brain analysis was limited in terms of poor sample size; this causes difficulty to conduct multivariate analysis with covariates such as sex, age, pH, and PMI, which can affect the results. Therefore, our postmortem brain analysis should be used as preliminary results. In addition, our analysis may have been affected by inadequate tissue quality. One study suggested that RIN values provide an incomplete measure of brain tissue quality (Sonntag et al., 2016). Additionally, RNA with RIN values ≥7 is regarded as optimal for most downstream molecular applications (Sellin Jeffries et al., 2014). Thus, the RIN threshold in this study may not have ensured the quality of our results regarding postmortem gene expression analysis.

In conclusion, we showed significant associations between *SIRT1* SNPs (rs12415800 and rs4746720) and female suicide completion after middle age in the Japanese population, consistent with the previous Chinese GWAS for recurrent MDD in women.

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Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.002.

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