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The Effect of Forkhead Box O1 Single Nucleotide Polymorphisms on Cortical Thickness and White Matter Integrity in High Suicide Risk Patients

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Objective Neuroinflammation's role is increasingly emphasized in the pathology of major depressive disorder (MDD), and its close association with the risk of suicide is being reported. The Forkhead Box O1 (FoxO1) gene is known to play a role in regulating mood and emotion and is associated with susceptibility to suicidality in relation to environmental stress. This research aims to explore the relationship between FoxO1 and the risk of suicide in individuals with MDD.

Methods We enrolled 127 healthy controls (HC) and 231 patients diagnosed with MDD, including 119 individuals with high suicide risk (HSR). All participants underwent the Hamilton Rating Scale for Depression Assessment and magnetic resonance imaging. Cortical thickness and white matter integrity were evaluated.

Results In the HSR group, cortical thinning was observed in the left triangular part of the inferior frontal gyrus and right transverse frontopolar gyrus compared to HC. Additionally, fractional anisotropy (FA) values were decreased in the left posterior thalamic radiation, sagittal stratum, and uncinate fasciculus. Although no differences were observed based on allele variations for the two FoxO1 single nucleotide polymorphisms (SNPs), those with the minor allele of FoxO1 rs34733279, especially in the HSR group, displayed increased cortical thinning and reduced FA values in the left cingulum.

Conclusion Our study reveals close association between the minor allele of the FoxO1 gene rs34733279 and suicide risk in the left cingulum highlights the potential key role of the FoxO1 gene rs34733279 in the context of suicidal vulnerability. Further investigations are warranted to elucidate the underlying biological mechanisms.
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Keywords Forkhead box protein O1; Single nucleotide polymorphisms; Suicide risk; Cortical thickness; Tract-based spatial statistics.

INTRODUCTION

Suicide is a severe social issue with a global age-standardized suicide rate of 10.5 per 100,000 in 2016, as per the World Health Organization report.[1] Suicide is the second most common cause of premature death among those aged 15–29, following traffic accidents, and the third most common cause among those aged 15–44.[2] Suicide leads to economic and emotional burdens for bereaved families.[3-6] And major depressive disorder (MDD) is the leading cause of suicide, with a 20-fold increase in suicide risk in individuals with MDD, and >50% of suicide deaths being linked to mood disorders.[7,8] Although the mechanisms underlying depression have been extensively studied, it is crucial to explore the biological mechanisms underlying suicide risk.

Previous studies have shed light on serotonergic mechanism abnormalities, including elevated serotonin receptor subtypes and reduced serotonin metabolites.[9-11] Moreover, elevated neuroinflammation, indicated by increased levels of inflammatory markers such as interleukin-6 and other cytokines in the bloodstream or cerebrospinal fluid, has been de-

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tected in suicide cases.[12] Research on the biological mechanisms of suicide has been further supported by magnetic resonance imaging (MRI) studies.[9,13] A qualitative analysis indicated that changes in the frontal, limbic, and temporal brain regions in individuals with suicidal thoughts were linked to difficulties in emotional processing and regulation. Additionally, alterations in the frontal, limbic, and parietal lobes and basal ganglia have been observed in individuals displaying suicidal behaviors, often related to deficits in decision-making abilities.[14]

Recent studies have elucidated the role of the Forkhead Box O (FoxO) gene, particularly FoxO1, in the pathophysiology of depressive disorders and other neuropsychiatric conditions.[15-17] FoxO genes are part of a family of transcription factors, characterized by a preserved DNA-binding region (known as the forkhead box) located at the protein's N-terminal region.[18,19] FoxOs bind to a conserved DNA-binding sequence in the promoter region of their target genes and control their transcription in response to external signals.[20,21] Four FoxO genes (FoxO1, FoxO3a, FoxO4, and FoxO6) have been identified in mammals. FoxO1 was initially discovered in studies on chromosomal translocations in human tumors. In addition to its role in oncogenesis, FoxO1 plays a vital role in regulating metabolic diseases, including gluconeogenesis, glycogenolysis, adipogenesis, thermogenesis, and feeding behavior.[17,22,23]

Among the various FoxO isoforms, FoxO1 is primarily expressed in the striatum and hippocampus.[24] Dysregulation of FoxO1 signaling has been observed in animal models of depression and stress, suggesting a potential involvement in mood disorders through its association with α2-macroglobulin and transforming growth factor-β1.[25] In transgenic mice, Sirt1/FoxO1-associated monoamine oxidase A (MAO-A) upregulation induced depressive-like behavior.[26] Furthermore, FoxO1 mediated psychological stress-induced neuroinflammation in mouse models,[27] and ameliorated neuroinflammation-induced depressive-like behavior by baicalin, via the PI3K/AKT/FoxO1 pathway.[28] Six single nucleotide polymorphisms (SNPs) within the FoxO1 gene were shown to be strongly linked with emotional stress in predicting depressive symptoms, according to a meta-analysis focusing on the interaction between FoxO1 SNPs and emotional stress. This shows that some FoxO1 gene variations may make a person more susceptible to the negative consequences of stress, which may raise the risk of suicide.[29]

As discussed above, FoxO1 and suicide are closely related to neuroinflammation, MAO-A, and Sirt1; however, studies on the relationship between FoxO1 and suicide are scarce. Herein, we investigated the association between FoxO1 and suicide risk. Our initial hypothesis was as follows. First, that the exon SNPs of FoxO1 could be associated with a high-risk group for suicide, and second, that FoxO polymorphisms are associated with reduced cortical thickness (CTh) and compromised white matter integrity in patients at a high risk of suicide. This study aimed to explore the biological basis of suicide by examining the relationship between two SNPs (rs3751436 and rs34733279) of FoxO1 and the risk of suicide.

METHODS

Participants

Between June 2018 and August 2021, 231 patients diagnosed with MDD and 127 healthy controls (HC) were included in this study. Board-certified psychiatrists diagnosed MDD (Ham BJ, Han KM) at Korea University Anam Hospital in Seoul, Republic of Korea, following the guidelines of the Structured Clinical Interview and based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders. Patients with MDD exhibited an average score of 13.146 with a standard deviation (SD) of 9.043 on the Beck Scale for Suicide Ideation (BSS). Patients with depression with a score ≥14 (n=119) were classified into the high suicide risk (HSR) group.

The exclusion criteria were the presence of any additional major psychiatric disorders, psychotic symptoms such as delusions or hallucinations, a history of severe or uncontrolled medical conditions, any underlying neurological disorders, or any factors that would prevent brain scanning for physiological (e.g., metal implants) or psychological reasons (e.g., claustrophobia). In addition, subjects with a Hamilton Depression Rating Scale (HDRS) score of ≥8 points in the normal group were judged to have mild but existing depressive symptoms and were excluded; in the case of a HDRS score ≤7 in the depressed patient group, the depressive symptoms were judged to be in remission, and patients were excluded.[30]

All the participants provided voluntary consent and signed written informed consent forms acknowledging their right to withdraw from the study at any point. The study procedures followed the ethical guidelines outlined in the Declaration of Helsinki and were approved by the Institutional Review Board of Korea University Anam Hospital (IRB Nos. 2017AN0185, 2019AN0174, 2020AN0335, and 2022AN0540).

Clinical assessments

The HDRS was used to assess depressive symptoms in the patient and control groups.[31] The HDRS has been broadly used in empirical research with psychiatric patients and is a well-accepted translated version with discriminant validity and reliable consistency.[32] The HDRS scale consists of 17 items rated on three- or five-point scales. In this study, the sum of the answers to all 17 questions was categorized as follows: 0−7: no depressive symptoms, 8−16: mild depression, 17−23:mod-

erate depression, ≥24: severe depressive symptoms.[30]

All patients with depression were assessed for the risk of suicidal ideation (SI) using the BSS. BSS is a self-report scale developed by Beck et al.[33,34] and is composed of a 19-item scale preceded by five screening items based on the "scale for suicide ideation". The BSS has satisfactory internal consistency, test-retest reliability, and various positive psychometric properties, including discriminant and convergent validity. The Korean version of the BSS has been also validated.[35,36] Out of more than 60 suicidal behavior assessment tools, only a limited number have shown predictive capability for suicide attempts (SAs); among these, the BSS has been suggested as a dependable tool.[37] There are no established cutoff scores for categorizing severity or guiding patient treatment. Higher scores indicate an increased risk of suicide, and any affirmative response should be thoroughly investigated. Therefore, in this study, based on the mean BSS score of 13.146 in patients with depression, we defined individuals with a score of 14 or higher as the HSR group. Based on previous studies, the cutoff score for the BSS was suggested to be approximately 2−8 points. Therefore, the cutoff score employed in this study was relatively high, indicating that it defined a group with a significant risk of suicide.[38,39]

MRI

MRI data acquisition

MRI scans were obtained at the Korea University Magnetic Resonance Imaging Center using a 3.0-Tesla Siemens Trio whole-body imaging system (Siemens Medical Systems, Iselin, NJ, USA). For T1-weighted magnetization-prepared rapid gradient-echo scans, the following parameters were used: repetition time (TR), 1,900 ms; echo time (TE), 2.6 ms; field of view (FOV), 220 mm; matrix size, 256×256; acquisition of 176 coronal slices without gaps; voxel size, 1×1×1 mm^3; flip angle, 16°; and single excitation. Diffusion tensor images were acquired using an echo-planar imaging sequence with parameters including a TR of 6,300 ms, TE of 84 ms, FOV of 230 mm, matrix size of 128×128, 3 mm slice thickness without gaps, voxel size of 1.8×1.8×3.0 mm^3, 20 diffusion directions, 50 slices, b-values of 0 and 600 s/mm^2, an acceleration factor (iPAT-GRAPPA) of 2 with 38 reference lines for phase encoding direction, and 6/8-phase partial Fourier.

CTh extraction

CTh analyses were conducted on a three-dimensional model of cortical surface reconstructions, which were generated from T1 images using FreeSurfer software (version 6.0) (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA; http://surfer.nmr.mgh.harvard.edu).[40] The processing stream utilized for the implantation procedure includes correcting motion in the volumetric T1-weighted images, eliminating non-brain tissue using a hybrid watershed/surface deformation method, performing Talairach transformation to align each partcipant's brain, segmenting volumetric structures of gray matter and white matter, inflating the cortical surface to a standardized spherical surface to locate the pial surface and the boundary between the gray and the white matter, normalizing intensity, and implementing automated topology correction.[41,42] The transition between gray and white matter and the pial boundary was identified by detecting the most significant intensity shift using surface deformation. The cortical reconstructions of each patient were visually inspected for errors and manually corrected if significant topological inaccuracies were observed. CTh was measured as the shortest distance between the gray/white matter boundary and the pial surface at each vertex across the cortex.[43] Gaussian smoothing was applied to the cortical maps with a 20 mm full width at half-maximum kernel. FreeSurfer also automatically parcellates the cortex based on the Destrieux atlas, and 76 gyri were analyzed in this study.[44]

Tract-based spatial statistics extraction

Voxel-based statistical analysis of the fractional anisotropy (FA) data was performed using tract-based spatial statistics (TBSS), which is a component of the FMRIB Software Library.[45,46] The FA images were generated by fitting a tensor model to the raw diffusion data using frequency-doubling technology. These images were then extracted using a brain extraction tool.[47] To align the FA data from all the participants, a nonlinear registration tool called FNIRT (https://ftp.nmr.mgh.harvard.edu/pub/dist/freesurfer/tutorial_packages/centos6/fsl_507/doc/wiki/FNIRT(2f)UserGuide.html) was used, which employs a B-spline representation of the registration warp field.[48] A mean FA image was subsequently created and thinned to generate a mean FA skeleton representing the common centers of all tracts within the group. Each participant's FA data aligned to this skeleton were projected onto it, and the resulting data were subjected to voxel-wise cross-subject statistics.[49]

Candidate SNP selection and genotyping

Genomic DNA was extracted from the participants' peripheral blood using an Agilent SureSelect Human All Exome V5 kit (Agilent Technologies, Santa Clara, CA, USA). SNPs sequencing of FoxO1 genes was performed using HiSeq2000, HiSeq2500, and HiSeq4000 (Illumina, San Diego, CA, USA) for paired-end 101 bp reads. The read quality was assessed using FastQC (https://www.bioinformatics.babraham.ac.uk/

projects/fastqc/). Trimmomatic[50] was used to remove low-quality bases and adapter sequences. The Burrows-Wheeler Aligner-Maximal Exact Match (BWA-MEM, v0.7.17-r1188)[51] was used to align the reads to the human reference genome (hg38), and the Genome Analysis Toolkit (GATK, v4.2.0.0)[52] was used to remove duplicates and perform base quality score recalibration. Aligned reads with mapping quality less than 20 were discarded using Samtools (v1.10).[53]

Germline variant calling was performed using the GATK HaplotypeCaller[52] for joint genotyping. Germline variants were annotated for gene name, SNP, mutation region (exonic), and exonic function (non-synonymous single nucleotide variant) using ANNOVAR.[54] Among the exon SNPs of FoxO1gene extracted in this way, two SNPs, rs3751436 and rs34733279, were selected for analysis according to the P allele frequency.

Statistical analysis

A chi-test was performed for categorical variables (sex, education level), and a t-test was applied for continuous variables (age). For the analysis of MRI data and SNPs, a two-way analysis of covariance (ANCOVA) model was employed to examine the impact of genotype and/or interactions between groups and genotypes on CTh and white matter integrity. CTh and FA were the variables of interest, with group and genotype as independent variables. Age, sex, educational level, and demeaned total intracranial cavity volume (eTIV) were incorporated as covariates.[55] Separate ANCOVAs were conducted for each genotype and brain structural parameter. To account for multiple comparisons, Bonferroni corrections were employed for the analysis of genotype or diagnosis-by-genotype interaction effects on cortical volume ($p<0.05$ divided by 76 cortical regions multiplied by two genetic polymorphisms, resulting in a significance threshold of 0.00033) and FA ($p<0.05$ divided by 42 white matter tracts multiplied by two genetic polymorphisms, resulting in a significance threshold of 0.00060).[56] When significant group-by-genotype interaction effects were observed, post hoc analyses were conducted within each group to examine the impact of the genotype on CTh and FA. These post hoc analyses utilized one-way ANCOVAs with the same covariates as those employed in the main analysis. All statistical analyses were conducted using IBM SPSS Statistics for Windows (version 24.0; IBM Corp., Armonk, NY, USA).

RESULTS

Participants' characteristics

HC and HSR did not show statistically significant differences in terms of sex, age, educational level, and eTIV. However, the HSR group exhibited significantly higher depression scores. In addition, the allele frequencies of rs3751436 and rs34733279 were not significantly different in either group (Table 1).

Effects of HSR and genotype on CTh and white matter tract

In the control group, the mean thickness of the left triangular parts of the inferior frontal gyrus (IFG) was 2.691 mm with a standard deviation of 0.154 mm, while in the HSR group, the mean thickness was 2.633 mm with a standard deviation of 0.156 mm. For the right transverse frontopolar gyrus, the mean thickness in the control group was 2.700 mm with a standard deviation of 0.167 mm, compared to the HSR group, where the mean thickness was 2.638 mm with a standard deviation of 0.156 mm. Even after applying the Bonferroni correction, a significant thinning in CTh was still observed in the two gyrus regions (specifically, the left triangular parts of the IFG [p=5.17.E-04] and the right transverse frontopolar gyrus [p=3.09.E-04]) in the HSR group compared to the HC group (Table 2).

Effect of group-by-genotype interactions on CTh and white matter tracts

No significant differences in CTh were observed among the genotypes. However, the interaction between the group and genotype showed a statistically significant difference in the left posterior-ventral part of the cingulate gyrus (LPVC), whereby a significant interaction effect was detected between the group and FoxO1 rs34733279 (Table 2 and Supplementary Table 1).

Neither SNPs showed statistically significant tracts in the FA analysis of TBSS. However, a statistically significant interaction between the group and FoxO1 rs34733279 was observed in the left cingulate tract (LCG) (Table 3 and Supplementary Table 2).

Secondary analysis of group and genotype interactions

When the CTh of the LPVC was divided based on the rs34733279 major allele and T allele carrier status, a post hoc analysis revealed that in the HC group, individuals with the T allele carrier had significantly thicker CTh in the LPVC (mean of TT+CT: 2.697, SD 0.188) compared to those with the CC genotype (mean: 2.559, SD 0.289) with a p of 0.006. However, in the HSR group, individuals with the T allele carrier showed a thinner CTh (mean: 2.404, SD 0.395) compared to those with the CC allele (mean: 2.614, SD 0.232) with a p of 0.015 (Figure 1). In individuals with the T allele, a higher suicide risk was associated with a more pronounced reduction in CTh than in those with the CC allele (Figure 2).

Furthermore, FA values of the LCG tract did not show sta-

Table 1. Demographics and clinical characteristics between HC and HSR

	HC (N=127)	HSR (N=119)	p
Age (yr)	37.024±14.015	35.050±13.186	0.26
Sex			0.90
Male	47 (37.0)	45 (37.8)	
Female	80 (63.0)	74 (62.2)	
Education			0.13
Under 9 years	4 (3.1)	7 (5.9)	
10 to 16 years	107 (84.3)	105 (88.2)	
Above 17 years	16 (12.6)	7 (5.9)	
eTIV	1465.288±154.320	1453.279±164.101	0.56
HDRS	0.984±1.746	16.916±5.985	<0.001***
FoxO1 rs3751436			0.33
CC	11 (8.7)	16 (13.4)	
CT	56 (44.1)	56 (47.1)	
TT	60 (47.2)	47 (39.5)	
HWE	0.684	0.916	
FoxO1 rs3751436			0.22
CC+CT	67 (52.8)	72 (60.5)	
TT	60 (47.2)	47 (39.5)	
FoxO1 rs34733279			0.85
TT	2 (1.6)	2 (1.7)	
TC	22 (17.3)	24 (20.2)	
CC	103 (81.1)	93 (78.2)	
HWE	0.518	0.755	
FoxO1 rs34733279			0.57
TT+TC	24 (18.9)	26 (21.8)	
CC	103 (81.1)	93 (78.2)	

Data are presented as mean±standard deviation or number (%). FoxO1 rs3751436 allele frequencies (T/C): HC 0.693/0.307, HSR 0.630/0.370. FoxO1 rs34733279 allele frequencies (C/T): HC 0.898/0.102, HSR 0.882/0.118. ***p<0.001. HC, healthy control; HSR, high suicide risk; eTIV, intracranial cavity volume; HDRS, Hamilton Depression Rating Scale, HWE, Hardy-Weinberg Equilibrium

tistically significant differences based on the rs34733279 allele in the total participants. However, there was a statistically significant difference between the rs34733279 allele groups within the HC group (p=0.042), and this association was reversed in the HSR group (p=0.023) (Figure 3). In the presence of HSR, individuals carrying the minor allele exhibited a significant reduction in the FA values of the LCG, which is distinct from the observations in the HC (Figure 4).

HC and low suicide risk group analysis

The low suicide risk (LSR) group exhibited a significantly higher mean age of 43.679 (SD 13.532) years compared to the HC group, which had a mean age of 37.024 (SD 14.015) years (p<0.001). Additionally, compared to the HC group, the LSR group exhibited a significantly lower educational attainment (p<0.001), as well as a significantly higher mean HDRS score of 14.107 (SD 6.971) (Supplementary Table 3).

Despite considering statistically significant demographic variables such as age and educational level and accounting for covariates such as sex and eTIV, CTh analysis did not reveal any statistically significant differences in regions between the groups or based on the FoxO1 gene. Additionally, the group and FoxO1 interaction showed no statistically significant differences in CTh (Supplementary Table 4). Similarly, TBSS analysis showed no statistically significant differences between groups. However, a statistically significant difference in the interaction between FoxO1 rs34733279 and group within the left sagittal stratum (F 12.977, p 3.86×10^{-4}) was depicted (Supplementary Table 5).

Table 2. Cortical thickness between HC and HSR

	Group (HC vs. HSR)†			FoxO1_ rs3751436†		FoxO1_ rs34733279†		Group by FoxO1_ rs3751436‡		Group by FoxO1_ rs34733279‡	
	F	p		F	p	F	p	F	p	F	p
L. posterior-ventral part of the cingulate gyrus*	0.981	0.323		0.647	0.42	<0.001	0.99	1.185	0.28	16.871	5.50.E-05*
L. triangular part of the inferior frontal gyrus*	12.387	5.17.E-04	HSR<HC*	0.496	0.48	2.136	0.15	3.128	0.08	5.014	0.03
R. transverse frontopolar gyrus*	13.406	3.09.E-04	HSR<HC*	1.366	0.24	1.591	0.21	0.426	0.52	0.459	0.50

A two-way analysis of covariance was performed with adjustment for age, sex, educational level, and total intracranial cavity volume as covariates. *regions that remained significant after the Bonferroni correction are marked with asterisks; †Bonferroni correction was applied to the effect of diagnosis: p<0.05/(76 cortical regions)=0.00066; ‡Bonferroni correction was applied to the effect of the diagnosis-genotype interaction: p<0.05/(76 cortical regions×2 genetic polymorphisms)=0.00033. HC, healthy control; HSR, high suicide risk; L, left; R, right

Table 3. TBSS between HC and HSR

	Group (HC vs. HSR)†			FoxO1_ rs3751436†		FoxO1_ rs34733279†		Group by FoxO1_ rs3751436‡		Group by FoxO1_ rs34733279‡	
	F	p		F	p	F	p	F	p	F	p
L. cingulum (cingulate gyrus)	0.263	0.61		0.682	0.41	0.022	0.881	8.292	0.004	12.396	5.16.E-04*
R. cingulum (cingulate gyrus)	0.210	0.65		1.411	0.24	0.939	0.334	3.468	0.06	12.004	0.001
L. posterior thalamic radiation	12.581	4.69.E-04	HSR<HC*	0.013	0.91	0.428	0.513	2.916	0.09	5.015	0.03
R. posterior thalamic radiation	8.137	0.01		0.002	0.97	0.015	0.901	0.611	0.44	0.197	0.66
L. sagittal stratum	11.357	8.77.E-04	HSR<HC*	0.215	0.64	0.285	0.594	3.636	0.06	8.850	0.003
R. sagittal stratum	3.079	0.08		0.118	0.73	0.561	0.455	1.283	0.26	3.993	0.05
L. uncinate fasciculus	11.346	8.82.E-04	HSR<HC*	0.272	0.60	0.610	0.435	0.274	0.60	0.704	0.40
R. uncinate fasciculus	5.694	0.02		0.010	0.92	0.590	0.44	0.342	0.56	0.395	0.53

A two-way analysis of covariance was performed with adjustment for age, sex, educational level, and total intracranial cavity volume as covariates. *regions that remained significant after Bonferroni correction are marked with asterisks; †Bonferroni correction was applied to the effect of diagnosis: p<0.05/(42 tracts)=0.00119; ‡Bonferroni correction was applied to the effect of the diagnosis-genotype interaction: p<0.05/(42 tracts×2 genetic polymorphisms)=0.00060. TBSS, tract-based spatial statistics; HC, healthy control; HSR, high suicide risk; L, left; R, right

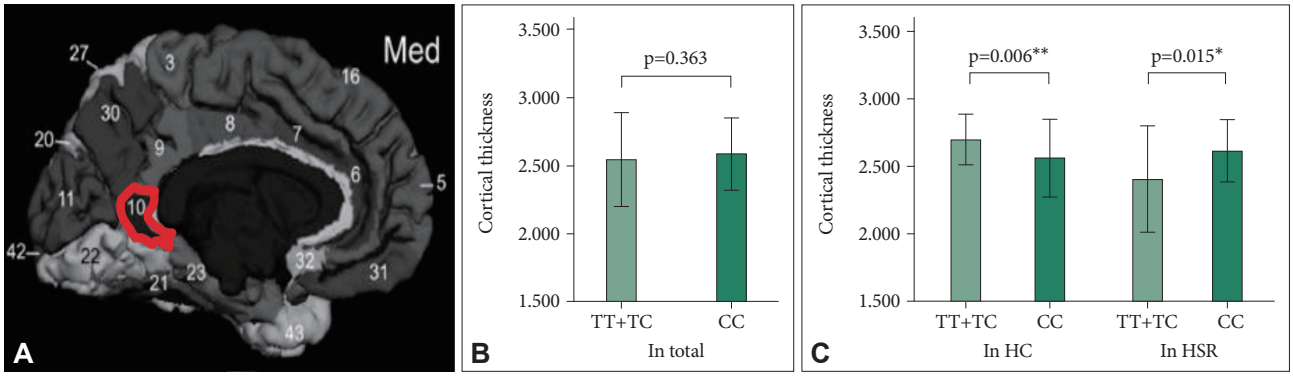

Figure 1. Cortical thickness of LPVC between HC and HSR. A: Anatomical location of the LPVC. B: Cortical thickness in total participants. C: Cortical thickness in HC and HSR group. *p<0.05; **p<0.01. LPVC, left posterior-ventral part of the cingulate gyrus; HC, healthy control; HSR, high suicide risk group, bars mean 1 standard deviation.

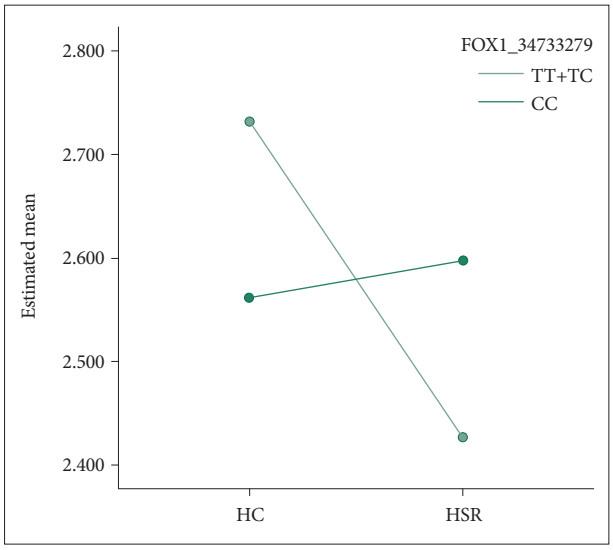

Figure 2. Estimated mean of cortical thickness of LPVC. LPVC, left posterior-ventral part of the cin-gulate gyrus; HC, healthy control; HSR, high-suicide risk group.

DISCUSSION

In this study, no significant differences in the frequency distribution of FoxO1's two SNPs, rs3751436 and rs34733279, between the HSR and HC groups were depicted. In the HSR group, a statistically significant thinning of CTh was observed in the left triangular parts of the IFG and the right transverse frontopolar gyrus, even after incorporating covariates and conducting Bonferroni correction. In the HSR group, the FA value was significantly lower in the left posterior thalamic radiation, left sagittal stratum, and left uncinate fasciculus than in the HC. Furthermore, in the HSR group, individuals carrying the minor allele (T allele) of the FoxO1 exon SNP rs34733279 exhibited a more pronounced reduction in CTh, specifically in the left posterior-ventral cingulate gyrus compared to individuals carrying the CC allele. Moreover, in those carrying the T allele, a higher suicide risk was associated with a greater reduction in left cingulate FA values.

Notably, CTh thinning in the triangular parts of the IFG, which is recognized as a component of the left ventrolateral prefrontal cortex (VLPFC) observed in the HSR group aligns with previous findings.[57-59] Furthermore, in the HSR group, a significant CTh reduction was observed in the right transverse frontopolar gyrus, a part of the right medial orbito-frontal cortex (rOFC). These findings are consistent with existing meta-analyses showing cortical thinning in individuals with depression.[60] While there have been no direct associations between cortical thinning in the rOFC and suicide risk in the literature, it has been established that a reduced OFC volume including both the right and left regions, is evident in individuals at risk of suicide.[61] Previous Positron Emission Tomography studies on SAs with high lethality or intent have revealed changes in serotonin (5-HT) production, transporters, and 5-HT1a receptors within the VLPFC and Ventromedial Prefrontal Cortex.[62] Furthermore, individuals with MDD and a history of SAs exhibited a reduction in 5-HT1a binding in the OFC, associated with an increased risk of SI during a 2-year follow-up period.[62] This indicates a strong correlation between the risk of suicide and the biological mechanisms underlying VLPCF and OFC.

In addition to the biological evidence, MRI studies have consistently demonstrated an association between VLPFC and OFC with suicide. The VLPFC, in conjunction with the dorsal-anterior insula, is associated with the "suppression" function of emotion regulation, directing the inhibition of emotional responses.[63] The rOFC is involved in response inhibition in healthy individuals, the cingulate cortex, and the inferior parietal lobule.[64] Adults with MDD with a history of SAs showed heightened activation in the IFG and the lateral and medial regions of the OFC, specifically in response to angry faces.[65] This evidence, including the findings of this study, suggests that emotion dysregulation plays a crucial role in the development of suicidal thoughts and behaviors. Emotional

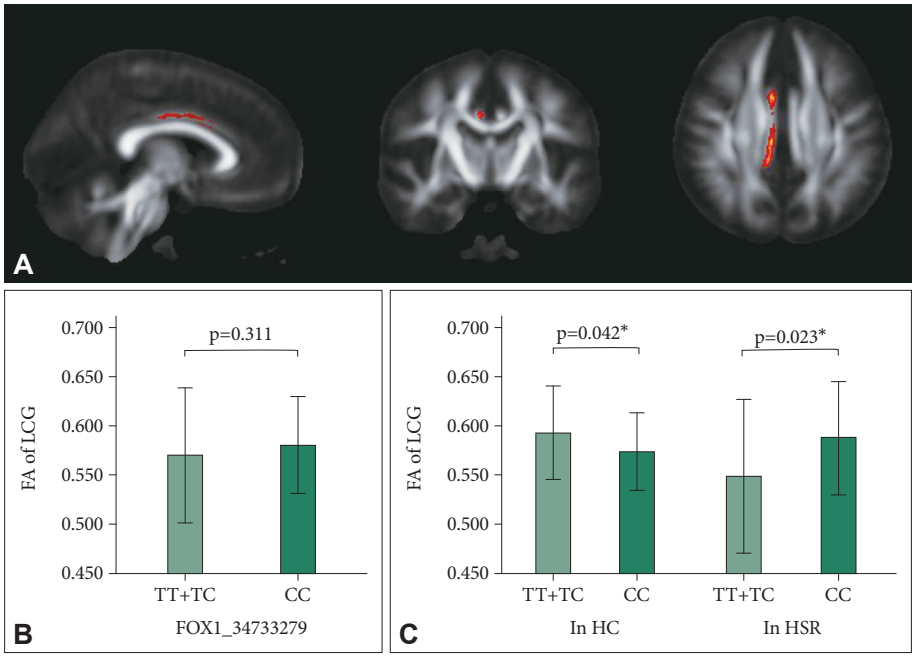

Figure 3. FA of LCG. A: Anatomical location of the tract of LCG. B: FA of LCG in total participants. C: FA of LCG in HC and HSR group. *p<0.05. LCG, left cingulate tract; HC, healthy con-trol; HSR, high suicide risk group; bars mean 1 standard deviation.

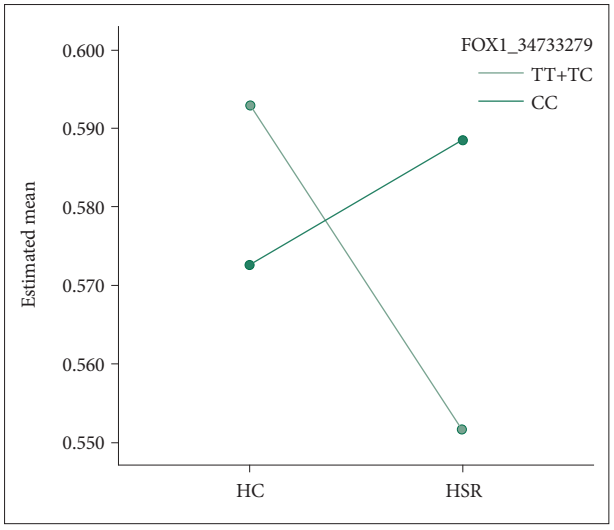

Figure 4. Estimated mean of FA of LCG. LCG of the right cingulum (cingulate gyrus). LCG, left cingulate tract; HC, healthy control, HSR, high suicide risk group.

dysregulation includes heightened negative emotions, diminished positive emotions, altered self-referential thoughts, and modified responses to emotional stimuli.[66]

Moreover, in the HSR group, there was a significant decrease in FA values within the left posterior thalamic radiation, left sagittal stratum, and left uncinate fasciculus, which is controversial compared to previous research findings in HCs. Among individuals with psychosis and panic disorder, those who have attempted suicide have been observed to exhibit higher FA values than non-suicidal individuals.[67,68] Furthermore, in cases of military personnel with comorbid traumatic brain injury and suicidal behavior, an increase in thalamic enlargement and FA values of related tracts has been reported.[69] In contrast to these findings, in patients with MDD with a history of SAs, a decrease in FA values has also been observed in the thalamic region.[70] Additionally, in cases where SAs were made by individuals with bipolar disorder, FA values within the hippocampal cingulum were reduced. In contrast, no differences were noted in the uncinate fasciculus compared to non-suicidal individuals.[71] Previous studies have consistently demonstrated a notable reduction in FA within the posterior thalamic radiation and sagittal stratum.[72,73] Furthermore, the left uncinate fasciculus has been studied primarily in memory processing, and its association with impaired emotional recognition has been elucidated.[74] Collectively, changes in FA values based on the risk of suicide across various conditions remain controversial. Nevertheless, when examining the function of the left posterior thalamic radiation, sagittal stratum, and uncinate fasciculus in this study, the decrease in FA values among individuals at risk of suicide could be a significant biomarker.

In our study, we observed thinning of the CTh of LPVC and a decrease in FA values within the left cingulum bundle in individuals at high risk for suicide who carried the minor allele of the FoxO1 SNPs (rs34733279 T allele). Cortical thinning in the posterior cingulate gyrus is known to be associated not only with suicide risk[75] but also with bipolar depression and

the progression of Alzheimer's and Parkinson's diseases.[76-78] Furthermore, the posterior cingulate gyrus is thinner in healthy individuals with a family history of MDD than in those without a family history, suggesting a close relationship between early pathological changes in neuropsychiatric symptoms and cognitive function.[79] In addition to structural changes, functional changes in the posterior cingulate gyrus have also been observed in suicide risk schizophrenia patients.[80] The left posterior cingulate gyrus shows higher activity during negative imagery generation than during positive imagery, and this activation is negatively correlated with the vividness of negative imagery, suggesting a potential role for the posterior cingulate gyrus in reducing the intensity of negative imagery.[81] In addition, when there is SI in adolescents, the activity of the posterior cingulate gyrus may be reduced; in adult SAs, the posterior cingulate (PCC) reaction to the sight of a knife is increased, and the PCC is closely related to suicide.[82,83] Thus, structural and functional changes in the left posterior cingulum are associated with suicide. The results of this study suggest that this association may be amplified when a minor allele of FoxO1 is present.

There have also been reported about the association of the cingula and depression.[84-86] Previous studies consistently point to cingulum to be involved in executive functioning and interrelated neuropsychological risk factor for suicidal behavior.[87,88] Decreased FA values and CTh in the cingulum of individuals with suicidal tendencies has been frequently reported.[75,89] Although it has not yet been extensively studied, the alterations in the CTh and white matter tract, notably in the cingulum, reflects the pathological changes in neuropsychiatric symptoms and cognitive function. Consequently, it is highly likely that its association with FoxO1 gene in the cortical and white matter alterations in the cingulum may be further implying the relationship between the brain, FoxO1, and suicidal behavior. A correlation has also been reported between decreased FA in the genu of the corpus callosum and the internal capsule in patients with a history of SA.[90,91] Furthermore, given the well-established evidence of a significant reduction in FA values within the left cingulum among individuals with depression who are at risk of suicide, the findings from our study suggest that carriers of the minor allele of the FoxO1 rs4733279 SNP may elicit a more severe pathological response to suicide than individuals with the major allele.[92]

This study elucidates the potential association between FoxO1 gene exon SNP and suicide risk. Ultimately, the minor allele of FoxO1 rs34733279 worsened LCG abnormalities and cortical thinning in the left cingulum. Collectively, these findings suggest that minor alleles of FoxO1 exon SNPs may play a significant biological role in suicide risk in the left cingulum. Moreover, additional analyses showed that the association between FoxO1 and suicide risk was not evident in HCs and LSR groups, confirming that these characteristics are unique to the HSR group. Numerous studies have reported that FoxO1 is closely associated with regulating apoptosis, differentiation, oxidative stress, homeostasis, and inflammatory responses.[93,94] In particular, depressive symptoms are associated with the cAMP/PKA and cAMP/ERK signaling pathways, affecting the function of FoxO through phosphorylation by PKA and ERK. Interactions between serotonergic and adrenergic receptors influence cellular cAMP levels and the FoxO's physiological role.[95-98] The findings of this study indicate that individuals carrying the minor alleles of FoxO1 SNPs (rs34733279) in the HSR group may elicit a more severe disruption in the white matter tract and CTh of the left cingulum. This suggests that beyond its association with depressive symptoms, the FoxO1 gene also influences mechanisms that elevate the risk of suicide. Additionally, based on the cellular apoptosis and inflammatory response mechanisms of FoxO1, it can be inferred that it may impact suicide, implying that suicide is a phenomenon with underlying biological mechanisms. However, there has been no evidence linking FoxO1 SNPs to human psychiatric disorders. Because previous studies have mostly focused on intron SNPs, future investigations are warranted to explore the psychiatric mechanisms related to exon SNPs, which would provide valuable insights into this area.

Limitations

This study has several limitations, one is that it utilized a targeted approach, analyzing only two specific SNPs of FoxO1, rather than conducting a more comprehensive analysis, such as whole-exome sequencing. This limited approach may not capture the full spectrum of genetic variations within a gene, potentially overlooking other relevant single SNPs or genetic factors that may contribute to suicide risk.

Second, the potential impact of medication on the observed results was not considered, which could have confounded the findings and limited the ability to draw definitive conclusions about the relationship between FoxO1 and suicide risk. Antidepressants can increase the prefrontal cortex's volume and increase CTh.[99,100] which warrants further investigation to better understand the complexities of changes in CTh in the context of suicide risk.

Third, the HSR group was extracted from the population of patients with depression and compared with an HC group. To provide a more comprehensive analysis, it would have been beneficial to conduct statistical comparisons among all three groups: HCs, the LSR group, and the high suicidal risk group. When conducting MRI studies that compare multiple brain regions or genetic factors, applying Bonferroni correction for controlling type 1 error could be overly stringent, es-

pecially when dealing with multiple groups. This correction may lead to an increased risk of false negatives and, as a result, significant findings can be disregarded. In such cases, researchers should consider alternative approaches to balance the trade-off between controlling for type 1 errors and detecting meaningful results. Therefore, instead of directly comparing all three groups simultaneously, this study employed a stepwise approach to compare the HC group with the HSR group. Subsequently, the significant findings were further validated by comparing the HC group with the LSR group, confirming the results' robustness and credibility.

Fourth, owing to the absence of differences in the frequency distribution of the two SNPs, a direct association between these FoxO1 SNPs and the risk of suicide could not be established. However, it is possible that the current sample size may not have provided sufficient statistical power to assess the impact of these SNPs on the risk of suicide risk. Therefore, further research involving a larger sample of subjects will be necessary to investigate the association between FoxO1 SNPs and the risk of suicide.

Lastly, due to the nature of a cross-sectional study, we were unable to fully encompass environmental factors in determining the relationship between FoxO1 gene and suicide risk in individuals with MDD. We highly suggest longitudinal studies to be designed in the future to fully understand the developmental changes in the genetic and suicidal risk in patients with MDD.

Despite these limitations, the present study successfully demonstrated that rs32733279 in the FoxO1 gene are associated with the left cingulum in individuals at HSR. Moreover, this study established a strong association between FoxO1 and suicide risk in the left cingulum. Further studies are required to explore the biological mechanisms underlying these correlations. Investigating the specific pathways through which the FoxO1 gene and the left cingulum are associated with suicide risk could provide valuable insights into the neurobiological underpinnings of this association. Conducting more in-depth studies, such as functional connectivity analyses, gene expression profiling, or neuroimaging techniques, could shed light on the intricate interplay between FoxO1, the left cingulum, and suicide risk, ultimately contributing to a deeper understanding of the biological factors that influence suicide vulnerability in individuals with depression.

Conclusion

While there were no differences in the distribution of FoxO1 SNPs between the groups at a higher risk of suicide and the HC group, individuals at a higher risk exhibited a reduction in CTh in the VLPFC and OFC. Additionally, decreased FA values were observed in the left posterior thalamic radiation, sagittal stratum, and uncinate fasciculus. Among the two exon SNPs of the FoxO1 gene, rs3751436 and rs34733279, it has been observed that in the high-risk group for suicide, both cortical thinning and decreased FA in the left cingulum are further exacerbated in the presence of the minor allele of the FoxO1 gene's rs34733279. Therefore, the FoxO1 gene, rs34733279 exhibits close associations with suicide risk, reaffirming that suicide is a phenomenon with underlying biological mechanisms.

Supplementary Materials

The Supplement is available with this article at https://doi.org/10.30773/pi.2024.0044.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Kyu-Man Han, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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