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ORIGINAL ARTICLE

Association of two variable number of tandem repeats in the monoamine oxidase A gene promoter with suicide completion: The present study and meta-analysis

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Abstract

Background: One potential cause of suicide is serotonergic dysfunction. Sex differences have been reported to modulate the effects of serotonergic polymorphisms. Monoamine oxidase A (MAOA) is an enzyme that degrades serotonin and is located on the X chromosome. A previous study indicated that the upstream (u) variable number of tandem repeat (VNTR) in the *MAOA* gene promoter may be associated with suicide. However, a meta-analysis showed that this polymorphism may not be related to suicide. According to a recent study, compared with the uVNTR, the distal (d)VNTR and the haplotypes of the two VNTRs modulate MAOA expression.

Methods: We examined the two VNTRs in the *MAOA* gene promoter in 1007 subjects who committed suicide and 844 healthy controls. We analyzed the two VNTRs using fluorescence-based polymerase chain reaction assays. We conducted a meta-analysis for the two VNTRs to update it.

Results: Our results demonstrated that neither the genotype-based associations nor allele/haplotype frequencies of the two VNTRs were significantly associated with suicide. In the meta-analysis, we did not indicate relationships between uVNTR and suicide nor did we identify articles analyzing dVNTR in suicide.

Conclusion: Overall, we did not find a relationship between the two VNTRs in the *MAOA* promoter and suicide completion; thus, warranting further studies are required.

KEYWORDS
genetics: human, monoamine oxidase A, suicide: basic/clinical, variable number of tandem repeats

Masashi Hasegawa and Takaki Tanifuji equally contributed to the work.

1 | INTRODUCTION

The World Health Organization (WHO) reported that suicide is a major public health issue and one of the leading causes of death worldwide, with approximately 800 000 deaths reported annually.[1] Well-known risk factors include psychiatric disorders, drug and alcohol misuse, and family history of suicidal behavior.[2] Other important risk factors for suicide include personality traits, such as impulsivity, and social factors, such as childhood maltreatment and negative life events.[3,4] To address this public health crisis effectively, it is necessary to elucidate the biological basis of suicide in order to develop and use medical technologies for its prevention.

Twin and adoption studies have found that suicidal behavior is related to genetic factors.[5] Additionally, population-based epidemiological studies have indicated that suicidal behavior, including suicidal thoughts, plans, and attempts, has an estimated heritability of 30%–55%.[6] Genome-wide association studies (GWAS) have demonstrated small but significant SNP heritability estimates for suicide attempts, indicating a polygenic structure of the traits related to suicide.[7–9]

Neurobiological evidence suggests that serotonergic dysfunction is involved in suicidality because patients who attempted suicide have low levels of the main serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in cerebrospinal fluid (CSF), which predicts an approximately five-fold increase in the odds ratio of suicide.[10] Serotonin is degraded by monoamine oxidase A (MAOA), a mitochondrial outer membrane enzyme.[11] In a systematic review of the relationship between serotonergic genes and suicide, the *MAOA* gene was found to increase the risk of suicidal behavior.[12]

The *MAOA* promoter contains an upstream (u) variable number of tandem repeat (VNTR) domain and a distal (d)VNTR domain.[13,14] The uVNTR polymorphism in *MAOA* may affect suicidal behavior, but contrasting results have also been reported.[15–17] According to a meta-analysis of the relationships between uVNTR polymorphism in *MAOA* and suicidal behavior, suicidal behavior was not significantly attributable to the uVNTR.[11] Although the uVNTR is a well-studied polymorphism,[11,15–17] it is necessary to investigate both uVNTR and dVNTR because dVNTR and the haplotypes of the two VNTRs are more linked to MAOA expression.[18] Specifically, the dVNTR increased and two VNTR haplotypes decreased the expression of the MAOA isoform.[18] We previously reported that the dVNTR and uVNTR are significantly associated with schizophrenia in females.[19]

Genome-wide association studies have not included the two VNTRs[7–9]; VNTR polymorphisms can lead to sex differences because the *MAOA* gene is located on the X chromosome.[20] In recent years, increased attention has been paid to sex differences in the pathophysiology and treatment of various psychiatric conditions.[21–27] The ratio of male-to-female suicides is markedly different among all age groups worldwide,[28] and sex differences have also been observed in major depressive disorders and serotonin levels, which are known risk factors for suicide.[2,10,21,24,26,29,30] Moreover, a recent study identified sex-specific gene expression in suicide completers.[31] We hypothesized that suicide would be significantly associated with haplotype and allele polymorphisms reported to degrade serotonin actively. In the present study, we investigated the association between the two VNTRs of the *MAOA* promoter and suicide, with a focus on sex differences.[32]

2 | METHODS

2.1 | Participants

This study population included 1007 suicide completers (667 males: median age [IQR], 51.0 [37.5–65.0]; 340 females: 54.0 [40.0–68.0]) and 844 healthy controls (399 males: median age [IQR], 52.0 [35.0–67.0]; 445 females: 54.5 [38.0–67.0]) of Japanese descent. The suicide methods used were neck hanging (642), jumping from a height (173), gas suffocation (50), drowning (21), jumping in front of a vehicle (18), self-inflicted penetrating wounds (17), self-burning (7), consuming poison (2), drug overdose (11), other methods (11), and unknown (63). The demographic data are summarized in Table 1.

A case was defined as a suicide based on the medicolegal examinations and police investigations as per Japanese law. Autopsies of the suicide victims were performed at the Department of Legal Medicine, Kobe University Graduate School of Medicine. To obtain background information on the suicide completers, we used the data collected by staff at the Medical Examiner's Office of Hyogo Prefecture and the Division of Legal Medicine at Kobe University. To screen control subjects for psychiatric disorders, at least two psychiatrists evaluated healthy volunteers using unstructured interviews; the inclusion criteria were as follows: those without a present, past, and family history (first-degree relatives) of psychiatric disorders or substance abuse diagnosis (excluding nicotine dependence). The above procedures were performed as described previously.[33]

2.2 | Genotyping of the two VNTRs

We obtained peripheral blood samples from all suicide completers and healthy controls and stored them at −80°C. DNA was extracted from these samples using a QIAamp DNA Blood Midi Kit (Qiagen, Valencia, CA, USA). The DNA quantity and purity were examined using NanoDrop (Thermo Fisher Scientific, Wilmington, DE, USA).

We used the genotyping methods and procedures described previously.[19] The uVNTR situated 1.2 kb upstream of the *MAOA* gene comprises 30-bp repeat unit and low-expression alleles (2 repeats [R], 3R, and 5R) and high-expression alleles (3.5R and 4R).[14,18] The dVNTR situated approximately 500-bp upstream of uVNTR comprises 10-bp repeat unit and the following polymorphisms: 9R and 10R indicate the highest- and lowest-expression alleles, respectively, whereas 8R and 11R indicate moderate expression alleles, and 12R is unknown.[13,18]

We performed fluorescence-based fragment assays for genotyping of the two VNTRs. The dVNTR PCR assay volume (20 μL) contained 10 ng of genomic DNA, 10 μL of AmpliTaq Gold Master Mix with

TABLE 1 Demographic and clinical characteristics of participants.

	CTL ($n=844$)	SCD ($n=1007$)	p-value
Sex (male/female)	399/445	667/340	<0.001[a]
Age/all (years), median (IQR)	53.0 (36.0, 67.0)	52.0 (38.8, 67.0)	0.854[b]
Age/male, median (IQR)	52.0 (35.0, 67.0)	51.0 (37.5, 65.0)	0.847[b]
Age/female, median (IQR)	54.5 (38.0, 67.0)	54.0 (40.0, 68.0)	0.430[b]
Suicide methods[c]			
Neck hanging		642	
Jumping from a height		173	
Gas suffocation		50	
Drowning		21	
Jumping in front of a vehicle		18	
Self-inflicted penetrating wounds		17	
Self-burning		7	
Consuming poison		2	
Drug overdose		11	
Other		11	
Unknown		63	

Note: We obtained information about age from the clinical records of 828 (98%) of the 844 healthy controls and 988 (98%) out 1007 of patients with suicide.

Abbreviations: CTL, healthy controls; IQR, interquartile range; SCD, suicide.

[a]p-value was analyzed using the χ^2 test.

[b]p-values were analyzed using the Mann–Whitney U test.

[c]Those having two or more suicide methods: jumping from a height and self-inflicted penetrating wounds, one person; neck hanging and self-inflicted penetrating wound, two persons; neck hanging, self-inflicted penetrating wound, and drug overdose, one person; self-inflicted penetrating wounds and self-burning, one person; gas suffocation and self-burning, one person; gas suffocation and drug overdose, one person.

10% GC enhancer (Applied Biosystems, Foster City, CA, USA), 0.1 μM 7deaza-dGTP (New England Bio Labs, Ipswich, MA, USA), and 25 pmol of each the primers: 5′-GGG TTA AGC GCC TCA GCT TC-3′ (forward primer labeled with 6-Fluorescence [FAM]) and 5′-CAA GAG TGG ACT TAA GGA AGC AG-3′ (reverse primer) (Invitrogen, Carlsbad, CA, USA). The thermal cycling reaction comprised 10 min of initial denaturing at 95°C, 10 cycles at 95°C for 20 s; touchdown annealing from 65°C to −56°C for 20 s, and 72°C for 30 s; followed 35 cycles at 95°C for 20 s, 55°C for 20 s, and 72°C for 30 s; and a final extension at 72°C for 7 min. The uVNTRs PCR assay volume (10 μL) comprised 1 ng of genomic DNA, 5 μL of AmpliTaq Gold Master Mix (Applied Biosystems), and 15 pmol each of the following primers: 5′-GAA CGG ACG CTC CAT TCG GA-3′ (forward primer labeled with 6-FAM) and 5′-ACA GCC TGA CCG TGG AGA AG-3′ (reverse primer) (Invitrogen). The thermal cycling reaction comprised 10 min of initial denaturing at 95°C, followed by 40 cycles of 95°C for 30 s, 55°C for 30 s, and 72°C for 30 s, and a final extension step at 72°C for 7 min. Both PCR products were analyzed using a SeqStudio Genetic Analyzer (Applied Biosystems) and the GeneMapper Software version 6 (Applied Biosystems). The dVNTR PCR product sizes were 339, 349, 359, 369, and 379 bp in length, corresponding to 8, 9, 10, 11, and 12R, respectively, in accordance with previous studies.[13,18] The uVNTR products were 286, 316, 346, and 376 bp in length, corresponding to 2, 3, 4, and 5R, respectively.[14,18]

2.3 | Statistical analysis

Data were analyzed using R version 4.2.2 (R Development Core Team, Vienna, Austria) and EZR software (version 1.61; Jichi Medical University, Saitama, Japan).[34] We analyzed frequencies of allele/haplotype and genetic associations in females using Haploview version 4.2 (Dlay Lab, Broad Institute, Cambridge, MA, USA).[35] We analyzed continuous and categorical variables between the two groups using the χ^2 test and Mann–Whitney U test. We analyzed genotype-based associations, and frequencies of allele/haplotype using the Cochran–Armitage trend test and χ^2 test, respectively. We assessed the Hardy–Weinberg equilibrium (HWE) in females using Fisher's exact test. We defined statistical significance as a two-tailed $p<0.05$ and performed permutation tests based on 10 000 replications for precision, as necessary.

2.4 | Meta-analysis of the suicide and two VNTRs

We searched candidate articles via a PubMed search through March 17, 2023, using the following search terms: ("suicide" OR "suicidal ideation" OR "suicide, completed" OR "suicidal" OR "suicidally") AND ("monoamine oxidase A" OR "MAOA"). This meta-analysis was

TABLE 2 Allelic and genotypic distribution of the polymorphisms in the *MAOA* promoter in healthy controls and suicide completers.

	CTL ($n=844$)				SCD ($n=1007$)							
	Genotype distribution[a]				Genotype distribution[a]							
Polymorphism	x/x	x/−	−/−	Allele freq	x/x	x/−	−/−	Allele freq	Genotype *p*-value[b]	Allele *p*-value[c]	Odds ratio (95% CI)	Power
Male (CTL, $n=399$; SCD, $n=667$)												
$dVNTR_{8R-12R}$												
8R		1	398	0.003		1	666	0.001		0.713	0.598 (0.037–9.581)	0.144
9R		166	233	0.416		293	374	0.439		0.458	1.100 (0.856–1.413)	0.110
10R		226	173	0.566		368	299	0.552		0.640	0.942 (0.734–1.210)	0.065
11R		4	395	0.010		4	663	0.006		0.461	0.596 (0.148–2.396)	0.124
12R		2	397	0.005		1	666	0.001		0.295	0.298 (0.269–3.298)	0.120
$uVNTR_{2R-4R}$												
2R		3	396	0.008		8	659	0.012		0.484	1.602 (0.423–6.075)	0.080
3R		236	163	0.591		387	280	0.580		0.718	0.955 (0.742–1.228)	0.054
4R		160	239	0.401		270	397	0.405		0.903	1.016 (0.789–1.417)	0.034
5R		0	399	0.000		2	665	0.003		0.274	N/A	0.132
Female (CTL, $n=445$; SCD, $n=340$)												
$dVNTR_{8R-12R}$												
8R	0	0	445	0.000	0	1	339	0.001	N/A	0.253	N/A	0.129
9R	83	191	171	0.401	63	162	115	0.424	0.388	0.371	1.097 (0.895–1.343)	0.095
10R	166	194	85	0.591	113	161	66	0.569	0.400	0.384	0.914 (0.747–1.119)	0.090
11R	0	5	440	0.006	0	3	337	0.004	N/A	0.739	0.784 (0.187–3.293)	0.053
12R	0	2	443	0.002	0	1	339	0.001	N/A	0.727	0.652 (0.059–7.202)	0.046
$uVNTR_{2R-4R}$												
2R	0	5	440	0.006	0	4	336	0.006	N/A	0.945	1.047 (0.280–3.915)	N/A
3R	181	190	74	0.620	130	149	61	0.601	0.469	0.450	0.924 (0.753–1.134)	0.078
4R	71	190	184	0.373	61	145	134	0.393	0.449	0.428	1.870 (0.884–1.334)	0.083
5R	0	1	444	0.001	0	0	340	0.000	N/A	0.382	N/A	0.058

Abbreviations: CI, confidence interval; CTL, healthy controls; Freq, frequency; MAOA, monoamine oxidase A; N/A, not applicable; SCD, suicide.

[a]This column show reference allele homozygotes, heterozygotes, and others as x/x, x/−, and −/−, respectively. The x/x was not available for male samples because of the *MAOA* gene situated on the X chromosome.

[b]*p*-values were analyzed using the Cochran-Armitage trend test.

[c]Allelic *p*-values were analyzed using the χ^2 test. If the nominal *p*-value showed a significant difference ($p<0.05$), the strict *p*-value for multiple testing (10000 permutations) was used, as necessary.

not registered. Studies in the meta-analysis were included based on the following criteria: (1) case–control design, (2) MAOA-uVNTR or -dVNTR polymorphism between suicide subjects and controls, (3) independent study from other studies, and (4) adequate and sufficient information for performing data synthesis. Language of the included studies was limited to English. We scrutinized reference lists of identified papers and relevant review articles and included studies not sourced in the search, as necessary. We screened titles and abstracts and assessed the full text, as necessary; nonrequirement studies were excluded according to our criteria. Studies were screened independently by two reviewers (T.T. and T.S.); disagreements were resolved by discussion and, if necessary, mediated by S.O.

Phenotypes were divided into suicide subjects vs. controls; allelic distributions were classified as follows: **uVNTR' alleles**, low-expression alleles (2R repeats [R], 3R, and 5R), and high-expression alleles (3.5R and 4R),[14,18] and **dVNTR' alleles**, low-expression alleles (10R), high-expression alleles (9R), moderate expression alleles (8R and 11R), and unknown (12R).[13,18] We performed a meta-analysis with Review Manager 5.4.1 (RevMan 2020) using the Mantel–Haenszel method. The meta-analysis used a random effects model and assessed the strength of association between polymorphisms and phenotype through odds ratio (OR). I^2 values were used to evaluate heterogeneity (I^2 values of 0%–40%: might not be important; 30%–60%: may present moderate heterogeneity; 50%–90%: may present substantial heterogeneity; 75%–100%: is considerable heterogeneity),[36] whereas a funnel plot was used to detect publication bias.

3 | RESULTS

The HWEs of the VNTR polymorphisms did not show any deviation in the females and were as follows: dVNTR; control, $p=0.782$

TABLE 3 Haplotypic distribution of the polymorphisms in the *MAOA* promoter in controls and suicide completers.

	CTL ($n=844$)		SCD ($n=1007$)				
Polymorphism	***n***	**Frequency**	***n***	**Frequency**	***p*-value**[a]	**Odds ratio (95% CI)**	**Power**
Male (CTL, $n=399$; SCD, $n=667$)							
8R-3R	1	0.003	1	0.001	0.713	0.598 (0.037–9.581)	0.144
9R-3R	17	0.043	37	0.055	0.354	1.320 (0.733–2.376)	0.130
9R-4R	149	0.373	254	0.381	0.810	1.032 (0.799–1.333)	0.045
9R-5R	0	0.000	2	0.003	0.274	N/A	0.132
10R-2R	3	0.008	8	0.012	0.484	1.602 (0.423–6.075)	0.080
10R-3R	212	0.531	344	0.516	0.622	0.939 (0.733–1.204)	0.069
10R-4R	11	0.028	16	0.024	0.719	0.867 (0.398–1.887)	0.063
11R-3R	4	0.010	4	0.006	0.461	0.596 (0.148–2.396)	0.124
12R-3R	2	0.005	1	0.001	0.295	0.298 (0.027–3.298)	0.279
Female (CTL, $n=445$; SCD, $n=340$)							
9R-3R	50	0.056	40	0.059	0.761	1.050 (0.684–1.611)	0.038
9R-4R	307	0.345	248	0.365	0.412	1.090 (0.885–1.343)	0.084
10R-2R	5	0.006	4	0.006	0.945	1.047 (0.280–3.915)	N/A
10R-3R	497	0.559	364	0.535	0.343	0.911 (0.745–1.113)	0.099
10R-4R	23	0.026	19	0.028	0.823	1.084 (0.585–2.006)	0.038
11R-3R	5	0.006	3	0.004	0.739	0.784 (0.187–3.293)	0.053
12R-3R	2	0.002	1	0.001	0.727	0.654 (0.059–7.226)	0.046

Abbreviations: CI, confidence interval; CTL, healthy controls; MAOA, monoamine oxidase A; N/A, not applicable; SCD, suicide.

[a]Haplotypic *p*-values were analyzed using the χ^2 test. If the nominal *p*-value showed a significant difference ($p<0.05$), a strict *p*-value for multiple testing (10000 permutations) was calculated.

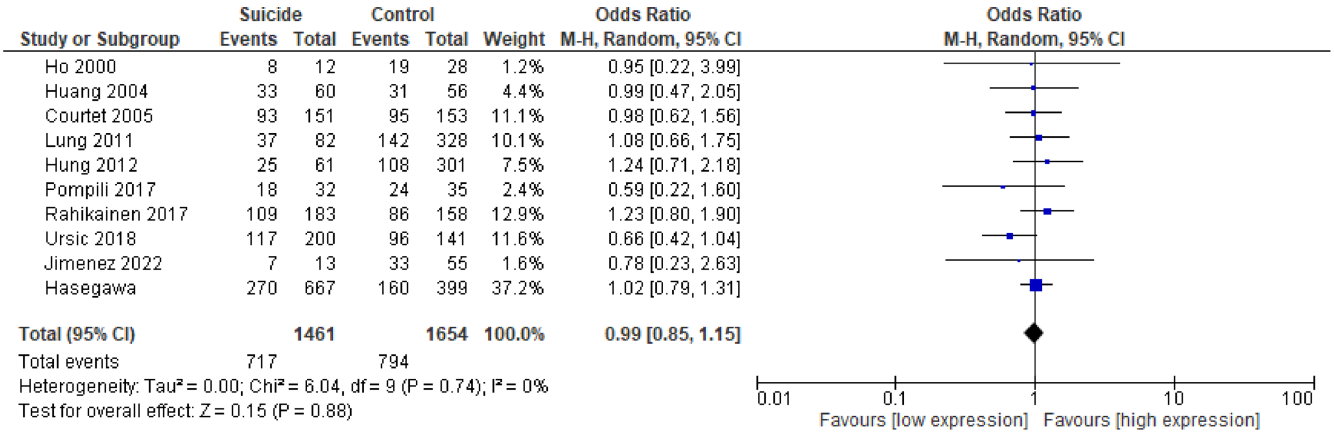

FIGURE 1 Forest plot analyzing an upstream variable number of tandem repeat (u-VNTR) polymorphism in the monoamine oxidase A gene (*MAOA*) in male suicide subjects and controls.

and suicide, $p=0.964$; uVNTR; control, $p=0.810$ and suicide, $p=0.431$.

The genotype-based associations and allele frequencies are presented in Table 2. Neither the genotype nor the allelic frequency of uVNTR and dVNTR was significantly related to suicide completion.

The distribution of the haplotypes of the two VNTRs was not significantly associated with completed suicides (Table 3).

In the meta-analysis, we identified 79 articles via PubMed and included our results in the present study. However, we did not identify articles of analysis between dVNTR in *MAOA* and suicide. Following screening of titles and abstracts, 48 articles were excluded; we assessed the full text of 32 articles, including 10 articles in the meta-analysis (Table S1 and Figure S1).[11,15,17,37–42] This meta-analysis did not show relationships between uVNTR in *MAOA* and suicide (Figures 1 and 2). Additionally, we performed subgroup

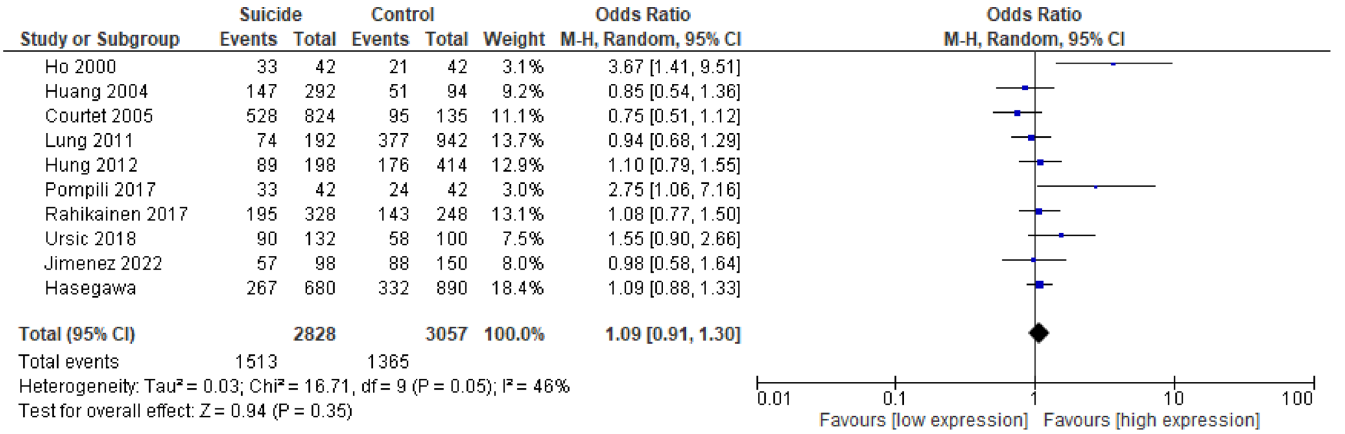

FIGURE 2 Forest plot analyzing an upstream variable number of tandem repeat (u-VNTR) polymorphism in the monoamine oxidase A gene (*MAOA*) in female suicide subjects and controls.

analysis between only healthy controls and suicide subjects, which did not show significantly different outcomes (Figures S2 and S3). The funnel plots indicate the publication bias (Figures S4–S7).

4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate the relationship between the two VNTRs in the *MAOA* promoter and suicide completion. The meta-analysis did not indicate relationships between uVNTR in *MAOA* and suicide, and we failed to find associations between the two VNTRs in *MAOA* and suicide.

We hypothesized that suicide would be significantly associated with 3.5R and 4R of the MAOA's high-expression uVNTR, 9R of the MAOA's highest-expression dVNTR, and a combination of haplotypes of the two VNTRs. One reported cause of suicide is serotonergic dysfunction such as low serotonin levels.[10] In theory, higher MAOA expression would lead to a higher serotonin degradation, resulting in a reduction in serotonin levels. However, our hypothesis was not validated because of several limitations.

We reviewed articles to perform a meta-analysis of the association between suicide and two VNTRs in *MAOA*. Numerous studies have investigated the uVNTR,[11,15–17] but very few studies have examined dVNTR and the haplotypes of the two VNTRs. The meta-analysis of uVNTR did not show any associations with suicide, whereas we did not identify articles of analysis between dVNTR and suicide. Therefore, the relationship between dVNTR and psychiatric diseases including suicide remain unclear, warranting further studies.

This study has several limitations. First, our sample size was very small, resulting in the analysis of the two VNTRs polymorphisms having low statistical power. Second, GWAS have indicated the need to consider polygenic structures.[7–9] It is challenging to use only a candidate gene approach to identify susceptibility genes for complex diseases such as suicide. Our findings were limited to two allele polymorphisms in the *MAOA* gene, and we could not clarify the association between polymorphisms and suicide based on multiple genes. Third, we did not directly measure serotonin levels to validate our hypothesis. Fourth, our study comprised only Japanese participants and did not consider other ethnicities.

5 | CONCLUSION

We investigated the relationship between the two VNTRs in the *MAOA* promoter and suicide completion but did not find a significant association. Therefore, this finding necessitates further studies focused on larger sample sizes and polygenic structures.

AUTHOR CONTRIBUTIONS

Conceptualization: Satoshi Okazaki and Akitoyo Hishimoto. **Data curation:** Masashi Hasegawa, Takaki Tanifuji, and Toshiyuki Shirai. **Formal Analysis:** Masashi Hasegawa, Takaki Tanifuji, and dToshiyuki Shirai. **Funding acquisition:** Satoshi Okazaki, Ikuo Otsuka, andAkitoyo Hishimoto. **Investigation:** Masashi Hasegawa and Takaki Tanifuji. **Project administration:** Satoshi Okazaki. **Resources:** Masahi Hasegawa, Takaki Tanifuji, Satoshi Okazaki, Ikuo Otsuka, Ryota Shindo, Tadsu Horai, Kentaro Mouri, Motonori Takahashi, Takeshi Kondo, and Yasuhiro Ueno. **Supervision:** Akitoyo Hishimoto. **Writing—original draft:** Masashi Hasegawa and Takaki Tanifuji. **Writing—review and editing:** Satoshi Okazaki and Akitoyo Hishimoto.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

ETHICS STATEMENT

Approval of the Research Protocol by an Institutional Review Board: The study design and related procedures were performed in accordance with the Declaration of Helsinki. This study was approved by the Ethical Committee for Genetic Studies of Kobe University Graduate School of Medicine (Approval No. 180240).

Informed Consent: Informed consent was obtained from all living participants and families of the suicide victims.

Registry and the Registration No. of the Study: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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