Association and Interaction of the MAOA Promoter uVNTR Polymorphism with Suicide Attempts in Patients with Major Depressive Disorder

For-Wey Lung\textsuperscript{1,2,3,4}, Dong-Sheng Tzeng\textsuperscript{1,5}, Mei-Feng Huang\textsuperscript{6}, Ming-Been Lee\textsuperscript{7,8}

\textsuperscript{a}Department of Psychiatry, Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan
\textsuperscript{b}Department of Neurology, Kaohsiung Medical University, Kaohsiung, Taiwan
\textsuperscript{c}Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan
\textsuperscript{d}Calo Psychiatric Center, Pingtung County, Taiwan
\textsuperscript{e}Graduate Institute of Undersea Medicine, National Defense Medical Center, Taipei, Taiwan
\textsuperscript{f}Department of Psychiatry, Kai-Suan Psychiatric Hospital, Kaohsiung, Taiwan
\textsuperscript{g}Departments of Psychiatry and Social Medicine, National Taiwan University College of Medicine, Taipei, Taiwan
\textsuperscript{h}Director of Taiwan Suicide Prevention Center, Taipei, Taiwan

Corresponding Author: Ming-Been Lee, No. 2 Chung Cheng 1\textsuperscript{st} Rd., Kaohsiung City, Taiwan
Tel: 886-7-7490056; Fax: 886-7-7493767; E-mail: forweylung@gmail.com

Running head: MAOA uVNTR in relation to suicide attempts
Abstract

**Background:** This study aimed to explore the association between alleles of the MAOA uVNTR polymorphism and patients with major depressive disorder (MDD) who had attempted suicide, using multiple controls. The symptom profiles and personal characteristics in each group were also compared.

**Methods:** Four different groups was included: 432 community controls, 385 patients with MDD who had not attempted suicide, 96 community subjects without mental disorders who had attempted suicide from emergency room in a general hospital, and 109 patients with MDD who had attempted suicide.

**Results:** An intergroup difference in allelic frequency was found between female suicidal subjects from the community and female suicidal subjects with MDD (P = 0.028): heterozygosity for the long-form variant of the MAOA polymorphism (≧ 3.5 repeats) was found to be a potential protective factor against MDD among female suicidal subjects (OR = 0.396). By multivariate logistic regression analysis, the long-form variant was found to be associated with suicide after controlling for the effect of gender (P = 0.004). An interaction was also found between depression and suicide that showed a negative correlation with the MAOA long-form variant (P = 0.045, OR = 0.503). Structural equation modeling showed, neuroticism, extraversion, low levels of anxiety, high levels of depressive symptoms, and smoking were associated with suicidal behavior in MDD group, not in the group of subjects without MDD.

**Conclusion:** The MAOA long-form variant was associated with enhanced vulnerability to suicide in the general population. Depressive symptoms and smoking were associated with suicide attempts, whereas anxiety was a protective factor against suicidal behavior in participants with MDD. Furthermore, we found that the MAOA long- and short-form variants had different effects in controls and in patients with MDD, and the reverse effect of the long-form MAOA variant on MDD patients who had attempted suicide was revealed only by analysis of interactions. The results
of our study explain why inaccurate diagnostic grouping and lack of investigation of
interaction effects can yield inconsistent results. Further large-scale studies are needed to verify the
psychopathology of the relationships among alleles of the MAOA polymorphism, symptom profiles,
and suicidal behavior.

**Key Words:** MAOA u-VNTR Polymorphisms, Suicide Attempts, Major Depressive Disorder
Background

According to the results of a population-based survey, 16.3% of young adults in the general population in the USA and 25.2% of individuals with a general medical condition develop suicidal ideation [1]. In Taiwan, depressive symptoms has been reported to be one of the three major predictors related to the development of suicidal ideation in psychiatric subjects [2]. It was also reported that serious suicidal behavior might occur more readily in those patients with mental illness or psychiatric comorbidity during their lifetime; however, the relationship between psychiatric comorbidity and risk of suicide varies with age and gender [3]. Individuals sometimes also commit suicide in the absence of psychiatric disorders [1,2]. Furthermore, Lung and Lee [2] found that different factors contribute to the risk of suicide in different groups. Depression, hostility, and feelings of inferiority predict suicide in patients with psychiatric illness, whereas hostility, feelings of inferiority, and insomnia predict suicide in subjects from the community [2]. This demonstrates that the factors that affect attempted suicide in psychiatric patients and in the general population may differ.

In addition to the above-mentioned proximal factors, personal characteristics, which include gender, socioeconomic status, age, education, and personality, are important factors that are associated with suicidal behavior. Some studies have found that neuroticism is associated with increased rates of suicide [4,5], whereas extraversion has a negative association [5]. Moreover, few studies of suicide have included the proximal psychological autopsy and distal predisposing factors among the factors investigated [6,7].

A family history of suicidal behavior and genetic consequences are linked to the development of suicidal ideation [8,9]. Increasingly, studies have indicated that gene–environment interactions may play a fundamental role in the occurrence of suicide attempts [10]. Abnormalities of the serotonergic system have been found to be involved in the risk of suicide. For example, the 102C allele of the 5-HT2A serotonin receptor is associated with suicidal ideation in depressive patients,
and the L/L (long/long) genotype of the 5-HTTLPR polymorphism of the serotonin transporter gene is associated significantly with completed suicide, whereas the S/S (short/short) genotype is found more frequently in individuals who have attempted suicide but failed and have further suicidal behavior than in those who have not [11,12]. The gene for monoamine oxidase A (MAOA), which is located on chromosome Xp21-p11 [13] and is involved in the serotonergic pathway, contains a region within its promoter that is polymorphic for the number of copies of a 30-bp repeat. The alleles identified for this upstream variable number of tandem repeats (uVNTR) polymorphism include alleles with 3, 3.5, 4, and 5 repeats (3R, 3.5R, 4R, and 5R) [14]. These different uVNTR variants are associated with different transcriptional activities of the MAOA promoter [15], which in turn result in different levels of expression of the MAOA gene. The allele of the MAOA uVNTR polymorphism that results in high levels of expression (high activity allele) has been reported to be associated in males with suicide caused by depression [16]. In addition, postmortem results have shown an increased level of MAOA activity in the hypothalamus of the brains of suicide victims with depressive disorder [17]. By contrast, in a population of healthy subjects from the community, male carriers of the low activity alleles (3R and 5R) showed lower scores on a composite measure of dispositional aggressiveness and impulsivity, and showed a greater responsiveness to serotonin in the central nervous system (CNS) than men with the high activity allele [18].

The MAOA uVNTR polymorphism has been identified as a genetic factor that can modulate the risk for depression, suicide, or both by influencing monoaminergic activity in a sexually dimorphic manner [16]. However, little is known about whether the MAOA uVNTR polymorphism confers vulnerability to major depressive disorder (MDD) or suicidal behavior in the Taiwanese population.

Gene–gene interactions are common in human disease. For example, the apolipoprotein (Apo) ε2 allele is a potential confounding covariate for the MAOA uVNTR polymorphism in MDD: the
high-activity MAOA uVNTR alleles are associated with MDD when the Apo ε2 allele, which is a protective factor for MDD, is adjusted for [19]. Moreover, gene–environment interactions are also an important factor. For example, Lin and colleagues also identified a sex-specific interaction between the MAOA uVNTR polymorphism and MDD [19]. In addition, maltreated children who carry the high-activity alleles of the MAOA uVNTR are less likely to develop antisocial problems and behaviors than maltreated children who carry the low activity alleles [20].

Therefore, in this study, we aimed to investigate the role of the different MAOA variants in relation to MDD and/or attempted suicide. We used structural equation modeling to investigate the relationships among personality traits, and other demographic factors in participants with MDD and those from the community who had or had not attempted suicide.

Materials and Methods

Sample Collection

We recruited four groups of participants: 1) controls from the community, 2) patients with MDD, 3) subjects without mental disorders who had attempted suicide from the emergency room, and 4) patients with MDD who had attempted suicide. There were 1022 participants in total: the community control group included 432 participants; the MDD group, 385 participants; the community who had attempted suicide group, 96 participants; and the MDD who had attempted suicide group, 109 participants. The patients with MDD were recruited from a teaching hospital in southern Taiwan from April 2001 to March 2006. All the participants were interviewed by two senior psychiatrists and research assistants to ensure that they did or did not meet the psychiatric diagnosis of MDD, according to the Diagnostic and Statistical Manual of Mental Disorders [21].

Materials

Personality and symptom profiles were collected. Personality was assessed using the
Eysenck Personality Questionnaire (EPQ), which is a 25-item self-report inventory that measures the personality traits of extraversion and neuroticism. There are 14 neuroticism items, which measure the emotional dysfunction of an individual, and 11 extraversion items, which measure the sociability of an individual. The Chinese-language version of the EPQ has demonstrated a high internal consistency of 0.90 [22].

Symptom profiles were assessed using the Chinese Health Questionnaire (CHQ). The CHQ is a 12-item screening instrument that is used to identify minor psychiatric disorders in individuals in the community or in non-psychiatric departments. The CHQ includes assessment of anxiety and depression. Cheng, Wu, Chong, and Williams [23] have demonstrated an internal consistency of 0.79 for the Chinese-language version of the CHQ.

The study protocol was approved by the Institutional Review Board of a teaching hospital in southern Taiwan. Informed consent was obtained from all participants before enrollment.

**DNA Extraction**

Genomic DNA was extracted from 3.5 ml of peripheral blood from each participant using a QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, USA), according to the manufacturer’s protocol. The extracted DNA was stored at –70°C until further use.

**Genotyping**

Amplification by the polymerase chain reaction (PCR) was performed in a final volume of 25 µl, which contained 50–100 ng of DNA, 50 mM KCl, 1.5 mM MgCl₂, 200 µM each of dATP, dCTP, and dTTP, 50 µM dGTP, 150 µM 7-deaza-dGTP, 10 pmol each of two primers (MAOA-F: 5’-ACAGCCTCGCCGTGGAGAAG-3’ and MAOA-R: 5’-GAACGGACGCTCCATTCGGA-3’), and 1 U of Taq polymerase (Biolab USA Inc, San Francisco, USA). The PCR was performed on a Hybaid PXE Thermal Cycler (Thermo Fisher Scientific, Barrington, USA) with the following cycling conditions: 35 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 30 s, and extension at 72°C for 30 s. The PCR products were subjected to gel electrophoresis on a 2.5%
agarose gel (Amresco, Ohio, USA) with 0.5× TBE running buffer. The gels were stained with ethidium bromide and visualized using an ImageMaster VDS gel documentation system (Pharmacia Biotech, Uppsala, Sweden). The MAOA promoter uVNTR polymorphism was interpreted on the basis of the results of our previous study [24], in which the sizes of the PCR products of the 2R, 3R, 4R, and 5R allelic variants were 320 bp, 350 bp, 380 bp, and 410 bp, respectively. The 2R and 3R allelic variants were defined as short-form variants, and the remaining variants, with a repeat number greater than three, were defined as long-form variants.

**Statistical Analysis**

In the descriptive analysis, continuous variables were expressed as the mean ± SD and categorical variables were shown as proportions. We used the algorithm developed by Guo and Thompson [25], which allows an exact test to be performed for traits that are encoded by multiple alleles, to test whether the allelic frequency of the MAOA uVNTR polymorphism in females was in Hardy–Weinberg equilibrium. The maximum likelihood chi-square test was applied to distinguish differences among the four groups studied. Moreover, the allelic variants were categorized further into two groups according to their transcriptional activity, as described elsewhere [14]. Genotypes that contained at least one short-form allele were defined as the low activity group, whereas female homozygotes of the long-form variants were classified as the high activity group. Pearson’s chi-square test was used to determine whether inter-group differences in allelic frequency between the short- and long-form variants were significant. Binary logistic regression analysis was carried out to clarify which factors among depression, suicide, and the interaction between depression and suicide were associated with the high activity allelic variants after controlling for age and gender. P values that were less than 0.05 were considered statistically significant. These statistical analyses were carried out using the SPSS version 17.0 for Windows software package. Structural equation modeling (SEM) was performed using the AMOS 7.0 for Windows software package to illustrate the interrelationships between the variables studied, which included personality scores, depression,
anxiety, suicidal behavior, MDD, and the presence of the MAOA short-form allele. A P value greater than 0.05 and an adjusted goodness-of-fit index greater than 0.9 implied that the null hypothesized structure was related closely to the true structure.

**Results**

One hundred and eighty-nine of the 432 participants in the community control group were male, and this group had a mean age of 45.36 years (SD = 13.91); 149 of the 385 MDD subjects who had not attempted suicide were male, with a mean age of 45.17 years (SD = 15.25); 43 of the 96 community controls who had attempted suicide were male, with a mean age of 45.48 years (SD = 20.53); and 47 of the 109 MDD subjects who had attempted suicide were male, with a mean age of 39.73 years (SD = 14.71). (these data can be included in a table, rather than in the text) Overall, the female-to-male ratio was 1.385 (568/410).

We detected the following MAOA uVNTR allelic variants among the participants: 2R, 3R, 4R, and 5R. We did not identify any 3.5R alleles among the subjects. The allelic frequencies and genotype distribution of the MAOA uVNTR polymorphism are shown by gender and group in Table 1. The frequency of the 2R and 5R alleles was extremely low in each group. Three females with MDD carried at least one 2R allele and three community control females harbored one 5R allele. Among the male participants, there were two carriers of the 2R allele in each group, with the exception of the community control group. Only one carrier of the 5R allele, in the community control group, was found among the male participants. The genotype distribution of the MAOA uVNTR polymorphism among the female community controls was in Hardy–Weinberg equilibrium (P = 0.367, data not shown). In the female participants, the most frequent genotype was 3R/4R, followed by 4R/4R and 3R/3R. The 3R allele was frequent in the male community controls (60.98%) and community suicide subjects (52.78%), but not in the other two groups. The allelic frequency of the MAOA uVNTR polymorphism among the male community controls was
significantly different from that in the other groups of male participants (community controls vs. MDD: chi-square = 8.603, P = 0.035; community controls vs. community subjects who attempted suicide: chi-square = 7.994, P = 0.046; community controls vs. MDD subjects who attempted suicide: chi-square = 8.763, P = 0.033). This finding suggested that high activity variants of the MAOA uVNTR polymorphism were more prevalent in male MDD patients, whether or not they had attempted suicide.

We subdivided the allelic variants further into dichotomous groups, which included female homozygotes for the long-form variant or male carriers of the long-form variant (high activity group) and carriers of the short-form variant (low activity group). The allelic frequencies of the short-form variants vs. long-form variants in the four groups studied are shown in Table 2. The high activity variant occurred more frequently among the community subjects who had attempted suicide (M: 51.2%, F: 37.7%) than among the members of the three other groups (M: 41.3–50.3%, F: 18.2–19.4%). Moreover, there were more homozygotes for the long-form variant among the females in the community suicide group than among those in the community control group (37.7% vs. 18.9%). A significant difference was found with respect to the allelic frequencies of the long- and short-form variants between the female community controls and female community subjects who had attempted suicide (chi-square = 8.881, P = 0.003). Females from the community who were homozygous for the MAOA long-form allele were estimated to have more than double the risk of attempted suicide than those who were homozygous or heterozygous for the short-form allele (OR = 2.596, 95% C.I. = 1.375–4.906). However, a significant difference was also observed with respect to the allelic frequencies of the long- and short-form variants between female subjects from the community who had attempted suicide and female patients with MDD who had attempted suicide (chi-square = 4.807, P = 0.028). There were fewer homozygotes for the long-form variant among the MDD patients who had attempted suicide than among the community subjects who had attempted suicide (19.4% vs. 37.7%), and homozygosity for the long-form allele appeared to be a
protective factor against the development of MDD among the female subjects who had attempted suicide (OR = 0.396, 95% C.I. = 0.173–0.909).

In the multivariate logistic regression analysis, the long-form variant was associated with attempted suicide rather than MDD after controlling for the effect of gender (suicide: B = 0.703, P = 0.004, MDD: B = 0.167, P = 0.295), as shown in Table 3. In general, gender did affect the allelic frequency of the long- and short-form variants of the MAOA uVNTR polymorphism (B = –1.223, P < 0.001); females less frequently harbored the long-form allele and may be at a lower risk of attempted suicide (OR = 0.294). Those individuals who carried the homozygous long-form allele and/or long-form allele were estimated to have a double the risk of developing suicidal behavior. In addition, an interaction was found between MDD and suicide, which may predispose patients with MDD to develop suicidal behavior. However, this interaction was negatively correlated with homozygosity for the MAOA long-form variant. It was suggested that carrying a homozygous long-form allele and/or long-form allele was a plausible protective factor against MDD development in the participants who showed suicidal behavior (B = -0.688, P = 0.045, OR = 0.503).

The pathways among the demographics, personality traits, depressive symptoms, anxiety levels, and the frequency of the MAOA short-form variant among the subjects with MDD who either had or had not attempted suicide were analyzed by structural equation modeling. The model resulted in a P value of 0.421 (>0.05) and an adjusted goodness-of-fit index of 0.986 (>0.9), as shown in Figure 1. The model showed that the factors that affected attempted suicidal behavior directly included anxiety, depressive symptoms, and smoking. Individuals who were more neurotic or more extraverted, had lower levels of anxiety, a higher level of depression, and who smoked more were more likely to attempt suicide than individuals who did not exhibit these characteristics ($\beta = -0.11, P = 0.018; \beta = -0.15, P = 0.003; \beta = 0.21, P < 0.001; \beta = -0.24, P < 0.001; \beta = -0.30, P < 0.001$).
Discussion

The results of our study showed that, in general, the MAOA long-form variant was associated with increased vulnerability to suicide in the general population. However, in MDD subjects, suicidal behavior was associated with the MAOA short-form variant. Additional risk factors, other than the length of the MAOA uVNTR polymorphism, were identified for the MDD and control groups. Depressive symptoms were associated with suicidal behavior in the participants with MDD, whereas anxiety was found to have a protective effect. However, neither anxiety nor depression affected suicidal behavior in the community groups.

In this study, we detected four different alleles of the MAOA promoter uVNTR polymorphism (2R, 3R, 4R and 5R), but we did not detect the 3.5R allele in our sample. It has been reported that the 3R and 4R alleles are the most common alleles among different ethnic populations [14]. In our population of 1022 participants, 71.29% of the participants in the community control group were found to carry at least one 3R allele, and 50.69% carried at least one 4R allele. By contrast, only nine and four individuals carried the 2R and 5R alleles, respectively. The allelic frequencies of the MAOA uVNTR polymorphism in our population were consistent with those described previously [14,19].

The MAOA high activity alleles, especially the 4R allele, were found to be associated with attempted suicide. This was consistent with the findings of a previous study by Du et al. [16]. In addition, homozygosity for the long form of the MAOA uVNTR polymorphism was a risk factor for developing suicidal behavior. Subjects who are homozygous for the MAOA long-form allele are assumed to have excess MAOA activity (which may result in abnormal serotonin metabolism in the CNS). Furthermore, a high activity allele has been linked to high levels of aggressiveness and impulsivity, as well as poor responsiveness to serotonin in the CNS [18]. Thus, the higher risk of suicidal ideation or attempts in subjects who carry an MAOA high activity allele may be due to a high level of aggressiveness and impulsivity, and low responsiveness to serotonin, in these
individuals. Moreover, the MAOA uVNTR polymorphism has been recognized as one of four serotonin-related SNPs that may affect the decision-making ability of individuals, and thus modulate vulnerability to suicide [26].

From the intergroup comparisons, we found that the MAOA long-form allele was not common in subjects with MDD who had attempted suicide, and it is likely to act as a protective factor against MDD in suicidal subjects. Although it has been suggested that the MAOA long-form allele is linked directly to high levels of aggression and impulsivity and low levels of responsiveness to serotonin in males without MDD, it was unclear whether homozygosity for the long-form allele conferred a protective effect against MDD in suicidal subjects. We speculate that serotonergic signaling may be abnormal in carriers of the MAOA long-form allele with a history of attempted suicide; this, in turn, may lead to a phenotype of aggression and impulsivity as a consequence of multi-factorial interactions, and may exert a protective effect against MDD. Logistic regression analysis further showed that homozygosity of the long-form allele and/or the long-form allele was associated with suicide, but not depression after controlling for the gender effect. Thus we found that, in the general population, the MAOA long-form variant was a risk factor for suicide, whereas the short-form variant was a risk factor for suicide in patients with MDD. The results of previous studies have shown inconsistencies with respect to the association between MAOA and suicide. Ono and colleagues [27] and Kunugi and colleagues [28] both failed to find an association between the MAOA polymorphism and suicide. However, Du et al. [16] showed that the high-activity allele was associated with depression-related suicide in male subjects, and indicated that carriers of the high-activity allele had a 3.1 times greater risk of developing suicide than non-carriers. Regarding the negative finding of an association between the MAOA uVNTR polymorphism and major depression, our result was partly consistent with that from another MAOA population-based SNP-association study using Han Chinese subjects in Taiwan [29]. These authors found that the MAOA uVNTR polymorphism had only a borderline significant association with severe MDD, and
they concluded that the polymorphism does not play a major role in the pathogenesis of MDD. By contrast, the high activity allele of the MAOA uVNTR was reported to be associated with MDD in German females [30]. The 4R allele was also reported to occur at a significantly higher frequency in Chinese female subjects with MDD than in controls [31]. In addition, the high activity allele was found at a significantly higher frequency in female subjects affected by mood disorders who presented a seasonal pattern or psychotic symptoms in their episodes than in subjects who did not show these characteristics [32]. Due to the fact that we found that the long- and short-form variants of the MAOA polymorphism had different effects in patients with MDD and in controls, the reverse effect of the long-form MAOA variant on MDD patients who had attempted suicide was revealed only by the analysis of the interaction. The results of our study explain why inaccurate diagnostic grouping and a lack of investigation of interaction effects may yield inconsistent results.

Comparison of the two groups of patients with MDD (those who had or had not attempted suicide) revealed that depressive symptoms increased the risk of suicidal behavior, whereas anxiety decreased the risk. This result was consistent with the findings of a previous study, in which depressive symptoms was shown to be an important predictor of suicidal ideation in groups of patients with psychiatric or general medical conditions, but not in community controls, and anxiety was found to be a protective factor against suicidal behavior in the psychiatric group [2]. In another study that investigated subjects with MDD, the severity of depression was identified as a predictor of suicidal ideation [33]. Several studies have shown that personality traits may be related to attempted suicide; for example, neuroticism shows a positive association [4,5], whereas extraversion shows a negative association [5].

The model produced was also applied to the community participants (data not shown), and neither depression nor anxiety was found to affect suicidal behavior in the community group. Lung and Lee [2] also reported previously that risk factors for suicidal behavior differed between
psychiatric and community groups. Thus, the hypothesis that depressive symptoms are associated with suicidal behavior in the general population is not supported by these studies.

In this study, we analyzed various factors associated with suicide, such as cigarette smoking and alcohol consumption, for intergroup differences. A significant difference was found between the MDD subjects who had and had not attempted suicide: the participants with MDD who had attempted suicide consumed more cigarettes and alcohol than the group who had not attempted suicide. Similar findings have been reported for college students [4,6] and patients with bipolar disorder [34]. According to previous studies, alcohol abuse, drug use, or smoking induces an increase in aggressive or impulsive behavior [34,35]. In a national comorbidity survey panel study, smoking was related to suicide ideation or attempts that had more common causes than those of the causal effects of smoking [36]. In fact, many genetic factors and behavioral traits have been shown to contribute to nicotine dependence in complex ways [37].

The results of our study demonstrated some new aspects of the association between the MAOA uVNTR polymorphism and suicidal behavior in patients with MDD when gender differences were controlled for, and revealed a parsimonious model of interrelationships among the factors that were associated with attempted suicide. However, our results should be viewed in the light of some experimental limitations. First, we did not investigate polymorphism in other genes that are involved in the serotonergic pathway; the lack of this genetic information for data stratification may lead to bias, because the allelic variants of the MAOA uVNTR polymorphism are correlated with serotonin activity in the CNS. Second, the MAOA uVNTR variants are well known to be associated with different mental symptoms and genetic effects that vary with gender and age. We performed data stratification using gender as a covariate; however, data stratification may result in false positive or false negative findings. Third, the community controls did not undergo a medical interview to assess their family history of psychiatric disorders; the required information was obtained simply from the self-reports of the participants. Thus, the information gathered may
be incorrect. Fourth, the survival effect may have influenced the results of this study. Individuals who had died as a result of suicide could not be studied, and para-suicidal persons might have been omitted from the present study.

Conclusion

In conclusion, we have demonstrated that the long-form variant of the MAOA uVNTR polymorphism is associated with enhanced vulnerability to suicide in the general population. However, it also serves as a protective factor against MDD among ethnic Chinese suicidal subjects. The severity of depression was associated with suicide in participants with MDD, whereas anxiety was found to be a protective factor against suicide. However, neither depression nor anxiety affected suicidal behavior in the community group. Further large-scale studies are needed to verify the psychopathology of the relationships among the MAOA polymorphism, symptom profiles, and attempts at suicide.

Abbreviations

None

Competing interests

All authors declare that they have no conflicts of interest.

Contributors

All authors contributed to the design of the study. FW participated in the design of the study, performed the statistical analysis, and drafted the manuscript. DS participated in the design of the study, collected the data, and helped to draft the manuscript. MF carried out the molecular genetic studies and helped to draft the manuscript. MB conceived the study, participated in its design, and drafted the manuscript. All authors have reviewed the manuscript and have approved the final
version.

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The funding organization had no role in the design or conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
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Table 1. Allelic frequencies and genotype distribution of the MAOA uVNTR polymorphism in the four groups of participants, i.e. community controls and patients with major depressive disorder who had or had not attempted suicide

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<td>2</td>
<td>72</td>
<td>72</td>
<td>1</td>
<td>8.603</td>
<td>0.035*</td>
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<td>149</td>
<td>146</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>236</td>
<td>233</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>81</td>
<td>109</td>
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<tr>
<td>Comm-suic</td>
<td>96</td>
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</tr>
</tbody>
</table>
Male 43 36 2(5.55%) 19(52.78%) 15(41.67%)  7.994 0.046*  2.252 0.324

Female 53 38 11(21.5%) 22(43.1%) 5(9.8%)  3.010 0.556  2.376 0.795

MDD-suic 109

Male 47 46 2(4.34%) 22(47.83%) 22(47.83%)  8.763 0.033*  1.298 0.523  0.329 0.848

Female 62 58 24(39.3%) 26(42.6%) 8(13.1%)  2.128 0.712  2.251 0.813  1.781 0.410

Comm-contl: community controls; MDD: subjects with major depressive disorder; Comm-suic: community subjects who had attempted suicide; MDD-suic: subjects with major depressive disorder who had attempted suicide; N: the number of recruited subjects; n: the number of genotyped subjects; $\chi^2$: the chi-squared value from the maximum likelihood method; asterisk indicates statistical significance.
Table 2. Allelic frequencies of short-form variants vs. long-form variants in the four groups of participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Allelic frequency, N (%)</th>
<th>Comm-contl</th>
<th>MDD</th>
<th>Comm-suic</th>
<th>OR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-form</td>
<td>Long-form</td>
<td>χ²</td>
<td>P</td>
<td>χ²</td>
<td>P</td>
</tr>
<tr>
<td>Comm-contl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>111(58.7%)</td>
<td>78(41.3%)</td>
<td>2.764</td>
<td>0.096</td>
<td>1.398</td>
<td>0.237</td>
</tr>
<tr>
<td>Female</td>
<td>197(81.1%)</td>
<td>46(18.9%)</td>
<td>0.04</td>
<td>0.907</td>
<td>8.881</td>
<td>0.003**</td>
</tr>
<tr>
<td>MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74(49.7%)</td>
<td>75(50.3%)</td>
<td>1.398</td>
<td>0.237</td>
<td>0.028</td>
<td>0.5</td>
</tr>
<tr>
<td>Female</td>
<td>193(81.8%)</td>
<td>43(18.2%)</td>
<td>8.881</td>
<td>0.003**</td>
<td>4.807</td>
<td>0.028*</td>
</tr>
<tr>
<td>Comm-suic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21(48.8%)</td>
<td>22(51.2%)</td>
<td>0.904</td>
<td>0.342</td>
<td>0.028</td>
<td>0.5</td>
</tr>
<tr>
<td>Female</td>
<td>33(62.3%)</td>
<td>20(37.7%)</td>
<td>0.006</td>
<td>0.939</td>
<td>0.042</td>
<td>0.838</td>
</tr>
</tbody>
</table>

Long-form: homozygous for long-repeat variants (≧3.5 repeat); short-form: carrier of short-repeat variants; OR: relative odds ratio; 95% C.I.: 95% confidence interval; a: odds ratio of long-form variants to short-form variants in relation to suicide in females; b. odds ratio of long-form variants to short-form variants in relation to female patients with MDD who had attempted suicide.
Table 3. Multivariate logistic regression analysis in the total (four
groups) participants

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>P-value</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>-1.223</td>
<td>0.142</td>
<td>74.632</td>
<td>1</td>
<td>&lt; 0.001</td>
<td>0.294</td>
</tr>
<tr>
<td>MD</td>
<td>0.167</td>
<td>0.160</td>
<td>1.097</td>
<td>1</td>
<td>0.295</td>
<td>1.182</td>
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<tr>
<td>Suicide</td>
<td>0.703</td>
<td>0.242</td>
<td>8.423</td>
<td>1</td>
<td>0.004</td>
<td>2.020</td>
</tr>
<tr>
<td>MD by suicide</td>
<td>-0.688</td>
<td>0.343</td>
<td>4.020</td>
<td>1</td>
<td>0.045</td>
<td>0.503</td>
</tr>
<tr>
<td>Constant</td>
<td>0.924</td>
<td>0.231</td>
<td>15.953</td>
<td>1</td>
<td>&lt;0.001</td>
<td>2.520</td>
</tr>
</tbody>
</table>

MD=Major Depression

MD by suicide: synergistic effect of Major Depression and suicide attributed to their interaction term;
dependent variable: 1: MAOA long-form variant; 0: MAOA short-form variant;
B: the regression weight; S.E.: standard error; Wald: the index of regression; Exp(B): odds ratio
corresponding to MAOA long-form variants.
Figure 1. Structural equation modeling of the relationships among personality traits, demographics, anxiety, and depression in patients with major depressive disorder who had or had not attempted suicide.

AGFI: adjusted goodness-of-fit. Dummy variables for suicide: 0 = no suicide attempt, 1 = attempted suicide.