

Association Study of a *Monoamine Oxidase A* Gene Promoter Polymorphism with Major Depressive Disorder and Antidepressant Response

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Monoamine oxidase A (MAOA), a mitochondrial enzyme involved in the degradation of biogenic amines, may be implicated in the pathogenesis of major depressive disorder (MDD) and be related to the therapeutic effects of antidepressants. To elucidate a genetic predisposition of MDD, we studied a variable-number-tandem-repeat (VNTR) polymorphism in the promoter region of the MAOA gene in a Chinese population of 230 MDD patients and 217 controls. We also examined the association of this polymorphism and antidepressant therapeutic response in the MDD patients who underwent a 4-week fluoxetine treatment. Our results showed a significantly increased frequency of 4-repeat (4R) allele in MDD patients, especially in the female population. Furthermore, MDD female patients who were 3R homozygotes had a significantly better response to 4-week fluoxetine treatment when compared to 4R carriers ($p = 0.024$), but there was a nonsignificant difference found in male patients ($p = 0.081$). Since the 4R allele transcribed 2–10 times more efficiently than those with 3R allele, our findings suggest that the MAOA-uVNTR may be involved in the pathogenesis of MDD and the antidepressant therapeutic mechanisms in Chinese population, and that there may be a gender effect in this association.

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INTRODUCTION

Monoamine oxidase (MAO) is a mitochondrial outer membrane enzyme that degrades biogenic amines, including neurotransmitters such as norepinephrine, dopamine, and serotonin. Two forms of the enzyme, MAOA and MAOB, are found in the brain where under physiological conditions, norepinephrine and serotonin are preferentially metabolized by MAOA, and dopamine by both forms of the enzyme. Several lines of evidences indicate that MAOA may be involved in the pathogenesis of major depressive disorder (MDD). First, a significant elevation of MAOA activity was found in the hypothalamic region of post-mortem brain from suicide victims (Sherif *et al*, 1991). The difference was more pronounced in the subgroup of

suicides with a record of depressive disorder. Second, MAO inhibitors are effective drugs for the treatment of MDD. Third, since MAOA plays an important role in the metabolism and regulation of central serotonin and norepinephrine, which are important for the pathogenesis of MDD (Meltzer, 1989), it is likely that MAOA will play important role in the pathogenesis of MDD.

The MAOA gene has been mapped to the short arm of X chromosome (Lan *et al*, 1989), and a variable-number-tandem-repeat (VNTR) polymorphism in the promoter region of the MAOA gene (MAOA-uVNTR) has been identified (Zhu *et al*, 1992). The polymorphism, which is located 1.2 kb upstream of the MAOA coding sequences, consists of 30-bp repeated sequence present in 2, 3, 3.5, 4, or 5 repeats (R). This polymorphism is functional in that 3.5R or 4R transcribed 2–10 times more efficiently than those with 2, 3, or 5R (Sabol *et al*, 1998). Although there are several negative association studies between MAOA-uVNTR gene polymorphism and psychiatric phenotype (Furlong *et al*, 1999; Yoshida *et al*, 2002b; Kunugi *et al*, 1999; Sygailo *et al*, 2001; Garpenstrand *et al*, 2002) including an alcoholism study in Han Chinese males (Lu *et al*, 2002), previous reports demonstrated that this polymorphism may

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be associated with monoamine metabolite concentrations in the CSF of healthy volunteers (Jonsson *et al*, 2000) as well as psychiatric diseases such as panic disorder (Deckert *et al*, 1999), obsessive-compulsive disorder (Camarena *et al*, 1998), bipolar disorder (Preisig *et al*, 2000), Alzheimer's disease (Takehashi *et al*, 2002), and schizophrenia (Jonsson *et al*, 2003). Considering the possible role of MAOA in the pathogenesis and therapeutic mechanisms, in this study, we investigated the possible association of the MAOA-uVNTR polymorphism with MDD and its antidepressant therapeutic response.

METHODS

The study was an add-on to another research project (Yu *et al*, 2002) and was approved by the Institution Review Board of the Taipei Veteran General Hospital. A total of 230 psychiatric outpatients (age range 18–79 years) who met the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) criteria for MDD were studied. The diagnoses were based on clinical interviews and bipolar depressive patients were excluded. Other inclusion criteria were (1) minimum baseline score of 18 on the 21-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967) and (2) presence of depressive symptoms for at least 2 weeks before entry into the study, without antidepressant treatment (patients were fresh cases or had quit antidepressant treatment for more than 2 weeks). Exclusion criteria were additional diagnoses on Axis I (including substance abuse, generalized anxiety disorders, panic disorders, or obsessive compulsive disorders) of the DSM-IV, personality disorders, pregnancy, attempted suicide, and major medical and/or neurological disorders. In total, 217 normal controls were recruited to be included for association study. Most of the normal controls were medical staff and they were each interviewed to rule out psychotic or mood disorders. Assessment of MDD patients was performed by a senior psychiatrist who is an expert in psychiatric rating (YWY). The sample consisted entirely of ethnic Han Chinese. Informed consents were obtained from all participants.

All 230 MDD patients took fluoxetine (range: 20–40 mg/day; mean 25.7 (9.0) mg/day) and received treatment efficacy evaluation with the HAM-D before and after the 4-week fluoxetine treatment by one investigator (YWY) who was blinded to the patient's genotype. Therapeutic response was evaluated by the percentage score reduction in HAM-D scores ((baseline score–4-week score) \times 100/baseline score).

For MAOA-uVNTR genotyping, genomic DNA was extracted from EDTA-containing venous blood samples according to standard procedures. The fragments of MAOA-uVNTR were amplified by polymerase chain reaction (PCR) using the forward primers of 5'-CCCAGGCTGCTCCA GAAAC-3' and a reverse primer of 5'-GGACCTGGG CAGTTGTGC-3'. Polymorphisms of MAOA-uVNTR were determined according to size, which was determined from 3% agarose-gel electrophoresis. The 30-bp repeat polymorphism consists of five alleles: 2R: 179 bp; 3R: 209; 4R: 239 bp; 5R: 269 bp. Furthermore, a 3.5R allele has been observed containing three 30-bp repeat and an additional

18-bp of an incomplete repeat unit (227 bp) (Samochowiec *et al*, 1999).

The categorical data were analyzed using the χ^2 test or the Fisher's exact test, as appropriate. Differences in continuous variables were evaluated by Student's *t*-test (eg age difference between the MDD and control; comparison of the HAM-D change after fluoxetine treatment between two genotypic groups in male MDD) or one-way analysis of variance followed by the LSD multiple range tests for comparison among groups (eg comparison of the HAM-D change after fluoxetine treatment among three genotypic groups in female MDD). The criterion for significance was set at $p < 0.050$ for all of the tests. Data are presented as mean (SD).

RESULTS

The frequency of 3.5R allele was zero; in addition, 2R and 5R allele were rare in this study. Thus, six individuals who carried 2R or 5R alleles (two MDD female patients carried one 2R allele, three normal female subjects carried one 2R allele, and one normal female carried one 5R) were excluded in the following statistical analyses (thus, MDD = 228 and Normal = 213). The age (MDD: 44.3 ± 16.8 years; controls: 41.8 ± 10.3 years) and sex (male/female: MDD: 95/133; controls: 110/103) distributions of the MDD patients and the control population were similar ($t = 1.83$, $df = 439$, $p = 0.063$ and $\chi^2 = 0.17$, $df = 1$, $p = 0.20$, respectively). Owing to the fact that MAOA-uVNTR is on the X chromosome, we divided the total sample into two groups according to gender for analysis. The genotypes and allele distribution for the MAOA-uVNTR polymorphism for the MDD group and controls are shown in Table 1. The distributions of the MAOA genotypes for the female MDD cases and the female controls were each in Hardy-Weinberg equilibrium. Comparison of the MAOA-uVNTR polymorphism among female subjects showed significant differences for the genotype distribution between the two groups ($\chi^2 = 9.65$, $df = 2$, $p = 0.008$) with 4R carriers more common in the MDD group (Table 1). Using 3R homozygote as a baseline, the odds ratio for bearers of 4R allele was 2.39 (95% CI 1.36–4.02). Analysis of the allele frequency demonstrated that 4R allele is more common in the MDD group when compared with the control group ($\chi^2 = 6.93$, $df = 1$, $p = 0.009$). Similarly, for males, 4R is more common in the MDD group compared with the control group ($\chi^2 = 6.27$, $df = 1$, $p = 0.015$ (Fisher's exact test) (Table 1). Using 3R carriers as baseline, the odds ratio for bearers of 4R allele was 1.97 (95% CI, 1.17–3.67). When comparing the total sample, including female and male subjects, there are still significant differences found for the allele distribution between the two groups ($\chi^2 = 12.48$, $df = 1$, $p < 0.001$), with 4R carriers more common in the MDD group (Table 1). However, when considering the issue of X-inactivation at the MAOA locus, we used another alternative approach combining total males and only homozygous female subjects. The result also demonstrated significant differences between the two groups ($\chi^2 = 10.72$, $df = 1$, $p = 0.001$) with 4R carriers more common in the MDD group. In this study, the MAOA-uVNTR allele frequency is different for this Chinese population as compared to European-

Table 1 Monoamine Oxidase A uVNTR Allele and Genotype Distributions in Major Depressive Disorder (MDD) Patients and Normal Control Subjects

	Allele frequencies								
	Male			Female			Total		
	3R	4R	<i>p</i>	3R	4R	<i>p</i>	3R	4R	<i>p</i>
MDD	46	49	0.015	144	122	0.009	190 (52.6%)	171 (47.4%)	<0.001
Control	68	35		145	75		213 (65.9%)	110 (34.1%)	

Genotype distribution (the female subjects)				
	3R/3R	3R/4R	4R/4R	<i>p</i>
MDD	34 (25.6%)	76 (57.1%)	23 (17.3%)	0.008
Control	49 (44.5%)	47 (42.7%)	14 (12.7%)	

American samples; however, our results are similar to the Japanese analog in which a high 3R allele frequency was demonstrated (3R allele frequency of control group: 65.9% in this study, 60% in the Japanese sample, and 25–38% in the European–American samples; 3R repeats allele frequency of major depressive group: 52.6% in this study, 58.4–59% in the Japanese sample, and 32% in the European–American samples) (Samochowiec *et al*, 2004; Schulze *et al*, 2000; Kunugi *et al*, 1999; Yoshida *et al*, 2002b).

Therapeutically, female patients bearing the 3R homozygous genotype had a significantly better response to antidepressants when compared with four repeats allele carriers, as evaluated on the HAM-D change after 4 weeks of fluoxetine treatment (3R/3R: $46.9 \pm 19.0\%$, 3R/4R: $37.3 \pm 19.8\%$, 4R/4R: $34.1 \pm 19.4\%$, respectively, $p = 0.024$). A multiple linear-regression analysis was performed using HAM-D change after fluoxetine treatment as the dependent variable, and age and MAOA-uVNTR genotype as the predictor variables. We included age as predictor variable because our earlier study found that age may have some effect on antidepressant therapeutic response (Yu *et al*, 2002). The results demonstrated that the MAOA-uVNTR genotype was a significant predictor of therapeutic response ($p = 0.010$; $r^2 = 0.049$). When comparing the 3R genotype with the 4R genotype group in male patients, there was nonsignificant difference found between 3R carriers and 4R carriers (3R: $39.1 \pm 21.0\%$, 4R: $31.0 \pm 23.6\%$, respectively, $p = 0.081$) according to the change of HAM-D.

DISCUSSION

The present study investigated the association between the MAOA-uVNTR polymorphism and MDD in a Chinese population. We found a significant association, suggesting that the MAOA-uVNTR gene polymorphism may be involved in the MDD susceptibility for our sample population. This finding of an association between MAOA-uVNTR gene polymorphism and MDD is similar with Schulze's study which demonstrated increments in

frequency of genotypes containing long alleles of MAOA-uVNTR in female patients with recurrent major depression (Schulze *et al*, 2000). However, our findings contrast with previous reports that showed no association between the two (Kunugi *et al*, 1999; Syagailo *et al*, 2001). One possible explanation for these discrepant results is that the association between MDD status and carriage of the MAOA-uVNTR polymorphism is in linkage disequilibrium with a functional polymorphism in or near the MAOA gene and the linkage disequilibrium is seen in some ethnic-groups, but not others. Another explanation is that our positive report is a false result due to population stratification. A potential limitation of this study is that case-control association studies can be influenced by undetected population stratification. We restricted the study cases to Han Chinese and focused on a polymorphism with demonstrated functional effects. Further studies with family-based designs or 'genomic control' analysis would be useful to confirm our findings. Finally, given the assumptions that MDD is probably multidetermined, if the MAOA-uVNTR polymorphism is an uncommon disease locus, or one of small effect, the power to detect the gene must consequently be reduced. The negative results in two previous reports could be due to lack of power because of the small sample size (Kunugi *et al*, 1999; Syagailo *et al*, 2001). Finally, the discrepancy may be due to the phenotypic heterogeneity of the MDD patients and the MAOA-uVNTR polymorphism may be just associated with a subgroup of MDD patients. Since the diagnosis of MDD is based on symptom-oriented criteria, selecting cases according to the diagnostic criteria does not assure an etiologically homogenous sample. For example, recent study had demonstrated that this MAOA-uVNTR polymorphism is related to impulsivity in male mood disorder patients (Huang *et al*, 2004).

Another finding of this study is that the female patients bearing the MAOA-uVNTR 3R/3R genotype had a better response to 4-week fluoxetine treatment than 4R allele carriers, and that a nonsignificant difference was found in male patients. When using another alternative approach

combining males and only homozygous female subjects, the results showed that 3R allele carriers had a better response than 4R allele carriers (3R allele carriers: $42.4 \pm 20.5\%$, 4R allele carriers: $31.9 \pm 22.3\%$, respectively, $p = 0.003$). Previously, Cusin *et al* (2002) reported no significant difference in response between MAOA-uVNTR genotypes in an Italy sample consisting of MDD or bipolar depressives treated with fluvoxamine or paroxetine for 6 weeks. Another study by Yoshida *et al* (2002b) reported no significant difference in antidepressant therapeutic response among the MAOA-uVNTR genotype groups in 66 Japanese MDD patients treated with fluvoxamine for 6 weeks. The differences in the study design among their studies and ours included the therapeutic-response assessment (Montgomery and Asberg Depression Rating Scale was used in Yoshida's study), duration of treatment (4 weeks in our study vs 6 weeks in the other two studies), sample (bipolar depression was also included in Cusin's study), and choice of antidepressant (fluoxetine vs fluvoxamine vs paroxetine; pindolol augmentation was used in Cusin's study), which may account for the different results. Furthermore, in our study, it was determined that the MAOA-uVNTR polymorphism accounts for 4.9% of the variance in antidepressant response. Our study using a larger sample, in a homogenous population (Chinese MDD), single medication (fluoxetine), and single rater are more likely to detect this difference. Recent study by Peters *et al*, (2004) consisted of 96 subjects with unipolar major depression treated with fluoxetine with response variables assessed after a 12-week trial. The results implicated the MAOA gene in the specificity of response to fluoxetine, which was more compatible with the results of our study.

In this study, we demonstrated that higher expression allele (4R) of MAOA is associated with MDD susceptibility and poorer antidepressant response. Since serotonin is chiefly metabolized by MAOA, 4R carriers who have higher central MAOA activity are likely to have lower central serotonin levels than those of 3R carriers. Our findings are in line with the report of a significant elevation of central MAOA activity in depressive suicide victims (Sherif *et al*, 1991), and data from previous research suggesting that lower serotonergic function could be the pathogenesis of MDD and drugs that can increase synaptic serotonin levels have antidepressant effects (for a review, see Meltzer, 1989).

In our study, the associations of MAOA-uVNTR polymorphism with MDD susceptibility and fluoxetine treatment response were more prominent in the female sample. The study of Jonsson *et al* (2000) investigated the relationship between MAOA-uVNTR polymorphism and CSF concentrations of 5-hydroxyindoleacetic acid in healthy volunteers. They found that female subjects containing alleles with 3.5 and/or 4 repeats reported to induce a more effective MAO transcription (Deckert *et al*, 1999; Sabol *et al*, 1998), and display higher concentrations of 5-hydroxyindoleacetic acid, but this relevance did not occur in men. Also, several previous reports demonstrated a gender effect in the association between this polymorphism and mental problems (Deckert *et al*, 1999; Camarena *et al*, 1998; Preisig *et al*, 2000; Takehashi *et al*, 2002; Huang *et al*, 2004; Cohen *et al*, 2003; Eley *et al*, 2003; Jonsson *et al*, 2003; Williams *et al*, 2003). From these reports and our findings, it seems

that there is a gender effect for MAOA-uVNTR polymorphism in psychiatric illness. Thus, it is important to take this gender effect into account while studying this polymorphism in mental diseases. The cause for the possible gender effect on this polymorphism is unknown. One possible explanation comes from the evidence that, in the transfected cell line, MAOA activity is reduced by estrogen treatment (Ma *et al*, 1993). Furthermore, the MAOA is on the X chromosome. Female subjects have two X chromosomes, but only one X chromosome is generally active (Willard, 2000). The X chromosome inactivation may have effect in the MAOA expression for the female MAOA-uVNTR heterozygotes. Nevertheless, as many as 10–15% of chromosome in all cells, females are epigenetic mosaics (that is, some cells show one pattern, whereas other cells show a different pattern). A further consideration is that because inactivation takes place not at the point of conception, but rather later on near the time of implantation, there is a developmental window that allows for the development of differences in cellular chemistry between male and female subjects. Although inactivation is largely random in operation, it seems that environment can sometimes influence the inactivation pattern. These speculations may need further exploration. Finally, genetic influences are not determined by the genes inherited, but rather by the genes expressed. That is, the inherited DNA brings about its effects through the RNA that it influences in cells in which the gene is expressed. The relevance of this point is that gene expression is probably influenced by hormonal factors, among other features (Petronis, 2001).

Although this study produced several positive results, there were some limitations. First, the most obvious limitation of this study is that the duration for fluoxetine evaluation was 4 weeks, although there have also been some studies which used 4 weeks as the time point in short-term antidepressant treatment response evaluation (eg Minov *et al*, 2001; Serretti *et al*, 2001; Yoshida *et al*, 2002a). This is the minimal time expected for a treatment response and we may only identify rapid responders, not all responders, to fluoxetine treatment. Further study with a longer observation period is needed to identify all responders. Second, no correction was made in the obtained p -values for multiple testing in our study. After correction for multiple testing, the results of the association of MAOA-uVNTR polymorphism with fluoxetine treatment response stratified by gender were negative. Third, the MAOA-uVNTR polymorphism is proved to have putative functional nature, but we cannot exclude the effects of other polymorphisms for MAOA gene. Although strong linkage disequilibrium in the Chinese population was found between the MAOA-uVNTR and other MAOA gene polymorphism such as EcoRV polymorphism in exon 14 (Lu *et al*, 2002), using haplotypic analysis of multiple polymorphisms for MAOA gene in future studies will be greatly helpful to better explore the role of MAOA in depression.

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