ORIGINAL INVESTIGATION

# Effects of MAOA promoter methylation on susceptibility to paranoid schizophrenia

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**Abstract** This study was undertaken to analyze DNA methylation profiling at the monoamine oxidase A (MAOA) locus, in order to determine whether abnormal DNA methylation is involved in the development of schizophrenia. We recruited a total of 371 patients with paranoid schizophrenia (199 males and 172 females) and 288 unrelated control subjects (123 males and 165 females) for analysis of DNA methylation. Diagnosis was made based on the Structured Clinical Interview for DSM-VI. Genomic DNA extracted from peripheral blood was chemically modified using bisulfite, and DNA methylation profiles of the MAOA promoter were determined by BSP-sequencing. DNA methylation ratios of individual CpG residues and overall methylation ratios were measured on each subject. The results showed that there was no significant difference in overall DNA methylation ratios between patients and controls either in the female group ($P = 0.42$) or in the male group ($P = 0.24$). Of 15 CpG residues that showed significant differences in DNA methylation status between the patient group and the control group in females, eight of which had an increased level and seven, a decreased level, with a combined $P$ value of 1 ($df = 160$). In male subjects, however, six individual CpG residues showed an increased methylation level with a combined $P$ value of 5.80E−35 ($df = 158$). In conclusion, abnormalities of DNA methylation at the MAOA promoter may be associated with schizophrenia in males.

**Abbreviations**
MAOA   Monoamine oxidase A
MDD    Major depressive disorder
ADHD   Attention deficit hyperactivity disorder
SNP    Single nucleotide polymorphism
QUMA   Quantification tool for methylation analysis

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## Introduction

Schizophrenia is a devastating mental disorder which affects approximately 1% of the general population worldwide. In the past decades, a number of schizophrenia susceptibility genes have been identified (Shifman et al. 2008; Williams et al. 2009). Because of the complexity of schizophrenia, however, a specific gene responsible for the development of disease does not appear to be elucidated and the precise mechanism by which the genetic variation can increase disease susceptibility remains unknown.

The neurotransmitter hypothesis of schizophrenia has been predominant for several decades and dysfunction of the monoaminergic system in the brain has been a main focus in biochemical research into the disease (Marsden 2006). Monoamine oxidase A (MAOA) is a key enzyme that catalyzes oxidative deamination of biogenic amines (Shih et al. 1999), such as dopamine, serotonin, and

norepinephrine. During neurodevelopment, MAOA could influence many cellular processes, including neuronal proliferation and apoptosis, probably by regulating the turnover of monoamine neurotransmitters (Ou et al. 2006), and repression of MAOA can result in an apoptotic decrease. Animal model study showed that MAOA knockout mice had altered cortex structure, monoamine deficiency, and elevated anxiety-like behaviors (Cases et al. 1995; Kim et al. 1997). MAOA has been thought to be involved in mental disorders due to its role in the degradation of monoamine neurotransmitters. Genetic polymorphisms of the MAOA gene have been reported to be associated with diverse mental health conditions, including schizophrenia (Qiu et al. 2009), major depressive disorder (MDD) (Rivera et al. 2009; Schulze et al. 2000), aggressive behaviors (Brunner et al. 1993a, b) and attention deficit hyperactivity disorder (ADHD) (Jiang et al. 2001). In our previous work, we found that single nucleotide polymorphisms (SNPs) within the MAOA gene were associated with paranoid schizophrenia (Xu et al. 2004) although genetic analyses conducted by others have shown controversial results.

Epigenetic regulation is essential for establishing a tissue and stage-specific gene expression pattern during growth and development, which is thus potentially involved in disease pathogenesis and progression (Grewal and Moazed 2003; Henikoff and Matzke 1997; Nestler 2009); DNA methylation plays a crucial role in regulation of gene function, such as gene imprinting and X chromosome inactivation. It has been revealed that disturbances of DNA methylation may play a role in the pathogenesis of some neurodevelopmental disorders like Rett syndrome and fragile X syndrome (Amir et al. 1999; Das et al. 1997). In addition, methylation status remains highly variable in the adult brain, and epigenetic variation is related with synaptic plasticity and memory formation (Levenson et al. 2006; Lubin et al. 2008). A number of studies have investigated the relationship between DNA methylation and mental disorders and found that abnormal DNA methylation is associated with schizophrenia, bipolar disorder and depression (Abdolmaleky et al. 2006; Iwamoto et al. 2005; Mill et al. 2008). Accordingly, the present work was undertaken to study the relationship between DNA methylation at the MAOA promoter and schizophrenia.

With regard to the tissue-specific feature of epigenetic markers, it is reasonable to consider that white blood cell-based methylation analysis may not reflect the methylation status of neurons in the brain. However, there is increasing evidence that many epigenetic changes, which are associated with a disease, are not restricted to specific tissues or cell types (Kuratomi et al. 2008; Rosa et al. 2008). Although the correlation between epigenetic variations in the brain and peripheral tissues has yet to be explored, the studies with blood samples have some advantages over those using the post-mortem brain samples. For example, the DNA methylation status of lymphoblast and whole blood is vulnerable to smoking (Philibert et al. 2010), and has been found to be associated with some psychosis-related risk factors like alcohol and nicotine dependence (Philibert et al. 2008). In addition, peripheral blood is much easier to obtain from living subjects, which cannot only facilitate a large-scale study but also provide potential diagnostic targets.

## Materials and methods

### Subjects

A total of 371 individuals with paranoid schizophrenia (199 males and 172 females) were recruited through the Peking University Institute of Mental Health, Beijing, China, in the period between January 2006 and August 2009. Diagnosis was made by at least two consultant psychiatrists according to Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria based on the Structured Clinical Interview for DSM-IV (SCID) (APA 2000). Patients diagnosed as having alcohol abuse, epilepsy, brain trauma with loss of consciousness, neurological illness, or pregnant women were excluded from this study. Meanwhile, 288 unrelated subjects (123 males and 165 females) were also recruited as control subjects. These control subjects were interviewed for detailed information about their medical and family histories. Those who had history of major psychiatric or neurological disorders, psychiatric treatment or drug abuse, or family history of severe forms of psychiatric disorders were excluded. All case and control subjects were of Chinese Han origin from northern China. Written informed consent was obtained from each participant after detailed description of the study. This study was approved by the Ethics Committee of Chinese Academy of Medical Science and Peking Union Medical College.

### Analysis of DNA methylation

A 2-kb DNA sequence across the region between the MAOA gene promoter and exon 1 was retrieved using UCSC Genome Browser (http://genome.ucsc.edu). The location and size of CpG islands were determined using online software, CpG Island Searcher developed by University of Southern California Norris Comprehensive Cancer Center (http://www.uscnorris.com/cpgislands2/cpg.aspx). Based on the prediction of CpG Island Searcher, the MAOA gene contains two CpG islands harboring a total of 80 CpG residues. The first CpG island spans 1,173 bp of

DNA while the second one spans 519 bp covering whole exon 1 of the MAOA gene (Figure S1). The primers used for bisulfite sequencing were designed using online primer design software MethPrimer (sequence listed in Supplementary Table 1), and they were blasted using the MethBlast program (http://medgen.ugent.be/methBLAST/). The amplified regions are denoted in Figure S1.

Peripheral blood samples were taken from patients with schizophrenia and control subjects. Genomic DNA was extracted from the blood samples using the phenol–chloroform method and treated using the bisulfite-modifying DNA method modified by Frommer et al. (1992). In brief, 1 µg DNA of each sample was treated with 3.6 mM bisulfite (pH 5.0) for 16 h to convert unmethylated cytosine residues into uracil residues; the converted DNA was then purified and subsequently applied to desulfonation. During subsequent touch-down PCR amplification, uracil compliments adenosine so that thymidine is incorporated into the DNA sequence at the position of unmethylated cytosine residues. PCR products were sequenced bi-directionally on an ABI 3700 DNA sequencer (PerkinElmer, Applied Biosystems, Foster City, USA).

Statistical analysis

The methylation status of each CpG residue was determined by quantification tool for methylation analysis (QUMA) (Kumaki et al. 2008). Overall methylation ratios for individual subjects were calculated and compared using the Mann–Whitney test. The difference in methylation ratio at each CpG residue was analyzed between the case group and the control group using the $2 \times 2$ Chi-square ($\chi^2$) test and the $P$ value of <0.05 from the 1-$df$ test was corrected by the Bonferroni's correction. The Fisher's combined probability test was applied to analyze the significance levels by combining all individual $P$ values and the combined $P$ values were obtained using the equation:

$$\chi^2 = -2 \times \Sigma \ln P, \ df = 2\kappa,$$ of which $\kappa$ is the number of CpG residues tested in this study (Whitlock 2005).

## Results

The frequencies of methylated cytosine at each CpG residue are given in Fig. 1. As compared to male subjects, females had a higher methylation ratio nearly at all sites, which is consistent to the results reported previously (Philibert et al. 2008). The overall methylation ratios were compared between cases and controls. As shown in Fig. 2, there was no significant difference in the overall methylation ratios between control subjects and schizophrenia patients in either male samples ($P = 0.24$) or female samples ($P = 0.42$).

As shown in Fig. 3, 38 CpG residues showed significant differences in their methylation status between the patient group and the control group in female subjects, 15 of which survived the Bonferroni's corrections. In the female patients with paranoid schizophrenia, decreased methylation ratios were observed at CpG residues 10, 37, 38, 39, 56, 65, and 67, whereas CpG residues 21, 23, 25, 36, 45, 46, 47, and 48 had increased methylation ratios (Supplementary Table 2). The combined $P$ value for female population was 1 ($df = 160$). In the male subjects, interestingly, 32 individual CpG residues were found to have an increased methylation level, six of which survived the Bonferroni's correction, including CpG residues 18, 21, 25, 44, 45, and 50 (Supplementary Table 3). The combined $P$ value was 5.80E−35 ($df = 158$) in the male group.

## Discussion

During the past decades, the relationship between DNA methylation and schizophrenia has emerged (Amir et al.
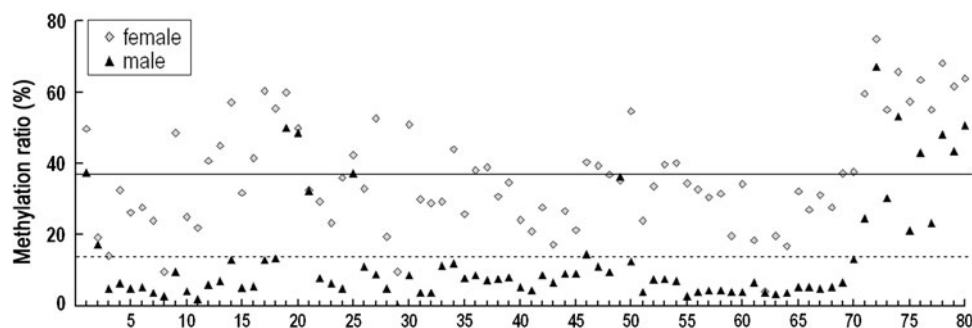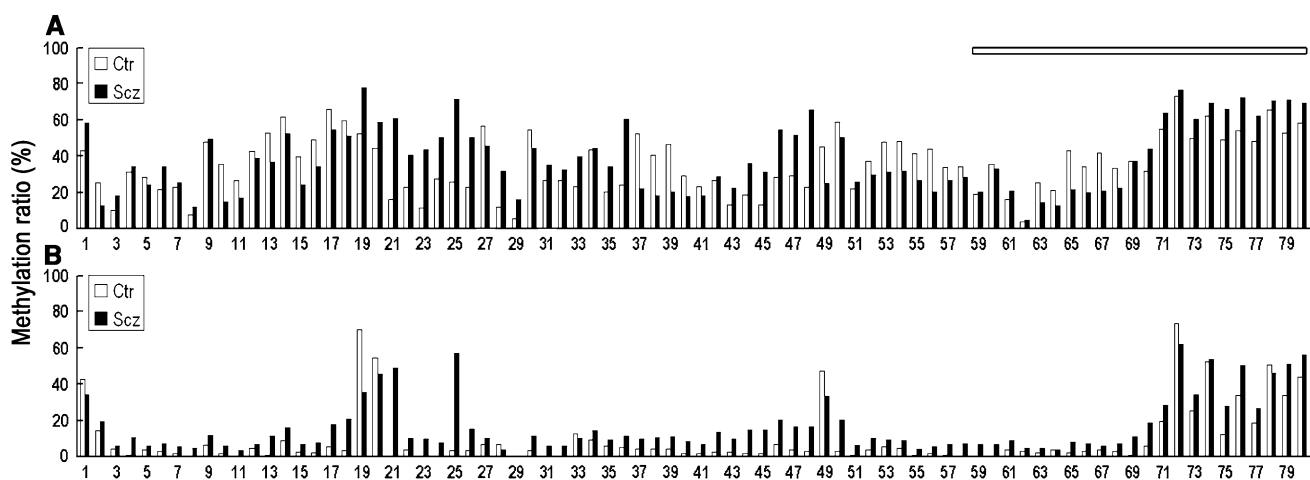


**Fig. 1** DNA methylation ratios at individual CpG residues. A total of 80 CpG residues are analyzed in this study, and the first CpG island consists of 18 residues while the rest of them reside in the second CpG island. *Gray diamonds* depict DNA methylation ratios at each residue in the female subjects, and *black triangles* depict the methylation ratios in the male subjects. The *solid line* depicts the mean methylation ratio in females (36.4%) and the *dashed line* indicates the mean methylation ratio in males (13.6%)
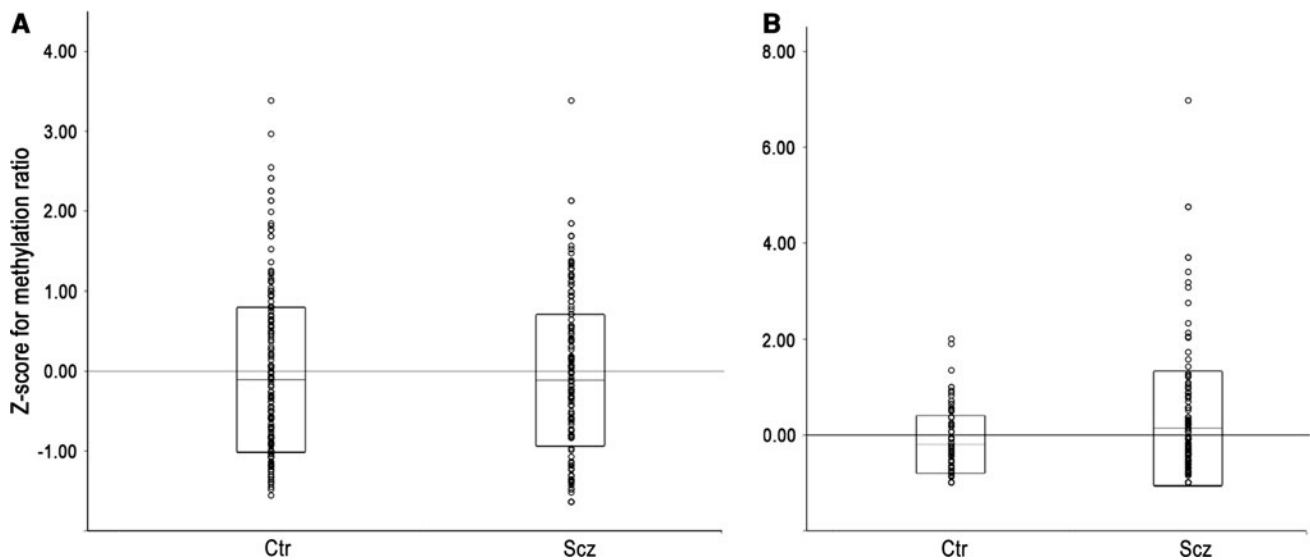
**Fig. 2** Comparison of overall DNA methylation ratios between control subjects and patients with schizophrenia. *Horizontal lines* indicate the mean methylation ratios of each group. There is no significant difference in overall DNA methylation ratios between the patient group and the control group in neither male ($P = 0.24$) nor female ($P = 0.42$) subjects



**Fig. 3** Comparison of methylation ratios at individual residues between cases and controls. The number on the X-axis represents a relative position of each CpG residue, and the *open box* on the *top* depicts exon 1 of the MAOA gene. DNA methylation ratios at each residue are analyzed using the $\chi^2$ test, followed by the Bonferroni's correction. **a** Of the 80 CpG residues analyzed in the female subjects, 15 are found to have a significant change in DNA methylation, including CpG residues 10, 21, 23, 25, 36-39, 45-48, 56, 65, and 67. **b** Of the 79 CpG residues analyzed in the male subjects, six show a significant change in DNA methylation, including CpG residues 18, 21, 25, 44, 45, and 50

1999; Das et al. 1997). Schizophrenia is a complex disease mainly affecting young and middle-aged people. It has been thought that the gene-environment (G × E) interaction is involved in the development of human diseases. In spite of the efforts made to identify environmental risk factors for schizophrenia, the specific causal factor for schizophrenia remains unknown. Epigenetic modifications are vulnerable to environmental factors, such as smoking (Philibert et al. 2008, 2010), and possibly serve as mediators of the G × E interaction. As epigenetic study does not need to assume specific environmental factors or pathological mechanisms, it is possible to conduct a study of the G × E interaction with unknown environmental factors for the disease. The present work confirms that methylation profiling of the MAOA gene promoter is strongly associated with susceptibility to schizophrenia in a Chinese Han population, and that increased methylation levels at the MAOA promoter may be involved in the development of paranoid schizophrenia although such a change significantly occurs only in male patients.

There are two monoamine oxidases in human, which are distinct in cerebral distributions and substrate preference. MAOA degrades predominantly norepinephrine and 5-HT and MAOB acts on phenylethylamine, whereas dopamine is degraded by both MAOA and MAOB (Bach et al. 1988).

Dopamine is a catecholaminergic neurotransmitter and plays a crucial role in cognitive function like attention working memory. On the basis of the prevailing dopamine hypothesis of schizophrenia, we have recently focused on investigating a number of the genes for the metabolic pathway of dopamine in schizophrenia. Our previous work suggests that the MAOA gene may be very important in conferring susceptibility to paranoid schizophrenia (Xu et al. 2004). While the polymorphisms of this gene have been reported to be associated with diverse mental health conditions, the precise mechanism has yet to be clarified. Investigation of methylation status of the MAOA gene promoter may lead to better understanding of a role of the MAOA gene in schizophrenia.

In addition, serotonergic system has also been implicated in the pathophysiology of schizophrenia. The interactions between these two systems are crucial in balancing neuronal activities in the brain, and the imbalance of these two systems has been proposed to be involved in the development of schizophrenia. Dysfunction of either of these two systems could be partially compensated by the other one and imbalance between the dopaminergic and serotonergic systems is very likely to contribute to a mental condition. It is speculated that a relative higher serotonergic activity than dopaminergic activity may be related to the development of the negative symptoms while relatively higher dopaminergic activity may lead to the positive symptoms (Meltzer 1989). Considering its role in both systems, abnormalities in regulation of the MAOA gene may have an impact on the balance between the dopamine system and the 5-HT system. It has been well shown that the dopaminergic and serotonergic systems modulate each other and that there is a reciprocal inhibitory effect between them (Meltzer 2000).

Work on gene structure shows that a 140 bp region, 50 bp upstream of the MAOA gene promoter, contains multiple Sp1 transcription factor binding sites, suggesting a high transcriptional activity (Zhu et al. 1992). The 240 bp core promoter region also shows bidirectional promoter activity (Zhu et al. 1994), and harbors 20 CpG residues (from residues 59 to 78). Increased level of promoter methylation is believed to correlate with gene silencing. Our results suggest that overall methylation levels at the MAOA promoter are not altered in neither male nor female schizophrenia subjects. However, methylation modification at specific CpG residues could potentially affect the affinity for transcription factors of nearing cis-elements. Thus, we have compared the difference in methylation ratios at individual residues between patients and controls, and observed altered methylation at multiple CpG residues. Although our results implicate a profound effect of DNA methylation at the MAOA promoter on susceptibility to schizophrenia in the Chinese Han population, it remains difficult to draw a firm conclusion fully interpreting their biological significance.

The major finding in this study is that individual CpG residues showed a significant increase of DNA methylation in male patients than male controls although such a change was not observed in the female subjects. The gender differences have been reported in a number of epigenetic studies. Shimabukuro et al. (2007) demonstrated that a lower level of genome-wide DNA methylation was associated with schizophrenia in male subjects but not in female subjects. The effect of gender on DNA methylation has been reported by several researchers in healthy subjects. Fuke et al. (2004) found that DNA methylation levels in peripheral blood cells from healthy male subjects were higher than those from healthy female subjects. Similarly, methylation levels of the MAOA gene were lower in males than females as reported by Philibert et al. (2008, 2010). Possibly, X-linked hemizygosity may bias the calculation of methylation ratios. Expression of the X-linked gene is regulated through different ways in males and females, because one of the two X chromosomes is subjected to inactivation in females, which may largely contribute to the difference in DNA methylation ratios calculated. In a study that profiled the expression of a number of the X-linked genes, about 15% genes were found to escape X-inactivation (Xi) to some degree and another 20% genes were not completely silenced in all cell lines tested, so that remarkable variability in Xi expression was observed among those genes (Carrel and Willard 2005). In the X-inactivation assay, the MAOA gene showed a moderate level of Xi expression (about 40% of Xa expression), and the Xi expression was detected in all the hybrids tested, implicating a high potential to escape X-inactivation. Accordingly, X-inactivation may serve as a confounding factor for analysis of DNA methylation in X-linked inheritable diseases in humans.

Taken together, our study shows a novel finding that abnormal DNA methylation at the MAOA gene promoter is very likely to be involved in schizophrenia, especially in the male subjects. This preliminary work may lead to the insight into a role of the MAOA gene in developing the disease. This model may be very useful for further investigation of the etiology of mental disorders so as to bridge the gap between environmental and heritable factors.

**Conflict of interest** None declared.

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