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No Evidence of an Association between a Functional Monoamine Oxidase A Gene Polymorphism and Completed Suicides

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Running title: MAOA gene polymorphism and suicide

ABSTRACT

Monoamine oxidase A (MAOA) has been implicated in the control of aggression and/or impulsivity in humans, and to be involved in suicide. This gene has a functional polymorphism in which there is a variable number tandem repeat (VNTR) in the upstream region (MAOA-u VNTR). We hypothesized that MAOA dysfunction due to this polymorphism was associated with suicide genetically through the disinhibition of aggression and/or impulsivity. We performed an association study between completed suicides and the MAOA-u VNTR polymorphism. No significant difference in genotype distribution or allele frequencies was found between completed suicides and comparison groups either in males or females. These results show no evidence of an association between the MAOA-uVNTR polymorphism and completed suicides, and suggest that MAOA is not involved in the susceptibility to suicide.

Key words: suicide, MAOA-uVNTR polymorphism, association study

Introduction

Biochemical studies have suggested that dysfunction in monoamine neurotransmissions is associated with suicide [Asberg M 1997, Brown et al. 1982, Mann et al. 1999]. Monoamine Oxidase A (MAOA) is one of the major enzymes responsible for the degradation of neurotransmitters such as noradrenaline, dopamine and serotonin. There have been several lines of evidence suggesting that MAOA plays an important role in the control of aggression and impulsivity. For example, a nonsense mutation in the MAOA gene is associated with mental retardation and impulsive aggressive behavior in affected males in a single large family studied in Holland [Brunner et al. 1993a.b]. As another example, transgenic mice with a deletion of the MAOA gene exhibit behavioral alterations, such as trembling and difficulty in righting as pups and increased aggression in adult males [Cases et al. 1995]. An inability to control aggression and/or impulsivity caused by MAOA induced dysfunction may result in suicide. In fact, many studies have suggested a correlation between low platelet MAOA levels and attempted or completed suicides [Gottfries et al. 1975, Sherif et al. 1991, Buchsbaum et al. 1976, 1977, Meltzer et al. 1986], while Mann et al. [1984] failed to find an association between platelet MAOA levels and completed suicides. Because of the potential effect of age, drugs, gender, diet, and other variables, on platelet enzyme levels [Fowler et al. 1982], the use of genetic polymorphisms at the MAOA gene may be more strategic than the use of enzyme levels.

The MAOA gene is localized on chromosome Xp [Ozelius et al. 1988] and

several different polymorphisms have previously been identified [Hinds et al. 1992, Konradi et al. 1992, Black et al. 1991, Brunner et al. 1993a.b.], among them a variable number tandem repeat (VNTR) located in upstream region of the MAOA gene (MAOA-u VNTR) is the only polymorphism associated with transcriptional activity. ‘Allele 3’, which contains four repetitive elements, was transcribed at 2.7-4.8 times the level of ‘allele 1’, which contains three repetitive elements [Sabol et al. 1998]. In addition, those carrying ‘allele 3’ showed significantly more serotonergic responsivity in the central nervous system (CNS) [Manuck et al. 2000]. Moreover, females with the alleles that are associated with more efficient transcription displayed higher concentrations of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) [Jonsson et al. 2000]. Therefore, to clarify the involvement of the MAOA gene in suicide, we examined whether this functional MAOA polymorphism is associated with suicide using completed suicide subjects.

MATERIALS AND METHODS

Subjects

The subjects for an association study consisted of 155 completed suicides (107 males: mean age $\pm$ SD, 48.6 ± 16.6 years; 48 females: mean age $\pm$ SD, 47.6 ± 19.9 years). The definition of suicide was based on the results of the medicolegal examination and the police investigation as required by Japanese law. Suicide methods were classified as violent or nonviolent according to Heilä et al. [1997]. Of the suicides, 134 (98 males, 36 females) died by violent methods (i.e., hanging, jumping from a high place, cutting, burning, and

jumping under a vehicle) and 21 (9 males, 12 females) died by non-violent methods (i.e., drug overdose, drowning, and inhaling carbon monoxide). The comparison group consisted of 162 unrelated healthy volunteers (109 males: mean age $\pm$ SD, 45.1 ± 15.3 years; 53 females: mean age $\pm$ SD, 48.4 ± 18.8 years). All subjects were ethnically Japanese. Blood samples of suicide victims were obtained from Department of Legal Medicine, Kobe University School of Medicine, and this study was conducted in accordance with the Ethical Code of the Japanese Society of Legal Medicine.

Identification of MAOA gene polymorphism

DNA was extracted from whole blood by the Sodium Iodide method using a DNA Extractor WB kit (Wako Chemicals, Tokyo, Japan). The genotype of the MAOA-uVNTR polymorphism was determined by the method of Sabol et al. [1998]. Target sequences were amplified using the polymerase chain reaction (PCR) with a Takara PCR Thermal Cycler MP (Takara Shuzo, Kyoto, Japan). The PCR products were separated into 'allele 3', which contains four 30 base pair (bp) repeats and 'allele 1', which contains three 30-bp repeats, by the electrophoresis on a 2% agarose gel and visualized by ethidium bromide staining and UV transillumination.

Statistical methods

The genotype distribution and Hardy-Weinberg equilibrium were tested by chi-square test for goodness of fit. Frequencies of the alleles were compared between the completed suicide and control subjects by using the two-sided Fisher's exact test. Probability differences of $P < 0.05$ were considered statistically significant.

RESULTS

We observed three alleles: the alleles 1,3 and a shorter variant containing two repeats which was not described in European Caucasians [Sabol et al. 1998], but was detected in a Japanese population by Kunugi et al. [1999]. The frequency of the shortest allele was very low. Only one male comparison subject and two female suicide subjects carried this allele. We excluded these subjects from the following statistical analyses.

As shown in Table 1, we detected no significant difference in allele frequencies between male completed suicides and the comparison group ($\chi^2=1.04$, $df=1$, $P=0.34$) or between female completed suicides and the comparison group ($\chi^2=0.85$, $df=1$, $P=0.40$). The genotype distribution in our female samples was in Hardy-Weinberg equilibrium with no difference as compared to the comparison group in female subjects $\chi^2=1.90$, $df=2$, $P=0.387$). Furthermore, we compared the genotype and allele frequencies of the MAOA-uVNTR between 130 violent completed suicides and the comparison group in male or female subjects. No significant differences were found in the genotype distribution or allele

frequencies between either of these groups and the comparison groups in male or female subjects (data not shown).

DISCUSSION

This is the first association study between functional MAOA polymorphism, MAOA-uVNTR polymorphism, and completed suicides. We found no significant difference in the genotype distribution or the allele frequencies of the MAOA-uVNTR polymorphism between completed suicides and the comparison group, for either males or females. We also found no significant difference between the violent completed suicides and the comparison group, for either sex.

In our samples, the number of the male suicide victims was larger than that of the female ones. This result is in line with the report suggesting that the rate of suicide victims is almost universally higher among males compared to females by aggregate ratio of 3.5 to 1 [Word Heath Organization 2001]. Some studies suggest that the rate of brain serotonin metabolism is higher in females than in males [Young et al.1980, Chugani et al. 1998]. Moreover, females with genotypes containing ‘allele 3’, which is reported to induce a more effective monoamine oxidase transcription [Sabol et al. 1998], were found to have higher levels of HVA and 5-HIAA, but males with this allele were not found to have higher levels of these monoamine metabolites [Jonsson et al. 2000]. Males might have lower serotonergic activity than females, which might be one of the risk factors of suicide.

Our results indicated that the MAOA-uVNTR polymorphism is unlikely to be

involved in the biological susceptibility to suicide, or aggression and/or impulsivity that are associated with suicide. To clarify the genetic influence of abnormal neurotransmission on suicide, further studies are needed to determine whether polymorphisms of other candidate genes related to aggression and impulsivity are associated with suicide.

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Table 1. Allele and Genotype Frequencies of the MAOA-uVNTR Polymorphism between Completed Suicides and Comparison Groups

	<u>Male</u>		<u>Female</u>	
	Completed suicides	Comparison group	Completed suicides	Comparison group
	(n=107)	(n=108)	(n=46)	(n=53)
Alleles				
allele 1 (%)	54 (50%)	62 (57%)	53 (58%)	54 (51%)
allele 3 (%)	53 (50%)	46 (43%)	39 (42%)	52 (49%)
Genotypes				
allele 1 / allele 1 (%)	-	-	15 (33%)	16 (30%)
allele 1 / allele 3 (%)	-	-	23 (50%)	22 (42%)
allele 3 / allele 3 (%)	-	-	8 (17%)	15 (28%)

Male, allele frequencies: $\chi^2=1.04$, df=1, P=0.34

Female, genotype distribution: $\chi^2=1.90$, df=2, P=0.387; allele frequencies: $\chi^2=0.85$, df=1, P=0.40