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Association between Catechol-*O*-Methyltransferase Functional Polymorphism and Male Suicide Completers

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Suicide has been suggested to involve catecholaminergic dysfunction and to be related to genetics. Catechol-*O*-methyltransferase (COMT) 158Val/Met polymorphism (GenBank Accession No. Z26491) is a polymorphism of the gene encoding COMT, a major enzyme in catecholamine inactivation. The COMT 158Val/Met polymorphism affects COMT activity, that is, the alleles encoding Val and Met are associated with relatively high and relatively low COMT activity, respectively. In this study, we hypothesized that the COMT 158Val/Met polymorphism is associated with suicide. The study population consisted of 163 suicide completers (112 males and 51 females). We found that the genotype distribution of the COMT 158Val/Met polymorphism was significantly different between male suicide completers and male controls ($p = 0.036$), while the frequency of the Val/Val genotype, a high-activity COMT genotype, was significantly less in male suicide completers than in male controls (OR: 0.52; 95% CL: 0.31–0.89; $p = 0.016$). However, this was not the case in females. Our results suggest that the Val/Val genotype is a protective factor against suicide in males.

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INTRODUCTION

Suicide has been suggested to involve catecholaminergic dysfunction and to be related to genetics. Catecholaminergic dysfunction has been observed in suicide. For example, low concentrations of 3-methoxy-4-hydroxyphenylglycol, a metabolite of norepinephrine, and homovanillic acid, a metabolite of dopamine, were observed in the cerebrospinal fluid of suicide attempters (Lester, 1995; Roy *et al*, 1986; Jones *et al*, 1990), and high concentrations of norepinephrine and decreased α2-adrenergic binding were observed in the prefrontal cortex of suicide victims (Arango *et al*, 1993). Genetic factors in suicide have been observed in family, twin, and adoption studies, and were found to be independent of psychiatric disorders (Roy *et al*, 1997).

Catecholaminergic dysfunction in suicide appears to be related to gene polymorphisms in catecholaminergic systems. Catechol-*O*-methyltransferase (COMT) is a major enzyme in catecholamine inactivation. COMT has a polymorphism named COMT 158Val/Met polymorphism (GenBank Accession No. Z26491), in which Val at codon 158 is replaced with Met. The alleles encoding Val and Met are associated with relatively high and relatively low COMT activity, respectively. The Val/Val genotype leads to a level of enzymatic activity three to four times that generated by the Met/Met genotype, while the Val/Met genotype leads to an intermediate activity (Lachman *et al*, 1996).

The COMT 158Val/Met polymorphism has been shown to be associated with suicide-related disorders. For example, the Met allele (low COMT activity) was associated with aggressive behaviors or violent suicide attempts in schizophrenic patients (Strous *et al*, 1997; Lachman *et al*, 1998; Kotler *et al*, 1999; Nolan *et al*, 2000). The Met allele was also associated with depressive disorders (Ohara *et al*, 1998), although other studies did not find such an association (Frisch *et al*, 1999; Kunugi *et al*, 1997b).

We hypothesized, therefore, that the COMT 158Val/Met polymorphism is associated with suicide, independently of psychiatric disorders. To test this hypothesis, we conducted a study of the association between the COMT 158Val/Met polymorphism and suicide completers in a Japanese population.

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Table 1 Genotype and Allele Frequencies of COMT 158Val/Met Polymorphism in Suicide Completers and Controls

	Genotype frequency			Allele frequency	
	Val/Val (%)	**Val/Met (%)**	**Met/Met (%)**	**Val (%)**	**Met (%)**
Suicide completers ($n=163$)	68 (42%)	79 (48%)	16 (10%)	215 (66%)	111 (34%)
Controls ($n=169$)	90 (53%)	61 (36%)	18 (11%)	241 (71%)	97 (29%)
Male suicide completers ($n=112$)	43 (38%)	60 (54%)	9 (8%)	146 (65%)	78 (35%)
Male controls ($n=114$)	62 (54%)	42 (37%)	10 (9%)	166 (73%)	62 (27%)
Female suicide completers ($n=51$)	25 (49%)	19 (37%)	7 (14%)	69 (68%)	33 (32%)
Female controls ($n=55$)	28 (50%)	19 (35%)	8 (15%)	75 (68%)	35 (32%)

METHODS

Subjects

The study population consisted of 163 suicide completers (112 males: mean age $\pm$ SD, 48.68 $\pm$ 16.9 years; 51 females: 47.12 $\pm$ 19.8 years), who were autopsied at the Division of Legal Medicine, Kobe University Graduate School of Medicine. All subjects were ethnically Japanese. The methods of suicide were hanging (80), jumping from heights (49), drug overdose (8), drowning (8), several deep cuts (5), jumping in front of a vehicle (4), burning (3), gas poisoning (2), and other methods (4). Most (155) of the cases were classified as violent suicides according to the criteria proposed by Asberg *et al* (1976). Accurate information about the clinical backgrounds of the suicide completers could not be obtained under our ethical code for genetic studies.

Control subjects (159 males, 223 females) were recruited from the general population of Kobe city area, Japan. All were healthy and of Japanese descent and none manifested psychiatric problems in brief interviews by psychiatrists. To match the age and gender of the suicide subjects, 169 subjects (114 males: 45.33 $\pm$ 15.5 years; 55 females: 48.9 $\pm$ 18.7 years; all unrelated) were randomly selected from the above group. Informed consent was obtained from each control subject. This study was approved by the Ethical Committee for Genetic Studies of Kobe University Graduate School of Medicine.

Genotyping

Peripheral blood was drawn from suicide completers and controls, and leukocyte DNA was extracted for genotype determination. The genotypes of the COMT 158Val/Met polymorphism were determined by the method of Daniels *et al* (1996).

Statistical Analyses

The genotype distribution and Hardy–Weinberg equilibrium were tested with the χ^2 test for quality of fit. Comparisons of the genotype or allele frequencies between groups were performed with a χ^2 test. The level of significance was set at $p=0.05$.

RESULTS

Table 1 shows the genotype and allele frequencies of the COMT 158Val/Met polymorphism in suicide completers and control subjects. There is a strong trend towards deviation from Hardy–Weinberg equilibrium in the male completers ($\chi^2=3.6$; df = 1, $p=0.057$), while the genotype distributions in male/female controls and female suicide completers are in Hardy–Weinberg equilibrium. The allele frequencies in the controls were similar to those previously established for a Japanese population (Kunugi *et al*, 1997a; Ohmori *et al*, 1998; Ohara *et al*, 1998).

When the results for both genders were combined, the genotype distribution tended to be different between suicide completers and controls, although the difference was not significant ($\chi^2=5.4$; df = 2, $p=0.068$). The allele frequencies were not different between suicide completers and controls ($\chi^2=2.2$; df = 1, $p=0.14$). Similar results were obtained when only the violent suicide completers (155 of 163 subjects) were considered (data not shown).

In males, the genotype distribution was significantly different between suicide completers and controls ($\chi^2=6.7$; df = 2, $p=0.036$). The genotype distribution of male suicide completers is also significantly different from controls of both genders combined ($\chi^2=8.40$; df = 2, $p=0.015$, statistically significant tests are those having p values less than 0.017, alpha = 0.05/3). The Val/Val genotype appeared less frequently in male suicide completers than in male controls. The Odds ratio for the Val/Val genotype *vs* the other genotypes was 0.52 (95% CL: 0.31–0.89; $p=0.016$) in male suicide completers. The Val/Met genotype appeared more frequently in male suicide completers than in male controls. The Odds ratio for the Val/Met genotype *vs* the other genotypes was 1.98 (95% CL: 1.16–3.37; $p=0.012$) in male suicide completers. In allele frequencies, the Val allele tended to appear less frequently in male suicide completers than in male controls ($\chi^2=3.08$; df = 1, $p=0.080$).

Among females, no significant differences were found between suicide completers and controls in either genotype distribution ($\chi^2=0.086$; df = 2, $p=0.96$), or in allele frequencies ($\chi^2=0.007$; df = 1, $p=0.93$).

DISCUSSION

This is the first study to examine the association between the COMT 158Val/Met polymorphism and suicide completers. We found that the Val/Val genotype, a high-activity COMT genotype, appeared less frequently in male suicide completers than in male controls. Among males, the risk for suicide in the Val/Val genotype carriers was only about half that in other genotype carriers (Odds ratio 0.52). However, this was not the case in females. Consequently, our results suggest that (1) the Val/Val genotype is a factor that protects against suicide, and (2) the COMT 158Val/Met polymorphism is associated with suicide, specifically in males.

Our finding that the Val/Val genotype is a factor that protects against suicide implies that the other genotypes including the Met allele, a low-activity COMT allele, increase suicide risk. This generally supports the results of previous reports that the Met allele is associated with suicide-related disorders (Ohara *et al*, 1998; Strous *et al*, 1997; Lachman *et al*, 1998; Kotler *et al*, 1999; Nolan *et al*, 2000). In our study, the Met allele tended to appear more common in suicide completers, although it did not reach statistical significance. The higher frequency of the Met allele was mainly due to the increased Val/Met genotype rather than to an increased Met/Met genotype. Why the Met/Met genotype did not increase is not clear. One possibility is that the frequency of the Met/Met genotype in our Japanese subjects is so low that the sample size is insufficient to detect a difference of the Met/Met genotype frequencies between suicide completers and controls. The frequency of the Met allele in Japanese subjects (approximately 0.3) is lower than that in Caucasian subjects (approximately 0.5) (Palmatier *et al*, 1999). Furthermore, in another Japanese study, the Val/Met genotype appeared more frequently in schizophrenics than in the controls, while the frequency of the Met/Met genotype was not significantly different between the two groups (Ohmori *et al*, 1998).

Our finding that the COMT 158Val/Met polymorphism is associated with suicide specifically in males implies that this polymorphism affects catecholaminergic systems differently in males and females. One possible explanation for the gender-specific association is that estrogen in females modulates neurotransmission and neuronal excitability of catecholaminergic systems (Balthazart *et al*, 1996). In previous studies, the COMT 158Val/Met polymorphism has been gender-specifically associated with several neuropsychiatric disorders: obsessive–compulsive disorders (Karayiorgou *et al*, 1999), narcolepsy (Dauvilliers *et al*, 2001), and attention deficit hyperactivity disorder (Qian *et al*, 2003). Moreover, the Met allele has been associated with violent suicide attempts specifically in male schizophrenic patients (Nolan *et al*, 2000).

In our study, the genotype distribution in the male suicide completers tended to deviate from Hardy–Weinberg equilibrium. There is little possibility of genotyping error only in the male suicide completers because the genotype distributions in other groups (male/female controls and female suicide completers) are in Hardy–Weinberg equilibrium. There is also little possibility of false-positive results due to population stratification in our study because the Japanese population is considered ethnically homogeneous due to its geographical and historical isolation (Katoh *et al*, 2002).

Our research contains some limitations. First, psychiatric diagnoses were not available in this study under our ethical code for genetic studies. We cannot completely exclude the possibility that the genotype differences are secondary to the different frequencies of psychiatric disorders and not directly related to risk for suicide. Second, we did not test several SNPs and haplotypes in the COMT gene. A haplotype analysis (Shifman *et al*, 2002) could have detected a smaller effect of the COMT 158Val/Met polymorphism on suicide completers. Third, the sample size of the subjects enrolled may be insufficient. Especially, in the comparison between female suicide completers and female controls, the power of the analysis was calculated to be 0.07. Considering that the COMT 158Val/Met polymorphism might have a very small effect on female suicide completers, we cannot completely exclude the possibility that our failure to find an association between the COMT 158Val/Met polymorphism and female suicide completers is due to a type II error. A more conclusive study with a substantially larger sample size may be required. Despite these limitations, our study provides new evidence regarding a protective factor for suicide.

In conclusion, we propose that the Val/Val genotype of the COMT 158Val/Met polymorphism, a high-activity COMT genotype, is a factor that protects against suicide specifically in males in the Japanese population.

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