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Serotonin 2A receptor gene polymorphism is not associated with completed suicide

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Running title: 5-HT2A receptor gene polymorphism and suicide

Abstract

Several lines of evidence indicate that a serotonergic dysfunction is involved in the biological susceptibility to suicide. Recently, the A–1438G polymorphism of the serotonin 2A (5-HT2A) receptor gene has been suggested to be associated with suicide, but the results are inconsistent. We examined whether the A–1438G polymorphism of the 5-HT2A receptor gene was associated with suicide itself using 151 Japanese completed suicides. No significant difference in genotype distribution or allele frequencies of the polymorphism was found between the completed suicides and the comparison group. We conclude that the A–1438G polymorphism of the 5-HT2A receptor gene is not likely to have a major effect on the biological susceptibility of suicide.

Key words: Suicide; Completed suicide; Genetics; Serotonin 2A receptor gene; Polymorphism; Association study

1. Introduction

Several lines of evidence suggest that a serotonergic dysfunction is involved in the biological susceptibility to suicide, especially in high-lethality suicide. First, the concentration of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin, has been reported to be lower in the cerebrospinal fluid (CSF) in higher lethality attempted suicides (Asberg et al., 1976 & Mann et al., 1997). Second, in healthy people, fenfluramine induces an increase in prolactin secretion, but in suicide attempters with a higher degree of lethality, the increase is more blunted (Malone et al., 1996). Because prolactin secretion is an indicator of central serotonergic function (Quattrone et al., 1983), the results of Malone et al. suggest some dysfunction in the serotonergic system in suicide attempters.

Because family, twin, and adoption studies have implicated genetic factors in suicide (Wender et al., 1986 & Roy et al., 1991), genes encoding proteins involved in the serotonergic system may be associated with suicide. An alteration of the density of the serotonin 2A (5-HT2A) receptor has been demonstrated in cortical and subcortical regions in postmortem brains of suicide victims (Gross-Isseroff R et al., 1998). Therefore, the 5-HT2A receptor gene is a prime candidate as a source of serotonergic dysfunction. Recently, Du et al. (2000) have reported that the T102C polymorphism of the 5-HT2A receptor gene was associated with suicidal ideation in subjects with major depressive disorder and they suggested the T102C polymorphism might confer increased risk of suicidality independent of psychiatric diagnoses. However, no association has been reported between the T102C

polymorphism and suicide victims (Du et al., 1999 & Bondy et al., 2000). As for the T102C polymorphism of the 5-HT2A receptor gene, which is in almost complete linkage disequilibrium with the T102C polymorphism (Spurlock G et al, 1998), Turekei et al. (1999) also reported that there was no association between the A–1438G polymorphism and completed suicides. Thus, it is still unclear whether the A–1438G/ T102C polymorphism of the 5-HT2A receptor gene is associated with suicide or not.

Completed suicides are more homogeneous in terms of higher-lethality and are thought to be more influenced by serotonergic mechanisms than attempted suicides. Therefore, we examined whether the A–1438G of the 5-HT2A receptor gene was associated with suicide using 151 completed suicides.

2. Materials and Methods

2.1. Subjects

The subjects for an association study consisted of 151 completed suicides (106 males: mean age ± SD, 49.1 ± 17.1 years; 45 females: mean age ± SD, 45.8 ± 19.2 years), all of which were ethnically Japanese. 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 methods (e.g., hanging, jumping from a high place, cutting, burning, and jumping under a vehicle) or nonviolent methods (e.g., drug overdose, drowning, and inhaling carbon monoxide) according to Heilä et al. (1997). Of the suicides, 132 (96 males, 36 females) died by violent methods and 19 (10 males, 9

females) died by non-violent methods. Prior to their deaths, forty-two of the completed suicides had been examined using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Each of 42 subjects was diagnosed with a single disorder as follows: 23 had mood disorders, 13 had schizophrenia, 2 had substance-related disorders, 1 had dementia, 1 had epilepsy, 1 had a borderline personality disorder, and 1 had an obsessive-compulsive disorder. Control subjects were recruited from the general population. All the control subjects were volunteers. One hundred sixty-three living comparison subjects (108 males: mean age ± SD, 44.9 ± 15.3 years; 55 females: mean age ± SD, 48.4 ± 18.8 years) were randomly selected from 386 control subjects for matching the age and the sex to the completed suicide samples. The control subjects, like the suicide victims, were ethnically Japanese.

Blood samples of suicides were obtained from the Department of Legal Medicine, Kobe University School of Medicine. This study was conducted in accordance with the ethical code of the Medico-Legal Society of Japan (1997).

2.2. Identification of 5-HT2A receptor gene polymorphisms

DNA was extracted from whole blood by the sodium iodide method using a DNA Extractor WB kit (Wako Chemicals, Tokyo, Japan). Genotyping for the A -1438 G polymorphism of the 5-HT2A receptor gene was performed based on the procedure of Collier et al. (1997). 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 digested with *Hpa*・, then electrophoresed on a 2% agarose gel. DNA was visualized by ethidium bromide staining and UV transillumination. The G allele was cleaved into 244 bp and 224 bp fragments by *Hpa*・, whereas the A allele was not digested.

2.3. Statistical methods

The genotype distribution and allele frequencies of the polymorphism were compared between the completed suicides and comparison subjects by using a chi-square test. P less than 0.05 was considered statistically significant.

3. Results

Table1 shows the genotype distribution and allele frequencies of the A–1438G polymorphism of the 5-HT2A receptor gene. The genotype distributions in both groups were in Hardy-Weinberg equilibrium and were similar to those among other Japanese populations previously found by other investigators (Sasaki et al.1996, Zhang et al.1997, Nakamura et al. 1999, Yamada et al. 2000).

The distribution of the A–1438G polymorphism showed no significant difference between the completed suicides and the comparison group. Even when the AA or the GG genotype of the A–1438G polymorphism was assumed to be a risk factor for suicide, no significant difference was observed between the completed suicides and the comparison group (data not shown).

4. Discussion

We performed an association study between the A–1438G polymorphism of the 5-HT2A receptor gene and 151 completed suicides independent of psychiatric diagnosis. We found no significant difference in the genotype distribution or the allele frequencies of the A–1438G polymorphism between completed suicides and the comparison group. We also identified the genotypes of the T102C polymorphism of the 5-HT2A receptor gene in all the samples and certified that the A–1438G polymorphism is in almost complete linkage disequilibrium with the T102C polymorphism in our Japanese samples (data not shown). Therefore, our results showed that the A–1438G/T102C polymorphism was not associated with suicide victims, and are in line with the results of Du et al. (1999), Turekei et al. (1999) and Bondy et al. (2000). In contrast, our data in suicide victims are in disagreement with the recent report of Du et al. (2000) that the allele –1438G/102C was significantly associated with suicidal ideation in major depressive disorder.

The conflicting findings concerning the association between the A–1438G/T102C polymorphism and suicidality may be due to various reasons, such as a weakness of case-control studies over incomplete penetrance or ethnic stratification. In this study, the power of the analysis was calculated 0.35 (Cohen's, 1988). Considering that the 5-HT2A receptor gene locus might have a small effect on suicide, we cannot completely exclude the possibility that our failure to find an association between the A–1438G/T102C polymorphism and suicide is due to a type II error. The allele frequencies of the A–1438G/ T102C polymorphism seem to be ethic–dependent (Tsai et al. 1999). In studies of Japanese

subjects, the frequencies of allele –1438A /102T is generally increased over allele –1438G/102C (Sasaki et al.1996, Zhang et al.1997, Nakamura et al. 1999, Yamada et al. 2000). In contrast, in studies of Caucasian subjects, the opposite frequencies were obtained: the frequency of –1438G/102C is higher than that of allele –1438A /102T (Erdmann et al. 1996, Verga et al 1997, Holmes et al.1998, Joober et al. 1999, Bondy et al.2000). However, Du et al.(2000) found a slightly higher frequency of the –1438A /102T allele than the –1438G/102C allele, even though their subjects were Caucasian. They also found that the frequency of allele –1438G/102C was significantly higher in depressed subjects with suicidal ideation.

Another reason for the discrepancy between our results and those of Du et al. (2000) may be due to a difference in subjects: Du et al. studied depressive patients with suicidal ideation, while we studied completed suicides. The A–1438G/T102C polymorphism of the 5-HT2A receptor gene may associate with suicidal ideation, but may not associate with completed suicide. We conclude that the A–1438G/T102C polymorphism of the 5-HT2A receptor gene is unlikely to be involved in the biological susceptibility to suicide. To clarify the genetic influence of abnormal neurotransmission on suicide itself, a larger number of the suicide subjects and further study is needed to determine whether the polymorphism of other candidate genes in the serotonergic system is associated with completed suicides.

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Table 1

Genotype distribution and allele frequencies of the A–1438G polymorphism of the 5-HT2A receptor gene in completed suicides and the comparison group

	Completed suicides (n=151)	Comparison group (n=163)
Genotypes		
AA	34 (23%)	42 (26%)
AG	77 (51%)	85 (52%)
GG	40 (26%)	36 (22%)
Alleles		
A	145 (48%)	169 (52%)
G	157 (52%)	157 (48%)

There was no significant difference between the suicide victims and the comparison group in either the genotype distribution (• ^{2}=0.99, df=2, p=0.61) or the allele frequencies (• ^{2}= 0.92, df=1, p=0.34).

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