

Sexually Dimorphic Relationship of a 5-HT_{2A} Promoter Polymorphism with Obsessive-Compulsive Disorder

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Background: *In an earlier analysis of 73 subjects from this study, the reduced activity catechol O-methyltransferase variant was shown to be associated with obsessive-compulsive disorder in men only. We hypothesized that the 5-HT_{2A} promoter polymorphism, -1438G>A, previously associated with anorexia nervosa, would be more abundant in women with obsessive-compulsive disorder.*

Methods: *One hundred and one Caucasian obsessive-compulsive disorder patients (48 women, 53 men) and 138 control subjects (77 women, 61 men), were genotyped. DSM-III-R psychiatric diagnoses were assigned based on the SCID-I.*

Results: *As hypothesized, the -1438A allele frequency was higher in obsessive-compulsive disorder women (.57) than female control subjects (.42) ($p = .015$). The genotype frequencies were also significantly different ($p = .020$). Allele frequencies did not differ between male obsessive-compulsive disorder patients (.44) and male control subjects (.41).*

Conclusions: *We have found that a 5-HT_{2A} promoter polymorphism is associated with obsessive-compulsive disorder in women but not in men, strengthening the argument that there may be fundamental gender differences in the genetic susceptibility to obsessive-compulsive disorder. Biol Psychiatry 2001;49:385-388 © 2001 Society of Biological Psychiatry*

Key Words: Obsessive-compulsive, gender, genes, serotonin, receptor

Introduction

Obsessive-compulsive disorder (OCD) is a disabling illness characterized by time-consuming, intrusive, recurrent obsessions and compulsions that cause marked distress and significant life-impairment. Symptoms are similar across cultures (Weissman et al 1994). Obsessive-

compulsive disorder is almost equally common in both genders, with a lifetime prevalence of 2.5%; however, male subjects have a somewhat earlier mean age of onset (21 years) compared with female subjects (24 years) (Antony et al 1998). Men have a higher frequency of obsessions with exactness and symmetry (Leckman et al 1997), sexual obsessions, and odd rituals (Lensi 1996), and anxious or meticulous personality traits (Castle et al 1995). Women have a higher frequency of aggressive obsessions at illness onset (Lensi 1996). Childhood onset OCD is associated with more checking and tics or ticlike compulsions (Pigott 1998), and may be a more severe form of the disease, particularly in male subjects (Flament et al 1988). Obsessive-compulsive disorder is familial, with a relative risk of 4-15 (Nestadt et al 2000; Pauls et al 1995; Sobin and Karayiorgou 1999). Heritability studies have been small in size and provide only modest evidence for differential concordance of monozygotic (MZ) and dizygotic (DZ) twins (Sobin and Karayiorgou 1999). An analysis of 14 OCD twin studies, including 80 MZ and 29 DZ twin pairs, found an MZ:DZ ratio of 2.19:1 (Billett et al 1998). Personality traits associated with OCD are also heritable; obsessiveness has a heritability of 0.47 (Clifford 1984).

It is likely that in a heterogeneous disorder such as OCD, common functional genetic variants influencing the expression of neurotransmitters will contribute to vulnerability or phenotype; however, the effects of genes may not be equal in men and women. Catechol O-methyltransferase (COMT) and monoamine-oxidase A (MAOA) are major enzymes involved in the metabolism of dopamine, noradrenaline, and adrenaline. A transmission disequilibrium test analysis of 110 nuclear OCD families revealed that both a reduced-activity COMT variant and high activity MAOA variant were associated with OCD in men but not women (Karayiorgou et al 1999). This study replicated the results of an earlier association analysis (Karayiorgou et al 1997). The 73 OCD patients from this earlier association analysis are part of the larger data set that comprises our study.

The effective pharmacotherapies for OCD and some genetic evidence (McDougle et al 1998) support a role for genetic variation of serotonin (5-HT) transmission in

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Table 1. Gender Distribution of 5-HT_{2A} Promoter Polymorphism -1438G>A in Patients with Obsessive–Compulsive Disorder (OCD) and Control Subjects

	Genotype frequency			Allele Frequency	
	A/A	A/G	G/G	A	G
OCD women (<i>n</i> = 48)	18 (.37)	19 (.40)	11 (.23)	55 (.57)	41 (.43)
OCD men (<i>n</i> = 53)	11 (.21)	25 (.47)	17 (.32)	47 (.44)	59 (.56)
Control women (<i>n</i> = 77)	12 (.16)	40 (.52)	25 (.32)	64 (.42)	90 (.58)
Control men (<i>n</i> = 61)	8 (.13)	33 (.54)	20 (.33)	49 (.40)	73 (.60)

χ^2 test for differences in allele frequency: female OCD vs. female control subjects; $\chi^2 = 5.869$, $p = .015$; female OCD vs. male OCD, $\chi^2 = 3.381$, $p = .066$. χ^2 test for differences in genotype frequency: female OCD vs. female control subjects, $\chi^2 = 7.811$, $p = .020$; female OCD vs. male OCD, $\chi^2 = 3.555$, $p = .169$.

OCD. The activation of postsynaptic 5-HT_{2A} and/or 5-HT_{2C} receptors may be important for the improvement of OCD symptoms after treatment with 5-HT re-uptake inhibitors (Greenberg et al 1998). Studies in OCD patients showing blunted prolactin and/or cortisol responses to 5-HT receptor agonists suggest postsynaptic impairment (Bastani et al 1990; Hollander 1992). The results of one study (Monteleone et al 1997) suggest that the postsynaptic impairment may be gender-specific: plasma cortisol response was significantly reduced only in female OCD patients and not in control subjects.

The 5-HT_{2A} promoter polymorphism, -1438G>A, has been associated with anorexia nervosa (AN) (Collier et al 1997; Enoch et al 1998; Sorbi et al 1998) in Caucasian women. Obsessive–compulsive disorder and AN are often comorbid (Jarry et al 1996), and AN and OCD patients tend to have personality traits in common, such as high harm avoidance, perfectionism, and obsessionality (Kaye et al 1992). For OCD itself, we reported an increased -1438A allele frequency, comparable to that in AN (Enoch et al 1998).

Because of the comorbidity and certain shared personality characteristics in women with OCD and AN, as well as the evidence reviewed above for serotonergic differences between men and women with OCD, we hypothesized that the 5-HT_{2A} promoter polymorphism -1438G>A would be more strongly associated with OCD in women than in men.

Methods and Materials

Patients meeting lifetime criteria for OCD were recruited from the outpatient clinic, a tertiary treatment center, of the National Institute of Mental Health (NIMH) (Bethesda, MD, USA). The control subjects were volunteers recruited from the local general population, independent of psychiatric diagnosis. All patients and control subjects were Caucasian and genetically unrelated. All study participants gave informed consent under human research protocols approved by the Institutional Review Boards of NIMH and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Venous blood was obtained from patients and control subjects.

Diagnoses for all subjects were made according to criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) following the (SCID-I) (Structured Clinical Interview for DSM-IV Axis I Disorders) (NIMH) or the SADS-L (Structured Clinical Interview for Affective Disorders and Schizophrenia-Lifetime Version) (NIAAA).

There were 101 patients with OCD: 48 women and 53 men. There was no gender difference in recruitment methodology. The mean age of women was 41.7 years (SD = 11.9), and men was 39.7 years (SD = 9.2). The age of onset of OCD was determined, retrospectively. As the interview was often several decades after OCD onset, this information was regarded as approximate. Women and men had the same mean age of onset: 14.8 years (SD = 9.0) and 13.1 years (SD = 7.2), respectively.

The control subjects were derived from two sources:

1. Thirty-eight volunteers (18 men, 20 women), recruited from the general population by the Laboratory of Clinical Science (LCS), NIMH and screened by the SCID-I; none had OCD. The mean ages were 34.6 years (SD = 12.3) for the women and 34.8 years (SD = 11.2) for the men.
2. One hundred volunteers (43 men, 57 women), recruited from the general population by the Laboratory of Neurogenetics (LNG), NIAAA. The mean ages were 43.4 years (SD = 13.6) for women and 45.7 years (SD = 12.7) for men. One-hundred five volunteers were originally interviewed with the SADS-L; five met DSM-III-R criteria for OCD and were excluded.

We followed previously published methods for genotyping DNA samples for the 5-HT_{2A} -1438G>A polymorphism (Enoch et al 1999).

The χ^2 test was used to compare genotype and allele frequencies between OCD patients and control subjects. We reasoned that because of the comorbidity and shared characteristics of OCD and AN women, and some evidence for gender-differences in 5-HT transmission, the 5-HT_{2A} promoter polymorphism would be associated with OCD in women but not men. We therefore did no analysis of the group of OCD patients as a whole, and hence a Bonferroni correction was not required.

Results

From Table 1 it can be seen that, as hypothesized, the frequency of the -1438A allele of the 5-HT_{2A} promoter

polymorphism is greater in women with OCD (.57) than in women without OCD (.42) ($p = .015$). The genotype frequencies are also significantly different ($p = .020$).

There is no difference in allele frequency between men with OCD (.44) and without OCD (.41). The genotype frequencies also did not differ between these groups.

The genotype distributions of OCD patients and control subjects were tested by χ^2 analyses and were found to be in Hardy-Weinberg equilibrium ($p > .71$).

Discussion

We have found that the 5-HT_{2A} -1438G>A promoter polymorphism is associated with OCD in Caucasian women but not in men. This is consistent both with the findings that OCD has different clinical features in men and women, and with the association of -1438G>A with AN. As previously discussed, AN is predominantly female, shares some personality traits with OCD, and the two disorders are often comorbid.

Our OCD patients had a lower mean age of onset (14 years) than OCD subjects ascertained from the general population (23 years) (Antony et al 1998). Earlier onset is associated with greater illness severity, and this is consistent with the disease profile for patients presenting at a tertiary treatment center such as NIMH. This study's positive genetic findings may therefore be representative of a more extreme group of individuals with OCD.

A sexually dimorphic association has already been found between OCD and the genes for COMT and MAOA, implicated in dopaminergic and adrenergic pathways. Those associations were with male OCD patients (Karayiorgou et al 1997, 1999). The majority of the patients in our study, 73/101 (42/53 male subjects, 31/48 female subjects), had previously been genotyped for the COMT association analysis (Karayiorgou et al 1997). Our finding of an association between a gene in the serotonergic pathway and female OCD patients in this largely identical group of subjects strengthens the argument that there are fundamental gender differences in genetic susceptibility to OCD.

It is unknown whether the -1438G>A 5-HT_{2A} promoter polymorphism is functional. The only data available so far are negative, but limited (Spurlock et al 1998); however, -1438G>A is in complete linkage disequilibrium with T102C (Spurlock et al 1998), a silent mutation located in the coding region. In the 1500+ nucleotides which lie between these two closely linked polymorphisms there will be multiple sites involved in the regulation of 5-HT_{2A} expression; for example, several promoter transcription initiation sites and a possible silencer of gene expression are localized here (Zhu et al 1995). Hence, -1438G>A

could be in linkage disequilibrium with an as yet unknown functional polymorphism in this region.

In conclusion, we have found that the -1438G>A 5-HT_{2A} promoter polymorphism is associated with OCD in Caucasian women but not men. However, this is only a modest-sized study, and although subjects were matched with control subjects, and the allele frequencies in our control subjects corresponded to those generally found in other population samples (Collier et al 1997; Spurlock et al 1998), there is always a possibility of false positives in case control studies due to population stratification. Therefore, these results should be tested with large intra-family (e.g., TDT) analyses.

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