



Association between the dopamine D₂ receptor TaqI A2 allele and low activity COMT allele with obsessive–compulsive disorder in males

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Abstract

Background: Mounting evidence suggests the involvement of the dopamine system in the pathophysiology of obsessive–compulsive disorder.

Method: The relationship of the dopamine D₂ receptor (DRD2) TaqI A, and catechol-O-methyltransferase (COMT) N1all High/Low activity polymorphism to obsessive–compulsive disorder (OCD) was examined in a sample of 150 patients and 150 controls.

Results: OCD patients did not show significant differences in genotype distribution and allele frequency for polymorphisms investigated relative to controls. However, when the sample was stratified by gender, there was a trend to a significant predominance of the DRD2 A2A2 genotype ($p=0.049$), and a higher frequency of the DRD2 A2 allele ($p=0.020$) and low-activity COMT allele ($p=0.035$) in male OCD patients compared to male controls. In addition, we observed an association of the DRD2 A2A2 genotype in patients with an early onset of disease (≤ 15 years) ($p=0.033$).

Conclusions: Our findings replicate previous reports and provide support for a potential role of the COMT and DRD2 locus in subgroup of male, early onset patients with OCD.

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1. Introduction

OCD is a common and severe, but still under-recognized, psychiatric disorder. Family and twin studies have provided evidence for the involvement of a genetic factor in OCD (Nestadt et al., 2000; Pauls et al., 1995). Although very little is known about the disorder's pathogenesis, both serotonergic and dopaminergic pathways may be implicated. A role for dopamine in the pathophysiology of OCD is supported by the observation that pharmacological agents enhancing dopamine release such as methylphenidate, cocaine, and bromocriptine may induce obsessive–compulsive symptoms (Crum and Anthony, 1993; Jenike et al., 1990; Satel and McDougle, 1991). In addition, evidence has accumulated that augmentation strategies with antipsychotics are beneficial for treatment-refractory OCD patients (Denys et al., 2002; McDougle et al., 1994, 2000). Recently, SPECT studies provided evidence for higher dopamine transporter densities and lower dopamine D₂ binding ratios in patients with OCD relative to controls (Denys et al., 2003; Kim et al., 2003; van der Wee et al., 2001). The combined results of these receptor-binding studies provide circumstantial *in vivo* evidence for an increased dopaminergic activity in OCD patients.

Catechol-*O*-methyl transferase (COMT) is an enzyme that has a crucial role in the elimination of dopamine. Since COMT is involved in the inactivation of dopamine, and higher dopamine levels may be implicated in OCD, the COMT gene is an attractive candidate for OCD. The G→A transition in codon 158 of the COMT gene results in a valine to methionine substitution and is associated with a three- to fourfold decrease in enzyme activity (valine=high-activity, methionine=low-activity) (Lotta et al., 1995). It has already been reported by Karayiorgou et al. (1997) that the low-activity COMT (COMT L) allele occurs significantly more frequently in male OCD patients, but opposing results have also been obtained (Erdal et al., 2003; Karayiorgou et al., 1999; Ohara et al., 1998). In addition, one might theorize that lower densities of the D₂ receptor in OCD patients are caused by genetic factors. The A1 allele of *TaqI* A polymorphism in the D₂ receptor (DRD2) gene locus has been suggested to be associated with reduced DRD2 receptor densities (Hitzemann, 1998; Jonsson et al., 1999). Data on the DRD2 *TaqI* A polymorphism in OCD are limited, but Nicolini et al. found a higher frequency of the DRD2 *TaqI* A2 allele in a small subgroup of OCD patients (*n* = 12) with tics, when compared to controls (Nicolini et al., 1996).

In light of the putative role of the dopamine system, and in particular the dopamine D₂ receptor in OCD, we tested the frequency of alleles and the distribution of genotypes of the DRD₂ receptor *TaqI* A and of COMT genes in an OCD sample of 150 patients. As a control population, we tested 150 ethnically matched Caucasian subjects. As there is evidence for gender specificity of the D₂ receptor and COMT gene and because previous findings have suggested gender differences in the clinical manifestation of OCD, males and females were analyzed separately (Castle et al., 1995; Kaasinen et al., 2001; Karayiorgou et al., 1999; Lensi et al., 1996). We firstly hypothesized that OCD patients would have higher frequencies of the COMT L allele, resulting in higher synaptic dopamine levels. Secondly, we hypothesized that

OCD patients would have higher frequencies of the DRD₂ receptor *TaqI* A1 allele, resulting in lower synaptic D₂ receptor density.

2. Material and methods

2.1. Study sample

The patient sample comprised 159 unrelated patients with OCD from consecutive referrals to the anxiety research unit of the department of psychiatry at the University Medical Centre Utrecht, who gave written informed consent for participation in this study that had been approved by the University of Utrecht Medical Ethical Review committee (Utrecht, The Netherlands). All patients were diagnosed with OCD according to DSM-IV criteria and the M.I.N.I., a clinical and structured interview, was used to confirm the diagnosis (Sheehan et al., 1998). Severity of obsessive–compulsive symptoms was rated with the Y-BOCS, depression with the HAM-D, and anxiety with the HAM-A (Goodman et al., 1989; Hamilton, 1959, 1960). Information on family history was obtained by direct interviews with the patients and the presence of vocal and/or motor tics was assessed during the clinical interview. The control sample was composed of 151 ethnically matched and unrelated Caucasian subjects, selected among healthy volunteers.

2.2. Genotyping and data analysis

Blood samples were collected from each subject and frozen at –80 °C. DNA was extracted from 10-ml samples of peripheral blood according to standard procedures. The total number of subjects genotyped for the genes in this study was 310. All subjects were genotyped at the University of Ghent (Belgium) based on a coded identification number. The COMT and DRD2 genotyping was performed following a standard protocol.

2.3. COMT

For detection of the *Nla*III polymorphism in codon 158, the following oligonucleotide primers were used (5'–TCACCATCGAGATCAACCCC–3' and 5'–ACAACGGGTCAGGCATGCA–3') to amplify a 96-bp region comprising the Val158Met polymorphism site. The PCR reaction was performed under the following conditions: 94 °C for 30 s, 64 °C for 1 min, 72 °C for 1 min per cycle, for a total of 35 cycles. Digestion of 9 µl of PCR product was accomplished by incubation for 3 to 4 hours with 5 units of *Nla*III restriction enzyme at 37 °C. Digestion with *Nla*III yields either two fragments (13 bp and 83 bp) for the Val-allele (COMT H) or three fragments (13 bp, 18 bp and 65 bp) for the Met-allele (COMT L). The fragments were resolved on a 2.5% agarose gel and visualized by ethidium bromide staining (Karayiorgou et al., 1997).

2.4. DRD2

For the detection of the polymorphism in the *TaqA* site in the DRD2 gene the oligonucleotide primers (5'–CCGTCGACGGCTGGC-CAAGTTGTCTA–3' and 5'–CCGTCGACCTTCTGAGTGTCATCA–3') were used to amplify a 310-bp region comprising the *TaqA* site (Grandy et al., 1993). The PCR reaction was performed under the following conditions: 94 °C for 1 min, 50 °C for 1 min, 72 °C for 1.5 min per cycle, for a total of 35 cycles. Digestion of 10 µl of PCR product was accomplished by overnight incubation with 5 units of *TaqI* restriction enzyme at 65 °C. After incubation with *TaqI*, the A1 allele remains intact while the A2 allele is cut into a 130-bp piece and a 180-bp piece. The fragments resulting from the digestion were resolved on a 1.5% agarose gel and visualized by staining with ethidium bromide.

Table 1 Allele frequencies and genotype distribution of the DRD2 *TaqI* A polymorphism

		<i>n</i>	Allele frequencies		<i>p</i> -value	Genotypes			<i>p</i> -value
			A1	A2		A1A1	A1A2	A2A2	
Total sample	Controls	135	0.20	0.80	0.218	5 (3.7%)	45 (33.3%)	85 (63.0%)	0.452
	Patients	141	0.16	0.84		3 (3.7%)	40 (28.4%)	98 (69.5%)	
Males	Controls	67	0.22	0.78	0.020	2 (3.0%)	26 (38.8%)	39 (58.2%)	0.049
	Patients	51	0.11	0.89		–	11 (21.6%)	40 (78.4%)	
Females	Controls	66	0.17	0.83	0.672	3 (4.5%)	17 (25.8%)	46 (69.7%)	0.692
	Patients	88	0.19	0.81		3 (3.4%)	28 (31.8%)	57 (64.8%)	

The association between the distribution of the genotypes and allele frequencies with the subjects, and expected frequencies to assess Hardy–Weinberg equilibrium, were ascertained by cross-tabulation and χ^2 analysis. Considering a partial Bonferroni's correction, the *p* value for statistical significance would be 0.036 with $\alpha=0.05$, 3 tests, *df*=2, and a correlation correction factor of 0.7.

3. Results

The patient sample was slightly skewed towards the female population (63%) with a mean \pm S.D. age at admission of 36.0 ± 11.0 years for both sexes. The mean age at onset of obsessive–compulsive symptoms in our sample was 17.7 ± 8.3 years, with a length of illness of 18.0 ± 11.0 years at entry. Males had a significantly earlier onset of illness than females (15.7 ± 8.0 years and 19.0 ± 8.3 years, respectively) ($\chi^2=5.85$, *df*=1, *p*=0.016). The mean Y-BOCS score for the whole sample was 24.9 ± 5.7 , with a mean HAM-D score of 9.5 ± 5.8 and a mean HAM-A score of 11.6 ± 6.7 . Twenty-seven percent (43 patients) of the sample had a first-degree relative with OCD and nine patients (6 males/3 females) reported comorbid tics at some time in their life.

The genotypic pattern of distribution and the allele frequencies of the DRD2 and COMT polymorphisms are shown in Tables 1 and 2. The representations of the polymorphism of the DRD2 receptor and the COMT gene were similar in patients and controls. No difference in frequencies of any of the alleles was observed between patients and controls. Both groups were in Hardy–Weinberg equilibrium at each locus investigated.

When the sample was stratified by gender, there was a statistically significant predominance of the DRD2 A2A2 genotype in the male patient group ($\chi^2=6.0$, *df*=2, *p*=0.049) and a higher frequency of the DRD2 A2 allele in male patients compared to male controls ($\chi^2=5.4$, *df*=2, *p*=0.020). In addition, a significant association was observed between the frequency of the COMT L allele and male

patients ($\chi^2=4.4$, *df*=2, *p*=0.035). Although the frequency of the COMT LL genotype was higher in male patients (37.5%) compared to male controls (21%), the difference failed to reach statistical significance ($\chi^2=4.6$, *df*=2, *p*=0.10).

4. Discussion

The findings of this study provide evidence for an association between the DRD2 *TaqI* A2 allele and the low-activity COMT allele on the one hand, OCD on the other, in male OCD patients.

Two previous studies have examined the association between the DRD2 *TaqI* A system and OCD. Nicolini et al. found no association in 67 patients with OCD, but observed a higher frequency of the A2 allele in a subgroup of OCD patients with tics (*n*=12) (Nicolini et al., 1996). Billet et al. (1998) did not find an association in a sample of 100 OCD patients either. Since the A1 allele of the DRD2 *TaqI* A system has been found to be associated with a variety of addictive, impulsive and compulsive disorders, the association of the A2 allele with our OCD-sample was unexpected (Comings and Blum, 2000). In addition, we presumed a higher frequency of the A1 allele, as it has been suggested that the A1 allele is associated with a mutation that decreases the D₂ receptor expression. This latter suggestion has been recently confirmed by Pohjalainen et al. (1998), but was contradicted by Laruelle et al. (1998). At the moment, it is still unclear whether or not the A1 allele is associated with lower D₂ expression (Hitzemann, 1998). Since other reports of associations between the A2 allele and similar neuropsychiatric disorders are scarce, the association of the A2 allele in our sample is difficult to interpret. The A2 allele has previously been related to hyperactive and impulsive symptoms in attention deficit hyperactivity disorder (ADHD) in a sample of 166 children and to compulsive smoking habits in 793 subjects (Rowe et al., 1999; Hamajima et al., 2002). Interestingly, the ADHD

Table 2 Allele frequencies and genotype distribution of the COMT polymorphism

		<i>n</i>	Allele frequencies		<i>p</i> -value	Genotypes			<i>p</i> -value
			L	H		LL	LH	HH	
Total sample	Controls	152	0.51	0.49	0.643	39 (25.7%)	77 (50.7%)	36 (23.7%)	0.779
	Patients	158	0.53	0.47		46 (29.1%)	75 (47.5%)	37 (23.4%)	
Males	Controls	79	0.47	0.53	0.035	17 (21.5%)	40 (50.6%)	22 (27.8%)	0.100
	Patients	56	0.60	0.40		21 (37.5%)	25 (44.6%)	10 (17.9%)	
Females	Controls	71	0.56	0.44	0.227	21 (29.6%)	37 (52.1%)	13 (18.3%)	0.440
	Patients	99	0.49	0.51		24 (24.2%)	49 (49.5%)	26 (26.3%)	

sample comprised 81% males, and the association with compulsive smoking was only significant for males. This suggests that the A2A2 genotype of the DRD2 *TaqI* A system, regardless of the diagnosis, is associated with a broad spectrum of impulsive/compulsive symptoms in a gender specific manner. On the other hand, without further evidence of its functional significance, and in the absence of other studies reporting similar associations, our finding of the association of the A2A2 genotype and OCD in male patients warrants replication in other samples, as well as family-based designs.

The COMT locus has been reported to be associated with OCD in several previous studies. Karayiorgou et al. (1997, 1999) found evidence for an association between the low-activity COMT allele and OCD in male OCD patients, in a case-control study and a family-based study, whereas Alsobrook et al. (2002) found evidence pointing to an association between the low-activity COMT allele and OCD in female OCD patients. Niehaus et al. (2001) reported a preponderance of COMT high/low heterozygotes in an Afrikaner population of 54 OCD patients, but did not observe gender differences. Schindler et al. (2000) did not find an association between any particular allele and OCD, but found a tendency for an association with homozygosity at the COMT locus. Ohara et al. (1998) did not find any association in a small sample of 24 Japanese patients and neither did Erdal et al. (2003) in a sample of 59 Turkish patients. A recent meta-analysis of the COMT gene in 144 OCD patients and 337 controls showed insufficient evidence to support an association (Azzam et al., 2002).

On the other hand, since a higher prevalence of the low-activity COMT allele in OCD patients has been established in different independent samples, the finding of an association between COMT and OCD remains interesting. Especially because the results are compatible with the assumption that increased dopamine levels are associated with obsessive–compulsive symptoms. It is possible that subjects with a low-activity COMT genotype have a longer lasting and more effective dopamine release, which makes them more vulnerable to the development of obsessive–compulsive symptoms. On the other hand, this is hard to reconcile with the observation that the association is gender specific. In this regard, it is remarkable that our results are strikingly similar to both reports by Karayiorgou et al. (1997, 1999), providing further evidence to the previously reported gender-selective association between COMT polymorphism and male patients. It is important to emphasize that in our control sample neither the COMT genotype distribution ($\chi^2=4.6$, $df=2$, $p=0.1$), nor the allele frequency ($\chi^2=4.6$, $df=2$, $p=0.1$) differed significantly between males and females. The significance of a gender specific association may not be easily explained. Karayiorgou et al. (1997, 1999) proposed that females have evolved mechanisms to compensate for their lower levels of COMT activity and are therefore less vulnerable to developing OCD in association with a low-activity COMT genotype. On the other hand, as has been noted by Schindler et al. (2000), the specific association in males may be a sampling phenomenon, since males typically demonstrate an earlier onset of OCD than females. In our sample, males (15.7 ± 8.0 years) had a significantly earlier age of onset than females (19.0 ± 8.3 years) and age of onset was significantly correlated with

gender ($r=0.18$, $p=0.033$). Since only 10 out of 54 male patients had an onset of disease later than 21 years, the bias of age of onset cannot be excluded.

To eliminate the possible confounding factor of age of onset, we dichotomized the patient population into an early-onset-group (≤ 15 years ($n=60$)), and a late-onset-group (≥ 21 years ($n=45$)). We found that the low-activity COMT genotype was significantly associated with the early-onset-group (36.7%), relative to late-onset-group (22.7%) ($\chi^2=6.83$, $df=2$, $p=0.033$), although allele frequencies did not significantly differ ($\chi^2=0.13$, $df=1$, $p=0.71$; data not shown). Fifty-five percent of the early-onset-group was female, which suggests that age of onset might be an independent factor in the association with the low-activity COMT genotype. Therefore, it is conceivable that both male gender and early age of onset represent different subgroups in OCD, which are independently related to the COMT gene.

Finally, some limitations of the study should be addressed. First, case-control studies are susceptible to false positive results due population stratification. Population stratification may be a confounding factor in case the individuals are selected from two genetically different populations in different proportions in cases and controls. The risk for population stratification in our study is limited since patients and controls are recruited from the same geographic region and are distributed equally. Second, although our sample is one of largest case-control samples in OCD, our analyses are limited and should be interpreted with caution due to the small number of subjects.

To summarize, this study suggests that DRD2 and COMT genes may be etiologically relevant in OCD, in a gender specific manner, and that early-onset-patients represent a genetically different subgroup. Further analysis of these phenotypic subtypes in larger samples is warranted to confirm our data.

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