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Association of the Val158Met Catechol *O*-Methyltransferase Genetic Polymorphism with Panic Disorder

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Genetic as well as clinical data suggest that catechol *O*-methyltransferase (COMT) is involved in multiple complex psychiatric conditions. Recent studies have described an association between the Val158Met COMT polymorphism and panic disorder. Other recent investigations provide evidence that there are other loci within or nearby the COMT gene that may contribute to the susceptibility to panic disorder. To further evaluate the influence of the Val158Met COMT polymorphism in panic disorder we genotyped this marker in the coding region of the COMT gene and two additional variants (rs737865 and rs165599) in the 5′ and the 3′ region, respectively, in two independent Canadian samples: 121 nuclear families, and 89 cases with matched controls. In the nuclear families, significant transmission disequilibrium for the valine allele was observed between the alleles of the Val158Met COMT polymorphism and panic disorder ($p < 0.01$). A significant excess of the valine allele was found in analysis of the case–control sample ($p < 0.01$). This effect was mainly derived from the subgroup of females. This finding, including the female effect, replicates earlier results in studies of the Val158Met polymorphism in panic disorder. No significant results were found for the other two markers. These results support the hypothesis that the valine allele of the Val158Met COMT polymorphism or a nearby locus is involved in the etiopathogenesis of panic disorder.
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INTRODUCTION

Panic disorder (PD) is a potentially disabling anxiety disorder defined by recurrent unexpected attacks of intense somatic and cognitive symptoms of anxiety, anticipatory anxiety, and phobic avoidance. The disorder is often associated with agoraphobia. This severe psychiatric condition has a life-time prevalence of 1–3% and a female:male ratio among affected of 2:1 (Eaton *et al*, 1994; Weissman *et al*, 1997). Family and twin studies suggest a genetic component in the etiopathogenesis of PD with an estimated heritability of up to 46% (Hettema *et al*, 2001). In genome-wide scans, several possible regions for panic disorder have been identified (Crowe *et al*, 1987; Gelernter *et al*, 2001; Hamilton *et al*, 2003; Knowles *et al*, 1998; Thorgeirsson *et al*, 2003), among them one locus on chromosome 11 in the region of the cholecystokinin-B receptor (CCKBR) gene (Gelernter *et al*, 2001). PD is considered a complex psychiatric disorder as there has been no simple Mendelian pattern of inheritance found in segregation studies (Vieland *et al*, 1996). Many genes of small effect may contribute to the disease susceptibility.

Association studies relating one single polymorphism with panic disorder often show inconclusive results. Nevertheless the COMT gene has been very consistently associated with panic disorder. COMT is an enzyme inactivating catecholamines, including adrenaline, noradrenaline and dopamine (Axelrod and Tomchick, 1958). The COMT gene is located on chromosome 22q11.2. A common nucleotide substitution polymorphism (guanine to adenosine), at the first position of codon 158 of the COMT gene results in a functional amino-acid change from valine to methionine (rs4680). The valine to methionine transition has been reported to be associated with a three- to four-fold difference in thermolability (Lotta *et al*, 1995). The valine allele shows higher COMT activity than the methionine allele (Lachman *et al*, 1996). The high activity allele has been associated with obsessive compulsive disorder (Karayiorgou *et al*, 1997) and phobic anxiety (McGrath *et al*, 2004).

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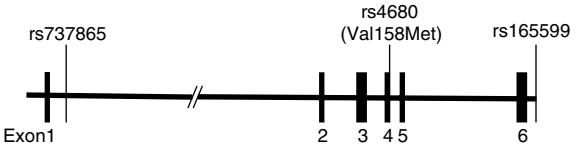

Figure 1 Map of the COMT gene (29 kb) with relative locations of the SNPs (not to scale).

In PD, the COMT Val158Met polymorphism has been investigated in several studies, with realtively high consistency. Recently, two studies reported an association between the high-activity valine allele and PD in Caucasians (Domschke *et al*, 2004; Hamilton *et al*, 2002). In contrast, Woo *et al* (2002) described a significant association ($p = 0.005$) of the low-activity allele in 51 PD patients of Korean origin. An additional study with a larger number of participants did not replicate this result ($p = 0.088$), but showed a borderline significant association ($p = 0.042$) with the low-activity Met/Met genotype in another Korean sample of 178 PD patients (Woo *et al*, 2004).

Recently, three markers of the COMT gene (Figure 1), including the Val158Met variant, were investigated for an association with anxiety-related personality traits in an extensive study of 497 college students (Stein *et al*, 2005). Two of the SNPs showed an association with low extraversion and high neuroticism, particularly in women. In addition, a COMT haplotype was defined by Stein *et al* that was associated with anxiety-related personality traits. In a case–control study the same three variants (rs737865, rs4680 and rs165599) were associated with schizophrenia in a large sample of schizophrenic patients (Shifman *et al*, 2002). Furthermore, Shifman *et al* identified a haplotype including these three SNPs that was strongly associated in another study of schizophrenia by Bray *et al* (2003).

As the COMT gene is a strong candidate gene for PD, we therefore tested the hypothesis of a possible association of COMT polymorphisms with PD in two independent Canadian samples.

METHOD

Subjects

In this study, we investigated two Canadian samples of PD patients. One sample consisted of 121 nuclear families (34 male patients, and 87 female patients) containing 79 complete trios (affected proband with both parents). In seven families at least one unaffected sibling was included. The other sample comprised of 89 cases (female, $n = 59$; male, $n = 30$) and case-matched controls to minimize population stratification. The participants were recruited via referrals or advertising from two university-based anxiety research units. Diagnosis of PD was assessed by a psychiatrist using DSM-IV criteria (American Psychiatric Association, 1994) and independently confirmed by a psychologist using a structured clinical interview (SCID, Structured Clinical Interview for DSM-IV). Ethnicity was determined from a short questionnaire that assesses birthplace of parents and grandparents, as well as primary language and religion. Both samples had the same predomination of European ancestry. The triad sample consisted of 93% European Caucasian, 5% Middle Eastern, and 2% West Indian subjects. The case–control sample included 96% European Caucasians, 1% African American, 1% Asian and 2% other subjects. The control group consisted of healthy individuals responding to local advertisements and screened for absence of major psychiatric disorder. The control subjects were screened by a trained psychiatric research nurse using a Mini-SCID (First *et al*, 1990). The PD patients were carefully matched with controls for age, gender, and ethnicity. Panic disorder was the primary and predominant diagnosis in all cases. Patients with comorbid depression or another anxiety disorder were included in the study as long as the comorbid condition was secondary to and clinically less prominent than PD. Informed written consent was obtained from all participating subjects. The study design complied with the revised Declaration of Helsinki and was approved by the local ethics committees.

Genotyping

Genomic DNA was extracted using standard high salt methods. The three single nucleotide polymorphisms of the COMT gene, rs737865, rs4820 and rs165599, were genotyped using Assays-by-Design® (ABI Applied Biosystems, Foster City, USA). PCR amplification and allelic discrimination were carried out on an ABI Prism 7000 Sequence Detection System (ABI Corporation, USA) using allele specific fluorescent labeled probes.

Statistics

The case–control sample was analyzed with a χ^2 statistic and a significance level set at $p = 0.05$. To correct for multiple testing we applied Bonferroni correction for χ^2 test and p-values were considered statistically significant for $p = 0.02$ in the patient–control group; for the comparison of female patients *vs* male patients, we set the significance level to $p = 0.01$. Fisher's Exact Test was applied when the frequency of any cell of a table was less than five. For the analysis of the nuclear families the transmission disequilibrium test (TDT) (Spielman *et al*, 1993) was used as well as the family-based association test (FBAT) (Laird *et al*, 2000). The latter was employed to allow inclusion of additional relatives. The extended transmission disequilibrium test (eTDT) was used to analyze maternal *vs* paternal transmission (Sham and Curtis, 1995). To estimate the overall effect of the valine allele in the two independent samples of nuclear families and case–controls, we converted the two χ^2 values to the corresponding z-scores, added the z-scores and used the inverse normal method to obtain the overall z-value (Hedges *et al*, 1985). Association analysis and haplotypes frequency estimation was carried out with the program COCAPHASE 2.35 for the case–control sample and TDTPHASE for the small families (Dudbridge, 2003).

RESULTS

The distribution of the genotypes did not differ significantly from those predicted by the Hardy–Weinberg equilibrium in patients and controls or in any subgroups.

The measure of the inter-marker linkage disequilibrium (LD), referred to as D', was calculated for both samples: in the sample of small families for rs787365 and rs4680 $D' = 0.22$, for rs787365 and rs165599 $D' = 0.27$ and for rs4680 and rs165599 $D' = 0.01$; in the case–control sample rs787365 and rs4680 $D' = 0.72$, for rs787365 and rs165599 $D' = 0.23$ and for rs4680 and rs165599 $D' = 0.62$.

The results of the association analysis are summarized in Table 1. The allele frequency of the controls for the Val158Met variant is consistent with recent findings in European Americans (Palmatier *et al*, 2004). An association was observed in the genotype and allele distribution with a relative excess of the valine allele in PD patients (genotype counts: $\chi^2 = 9.92$, df = 2, $p = 0.007$; allele counts: $\chi^2 = 7.71$, df = 1, $p = 0.005$). Analyzing subgroups we found that this effect was mainly due to the group of 59 female PD patients (genotype count: $p = 0.014$; allele count: $\chi^2 = 6.94$, df = 1, $p = 0.008$). There was no significant difference between the male patients ($n = 30$) and the healthy controls. In patients with PD with agoraphobia ($n = 68$) the valine allele was found to be significantly associated with the disease (genotype count: $p = 0.01$) (data not shown). TDT analysis (Table 2) revealed a more frequent transmission of the high-activity valine allele (58 *vs* 28) from the heterozygous parents of the PD patients, providing evidence for a significant allelic association ($\chi^2 = 10.47$, df = 1, $p = 0.005$). Furthermore, the FBAT analysis showed an association between panic disorder and the Val158Met polymorphism ($Z = 2.853$, $p = 0.004$; data not shown in Table 2).

Table 2 TDT for Transmission Disequilibrium between COMT Polymorphisms and Panic Disorder

Variant	Allele count		
rs737865	C	T	
Transmitted	45	31	
Untransmitted	31	45	0.108
rs4680	G	A	
Transmitted	58	28	
Untransmitted	28	58	0.005
rs4680	G	A	
Transmitted	35	31	
Untransmitted	31	35	0.623

Table 1 Allele and Genotype Counts of the COMT Polymorphisms

	Allele count			Genotype count			
Variant	**C**	**T**	***p*-value**	**C/C**	**C/T**	**T/T**	***p*-value**
rs737865							
Patients ($n = 89$)	52	126		7	38	44	
Controls ($n = 89$)	60	118	0.424	11	38	40	0.300
Male patients ($n = 30$)	17	43		2	13	15	
Male controls ($n = 30$)	17	43	0.698	4	9	17	0.715
Female patients ($n = 59$)	35	83		5	25	29	
Female controls ($n = 59$)	43	75	0.157	7	29	23	0.461
	Val(G)	**Met (A)**		**Val/Val**	**Val/Met**	**Met/Met**	
rs4680 (Val/Met)							
Patients ($n = 89$)	91	97		21	49	19	
Controls ($n = 89$)	65	113	0.005	7	51	31	0.007
Male patients ($n = 30$)	31	29		6	19	5	
Male controls ($n = 30$)	25	35	0.272	3	19	8	0.425
Female patients ($n = 59$)	60	58		15	30	14	
Female controls ($n = 59$)	40	78	0.008	4	32	23	0.014
	G	**A**		**G/G**	**G/A**	**A/A**	
rs165599							
Patients ($n = 88$)	60	116		9	42	37	
Controls ($n = 88$)	49	127	0.249	7	35	46	0.394
Male patients ($n = 30$)	21	39		4	13	13	
Male controls ($n = 30$)	18	42	0.697	3	12	15	0.877
Female patients ($n = 58$)	39	77		5	29	24	
Female controls ($n = 58$)	31	85	0.317	4	23	31	0.433

Table 3 Estimated Haplotype Frequencies in a Case Control Sample and a Nuclear Family Sample

			Frequency		
rs737865	**Val158Met**	**rs165599**	**Cases**	**Controls**	***p*-value**
Case control sample					
A	G	G	0.07	0.01	0.002
A	G	A	0.40	0.30	0.039
A	A	G	0.11	0.12	0.966
A	A	A	0.13	0.23	0.010
G	G	G	0.01	>0.01	0.177
G	G	A	0.03	0.04	0.918
G	A	G	0.15	0.14	0.848
G	A	A	0.10	0.15	0.050
					Global *p*-value 0.016
					df = 7
rs737865	**Val158Met**	**rs165599**	**Transmitted**	**Nontransmitted**	***p*-value**
Nuclear family sample					
A	G	G	0.08	0.04	0.284
A	G	A	0.29	0.24	0.265
A	A	G	0.08	0.11	0.266
A	A	A	0.22	0.39	0.001
G	G	G	0.13	0.05	0.017
G	G	A	0.11	0.07	0.094
G	A	G	0.03	0.07	0.114
G	A	A	0.06	0.03	0.267
					Global *p*-value 0.003
					df = 7

Combiniation of the *z*-scores of the two independent samples yields a higher significance ($z = 4.251$, $p = 0.00002$ (two-tailed)).

For the markers rs165599 and rs737865 no significant results were found in any of the samples (Tables 1 and 2).

The analysis of maternal and paternal transmission does not show significant results for the markers rs165599 and rs737865, whereas maternal and paternal transmission were significant for the Val158Met polymorphism (maternal transmission: $p = 0.019$; paternal transmission $p = 0.0006$).

The results of the haplotype analysis are summarized in Table 3. In the case–control sample two haplotypes reveal a significant association with PD. In the sample of nuclear families these two haplotypes did not show any significant results, whereas other haplotypes became significant.

DISCUSSION

The Val158Met polymorphism of the COMT gene has been studied widely in various disorders and in personality traits. In addition, several studies have found an association with PD yet (Domschke *et al*, 2004; Hamilton *et al*, 2002; Woo *et al*, 2002). Therefore, our a priori hypothesis was that this polymorphism is associated with PD. Recent studies imply that additional loci within or near the COMT gene may contribute to the etiopathogenesis of PD (Hamilton *et al*, 2002). Haplotypes have been described to be associated with schizophrenia (Palmatier *et al*, 2004; Shifman *et al*, 2002) and seem to have an influence on the susceptibility of anxiety-related personality traits (Stein *et al*, 2005). Therefore, we investigated, in addition to the Val158Met polymorphism, two markers of the COMT gene chosen in the above mentioned studies that might be associated with PD (Shifman *et al*, 2002; Stein *et al*, 2005).

We found a significant association between the valine allele of the Val158Met COMT polymorphism and PD in two independent samples, one of nuclear families and another of case–controls. In the case–control sample, we detected an excess of the valine allele in PD patients, especially in women. Furthermore, a significant transmission disequilibrium for the valine allele in the family-based sample was observed. The fact that the positive result has not only been in the case–controls but also in the family sample is important evidence that population stratification is probably not creating a false positive result. Furthermore, these findings are consistent with two previous studies reporting an association of this more active COMT allele with PD, in particular in women (Domschke *et al*, 2004; Hamilton *et al*, 2002). Our findings are in line with a recent study on phobic

anxiety that has been reported to be associated with the valine allele of the functional COMT polymorphism in a sample of 1234 women (McGrath *et al*, 2004). A recent association study of COMT and anxiety-related personality traits described two significant haplotypes which we found in our case–control sample significant as well (Stein *et al*, 2005). A study by Bray *et al* (2003) showed that apart from the Val/Met polymorphism, COMT variants are of functional importance. A haplotype of these variants was associated with risk for schizophrenia probably by down-regulation of COMT expression. Our haplotype frequencies were different from those of Bray *et al* One explanation for this might be due to the fact that the sample of Bray *et al* consisted of subjects from two European sites (Sweden and UK) and from the US. This could easily create allele and haplotype differences.

The high-activity valine allele is assumed to remove synaptic dopamine at a higher rate and thus effectively lower frontal dopamine activity. There is evidence that the valine allele of the Val158Met COMT polymorphism interferes with prefrontal function in healthy subjects (Malhotra *et al*, 2002). PD subjects display increased prefrontal responsivity compared to healthy volunteers in a fMRI study with threat-related words (Maddock *et al*, 2003). Furthermore, information-processing deficits seem to play a crucial role in the etiopathogenesis of PD (Ludewig *et al*, 2005). The COMT genetic variation may thus influence prefrontal cortical processes which are relevant not only for healthy subjects, but also for PD symptomatology.

In contrast to our findings of the Val158Met variant are the results of two Asian studies (Ohara *et al*, 1998; Woo *et al*, 2004). Ohara *et al* (1998) investigated a sample of anxiety disorder patients ($n = 108$) including a small number of PD patients ($n = 29$) and found no association. This small sample of PD patients had very low power to detect the COMT effect sizes observed in our study as well as in Domschke *et al* (2004) and Hamilton *et al* (2002). Furthermore, it is not clear whether matching of the control subjects concerning gender and age was carried out, since this information was not reported by the authors. Woo *et al* (2004) found a nominally significant association with the less active methionine allele in a clinically characterized Korean PD sample ($n = 178$). Different ethnic ancestry with low frequency of the less active methionine alleles in the Asian population might be an explanation for these diverse results.

Another important issue to raise is the one of specificity: it seems evident that the relationship between the Val158-Met polymorphism and psychopathology is not specific to PD. An association has been found also in schizophrenia (Goldberg *et al*, 2003; Shifman *et al*, 2002), major depression (Massat *et al*, 2005), rapid cycling in bipolar illness (Kirov *et al*, 1998) and anxiety-related personality traits (Stein *et al*, 2005). This might indicate that the involvement of COMT variants would be a 'general deficit' leading to several syndromes rather than to a 'specific deficit' associated to PD or any other particular syndrome. In contrast to the apparent general effects of COMT, the role of the CCK-B receptor gene seems to be implicated in a more specific way to PD (Hösing *et al*, 2004; Kennedy *et al*, 1999). There is ample evidence that cholecystokinin and the CCK-B receptor play a considerable role in the neurobiology in PD as described in animal studies, challenging studies, and genetic studies (Bourin and Dailly, 2004; Bradwejn and Koszycki, 2001). As the COMT variant as well as the CCK-B receptor CT repeat in the promoter region are associated with PD in Caucasians, the question arises as to whether PD is the result of a combination of general deficits, for example, COMT, or combined with specific ones, for example, cholecystokinin.

One limitation of this study is the small number in both samples. However, a major advantage of our investigation is that we replicated our results in two independent samples, which is a strong indication for the reliability of the results.

Finally, despite the replicating reports, the COMT Val158Met may not be the clinically relevant polymorphism on chromosome 22q11.2, but rather it may be in LD with another nearby marker involved in risk for PD.

Overall given that the role of COMT Val158Met variant in PD is now reported in four studies, including the present investigation, with sufficient power (Domschke *et al*, 2004; Hamilton *et al*, 2002; Woo *et al*, 2004), further investigations of the COMT gene and nearby markers on chromosome 22 are warranted to increase our understanding of the genetic basis of PD. If COMT is further proven to be involved then new targets for drug development may be uncovered leading to enhanced pharmacological treatment of panic disorder.

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