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*Brief Research Communication*

# Association Study of Candidate Variants of COMT With Neuroticism, Anxiety and Depression

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**The Val158Met polymorphism of the gene encoding catechol-*O*-methyltransferase (COMT) is one of the most widely tested variants for association with psychiatric disorders, but replication has been inconsistent including both sex limitation and heterogeneity of the associated allele. In this study we investigate the association between three SNPs from COMT and anxiety and depression disorders and neuroticism all measured within the same study sample. Participants were selected as sibling pairs (or multiples) that were either concordant or discordant for extreme neuroticism scores from a total sample of 18,742 Australian twin individuals and their siblings. All participants completed the Composite International Diagnostic Interview (CIDI) from which diagnoses of DSM-IV depression and anxiety disorders were determined. Of the participants, 674 had a diagnosis of anxiety and/or depression from 492 families. Study participants (n = 2,045 from 987 families) plus, where possible, their parents were genotyped for rs737865, rs4680 (Val158Met), and rs165599. Using family based tests we looked for association between these variants and neuroticism, depression, anxiety, panic disorder and agarophobia (PDAG) and obsessive compulsive disorder. We found no convincing evidence for association either in allelic or genotypic tests for the total sample or when the sample was stratified by sex. Haplotype T-G-G showed weak association ($P = 0.042$) with PDAG before correction for multiple testing; association between this haplotype and schizophrenia has been previously reported in an Australian sample.**



**KEY WORDS: association; anxiety; major depression; neuroticism; COMT**

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The gene encoding catechol-*O*-methyltransferase (COMT), a dopamine catabolic enzyme, is a functional candidate for a spectrum of psychiatric disorders, personality traits and cognitive function. A non-synonymous single nucleotide polymorphism (SNP) with bases G → A (rs4680, also referred to as rs165688) at codon 158 results in an amino acid substitution of valine (Val) to methionine (Met). This Val158Met variant has been extensively investigated in association studies but with inconsistent replication. Allele frequencies differ significantly between populations and this may have contributed to the high degree of heterogeneity between studies: the G allele has frequency of 0.48 in Caucasians and 0.75 in Japanese/Han Chinese [HapMap, 2003]. Nonetheless, meta-analyses have shown significant association between Val158Met and anxiety disorders but with both sex limitation and heterogeneity of the associated allele: the Val allele was associated with panic disorder (PD) in Caucasian women (Odds Ratio (OR) 1.54, 95% confidence interval (CI) 1.02–2.34, $P = 0.04$) [Domschke et al., 2007] but the Met allele was associated with obsessive compulsive disorder (OCD) in men (OR 1.88, 95% CI 1.45–2.44, $P < 0.001$) [Pooley et al., 2007]. Authors of both meta-analyses review the breadth of evidence supporting sexual dimorphism of COMT phenotypes relating to knock-out mice, enzyme activity and regulation by estrogens. However, both conclude that sample sizes are still too small to be definitive and that future studies should consider additional variants within the COMT gene.

Anxiety disorders are often comorbid with depression and are considered to have a common genetic basis with both depression and neuroticism, a dimension of personality that includes a tendency to anxiety, depression and low self-esteem [Levinson, 2006]. Of four association studies of major depressive disorder, two [Frisch et al., 1999; Cusin et al., 2002; Serretti et al., 2003] found no evidence for association with Val158Met, but the largest (222 early onset cases and 628 controls) [Massat et al., 2005] reported association with the Val variant (OR = 1.48, 95% CI 1.09–1.91, $P = 0.009$). Of four association studies for neuroticism in Caucasians [Henderson et al., 2000; Eley et al., 2003; Olsson et al., 2005; Stein et al., 2005], only one showed borderline evidence for association ($P = 0.05$) with the Met allele in females only. The only one of these studies to genotype additional SNPs in the COMT gene reported a sex limited association for haplotypes of rs737865, rs4680 and rs165599 (global $P = 0.002$ in women).

In this study we investigate the association between three SNPs from COMT and anxiety and depression disorders and neuroticism all measured within the same study sample. Our study participants were adult twins and their families recruited through the Australian Twin Registry. All participants provided written informed consent under study protocols approved by the Queensland Institute of Medical Research Human Research Ethics Committee. Over the period 1980–1995 participants completed self-report questionnaires which included either the full 90-item Eysenck Personality Questionnaire revised (EPQ-R) [Eysenck et al., 1985] with a 23 item neuroticism scale or a shortened questionnaire (EPQ-R-S) with a 12 item neuroticism scale. EPQ-R or EPQ-R-S neuroti-

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cism scores were available on 18,742 Australian twin individuals and their siblings. The relationship between the 12 and 23 item scales has been investigated for our samples; the correlation between the full 23 items and the 12 items included in the short version is 0.95 [Birley et al., 2006]. Sibling pairs that were either concordant or discordant for extreme normalized EPQ scores (one sibling in the top or bottom decile, the other sibling in the top or bottom quintile and excluding monozygotic twin pairs) were recruited and interviewed by telephone with the shortened Composite International Diagnostic Interview [CIDI, 1997]. Using these criteria, multiple siblings were selected from some families. This extreme discordant and concordant (EDAC) [Risch and Zhang, 1995] design is a cost efficient strategy for obtaining an informative data set for genetic studies [Purcell et al., 2001]. Blood (or buccal) samples were obtained where possible from the selected siblings and their parents. Self-report ancestry suggested participants to be of North European ancestry (>94% of all grandparents) which was confirmed in a formal test of genetic similarity of unrelated founders (n = 519) with a cohort from the Netherlands (n = 549) using 359 single tandem repeat polymorphisms ($F_{st} = 0.30\%$) [Sullivan et al., 2006]. Full details of the recruitment procedure for the study, including response rates and incidence of DSM-IV diagnoses for anxiety and depression related disorders have been reported previously [Kirk et al., 2000].

EPQ-R neuroticism scores (n = 1968) were analyzed as sex-standardized residuals of the averaged angular transformation [Freeman and Tukey, 1950] after regression of the transformed neuroticism scores on age, sex, age*sex, age$^2$ and age$^2$*sex calculated using the population sample from which the EDAC sample was selected. Individuals were identified who were in the top 10% (NEU = 2) or the bottom 10% (NEU = 1) of the population distribution, with all other individuals scored as missing (NEU = 0). Responses to the CIDI interview provided DSM-IV [DSM-IV, 1994] life-time diagnoses of depression (296.2: major depressive disorder, single episode, 296.3: major depressive disorder, recurrent episode or 300.4: dysthymic disorder) and anxiety (300.23: social phobia, 300.02: generalized anxiety disorder, 300.01: panic with agoraphobia, 300.21: panic without agoraphobia, 300.22: agoraphobia without panic, and 300.03: obsessive compulsive disorder). Standard clinical significance exclusion criteria [Andrews et al., 2001] were applied which help to ensure accurate prevalence rates of DSM-IV diagnoses. Diagnoses were coded as: 2 = affected, 1 = unaffected for all DSM-IV diagnoses, 0 = not scored or affected for a different DSM-IV diagnosis. The DSM-IV phenotypes used for association analysis were DEP (any depression diagnosis), ANX (any anxiety diagnosis) and DEPorANX (any depression or anxiety diagnosis, i.e., all cases in ANX and/or DEP) and two specific anxiety disorders OCD (obsessive compulsive disorder) and PDAG (panic disorder and/or agoraphobia). Although not selected as part of the EDAC design, 68 MZ twin pairs were included in the study when an additional sibling had been selected. Only one individual from each of these MZ twin pairs were used in the analysis, preferentially selecting the one with any DSM-IV diagnosis of anxiety or depression if they were discordant for affected status.

In total, our study sample comprises 2,045 study participants and a total of 2,832 genotyped individuals from 987 families of whom 674 individuals from 492 families qualified for a DEPorANX diagnosis. A description of the structure of the data with respect to family size and number of DEPorANX affected individuals is listed in Table I. The number of individuals who qualified as cases for each diagnosis is listed in Table II. This study is designed to be a replication study and therefore we could declare significance at the type I error rate to be 0.05. However, even within this replication study we are conducting multiple tests. At the other extreme our study sample has and will be used for other association studies and so genome-wide type I error rate of $5 \times 10^{-8}$ would be most conservative. Using these two extremes we consider the power of a case–control study with 492 cases and 495 controls, representing the number of independent families with some affecteds or no affecteds respectively. Such a study has more than 80% power to detect a causal variant with heterozygous genotype relative risk (GRR) of 1.5 (or 2.3) under a genetic model of multiplicative allelic action of frequency 0.1 using a genotyped marker of frequency 0.1 which is in complete LD with the causal variant assuming a type I error rate of 0.05 (or $5 \times 10^{-8}$) [Purcell et al., 2003]. These calculations provide a baseline indication of power as our study design includes many families with multiple affected sibs and/or unaffected sibs plus which should result in increased power [Martin et al., 2000] and 26% of families have both parents genotyped (Table I).

Three COMT SNPs rs737865, rs4680, and rs165599 were genotyped by primer extension reaction and MALDI-TOF mass spectrometry (MassARRAY, Sequenom, Inc., San Diego, CA) as described elsewhere [Handoko et al., 2005]. Genotypes from an additional 84 polymorphic markers were used to verify the pedigree relationships between study participants. Genotyping success rates were >99.5% for all SNPs after exclusion of any Mendelian errors. All SNPs were in Hardy–Weinberg equilibrium *PedStats* [Wigginton and Abecasis, 2005] using unrelated individuals from families with no affecteds.

TABLE I. Description of the Full Data Set of 987 Families With 2,045 Siblings With Both Genotypes and Phenotypes

| | | | % Families | | | | | | | % Families | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. of affecteds | | | | | | | No. parents genotyped | | |
| | | No. families | 0 | 1 | 2 | 3 | 4 | 5 | | 0 | 1 | 2 |
| No. measured per family | 1 | 221 | 67 | 33 | | | | | | 63 | 19 | 18 |
| | 2 | 548 | 48 | 36 | 16 | | | | | 52 | 23 | 25 |
| | 3 | 159 | 40 | 29 | 24 | 8 | | | | 38 | 26 | 35 |
| | 4 | 45 | 37 | 31 | 22 | 11 | 0 | | | 33 | 31 | 36 |
| | 5 | 13 | 39 | 15 | 23 | 15 | 8 | 0 | | 23 | 39 | 39 |
| | 6 | 1 | 0 | 0 | 0 | 0 | 0 | 100 | | 0 | 0 | 100 |
| Total | Number | 987[a] | 495 | 334 | 137 | 19 | 1 | 1 | Overall % | 51 | 23 | 26 |

Affecteds are those with any diagnosis of anxiety or depression.
[a]908 families were simple nuclear families, for the remaining 79 families the study participants were the children of a twin pair.

TABLE II. Number of Individuals and Families in the Study Sample for Each Diagnosis

| | Individual | | | Families | | |
|---|---|---|---|---|---|---|
| Diagnoses | Total | Male | Female | Total | Male | Female |
| None | 1371 | 521 | 850 | 495 | 265 | 390 |
| DEPorANX | 674 | 243 | 431 | 492 | 212 | 356 |
| DEP | 518 | 177 | 341 | 399 | 156 | 292 |
| ANX | 382 | 134 | 248 | 310 | 125 | 219 |
| PDAG | 105 | 29 | 76 | 101 | 29 | 73 |
| OCD | 114 | 50 | 64 | 105 | 49 | 61 |
| NEU low | 573 | 236 | 337 | 349[a] | 192[b] | 252[c] |
| NEU high | 518 | 213 | 305 | 312[a] | 174[b] | 228[c] |

The number of families listed for NEU low and high relate to the numbers of families with only low NEU or only high NEU scores, an additional (a) 98, (b) 19, (c) 37 families included individuals with both low and high scores.

Association analysis was undertaken using logistic regression as implemented in UNPHASED v3.10 [Dudbridge, 2003]. UNPHASED optimally combines all the information available (which differs between families, e.g., sibship size, number of parents genotyped, number of affected sibs per family including none) generating frequencies for "case" and "control" haplotypes from all parental chromosomes. The default settings of UNPHASED allow estimation of uncertain haplotype frequencies by the EM (expectation–maximization) algorithm and assume that transmissions are not independent in families with multiple siblings. Options used were: *–missing*, to allow imputation of missing parental genotypes, *–rare 0.01* to require haplotypes to have frequency greater than 1% in either cases or controls; *–window* to specify the number of SNPs used in haplotype analyses; *–individual* to generate *P*-values for each associated haplotype in addition to a global *P*-value from the test of the similarity in distributions of haplotype frequencies between "cases" and "controls." The option *–permutation* 10,000 was used to generate empirical *P*-values from 10,000 simulation permutations in situations where association was $<0.05$ as a check that given our family structure that the test statistic follows the asymptotic distribution. For analysis of individual SNPs the option *–genotype* was also used to allow association tests of individual single SNP genotypes, in which "control" genotypes are derived from the pair of non-transmitted alleles. Pairwise |D'| and $r^2$ measures of linkage disequilibrium (LD) between variants within genes were estimated from "control" chromosomes using the *–window 2 –LD* option.

Estimates of LD between the SNPs (Table III) were a little higher than those reported by Handoko et al. [2005] in a study of 50 Caucasian Australian families ascertained to have sib-pairs affected with schizophrenia. We note that the method used by Handoko et al. [2005] to estimate LD does not differentiate between chromosomes transmitted and non-transmitted to affected offspring. As they report two separate and interacting highly significant associations between schizophrenia and haplotypes of the three SNPs, differences in the pattern of LD compared to our control chromosomes are not unexpected. We found no differences in the allele frequencies between the sexes of the control group for any of the SNPs (Table IV). We found no evidence for association between any of the individual genotyped SNPs in either allelic or genotype tests and any of the anxiety or depression disorders either for both sexes combined (Table IV) or when stratified by sex (results not presented). No association was found between any of the SNP alleles or genotypes and neuroticism when considered as a quantitative trait (results not presented) or by considering extreme dichotomous scores (NEU; Table IV). Association analyses for the haplotypes of the three SNPs for both sexes combined showed weak evidence for association for haplotype T-G-G (Table V) and PDAG (empirical $P = 0.042$, frequency in "cases" 0.08 vs. 0.11 in "controls"). Any correction for multiple testing will make this weak association non-significant. However, we note that this is the same haplotype reported by Handoko et al. [2005] to be highly associated with schizophrenia in an Australian sample of 50 Caucasian affected sib-pair families ($P = 6.8 \times 10^{-6}$, transmitted frequency 0.01, non-transmitted frequency 0.19). No individual haplotype or global haplotype association tests had $P < 0.05$ when sexes were considered separately (results not presented).

In conclusion, we found no significant evidence for association between any of the COMT variants and any measure of anxiety or depression either in both sexes combined or sexes considered separately. Whilst our study sample is relatively large compared to many other studies, sample size and power remain a limitation. In particular, the numbers of affected individuals for PDAG and OCD are low, but nonetheless are higher than the numbers included in the majority of individual studies that have contributed to the meta-analyses for these disorders [Domschke et al., 2007; Pooley et al., 2007]. Family-based studies are often excluded from meta-analyses; our results could be included in future case–control meta-analyses by conservatively using the number of case and control families (Table II), together with the reported allele, genotype and haplotype frequencies and *P*-values.

TABLE III. Measures of Linkage Disequilibrium Between the Genotyped SNPs

| | Minor allele[a] | Major allele | Distance from rs737865 (kb) | LD: \|D′\| and $\mathbf{r^2}$ | | |
|---|---|---|---|---|---|---|
| | | | | rs737865 | rs4680 | rs165599 |
| rs737865 | C | T | 0 | | **0.28** | **0.07** |
| rs4680 | G | A | 21.2 | 0.77 | | **0.18** |
| rs165599 | G | A | 26.7 | 0.27 | 0.59 | |

[a]Based on coding (forward) strand.

TABLE IV. Allele and Genotype Frequencies and Association Analysis *P*-Values for Both Sexes Combined

| | Frequencies | | | | *P*-values | | | |
|---|---|---|---|---|---|---|---|---|
| rs737865 | C | C/C | C/T | T/T | Allele | C/C | T/T | Genotype |
| Control[a] | 0.28 | 0.08 | 0.40 | 0.52 | 0.92[b] | | | |
| DEPorANX | 0.29 | 0.09 | 0.39 | 0.52 | 0.28 | 0.23 | 0.62 | 0.46 |
| DEP | 0.29 | 0.10 | 0.39 | 0.52 | 0.48 | 0.16 | 0.98 | 0.38 |
| ANX | 0.28 | 0.09 | 0.39 | 0.53 | 0.62 | 0.50 | 0.87 | 0.81 |
| PDAG | 0.30 | 0.09 | 0.43 | 0.49 | 0.37 | 0.60 | 0.44 | 0.67 |
| OCD | 0.27 | 0.07 | 0.40 | 0.53 | 0.99 | 0.81 | 0.93 | 0.97 |
| NEU low | 0.27 | 0.07 | 0.39 | 0.54 | | | | |
| NEU high | 0.29 | 0.10 | 0.38 | 0.52 | 0.70 | 0.34 | 0.78 | 0.61 |
| rs4680 Val/Met | G | G/G | G/A | A/A | Allele | G/G | A/A | Genotype |
| Control | 0.48 | 0.24 | 0.50 | 0.27 | 0.27[b] | | | |
| DEPorANX | 0.50 | 0.25 | 0.49 | 0.26 | 0.34 | 0.51 | 0.48 | 0.64 |
| DEP | 0.50 | 0.25 | 0.49 | 0.26 | 0.28 | 0.38 | 0.48 | 0.55 |
| ANX | 0.47 | 0.22 | 0.50 | 0.28 | 0.54 | 0.62 | 0.69 | 0.83 |
| PDAG | 0.47 | 0.18 | 0.57 | 0.25 | 0.11 | 0.04[c] | 0.74 | 0.12 |
| OCD | 0.47 | 0.25 | 0.43 | 0.32 | 0.52 | 0.10 | 0.57 | 0.19 |
| NEU low | 0.47 | 0.22 | 0.51 | 0.27 | | | | |
| NEU high | 0.47 | 0.25 | 0.45 | 0.31 | 0.82 | 0.18 | 0.14 | 0.13 |
| rs165599 | G | G/G | G/A | A/A | Allele | G/G | A/A | Genotype |
| Control | 0.31 | 0.10 | 0.42 | 0.48 | 0.53[b] | | | |
| DEPorANX | 0.30 | 0.10 | 0.41 | 0.50 | 0.83 | 0.71 | 0.98 | 0.93 |
| DEP | 0.30 | 0.09 | 0.41 | 0.50 | 0.91 | 0.79 | 0.74 | 0.91 |
| ANX | 0.28 | 0.09 | 0.38 | 0.53 | 0.51 | 0.91 | 0.48 | 0.76 |
| PDAG | 0.29 | 0.10 | 0.39 | 0.51 | 0.62 | 0.71 | 0.72 | 0.88 |
| OCD | 0.26 | 0.08 | 0.36 | 0.56 | 0.82 | 0.41 | 0.82 | 0.64 |
| NEU low | 0.31 | 0.10 | 0.42 | 0.48 | | | | |
| NEU high | 0.30 | 0.09 | 0.41 | 0.50 | 0.29 | 0.41 | 0.46 | 0.55 |

*P*-values are the asymptotic *P*-values. When the asymptotic *P*-value was less than 0.05, the significance of the test was checked using 10,000 permutations.
[a]Within unphased V3.10 control frequencies are estimated from families with no case diagnoses, from chromosomes not transmitted from parents to case offspring and from chromosomes transmitted to non-affected siblings of cases. Case frequencies are derived from transmissions from parents to affected offspring.
[b]Hardy–Weinberg equilibrium test *P*-value in unrelated individuals from families with no affected diagnoses.
[c]The empirical *P*-value was 0.09.

TABLE V. Frequency of Haplotypes of SNPs rs737865-rs4680-rs165599, for Both Sexes Combined

| | Control | DEPorANX | DEP | ANX | PDAG | OCD | NEU low | NEU high |
|---|---|---|---|---|---|---|---|---|
| C-G-G | 0.13 | 0.13 | 0.13 | 0.13 | 0.13 | 0.10 | 0.13 | 0.13 |
| C-G-A | 0.12 | 0.12 | 0.14 | 0.12 | 0.12 | 0.14 | 0.11 | 0.12 |
| C-A-A | 0.03 | 0.03 | 0.03 | 0.03 | 0.05 | 0.04 | 0.03 | 0.03 |
| T-G-G | 0.11 | 0.10 | 0.10 | 0.09 | 0.08[a] | 0.10 | 0.11 | 0.10 |
| T-G-A | 0.13 | 0.13 | 0.13 | 0.13 | 0.13 | 0.13 | 0.12 | 0.12 |
| T-A-G | 0.06 | 0.06 | 0.06 | 0.06 | 0.07 | 0.06 | 0.07 | 0.07 |
| T-A-A | 0.42 | 0.41 | 0.41 | 0.43 | 0.42 | 0.44 | 0.43 | 0.43 |

No global test had *P*-value <0.05. Only one individual haplotype test (haplotype T-G-G with PDAG) had *P*-value <0.05.
[a]The empirical *P*-value for the individual test of this haplotype was 0.042.

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