Int J Psychiatry Clin Pract 2014; 18: 97–102. © 2014 Informa Healthcare
ISSN 1365-1501 print/ISSN 1471-1788 online. DOI: 10.3109/13651501.2014.894073

International Journal of
Psychiatry in
Clinical Practice
informahealthcare.com/ijpcp

ORIGINAL ARTICLE

Lack of influence of rs4680 (*COMT*) and rs6276 (*DRD2*) on diagnosis and clinical outcomes in patients with major depression

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Abstract
Objective. The gene coding for the catechol-O-methyltransferase (*COMT*) and the one coding for the dopamine receptor 2 (*DRD2*) have been linked with major depression (MD) and with the response to antidepressants in several studies. However, contrasting findings have been reported as well. The aim of the present study is, therefore, to investigate possible influences of rs4680 within *COMT* and rs6276 within *DRD2*, analyzed both individually and in combination, on the diagnosis and clinical outcomes in a sample of Korean MD patients treated with antidepressants. *Methods*. Totally, 184 Korean in-patients suffering from MD treated with either paroxetine or venlafaxine and 220 healthy control subjects were included in the present study. Depression severity was assessed by means of the Hamilton Rating Scale for Depression. *Results*. We were not able to find any association between the two variants under investigation and diagnosis of MD, as well as with antidepressant response. *Conclusions*. Although limited by several factors, including the small sample size and the impossibility to extend our findings to patients treated with different antidepressants, the results of our study provide support to the notion that these variants might not play a major role in the etiology and clinical outcomes of MD.

Key words: *COMT*, *DRD2*, antidepressants, major depression, response, epistasis

(Received 12 June 2013; accepted 31 January 2014)

Introduction

Major depression (MD) is a common mental disorder with an estimated likelihood of occurring over the life span as high as 12–20% (Kessler et al. 2003). Consistent evidence suggests that MD has a strong genetic etiology (Belmaker and Agam 2008) and that several genetic variants could reciprocally interact to modulate antidepressant response (Kato and Serretti 2008; Gvozdic et al. 2012).

One of the most commonly investigated genes in association with MD and antidepressant response is that coding for the catechol-O-methyltransferase (*COMT*), one of the several enzymes involved in the metabolism of catecholamines (dopamine, adrenaline, and noradrenaline) (Karhunen et al. 1995). *COMT* is located on chromosome 22q11, a chromosomal region of interest for several psychiatric disorders, including MD (Badner and Gershon 2002; Hashimoto et al. 2005). The *COMT* functional polymorphism val(158)met (rs4680) is one of the most studied variants in psychiatric genetics. Such polymorphism has been associated with a three- to -four-fold variation in *COMT* enzyme activity (Lachman et al. 1996), with a higher likelihood of developing MD (Ohara et al. 1998), particularly early onset MD (Massat et al. 2005, 2011), and with antidepressant response (e.g., Szegedi et al. 2005; Arias et al. 2006; Baune et al. 2008). It is noteworthy, however, that contrasting results have been reported as well (e.g., Cusin et al. 2002; Serretti et al. 2006; Kocabas et al. 2010).

More recently, increasing attention has been given to variations in the gene coding for the dopamine 2 receptor (*DRD2*; chromosome 11q23), both alone and in the combination with other genes involved in the same pathway, such as *COMT*, in association with psychiatric disorders. More in detail, variations within *DRD2* have been associated with delirium (van Munster et al. 2010), MD (Wang et al. 2012) and onset-time of antidepressant response (Wang et al. 2012). However, contrasting results have likewise been reported (e.g., Koks et al. 2006; Xu et al. 2011) and an association between *DRD2* and antidepressant response has not been unequivocally demonstrated so far.

As one can observe, results from studies focusing on single SNPs have been largely inconsistent or contradictory (Gvozdic et al. 2012). As a consequence, increasing emphasis has recently been given to the investigation of epistatic

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interactions between polymorphisms in candidate genes possibly influencing the etiology and treatment outcomes in complex diseases such as psychiatric disorders (e.g., Carlborg and Haley 2004; Segurado et al. 2011).

Epistasis is commonly defined as the functional interaction between genes. It encompasses various events including promoter activity, epigenetic control, chromatin remodeling, and many other molecular reactions (Phillips 2008). These events can impact cell lifecycles and complex traits and are orchestrated through genetically driven complex yet flexible activities (Phillips 2008). Accordingly, the research for epistatic interactions between different candidate genes could represent a significant advantage in comparison to the investigation of single genes as a way to understand the biological diversity that could influence, for instance, the development and clinical outcomes of MD.

The aim of the present work is, therefore, to investigate possible influences of rs4680 within *COMT* and rs6276 within *DRD2*, analyzed both individually and in combination with one another, on the diagnosis of MD and clinical outcomes, such as improvements on depressive symptoms and quality of life scores, in a sample of Korean MD patients treated with antidepressants.

Methods

The sample under investigation comprised 184 Korean inpatients suffering from MD according to DSM-IV criteria (Sheehan et al. 1998) who were consecutively recruited at the Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. All patients were treated with either paroxetine or venlafaxine. Patients were excluded if they had current severe or unstable medical and neurological conditions, current treatment with a long-acting antipsychotic, concomitant alcohol and substance use disorders and if they were not of Korean ethnicity.

All patients admitted to the hospital were administered with the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960), as a measure of depression severity, and with the EUROQoF scale (Kind 1996), as a measure of self-perceived quality of life. In accordance with previous studies, response was *a priori* defined as a $\geq 50\%$ symptoms' reduction from baseline to discharge (Riedel et al. 2010). Remission was defined as an HAM-D score less than 7 at discharge (Riedel et al. 2010). Further clinical and socio-demographic variables were likewise recorded (Table I).

A further sample of 220 Korean psychiatrically healthy subjects—who came from the same location as the psychiatric patients in the present study and who underwent the same assessment as psychiatric patients to exclude possible psychiatric disorders—was also included to investigate possible differences between genotype and allele frequencies between these subjects and MD patients. The study protocol was approved by the institutional review board.

The main outcome measures of the present study included: (1) possible differences between rs4680 (*COMT*) and rs6276 (*DRD2*) allele and genotype frequencies in MD patients and in controls and (2) possible influences of the same two variants on HAM-D improvement scores in MD patients. Secondary outcome measures focused the following issues: (1) whether rs4680 within *COMT* and rs6276 within *DRD2* allele and genotype frequencies in MD patients separately analyzed were associated with other clinical and socio-demographical variables included in the present study, such as response rates and EUROQoF scores, (2) whether patients and control groups could be distinguished from one another in terms of epistatic interaction frequencies between rs4680 and rs6276, (3) whether the epistatic interaction between the same two variants could influence HAM-D improvement scores in MD patients and (4) whether the epistatic interaction between the same two variants could influence other clinical and socio-demographical variables included in the present study.

Statistical analyses were performed using 'Statistica' package (StatSoft 1995). A multiple regression model was employed to investigate the existence of possible epistatic interactions between the two genotypes under investigation and clinical and socio-demographical variables included in the present study. Clinical improvement on HAM-D scores was calculated according to the following formula:

$$\left[\frac{(\text{HAM-D}_{\text{final}} - \text{HAM-D}_{\text{baseline}})}{\text{HAM-D}_{\text{baseline}}}\right] \times 100$$

All p values were two-tailed and statistical significance was conservatively set at the 0.003 level (approximately corresponding to the 16 variables outlined in Table I). With these parameters we had a sufficient power (0.80) to detect a small to medium effect size ($\acute{\omega} = 02$) that, as an example, corresponded to an odds ratio of 2.2 between MD patients and controls, and to detect a medium effect size ($d = 0.29$) for MD patients carrying the GG rs4680 genotype as compared with those carrying the GA genotype (Cohen 1988). Such effect size corresponded to the possibility of detecting final differences on HAM-D scores of 2.5 points.

Results

Genetic, socio-demographic, and clinical characteristics of the two samples included in the present study are reported in Table I. Overall, HAM-D scores improved from baseline to endpoint (Table II). Forty-nine patients (27%) showed minimal improvements ($< 20\%$), 70 patients (38%) showed moderate improvements ($\geq 20\%$ and $\leq 50\%$), and 65 patients (35%) showed large improvements ($< 50\%$). The two samples differed in terms of both gender and age (Table I). No significant difference was observed in terms of rs4680 and rs6276 allele and genotype frequencies between MD patients and controls. In addition, no epistatic interaction was observed between the same two variants and a diagnosis of MD (all p values > 0.003). Also, the same two variants, as well as their reciprocal interaction, were not found to influence either symptoms improvement or any other clinical and socio-demographic variables under investigation in the present study (all p values $= 0.003$; see Table II for more details: data not shown are available from the authors on request). In addition, the outcome measures under investigation in the present study were neither influenced by drugs assumed nor by drug dosages (all p values $= 0.003$). Adding gender and age as covariates did no alter the results.

Table I. Allele, genotype, clinical, and demographic characteristics of the sample.

Genetic, socio-demographic and clinical variables	MD patients N (%) or mean ± standard deviation ($n = 184$)	Controls N (%) or mean ± standard deviation ($n = 220$)	χ^2/t	*p* value
Allele frequencies				
Rs4680	G:261 (71%)	G:327 (74%)	1.16	0.28
	A:107 (29%)	A:113 (26%)		
Rs6276	C:250 (68%)	C:317 (72%)	1.62	0.20
	T:118 (32%)	T:123 (28%)		
Genotype frequencies				
Rs4680	GG:93 (50%)	GG:120 (54%)	1.42	0.49
	GA:75 (41%)	GA:87 (40%)		
	AA:16 (9%)	AA:13 (6%)		
Rs6276	CC:82 (45%)	CC:114 (52%)	2.11	0.34
	CT:86 (47%)	CT:89 (40%)		
	TT:16 (9%)	TT:17 (7%)		
Gender			7.86	0. 005
Males	56 (30%)	96 (44%)		
Females	128 (70%)	124 (56%)		
Age	43.62 ± 15.42	47.32 ± 11.51	2.75	0.006
Age of onset	41.34 ± 14.77		–	–
Family history for affective disorders			–	–
Positive	20 (10%)			
Negative	164 (90%)			
Current episode				
First	40 (22%)			
Recurrent	144 (78%)			
Suicidal behaviors			–	–
Positive	21 (11%)			
Negative	163 (89%)			
HAM-D scores			–	–
Baseline	21.71 ± 6.98			
Discharge	13.52 ± 6.86			
% Improvement	37.84 ± 24.90			
Response			–	–
Yes	65 (35%)			
No	119 (65%)			
Remission			–	–
Yes	50 (27%)			
No	134 (73%)			
EUROQ-5 scores			–	–
Baseline	9.21 ± 2.27			
Discharge	5.53 ± 3.71			
% Improvement	37.33 ± 42.90			
Drug			–	–
Paroxetine	132 (72%)			
Venlafaxine	52 (28%)			
Antidepressant dosages (mg)				
Paroxetine	20.52 ± 9.28			
Venlafaxine	158.25 ± 25.45			
Duration of admission (weeks)	7.42 ± 1.40		–	–

HAMD, Hamilton Rating Scale for Depression; MD, Major depression.

Discussion

First, we found that rs4680 and rs6276 allele and genotype frequencies did not differ between MD patients and controls. This finding is consistent with a number of studies showing similar findings (e.g., Cusin et al. 2002; Serretti et al. 2006; Illi et al. 2010). In addition, no epistatic interaction between the same two variants and a diagnosis of MD was observed as well.

Second, we found that rs4680 and rs6276, analyzed both individually and in combination with one another, were not associated with depressive symptoms' improvement in MD patients, as measured with the HAM-D. A possible explanation for this negative finding could be related to the moderately small sample size of our sample that could not allow us to detect subtle differences that are usually associated with single genes or gene–gene interactions in complex disorders (e.g., Risch et al. 2009). However, another possibility is that our negative finding could really reflect a lack of influence of these variants, as well as of their epistatic interaction, on clinical improvement, in accordance with some studies investigating the same genetic variants in MD patients (e.g., Illi et al. 2010; Kocabas et al. 2010; Wang et al. 2012). Finally, no significant association was observed in relationship with further clinical and socio-demographic variables included in the present study.

Table II. Main demographic and clinical outcomes of the present study displayed according to genotypes and epistatic interactions under examination in the present study.

Genotypes	Females (%)*	Age (years)	Baseline HAM-D scores	Final HAM-D scores	% HAM-D improvement scores	Response rates (%)	Remission rates (%)	Baseline EUROQoF scores	Final EUROQoF scores	% EUROQoF improvement scores
					COMT					
rs4680										
GG ($n = 92$)	55 (60%)	44.43 ± 16.58	21.67 ± 6.65	13.84 ± 6.02	35.68 ± 22.26	27 (29%)	17 (18%)	9.55 ± 2.26	6.16 ± 3.58	31.69 ± 41.67
GA ($n = 76$)	59 (78%)	42.46 ± 14.51	21.91 ± 7.57	13.67 ± 7.71	38.07 ± 26.21	28 (37%)	26 (35%)	9.03 ± 2.20	5.12 ± 3.91	41.51 ± 44.95
AA ($n = 16$)	14 (93%)	44.37 ± 12.97	21.06 ± 6.40	11.00 ± 7.10	49.30 ± 31.06	10 (62%)	7 (44%)	8.06 ± 2.27	3.81 ± 2.83	50.74 ± 36.67
					DRD2					
rs6276										
CC ($n = 82$)	54 (67%)	44.13 ± 16.31	21.84 ± 6.65	13.53 ± 6.82	38.53 ± 24.46	29 (35%)	21 (26%)	9.06 ± 2.17	5.76 ± 3.52	32.77 ± 42.24
TC ($n = 86$)	59 (69%)	43.43 ± 15.48	21.65 ± 7.29	13.56 ± 8.80	37.17 ± 24.59	30 (35%)	25 (29%)	9.42 ± 2.41	5.77 ± 3.87	37.09 ± 42.99
TT ($n = 16$)	15 (94%)	42.00 ± 10.06	21.37 ± 7.45	13.18 ± 7.75	37.91 ± 23.00	6 (38%)	4 (25%)	8.81 ± 2.01	3.00 ± 3.07	62.02 ± 39.80
					COMT-DRD2 interaction					
rs4680-rs6276										
GG-CC ($n = 60$)	37 (62%)	42.88 ± 17.09	21.90 ± 6.99	13.95 ± 6.55	36.61 ± 23.07	19 (32%)	12 (20%)	9.25 ± 2.06	6.18 ± 3.50	29.90 ± 42.41
GG-CT ($n = 31$)	17 (55%)	48.30 ± 15.42	21.61 ± 6.06	13.61 ± 5.16	35.53 ± 20.63	8 (26%)	5 (16%)	9.97 ± 2.51	6.53 ± 3.52	30.45 ± 38.22
GA-CC ($n = 19$)	15 (80%)	46.84 ± 12.97	21.89 ± 5.64	13.21 ± 7.60	40.05 ± 27.76	7 (37%)	7 (37%)	8.73 ± 2.21	4.73 ± 3.60	41.40 ± 43.60
GA-CT ($n = 52$)	40 (77%)	41.35 ± 15.01	21.90 ± 8.05	13.57 ± 7.63	21.90 ± 8.05	21 (40%)	19 (37%)	9.19 ± 2.26	5.48 ± 4.06	39.34 ± 46.07
Other ($n = 22$)	20 (95%)	42.86 ± 12.73	20.72 ± 7.04	12.36 ± 7.64	41.30 ± 30.03	10 (45%)	7 (31%)	8.50 ± 2.40	3.18 ± 2.85	58.73 ± 36.96

HAMD, Hamilton Rating Scale for Depression; EUROQoF, European Quality of Life Scale.

Several factors, including the different sample size, different severity of illness, and different ethnicity across different studies, might explain why discrepant findings have sometimes been observed in candidate genetic studies, such as the present one. However, the possibility that epistatic interaction among a higher number of genes belonging to same pathways could be more likely to provide an appropriate framework for the understanding of complex diseases, such as MD, cannot be ruled out. Such a possibility, in turn, raises significant computational and theoretical difficulties when considering all possible gene–gene interactions not to mention other forms of genetic expression controls (Serretti and Chiesa 2012).

Several limitations affecting the present study should be considered before firm conclusions are drawn. First, all patients included in the present study were treated with either paroxetine or venlafaxine, both of which act upon the serotonergic system (Dechant and Clissold 1991; Andrews et al. 1996). Further studies could focus on patients treated with different antidepressants. Second, the lack of associations observed in the present study could be simply due to the lack of statistical power that, in turn, could obscure small effects exerted by single SNPs. This issue is particularly concerning if one considers that even among pharmacogenetic studies with a large sample size, the effects exerted by single SNPs or SNP combinations on such clinical outcomes as, for instance, depressive symptom improvements could be so small that it could be missed (e.g., Abou Jamra et al. 2008). Taking into account positive results observed in some studies (e.g., Szegedi et al. 2005; Arias et al. 2006), however, future studies focusing on larger samples of more homogenous groups of patients (e.g., patients treated with the same drug and/or patients with more homogeneous clinical characteristics at baseline) could reasonably help distinguish whether the negative findings observed in our study could actually depend on a lack of statistical power rather than on a clear lack of association between the genetic variants under investigation in the present study and clinical outcomes of interest. Also, the duration of hospitalization in the present study could be considered as insufficient to ascertain a lack of response and remission. However, this time frame is consistent with common clinical practice (Zimmerman et al. 2002). Finally, the different duration of hospitalization could raise concerns about the fact that clinical improvement could vary as a function of time rather than of genetic variants. However, we checked for such a possibility, finding no significant influence.

In conclusion, our findings preliminary suggest that rs4680 within *COMT* and rs6276 within *DRD2* are not associated with the development and clinical outcomes of MD. However, taking into account the limitations mentioned above, further studies focusing on more homogeneous group of patients might be warranted.

Key points

- *COMT* and *DRD2* could play a role into the etiology and clinical outcomes of major depression.

- Increasing emphasis has recently been given to epistatic interactions between genes.
- Our study does not lend support to an involvement of *COMT* and *DRD2* in MD.

Acknowledgments
None

Role of Funding Source
This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120004).

Statement of interest
None of the authors reports conflicts of interest.

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