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DAOA Variants on Diagnosis and Response to Treatment in Patients with Major Depressive Disorder and Bipolar Disorder

A Chiesa[1], C-U Pae[2,3], S Porcelli[1], C Han[4], S-J Lee[2], AA Patkar[3], MH Park[5], T-Y Jun[2] and A Serretti[1]

[1]Institute of Psychiatry, University of Bologna, Bologna, Italy; [2]Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; [3]Department of Psychiatry and Behavioural Sciences, Duke University Medical Center, Durham, North Carolina, USA; and [4]Department of Psychiatry, and [5]Department of Neurology, College of Medicine, Korea University, Ansan, Kyounggi-Do, Republic of Korea

OBJECTIVE: This study investigated whether selected D-amino acid oxidase activator *(DAOA)* gene single nucleotide polymorphisms (SNPs; rs3916966, rs3916967, rs2391191, rs3916968, rs7139958, rs9558571, rs778293) are associated with major depressive disorder (MDD) and bipolar disorder (BD), and whether they can predict clinical outcomes in Korean in-patients treated with antidepressants and mood stabilizers, respectively. METHODS: In total, 145 patients with MDD, 132 patients with BD and 170 psychiatrically healthy controls were genotyped for the *DAOA* SNPs. Baseline and final clinical assessments included the Montgomery–Asberg Depression Rating Scale and Young Mania Rating Scale for patients with MDD and BD, respectively. RESULTS: There was no association between *DAOA* SNP genotypes or alleles with diagnosis, clinical improvement, response rates or remission rates for MDD and BD. Haplotype analyses found no association with MDD or BD diagnosis or clinical outcomes. CONCLUSIONS: The findings suggest that the *DAOA* SNPs investigated may not affect MDD or BD phenotype, clinical symptoms or other clinical factors, and are unlikely to be involved in MDD or BD development and treatment outcomes. Given the study's limitations, further investigation should be carried out.

KEY WORDS: D-Amino acid oxidase activator (DAOA); Clinical improvement; Treatment response; Major depressive disorder; Bipolar disorder

Introduction

It has long been known that G72, also known as D-amino acid oxidase activator (DAOA), is associated with several psychiatric disorders, including major depressive disorder (MDD) and bipolar disorder (BD).[1] Early biological studies suggested that DAOA interacts with D-amino acid oxidase (DAO), a protein with an important role in neuronal migration and

synaptic plasticity[1] that is present in the human brain, where it oxidizes D-serine, a potent activator of the *N*-methyl-D-aspartate glutamate receptor.[2] Chumakov *et al.*[2] found that co-incubating DAOA and DAO *in vitro* yielded a functional interaction, with DAOA enhancing the activity of DAO. Subsequent studies have failed to replicate these findings.[3–5]

The association of the *DAOA* gene with MDD and BD has been investigated. Support for an association between *DAOA* and BD and schizophrenia has been reported in several independent datasets and a meta-analysis although, for schizophrenia, it is clear that there is no association with specific alleles or haplotypes.[4] According to a recent review, *DAOA* does not have a major effect on susceptibility to BD in general, but may contribute to BD susceptibility in some families.[6] Furthermore, based on the well-established familial clustering of MDD and BD and on the result of a large multicentre study showing a link between MDD and a locus on 13q31.1–q31.3 which is in the vicinity of *DAOA*, Rietschel *et al.*[7] investigated whether some single nucleotide polymorphisms (SNPs) within the *DAOA* gene previously linked with BD could also be associated with MDD and neuroticism. They found that a previously identified rs3918342–rs1421292 risk haplotype was significantly associated with both outcomes.[7] Additionally, variations in the *DAOA* gene could influence susceptibility to mood disorder episodes across the traditional BD categories or, alternatively, they could be linked to endophenotypes in different domains such as cognition, neurophysiology or neuroanatomy.[8,9] Further research is needed in these areas.

The present study explored whether specific SNPs within the *DAOA* gene, which have been previously investigated in association with MDD and BD, including rs3916966, rs3916967, rs2391191 and rs778293,[6,7,9,10] as well as additional SNPs that, to date, have received little or no attention including, rs3916968, rs7139958 and rs9558571,[11] could be associated with MDD and BD in an independent Korean sample population. The study also investigated whether such variants could predict clinical outcomes in groups of patients with MDD and BD treated with antidepressants and mood stabilizers, respectively.

Patients and methods

STUDY POPULATION

Data on consecutive in-patients with MDD or BD who had been treated at the Department of Psychiatry of The Catholic University of Korea College of Medicine, Seoul, Republic of Korea between January 2000 and December 2005 were included in the study. Eligibility for inclusion was a documented clinical diagnosis of MDD or BD according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria, as assessed by the Mini-International Neuropsychiatric Interview.[12] Data from a further cohort of psychiatrically healthy Korean subjects, who underwent the same assessment as the psychiatric patients to exclude possible psychiatric disorders and who originated from the same location as the psychiatric patients, were included for comparison of genotype and allele frequencies with the patient groups.

Treatments, concomitant comorbidities and first onset were not restricted versus subsequent disease episodes. Exclusion criteria comprised severe or unstable medical and neurological conditions, treatment with a long-acting antipsychotic, concomitant alcohol and substance abuse disorders, or if the patients were not Korean. All patients admitted to the hospital were assessed for

illness severity at baseline and at discharge by psychometric questionnaires specific for each condition. Severity of MDD was assessed by the Montgomery–Asberg Rating Scale for Depression (MADRS),[13] and mania severity in patients with BD was assessed by the Young Mania Rating Scale (YMRS).[14] Additionally, the following clinical and demographic variables were recorded: sex, age, clinical subtype, age at disorder onset, familial history of psychiatric disorders, lifetime suicide attempts, duration of admission, drugs at discharge and concomitant use of anxiolytics.

The study protocol was approved by the Institutional Review Board of Bucheon St Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea (approval No. HC10TISI0031). All patients provided written informed consent for inclusion of their data in the study.

STUDY ASSESSMENTS

The main outcome measures were: (i) differences between genotype and allele frequencies in the MDD or BD patients and healthy control subjects; and (ii) influences of the seven SNPs under investigation (rs3916966, rs3916967, rs2391191, rs3916968, rs7139958, rs9558571 and rs778293) on clinical improvement in the MDD or BD patients. The two groups of patients were analysed separately.

Additional outcomes included effects of the selected seven SNPs on the clinical and demographic variables, including baseline scores on each psychometric scale and response and remission rates. Both continuous and categorical analyses were performed. Based on previous studies, response was *a priori* defined as a $\geq$ 50% reduction in symptoms from baseline to discharge.[15–17] Remission was defined as a MADRS score $\leq$ 7 at discharge for patients with MDD[15] and as a YMRS score $\leq$ 12 for patients with BD.[18]

GENOTYPING OF *DAOA* SNPs

The SNPs were chosen from two groups of alleles: (i) those that had been investigated previously in association with MDD and BD and/or in response to pharmacological treatments of such diseases;[6,7,9,10] and (ii) those that had not previously (or had scarcely) been investigated but that had a reported prevalence of $\geq$ 5% for the variant allele among Asian populations (data obtained from the International Hapmap Project; http://hapmap.ncbi.nlm.nih.gov/).[11] Genomic DNA was extracted from blood and quantified using standard methods.[19] A high-throughput genotyping method using a pyrosequencer (Biotage, Uppsala, Sweden) was used for genotyping the seven *DAOA* SNPs (rs3916966, rs3916967, rs2391191, rs3916968, rs7139958, rs9558571 and rs778293). Polymerase chain reaction primers and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed using the Pyrosequencing Assay Design Software v1 (Biotage), and one primer of each primer set was biotinylated. Primer sequences are shown in Table 1.

STATISTICAL ANALYSES

Statistical analyses were performed using Statistica, version 5.0 (StatSoft Italia, Vigonza, Padua, Italy) for Windows®. Differences in the allele and genotype frequencies between healthy subjects and patients with MDD and BD and the effects of these variants on response and remission rates were calculated using the χ^2-test. Clinical improvements were calculated with a repeated-measures analysis of variance. In cases of positive findings, clinical variables associated with the outcome measure under investigation were added as covariates.

TABLE 1:
Primer sequences used in the study for genotyping the seven D-amino acid oxidase activator (*DAOA*) gene single nucleotide polymorphisms (SNPs)

DAOA SNP	Primer sequences
rs3916966	TTGCATAGCCACGTGGTTGGCTTCTATAGCATCACTTCACACTGTGGTCACCTGCCTTCT[A/C]CTCACTCAGGAACTTCTCTCCATTGAAGAAGTTCTTCTTCCCCATCTCCAGGGCTTTCCC
rs3916967	AATTTTTCACAGGACATGACTGCCATAGCCATGATAGGGTCCCTGGCTAATCTTTCAATT[A/G]TGATAGCATCATAAGATAATTTTGAATATGAGGAGAGAAGAATAACTCTAGAACTGCAAT
rs2391191	TTTCTTTAATTTTTAGATCCAGATATACATTGGGTAAAATCTACTTCATAGGTTTTCAAA[A/G]GAGCATTCTTCTGAGCAAATCTGAAAACTCTCTAAACTCTATTGGTATGTTACTCTTTAT
rs3916968	GCATTCATGGATCCAATTACGTTTTTTGTCATGGTAAAAGCCACAGTGGATATATTAAAT[A/G]AGAGTGTGGTTTAAGAATGAAGGCCCAGGAGTCTGGAGATCTGGTTTCTAAGGCTGACTT
rs7139958	GCGTTTACATAGGAATTTTAAATTCAGCTTGTCAATTTCCACAATGTAGCTTGCTGGGAT[A/T]ACAGGGAAGCTATAGATGAATTTGGGGACAACTGACATCTTAAGAATATTATCTTCCAAC
rs9558571	GTTGTAGCAGCCTAGGAAACAAACCCACTCCCATCCCCATCACCTTATTTTGACAAGAGC[T/C]ACTTCAGCTCCTATGTGCCACCTGGTATCGTGCTTAGTCCCTTTATATGCTACTCCAGGC
rs778293	TAGGATGTCAGACTTTATTCTAATGATTTCTCCTAGTTGCCCCCCAAAATTGTATTCTAC[A/G]GTGTGATTTTAAAGCTGAATTTTCAAGATGATATTTCATATCTATATTTTCACAAGCTTT

Haploview 3.2 was used to generate a linkage disequilibrium map and to test for Hardy–Weinberg equilibrium.[20] Tests for associations using multimarker haplotypes were performed using the package haplo.score in the statistics environment 'R' (http://www.R-project.org) to compare response and remission rates among different haplotypes. Permutations (n = 10 000) were performed to estimate the global significance of the results for all haplotype analyses and to validate the expectation-maximization values.

All P-values were two-tailed. Statistical significance was calculated using the false discovery rate, which allows for a correction of multiple testing without being as conservative as with the Bonferroni correction.[21] A value of $P < 0.05$ was considered to be statistically significant.

The study had sufficient power (0.80) to detect a small–medium effect size ($\omega = 0.16$), which corresponded to an odds ratio of 1.94 among the three groups of patients and controls and to detect medium to medium–large (d = 32 and 34) effect sizes for patients with MDD and BD, respectively, carrying the rs3916968GG genotype compared with those carrying the GA genotype.[22] Such effect sizes corresponded to the possibility of detecting final differences in MADRS and YMRS scores of 5.8 and 3.7 points, respectively.

Results

Data from 145 in-patients with MDD (52% males; mean ± SD age 41.4 ± 14.1 years), 132 in-patients with BD (66% males; mean ± SD age 36.4 ± 11.6 years) and 170 healthy controls (62% males; mean ± SD age 38.8 ± 12.8 years) were included in the study. Demographic parameters and other clinical variables (sex, age, clinical subtype, age at disorder onset, familial history of psychiatric disorders, lifetime suicide attempts, duration

of admission, drugs at discharge and concomitant use of anxiolytics) were not significantly different between the patient groups and healthy controls.

Mean ± SD total MADRS scores at baseline and at discharge were 34.4 ± 9.0 and 17.1 ± 10.1, respectively, in patients with MDD (mean ± SD hospitalization 32.3 days ± 20.6 days) and mean ± SD total YMRS scores at baseline and at discharge were 33.3 ± 9.1 and 19.8 ± 5.3, respectively, in patients with BD (mean ± SD hospitalization 33.7 ± 21.1 days). Response and remission were achieved in 78 (54%) and 22 (15%) patients with MDD, respectively, compared with 33 (25%) and 10 (8%) patients with BD, respectively. In the patient groups, 36 (25%) MDD patients and 22 (17%) BD individuals had a history of suicide attempts.

All SNPs within the *DAOA* gene were in Hardy–Weinberg equilibrium in the entire sample. Strong linkage disequilibrium was observed among rs3916966, rs3916967 and rs2391191, and between rs7139958 and rs9558571. Patients and healthy volunteers, who were analysed separately, yielded similar results (data not shown).

No differences were observed between allele and genotype frequencies in patients with MDD or BD compared with healthy controls (Table 2). Notably, genotype and allele frequencies in the sample of healthy control subjects did not differ significantly from those obtained for the general Asian population from CHIP Bioinformatics Tools, SNPper (http://snpper.chip.org) (Table 2).

There was no association between the seven genotypes or alleles under investigation and clinical improvement, response rates, remission rates, or final outcomes for either of the disorders (data not shown). Sliding window haplotype analyses also failed to provide evidence for any association (data not shown).

Discussion

The present study explored whether specific SNPs within the *DAOA* gene (rs3916966, rs3916967, rs2391191, rs3916968, rs7139958, rs9558571 and rs778293) were associated with MDD and BD, and whether these same variants could predict clinical outcomes in patients with MDD or BD treated with antidepressants and mood stabilizers, respectively.

In contrast to a number of published case–control association studies,[4,7,9,10] the present study did not provide evidence for an association of any of the SNPs with MDD and BD. A large number of such studies have, however, been performed in Caucasian patients and there is incomplete overlap between the SNPs selected for analysis in the present study and those investigated in previous studies. Furthermore a number of other studies have found no association between *DAOA* variants and MDD and BD.[6,9,10] Others have stated that there could be consistent variations with regard to risk alleles and genotypes across studies or, alternatively, that such polymorphisms could contribute to disease susceptibility in some specific families but not in others,[6] pointing to the necessity of further investigation aimed at exploring the relationship between specific genetic variants within *DAOA* and psychiatric disorders.[8,9]

The present study did not demonstrate any influence of the seven SNPs on clinical improvement, or response and remission to treatment. Considering the dearth of studies exploring the influence of *DAOA* variants on responses to antidepressants and mood stabilizers, these findings should be considered with caution and further studies on adjacent variants are needed to draw more definitive conclusions.

There were several limitations to the

TABLE 2:
Comparison of allele and genotype frequencies according to single nucleotide polymorphism (SNP) of the gene for D-amino acid oxidase activator *(DAOA)* in Korean subjects with major depressive disorder and bipolar disorder with the frequencies in healthy controls and in the general population

DAOA SNP	Major depressive disorder (n = 145)	Bipolar disorder (n = 132)	Healthy controls (n = 170)	General population[a]	χ^2	Statistical significance
Alleles						
rs3916966	C 189 (65%) A 101 (35%)	C 164 (62%) A 100 (38%)	C 221 (65%) A 119 (35%)	C 57% A 43%	0.73	NS
rs3916967	G 190 (65%) A 100 (35%)	G 163 (62%) A 101 (38%)	G 221 (65%) A 119 (35%)	G 58% A 42%	1.05	NS
rs2391191	A 191 (66%) G 99 (34%)	A 163 (62%) G 101 (38%)	A 221 (65%) G 119 (35%)	A 59% G 41%	1.20	NS
rs3916968	G 211 (73%) A 79 (27%)	G 186 (70%) A 78 (30%)	G 234 (69%) A 106 (31%)	G 79% A 21%	4.87	NS
rs7139958	A 177 (61%) T 113 (39%)	A 148 (56%) T 114 (44%)	A 209 (61%) T 131 (39%)	A 55% T 45%	1.77	NS
rs9558571	T 161 (55%) C 129 (45%)	T 132 (50%) C 130 (50%)	T 178 (52%) C 162 (48%)	T 51% C 49%	2.63	NS
rs778293	NA	A 193 (73%) G 71 (27%)	A 246 (72%) G 94 (28%)	A 68% G 32%	0.26	NS
Genotypes						
rs3916966	CC 65 (45%) CA 59 (41%) AA 21 (14%)	CC 50 (38%) CA 64 (48%) AA 18 (14%)	CC 76 (45%) CA 60 (40%) AA 25 (15%)	CC 36% CA 42% AA 22%	3.05	NS
rs3916967	GG 65 (45%) GA 60 (41%) AA 20 (14%)	GG 65 (49%) GA 49 (37%) AA 18 (14%)	GG 69 (41%) GA 76 (45%) AA 25 (15%)	GG 38% GA 40% AA 22%	3.44	NS
rs2391191	AA 59 (41%) AG 66 (45%) GG 20 (14%)	AA 49 (37%) AG 65 (49%) GG 18 (14%)	AA 76 (45%) AG 69 (40%) GG 25 (15%)	AA 38% AG 41% GG 21%	3.75	NS
rs3916968	GG 77 (53%) GA 57 (39%) AA 11 (8%)	GG 67 (51%) GA 52 (39%) AA 13 (10%)	GG 78 (46%) GA 78 (46%) AA 14 (8%)	GG 63% GA 32% AA 5%	6.21	NS
rs7139958	AA 53 (37%) AT 71 (49%) TT 21 (14%)	AA 39 (30%) AT 70 (53%) TT 22 (17%)	AA 63 (37%) AT 83 (49%) TT 24 (14%)	AA 32% AT 45% TT 23%	6.23	NS
rs9558571	TT 45 (31%) TC 71 (49%) CC 29 (20%)	TT 31 (24%) TC 70 (53%) CC 30 (23%)	TT 43 (25%) TC 92 (54%) CC 35 (21%)	TT 27% TC 48% CC 25%	8.16	NS
rs778293	NA	AA 69 (52%) AG 55 (42%) GG 8 (6%)	AA 88 (52%) AG 70 (41%) GG 12 (7%)	AA 46% AG 44% GG 10%	1.96	NS

[a]Percentages in the general Asian population were obtained from CHIP Bioinformatics Tools, SNPper (http://snpper.chip.org).
NA, data not available; NS, not statistically significant ($P \geq 0.05$).

present study that should be carefully considered. First, current genetic studies are associated with a high likelihood of false-positive or false-negative findings.[23] Accordingly, the lack of an association of the SNPs under investigation with diagnosis and clinical improvement could simply be related to the lack of statistical power, which could obscure small effects exerted by single SNPs. Genetic heterogeneity was not specifically controlled for, but the Korean population is considered quite homogeneous.[24] A further concern is related to the use of several drugs with different mechanisms of action by the different cohorts, which did not allow definitive conclusions with regard to the influence of the SNPs on specific drugs or classes of medications. The decision to include patients treated with different drugs could, however, have the advantage of being closer to actual clinical practice. The duration of hospitalization may have been insufficient to ascertain a lack of response and remission, although the timeframe was consistent with common clinical practice.[25] Finally, only seven SNPs (data obtained from http://hapmap.ncbi.nlm.nih.gov/) were investigated, but the *DAOA* gene includes 183 validated SNPs and, therefore, only 4% of the available genes were included.

The present study suggests that the seven *DAOA* gene SNPs investigated may not affect disease phenotypes, clinical improvement or other MDD and BD clinical factors, indicating that these seven SNPs are unlikely to be involved in the development and treatment outcomes of these disorders. Although there was no evidence to show that these seven *DAOA* gene SNPs were associated with the development and treatment of patients with MDD and BD, the results may help to define the limited effects that these seven *DAOA* variants have on the development and treatment of MDD and BD. It was clearly shown that MDD and BD are complex (multifactorial) disorders and that the discovery of predisposing genes is just as important as identifying environmental factors and should provide clues to pathogenesis, treatment and prevention.

Finally, further adequately powered, well-designed studies are needed to draw more definitive conclusions. We propose that future studies consider the small effects of such SNPs, include larger samples such as cohorts or trios, provide a biological rationale for the relationship of the DAOA variants to MDD and BD (select functional variants) and consider multiple comparison issues in a prospective clinical trial with control of medication and epistasis/epigenesis.

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Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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Author's address for correspondence
Dr Chi-Un Pae
Department of Psychiatry, Bucheon St Mary's Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Bucheon, Kyeonggi-Do 420-717, Republic of Korea.
E-mail: pae@catholic.ac.kr