Association of a Nonsynonymous Variant of *DAOA* with Visuospatial Ability in a Bipolar Family Sample

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Background: Bipolar disorder and schizophrenia are hypothesized to share some genetic background.

Methods: In a two-phase study, we evaluated the effect of five promising candidate genes for psychotic disorders, *DAOA*, *COMT*, *DTNBP1*, *NRG1,* and *AKT1*, on bipolar spectrum disorder, psychotic disorder, and related cognitive endophenotypes in a Finnish family-based sample ascertained for bipolar disorder.

Results: In initial screening of 362 individuals from 63 families, we found only marginal evidence for association with the diagnosis-based dichotomous classification. Those associations did not strengthen when we genotyped the complete sample of 723 individuals from 180 families. We observed a significant association of *DAOA* variants rs3916966 and rs2391191 with visuospatial ability (Quantitative Transmission Disequilibrium Test [QTDT]; $p = 4 \times 10^{-6}$ and 5×10^{-6}, respectively) ($n = 159$) with the two variants in almost complete linkage disequilibrium. The *COMT* variant rs165599 also associated with visuospatial ability, and in our dataset, we saw an additive effect of *DAOA* and *COMT* variants on this neuropsychological trait.

Conclusions: The ancestral allele (Arg) of the nonsynonymous common *DAOA* variant rs2391191 (Arg30Lys) was found to predispose to impaired performance. The *DAOA* gene may play a role in predisposing individuals to a mixed phenotype of psychosis and mania and to impairments in related neuropsychological traits.

Key Words: AKT1, bipolar disorder, COMT, DAOA, DTNBP1, G72, neuropsychological trait, NRG1

Bipolar disorder (BPD) is a severe mental disorder characterized by alternating episodes of depression and mania (bipolar type I [BPD-I]) or hypomania (bipolar type II [BPD-II]). Certain cognitive impairments such as poor executive functioning and verbal memory have been related to disease susceptibility (1). Despite being considered distinct clinical disorders, BPD and schizophrenia share many clinical features and treatment approaches. Sixty percent of BPD-I patients have psychotic symptoms during their lifetime (2). Bipolar disorder and schizophrenia co-segregate in many pedigrees (3), which suggest a shared genetic etiology of these two disorders at least to some extent.

In our previous study, we found evidence for contribution of distinct variants of the disrupted-in-schizophrenia 1 (*DISC1*) gene to features of bipolar spectrum and psychotic disorders in Finnish families ascertained for BPD (4). We screened the same set of BPD families for several promising candidate genes for psychotic disorders: d-amino acid oxidase activator (*DAOA* or *G72*) (5), catechol-O-methyl transferase (*COMT*) (6), dystrobrevin binding protein 1 (dysbindin or *DTNBP1*) (7), neuregulin 1 (*NRG1*) (8), and v-akt murine thymoma viral oncogene homolog 1 (*AKT1*) (9). Except for *AKT1*, these genes have been reported to associate with various neuropsychological traits within affected individuals or healthy control subjects (Supplement 1). We evaluated the effects of variations in these genes both on clinical diagnosis of bipolar spectrum disorder or psychotic disorder, as well as on cognitive functions considered as endophenotypes (or intermediate traits) for these disorders (10).

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Methods and Materials

Study Sample

The study sample includes 723 individuals from 180 families (4) (Table 1); neuropsychological test data were available altogether for 159 individuals from 65 of the families (11) (Table 1). Ascertainment strategy and sample collection are described in Supplement 2. The study was approved by the Ministry of Social Affairs and Health and the Ethical Committee of the National Public Health Institute.

Single Nucleotide Polymorphism Selection and Genotyping

We selected single nucleotide polymorphisms (SNPs) from published findings (5-9) and from the public SNP database, dbSNP (http://www.ncbi.nlm.nih.gov). Genotyping was done with homogeneous mass extension using the MassARRAY System (Sequenom, San Diego, California) in multiplexes of two to six SNPs. The *COMT* variants were genotyped by microarray-based allele-specific primer extension method (12). Genotyping was performed in two phases. Phase I was an initial screening involving 362 individuals from 63 families. In phase II, we examined an additional 361 individuals from 117 families.

Statistical Analysis

Association analyses using dichotomized diagnostic classes (bipolar spectrum disorder and psychotic disorder) were performed by haplotype relative risk (HRR) test of the ANALYZE package (13) for two-point analyses and by FBAT (14) for

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Table 1. Number of Individuals in Phase I and Phase II of the Study and the Total Number of Familial Cases

	Phase I		Phase II		Familial
	Female	Male	Female	Male	Cases[a]
Affected	78 (32)	89 (30)	65 (4)	84 (14)	258
Bipolar spectrum disorder[b]	59 (29)	68 (24)	50 (4)	50 (9)	173
Psychotic disorder[c]	66 (27)	65 (25)	51 (4)	69 (12)	212
In both categories[d]	47 (24)	44 (19)	36 (4)	35 (7)	127
Other mental disorder[e]	22 (14)	12 (8)	5 (2)	7 (3)	45
Unaffected	92 (29)	69 (21)	116 (1)	84 (1)	241
Total Genotyped	192 (75)	170 (59)	186 (7)	175 (18)	544

The number of neuropsychologically tested individuals is shown in parentheses.

BPD-I, bipolar disorder type I; BPD-II, bipolar disorder type II; NOS, not otherwise specified.

[a]The familial cases are from 118 families with more than one affected individual.

[b]Contains BPD-I ($n = 214$), BPD-II ($n = 5$), bipolar disorder NOS ($n = 6$), and cyclothymia ($n = 2$) cases.

[c]Contains BPD-I with intermittent psychotic features ($n = 162$), psychotic depression ($n = 15$), schizophrenia ($n = 14$), schizoaffective disorder ($n = 51$), and psychotic NOS ($n = 9$). Numbers are from the whole sample.

[d]Overlap between bipolar spectrum and psychotic disorder categories.

[e]Contains depression, alcohol-, related disorders and delusional, adjustment, dysthymic, and panic disorders.

haplotype analyses. Unaffected family members and individuals with other mental disorders were coded as unknown. Analyses were done using two different sample sets, the first including all individuals genotyped and the second including only familial cases, defined as cases from families with two or more affected members. We used the Quantitative Transmission Disequilibrium Test (QTDT) software package (15) with the polygenic variance component option and performed association analyses of quantitative traits with the total association model assuming no population stratification. Age, gender, and presence of psychosis (16) were used as covariates. Statistical comparisons of the results in different genotyped groups and diagnostic categories were analyzed by SPSS 14.0 (SPSS Inc., Chicago, Illinois) using one-way analysis of variance (ANOVA). Interaction analysis was done by logistic regression backward stepwise model.

Results

We initially screened 51 SNPs of the selected genes (Supplement 3) in 362 individuals from 63 families (Table 1). The most significant association of dichotomized phenotype was obtained for *COMT* variant rs165599 with bipolar spectrum disorder (HRR; $p = .003$) (Supplement 3). Adjacent 2-SNP haplotype analysis showed no evidence for association with either bipolar spectrum or psychotic disorder (Supplement 4). Several *DAOA* variants were associated with neuropsychological traits (Supplement 5). The strongest associations were seen between *DAOA* variants rs3916966 and rs2391191 (Arg30Lys) and visuospatial ability assessed with the Block Design test ($p = .0006$ and $p = .0008$, respectively).

We focused our analysis on *DAOA* and *COMT* and genotyped all 723 individuals from 180 families using six *DAOA* variants (rs3916966, rs2391191, rs2153674, rs701567, rs778326, and rs954580) and two *COMT* variants (rs165599 and rs4680, also known as valine [Val]158 methionine [Met]).

In the complete sample, the *COMT* variant rs4680 was the only variant that associated with bipolar spectrum disorder in the complete sample (Table 2). In the familial sample, both rs4680 and rs165599 showed suggestive evidence of association with bipolar spectrum disorder. D-amino acid oxidase activator (*DAOA*) variants rs701567 and rs778326 were suggestively associated with psychotic disorder in the familial sample. For both genes, analysis of 2-SNP haplotypes yielded no further evidence of association (data not shown).

Analysis of the full study sample strengthened the previously observed association between *DAOA* variants rs3916966 and rs2391191 (Arg30Lys) and visuospatial ability (Table 3). These two variants are in almost perfect linkage disequilibrium ($r^2 = .98$). Visuospatial performance differed significantly between the Arg and Lys genotype groups of rs2391191, with the worst performance observed in individual homozygotes for the ancestral G (Arg) allele (Table 4, Figure 1). All study subjects performing above the average, i.e., achieving over 40 points in the Block Design test ($n = 27$), were either homozygous or heterozygous for the A (Lys) allele.

Catechol-O-methyl transferase (*COMT*) variant rs165599 associated with visuospatial ability. Individuals homozygous for the G allele had the best test performance among the rs165599 genotype groups. This difference was statistically significant in the full sample and in the psychotic subgroup but not in the nonpsychotic subgroup (Table 4).

Table 2. Association Between Single SNP and Disease Status in Phase I, Combined Phase I and Phase II, and Familial Cases Using HRR Analysis

	Bipolar Spectrum Disorder			Psychotic Disorder		
	Phase I (62 Families)	Phase I + II (154 Families)	Familial Cases[a] (99 Families)	Phase I (57 Families)	Phase I + II (144 Families)	Familial Cases[a] (102 Families)
DAOA						
rs3916966	.696	.966	.906	.843	.839	.616
rs2391191	.889	.913	.735	.87	.891	.349
rs2153674	.072	.353	.095	.066	.700	.233
rs701567	.670	.593	.407	.278	.133	.031
rs778326	.025	.111	.024	.010	.186	.018
rs954580	.040	.107	.052	.049	.565	.252
COMT						
rs4680	.085	.046	.020	.340	.072	.149
rs165599	.003	.829	.035	.015	.396	.103

COMT, catechol-O-methyl transferase; *DAOA*, d-amino acid oxidase activator; HRR, haplotype relative risk; SNP, single nucleoide polymorphism.

[a]Familial cases include only families that contain at least two affected individuals.

Table 3. Association Between Neuropsychological Traits and Candidate Gene Variants Genotyped in the Combined Sample Using QTDT Analysis

	DAOA					*COMT*	
Neuropsychological Trait	rs3916966	rs2391191	rs2153674	rs701567	rs954580	rs4680	rs165599
General Intellectual Functioning (WAIS-R)							
General ability (Vocabulary)	.0015	.0002	.0086	.0083	.0051	.1381	.1801
Abstraction (Similarities)	.0010	.0003	.0063	.0173	.1428	.1191	.2103
Psychomotor speed (Digit Symbol)	.0013	.0034	.0953	.0125	.2591	.0986	.0051
Visuospatial ability (Block Design)	4.00E-06[a]	5.00E-06[a]	.0638	.0108	.0392	.0191	.0007
Attention, Working Memory (WMS-R)							
Auditory attention (Digit Span forward)	.0091	.0088	.0991	.1948	.0724	.2769	.5932
Verbal working memory (Digit Span backward)	.0298	.0213	.1089	.4111	.6239	.4017	.8425
Visual attention (Visual Span forward)	.1899	.1374	.6787	.2073	.2443	.8875	.9947
Visual working memory (Visual Span backward)	.7120	.5995	.9652	.7439	.5356	.7039	.4952
Verbal and Visual Memory (WMS-R)							
Immediate verbal memory (Logical Memory I)	.1176	.0602	.4636	.7139	.7698	.9536	.8925
Delayed verbal memory (Logical Memory II)	.1076	.0638	.8161	.5091	.4862	.5853	.4035
Immediate visual memory (Visual Reproduction I)	.0047	.0047	.2174	.2841	.1352	.0628	.1468
Delayed visual memory (Visual Reproduction II)	.0005	.0010	.2658	.1316	.2061	.1200	.2613
Verbal Learning and Memory (CVLT)							
Free short delay recall	.0032	.0024	.0537	.1016	.1397	.0891	.4644
Free long delay recall	.0443	.0206	.2987	.5264	.7442	.0054	.0570
Recognition memory	.0173	.0079	.1617	.4569	.5709	.1076	.4686
Retention	.9571	.4473	.4304	.8079	.2869	.0391	.0016
Executive Functions							
Stroop Interference score	.0162	.0060	.3567	.0047	.3510	.3090	.7938
Semantic fluency (COWAT)	.0195	.0239	.8410	.0168	.3594	.5887	.4003
Phonemic fluency (COWAT)	.4183	.4524	.0369	.4284	.4841	.6706	.5438

COMT, catechol-O-methyl transferase; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; *DAOA*, d-amino acid oxidase activator; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised; QTDT, Quantitative Transmission Disequilibrium Test.
[a] p values that remained significant ($p < .05$) after conservative Bonferroni correction.

As shown in Table 4, individuals homozygous for both the ancestral allele G (Arg) of *DAOA* variant rs2391191 and the T allele of *COMT* variant rs165599 performed worse in the Block Design test (mean test score = 15.6) than did subjects homozygous only for the *DAOA* rs2391191 G allele (mean test score = 24.8) or the *COMT* rs165599 T allele (mean test score = 28.6). However, backward stepwise logistic regression showed no evidence for significant interaction between the two variants ($p = .5$ for rs2391191*rs165599). Decreased test performance in the doubly homozygous subjects suggests a minor additive effect of *DAOA* and *COMT* variants on visuospatial ability, without evidence for epistasis.

Discussion

D-amino acid oxidase activator (*DAOA*) is a primate-specific gene encoding mitochondrial protein that promotes mitochondrial fragmentation and dendritic branching (17). D-amino acid oxidase activator (*DAOA*) may be involved in glutamate signaling (5), which has been shown to have multiple effects on learning and memory (18). Like some other genes encoding mitochondrial proteins in primates, the *DAOA* gene has evolved rapidly; the open reading frame of the human gene is twice as long as that of the chimpanzee homolog (5).

The strongest finding of our study was the association of a nonsynonymous *DAOA* variant, rs2391191 (Arg30Lys), with visuospatial ability, which remains significant after a conservative Bonferroni correction for multiple testing (corrected $p = .005$). In a recent study (19), the Arg allele associated with impairment in immediate and delayed verbal memory. In the present study, this allele showed only a trend for association with verbal memory ($p < 0.1$), but it predisposed to impairment with many other cognitive traits, most significantly with visuospatial ability. Thus, our data further strengthen the possibility that the Arg30Lys variation might affect cognitive functioning. Interestingly, the Lys allele that associated here with enhanced performance in the tests of general intellectual functioning is found only in humans, suggesting that *DAOA* might have played a part in the evolution of *Homo sapiens* when greater cognitive functions developed as the brain increased in size.

Catechol-O-methyl transferase (*COMT*) variant rs4680 (Val158Met) associated here nominally with familial bipolar spectrum disorder, but the risk allele (Met) was different from that reported by

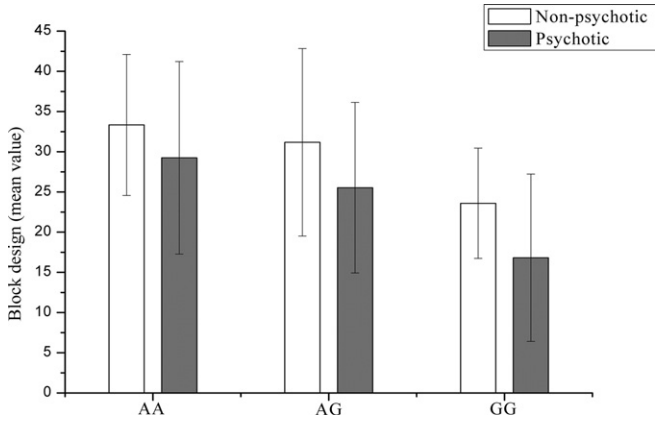

Figure 1. Block Design test results for *DAOA* rs2391191 genotype groups. Average values of nonpsychotic individuals (white bars) and individuals with psychotic disorder (gray bars) are shown. Also, the standard deviation bar is shown. *DAOA,* d-amino acid oxidase activator.

Table 4. The Effect of *DAOA* Variant rs2391191 and *COMT* Variant rs165599 on Visuospatial Ability (Block Design), Showing Mean Values of Block Design Test in Cross Table of *DAOA* rs2391191 and *COMT* rs165599 Genotypes in All Individuals and in Psychotic and Nonpsychotic Groups

	DAOA Variant rs2391191													
	All					Psychotic				Nonpsychotic				
COMT Variant rs165599	AA	AG	GG	Mean (*n*)	*p* value	AA	AG	GG	Mean (*n*)	*p* value	AA	AG	GG	Mean (*n*)	*p* value
CC	30.6 (7)	38.1 (8)	28.2 (5)	34.1 (22)	.009	35.7 (3)	40.5 (4)	22.0 (1)	33.2 (9)	.013	39.3 (4)	35.8 (4)	29.8 (4)	34.8 (139)	.252
CT	32.2 (16)	26.8 (28)	23.3 (12)	28.0 (61)		34.8 (5)	22.7 (12)	23.3 (4)	25.9 (22)		30.8 (11)	30.0 (16)	23.4 (8)	29.2 (39)	
TT	29.5 (20)	28.1 (37)	15.6 (16)	25.7 (73)		23.1 (8)	23.9 (16)	14.0 (11)	20.9 (36)		33.7 (12)	31.2 (21)	19.0 (5)	30.4 (37)	
Mean (*n*)	31.8 (43)	28.7 (73)	20.3 (33)			29.3 (16)	25.7 (33)	16.0 (15)			33.3 (27)	31.2 (40)	23.9 (18)		
p value		2.3E-05					.003					.008			

The numbers of individuals that belong to a specific genotype group are in parentheses. The mean scores and the *p* values from one-way ANOVA are shown for each genotype group separately.
ANOVA, analysis of variance; *COMT*, catechol-O-methyl transferase; *DAOA*, d-amino acid oxidase activator.

Shifman *et al.* (6). Variant rs165599 was also associated with visuospatial ability, with the best test performance seen in individuals homozygous for the C allele. An earlier study showed association of the *COMT* variant rs165599 with verbal memory in Caucasians (20), but better performance was associated with the T allele. The incoherence in findings on the effect of *COMT* on neuropsychological performance likely results from a relatively weak effect and the genetic heterogeneity behind these traits.

We found a minor additive effect of *DAOA* and *COMT* on visuospatial ability, a finding consistent with the hypothesis that interaction of glutamatergic (*DAOA*) and dopaminergic (*COMT*) neurotransmission is fundamental for many cognitive functions, particularly working memory (18). We recognize that all neuropsychological traits assessed in the present study may be state-dependent; however, many of the observed deviations are also found in euthymic BPD patients (1). Furthermore, our finding of association of *DAOA* with visuospatial ability did not result from an underlying effect of *DAOA* genotype to other illness-related parameters, such as medication or age of onset (data not shown). While there are no data for visuospatial ability being a good endophenotype for BPD, there is at least one study that showed impaired general intellectual function in relatives of psychotic patients (21). Other *DAOA* variants also associated weakly with psychotic disorder. The *DAOA* gene may play a role in predisposing individuals to a mixed phenotype of psychosis and mania and to impairments in related neuropsychological traits. However, further research is necessary to define the effect of *DAOA* on the complex processes of brain functions.

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Supplementary material cited in this article is available online.

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