Genetic Association Study of Treatment Response With Olanzapine/Fluoxetine Combination or Lamotrigine in Bipolar I Depression

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Objective: To evaluate common genetic variations for association with symptomatic improvement in bipolar I depression following treatment with olanzapine/fluoxetine combination (OFC) or lamotrigine.

Method: Symptom improvement was assessed in 88 OFC-treated and 85 lamotrigine-treated white patients with bipolar I depression in the 7-week acute period of a randomized, double-blind study comparing OFC (6/25, 6/50, 12/25, or 12/50 mg/d [olanzapine/fluoxetine]) with lamotrigine (titrated to 200 mg/d). The original study was conducted from November 2003 to August 2004. Single nucleotide polymorphisms (SNPs) were genotyped in a set of 19 candidate genes corresponding to known sites of activity for olanzapine and fluoxetine or previously associated with antidepressant or antipsychotic response. Primary outcome was the reduction in Montgomery-Asberg Depression Rating Scale (MADRS) total score as assessed by the difference by genotype from baseline to week 7 from a mixed-effects repeated measures analysis with terms for visit, genotype, genotype-by-visit interaction, and baseline MADRS score as a covariate.

Results: SNPs within the dopamine D_3 receptor and histamine H_1 receptor (*HRH1*) genes were significantly associated with response to OFC. SNPs within the dopamine D_2 receptor, *HRH1*, dopamine β-hydroxylase, glucocorticoid receptor, and melanocortin 2 receptor genes were significantly associated with response to lamotrigine.

Conclusions: SNPs in specific candidate genes were associated with symptomatic improvement in a treatment-specific fashion. These results suggest the importance of dopaminergic effects in the treatment of patients with bipolar I depression and the potential utility of genotyping in selection of pharmacologic treatments for bipolar depression.

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Major depressive episodes among patients with bipolar I depression are associated with significant morbidity, disability, and mortality.[1] The current American Psychiatric Association (APA) practice guidelines recommend either lithium or lamotrigine as first-line treatment for bipolar I depression, while olanzapine/fluoxetine combination (OFC) and quetiapine are currently the only treatments for acute bipolar I depression approved by the US Food & Drug Administration.[2–4] The efficacy and safety of OFC (N = 205) and lamotrigine (N = 205) were evaluated in the acute phase (7 weeks) of a multicenter, randomized, double-blind study[5] of inpatients or outpatients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[6] diagnostic criteria for bipolar I disorder, depressed. It was an option for patients in this study to consent to provide a sample for genetic analysis.

Both treatments showed significant interindividual variation in therapeutic efficacy. Variation in genes involved in the mechanism of action of individual medications may account for some of this interindividual variation.[7] For instance, polymorphisms in the dopamine D_3 receptor (*DRD3*) gene have been associated with greater positive symptom response to olanzapine in patients with schizophrenia.[8,9] The ability to predict treatment response in bipolar depression would be of great value in making rational therapeutic choices for individualized patient therapy. Therefore, this exploratory study examined variations in a set of candidate genes corresponding to known or putative mechanisms of actions of olanzapine and fluoxetine, as well as those previously reported to be predictors of response for antidepressant or antipsychotic medications, for association with depressive symptom improvement and remission.

METHOD

Subjects

Subjects were adult outpatients or hospital inpatients from a randomized, double-blind study conducted in the United States from November 2003 to August 2004 comparing OFC with lamotrigine treatment; details of the overall study population and design have been previously

Table 1. Baseline Characteristics of Patients Taking Lamotrigine or OFC for Bipolar Depression[a]

Characteristic	Genotyped Patients: Lamotrigine n = 85	Genotyped Patients: OFC n = 88	All Patients N = 173[a]	All Patients From Parent Trial N = 410
Male sex, n (%)	38 (44.7)	39 (44.3)	77 (44.5)	164 (40.0)
Age, mean (SD), y	36.6 (11.4)	35.5 (11.6)	36.0 (11.5)	37.0 (11.1)
CGI-S score, mean (SD)	4.8 (0.7)	4.7 (0.7)	4.8 (0.7)	4.6 (0.6)
MADRS total score, mean (SD)	32.3 (5.1)	31.4 (5.3)	31.9 (5.2)	31.0 (5.4)
YMRS total score, mean (SD)	5.0 (3.5)	4.7 (3.2)	4.8 (3.4)	4.9 (3.3)

[a]One patient was missing a value for therapy and was not included in the lamotrigine group or OFC group.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination, YMRS = Young Mania Rating Scale.

reported.[6] Relevant inclusion criteria included the following: patients met *DSM-IV-TR* diagnostic criteria for bipolar I disorder, depressed, on the basis of the *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-P)[10]; they had a minimum Montgomery-Asberg Depression Rating Scale (MADRS)[11] total score of 20; and they had a minimum Clinical Global Impressions-Severity of Illness (CGI-S)[12] score of 4 (moderate). Patients were randomly assigned in a 1:1 fashion to treatment with OFC (6/25, 6/50, 12/25, or 12/50 mg/d) and lamotrigine (titrated to 200 mg/d). The study protocol was approved by institutional review boards, and written informed consent was obtained from all participants prior to study entry. Of the 410 patients enrolled in the clinical trial, 212 consented at the initial study visit to donate a blood sample for genetic analysis. Of these subjects, 173 white subjects were used in this analysis (Table 1). Genotype association analysis was limited to white patients to minimize the effects of population stratification. Single nucleotide polymorphisms (SNPs) used to evaluate population substructure are typically selected with the understanding that they have no association with the endpoint being examined. All the SNPs examined here are within candidate genes, so we could not formally use them to assess population substructure. However, the inflation factor due to stratification, lambda,[13] was estimated to be 1.03 using all of the genotyped SNPs, suggesting only minor or no confounding effects of population substructure.

Clinical Assessments

Depressive symptoms were assessed at each weekly study visit with the MADRS.[11] Response was defined as mean change in MADRS total scores from baseline to the end of the acute treatment period at 7 weeks on the basis of repeated measures.

Genotyping

Nineteen genes were selected for genotyping (Table 2), including 5 serotonergic, 5 dopaminergic, 2 α-adrenergic, and 2 histamingeric genes. Genotyping was performed on a subset of white patients (n = 173) from the larger study who agreed to donate a DNA sample at baseline for analysis. Genotyping was performed by Cogenics (Newton, Massachusetts) using the MassArray platform[14] for SNPs and polymerase chain reaction (PCR) characterization for 2 length variation and 1 insertion/deletion polymorphisms: (1) Two major alleles (termed short [s] and long [l]) and 1 minor allele (termed extra long [xl]) correspond to the presence of 14 versus 16 versus 18 20–23 base pair repeat elements in the serotonin transporter gene-linked polymorphic region (*SLC6A4*)[15]; (2) a 48 base pair segment in exon 3 of the coding region of dopamine D_4 (receptor *DRD4*) is characterized by a varying number of direct imperfect 48 base pair repeats[16]; and (3) a 19 base pair insertion/deletion in the dopamine β-hydroxylase promoter characterized using Titanium Taq DNA polymerase[17] (Clontech, Leusden, The Netherlands).

Of 254 SNPs attempted, 232 were successfully genotyped in at least 190 individuals (90%); 99 of these SNPs were excluded prior to analysis because minor allele frequencies in the sample as a whole were less than 15%. A 15% minor allele frequency cutoff was used to ensure sufficient numbers of individuals per genotype and enhance the likelihood of results' having clinical utility. Likewise, of the 3 variable number tandem repeats (VNTRs) and insertion/deletion polymorphisms attempted, 3 were successfully genotyped in at least 190 individuals (90%). Four SNPs were out of Hardy-Weinberg Equilibrium ($P < .0001$)[18] and were excluded from analysis, leaving 129 SNPs that passed quality control (QC). Finally, 2 individuals were excluded from analysis because of a genotyping rate less than 85%. Among the remaining individuals, genotyping pass rates were above 89.5%. Of these individuals, 173 were white (on the basis of self-report).

Statistical Analyses

The assessment of the effect of genotype on change in MADRS scores was evaluated using the *P* value for a difference between genotype means at 7 weeks from a mixed-effects repeated measures (MMRM) analysis of variance with terms for visit, SNP, SNP-by-visit interaction, and baseline score as a covariate. For the term *SNP* in the MMRM model, SNP was entered as the number of variant alleles a subject had and was handled as a continuous variable. For the *SCL6A4* polymorphism, the genotypes s/s, s/l, l/l, and l/xl were coded as 0, 1, 2, and 3, respectively, and placed into the MMRM as a continuous variable. For the *DRD4* VNTR, the allele with the largest and smallest number of repeats was entered into the MMRM as a continuous variable. Correction for multiple testing within each gene was performed using the effective number of

Table 2. Mean (SD) Change in MADRS Total Score From Baseline to 7 Weeks of OFC or Lamotrigine Treatment in Patients With Bipolar I Depression by Significant (uncorrected $P < .05$ for at least 1 treatment group) Candidate Genotypes

Gene SNP (bp) (A/B)[a]	OFC Genotype AA	n	AB	n	BB	n	*P* Value	Corrected *P*[b]	Lamotrigine Genotype AA	n	AB	n	BB	n	*P* Value	Corrected *P*[b]
DRD3																
rs167770 (A/G)[c]	−17.9 (11.6)	27	−24.6 (7.8)	28	−24.8 (6.9)	5	.001	.007	−15.9 (9.9)	38	−22.2 (11.7)	21	−24.0 (8.5)	6	.019	.103
rs6280 (C/T)	−22.7 (7.9)	9	−23.6 (8.4)	25	−19.4 (11.7)	24	.033	.181	−21.9 (12.1)	8	−20.4 (11.3)	23	−16.8 (10.1)	34	0.215	1.000
HRH1																
rs346070 (C/T)[d]	−21.7 (10.8)	42	−21.7 (7.1)	13	−8.0 (0.0)	2	.043	.043	−19.9 (10.7)	44	−17.6 (10.6)	18	−8.0 (7.9)	3	.039	.039
ANKK1																
rs11214601 (C/T)	−22.4 (10.5)	36	−19.9 (9.5)	23	…	0	.615	1.0	−16.9 (10.9)	45	−22.5 (8.8)	18	…	0	.021	.044
rs1800497 (*Taq*1A) (C/T)	−23.4 (10.5)	33	−19.6 (9.9)	22	−18.4 (6.8)	5	.246	.513	−16.6 (11.1)	38	−22.5 (9.7)	23	−19.5 (7.8)	2	.019	.040
DRD2																
rs4245147 (C/T)	−21.9 (9.1)	10	−20.4 (10.6)	28	−23.0 (10.1)	22	.557	1.0	−11.4 (10.9)	14	−19.1 (9.4)	34	−24.0 (10.5)	1	<.0001	.010
DRD4																
rs936461 (A/G)	−24.0 (10.7)	5	−21.6 (9.5)	27	−19.6 (10.9)	24	.335	.335	−9.3 (16.6)	3	−18.2 (9.9)	33	−21.6 (10.9)	25	.046	.046
DBH																
rs1076153 (G/T)	−21.0 (10.6)	41	−23.0 (9.0)	19	…	0	.289	.289	−17.1 (10.8)	38	−20.5 (10.3)	26	−34.0 (NA)	1	.038	.038
MC2R																
rs4464147 (A/G)	−8.0 (NA)	1	−20.4 (11.2)	25	−22.2 (9.2)	26	.0200	.038	−20.3 (8.9)	8	−19.1 (10.1)	31	−16.6 (12.0)	24	.106	.199
rs7228339[e] (C/G)	−22.0 (9.7)	15	−21.7 (10.9)	29	−21.1 (9.4)	16	.548	1.00	−22.4 (8.7)	14	−19.1 (10.2)	32	−16.3 (12.2)	18	.015	.028
rs5823275 (D/I)	−22.2 (9.2)	26	−21.0 (11.3)	26	−21.8 (9.8)	8	.285	.534	−16.7 (12.0)	26	−19.2 (10.0)	29	−22.5 (9.3)	10	.032	.059
NR3C1																
rs258747 (C/T)[f]	−20.0 (11.6)	17	−21.7 (10.0)	37	−25.7 (5.2)	6	.265	.269	−22.4 (9.7)	18	−19.0 (10.5)	37	−10.9 (10.5)	10	.004	.004
rs6198 (A/G)	−20.9 (9.9)	42	−21.9 (11.0)	15	−30.3 (2.3)	3	.151	.153	−17.1 (11.2)	44	−22.0 (9.2)	21	…	0	.024	.025

[a]Total number of polymorphisms analyzed across the genes: *ADRA1A* (22 SNPs), *ADRA2A* (2 SNPs), *ANKK1* (4 SNPs), *COMT* (1 SNP), *DBH* (1 SNP and 1 insertion/deletion), *DRD1* (4 SNPs), *DRD2* (33 SNPs), *DRD3* (12 SNPs), *DRD4* (2 SNPs and 1 VNTR), *HRH1* (2 SNPs), *HTR1A* (5 SNPs), *HRH2A* (6 SNPs), *HTR2C* (9 SNPs), *HTR6* (6 SNPs), *LEPR* (5 SNPs), *MC2R* (11 SNPs), *NPAS3* (1 SNP), *NR3C1* (3 SNPs), *SLC6A4* (2 SNPs).

[b]Correction for multiple testing within the gene was performed using the effective number of independent SNPs (M_{eff}) × *P* as described by Nyholt.[19]

[c]In strong linkage disequilibrium (LD) with the following SNPs, which were also significantly associated with response to OFC and moderately associated with response to lamotrigine, respectively: rs324023 ($P = .009$ and .054) and rs324029 ($P = .009$ and .103).

[d]In strong LD with a Cogenics SNP, which was significantly associated with response to lamotrigine but not OFC (*P*: . 037 and .350, respectively).

[e]In strong LD with the following SNPs, which were also not significantly associated with response to OFC but were to lamotrigine, respectively: rs3888305 ($P = 1.000$ and .036), rs10853245 ($P = 1.000$ and .036), rs10853246 ($P = 1.000$ and .036), rs1940907 ($P = 1.000$ and .036), rs4308014 ($P = 1.000$ and .036), and rs4797825 ($P = 1.000$ and .036).

[f]In strong LD with rs6191, which was significantly associated with response to lamotrigine but not OFC ($P = .007$ and .340), respectively.

Abbreviations: bp = base pair, *DRD2* = dopamine D_2 receptor gene, *DRD3* = dopamine D_3 receptor gene, *DRD4* = dopamine D_4 receptor gene, *HRH1* = histamine H_1 receptor gene, NA = not applicable, OFC = olanzapine/fluoxetine combination, SNP = single nucleotide polymorphism.

independent SNPs (M_{eff}) × P as described by Nyholt.[19] Because the statistical power to detect associations was low, no experiment-wise correction was applied, as this was an exploratory analysis with a limited number of candidate genes with high prior probability of association and we were more concerned about type II than type I error. For the primary analysis, OFC- and lamotrigine-treated patients were analyzed separately. When the minor allele was associated with greater response in comparison to the more common allele, the genetic interaction was termed an association with response. When the minor allele was associated with less response in comparison to the more common allele, the genetic interaction was termed an association with nonresponse. Linkage disequilibrium (LD) was calculated with Haploview software (Broad Institute, Cambridge, Massachusetts).[20]

RESULTS

Subjects and Clinical Assessment

Genotyping was completed for 88 OFC- and 85 lamotrigine-treated white patients. Baseline patient and illness characteristics are shown in Table 1. The age, sex, and illness severity of genotyped patients appeared similar to that of the entire clinical cohort. The proportion of genotyped patients completing the 7-week acute phase of the study was 68.2% (60/88) for the OFC group and 77.6% (66/85) for the lamotrigine group.

Genotyping and Genetic Analyses

One hundred twenty-nine SNPs, 1 insertion/deletion polymorphism, and 2 length variation polymorphisms from 19 candidate genes met QC criteria and were used for analysis.

Association With Response

The *DRD3* SNP rs167770 and 2 other *DRD3* SNPs in strong LD were significantly associated with differences in depressive symptom response to OFC (Table 2). All 3 of these SNPs had a modest effect on lamotrigine response with a similar response pattern by genotype as OFC, but this association was not significant after correction for multiple testing. Two additional *DRD3* candidate SNPs were examined that were not significant at the gene-wise level. The SNP rs6280, which results in a ser/gly substitution (ser-9-gly), was in modest LD with the 3 SNPs significantly associated with OFC response: rs16770 (r^2 = .747), rs324029 (r^2 = .760), and rs324023 (r^2 = .762). There was a marginally significant effect for the rs6280 genotype on OFC response (uncorrected P = .033) but not for the lamotrigine arm (uncorrected P = .215). Another candidate *DRD3* SNP, rs2134655, in a different region of the gene, was also marginally associated with response to OFC (uncorrected P = .019) but not to lamotrigine (uncorrected P = .434).

Two histamine H_1 receptor (*HRH1*) SNPs in strong LD were associated with depressive symptom nonresponse to both OFC and lamotrigine (Table 2).

Finally, other polymorphisms associated with depressive symptom nonresponse to lamotrigine but not OFC included 3 SNPs in the dopamine D_2 receptor gene (*DRD2*)/*ANKK1*, 1 SNP in *DRD4*, 1 SNP in the dopamine β-hydroxylase gene (*DBH*), 3 SNPs in the glucocorticoid receptor gene (*NR3C1*), and a block of 7 strongly linked SNPs and 1 moderately linked SNP in the melanocortin 2 receptor gene (*MC2R*) (Table 2). Although none of these melanocortin SNPs associated with lamotrigine response were associated with response to OFC, an additional *MC2R* SNP rs4464147 was associated with response to OFC, but not to lamotrigine.

Only the *DRD3* SNPs rs16770, rs324029 and rs324023 were significantly associated with baseline MADRS (P = .038, .042, and 0.042, respectively), although not after adjustment for multiple comparisons. The clinical impact of these 3 SNPs was modest. For example, the mean ± SD baseline MADRS score was 31.2 ± 5.1 (n = 93), 32.0 ± 5.0 (n = 64), and 34.1 ± 6.1 (n = 18) for the AA, AG, and GG genotypes of rs16770, respectively.

DISCUSSION

This genetic association study, which is one of the first to examine treatment response in bipolar I depression, identified polymorphisms in 3 genes that were nominally associated with response to OFC and 5 genes nominally associated with response to lamotrigine. The SNPs in 2 genes were associated with response in both treatment arms.

A block of 3 intronic *DRD3* SNPs in strong LD were associated with response to OFC. These SNPs were in moderate LD with the frequently studied nonsynonymous ser-9-gly (rs6280) SNP. The minor gly allele of the ser-9-gly SNP and other minor SNP alleles in moderate LD were associated with greater response, whereas the minor rs2134655 allele in a separate haplotype block was associated with nonresponse (nonsignificant at gene-wise level). This pattern of association with OFC response in patients with bipolar disorder is similar to that shown in prior studies of olanzapine response in schizophrenia, which suggested that polymorphisms in the *DRD3* gene (including ser-9-gly) were associated with olanzapine positive symptom response (the gly allele being associated with greater response in both patient populations),[8,9] and the minor rs2314655 allele was associated with olanzapine positive symptom nonresponse.[9] Thus, it is very likely that the observed association with OFC response in the current study is due to the olanzapine component of OFC, although the results need to be confirmed. Olanzapine has moderate affinity for *DRD3* (K_i = 43.7 ± 8.95 nM), approximately 4-fold less than its affinity at *DRD2* (K_i = 10.5 ± 0.22 nM),[21] and *DRD3* antagonism may be an important site for olanzapine therapeutic efficacy. More broadly, dopaminergic neurotransmission has been implicated in the

pathophysiology of affective disorders, and dopaminergic modulation may be an important pathway for antidepressant mechanism of action.[22–24] *DRD3* may be particularly related to antidepressant activity due to its neuroanatomical localization in limbic regions of the brain. Vogel et al[25] found a decrease in *DRD3* messenger RNA (mRNA) in the lymphocytes of patients with schizophrenia or bipolar disorder compared to controls that reversed with treatment. The *DRD3* gene should therefore be considered a candidate for further studies of treatment response in bipolar disorder.

Both the *HRH1* SNP rs346070 and the *MC2R* SNP rs4464147 were also associated with OFC response. Olanzapine has significant affinity at the *HRH1* receptor.[21] The *HRH1* SNP associated with both OFC and lamotrigine response in the present study is in an untranslated region of exon 3. It is unclear what function variations in the *HRH1* gene may play in the response to OFC or lamotrigine. Although *HRH1* antagonism has been linked to sedation and possibly weight gain associated with antipsychotic treatment, it is unclear what role this receptor plays in therapeutic response.

The precise mechanism of action of lamotrigine in bipolar disorder is not known but may be related to its inhibition of neuronal sodium and calcium channels and indirect modulation of γ-aminobutyric acid neurotransmission. Lamotrigine response was associated with SNPs in several genes involved in catecholamine signaling, including the *DRD2*, *ANKK1*, *DRD4*, and *DBH* genes. Lamotrigine does not have substantial affinity at dopamine receptors, so the functional consequence of the dopaminergic gene SNPs that were observed to be associated with response are not obvious and very likely indirect. *ANKK1* is a serine/threonine kinase gene downstream of *DRD2,* and it lies in the same haplotype block.[26] The *ANKK1* SNP (rs11214601) that was associated with lamotrigine response is in the downstream untranslated portion of the *ANKK1* gene near the *DRD2* genomic region. It is downstream of the frequently studied *Taq*1A polymorphism in the *ANKK1* gene, which was also associated with lamotrigine response and has been associated with smoking behavior and alcoholism.[27] SNPs in *ANKK1* have also recently been associated with nicotine dependence.[26] Additional studies with denser SNP genotyping are needed to confirm the association of *DRD2* and/or *ANKK1* variants in lamotrigine response in bipolar depression, in order to more precisely identify the gene location that may affect treatment response. A single SNP in the 5′ upstream region of *DBH* was also associated with lamotrigine response. *DBH* catalyzes the conversion of dopamine to norepinephrine.

Lamotrigine response was also associated with SNPs in 2 genes involved in the hypothalamic-pituitary-adrenal (HPA) axis signaling. Three SNPs in an untranslated region of exon 9 or downstream of exon 9 of the glucocorticoid receptor (GR) coding gene (*NR3C1*) were associated with lamotrigine response. Dysregulation of the HPA axis is a common finding in affective disorders, including bipolar disorder. GR regulation of this pathway is critical for normal physiologic response to stress, and it has been suggested that this receptor plays a role in antidepressant response. Lithium and some antidepressants have been shown to alter GR expression in cells and animal models.[28] A postmortem study found region-specific alterations in GR mRNA in subjects with bipolar disorder compared with controls and subjects with schizophrenia and depression.[29] In addition, GR protein levels and DNA binding were altered in lymphocytes of patients with bipolar depression receiving pharmacologic treatment compared to matched controls and compared to euthymic patients, suggesting that response to therapy may normalize GR signaling.[30] This study adds to the body of literature suggesting a role for the GR in affective disorders by identifying a potential association of specific polymorphisms in the GR coding *NR3C1* gene with lamotrigine response.

It is intriguing that variations in a second gene that codes for a receptor that is part of the HPA axis were associated with lamotrigine response. *MC2R* is selectively expressed in the adrenal cortex and regulates cortisol release via the adrenocorticotropic hormone. A block of *MC2R* SNPs, including the SNPs associated with depressive response in patients with bipolar depression in the present study, was previously observed to be associated with depressive symptom response to olanzapine in patients with schizophrenia and moderate depressive symptoms at baseline.[31] None of the associated SNPs are in coding regions of the gene, but *MC2R* rs4797825 and rs4308014 are in the 3′ untranslated region. SNP rs4464147, which was associated with OFC response, is also in the 3′ untranslated region.

There was some overlap in the SNPs that were associated with response to either treatment. The SNPs in the *DRD3* gene that were significantly associated with response to OFC were modestly associated with lamotrigine response, but these associations were not significant after correcting for within-gene multiple testing, suggesting that *DRD3* may have a more selective role in OFC mechanisms of action and *DRD3* variations may have a greater effect on OFC response than on lamotrigine response. Likewise, both lamotrigine and OFC response were associated with *HRH1* SNPs. These results suggest that both drugs have effects on bipolar depression mediated by *HRH1* or that *HRH1* variations are markers of nonspecific or placebo response.

This study had a number of limitations, including the lack of a placebo control group. Thus, the possibility that the observed associations with treatment response were actually due to placebo response cannot be excluded, in particular for the SNPs that were associated with both OFC and lamotrigine response. Of course, any association with treatment response, regardless of specificity, could be of tremendous clinical utility. In addition, the sample size for the study was small, so the risk of type II error is high. Likewise, as the SNPs in these genes were not selected to tag haplotype blocks and thus capture all common variation, the

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associations with other, untyped SNPs in these genes cannot be excluded. Coverage of the *DRD2-ANKK1* block and of *DRD3* was relatively good. In *DRD2*, of the 85 HapMap SNPs, 81% were captured with $r^2 > 0.8$, and mean r^2 between typed SNPs and HapMap SNPs was .90. Likewise, in *DRD3*, of the 44 HapMap SNPs, 68% were captured with $r^2 > 0.8$, and mean r^2 was 0.77. (HapMap provides a list of common SNPs in the human genome that can be used to develop a haplotype plot.[32]) Tagging efficiency for most other genes was less than 50%. Because statistical power to detect associations was recognized to be low, this study did not correct for examining multiple genes, as there was more concern about type II than type I error. This study also did not examine association with adverse events because of the small sample size. For the significant associations with OFC, it would be beneficial to have had separate olanzapine and fluoxetine treatment groups to determine which compound might be primarily responsible for the associations. Finally, the risk of population stratification, despite exclusion of nonwhite subjects, is recognized. With these caveats in mind, replication in independent cohorts will be required. Nonetheless, the results of this study suggest that genes related to dopaminergic neurotransmission are associated with symptomatic improvement in bipolar depression. If confirmed in larger studies, these genes may represent targets for future treatment development or means of identifying patients more likely to respond to a specific treatment.

Drug names: fluoxetine (Prozac, Sarafem, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), quetiapine (Seroquel).

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