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Neurotransmission and Bipolar Disorder: A Systematic Family-based Association Study

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Abstract

Neurotransmission pathways/systems have been proposed to be involved in the pathophysiology and treatment of bipolar disorder for over forty years. In order to test the hypothesis that common variants of genes in one or more of five neurotransmission systems confer risk for bipolar disorder, we analyzed 1005 tag single nucleotide polymorphisms in 90 genes from dopaminergic, serotonergic, noradrenergic, GABAergic and glutamatergic neurotransmitter systems in 101 trios and 203 quads from Caucasian bipolar families. Our sample has 80% power to detect ORs ≥ 1.82 and ≥ 1.57 for minor allele frequencies of 0.1 and 0.5, respectively. Nominally significant allelic and haplotypic associations were found for genes from each neurotransmission system, with several reaching gene-wide significance (allelic: *GRIA1*, *GRIN2D*, and *QDPR*; haplotypic: *GRIN2C*, *QDPR*, and *SLC6A3*). However, none of these associations survived correction for multiple testing in an individual system, or in all systems considered together. Significant single nucleotide polymorphism associations were not found with sub-phenotypes (alcoholism, psychosis, substance abuse, and suicide attempts) or significant gene-gene interactions. These results suggest that, within the detectable odds ratios of this study, common variants of the selected genes in the five neurotransmission systems do not play major roles in influencing the risk for bipolar disorder or comorbid sub-phenotypes.

Keywords

bipolar disorder; neurotransmitter; single nucleotide polymorphism; monoamine; amino acid

INTRODUCTION

Bipolar disorder (BP) is a complex psychiatric condition with a significant genetic component [Craddock and Jones, 1999; Taylor et al., 2002]. However, the search for specific susceptibility gene(s) in the last several decades has produced promising but inconsistent results [Craddock

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and Forty, 2006; Farmer et al., 2007; Hayden and Nurnberger, Jr., 2006]. Genes in several neurotransmission pathways/systems have long been a focus of candidate association studies in BP [Craddock et al., 2001], due to the effects of antidepressants on monoamine neurotransmission and of anti-manic drugs on glutamate and -amino butyric acid (GABA) transmission as well as on monoaminergic transmission [Hattori et al., 2005].

The serotonin and norepinephrine systems

The original monoamine hypothesis of depression postulated a deficiency of monoamines 5-hydroxytryptamine (5-HT, serotonin) or norepinephrine (NE) in the pathophysiology of depression [Bunney, Jr. and Davis, 1965; Coppen, 1969; Schildkraut, 1965]. Current evidence is based on the continued effect of most antidepressant drugs on these systems [Berton and Nestler, 2006; Nutt, 2002], brain imaging studies with specific ligands [Bremner et al., 2003; Cannon et al., 2007; Zipursky et al., 2007], transgenic mouse models with key 5HT or NE genes knocked out [El and Vaugeois, 2007; Lesch and Mossner, 2006; Urani et al., 2005], and genetic association studies [Craddock et al., 2001; Kato, 2007; Levinson, 2006]. In addition, gene expression data from the Stanley Medical Research Institute's (SMRI) brain collections reveal abnormal expression of several NE- and 5-HT-related genes in BP patients in contrast to mentally healthy controls [Higgs et al., 2006] (Supplementary Table 1). However, some experimental data do not support the role of serotonergic or noradrenergic systems in mood disorders [Craddock and Forty, 2006; Hayden and Nurnberger, Jr., 2006; Levinson, 2006].

The dopamine (DA) system

Dopaminergic dysfunction has also been proposed to contribute to the etiology of mood disorders [Brugue and Vieta, 2007; Dunlop and Nemeroff, 2007; Gershon et al., 2007; Nutt, 2006]. Some drugs targeting DA neurotransmission been shown to induce manic or major depressive episodes, as well as alleviate manic or depressive symptoms [Diehl and Gershon, 1992; Gao et al., 2005; Kapur and Mann, 1992]. Gene expression analysis of postmortem brains of BP patients (Supplementary Table 1), neuroimaging studies, and genetic association studies provide suggestive evidence for a dopaminergic disturbance in mood disorders (see reviews [Craddock et al., 2001; Dunlop and Nemeroff, 2007; Stoll et al., 2000]).

The GABA system

Evidence for a GABAergic deficit in the pathophysiology and treatment of mood disorders includes stress-induced GABAergic functional changes in animal studies, the role of GABA receptor agonists and antagonists in improving the behavioral deficits of animal models of depression, the effects of available antidepressants and mood stabilizers on GABA function, genetic, neurobiochemical, and neuroimaging abnormalities of GABA system in patients with mood disorders, and the mood-modulating efficacy of drugs targeting the GABA system [Brambilla et al., 2003; Krystal et al., 2002; Sanacora and Saricicek, 2007].

The glutamate system

Findings from pharmacological studies [Berton and Nestler, 2006; Krystal et al., 2002; Paul and Skolnick, 2003], neuroimaging studies [Dager et al., 2004; Krystal et al., 2002], gene expression analysis of postmortem brains of BP patients ([Knable et al., 2004; McCullumsmith et al., 2007; McCullumsmith and Meador-Woodruff, 2002; Woo et al., 2004] and Supplementary Table 1), and genetic association studies [Blackwood et al., 2007; Fallin et al., 2005; Pickard et al., 2006] also support the glutamate deficit hypothesis of mood disorders [Krystal et al., 2002; Kugaya and Sanacora, 2005; Paul and Skolnick, 2003; Stewart and Reid, 2002].

Other neurotransmission systems (*e.g.*, cholinergic) may also be involved in the pathophysiology and treatment of mood disorders [Belzung et al., 2006; Berton and Nestler, 2006; Hauger et al., 2006; Young, 2006], but have been studied separately (cholinergic system in [Shi et al., 2007]). It has been hypothesized that imbalance of the interacting neurotransmission systems (*e.g.*, monoamine and amino acids) may result in neuropsychiatric diseases such as Parkinson disease, schizophrenia and depression [Carlsson et al., 2001; Carlsson, 2006; Charney and Manji, 2004; Pralong et al., 2002]. Variants in genes from one or several of the neurotransmission systems described here may contribute to BP susceptibility [Hattori et al., 2005]. We tested this hypothesis in three monoamine (NE, DA and 5-HT) and two amino acid systems (glutamate and GABA) in a familial BP sample. We also investigated the relationship between variants in these neurotransmission genes and several comorbid conditions: alcoholism, psychosis, substance abuse and suicide attempts [Baldassano, 2006; Potash et al., 2007].

Materials and Methods

Subjects

The sample was composed of 1115 individuals, including six trios (parents plus one affected child) and seven quads (parents plus two affected children) from the Clinical Neurogenetics (CNG) collections [Berrettini et al., 1991], 53 trios and 170 quads from the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder collections waves 1–4 (<http://www.nimhgenetics.org/>) [Dick et al., 2003; Nurnberger, Jr. et al., 1997], and 42 trios and 26 quads from the Chicago-Hopkins-Intramural Program (CHIP) collections [Potash et al., 2007]. Ascertainment and diagnostic methods for participants from the CNG, the NIMH waves 1–4 and the CHIP collections have been described in detail elsewhere [Berrettini et al., 1991; Potash et al., 2007]. All individuals are of European ancestry based on self-reported ancestry and further confirmed by STRUCTURE [Pritchard et al., 2000] analysis using 254 unlinked single nucleotide polymorphisms (SNPs) (data not shown). As BPII has been postulated to be an etiologically distinct mood disorder [Berk and Dodd, 2005; Hadjipavlou et al., 2004; Heun and Maier, 1993; McMahon et al., 2001; Nwulia et al., 2007], we analyzed only those families with affected offspring of either BPI or schizoaffective disorder bipolar type (SAB). Of 507 affected offspring from 101 trios and 203 quads, 481 met DSM-III-R or DSM-IV criteria for BPI and 26 for SAB. Three hundred were females and 207 were males.

Candidate Gene Selection

Gene selection from the dopaminergic, serotonergic, noradrenergic, glutamatergic and GABAergic neurotransmission systems have been previously described [Hattori et al., 2005], where genes of various neurobiological pathways were culled by literature mining along with use of two databases, the Kyoto Encyclopedia of Genes and Genomes (KEGG) [Kanehisa et al., 2006] and the Gene Ontology database (<http://www.geneontology.org/>). The selection focused on metabolic enzymes, receptors, transporters, and intracellular signaling molecules. Five genes (*ADCY1*, *ARRB2*, *GRIN3B*, *GRINA* and *PAWR*) were added following further literature review [Chatterton et al., 2002; Grange-Midroit et al., 2003; Hardingham et al., 2002; Lu et al., 2003; Park et al., 2005]. A total of 90 genes were chosen for this study (Supplementary Table 2).

Single Nucleotide Polymorphism Selection and Genotyping

We used a series of bioinformatics tools (<http://bioinfo.bsd.uchicago.edu/index.html>) to select tag SNPs (tSNPs), as described previously [Shi et al., 2007]. Briefly, we first downloaded the 30 Centre d'Etude du Polymorphisme Humain (CEPH) trios' HapMap genotype data for SNPs within each genic region and within 10 kb sequences flanking each gene (Rel16c.1/phaseI June 05, on NCBI B34 assembly, dbSNP b124). Linkage disequilibrium (LD) was estimated for

SNPs with minor allele frequencies (MAF) greater than 0.1. Next, we used the ldSelect algorithm [Carlson et al., 2004] to select tSNPs, which are SNPs that capture most of the genetic variation in a region due to high LD with other SNPs. A criterion of $r^2 = 0.85$ was set to define the bins. We selected tSNPs and singleton SNPs (only one SNP in each bin) for genotyping. Some originally selected SNPs that failed the Illumina check system (Illumina Inc., San Diego, CA) were replaced with alternative tSNPs residing in the same LD bins. Finally, 1099 SNPs in neurotransmission system genes were chosen for genotyping. Genotyping was performed using the Illumina BeadArray technology [Oliphant et al., 2002].

For quality control of genotyping, DNA from 46 HapMap European ancestry subjects, 15 never mentally ill individuals (11 from the NIMH collections, one from the CNG collections, and three from the CHIP collections), and 45 blank controls (using water instead of DNA) were used. Of 1099 SNPs tested, 94 failed in genotyping or appeared as monomorphic. We used PedCheck1.1 to detect any Mendelian inconsistencies [O'Connell and Weeks, 1998], and Merlin to detect any unlikely recombinants [Abecasis et al., 2002]. All genotype errors were manually resolved by assigning problematic genotypes as missing prior to statistical analysis. The genotype data finally included had an average genotyping success rate of > 99.85% for 1005 SNPs.

Statistical Analysis

Pairwise LD, using the standard LD coefficient D' , was estimated between every pair of markers in each gene using Haploview (version 4.0) [Barrett et al., 2005]. Haplotype blocks were identified using the solid spine of LD method implemented in Haploview [Barrett et al., 2005]. This method searches for strong LD (a solid spine of $D' > 0.80$ was set in our analysis), such that the first and last markers in a block are in strong LD with all intermediate markers, but the intermediate markers are not necessarily in LD with each other. All the following analyses were accomplished using the whole genome data analysis tool set PLINK [Purcell et al., 2007], except where noted.

Allelic and haplotypic transmission disequilibrium tests (TDTs) were carried out for the disease trait. Permutations correcting for multiple testing were performed for individual SNPs and for all the SNPs and haplotypes in each gene, for each neurotransmission system, and for the five systems as a whole. To incorporate haplotypes into the permutation analysis, the most likely haplotypes were imputed using the hap-impute option in PLINK. These data were permuted to obtain analysis-wide p -values. Haplotypic imputations and association analyses could not be performed for the five genes on the X-chromosome.

We used two different approaches to test potential effects of sub-phenotypes including alcoholism, psychosis, substance abuse and suicide attempts, on the SNP associations. The first method was the logistic regression analysis, using the sub-phenotypes as covariates. The second method was the heterogeneity test. For each covariate (e.g. psychosis), the sample was divided into two groups (strata). Then, association was tested within each stratum and across the two strata. The odds ratios from the groups with and without the covariate were compared (test of heterogeneity).

We also performed epistasis analysis to detect potential gene-gene interactions. First, we used the "focused interaction testing framework" (FITF) prescreening approach [Millstein et al., 2006] to test deviations in genotype distributions of pairs of SNPs from what is expected. This step helps to reduce the number of tests, which may enhance power. We selected the top 5% of pairs from this prescreening. We also analyzed SNP pairs in which both had an association with p -value < 0.05. This combined prescreening picks up interactions that may have no main order effects (from FITF prescreening) as well as those with main order effects (from individually nominally significant SNPs). A false discovery rate (FDR) of < 0.025 (for two

sets of epistatic analyses) in either analysis would be considered statistically significant. We estimated the FDR using the Statistical Analysis System (SAS Institute Inc., Cary, NC).

Both the covariate and epistasis analyses were accomplished by taking one case per family and creating a pseudo-control of the untransmitted alleles and performing case-control analyses.

Comparison with genome-wide association study (GWAS) data

We also reviewed the summary data from the GWAS on BP using an independent sample with 2000 cases and 3000 controls [Wellcome Trust Case Control Consortium, 2007], and compared these results with our data to see whether there were overlapping genes or SNPs showing nominally significant allelic association. We did not compare our data with another GWA study [Baum et al., 2008] because of overlap between our samples and those in that study.

RESULTS

Results of SNP and haplotype association analyses of 1005 SNPs in selected genes from five neurotransmission systems are summarized in Supplementary Table 3. Single nucleotide polymorphisms showing nominal association with BP are presented in Table 1. Of them, rs2926835 in the *GRI1* gene, rs1799281 in the *GRIN2D* gene and rs744731 in the *QDPR* gene reached gene-wide association (permutation $p < 0.05$ for all SNPs of each gene). None of these associations survived multiple testing for its own system (e.g. glutamatergic or serotonergic) or all the five systems taken together (permutation adjusted $p > 0.05$) (Supplementary Table 3). Table 2 shows the gene-wide significant haplotypic associations with BP. Again, none of these associations survived correction for multiple testing (Supplementary Table 3).

Logistic regression analyses revealed that none of the covariates/sub-phenotypes (alcoholism, psychosis, substance abuse, and suicide attempts) produced significant associations for any SNP (data not shown). For the sub-phenotypes analyzed, none of the SNPs had a p -value less than the lowest p -value in the TDT test for the disease trait, implying that none of the associations would be significant after correction for multiple testing. While some sub-phenotype or covariate associations appeared to be present in one stratum but not the other in the heterogeneity tests, the difference was not significant, indicating no influence of these covariates on SNP associations.

We did not detect any significant gene-gene interaction, as shown by FDR correction for multiple testing of the results generated by FITF analysis (data not shown). Several genes from neurotransmission systems tested showed nominal allelic association with BP in this study or in the WTCCC GWA data ($0.0001 < p < 0.05$, Supplementary Table 4). However, only one SNP was nominally significant in both studies (rs623580 in *TPH1*, this study $p < 0.0413$; WTCCC $p < 0.049$ (allelic)), and would not be considered significant when multiple tests are corrected for.

DISCUSSION

This is the first association study to test five pathway/system disturbance hypotheses of BP, by systematically interrogating tSNPs in genes from each neurotransmission system. Several genes (*GRI1*, *GRIN2C*, *GRIN2D*, *QDPR*, and *SLC6A3*) may have weak effects on risk for bipolar disorder (Tables 1 and 2). The allelic or haplotypic associations shown in these gene region could survive correction for multiple tests for each gene but neither for corresponding individual system nor for all the five systems as a whole (Supplementary Table 3). We did not detect significant SNP association with sub-phenotypes/covariates including alcoholism, psychosis, substance abuse, and suicide attempts or gene-gene interactions in influencing such

disease risk. These results suggest that, within the detectable odds ratios (ORs) of this study, common variants of the selected genes in the five neurotransmission systems do not have major effects on etiology of BP or comorbid conditions.

Although multiple genes from the monoamine and amino-acid systems have been frequently tested in BP during the last two decades, no consistent association has yet been discovered [Cho et al., 2005; Craddock et al., 2001; Craddock et al., 2006; Lasky-Su et al., 2005; Levinson, 2005; Preisig et al., 2005]. For example, a meta-analysis of 13 studies including 2,319 cases and 7,810 controls did not identify significant association of the functional Val158Met polymorphism (rs4680) in the catechol-O-methyltransferase (*COMT*) gene with BP [Craddock et al., 2006]. Our analysis of rs4680 in a sample of 376 trios overlapping with the samples used in the current study (unpublished data) did not show significant results. Two recent GWA studies [Baum et al., 2008; Wellcome Trust Case Control Consortium, 2007] did not detect any significant allelic association with BP either. As another example, the intron-2 variable number tandem repeats and gene-linked polymorphic region polymorphisms in the serotonin transporter gene (*5-HTT*, also known as *SLC6A4*) have shown significant association with BP in a meta-analysis (both with OR of 1.12) [Cho et al., 2005]. However, we did not identify any disease association in this gene region (Supplementary Table 3), and only one SNP (rs7224199) in the *5-HTT* gene showed a nominal association (OR = 1.10, $p = 0.031$) in the WTCCC GWA study [Wellcome Trust Case Control Consortium, 2007]. These results also imply that the effects of the neurotransmission system genes on BP susceptibility are relatively weak (e.g., OR of 1.1), if any exist.

Several genes with gene-wide significant association in the present study may deserve further investigation. For example, *QDPR*, encoding quinoid dihydropteridine reductase, is an essential cofactor for the metabolism of phenylalanine, tyrosine, and tryptophan hydroxylases of the serotonin system. Decreased gene expression has been shown in postmortem brain tissues of BP patients (Supplementary Table 1). In addition, *QDPR* is located on 4p15, a BP linked chromosomal region [Detera-Wadleigh et al., 1997]. *GRIA1* encodes an ionotropic AMPA glutamate receptor, which has been shown to play an important role in controlling synaptic plasticity [Du et al., 2004; Lee et al., 2003; Zamanillo et al., 1999]. An impairment of synaptic plasticity has been implicated in BP pathophysiology [Carlson et al., 2006; Duman, 2002; Kempermann and Kronenberg, 2003]. *SLC6A3*, encoding the dopamine transporter, is mapped to 5p15, which has been linked to BP [Kelsoe et al., 2001; Shink et al., 2002]. The dopamine transporter, an essential regulator of dopamine transmission, is the target of several psychostimulants [Iversen, 2006; Williams and Galli, 2006]. Furthermore, *SLC6A3* has been associated to BP in several studies [Greenwood et al., 2006; Keikhaee et al., 2005; Ohadi et al., 2007; Stober et al., 2006; Waldman et al., 1997], but not in others [Bocchetta et al., 1999; Georgieva et al., 2002; Gomez-Casero et al., 1996; Souery et al., 1996].

Three serotonergic genes, *ABCG1*, *HTR4* and *TPH1*, demonstrate nominally significant allelic association with BP in both the WTCCC GWA study and our family-based study (Table 1 and Supplementary Table 4). These three genes are also implicated by their location in BP-linked chromosomal regions [Aita et al., 1999; Hong et al., 2004; Zandi et al., 2003], by previous association evidence [Bellivier et al., 1998; Kirov et al., 2001; Ohtsuki et al., 2002], and by abnormal expression in postmortem brains of patients (Supplementary Table 1).

The present study has several limitations. First, our sample has modest statistical power to detect associations with relatively weak effects at the study-wide significance level. For example, using PBAT (<http://www.biostat.harvard.edu/~clang/default.htm>), under a multiplicative model and at $p < 0.00005$ (Bonferroni adjustment for 1005 SNPs), our sample of 101 trios and 203 quads has 80% power to detect ORs of ≥ 1.82 and ≥ 1.57 for minor allele frequencies of 0.1 and 0.5, respectively. Second, SNP coverage for each gene is modest (on

average, 9.3 kb/SNP) because we selected tSNPs from HapMap Phase I genotype data, which was the only data available at the time. Thus, we may have overlooked potential signals in the genes tested, although no strong association was identified by the WTCCC GWA study, which had denser coverage in some of the genes we studied [Wellcome Trust Case Control Consortium, 2007] (Supplementary Table 4). Lastly, we did not test all functionally interesting gene systems. For example, intracellular signaling molecules [Tanis and Duman, 2007], such as those encoding dystrobrevin-binding protein 1 (*DTNBPI*), neuregulin 1 (*NRG1*) and regulator of G-protein signaling 4 (*RGS4*) have been reported to influence NMDAR-mediated glutamatergic transmission and influence susceptibility to schizophrenia [Carter, 2006; Harrison and Weinberger, 2005], as well as to BP [Breen et al., 2006; Cordeiro et al., 2005; Fallin et al., 2005; Joo et al., 2007; Pae et al., 2007; Thomson et al., 2007]. Pathway analysis using tools such as KEGG, Protein ANalysis THrough Evolutionary Relationships (PANTHER) [Mi et al., 2007], and Ingenuity.com (<http://www.ingenuity.com/>), together with other lines of evidence may help to select such potential candidate genes for future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference List

- Abecasis GR, Cherny SS, Cookson WO, Cardon LR. Merlin--rapid analysis of dense genetic maps using sparse gene flow trees. *Nat Genet* 2002;30:97–101. [PubMed: 11731797]
- Aita VM, Liu J, Knowles JA, Terwilliger JD, Baltazar R, Grunn A, Loth JE, Kanyas K, Lerer B, Endicott J, Wang Z, Penchaszadeh G, Gilliam TC, Baron M. A comprehensive linkage analysis of chromosome 21q22 supports prior evidence for a putative bipolar affective disorder locus. *Am J Hum Genet* 1999;64:210–217. [PubMed: 9915960]
- Baldassano CF. Illness course, comorbidity, gender, and suicidality in patients with bipolar disorder. *J Clin Psychiatry* 2006;67(Suppl 11):8–11. [PubMed: 17029490]
- Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005;21:263–265. [PubMed: 15297300]
- Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, Schulze TG, Cichon S, Rietschel M, Nothen MM, Georgi A, Schumacher J, Schwarz M, Abou JR, Hofels S, Propping P, Satagopan J, tera-Wadleigh SD, Hardy J, McMahon FJ. A genome-wide association study implicates diacylglycerol kinase eta (*DGKH*) and several other genes in the etiology of bipolar disorder. *Mol Psychiatry* 2008;13:197–207. [PubMed: 17486107]
- Bellivier F, Leboyer M, Courtet P, Buresi C, Beaufils B, Samolyk D, Allilaire JF, Feingold J, Mallet J, Malafosse A. Association between the tryptophan hydroxylase gene and manic-depressive illness. *Arch Gen Psychiatry* 1998;55:33–37. [PubMed: 9435758]
- Belzung C, Yalcin I, Griebel G, Surget A, Leman S. Neuropeptides in psychiatric diseases: an overview with a particular focus on depression and anxiety disorders. *CNS Neurol Disord Drug Targets* 2006;5:135–145. [PubMed: 16611088]

- Berk M, Dodd S. Bipolar II disorder: a review. *Bipolar Disord* 2005;7:11–21. [PubMed: 15654928]
- Berrettini WH, Goldin LR, Martinez MM, Maxwell ME, Smith AL, Guroff JJ, Kazuba DM, Nurnberger JI Jr, Hamovit J, Simmons-Allings S, Muniec D, Choi H, York C, Robb AS, Gershon ES. A bipolar pedigree series for genomic mapping of disease genes: Diagnostic and analytic considerations. *Psychiatric Genetics* 1991;2:125–160.
- Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. *Nat Rev Neurosci* 2006;7:137–151. [PubMed: 16429123]
- Blackwood DH, Pickard BJ, Thomson PA, Evans KL, Porteous DJ, Muir WJ. Are some genetic risk factors common to schizophrenia, bipolar disorder and depression? Evidence from DISC1, GRIK4 and NRG1. *Neurotox Res* 2007;11:73–83. [PubMed: 17449450]
- Bocchetta A, Piccardi MP, Palmas MA, Chillotti C, Oi A, Del ZM. Family-based association study between bipolar disorder and DRD2, DRD4, DAT, and SERT in Sardinia. *Am J Med Genet* 1999;88:522–526. [PubMed: 10490710]
- Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. *Mol Psychiatry* 2003;8:721–37. 715. [PubMed: 12888801]
- Breen G, Prata D, Osborne S, Munro J, Sinclair M, Li T, Staddon S, Dempster D, Sainz R, Arroyo B, Kerwin RW, St Clair D, Collier D. Association of the dysbindin gene with bipolar affective disorder. *Am J Psychiatry* 2006;163:1636–1638. [PubMed: 16946192]
- Bremner JD, Vythilingam M, Ng CK, Vermetten E, Nazeer A, Oren DA, Berman RM, Charney DS. Regional brain metabolic correlates of alpha-methylparatyrosine-induced depressive symptoms: implications for the neural circuitry of depression. *JAMA* 2003;289:3125–3134. [PubMed: 12813118]
- Brugue E, Vieta E. Atypical antipsychotics in bipolar depression: neurobiological basis and clinical implications. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:275–282. [PubMed: 16876306]
- Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions. A review. *Arch Gen Psychiatry* 1965;13:483–494. [PubMed: 5320621]
- Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC. Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [11C]DASB; comparison with bipolar disorder. *Biol Psychiatry* 2007;62:870–877. [PubMed: 17678634]
- Carlson CS, Eberle MA, Rieder MJ, Yi Q, Kruglyak L, Nickerson DA. Selecting a maximally informative set of single-nucleotide polymorphisms for association analyses using linkage disequilibrium. *Am J Hum Genet* 2004;74:106–120. [PubMed: 14681826]
- Carlson PJ, Singh JB, Zarate CA Jr, Drevets WC, Manji HK. Neural circuitry and neuroplasticity in mood disorders: insights for novel therapeutic targets. *NeuroRx* 2006;3:22–41. [PubMed: 16490411]
- Carlsson A. The neurochemical circuitry of schizophrenia. *Pharmacopsychiatry* 2006;39(Suppl 1):S10–S14. [PubMed: 16508890]
- Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* 2001;41:237–260. [PubMed: 11264457]
- Carter CJ. Schizophrenia susceptibility genes converge on interlinked pathways related to glutamatergic transmission and long-term potentiation, oxidative stress and oligodendrocyte viability. *Schizophr Res* 2006;86:1–14. [PubMed: 16842972]
- Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. *Sci STKE* 2004;2004:re5. [PubMed: 15039492]
- Chatterton JE, Awobuluyi M, Premkumar LS, Takahashi H, Talantova M, Shin Y, Cui J, Tu S, Sevarino KA, Nakanishi N, Tong G, Lipton SA, Zhang D. Excitatory glycine receptors containing the NR3 family of NMDA receptor subunits. *Nature* 2002;415:793–798. [PubMed: 11823786]
- Cho HJ, Meira-Lima I, Cordeiro Q, Michelon L, Sham P, Vallada H, Collier DA. Population-based and family-based studies on the serotonin transporter gene polymorphisms and bipolar disorder: a systematic review and meta-analysis. *Mol Psychiatry* 2005;10:771–781. [PubMed: 15824745]
- Coppen AJ. Biochemical aspects of depression. *Int Psychiatry Clin* 1969;6:53–81. [PubMed: 5817856]

- Cordeiro Q, Talkowski ME, Chowdari KV, Wood J, Nimgaonkar V, Vallada H. Association and linkage analysis of RGS4 polymorphisms with schizophrenia and bipolar disorder in Brazil. *Genes Brain Behav* 2005;4:45–50. [PubMed: 15660667]
- Craddock N, Dave S, Greening J. Association studies of bipolar disorder. *Bipolar Disord* 2001;3:284–298. [PubMed: 11843779]
- Craddock N, Forty L. Genetics of affective (mood) disorders. *Eur J Hum Genet* 2006;14:660–668. [PubMed: 16721402]
- Craddock N, Jones I. Genetics of bipolar disorder. *J Med Genet* 1999;36:585–594. [PubMed: 10465107]
- Craddock N, Owen MJ, O'Donovan MC. The catechol-O-methyl transferase (COMT) gene as a candidate for psychiatric phenotypes: evidence and lessons. *Mol Psychiatry* 2006;11:446–458. [PubMed: 16505837]
- Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, Dunner DL, Renshaw PF. Brain metabolic alterations in medication-free patients with bipolar disorder. *Arch Gen Psychiatry* 2004;61:450–458. [PubMed: 15123489]
- Detera-Wadleigh SD, Badner JA, Yoshikawa T, Sanders AR, Goldin LR, Turner G, Rollins DY, Moses T, Guroff JJ, Kazuba D, Maxwell ME, Edenberg HJ, Foroud T, Lahiri D, Nurnberger JI Jr, Stine OC, McMahon F, Meyers DA, MacKinnon D, Simpson S, McInnis M, DePaulo JR, Rice J, Goate A, Gershon ES. Initial genome scan of the NIMH genetics initiative bipolar pedigrees: chromosomes 4, 7, 9, 18, 19, 20, and 21q. *Am J Med Genet* 1997;74:254–262. [PubMed: 9184307]
- Dick DM, Foroud T, Flury L, Bowman ES, Miller MJ, Rau NL, Moe PR, Samavedy N, El-Mallakh R, Manji H, Glitz DA, Meyer ET, Smiley C, Hahn R, Widmark C, McKinney R, Sutton L, Ballas C, Grice D, Berrettini W, Byerley W, Coryell W, DePaulo R, MacKinnon DF, Gershon ES, Kelsoe JR, McMahon FJ, McInnis M, Murphy DL, Reich T, Scheftner W, Nurnberger JI Jr. Genomewide linkage analyses of bipolar disorder: a new sample of 250 pedigrees from the National Institute of Mental Health Genetics Initiative. *Am J Hum Genet* 2003;73:107–114. [PubMed: 12772088]
- Diehl DJ, Gershon S. The role of dopamine in mood disorders. *Compr Psychiatry* 1992;33:115–120. [PubMed: 1347497]
- Du J, Gray NA, Falke CA, Chen W, Yuan P, Szabo ST, Einat H, Manji HK. Modulation of synaptic plasticity by antimanic agents: the role of AMPA glutamate receptor subunit 1 synaptic expression. *J Neurosci* 2004;24:6578–6589. [PubMed: 15269270]
- Duman RS. Pathophysiology of depression: the concept of synaptic plasticity. *Eur Psychiatry* 2002;17 (Suppl 3):306–310. [PubMed: 15177086]
- Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry* 2007;64:327–337. [PubMed: 17339521]
- El YM, Vaugeois JM. Genetic rodent models of depression. *Curr Opin Pharmacol* 2007;7:3–7. [PubMed: 17169613]
- Fallin MD, Lasseter VK, Avramopoulos D, Nicodemus KK, Wolyniec PS, McGrath JA, Steel G, Nestadt G, Liang KY, Hagan RL, Valle D, Pulver AE. Bipolar I disorder and schizophrenia: a 440-single-nucleotide polymorphism screen of 64 candidate genes among Ashkenazi Jewish case-parent trios. *Am J Hum Genet* 2005;77:918–936. [PubMed: 16380905]
- Farmer A, Elkin A, McGuffin P. The genetics of bipolar affective disorder. *Curr Opin Psychiatry* 2007;20:8–12. [PubMed: 17143075]
- Gao K, Gajwani P, Elhaj O, Calabrese JR. Typical and atypical antipsychotics in bipolar depression. *J Clin Psychiatry* 2005;66:1376–1385. [PubMed: 16420074]
- Georgieva L, Dimitrova A, Nikolov I, Koleva S, Tsvetkova R, Owen MJ, Toncheva D, Kirov G. Dopamine transporter gene (DAT1) VNTR polymorphism in major psychiatric disorders: family-based association study in the Bulgarian population. *Acta Psychiatr Scand* 2002;105:396–399. [PubMed: 11942948]
- Gershon AA, Vishne T, Grunhaus L. Dopamine D2-like receptors and the antidepressant response. *Biol Psychiatry* 2007;61:145–153. [PubMed: 16934770]
- Gomez-Casero E, Perez dC I, Saiz-Ruiz J, Llinares C, Fernandez-Piqueras J. No association between particular DRD3 and DAT gene polymorphisms and manic-depressive illness in a Spanish sample. *Psychiatr Genet* 1996;6:209–212. [PubMed: 9149327]

- Grange-Midroit M, Garcia-Sevilla JA, Ferrer-Alcon M, La HR, Huguelet P, Guimon J. Regulation of GRK 2 and 6, beta-arrestin-2 and associated proteins in the prefrontal cortex of drug-free and antidepressant drug-treated subjects with major depression. *Brain Res Mol Brain Res* 2003;111:31–41. [PubMed: 12654503]
- Greenwood TA, Schork NJ, Eskin E, Kelsoe JR. Identification of additional variants within the human dopamine transporter gene provides further evidence for an association with bipolar disorder in two independent samples. *Mol Psychiatry* 2006;11:125–33. 115. [PubMed: 16261167]
- Hadjipavlou G, Mok H, Yatham LN. Bipolar II disorder: an overview of recent developments. *Can J Psychiatry* 2004;49:802–812. [PubMed: 15679203]
- Hardingham GE, Fukunaga Y, Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nat Neurosci* 2002;5:405–414. [PubMed: 11953750]
- Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 2005;10:40–68. [PubMed: 15263907]
- Hattori E, Liu C, Zhu H, Gershon ES. Genetic tests of biologic systems in affective disorders. *Mol Psychiatry* 2005;10:719–740. [PubMed: 15940293]
- Hauger RL, Risbrough V, Brauns O, Dautzenberg FM. Corticotropin releasing factor (CRF) receptor signaling in the central nervous system: new molecular targets. *CNS Neurol Disord Drug Targets* 2006;5:453–479. [PubMed: 16918397]
- Hayden EP, Nurnberger Jr. Molecular genetics of bipolar disorder. *Genes Brain Behav* 2006;5:85–95. [PubMed: 16436192]
- Heun R, Maier W. The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: results of a controlled family study. *Acta Psychiatr Scand* 1993;87:279–284. [PubMed: 8488750]
- Higgs BW, Elashoff M, Richman S, Barci B. An online database for brain disease research. *BMC Genomics* 2006;7:70. [PubMed: 16594998]
- Hong KS, McInnes LA, Service SK, Song T, Lucas J, Silva S, Fournier E, Leon P, Molina J, Reus VI, Sandkuijl LA, Freimer NB. Genetic mapping using haplotype and model-free linkage analysis supports previous evidence for a locus predisposing to severe bipolar disorder at 5q31–33. *Am J Med Genet B Neuropsychiatr Genet* 2004;125:83–86. [PubMed: 14755450]
- Iversen L. Neurotransmitter transporters and their impact on the development of psychopharmacology. *Br J Pharmacol* 2006;147(Suppl 1):S82–S88. [PubMed: 16402124]
- Joo EJ, Lee KY, Jeong SH, Chang JS, Ahn YM, Koo YJ, Kim YS. Dysbindin gene variants are associated with bipolar I disorder in a Korean population. *Neurosci Lett* 2007;418:272–275. [PubMed: 17433541]
- Kanehisa M, Goto S, Hattori M, Ito K, Kinoshita KF, Itoh M, Kawashima S, Katayama T, Araki M, Hirakawa M. From genomics to chemical genomics: new developments in KEGG. *Nucleic Acids Res* 2006;34:D354–D357. [PubMed: 16381885]
- Kapur S, Mann JJ. Role of the dopaminergic system in depression. *Biol Psychiatry* 1992;32:1–17. [PubMed: 1391289]
- Kato T. Molecular genetics of bipolar disorder and depression. *Psychiatry Clin Neurosci* 2007;61:3–19. [PubMed: 17239033]
- Keikhaee MR, Fadaei F, Sargolzaee MR, Javanbakht A, Najmabadi H, Ohadi M. Association analysis of the dopamine transporter (DAT1)-67A/T polymorphism in bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 2005;135:47–49. [PubMed: 15768394]
- Kelsoe JR, Spence MA, Loetscher E, Foguet M, Sadovnick AD, Remick RA, Flodman P, Khristich J, Mroczkowski-Parker Z, Brown JL, Masser D, Ungerleider S, Rapaport MH, Wishart WL, Luebbert H. A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. *Proc Natl Acad Sci U S A* 2001;98:585–590. [PubMed: 11149935]
- Kempermann G, Kronenberg G. Depressed new neurons--adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. *Biol Psychiatry* 2003;54:499–503. [PubMed: 12946878]
- Kirov G, Lowry CA, Stephens M, Oldfield S, O'Donovan MC, Lightman SL, Owen MJ. Screening ABCG1, the human homologue of the *Drosophila* white gene, for polymorphisms and association with bipolar affective disorder. *Mol Psychiatry* 2001;6:671–677. [PubMed: 11673795]

- Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. *Mol Psychiatry* 2004;9:609–20. 544. [PubMed: 14708030]
- Krystal JH, Sanacora G, Blumberg H, Anand A, Charney DS, Marek G, Epperson CN, Goddard A, Mason GF. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Mol Psychiatry* 2002;7(Suppl 1):S71–S80. [PubMed: 11986998]
- Kugaya A, Sanacora G. Beyond monoamines: glutamatergic function in mood disorders. *CNS Spectr* 2005;10:808–819. [PubMed: 16400244]
- Lasky-Su JA, Faraone SV, Glatt SJ, Tsuang MT. Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. *Am J Med Genet B Neuropsychiatr Genet* 2005;133:110–115. [PubMed: 15578606]
- Lee HK, Takamiya K, Han JS, Man H, Kim CH, Rumbaugh G, Yu S, Ding L, He C, Petralia RS, Wenthold RJ, Gallagher M, Huganir RL. Phosphorylation of the AMPA receptor GluR1 subunit is required for synaptic plasticity and retention of spatial memory. *Cell* 2003;112:631–643. [PubMed: 12628184]
- Lesch KP, Mossner R. Inactivation of 5HT transport in mice: modeling altered 5HT homeostasis implicated in emotional dysfunction, affective disorders, and somatic syndromes. *Handb Exp Pharmacol* 2006;417–456. [PubMed: 16722245]
- Levinson DF. Meta-analysis in psychiatric genetics. *Curr Psychiatry Rep* 2005;7:143–151. [PubMed: 15802092]
- Levinson DF. The genetics of depression: a review. *Biol Psychiatry* 2006;60:84–92. [PubMed: 16300747]
- Lu HC, She WC, Plas DT, Neumann PE, Janz R, Crair MC. Adenylyl cyclase I regulates AMPA receptor trafficking during mouse cortical ‘barrel’ map development. *Nat Neurosci* 2003;6:939–947. [PubMed: 12897788]
- McCullumsmith RE, Kristiansen LV, Beneyto M, Scarr E, Dean B, Meador-Woodruff JH. Decreased NR1, NR2A, and SAP102 transcript expression in the hippocampus in bipolar disorder. *Brain Res* 2007;1127:108–118. [PubMed: 17113057]
- McCullumsmith RE, Meador-Woodruff JH. Striatal excitatory amino acid transporter transcript expression in schizophrenia, bipolar disorder, and major depressive disorder. *Neuropsychopharmacology* 2002;26:368–375. [PubMed: 11850151]
- McMahon FJ, Simpson SG, McInnis MG, Badner JA, MacKinnon DF, DePaulo JR. Linkage of bipolar disorder to chromosome 18q and the validity of bipolar II disorder. *Arch Gen Psychiatry* 2001;58:1025–1031. [PubMed: 11695948]
- Mi H, Guo N, Kejariwal A, Thomas PD. PANTHER version 6: protein sequence and function evolution data with expanded representation of biological pathways. *Nucleic Acids Res* 2007;35:D247–D252. [PubMed: 17130144]
- Millstein J, Conti DV, Gilliland FD, Gauderman WJ. A testing framework for identifying susceptibility genes in the presence of epistasis. *Am J Hum Genet* 2006;78:15–27. [PubMed: 16385446]
- Nurnberger JI Jr, DePaulo JR, Gershon ES, Reich T, Blehar MC, Edenberg HJ, Foroud T, Miller M, Bowman E, Mayeda A, Rao NL, Smiley C, Conneally PM, McMahon F, Meyers D, Simpson S, McInnis M, Stine OC, Detera-Wadleigh SD, Goldin L, Gurroff J, Maxwell E, Kazuba D, Gejman PV, Badner J, Sanders A, Rice J, Bierut L, Goate A. Genomic survey of bipolar illness in the NIMH genetics initiative pedigrees: a preliminary report. *Am J Med Genet* 1997;74:227–237. [PubMed: 9184304]
- Nutt DJ. The neuropharmacology of serotonin and noradrenaline in depression. *Int Clin Psychopharmacol* 2002;17(Suppl 1):S1–12. [PubMed: 12369606]
- Nutt DJ. The role of dopamine and norepinephrine in depression and antidepressant treatment. *J Clin Psychiatry* 2006;67(Suppl 6):3–8. [PubMed: 16848670]
- Nwulia EA, Miao K, Zandi PP, MacKinnon DF, Raymond DJ Jr, McInnis MG. Genome-wide scan of bipolar II disorder. *Bipolar Disord* 2007;9:580–588. [PubMed: 17845272]
- O’Connell JR, Weeks DE. PedCheck: a program for identification of genotype incompatibilities in linkage analysis. *Am J Hum Genet* 1998;63:259–266. [PubMed: 9634505]
- Ohadi M, Keikhaee MR, Javanbakht A, Sargolzaee MR, Robabeh M, Najmabadi H. Gender dimorphism in the DAT1 -67 T-allele homozygosity and predisposition to bipolar disorder. *Brain Res* 2007;1144:142–145. [PubMed: 17316573]

- Ohtsuki T, Ishiguro H, Iwata-Wadleigh SD, Toyota T, Shimizu H, Yamada K, Yoshitsugu K, Hattori E, Yoshikawa T, Arinami T. Association between serotonin 4 receptor gene polymorphisms and bipolar disorder in Japanese case-control samples and the NIMH Genetics Initiative Bipolar Pedigrees. *Mol Psychiatry* 2002;7:954–961. [PubMed: 12399948]
- Oliphant A, Barker DL, Stuelpnagel JR, Chee MS. BeadArray technology: enabling an accurate, cost-effective approach to high-throughput genotyping. *Biotechniques* 2002;32(Suppl):56–58. 60–61. [PubMed: 11808699]
- Pae CU, Serretti A, Mandelli L, Yu HS, Patkar AA, Lee CU, Lee SJ, Jun TY, Lee C, Paik IH, Kim JJ. Effect of 5-haplotype of dysbindin gene (DTNBP1) polymorphisms for the susceptibility to bipolar I disorder. *Am J Med Genet B Neuropsychiatr Genet* 2007;144:701–703. [PubMed: 17192893]
- Park SK, Nguyen MD, Fischer A, Luke MP, Affar eB, Dieffenbach PB, Tseng HC, Shi Y, Tsai LH. Par-4 links dopamine signaling and depression. *Cell* 2005;122:275–287. [PubMed: 16051151]
- Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci* 2003;1003:250–272. [PubMed: 14684451]
- Pickard BS, Malloy MP, Christoforou A, Thomson PA, Evans KL, Morris SW, Hampson M, Porteous DJ, Blackwood DH, Muir WJ. Cytogenetic and genetic evidence supports a role for the kainate-type glutamate receptor gene, GRIK4, in schizophrenia and bipolar disorder. *Mol Psychiatry* 2006;11:847–857. [PubMed: 16819533]
- Potash JB, Toolan J, Steele J, Miller EB, Pearl J, Zandi PP, Schulze TG, Kassem L, Simpson SG, Lopez V, MacKinnon DF, McMahon FJ. The bipolar disorder phenotype database: a resource for genetic studies. *Am J Psychiatry* 2007;164:1229–1237. [PubMed: 17671286]
- Pralong E, Magistretti P, Stoop R. Cellular perspectives on the glutamate-monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders. *Prog Neurobiol* 2002;67:173–202. [PubMed: 12169296]
- Preisig M, Ferrero F, Malafosse A. Monoamine oxidase a and tryptophan hydroxylase gene polymorphisms: are they associated with bipolar disorder? *Am J Pharmacogenomics* 2005;5:45–52. [PubMed: 15727488]
- Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics* 2000;155:945–959. [PubMed: 10835412]
- Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *Am J Hum Genet* 2007;81:559–575. [PubMed: 17701901]
- Sanacora G, Saricicek A. GABAergic contributions to the pathophysiology of depression and the mechanism of antidepressant action. *CNS Neurol Disord Drug Targets* 2007;6:127–140. [PubMed: 17430150]
- Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 1965;122:509–522. [PubMed: 5319766]
- Shi J, Hattori E, Zou H, Badner JA, Christian SL, Gershon ES, Liu C. No evidence for association between 19 cholinergic genes and bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B:715–723. [PubMed: 17373692]
- Shink E, Morissette J, Villeneuve A, Bordeleau L, Rochette D, Gagne B, Laprise C, Plante M, Barden N. Support for the presence of bipolar disorder susceptibility loci on chromosome 5: heterogeneity in a homogeneous population in Quebec. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:1273–1277. [PubMed: 12502013]
- Souery D, Lipp O, Mahieu B, Mendelbaum K, De Martelaer V, Van BC, Mendlewicz J. Association study of bipolar disorder with candidate genes involved in catecholamine neurotransmission: DRD2, DRD3, DAT1, and TH genes. *Am J Med Genet* 1996;67:551–555. [PubMed: 8950413]
- Stewart CA, Reid IC. Antidepressant mechanisms: functional and molecular correlates of excitatory amino acid neurotransmission. *Mol Psychiatry* 2002;7(Suppl 1):S15–S22. [PubMed: 11986991]
- Stober G, Sprandel J, Schmidt F, Faul T, Jabs B, Knapp M. Association study of 5'-UTR polymorphisms of the human dopamine transporter gene with manic depression. *Bipolar Disord* 2006;8:490–495. [PubMed: 17042887]
- Stoll AL, Renshaw PF, Yurgelun-Todd DA, Cohen BM. Neuroimaging in bipolar disorder: what have we learned? *Biol Psychiatry* 2000;48:505–517. [PubMed: 11018223]

- Tanis KQ, Duman RS. Intracellular signaling pathways pave roads to recovery for mood disorders. *Ann Med* 2007;39:531–544. [PubMed: 17852035]
- Taylor L, Faraone SV, Tsuang MT. Family, twin, and adoption studies of bipolar disease. *Curr Psychiatry Rep* 2002;4:130–133. [PubMed: 11914174]
- Thomson PA, Christoforou A, Morris SW, Adie E, Pickard BS, Porteous DJ, Muir WJ, Blackwood DH, Evans KL. Association of Neuregulin 1 with schizophrenia and bipolar disorder in a second cohort from the Scottish population. *Mol Psychiatry* 2007;12:94–104. [PubMed: 16940976]
- Urani A, Chourbaji S, Gass P. Mutant mouse models of depression: candidate genes and current mouse lines. *Neurosci Biobehav Rev* 2005;29:805–828. [PubMed: 15925701]
- Waldman ID, Robinson BF, Feigon SA. Linkage disequilibrium between the dopamine transporter gene (DAT1) and bipolar disorder: extending the transmission disequilibrium test (TDT) to examine genetic heterogeneity. *Genet Epidemiol* 1997;14:699–704. [PubMed: 9433566]
- Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007;447:661–678. [PubMed: 17554300]
- Williams JM, Galli A. The dopamine transporter: a vigilant border control for psychostimulant action. *Handb Exp Pharmacol* 2006;215–232. [PubMed: 16722238]
- Woo TU, Walsh JP, Benes FM. Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. *Arch Gen Psychiatry* 2004;61:649–657. [PubMed: 15237077]
- Young AH. Antiglucocorticoid treatments for depression. *Aust N Z J Psychiatry* 2006;40:402–405. [PubMed: 16683965]
- Zamanillo D, Sprengel R, Hvalby O, Jensen V, Burnashev N, Rozov A, Kaiser KM, Koster HJ, Borchardt T, Worley P, Lubke J, Frotscher M, Kelly PH, Sommer B, Andersen P, Seeburg PH, Sakmann B. Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial learning. *Science* 1999;284:1805–1811. [PubMed: 10364547]
- Zandi PP, Willour VL, Huo Y, Chellis J, Potash JB, MacKinnon DF, Simpson SG, McMahon FJ, Gershon E, Reich T, Foroud T, Nurnberger J Jr, DePaulo JR Jr, McInnis MG. Genome scan of a second wave of NIMH genetics initiative bipolar pedigrees: chromosomes 2, 11, 13, 14, and X. *Am J Med Genet B Neuropsychiatr Genet* 2003;119:69–76. [PubMed: 12707942]
- Zipursky RB, Meyer JH, Verhoeff NP. PET and SPECT imaging in psychiatric disorders. *Can J Psychiatry* 2007;52:146–157. [PubMed: 17479522]

Nominally Significant Allelic Association of Neurotransmission Systems Genes with Bipolar Disorder

Table 1

SNP	Gene	CHR	Position ^a	System	Alleles (1/2) ^b	T/UT ^c	TDT p-value	Gene-wide significance ^d
rs2453737	DRD1	5	174791508	Dopamine	A/G	158/130	0.0233	0.0989
rs2168631	DRD1	5	174808608	Dopamine	A/G	84/105	0.0475	0.1898
rs37022	SLC6A3	5	1468629	Dopamine	A/T	88/104	0.0371	0.2108
rs2036109	ADRA1A	8	26672701	Norepinephrine	A/C	157/126	0.0268	0.1728
rs10102186	ADRA1A	8	26680568	Norepinephrine	A/G	142/120	0.0139	0.1728
rs1048101	ADRA1A	8	26683945	Norepinephrine	A/G	166/140	0.0306	0.1888
rs915841	ABCG1	21	42552507	5-HT	A/G	104/70	0.0494	0.5205
rs9450594	HTR1E	6	87695058	5-HT	A/C	44/72	0.0248	0.0579
rs5028114	HTR4	5	147991932	5-HT	A/G	137/170	0.0432	0.2378
rs744731	QDPR	4	17169112	5-HT	A/G	94/138	0.0055	0.0140
rs623580	TPH1	11	18020553	5-HT	A/T	138/119	0.0413	0.0809
rs10743152	TH	11	2152557	Metabolic enzyme	A/G	149/126	0.0490	0.2058
rs1042009	ADCY1	7	45477211	cAMP signaling	A/G	109/145	0.0122	0.0829
rs12754	ADCY1	7	45534434	cAMP signaling	A/C	71/99	0.0070	0.1099
rs4790694	ARRB2	17	4573103	cAMP signaling	A/C	89/66	0.0251	0.0669
rs9456	ABAT	16	8785092	GABA	A/T	75/62	0.0049	0.0859
rs1273394	ABAT	16	8720788	GABA	A/C	110/131	0.0345	0.6224
rs925155	GABRA3	X	151128486	GABA	A/G	65/80	0.0359	0.2428
rs252952	GABRB2	5	160646912	GABA	A/C	125/103	0.0066	0.1039
rs592403	GABRB2	5	160652562	GABA	A/C	159/133	0.0198	0.2517
rs10515827	GABRB2	5	160687535	GABA	A/G	88/110	0.0206	0.1409
rs967771	GABRB2	5	160694752	GABA	A/G	98/121	0.0278	0.2058
rs6580038	GRIAI	5	153113034	Glutamate	A/G	162/120	0.0264	0.3586
rs2926837	GRIAI	5	153151993	Glutamate	C/G	148/103	0.0294	0.3127
rs1461225	GRIAI	5	153162918	Glutamate	A/C	102/136	0.0056	0.0769
rs2926835	GRIAI	5	153169123	Glutamate	A/T	71/107	0.0036	0.0290
rs592807	GRIAI	X	122317191	Glutamate	A/G	44/58	0.0267	0.4036
rs220592	GRIN2B	12	13856575	Glutamate	A/C	168/140	0.0449	0.7223
rs2268115	GRIN2B	12	13760992	Glutamate	A/C	159/141	0.0352	0.6743
rs1799281	GRIN2D	19	53640582	Glutamate	A/G	143/112	0.0029	0.0260
rs362853	GRM1	6	146754791	Glutamate	A/C	148/123	0.0443	0.3766
rs733457	GRM4	6	34176386	Glutamate	A/C	122/159	0.0249	0.1399
rs6443074	GRM7	3	6882193	Glutamate	A/G	42/49	0.0300	0.5674
rs329037	GRM7	3	7738386	Glutamate	A/C	176/131	0.0059	0.3766
rs162724	GRM7	3	7744282	Glutamate	A/G	65/96	0.0205	0.3037
rs3818275	SLC1A2	11	35265359	Glutamate	A/G	172/131	0.0325	0.3556
rs2731877	SLC1A3	5	36637612	Glutamate	A/G	150/166	0.0224	0.1948
rs1645660	SLC1A3	5	36680057	Glutamate	A/G	147/147	0.0292	0.2927

^aChromosome position is based on the human genome assembly B35 (hg17).

^bMinor allele for each SNP in unrelated parents is underlined.

^cNumbers of Transmitted and Untransmitted alleles from heterozygous parents to the first affected child in each family are presented. The T and UT counts for all affected offspring are not presented because they will not give accurate estimates of odds ratios when there is correlation between sibs due to any linkage.

^dp-values were based on permutation for all SNPs in each gene.

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; T, transmitted; UT, untransmitted; TDT, transmission/disequilibrium test.

Table II
Gene-wide Significant Haplotype Association with Bipolar Disorder

SNPs/Haplotype	Gene	System	T/U/T	TDI <i>p</i> -value	Gene-wide significance ^a
rs37022 rs2042449/TG	<i>SLC6A3</i>	Dopamine	159/118	0.0068	0.0340
rs1568447 rs690533 rs516035/GGA	<i>GRIN2C</i>	Glutamate	30/42	0.0110	0.0410
rs2597758 rs1031326 rs744731 rs2597778/AGGA	<i>QDPR</i>	5-HT	93/134	0.0064	0.0499

^a *P* values in bold, which reached gene-wide significance ($P < 0.05$), were based on permutation for multiple tests for all the single nucleotide polymorphisms and haplotypes in each gene.