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Convergent Functional Genomics of Genome-Wide Association Data for Bipolar Disorder: Comprehensive Identification of Candidate Genes, Pathways and Mechanisms

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Given the mounting convergent evidence implicating many more genes in complex disorders such as bipolar disorder than the small number identified unambiguously by the first-generation Genome-Wide Association studies (GWAS) to date, there is a strong need for improvements in methodology. One strategy is to include in the next generation GWAS larger numbers of subjects, and/or to pool independent studies into meta-analyses. We propose and provide proof of principle for the use of a complementary approach, convergent functional genomics (CFG), as a way of mining the existing GWAS datasets for signals that are there already, but did not reach significance using a genetics-only approach. With the CFG approach, the integration of genetics with genomics, of human and animal model data, and of multiple independent lines of evidence converging on the same genes offers a way of extracting signal from noise and prioritizing candidates. In essence our analysis is the most comprehensive integration of genetics and functional genomics to date in the field of bipolar disorder, yielding a series of novel (such as Klf12, Aldh1a1, A2bp1, Ak3l1, Rorb, Rora) and previously known (such as Bdnf, Arntl, Gsk3b, Disc1, Nrg1, Htr2a) candidate genes, blood biomarkers, as well as a comprehensive identification of pathways and mechanisms. These become prime targets for hypothesis driven follow-up studies, new drug development and personalized medicine approaches.

Key words: gene expression; genetics; convergent functional genomics; genome-wide association; brain; blood; bipolar

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INTRODUCTION

The recent availability of massively parallel genotyping technologies has made genome wide association studies (GWAS) feasible, with initial interesting results reported in a variety of complex disorders [GWAS, 2007; McPherson et al., 2007; Kingsmore et al., 2008; Willer et al., 2008]. However, the number of SNPs identified unambiguously, after correction for multiple comparisons, is relatively small, and the number of known genes unambiguously implicated by them is even smaller [Zeggini et al., 2007]. At least part of the problem facing genetic-only approaches in complex disorders may be related to extreme genetic heterogeneity [Walsh et al., 2008]. Given the mounting convergent evidence implicating many more genes in complex disorders [Walsh et al., 2008; Sun et al., 2008a] than the small number identified by the first-generation GWAS to date, there is a strong need for improvements in methodology. One strategy is to include in the next generation of GWAS larger number of subjects, and/or pool independent studies into meta-analyses [Zeggini et al., 2008]. We propose the use of a complementary approach, convergent functional genomics (CFG) [Niculescu et al., 2000a; Ogden et al., 2004; Le-Niculescu et al., 2007a,b; Le-Niculescu et al., 2008a,b], as a way of mining the existing GWAS datasets for signals that are there already, but did not reach significance using a genetics-only approach. With the CFG approach, the integration of genetics with genomics, of human and animal model data, and of multiple independent lines of evidence converging on the same genes offers a way of extracting signal from noise, and prioritizing candidates for future focused validatory studies-individual candidate gene association studies with more SNPs tested per gene, deep re-sequencing, and/or biological validation such as transgenic animal work [Le-Niculescu et al., 2008b].

As part of a CFG strategy, we have used data from three published GWAS datasets for bipolar disorder [GWAS, 2007; Baum et al., 2008]. We integrated those data with human postmortem brain gene expression data and human blood gene expression data, as well as with relevant animal model brain and blood gene expression data generated by our group [Niculescu et al., 2000a; Ogden et al., 2004; Le-Niculescu et al., 2007b, 2008a,b]. In addition, we have integrated as part of this comprehensive approach other published human genetic (linkage or association) data for bipolar and related disorders to date, and relevant mouse genetic (QTL or transgenic) data. Genes were prioritized based on a scoring of multiple independent lines of evidence, followed by pathway analyses of the top candidate genes. Finally, we have looked at whether the top candidate genes identified by our analysis are represented in a recently published independent GWAS [Sklar et al., 2008].

METHODS

Genome-Wide Association Data for Bipolar Disorder

The GWA data for the bipolar study from the Wellcome Trust is available at http://www.wtccc.org.uk/info/access_to_data_samples.shtml [2007]. The GWA data from NIMH and German studies is available at http://mapgenetics.nimh.nih.gov/bp_pooling [Baum et al., 2008]. We have used the genotypic test *P*-value (standard analysis). We used two nominal *P*-value thresholds for SNP selection-a lower stringency threshold ($P < 0.05$), and a higher stringency threshold ($P < 0.001$). The GWA data from the STEP-BD study, used as a replication cohort to test our top findings, is available at http://pngu.mgh.harvard.edu/~purcell/bpwgas. No Bonferroni correction for number of SNPs tested was performed.

Gene Identification

To identify the genes that correspond to the selected SNPs, the lists of SNPs from the GWAS was uploaded to the SNPPER website (http://snpper.chip.org). In the cases where a SNP mapped to a region close to multiple genes, we selected all the genes that were provided by SNPper. SNPs for which no gene was identified were not included in our subsequent analysis.

Human Postmortem Brain Gene Expression

Information about our candidate genes was obtained using GeneCards (http://www.genecards.org), the Online Mendelian Inheritance of Man database (http://ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM), as well as database searches using PubMed (http://ncbi.nlm.nih.gov/PubMed) and various combinations of keywords (gene name, bipolar, depression, human, postmortem, brain).

Human Genetic (Linkage, Association) Convergence

To designate convergence for a particular gene, the gene had to map within 10 cM [see Niculescu et al., 2000b for detailed discussion] of a microsatellite marker for which at least one published study showed evidence for linkage for bipolar disorder or depression, or a positive association study for the gene itself was reported in the literature. The University of Southampton's sequence-based integrated map of the human genome (The Genetic Epidemiological Group, Human Genetics Division, University of Southampton: http://cedar.genetics.soton.ac.uk/public_html/) was used to obtain cM locations for both genes and markers. The sex-averaged cM value was calculated and used to determine convergence to a particular marker. For markers that were not present in the Southampton database, the Marshfield database (Center for Medical Genetics, Marshfield, WI: http://research.marshfieldclinic.org/genetics) was used with the NCBI Map Viewer web-site to evaluate linkage convergence.

We have established in the lab manually curated databases of all the published human postmortem and human genetic literature to date on bipolar and related disorders. These large databases have been used in our CFG cross-validation analyses.

Animal Model Brain and Blood Gene Expression Data

For animal model brain and blood gene expression evidence, we have used previously generated data from two different animal models for bipolar disorder developed by our group, one

pharmacogenomic and one transgenic [Ogden et al., 2004; Le-Niculescu et al., 2007a,b, 2008a,b].

Mouse Genetic (QTL, Transgenic) Convergence

To search for mouse genetic evidence—quantitative trait loci (QTL) or transgenic—for our candidate genes, we utilized the MGI_3.54—Mouse Genome Informatics (Jackson Laboratory, Bar Harbor, ME) and used the search menu for mouse phenotypes and mouse models of human disease/abnormal behaviors, using the following sub-categories: abnormal emotion/affect behavior and abnormal sleep pattern/circadian rhythm. To designate convergence for a particular gene, the gene had to map within 10 cM of a QTL marker for the abnormal behavior, or a transgenic mouse of the gene itself displayed that behavior.

Convergent Functional Genomics (CFG) Analysis Scoring

Genes from GWAS data that had SNPs with nominal *P*-values of <0.05 received 1 point; those that had SNPs with nominal *P*-values of <0.001 received 2 points (see Fig. 1). All other cross-validating lines of evidence (other human data, animal model data) received a maximum of 1 point each (for human genetic data, 0.5 points if it is linkage, 1 point if it is association; for mouse genetic data, 0.5 points if it is QTL, 1 point if it is transgenic). Thus the maximum possible CFG score for each gene is 12 ($6 = 2 \times 3$ points from the three GWAS, and 6 points from the other lines of evidence). As we are interested in discovering signal in GWAS, we weighted data from GWAS more heavily, bringing the data from this one methodological approach on par with the data from all the other methodological approaches combined. It has not escaped our attention that other ways of weighing the scores of line of evidence may give slightly different results in terms of prioritization, if not in terms of the list of genes per se. Nevertheless, we feel this simple scoring system provides a good separation of genes based on our focus on identifying signal in the GWAS.

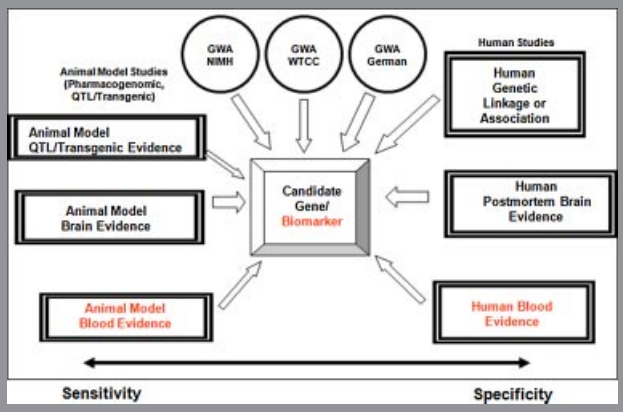

FIG. 1. Convergent functional genomics. Multiple independent lines of evidence for Bayesian cross-validation of GWAS data.

Pathway Analysis

Ingenuity 6.0 (Ingenuity Systems, Redwood City, CA) was employed to analyze the molecular networks, biological functions and canonical pathways of the top candidate genes resulting from our CFG analysis (Fig. 3), as well as to identify genes in our datasets that are the target of existing drugs (Table IIS).

We have also used another independent pathway analysis package, MetaCore (GeneGo, Encinitas, CA) to analyze genes functions in diseases (Fig. 5).

RESULTS

Top Candidate Genes

In order to minimize false negatives, we initially cast a wide net, using as a filter a minimal requirement for a gene to have both some genetic and some functional genomic evidence (Table IS). We thus generated an initial list of 1,529 unique genes with $P < 0.05$ in at least one of the three primary GWAS analyzed, that also had some functional (gene expression) evidence (human or animal model data), implicating them in bipolar disorder or depression. Of interest, a similar analysis for a recent independent GWAS (STEP-BD) [Sklar et al., 2008] yielded just 96 additional new genes (see Supplementary Information—Table IS) over the 1,529 we originally identified, suggesting that: (1) with our genetic-genomic filtering of the three GWAS in the primary analysis we are already capturing most of the genes that may be involved in bipolar disorder, with additional studies providing an asymptotic contribution beyond this point; and (2) that the number of genes potentially involved, directly or indirectly, in bipolar disorder may be indeed quite large, up to 10% of the genome.

In order to minimize false positive, we then used a CFG analysis integrating multiple lines of evidence to prioritize this initial list of 1,529 genes, and focused our subsequent analyses on only the top CFG scoring candidate genes. Forty-one genes had a CFG score of 6 and above ($\geq$50% of maximum possible score) (Fig. 2). One hundred thirteen genes had a CFG score of 5 and above ($\geq 2 + 2 + 1 =$ maximum score for gene expression data in human brain and blood + maximum score for gene expression data in animal models brain and blood + at least one nominal *P*-value signal in a GWAS) (Table I).

As a way of testing the validity of our approach, we have examined if our top findings were over-represented in an independent GWAS of bipolar disorder [Sklar et al., 2008]. Thirty of the top 41 genes identified by our approach had a *P*-value of <0.05 in that independent study, an estimated fourfold enrichment over what would be expected by chance alone in that study (see Table II).

Candidate Blood Biomarkers

Of the top candidate genes from Table I (see also Fig. 2), 32 out of 113 have prior blood gene expression evidence implicating them as potential blood biomarkers. The additional evidence provided by GWAS data indicates a genetic rather than purely environmental (medications, stress) basis for their alteration in disease, and their potential utility as trait rather than purely state markers.

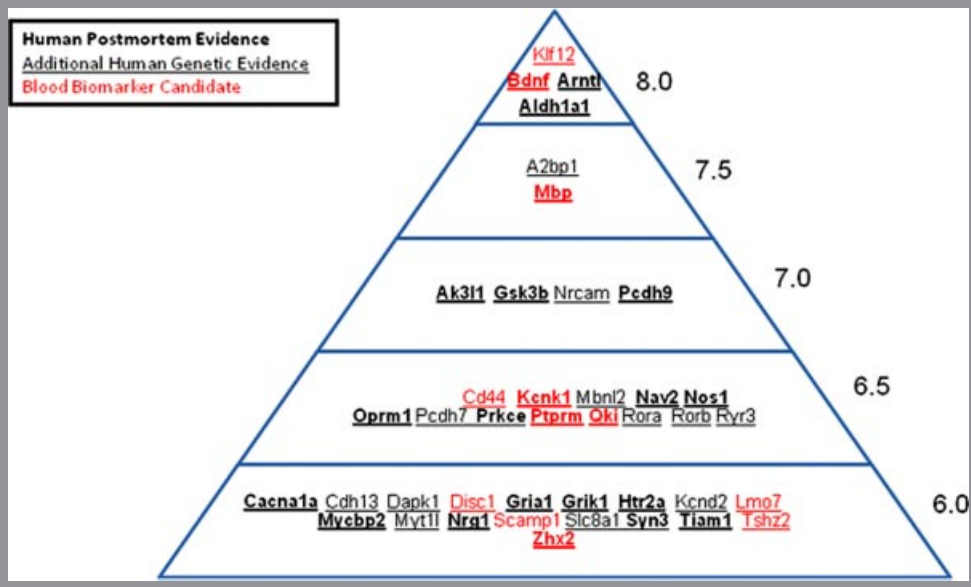

FIG. 2. Top candidate genes for bipolar disorder identified by CFG of GWAS data. CFG score depicted on the right side of the pyramid. Bold font—the gene has human postmortem evidence. Underlined—the gene has additional human genetic evidence beyond the GWAS data. Red—the gene has blood evidence making it a possible biomarker.

Pathways and Mechanisms

We classified our top candidate genes from Table I into biological groups of interest previously reported to have relevance to the pathophysiology of bipolar and related disorders (see Table III). Ingenuity pathway analysis was carried out on the top 41 genes (Fig. 3A), as well as on the more extensive list of 113 top genes (Fig. 3B). Ingenuity was employed to analyze the molecular networks, biological functions and canonical pathways of the top candidate genes resulting from our CFG analysis (Fig. 3A,B), as well as to identify genes in our datasets that are the target of existing drugs (Table IIS). We have also used another independent pathway analysis package, MetaCore (GeneGo, Encinitas, CA) to analyze genes functions in diseases (Fig. 5). Finally, a model summarizing the data is depicted in Figure 4.

DISCUSSION

Our CFG approach helped prioritize, as expected, genes for which there was consistent evidence among the three GWAS datasets, or stronger evidence in one or another of the datasets. However, it also prioritized genes with weaker evidence in the GWAS data, but with strong independent evidence in terms of gene expression studies and other prior human or animal genetic work.

At the top of our list of candidate genes we have four genes: Arntl, Bdnf, Aldh1a1, and Klf12. Notably, of the four top candidate genes for bipolar disorder identified by our combined approach (Klf12, Arntl, Bdnf, Aldh1a1) (Fig. 2), one of them—Klf12 (Kruppel-like factor 12), had not been previously suspected to be involved in bipolar disorder, or indeed in neuropsychiatric disorders. It shows modest but consistent signal ($P < 10^{-3}$, 10^{-4}) across all three primary GWAS datasets. Klf12 maps to a mouse QTL for abnormal emotion/affect behavior, and to a linkage locus on chromosome 13q22.1 previously implicated in bipolar disorder [Potash et al., 2003]. Klf12 is a transcription factor, more specifically a zinc finger transcriptional repressor. Other transcription factor top candidate genes identified by our analysis include Mytl1, Tshz2, and Zhx2 (Fig. 2, and Tables I and III). Transcription factors are particularly interesting as effectors of broad phenotypic changes, due to the large number of genes they regulate. It is thus possible that by themselves, or in oligogenic combinations, they can account for complex disorders such as bipolar disorder. In our own animal model work, Klf12 was inversely changed in the pre-frontal cortex (decreased) and the amygdala (increased) of Dbp KO ST manic-like mice [Le-Niculescu et al., 2008b]. We have also identified Klf12 as a candidate blood biomarker in recent human studies, increased in expression in low mood (depression) [Le-Niculescu et al., 2008a]. The model that emerges, then, is that Klf12 may be involved in suppressing genes involved in elevated mood. Gain of function mutations or promoter mutations that lead to overexpression are likely to manifest as depressive phenotypes, and loss of function mutations or promoter mutations that lead to decreased expression, as manic phenotypes.

Arntl (aryl hydrocarbon receptor nuclear translocator-like), also a transcription factor, is a circadian clock gene. Other circadian top candidate genes identified by our analysis include Rorb, Rora, and Rxrg (Fig. 2, and Tables I and III). Circadian rhythm and sleep abnormalities have long been described in bipolar disorder—excessive sleep in the depressive phase, reduced need for sleep in the manic phase [Bauer et al., 2006]. Sleep deprivation is one of the more powerful and rapid acting treatment modalities for severe depression, and can lead to precipitation of manic episodes

TABLE I. Top Candidate Genes for Bipolar Disorder Identified by Convergent Functional Genomics (CFG) of Genome-Wide Association Studies (GWAS) Data

Gene symbol/ name	GWAS WTC *P*-value	GWAS NIMH *P*-value	GWAS German *P*-value	Mouse genetic evidence (QTL, TG)	Mouse models brain evidence [Ogden et al., 2004; Le-Niculescu et al., 2008b]	Mouse models blood evidence [Le-Niculescu et al., 2008a,b]	Additional human genetic evidence (linkage or association)	Human postmortem brain evidence	Human blood evidence [Le-Niculescu et al., 2008a]	CFG score
Klf12 Kruppel-like factor 12	2.76E-03	**6.77E-04**	**1.68E-04**	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm	DBP ST AMY (I) DBP ST PFC (D) [Le-Niculescu et al., 2008b]		13q22.1 BP [Potash et al., 2003]		(D) [Le-Niculescu et al., 2008a]	8.0
Arntl aryl hydrocarbon receptor nuclear translocator-like	**7.71E-04**	3.84E-02	3.72E-02	(TG) Abnormal Sleep Pattern/ Circadian Rhythm	PFC Meth (D) [Ogden et al., 2004]		11p15.2 (Assoc) BP [Mansour et al., 2006; Nievergelt et al., 2006]	(I) BP [Nakatani et al., 2006]		8.0
Bdnf brain-derived neurotrophic factor	1.05E-02	3.76E-02	1.91E-03	(TG) Abnormal emotion/affect behavior	PFC Meth (D) [Ogden et al., 2004]		11p14.1 (Assoc) BP [Sklar et al., 2002; Liu et al., 2008, in press] (Assoc) MDD [Schumacher et al., 2005] BP [McInnes et al., 1996; Detera-Wadleigh et al., 1999; Neves-Pereira et al., 2002]	(D) MDD [Duman and Monteggia, 2006] (D) BP [Knable et al., 2004; Torrey et al., 2005]	(D) BP [Karege et al., 2004]	8.0
Aldh1a1 aldehyde dehydrogenase family 1, subfamily A1	1.29E-02	**1.58E-04**	3.34E-02	Abnormal sleep pattern/circadian rhythm	DBP NST PFC (D) DBP ST AMY (I) [Le-Niculescu et al., 2008b]	Meth (D)	9q21.13 BP [Macgregor et al., 2004]	(I) BP [Pennington et al., 2007]		8.0
A2bp1 ataxin-2-binding protein 1	**3.42E-05**	**4.23E-04**	**1.59E-04**		VT VPA (D) [Ogden et al., 2004]		16p13.2 BP [Ewald et al., 2002]			7.5
Mbp myelin basic protein		8.30E-03	**8.19E-04**		DBP NST PFC (D) DBP ST PFC (D) DBP ST AMY (I) [Le-Niculescu et al., 2008b]	Meth (I)	18q23 BP [Freimer et al., 1996; Ewald et al., 1999; Baron, 2001; Schulze et al., 2003] MDD [Coon et al., 1996]	(D) BP [Tkachev et al., 2003; Sun et al., 2006] (D) Female BP, (I) Male BP [Chambers and Perrone-Bizzozero, 2004]	(I) [Le-Niculescu et al., 2008a]	7.5
Ak3l1 adenylate kinase 3 alpha-like 1	**9.80E-05**	1.79E-02	2.57E-02	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm	DBP ST AMY (D) DBP ST PFC (I) DBP ST AMY (D) [Le-Niculescu et al., 2008b]		1p31.3 BP [Rice et al., 1997; Ewald et al., 2002] MDD [Nurnberger et al., 2001]	(D) MDD [Klempan et al., 2007]		7.0

(*Continued*)

TABLE I. (*Continued*)

Gene symbol/ name	GWAS WTC *P*-value	GWAS NIMH *P*-value	GWAS German *P*-value	Mouse genetic evidence (QTL, TG)	Mouse models brain evidence [Ogden et al., 2004; Le-Niculescu et al., 2008b]	Mouse models blood evidence [Le-Niculescu et al., 2008a,b]	Additional human genetic evidence (linkage or association)	Human postmortem brain evidence	Human blood evidence [Le-Niculescu et al., 2008a]	CFG score
Gsk3b glycogen synthase kinase 3 beta	9.82E-03	1.62E-02	6.72E-03	(TG) Abnormal emotion/affect behavior	CP VPA (D) [Ogden et al., 2004] PFC Meth (D) [Ogden et al., 2004] DBP NST PFC (D) DBP NST AMY (I) [Le-Niculescu et al., 2008b]		3q13.33 (Assoc) BP [Szczepankiewicz et al., 2006; Lachman et al., 2007] BP [Bailer et al., 2002; Benedetti et al., 2004; Maziade et al., 2005; Nishiguchi et al., 2006]	(D) BP [Nakatani et al., 2006; Vawter et al., 2006] (I) MDD [Vawter et al., 2006]		7.0
Nrcam neuronal cell adhesion molecule	1.63E-03	**5.94E-04**	**8.60E-04**	Abnormal sleep pattern/circadian rhythm	DBP NST AMY (I) [Le-Niculescu et al., 2008b]		7q31.1 BP [Detera-Wadleigh et al., 1999; Evans et al., 2007]			7.0
Pcdh9 Protocadherin 9	9.77E-03	1.19E-03	**4.80E-04**	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm	DBP NST AMY (I) [Le-Niculescu et al., 2008b]		13q21.32 BP [Potash et al., 2003]	(D) MDD [Klempan et al., 2007]		7.0
Cd44 CD44 antigen (homing function and Indian blood group system)	3.48E-02	3.94E-03	1.06E-02		CP Meth (I) [Ogden et al., 2004]	Meth (D)	11p13 BP [McInnes et al., 1996]		(I) BP [Middleton et al., 2005]	6.5
Kcnk1 potassium channel, subfamily K, member 1	1.89E-02	7.60E-03	**3.47E-04**				1q42.2 BP [Curtis et al., 2003; Macgregor et al., 2004]	(D) BP [Jurata et al., 2004]	(I) BP [Matigian et al., 2007]	6.5
Mbnl2 muscleblind-like 2 (Drosophila)	2.94E-03	4.64E-02	**4.02E-04**		AMY VPA (D) [Ogden et al., 2004]	DBP NST (D) [Le-Niculescu et al., 2008b]	13q32.1 BP [Liu et al., 2003; Maziade et al., 2005; Goes et al., 2007]			6.5
Nav2 neuron navigator 2	4.16E-03	**5.77E-04**	2.04E-03	(TG) Abnormal emotion/affect behavior			11p15.1 BP [Detera-Wadleigh et al., 1999]	(D) BP [Kim et al., 2007]		6.5
Nos1 Nitric oxide synthase 1, neuronal (Nos1), mRNA	1.72E-02	3.73E-02	4.56E-02	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm	DBP NST AMY (D) [Le-Niculescu et al., 2008b]		12q24.22 (Assoc) BP [Fallin et al., 2005] BP [Morissette et al., 1999; Chagnon et al., 2004; Fallin et al., 2005]	(I) BP [Benes et al., 2006]		6.5
Oprm1 Opioid receptor, mu 1	**7.82E-04**	7.31E-03	1.90E-03	(TG) Abnormal emotion/ affect behavior			6q25.2 BP [Cheng et al., 2006]	(I) BP [Ryan et al., 2006]		6.5
Pcdh7 Protocadherin 7	**4.08E-04**	1.71E-02	**8.05E-04**		AMY VPA (D) [Ogden et al., 2004]		4p15.1 BP [Detera-Wadleigh et al., 1999; Lambert et al., 2005]			6.5

Prkce protein kinase C, epsilon	4.59E-03	**2.37E-04**	1.20E-02	(TG) Abnormal emotion/affect behavior		2p21 BP [Etain et al., 2006]	(D) BP [Torrey et al., 2005]		6.5
Ptprm protein tyrosine phosphatase, receptor type, M	1.74E-02	1.10E-02	**2.41E-04**			18p11.23 BP [Segurado et al., 2003]	(I) BP [Nakatani et al., 2006]	(D) [Le-Niculescu et al., 2008a]	6.5
Qki quaking homolog, KH domain RNA binding (mouse)	3.06E-02		**7.74E-05**		CP VPA (I) [Ogden et al., 2004] DBP AMY (I) [Le-Niculescu et al., 2008b]	6q26 BP [Cheng et al., 2006]	(D) MDD [Klempan et al., 2007]	(D) BP [Matigian et al., 2007]	6.5
Rora RAR-related orphan receptor alpha	**1.90E-04**	**3.55E-04**	6.36E-03		DBP NST AMY (I) DBP ST AMY (I) DBP ST PFC (D) [Le-Niculescu et al., 2008b]	15q21-q22 MDD [Zubenko et al., 2002]			6.5
Rorb RAR-related orphan receptor beta	1.29E-02	**5.88E-04**	1.95E-02	(TG) Abnormal emotion/affect behavior	DBP ST AMY(I) DBP ST PFC (D) [Le-Niculescu et al., 2008b]	9q21.13 BP [Macgregor et al., 2004]			6.5
Ryr3 ryanodine receptor 3	1.21E-03	**2.89E-04**	6.09E-03	(TG) Abnormal emotion/affect behavior	CP VPA (I) [Ogden et al., 2004]	15q13.3 MDD [Levinson et al., 2007]			6.5
Cacna1a calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	2.99E-02	2.12E-02	**7.04E-04**	Abnormal emotion/affect behavior		19p13.13 MDD [Zubenko et al., 2003]	(D) BP [Iwamoto et al., 2004]		6.0
Cdh13 cadherin 13	5.89E-03	2.50E-03	**9.08E-04**	Abnormal emotion/affect behavior	DBP NST AMY (D) [Le-Niculescu et al., 2008b]	16q23.3 BP [Etain et al., 2006]			6.0
Dapk1 death-associated protein kinase 1	4.02E-02	**5.97E-05**	4.04E-02	Abnormal emotion/affect behavior	AMY VPA (D) [Ogden et al., 2004]	9q21.33 BP [Segurado et al., 2003]			6.0
Disc1 disrupted in schizophrenia 1	1.31E-02	2.99E-03	6.08E-03	(TG) Abnormal emotion/affect behavior		1q42.2 (Assoc) BP [Hodgkinson et al., 2004; Maeda et al., 2006; Millar et al., 2007; Hennah et al., 2008] BP [Curtis et al., 2003; Macgregor et al., 2004]		(D) BP [Maeda et al., 2006]	6.0
Gria1 glutamate receptor, ionotropic, AMPA1 (alpha 1)	1.47E-02	6.55E-03	9.19E-03	Abnormal emotion/affect behavior	VT Meth (D) [Ogden et al., 2004]	5q33.2 BP [Morissette et al., 1999; Sklar et al., 2004; Etain et al., 2006]	(I) BP, MDD [Choudary et al., 2005]		6.0
Grik1 glutamate receptor, ionotropic, kainate 1	**5.39E-04**	2.79E-03	3.36E-02	Abnormal emotion/affect behavior		21q21.3 BP [Detera-Wadleigh et al., 1999; Morissette et al., 1999]	(D) BP [Iwamoto et al., 2004; Nakatani et al., 2006] (I) DLPFC -MDD [Choudary et al., 2005]		6.0

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TABLE I. (*Continued*)

Gene symbol/ name	GWAS WTC *P*-value	GWAS NIMH *P*-value	GWAS German *P*-value	Mouse genetic evidence (QTL, TG)	Mouse models brain evidence [Ogden et al., 2004; Le-Niculescu et al., 2008b]	Mouse models blood evidence [Le-Niculescu et al., 2008a,b]	Additional human genetic evidence (linkage or association)	Human postmortem brain evidence	Human blood evidence [Le-Niculescu et al., 2008a]	CFG score
								(D) AnCg—BP [Choudary et al., 2005]		
Htr2a Seratonin receptor 2A	1.86E-02	4.52E-02	1.65E-03	(TG) Abnormal emotion/affect behavior Abnormal sleep pattern/ circadian rhythm			13q14.2 (Assoc) BP [Ranade et al., 2003]0, [Ranade et al., 2003] BP [Arranz et al., 1997; Badenhop et al., 2002]	(D) BP [Knable et al., 2004; Torrey et al., 2005] (D) MDD [Klempan et al., 2007]		6.0
Kcnd2 Potassium voltage-gated channel, Shal-related family, member 2 (Kcnd2), mRNA	5.78E-03	4.08E-03	**5.24E-05**	Abnormal emotion/ affect behavior	DBP ST PFC (D) [Le-Niculescu et al., 2008b]		7q31.31 BP [Detera-Wadleigh et al., 1999; Evans et al., 2007]			6.0
Lmo7 LIM domain only 7	**6.62E-05**	1.11E-02	8.17E-03	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm			13q22.2 BP [Potash et al., 2003]		(D) Anti-depressant treatment [Kalman et al., 2005]	6.0
Mycbp2 MYC binding protein 2	**5.66E-04**	2.92E-02	2.39E-02	Abnormal emotion/ affect behavior			13q22.3 BP [Potash et al., 2003]; MDD [Zubenko et al., 2003]	(I) BP [Pennington et al., 2007]		6.0
Myt1l myelin transcription factor 1-like	**2.25E-04**	1.31E-02	1.25E-02	Abnormal sleep pattern/circadian rhythm	DBP ST PFC (D) [Le-Niculescu et al., 2008b]		2p25.3 BP [Detera-Wadleigh et al., 1999]			6.0
Nrg1 neuregulin 1	**1.07E-05**	2.19E-03	4.51E-03				8p12 (Assoc) BP [Green et al., 2005; Walss-Bass et al., 2006; Thomson et al., 2007] BP [Cichon et al., 2001; Zubenko et al., 2003; Park et al., 2004]	(I) BP [Tkachev et al., 2003] (D) MDD [Bertram et al., 2007]		6.0
Scamp1 secretory carrier membrane protein 1	1.71E-02	1.31E-02	2.46E-03		DBP ST PFC (D) [Le-Niculescu et al., 2008b]	DBP NST (D) [Le-Niculescu et al., 2008b]	5q14.1		(D) [Le-Niculescu et al., 2008a]	6.0
Slc8a1 solute carrier family 8 (sodium/calcium exchanger), member 1	4.57E-03	**2.77E-04**	2.28E-02	Abnormal emotion/af- fect behavior	DBP ST AMY (I) DBP ST AMY (D) [Le-Niculescu et al., 2008b]		2p22.1 BP [Etain et al., 2006]			6.0

Syn3 synapsin IIIa	**1.67E-04**	4.94E-03	4.17E-03			22q12.3 (Assoc) BP [Lachman et al., 2006] BP [Kelsoe et al., 2001; Potash et al., 2003; Lachman et al., 2006]	(D) BP [Vawter et al., 2002]		6.0
Tiam1 T-cell lymphoma invasion and metastasis 1	**7.39E-05**	1.82E-03	2.65E-03	Abnormal emotion/ affect behavior		21q22.11 BP [Detera-Wadleigh et al., 1999; Morissette et al., 1999]	(D) MDD [Aston et al., 2005]		6.0
Tshz2 teashirt family zinc finger 2	1.98E-02	8.22E-03	**3.58E-04**	Abnormal emotion/ affect behavior		20q13.2 BP [Radhakrishna et al., 2001]		(D) [Le-Niculescu et al., 2008a]	6.0
Zhx2 Zinc fingers and homeoboxes 2	2.47E-03	2.86E-02	1.69E-03	Abnormal emotion/ affect behavior		8q24.13 BP [Cichon et al., 2001; Badenhop et al., 2002; Park et al., 2004]	(D) BP [Kim et al., 2007]	(I) BP [Middleton et al., 2005]	6.0
Acacb acetyl-Coenzyme A carboxylase beta	2.94E-02	**7.84E-04**	1.42E-03			12q24.11 BP [Chagnon et al., 2004; Maziade et al., 2005]		(D) [Le-Niculescu et al., 2008a]	5.5
App amyloid beta (A4) precursor protein	3.37E-02	9.86E-03	7.81E-03	(TG) Abnormal emotion/affect behavior (TG) Abnormal sleep pattern/circadian rhythm		21q21.3 BP [Morissette et al., 1999]	(I) BP [Jurata et al., 2004]		5.5
Atxn1 Ataxin 1	1.11E-03	5.55E-03	6.58E-03		CP METH (D) [Ogden et al., 2004] DBP PFC (D) [Le-Niculescu et al., 2008b]	6p22.3 BP [Turecki et al., 2001]		(I) [Le-Niculescu et al., 2008a]	5.5
C14orf145 chromosome 14 open reading frame 145	**2.27E-04**	1.89E-02	1.03E-03			14q31.1 BP [Segurado et al., 2003]		(D) [Le-Niculescu et al., 2008a]	5.5
C18orf1 Chromosome 18 open reading frame 1	**1.16E-04**	4.21E-03	3.04E-03			18p11.21 BP [Detera-Wadleigh et al., 1999; Baron, 2001]		(D) [Le-Niculescu et al., 2008a]	5.5
Cacnb2 calcium channel, voltage-dependent, beta 2 subunit	**2.40E-09**	6.57E-03	4.23E-02		AMY VPA (D) [Ogden et al., 2004] CP VPA (I) [Ogden et al., 2004] DBP NST AMY (D) [Le-Niculescu et al., 2008b]	10p12.33 BP [Rice et al., 1997; Faraone et al., 1998; Foroud et al., 2000; Baron, 2001; McInnis et al., 2003; Lambert et al., 2005; Etain et al., 2006]			5.5

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Camk2a calcium/calmodulin-dependent protein kinase II alpha		1.76E-02	3.62E-02	(TG) Abnormal emotion/affect behavior (TG) Abnormal sleep pattern/ circadian rhythm	DBP NST AMY (I) DBP ST PFC (I) [Le-Niculescu et al., 2008b]		5q32 BP [Sklar et al., 2004; Etain et al., 2006]	(D) BP [Xing et al., 2002] (I) MDD [Novak et al., 2006] (I) MDD [Tochigi et al., 2008]		5.5
Camk2d calcium/calmodulin-dependent protein kinase II, delta	1.69E-02	1.20E-03	2.90E-03		DBP ST PFC (I) [Le-Niculescu et al., 2008b]		4q26 BP [Lambert et al., 2005]		(I) [Le-Niculescu et al., 2008a]	5.5
Celsr1 Cadherin, EGF LAG seven-pass G-type receptor 1 (flamingo homolog, Drosophila)	1.85E-03	**8.84E-04**	4.85E-02	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm			22q13.31	(I) BP [Ryan et al., 2006]		5.5
Clstn2 calsyntenin 2	7.57E-03	**4.25E-04**	1.33E-02		DBP NST AMY (I) [Le-Niculescu et al., 2008b]		3q23 BP [Dick et al., 2003]			5.5
Crebbp CREB binding protein	5.02E-03	1.39E-03	3.64E-03	(TG) Abnormal emotion/affect behavior	DBP ST PFC (D) [Le-Niculescu et al., 2008b]		16p13.3 BP [Ewald et al., 2002]			5.5
Cugbp2 CUG triplet repeat, RNA binding protein 2	**2.84E-05**	3.38E-03	2.66E-02				10p14 MDD [Zubenko et al., 2003] BP [Etain et al., 2006]		(I) BP [Matigian et al., 2007]	5.5
Dcamkl1 doublecortin and CaM kinase-like 1	8.55E-03	2.36E-03	5.27E-03		AMY VPA (D) [Ogden et al., 2004]	DBP NST (D) [Le-Niculescu et al., 2008b]	13q13.3 BP [Maziade et al., 2005]			5.5
Diaph1 diaphanous homolog 1 (Drosophila)	2.62E-02	4.70E-02	3.38E-03		CP VPA (I) [Ogden et al., 2004]		5q31.3 MDD [Zubenko et al., 2003]		(I) BP [Matigian et al., 2007]	5.5
Dpp10 dipeptidylpeptidase 10	**1.31E-05**	1.67E-03	2.70E-03		DBP NST AMY (I) [Le-Niculescu et al., 2008b]		2q14.1 BP [Maziade et al., 2005; Etain et al., 2006]			5.5
Eif2c2 eukaryotic translation initiation factor 2C, 2	1.81E-02		**2.48E-04**		DBP ST AMY (I) DBP ST PFC (D) [Le-Niculescu et al., 2008b]		8q24.3 BP [Segurado et al., 2003]			5.5
Fam13a1 family with sequence similarity 13, member A1	3.37E-03	**4.77E-05**	3.94E-02				4q22.1 BP [Curtis et al., 2003]		(D) [Le-Niculescu et al., 2008a]	5.5
Fgf12 fibroblast growth factor 12	**6.14E-04**	2.50E-03	9.57E-03				3q28 BP [Bailer et al., 2002; Liu et al., 2003; Schosser et al., 2004; Maziade et al., 2005]	(D) MDD [Evans et al., 2004]		5.5
FLJ10986 hypothetical protein FLJ10986	9.77E-03	2.09E-03	**2.29E-04**				1p32.1 BP [Cichon et al., 2001]		(I) [Le-Niculescu et al., 2008a]	5.5

Foxp1 Forkhead box P1 (Foxp1), mRNA	4.80E-03	**9.66E-04**	5.33E-03		DBP NST AMY (D) DBP ST PFC (D) [Le-Niculescu et al., 2008b]		3p13 BP [McInnes et al., 1996; Etain et al., 2006; Evans et al., 2007]			5.5
Fut9 fucosyltransferase 9 (alpha (1,3) fucosyltransferas)	4.03E-03	**6.07E-04**	5.34E-03		CP Meth (I) [Ogden et al., 2004] DBP NST PFC (I) DBP ST PFC (D) DBP ST AMY (I) [Le-Niculescu et al., 2008b]		6q16.1 BP [Schulze et al., 2004; Lambert et al., 2005; Goes et al., 2007] MDD [Camp et al., 2005]			5.5
Gnai1 guanine nucleotide binding protein, alpha inhibiting 1	4.98E-03	7.55E-03	1.55E-02		DBP ST PFC (D) [Le-Niculescu et al., 2008b]		7q21.11 BP [Lambert et al., 2005]	(D) BP [Jurata et al., 2004]		5.5
Grm1 glutamate receptor, metabotropic 1	1.28E-03	3.67E-03	5.74E-03	(TG) Abnormal emotion/affect behavior			6q24.3 BP [Rice et al., 1997; Ewald et al., 2002]	(D) BP [Iwamoto et al., 2004]		5.5
Grm3 glutamate receptor, metabotropic 3	3.43E-02	3.18E-03	7.36E-03		PFC VPA (D) [Ogden et al., 2004] DBP ST AMY (I) [Le-Niculescu et al., 2008b]		7q21.12 BP [Lambert et al., 2005; Etain et al., 2006]	(I) BP [Choudary et al., 2005] (D) MDD [Klempan et al., 2007]		5.5
Gsta2 glutathione S-transferase, alpha 2 (Yc2)	1.14E-03	1.93E-03	1.89E-03			VPA (D)	6p12.2 BP [Lambert et al., 2005]	(I) BP [Benes et al., 2006]		5.5
Iqgap2 IQ motif and Sec7 domain 1	8.17E-03	5.83E-03	**6.65E-04**	Abnormal emotion/affect behavior	DBP ST AMY (D) [Le-Niculescu et al., 2008b]		5q13.3			5.5
Itgav integrin beta 1 (fibronectin receptor beta)	4.68E-02	1.09E-02	1.56E-02		DBP NST AMY (I) [Le-Niculescu et al., 2008b]		2q32.1 BP [Cichon et al., 2001]		(I) BP [Middleton et al., 2005]	5.5
Kif1A kinesin family member 1A	**5.31E-04**	6.77E-03	1.00E-02		CP VPA (I) [Ogden et al., 2004]		2q37.3 BP [Lambert et al., 2005]			5.5
Ndufs2 NADH dehydrogenase (ubiqui) Fe-S protein 2, 49kDa (NADH-coenzyme Q reductase)	4.27E-02	1.08E-02	4.67E-02		AMY VPA (I) [Ogden et al., 2004]		1q23 BP [Fallin et al., 2004]		(D) BP [Middleton et al., 2005]	5.5
Nfib nuclear factor I/B		3.47E-03	**1.44E-04**		DBP ST AMY (I) [Le-Niculescu et al., 2008b]		9p24.1 BP [Segurado et al., 2003]		(D) [Le-Niculescu et al., 2008a]	5.5
Nr3c1 nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	4.03E-03	3.71E-02	2.96E-02	(TG) Abnormal emotion/affect behavior			5q31.3 BP [Etain et al., 2006] MDD [van West et al., 2006]	(D) BP,MDD [Torrey et al., 2005] (D) BP [Knable et al., 2004] (I) MDD [Sequeira et al., 2007]		5.5

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Pde10a phosphodiesterase 10A	1.50E-02	9.64E-03	1.50E-03	(TG) Abnormal emotion/affect behavior	DBP NST AMY (D) DBP ST PFC (D) [Le-Niculescu et al., 2008b]		6q27 BP [Cheng et al., 2006]			5.5
Pftk1 PFTAIRE protein kinase 1	**6.54E-04**	1.55E-03	2.26E-03		DBP ST AMY (D) [Le-Niculescu et al., 2008b]		7q21.13 BP [Lambert et al., 2005; Etain et al., 2006]			5.5
Pik3r1 phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)		**6.99E-04**	9.97E-03	Abnormal emotion/ affect behavior	DBP ST PFC (D) [Le-Niculescu et al., 2008b]		5q13.1	(D) MDD [Aston et al., 2005]		5.5
Plxna2 Plexin A2	2.98E-02	**4.71E-04**	3.18E-02				1q32.2 BP [Segurado et al., 2003]		(D) [Le-Niculescu et al., 2008a]	5.5
Ptn pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	2.85E-02	1.90E-02	4.56E-03		CP Meth (I) [Ogden et al., 2004]		7q33 BP [Segurado et al., 2003]	(I) MDD [Tochigi et al., 2008]		5.5
Ptprt Protein tyrosine phosphatase, receptor type, T	6.27E-03	3.45E-03	1.12E-02		DBP ST AMY (I) [Le-Niculescu et al., 2008b]		20q12 BP [Radhakrishna et al., 2001]	(D) MDD [Aston et al., 2005] (I) MDD-suicide [Sequeira et al., 2007]		5.5
Rasgrf2 Ras protein-specific guanine nucleotide-releasing factor 2	1.27E-02	2.35E-02	**9.06E-04**	Abnormal emotion/ affect behavior			5q14.1		(D) [Le-Niculescu et al., 2008a]	5.5
Sod1 superoxide dismutase 1, soluble			1.58E-02	(TG) Abnormal emotion/affect behavior	AMY VPA (I) [Ogden et al., 2004]	DBP NST (D) [Le-Niculescu et al., 2008b]	21q22.11 BP [Detera-Wadleigh et al., 1999; Morissette et al., 1999]	(D) BP [Benes et al., 2006]		5.5
Spast spastin	9.86E-03	5.03E-03	3.76E-02			Meth (D)	2p22.3 BP [Etain et al., 2006]	(I) BP [Nakatani et al., 2006]		5.5
Syne1 synaptic nuclear envelope 1	**1.92E-05**	1.31E-03	3.29E-03				6q25.1 BP [Cheng et al., 2006]		(D) [Le-Niculescu et al., 2008a]	5.5
Tnik TRAF2 and NCK interacting kinase	1.67E-02	**7.43E-04**	7.05E-03				3q26.2 BP [Cichon et al., 2001]		(I) BP [Matigian et al., 2007]	5.5
Trpm3 transient receptor potential cation channel, subfamily M, member 3	6.42E-03	**3.49E-04**	2.61E-03			VPA (D)	9q21.13 BP [Macgregor et al., 2004]			5.5
Zdhhc14 zinc finger, DHHC domain containing 14	4.09E-03	4.59E-03	3.56E-02		DBP ST AMY (I) [Le-Niculescu et al., 2008b]		6q25.3 BP [Cheng et al., 2006]		(D) [Le-Niculescu et al., 2008a]	5.5

Adcy1 adenylate cyclase 1	1.88E-02	1.18E-03	3.58E-02	(TG) Abnormal emotion/affect behavior		7p13	(I) BP [Bezchlibnyk et al., 2001]		5.0
Adcyap1 adenylate cyclase activating polypeptide 1	2.38E-02	1.32E-02		(TG) Abnormal emotion/affect behavior (TG) Abnormal sleep pattern/circadian rhythm	VT VPA (D) [Ogden et al., 2004]	18p11.32 (Assoc) BP [Ishiguro et al., 2001]			5.0
Ank2 ankyrin 2, brain	**4.77E-04**	1.34E-02	8.90E-03	Abnormal emotion/affect behavior	DBP ST PFC (I) [Le-Niculescu et al., 2008b]	4q25 BP [Lambert et al., 2005]			5.0
Chrna7 cholinergic receptor, nicotinic, alpha 7		2.03E-03	1.33E-02	(TG) Abnormal emotion/affect behavior		15q13.3 (Assoc) BP [Hong et al., 2004] MDD [Lai et al., 2001; Levinson et al., 2007]	BP [De Luca et al., 2006]		5.0
Drd2 dopamine receptor 2		1.20E-02	5.78E-03	(TG) Abnormal emotion/affect behavior		11q23.2 (Assoc) BP [Li et al., 1999; Massat et al., 2002] BP [Craddock et al., 1995; Peroutka et al., 1998; Serretti et al., 2000]	(I) BP [Ryan et al., 2006] (D) MDD [Torrey et al., 2005]		5.0
Dst dystonin	2.56E-02	3.29E-02	4.12E-03	(TG) Abnormal emotion/affect behavior		6p12.1		(D) [Le-Niculescu et al., 2008a]	5.0
Elavl2 ELAV (embryonic lethal, abnormal vision, Drosophila)-like 2 (Hu antigen B)	2.26E-02	4.47E-03	4.53E-02	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm	AMY VPA (D) [Ogden et al., 2004]	9p21.3 BP [Lambert et al., 2005; McQueen et al., 2005]			5.0
Epha5 EPH receptor A5	3.28E-02	1.61E-02	1.88E-02	Abnormal emotion/affect behavior		4q13.1 BP [Zubenko et al., 2003; Lambert et al., 2005] BP [Etain et al., 2006]	(D) MDD [Aston et al., 2005]		5.0
Gaa glucosidase, alpha, acid	1.48E-02	2.91E-02	1.01E-02	Abnormal emotion/affect behavior	DBP NST AMY (I) [Le-Niculescu et al., 2008b]	17q25.3 MDD [Curtis et al., 2003; Camp et al., 2005] BP [Dick et al., 2003; Schulze et al., 2004]			5.0
Gna12 guanine nucleotide binding protein, alpha 12	6.67E-03	1.57E-02	3.18E-03	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm		7p22.2 MDD [Camp et al., 2005]		(I) BP [Middleton et al., 2005]	5.0

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Hmox1 heme oxygenase (decycling) 1		2.87E-02	**1.89E-05**	Abnormal emotion/ affect behavior			22q12.3 BP [Detera-Wadleigh et al., 1999; Baron, 2001; Kelsoe et al., 2001; Potash et al., 2003]	(I) BP [Benes et al., 2006]		5.0
Impa2 inositol monophosphatase (IMPase)	3.93E-02	3.18E-02	1.44E-02				18p11.21 (Assoc) BP [Sjoholt et al., 2004; Ohnishi et al., 2007]	(D) BP [Yoon et al., 2001]		5.0
Kcnab1 potassium voltage-gated channel, shaker-related subfamily, beta member 1	1.65E-02	6.37E-03	2.39E-02	Abnormal emotion/ affect behavior	VT VPA (I) [Ogden et al., 2004] DBP NST AMY (D) DBP ST PFC (D) [Le-Niculescu et al., 2008b]		3q25.31 BP [Badenhop et al., 2002; Curtis et al., 2003]			5.0
Kcnb1 potassium voltage gated channel, Shab-related subfamily, member 1	1.61E-03	1.90E-02	2.25E-03	Abnormal emotion/ affect behavior	DBP NST PFC (I) DBP NST AMY (I) DBP ST PFC (D) DBP ST AMY (I) [Le-Niculescu et al., 2008b]		20q13.13 BP [Radhakrishna et al., 2001]			5.0
Large like-glycosyltransferase	4.32E-03	3.50E-03	2.75E-03	Abnormal emotion/ affect behavior			22q12.3 BP [Detera-Wadleigh et al., 1999; Baron, 2001; Kelsoe et al., 2001; Potash et al., 2003]		(D) Anti-depressant treatment [Kalman et al., 2005]	5.0
Lef1 lymphoid enhancer-binding factor 1		**3.84E-04**	2.23E-02	Abnormal emotion/ affect behavior			4q25 BP [Lambert et al., 2005]	(D) BP [Benes, 2007]		5.0
Mdh1 malate dehydrogenase 1, NAD (soluble)		**8.45E-04**		Abnormal emotion/ affect behavior		VPA (D)	2p15 BP [Liu et al., 2003; Maziade et al., 2005]	(D) BP [Jurata et al., 2004] (I) MDD [Beasley et al., 2006]		5.0
Ncam1 Neural cell adhesion molecule 1	2.77E-02	2.61E-02	8.62E-03				11q23.1 (Assoc) BP [Arai et al., 2004; Atz et al., 2007]	(D) BP [Atz et al., 2007] (D) MDD [Tochigi et al., 2008]		5.0
Nfia nuclear factor I/A	3.96E-02	8.70E-03	1.09E-02	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm	DBP NST AMY (I) [Le-Niculescu et al., 2008b]		1p31.3 BP [Cichon et al., 2001]			5.0
Olig2 oligodendrocyte lineage transcription factor 2	1.49E-02	8.96E-03	8.47E-03	Abnormal emotion/ affect behavior			21q22.11 BP [Detera-Wadleigh et al., 1999; Morissette et al., 1999]	(D) BP [Tkachev et al., 2003] (D) MDD [Aston et al., 2005]		5.0

Pard3 Par-3 partitioning defective 3 homolog (C. elegans)	1.58E-02	3.48E-02	1.38E-02	Abnormal emotion/ affect behavior			10p11.22 BP [Rice et al., 1997]	(I) BP [Ryan et al., 2006]	5.0
Pdlim5 PDZ and LIM domain 5	1.39E-03	1.73E-03	1.50E-03				4q22.3 (Assoc) BP [Kato et al., 2005]	(D) MDD [Iga et al., 2006]	5.0
Ppm1b protein phosphatase 1B, magnesium dependent, beta isoform	7.73E-03	4.62E-02	1.31E-02	Abnormal emotion/ affect behavior	CP VPA (I) [Ogden et al., 2004]		2p21 BP [Etain et al., 2006]		5.0
Ptprk protein tyrosine phosphatase, receptor type, K	2.50E-02	1.37E-03	1.54E-03	Abnormal emotion/ affect behavior	DBP ST AMY (D) [Le-Niculescu et al., 2008b]		6q22.33 BP [Park et al., 2004]		5.0
Rxrg retinoid X receptor gamma	1.43E-03	1.83E-02	3.04E-02	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm	DBP ST PFC (D) [Le-Niculescu et al., 2008b]		1q23.3 BP [Fallin et al., 2004]		5.0
Sparc secreted protein, acidic, cysteine-rich (osteonectin)		1.11E-02	4.55E-02	Abnormal emotion/ affect behavior	NAC Meth (I) [Ogden et al., 2004] DBP NST AMY (D) [Le-Niculescu et al., 2008b]		5q33.1 BP [Morissette et al., 1999; Etain et al., 2006]	(I) BP [Iwamoto et al., 2004]	5.0
Stk24 serine/threonine kinase 24 (STE20 homolog, yeast)	7.83E-03	1.70E-02	7.95E-03	Abnormal emotion/ affect behavior		Meth (D)	13q32.2 BP [Detera-Wadleigh et al., 1999; Kelsoe et al., 2001; Liu et al., 2003; Maziade et al., 2005]		5.0
Tpst2 Tyrosylprotein sulfotransferase 3	4.36E-03	6.59E-03	4.67E-02	Abnormal emotion/ affect behavior Abnormal sleep pattern/circadian rhythm			22q12.1 BP [Kelsoe et al., 2001]	(I) BP [Nakatani et al., 2006]	5.0

I, increased; D, decreased in expression. For human blood data: I, increased in high mood (mania); D, decreased in high mood (mania)/increased in low mood (depression). [For human blood data, where references other than Le-Niculescu et al., 2008a are cited, the studies are in lymphoblastoid cell lines without correlation with mood state, I, increased; D, decreased]. In METH, methamphetamine, VPA, valproate; PFC, prefrontal cortex; AMY, amygdala; CP, caudate putamen; NAC, nucleus accumbens; VT, ventral tegmentum; DBP, DBP knock-out mice; NST, nonstressed; ST, stressed; BP, bipolar disorder; MDD, major depressive disorder; TG, transgenic. For additional human genetic evidence, (Assoc)—genetic association evidence; where that is not mentioned, the evidence is only linkage.
Gene symbols underlined are blood biomarker candidate genes.
Bold values signify $P < 0.001$.

TABLE II. Replication of Findings

Gene symbol/name	CFG score	*P*-value <0.05 in an independent GWAS [Sklar et al., 2008]
Klf12/Kruppel-like factor 12	8.0	
Arntl/aryl hydrocarbon receptor nuclear translocator-like	8.0	0.0255
Bdnf/brain-derived neurotrophic factor	8.0	
Aldh1a1/aldehyde dehydrogenase family 1, subfamily A1	8.0	
A2bp1/ataxin-2-binding protein 1	7.5	0.004176
Mbp/myelin basic protein	7.5	0.001165
Ak3l1/adenylate kinase 3 alpha-like 1	7.0	
Gsk3b/glycogen synthase kinase 3 beta	7.0	
Nrcam/neuronal cell adhesion molecule	7.0	0.04352
Pcdh9/Protocadherin 9	7.0	
Cd44/CD44 antigen	6.5	
Kcnk1/potassium channel, subfamily K, member 1	6.5	0.04384
Mbnl2/muscleblind-like 2	6.5	0.01614
Nav2/neuron navigator 2	6.5	0.001869
Nos1/Nitric oxide synthase 1	6.5	0.02122
Oprm1/Opioid receptor, mu 1	6.5	0.02105
Pcdh7/Protocadherin 7	6.5	
Prkce/protein kinase C, epsilon	6.5	0.02484
Ptprm/protein tyrosine phosphatase, receptor type, M	6.5	0.0101
Qki/quaking homolog, KH domain RNA binding	6.5	
Rora/RAR-related orphan receptor alpha	6.5	0.01628
Rorb/RAR-related orphan receptor beta	6.5	0.0008992
Ryr3/ryanodine receptor 3	6.5	0.008071
Cacna1a/calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	6.0	0.002702
Cdh13/cadherin 13	6.0	0.00801
Dapk1/death-associated protein kinase 1	6.0	0.001561
Disc1/disrupted in schizophrenia 1	6.0	0.008606
Gria1/glutamate receptor, ionotropic, AMPA1 (alpha 1)	6.0	0.006843
Grik1/glutamate receptor, ionotropic, kainate 1	6.0	0.04468
Htr2a/Seratonin receptor 2A	6.0	0.005598
Kcnd2/Potassium voltage-gated channel, Shal-related family, member 2 (Kcnd2), mRNA	6.0	0.03855
Lmo7/LIM domain only 7	6.0	0.006589
Mycbp2/MYC binding protein 2	6.0	
Myt1l/myelin transcription factor 1-like	6.0	0.01648
Nrg1/neuregulin 1	6.0	0.0008814
Scamp1/secretory carrier membrane protein 1	6.0	0.02253
Slc8a1/solute carrier family 8 (sodium/calcium exchanger), member 1	6.0	0.007436
Syn3/synapsin IIIa	6.0	0.02029
Tiam1/T-cell lymphoma invasion and metastasis 1	6.0	0.002492
Tshz2/teashirt family zinc finger 2	6.0	0.01729
Zhx2/Zinc fingers and homeoboxes 2	6.0	

Examination of our top candidate genes from Figure 2 in an independent bipolar GWAS [Sklar et al., 2008]. Thirty of our top 41 genes had a $P < 0.05$ in the Sklar et al. study. As there were 3,654 genes at $P < 0.05$ in that study, and the number of genes in the human genome is estimated at 20,500 [Clamp et al., 2007], the enrichment factor provided by our approach is (30/41)/(3654/20500) = 4.1-fold.

TABLE III. Top Candidate Genes and Biological Roles

Entrez genes	Gene /Name
	NEUROTRANSMITTERS/ SIGNALING
	Glutamate signaling
2890	**Gria1** glutamate receptor, ionotropic, AMPA1 (alpha 1)
2897	**Grik1** glutamate receptor, ionotropic, kainate 1
2911	**Grm1** glutamate receptor, metabotropic 1
2913	**Grm3** glutamate receptor, metabotropic 3
	Serotonin signaling
3356	**Htr2a** Seratonin receptor 2A
	Cholinergic signaling
1139	**Chrna7** cholinergic receptor, nicotinic, alpha 7
	Dopamine signaling
1813	**Drd2** dopamine receptor 2
	Opioid signaling
4988	**Oprm1** Opioid receptor, mu 1
	Synaptic function
4842	**Nos1** Nitric oxide synthase 1, neuronal (Nos1), mRNA
8224	**Syn3** synapsin IIIa
	OTHER PHYSIOLOGICAL FUNCTIONS AND CELLULAR MECHANISM
	Growth factor signaling
627	**Bdnf** brain-derived neurotrophic factor
2257	**Fgf12** fibroblast growth factor 12
3084	**Nrg1** neuregulin 1
5764	**Ptn** pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)
	Circadian clock genes
406	**Arntl** aryl hydrocarbon receptor nuclear translocator-like
6095	**Rora** RAR-related orphan receptor alpha
6096	**Rorb** RAR-related orphan receptor beta
6258	**Rxrg** retinoid X receptor gamma
	Mitochondrial function
32	**Acacb** acetyl-Coenzyme A carboxylase beta
205	**Ak3l1** adenylate kinase 3 alpha-like 1
4720	**Ndufs2** NADH dehydrogenase (ubiqui) Fe-S protein 2, 49kDa
	Cell survival /Cell death
54715	**A2bp1** ataxin-2-binding protein 1
6310	**Atxn1** Ataxin 1
773	**Cacna1a** calcium channel, voltage-dependent,P/Q type, alpha 1A subunit
10659	**Cugbp2** CUG triplet repeat, RNA binding protein 2
1612	**Dapk1** death-associated protein kinase 1
2932	**Gsk3b** glycogen synthase kinase 3 beta
5218	**Pftk1** PFTAIRE protein kinase 1
8428	**Stk24** serine/threonine kinase 24 (STE20 homolog, yeast)
	Neuronal Development
27185	**Disc1** disrupted in schizophrenia
1993	**Elavl2** ELAV (embryonic lethal, abnormal vision, Drosophila)-like 2
89797	**Nav2** neuron navigator 2
	Glia/Myelin
3084	**Nrg1** neuregulin 1
4155	**Mbp** myelin basic protein
23040	**Myt1l** myelin transcription factor 1-like
10215	**Olig2** oligodendrocyte lineage transcription factor 2
9444	**Qki** quaking homolog, KH domain RNA binding
	Cellular adhesion
287	**Ank2** ankyrin 2, brain
351	**App** amyloid beta (A4) precursor protein
960	**Cd44** CD44 antigen
1012	**Cdh13** cadherin 13
64084	**Clstn2** calsyntenin 2
2044	**Epha5** EPH receptor A5
3685	**Itgav** integrin, alpha V
4684	**Ncam1** Neural cell adhesion molecule 1
4897	**Nrcam** neuronal cell adhesion molecule
5099	**Pcdh7** protocadherin 7
5101	**Pcdh9** Protocadherin 9
5362	**Plxna2** Plexin A2
5796	**Ptprk** protein tyrosine phosphatase, receptor type, K
5797	**Ptprm** protein tyrosine phosphatase, receptor type, M
11122	**Ptprt** protein tyrosine phosphatase, receptor type, T
6678	**Sparc** secreted protein, acidic, cysteine-rich (osteonectin)
23345	**Syne1** synaptic nuclear envelope 1

Entrez genes	Gene /Name
	G-protein coupled receptor related genes
9620	**Celsr1** Cadherin, EGF LAG seven-pass G-type receptor 1
2768	**Gna12** guanine nucleotide binding protein, alpha 12
2770	**Gnai1** guanine nucleotide binding protein, alpha inhibiting 1
10788	**Iqgap2** IQ motif and Sec7 domain 1
56288	**Pard3** Par-3 partitioning defective 3 homolog
5924	**Rasgrf2** Ras protein-specific guanine nucleotide-releasing factor 2
7074	**Tiam1** T-cell lymphoma invasion and metastasis 1
	Signal transduction
107	**Adcy1** adenylate cyclase 1
116	**Adcyap1** adenylate cyclase activating polypeptide 1
3613	**Impa2** inositol monophosphatase (IMPase)
10846	**Pde10A** phosphodiesterase 10A
5581	**Prkce** protein kinase C, epsilon
5295	**Pik3r1** phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1
11122	**Ptprt** protein tyrosine phosphatase, receptor type, T
23043	**Tnik** TRAF2 and NCK interacting kinase
	Transcriptional regulation
1387	**Crebbp** CREB binding protein
27086	**Foxp1** Forkhead box P1 (Foxp1), mRNA
51176	**Lef1** lymphoid enhancer-binding factor 1
4008	**Lmo7** LIM domain only 7
11278	**Klf12** Kruppel-like factor 12
10150	**Mbnl2** muscleblind-like 2 (Drosophila)
4774	**Nfia** nuclear factor I/A
4781	**Nfib** nuclear factor I/B
2908	**Nr3c1** nuclear receptor subfamily 3, group C, member 1
10215	**Olig2** oligodendrocyte lineage transcription factor 2
6095	**Rora** RAR-related orphan receptor alpha
6258	**Rxrg** retinoid X receptor gamma
128553	**Tshz2** teashirt zinc finger homeobox 2
22882	**Zhx2** Zinc fingers and homeoboxes 3
	Calcium regulation
773	**Cacna1a** calcium channel, voltage-dependent, P/Q type, alpha 1A subunit
783	**Cacnb2** calcium channel, voltage-dependent, beta 2 subunit
815	**Camk2a** calcium/calmodulin-dependent protein kinase II alpha
817	**Camk2d** calcium/calmodulin-dependent protein kinase II, delta
9201	**Dcamkl1/Dclk1** Doublecortin-like and CAM kinase-like 1
6263	**Ryr3** ryanodine receptor 3
6546	**Slc8a1** solute carrier family 8 (sodium/calcium exchanger), member 1
80036	**Trpm3** transient receptor potential cation channel, subfamily M, member 3
	Potassium regulation
57628	**Dpp10** dipeptidylpeptidase 10
7881	**Kcnab1** potassium voltage-gated channel, shaker-related subfamily, beta member 1
3745	**Kcnb1** potassium voltage gated channel,Shab-related subfamily,member 1
3751	**Kcnd2** Potassium voltage-gated channel, Shal-related family, member 2
3775	**Kcnk1** potassium channel, subfamily K, member 1
	Cell organization/biogenesis
1729	**Diaph1** diaphanous homolog 1 (Drosophila)
27185	**Disc1** disrupted in schizophrenia
667	**Dst** dystonin
547	**Kif1a** kinesin family member 1A
10611	**Pdlim5** PDZ and LIM domain 5
6683	**Spast** spastin
	Oxidative stress
3162	**Hmox1** heme oxygenase (decycling) 1
9215	**Large** like-glycosyltransferase
6647	**Sod1** superoxide dismutase 1, soluble
	Catalytic enzyme
216	**Aldh1a1**aldehyde dehydrogenase 1 family, member A1
10690	**Fut9** fucosyltransferase 9 (alpha (1,3) fucosyltransferas)
2548	**Gaa** glucosidase, alpha, acid
2939	**Gsta2** glutathione S-transferase, alpha 2 (Yc2)
4190	**Mdh1** malate dehydrogenase 1, NAD (soluble)
5495	**Ppm1b** protein phosphatase 1B, magnesium dependent, beta isoform
8459	**Tpst2** Tyrosylprotein sulfotransferase 2

Top candidate genes (CFG score 5 and above—Table I) were classified into biological groups of interest previously reported to have relevance to the pathophysiology of bipolar and related disorders. Blue dots indicate there is also data showing alterations in expression of that gene in brains from subjects with bipolar and related disorders. Red dots indicate there is also data showing alterations in expression of that gene in bloods from subjects with bipolar and related disorders.

in bipolar patients [Wirz-Justice et al., 2004]. Clock genes expression levels (Dbp, Per1, and Per2) have been reported to be changed by sleep deprivation in rodents [Wisor et al., 2002]. Seasonal affective disorder (SAD), a variant of bipolar disorder [Magnusson and Partonen, 2005], is tied to the amount of daylight, which is a primary regulator of circadian rhythms and clock gene expression; associations between polymorphisms in the clock genes Arntl, Per2, and Npas2 and SAD have previously been reported [Johansson et al., 2003; Partonen et al., 2007]. We had previously described the identification of clock gene D-box binding protein

A

Top Networks	Score
Psychological Disorders, Behavior, Neurological Disease	42
Cancer, Cellular Growth and Proliferation, Cellular Development	28
Cancer, Cell Morphology, Cellular Growth and Proliferation	11
Cell-To-Cell Signaling and Interaction, Cellular Assembly and Organization, Nervous System Development and Function	2

Top Bio Functions Diseases and Disorders	p-value	Number of Molecules
Neurological Disease	5.86E-10 - 9.96E-03	20
Psychological Disorders	5.86E-10 - 6.65E-03	14
Organismal Injury and Abnormalities	2.53E-05 - 3.33E-03	5
Cancer	1.17E-04 - 9.96E-03	16
Dermatological Diseases and Conditions	2.99E-04 - 3.96E-03	4
Molecular and Cellular Functions	**p-value**	**Number of Molecules**
Cell-To-Cell Signaling and Interaction	5.90e-08 - 9.96e-03	19
Cellular Assembly and Organization	7.72E-06 - 9.96E-03	15
Cellular Movement	1.86E-05 - 9.96E-03	8
Cell Death	7.76E-05 - 9.96E-03	19
Molecular Transport	1.28E-04 - 8.38E-03	13
Physiological System Development and Function	**p-value**	**Number of Molecules**
Nervous System Development and Function	5.90E-08 - 9.96E-03	23
Organismal Functions	1.43E-06 - 4.73E-03	6
Behavior	2.89E-06 - 9.96E-03	9
Immune Response	1.07E-04 - 9.96E-03	5
Hair and Skin Development and Function	1.61E-04 - 6.65E-03	3

Top Canonical Pathways	p-value	Ratio
Synaptic Long Term Depression	1.07E-03	4/162 (0.025)
Calcium Signaling	2.32E-03	4/203 (0.02)
Amyloid Processing	1.24E-02	2/52 (0.038)
Glutamate Receptor Signaling	1.44E-02	2/67 (0.03)
Cell Cycle: G1/S Checkpoint Regulation	1.54E-02	2/60 (0.033)

B

Top Networks	Score
Psychological Disorders, Neurological Disease, Cellular Development	43
Behavior, Nervous System Development and Function, Neurological Disease	38
Behavior, Organismal Functions, Neurological Disease	30
Neurological Disease, Nervous System Development and Function, Cell-To-Cell Signaling and Interaction	26
Gene Expression, Cancer, Cell Cycle	17

Top Bio Functions Diseases and Disorders	p-value	Number of Molecules
Neurological Disease	2.37E-16 - 5.13E-03	47
Psychological Disorders	2.37E-16 - 4.12E-03	28
Cancer	1.30E-06 - 5.03E-03	41
Organismal Injury and Abnormalities	1.01E-04 - 5.03E-03	10
Nutritional Disease	1.33E-04 - 1.96E-03	10
Molecular and Cellular Functions	**p-value**	**Number of Molecules**
Cell-To-Cell Signaling and Interaction	5.12E-09 - 4.84E-03	32
Cellular Movement	4.84E-08 - 4.99E-03	22
DNA Replication, Recombination, and Repair	5.67E-08 - 1.64E-04	11
Cell Signaling	5.74E-07 - 3.46E-03	25
Molecular Transport	5.74E-07 - 4.84E-03	33
Physiological System Development and Function	**p-value**	**Number of Molecules**
Behavior	9.14E-14 - 2.20E-03	26
Organismal Functions	4.34E-11 - 2.68E-03	13
Nervous System Development and Function	4.36E-10 - 5.03E-03	52
Tissue Morphology	2.72E-05 - 4.21E-03	26
Skeletal and Muscular System Development and Function	5.78E-05 - 5.03E-03	16

Top Canonical Pathways	p-value	Ratio
G-Protein Coupled Receptor Signaling	1.04E-07	12/199 (0.06)
Synaptic Long Term Potentiation	3.94E-06	8/111 (0.072)
Synaptic Long Term Depression	3.22E-05	8/162 (0.049)
cAMP-mediated Signaling	6.76E-05	8/159 (0.05)
Calcium Signaling	1.42E-04	8/203 (0.039)

FIG. 3. Ingenuity Pathway Analysis of top candidate genes. A: Analysis of top 41 candidate genes (CFG score of 6 and above). B: Analysis of top 113 candidate genes (CFG score of 5 and above).

(Dbp) as a potential candidate gene for bipolar disorder [Niculescu et al., 2000b], using a CFG approach. Dbp was changed in expression by acute methamphetamine treatment in rat pre-frontal cortex (PFC) [Niculescu et al., 2000b], and mapped near a human genetic linkage locus for bipolar disorder [Morissette et al., 1999] and for depression [Zubenko et al., 2002] on chromosome 19q13. Subsequently, Dbp was also reported changed in expression by acute and chronic amphetamine treatments in mice [Sokolov et al., 2003]. Moreover, Dbp knock-out mice have abnormal circadian and homeostatic aspects of sleep regulation [Franken et al., 2000]. More recently, we have conducted extensive behavioral and gene expression studies in Dbp KO mice. These mice display a bipolar-like phenotype [Le-Niculescu et al., 2008b], which is modulated by stress. Decreases in Dbp expression have also been recently reported in fibroblasts from bipolar subjects [Yang et al., 2008]. In parallel, work carried out by us using an expanded CFG approach in a mouse pharmacogenomic model for bipolar disorder identified Arntl and a series of other clock genes (Cry2, Csnk1d, and Ccr4/nocturnin), as potential bipolar candidate genes [Ogden et al., 2004]. Following that, three independent reports have shown some suggestive association for Arntl in human bipolar samples [Mansour et al., 2006; Nievergelt et al., 2006; Shi et al., 2008]. Arntl is upstream of Dbp in the circadian clock intracellular molecular machinery, driving the transcription of Dbp [Ripperger and Schibler, 2006; van der Veen et al., 2006]. An increase in Arntl gene expression was reported in postmortem brains from bipolar subjects [Nakatani et al., 2006]. Overall, Arntl and related circadian clock genes are compelling candidates for involvement in bipolar disorders, especially the core clinical phenomenology of cycling and switching from depression to mania [Bunney and Bunney, 2000; Wager-Smith and Kay, 2000; Niculescu et al., 2000b; Niculescu and Kelsoe, 2001; Kelsoe and Niculescu, 2002; Lenox et al., 2002; Hasler et al., 2006; Wirz-Justice, 2006; McClung, 2007; Le-Niculescu et al., 2008b].

Bdnf is a growth factor involved in neurotrophicity and synaptic transmission. Other growth factor top candidate genes identified by our analysis include Nrg1, Fgf12, and Ptn (Fig. 2, and Tables I and III). Bdnf has been previously implicated in a variety of neuropsychiatric disorders, by both animal model and human studies: depression [Pezawas et al., 2008; Sen et al., 2008], bipolar disorder [Ogden et al., 2004], anxiety, alcoholism [Rodd et al., 2007], and schizophrenia [Le-Niculescu et al., 2007a; Chao et al., 2008]. Notably, there are several candidate gene association studies to date implicating Bdnf in bipolar disorder [Fan and Sklar, 2008; Liu et al., in press].

Aldh1a1 has been previously implicated in brain development [Denisenko-Nehrbass et al., 2000], schizophrenia [Galter et al., 2003], and alcoholism [Moore et al., 2007]. An intriguing finding is that of Oprm1 (opioid receptor mu 1) as a top candidate gene for bipolar. Oprm1 has been implicated in pain regulation [Oertel and Lotsch, 2008], substance abuse disorders [Luo et al., 2008], attachment behaviors [Barr et al., 2008], and suicide [Hishimoto et al., 2008]. Earlier work by us using animal models and a CFG approach had identified an overlap between candidate genes involved in mood regulation and pain regulation, such as Penk (preproenkephalin) [Ogden et al., 2004; Le-Niculescu et al., 2008b].

A surprising finding is that of amyloid beta precursor protein (App), an Alzheimer disease (AD) candidate gene, among the top candidate gene for bipolar disorder (Table I), as well as the overall amyloid pathway being among the top canonical pathways identified (Fig. 3A). Another key gene involved in AD, Gsk3b, is also present on our list of top candidate genes. There is an interesting epidemiological literature showing increased AD in bipolar patients, and the prophylactic effect of the mood stabilizer lithium on the incidence of AD in bipolar patients [Nunes et al., 2007]. Notably, Gsk3b is a target of lithium treatment [Beaulieu

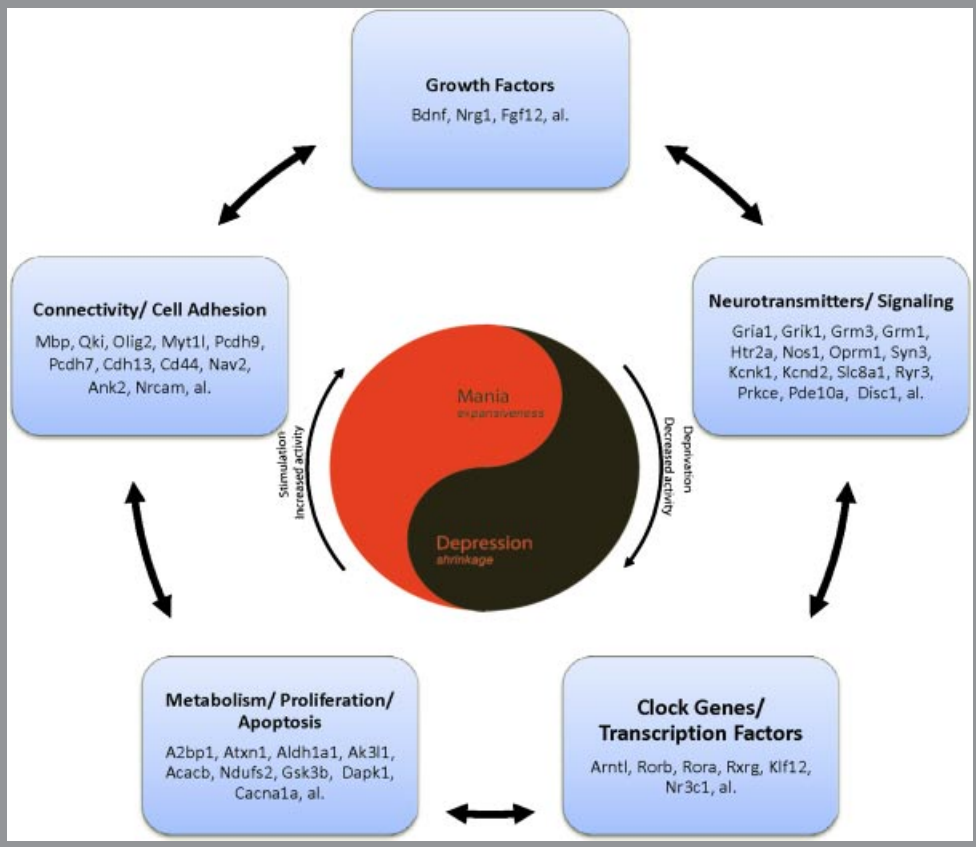

FIG. 4. A comprehensive model for bipolar disorder pathophysiology.

et al., 2008a], as well as of serotonergic anti-depressants [Beaulieu et al., 2008b]. App has recently been shown to have a neurotrophic role [Oh et al., 2008], similar in some ways to growth factors such as Bdnf. App has also been reported to be increased in expression in bipolar postmortem brains compared to normal controls [Jurata et al., 2004]. It remains unclear if App's role in AD is pathogenic or is in fact a defense/compensatory mechanisms to try to maintain neuronal survival [Rohn et al., 2008]. If the later scenario is true, new compounds being developed for AD that target App might not stop the illness. Regardless if that turns out to be the case or not, drugs that regulate App levels may have an impact on mood (i.e., downregulation of App may be depressogenic), a particular concern given the prevalence of depression in the elderly in general [Alexopoulos et al., 2005], and in AD patients in particular [Sun et al., 2008b].

Limitations and Confounds

No correction of best *P*-values for number of SNPs tested/gene size effect was performed. While this is arguably a valid statistical issue for genetic studies by themselves, some of the multiple SNPs tested per gene could be in linkage disequilibrium, and the Bonferroni correction might be too conservative [Rice et al., 2008]. Moreover, it could introduce a bias against large-size genes, which generally have more SNPs tested than smaller genes. Of course, the converse is true if we do not correct for number of SNPs tested and one would expect some noise due to gene size effects. However, we did not observe a significant correlation between gene size and our top candidate genes (Supplementary Information—Fig. 1S and Table IIIS). That may be due to the fact that we are using this evidence for integration across platforms and modalities, along with a series of other lines of evidence that have their own attendant noise, as part of a Bayesian-like approach to pull signal from noise and prioritize findings. The convergence of lines of evidence arguably factors out the noise of the different individual approaches, and makes our network-like CFG approach relatively resilient to error even when one or another of the nodes (lines of evidence) is weak (Fig. 1).

Our approach relies on a list of genes from the GWAS datasets generated by SNPPER identifying SNPs in genes. We may thus be missing genes where the assignment is not made by the software, and discarding SNPs that fall into regulatory regions, such as promoter or enhancer regions. Moreover, genes where the illnesses associated SNPs do not lead to a change in expression levels are not included in our CFG-GWA cross-validation. Similarly, genes that have changes in expression levels but no intragenic SNP in the GWAS datasets are not included. Interestingly, some of these later

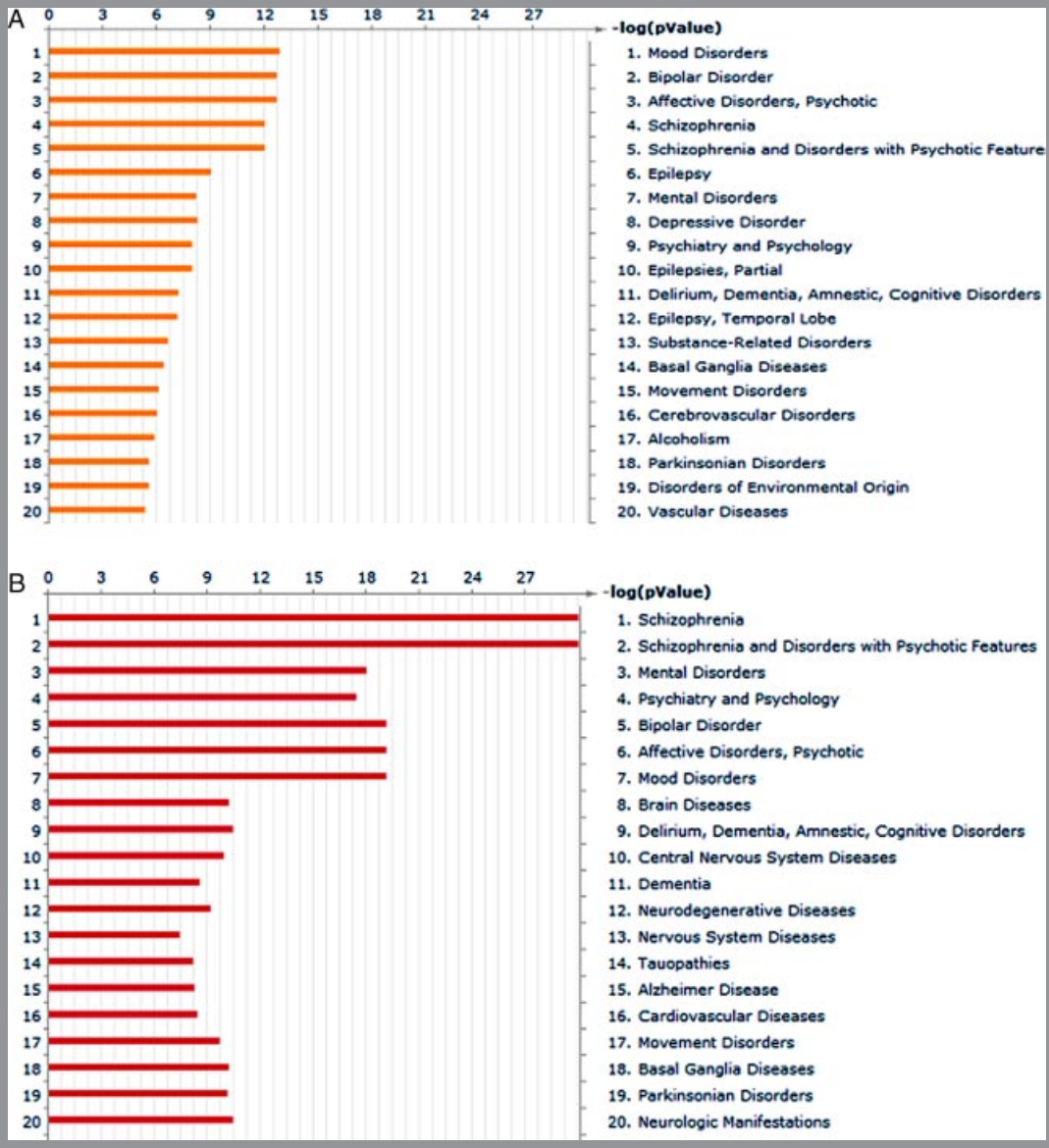

FIG. 5. Genetic co-morbidity. MetaCore analysis (GeneGo, Encinitas, CA) of top candidate genes involvement in diseases. A: Analysis of top 41 candidate genes (CFG score of 6 and above). B: Analysis of top 113 candidate genes (CFG score of 5 and above). *P*-value indicates over-representation of these genes in different disease categories, based on bioinformatic analyses of published literature—derived connections.

genes may be changed in expression as a consequence of distal regulatory SNPs or other genes in a network, an exciting area for future system biology studies awaiting better bioinformatic tools and data analysis now on the horizon [Stumpf et al., 2008].

Other animal models data could potentially be used for CFG cross-validation, in addition to the data from the pharmacogenomic (methamphetamine/valproate) [Ogden et al., 2004] and the genetic (DBP knock-out mouse) [Le-Niculescu et al., 2008b] models that we generated and used. However, these are some of the best animal models with corresponding comprehensive brain and blood gene expression datasets published to date. Moreover, we relied, as an additional line of evidence, on an extensive public mouse QTL/transgenic database.

As new human blood, postmortem brain, and human genetic studies are published, new evidence will be available for some of the genes we have identified. However, any new evidence will not remove genes from our results, but rather move them up higher in the prioritization list/pyramid (Fig. 2).

Different ways of weighing the lines of evidence included in the CFG analysis rather than the equal weight approach we have used may become available in the future, based on more empirical and quantitative methods. Other ways of weighing the scores of line of evidence may give slightly different results in terms of prioritization, if not in terms of the list of top genes per se.

Pathways identified by Ingenuity and GeneGo may be based on some of the same body of knowledge and published literature used

in our direct CFG scoring. However, it is reassuring to see that different independent systematization and curation efforts lead to a consistent picture of genes involved in behavior, neurological disease, psychological disorders, and nervous system development coming up at the top of the over-represented pathways from our top candidate genes for bipolar disorder identified by our genetic–genomic combined approach.

Conclusions and Future Directions

In spite of these notable limitations, our analysis is arguably the most comprehensive integration of genetics and functional genomics to date in the field of bipolar disorder, yielding a series of candidate genes, blood biomarkers, pathways and mechanisms, that are prime targets for follow-up hypothesis driven studies. Such studies may include individual candidate gene association studies with more SNPs tested per gene, deep re-sequencing, and/or biological validation such as cell culture [Pletnikov et al., 2007] and transgenic animal work [Hikida et al., 2007; Le-Niculescu et al., 2008b].

First, the model that emerges from this work (Fig. 4) is consistent with mood being a function of trophicity [Niculescu, 2005], through energy metabolism [Quiroz et al., 2008] as well as cellular growth and proliferation [Le-Niculescu et al., 2008a]. Speculatively, from an evolutionary standpoint, it may make sense for the organism to react to a favorable environment by activity and expansion, and to an unfavorable environment by inactivity and retraction-the "mood as a muscle" model [Niculescu, 2005]. In this view, high resources translate into high mood and high libido, as the environment is favorable and can support growth, expansion and progeny. The threshold to pain may be elevated [Ogden et al., 2004], so activity can occur even in the face of actual injuries. Conversely, low resources translate into a low mood and low libido, as the environment is unfavorable and cannot support more growth, expansion and progeny. The threshold to pain is reduced, so one can react and retract in the face of potential injuries [Niculescu and Akiskal, 2001a,b]. In clinical illness (bipolar disorder, depression), this congruence between mood and environment is arguably lost and/or the mood reaction to environmental cues is disproportionate.

Second, despite the fact that our analysis uses only data from human and animal studies focused on bipolar and related disorders, it is likely that some of the genes and pathways identified in this report are not implicated only in bipolar disorder and depression, but also in other psychiatric disorders, such as schizophrenia [Le-Niculescu et al., 2007a]. Indeed, we provide some evidence for that (Fig. 5). While some of this overlap might be due to limitations in precision of diagnostic ascertainments in human studies and limitations in specificity to a disorder in animal studies, an alternative and more compelling explanation is that the genetic and neurobiological structure of psychiatric disorders is modular in a Lego-like fashion [Niculescu et al., 2006], with building blocks in different permutations leading to different clinical disorders.

Third, our work provides additional integrated evidence focusing attention on and prioritizing a number of genes as candidate blood biomarkers for bipolar disorder, with an inherited genetic basis (Table I). While prior evidence existed as to alterations in gene expression levels of those genes in whole-blood samples or lymphoblastoid cell lines (LCLs) from mood disorders patients, it was unclear prior to our analysis whether those alterations were truly related to the disorder or were instead related to medication effects and environmental factors, or indeed were frankly artifactual.

Last but not least, our work provides a proof of principle for how such a combined approach, integrating functional and genotypic data, can be used for other complex disorders-psychiatric and non-psychiatric. What we are beginning to see across GWAS of complex disorders are not necessarily the same genes showing the strongest signal, but rather consistency at the level of gene families or biological pathways. The distance from genotype to phenotype may be a bridge too far for genetic-only approaches, given the intervening complex layers of epigenetics, gene expression regulation and endophenotypes [Tan et al., 2008]. Using GWAS data in conjunction with gene expression data as part of CFG or integrative genomics [Degnan et al., 2008] approaches, followed by pathway—level analysis of the prioritized candidate genes, can serve as the necessary Rosetta Stone for unraveling the genetic code of complex disorders such as bipolar disorder. A whole body of work will then need to follow in terms of personalizing diagnosis and treatment based on particular combinations of genes and gene expression patterns, leading to major re-evaluations of current clinical nosology.

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Figure 1S. Top candidate genes - gene size. Top candidate genes (n=113) from Table 1 are depicted. There is no significant correlation between gene size and the identification/prioritization of candidate genes using our CFG approach.

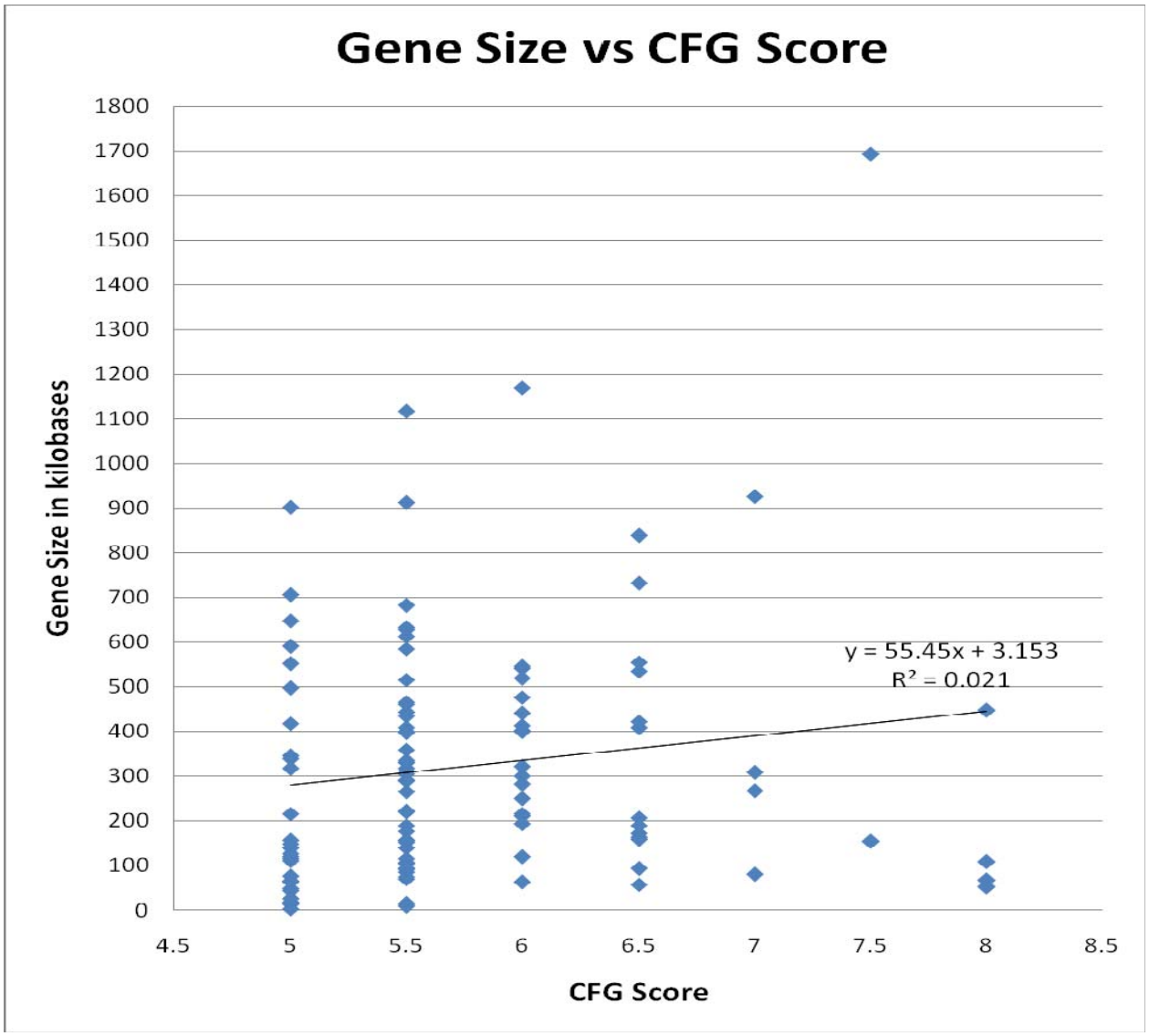

Table 1S. Overlap of genetic and functional genomic evidence.

GWAS	Number of SNPs at p<0.05	Number of genes with at least one SNP at p<0.05	Number of these genes for which there is published gene expression evidence in bipolar and related disorders (animal models and/or human data)
NIMH	35,389	6,541	936
German	29,296	6,202	865
WTCC	28,345	4,951	723
			Unique genes combining the 3 above studies: 1529
STEP-BD	20,991	3,654	572
			Extra genes identified by STEP-BD in addition to those identified by the 3 GWAS used in the primary analysis: 96

Table 2S. Top candidate genes and existing drugs. Genes in Table 1 that are targets of existing drugs (Ingenuity analysis).

Gene Symbol/ Name	Type	Drugs
Aldh1a1 aldehyde dehydrogenase 1 family, member A1	enzyme	disulfiram, chlorpropamide
App amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease)	other	AAB-001
Gria1 glutamate receptor, ionotropic, AMPA 1	ion channel	talampanel, Org 24448, LY451395, LY 293558
Grm1 glutamate receptor, metabotropic 1	G-protein coupled receptor	fasoracetam
Grm3 glutamate receptor, metabotropic 3	G-protein coupled receptor	fasoracetam
Gsk3b glycogen synthase kinase 3 beta	kinase	enzastaurin
Hmox1 heme oxygenase (decycling) 1	enzyme	tin mesoporphyrin
Htr2a 5-hydroxytryptamine (serotonin) receptor 2A	G-protein coupled receptor	paliperidone, risperidone, buspirone, caffeine/ergotamine, eplivanserin, blonanserin, flibanserin, asenapine, ocaperidone, abaperidone, psilocybine, APD125, trazodone, cyproheptadine, fluoxetine/olanzapine, epinastine, fenfluramine, quetiapine, olanzapine, nefazodone, mirtazapine, ziprasidone, aripiprazole, dihydroergotamine, apomorphine, ergotamine, azatadine
Itgav integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	other	abciximab, CNTO 95, EMD121974
Nos1 nitric oxide synthase 1 (neuronal)	enzyme	GW 273629, omega-N-methylarginine
Nr3c1 nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	ligand-dependent nuclear receptor	rimexolone, medrysone, clocortolone pivalate, diflorasone diacetate, fluorometholone, dexamethasone phosphate, cortisone acetate, halcinonide, flurandrenolide, desoximetasone, desonide, prednisolone, clobetasol propionate, fluocinolone acetonide, prednisone, hydrocortisone, triamcinolone, dexamethasone 21-acetate, 11beta hydrocortisone acetate, betamethasone,
Oprm1 opioid receptor, mu 1	G-protein coupled receptor	dihydrocodeine, morphine/dextromethorphan, alvimopan, hydrocodone, propoxyphene, fentanyl, sufentanil, alfentanil, methadone, codeine, tramadol,
Rxrg retinoid X receptor, gamma	ligand-dependent nuclear receptor	bexarotene, retinoic acid, 9-cis-retinoic acid

Table 3S. Gene size and number of SNPs tested for top candidate genes from Table 1.

Gene Symbol/ Name	Gene Size (kilobases)	GWAS WTC Best p-value Number of SNPs tested	GWAS NIMH Best p-value Number of SNPs tested	GWAS German Best p-value Number of SNPs tested	CFG Score
Klf12 Kruppel-like factor 12	448 kb	2.76E-03 112	**6.77E-04** 139	**1.68E-04** 139	8.0
Arntl aryl hydrocarbon receptor nuclear translocator-like	109 kb	**7.71E-04** 24	3.84E-02 27	3.72E-02 27	8.0
Bdnf brain-derived neurotrophic factor	67 kb	1.05E-02 9	3.76E-02 13	1.91E-03 13	8.0
Aldh1a1 aldehyde dehydrogenase family 1, subfamily A1	52 kb	1.29E-02 17	**1.58E-04** 22	3.34E-02 22	8.0
A2bp1 ataxin-2-binding protein 1	1,693 kb	**3.42E-05** 747	**4.23E-04** 583	**1.59E-04** 583	7.5
Mbp myelin basic protein	154 kb		8.30E-03 31	**8.19E-04** 31	7.5
Ak3l1 adenylate kinase 3 alpha-like 1	80 kb	**9.80E-05** 13	1.79E-02 18	2.57E-02 18	7.0
Gsk3b glycogen synthase kinase 3 beta	267 kb	9.82E-03 20	1.62E-02 20	6.72E-03 20	7.0
Nrcam neuronal cell adhesion molecule	309 kb	1.63E-03 96	**5.94E-04** 107	**8.60E-04** 107	7.0
Pcdh9 Protocadherin 9	927 kb	9.77E-03 158	1.19E-03 189	**4.80E-04** 183	7.0
Cd44 CD44 antigen	94 kb	3.48E-02 29	3.94E-03 56	1.06E-02 56	6.5
Kcnk1 potassium channel, subfamily K, member 1	58 kb	1.89E-02 26	7.60E-03 31	**3.47E-04** 31	6.5
Mbnl2 muscleblind-like 2 (Drosophila)	173 kb	2.94E-03 48	4.64E-02 51	**4.02E-04** 51	6.5
Nav2 neuron navigator 2	408 kb	4.16E-03 141	**5.77E-04** 210	2.04E-03 210	6.5
Nos1 Nitric oxide synthase 1, neuronal (Nos1), mRNA	163 kb	1.72E-02 29	3.73E-02 50	4.56E-02 50	6.5
Oprm1 Opioid receptor, mu 1	208 kb	**7.82E-04** 60	7.31E-03 73	1.90E-03 73	6.5
Pcdh7 Protocadherin 7	423 kb	**4.08E-04** 51	1.71E-02 79	**8.05E-04** 79	6.5
Prkce protein kinase C, epsilon	536 kb	4.59E-03 157	**2.37E-04** 248	1.20E-02 248	6.5
Ptprm protein tyrosine phosphatase, receptor type, M	839 kb	1.74E-02 168	1.10E-02 128	**2.41E-04** 128	6.5
Qki quaking homolog, KH domain RNA binding (mouse)	159 kb	3.06E-02 22		**7.74E-05** 29	6.5
Rora RAR-related orphan receptor alpha	732 kb	**1.90E-04** 216	**3.55E-04** 172	6.36E-03 172	6.5
Rorb RAR-related orphan receptor beta	190 kb	1.29E-02 43	**5.88E-04** 48	1.95E-02 48	6.5
Ryr3 ryanodine receptor 3	555 kb	1.21E-03 187	**2.89E-04** 161	6.09E-03 161	6.5
Cacna1a calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	300 kb	2.99E-02 54	2.12E-02 49	**7.04E-04** 49	6.0
Cdh13 cadherin 13	1,170 kb	5.89E-03 575	2.50E-03 465	**9.08E-04** 465	6.0
Dapk1 death-associated protein kinase 1	211 kb	4.02E-02 94	**5.97E-05** 98	4.04E-02 98	6.0
Disc1 disrupted in schizophrenia 1	414 kb	1.31E-02 93	2.99E-03 110	6.08E-03 110	6.0
Gria1 glutamate receptor, ionotropic, AMPA1 (alpha 1)	321 kb	1.47E-02 104	6.55E-03 104	9.19E-03 104	6.0
Grik1 glutamate receptor, ionotropic, kainate 1	403 kb	**5.39E-04** 112	2.79E-03 118	3.36E-02 118	6.0
Htr2a Seratonin receptor 2A	63 kb	1.86E-02 36	4.52E-02 42	1.65E-03 42	6.0
Kcnd2 Potassium voltage-gated channel, Shal-related family, member 2 (Kcnd2), mRNA	477 kb	5.78E-03 56	4.08E-03 62	**5.24E-05** 62	6.0
Lmo7 LIM domain only 7	250 kb	**6.62E-05** 58	1.11E-02 51	8.17E-03 51	6.0
Mycbp2 MYC binding protein 2	282 kb	**5.66E-04** 23	2.92E-02 22	2.39E-02 22	6.0
Myt1l myelin transcription factor 1-like	542 kb	**2.25E-04** 88	1.31E-02 95	1.25E-02 95	6.0
Nrg1 neuregulin 1	216 kb	**1.07E-05** 304	2.19E-03 297	4.51E-03 297	6.0
Scamp1 secretory carrier membrane protein 1	120 kb	1.71E-02 27	1.31E-02 14	2.46E-03 14	6.0
Slc8a1 solute carrier family 8 (sodium/calcium exchanger), member 1	400 kb	4.57E-03 112	**2.77E-04** 134	2.28E-02 134	6.0
Syn3 synapsin IIIa	546 kb	**1.67E-04** 143	4.94E-03 213	4.17E-03 213	6.0
Tiam1 T-cell lymphoma invasion and metastasis 1	441 kb	**7.39E-05** 141	1.82E-03 149	2.65E-03 149	6.0
Tshz2 teashirt family zinc finger 2	519 kb	1.98E-02 172	8.22E-03 172	**3.58E-04** 172	6.0
Zhx2 Zinc fingers and homeoboxes 2	193 kb	2.47E-03 37	2.86E-02 52	1.69E-03 52	6.0
Acacb acetyl-Coenzyme A carboxylase beta	152 kb	2.94E-02 28	**7.84E-04** 44	1.42E-03 44	5.5
App amyloid beta (A4) precursor protein	290 kb	3.37E-02 71	9.86E-03 70	7.81E-03 70	5.5
Atxn1 Ataxin 1	462 kb	1.11E-03 121	5.55E-03 189	6.58E-03 189	5.5
C14orf145 chromosome 14 open reading frame 145	443 kb	**2.27E-04** 78	1.89E-02 96	1.03E-03 96	5.5
C18orf1 Chromosome 18 open reading frame 1	434 kb	**1.16E-04** 96	4.21E-03 78	3.04E-03 78	5.5
Cacnb2 calcium channel, voltage-dependent, beta 2 subunit	401 kb	**2.40E-09** 137	6.57E-03 164	4.23E-02 164	5.5
Camk2a calcium/calmodulin-dependent protein kinase II alpha	71 kb		1.76E-02 33	3.62E-02 33	5.5
Camk2d calcium/calmodulin-dependent protein kinase II, delta	311 kb	1.69E-02 72	1.20E-03 67	2.90E-03 67	5.5