American Journal of Medical Genetics
Part B: Neuropsychiatric Genetics

Coming to Grips with Complex Disorders: Genetic Risk Prediction in Bipolar Disorder Using Panels of Genes Identified Through Convergent Functional Genomics

Journal:	*American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*
Manuscript ID:	NPG-10-0022.R1
Wiley - Manuscript type:	Rapid Publication
Date Submitted by the Author:	19-Feb-2010
Complete List of Authors:	Patel, Sagar; IU School of Medicine, Psychiatry Le-Niculescu, Helen; IU School of Medicine, Psychiatry Koller, Daniel L.; IU School of Medicine, Medical and Molecular Genetics Green, Steven; IU School of Medicine, Psychiatry Lahiri, Debomoy; Indiana University School of Medicine, Psychiatry and Medical and Molecular Genetics McMahon, Francis J. Nurnberger, John; Indiana University School of Medicine, Department of Psychiatry Niculescu, Alexander; IU School of Medicine, Psychiatry
Keywords:	convergent functional genomics, pathways, epistasis, genetic risk prediction, bipolar

Coming to Grips with Complex Disorders: Genetic Risk Prediction in Bipolar Disorder Using Panels of Genes Identified Through Convergent Functional Genomics

S.D. Patel [1,3], H. Le-Niculescu[1, 2, 3], D. L. Koller [4], S. D. Green[1,3], D. K. Lahiri[3], F. McMahon[5], J. I. Nurnberger Jr[3] and A. B. Niculescu[1, 2, 3, 6 ¶]

[1]Laboratory of Neurophenomics, [2]INBRAIN, [3]Institute of Psychiatric Research, Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN 46202; [4]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN 46202; [5]Mood and Anxiety Disorders Branch, NIMH, Bethesda, MD; [6]Indianapolis VA Medical Center, Indianapolis, IN 46202.

[¶] Corresponding author, E-mail: anicules@iupui.edu

Running title: Genetic Risk Prediction in Bipolar Disorder

Keywords: convergent functional genomics; pathways; epistasis; genetic risk; prediction; bipolar disorder

Correspondence:

Alexander B. Niculescu III, MD, PhD
Assistant Professor of Psychiatry and Medical Neuroscience
Indiana University School of Medicine
Staff Psychiatrist, Indianapolis VA Medical Center
Director, INBRAIN and Laboratory of Neurophenomics
Institute of Psychiatric Research
791 Union Drive, Indianapolis,
IN 46202-4887
tel. 317 274-6544;
fax. 317 274-1365;
e-mail: anicules@iupui.edu

Abstract

We previously proposed and provided proof of principle for the use of a complementary approach, Convergent Functional Genomics (CFG), combining gene expression and genetic data, from human and animal model studies, 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 (Le-Niculescu et al. 2009). CFG provides a fit-to-disease prioritization of genes that leads to generalizability in independent cohorts, and counterbalances the fit-to-cohort prioritization inherent in classic genetic-only approaches, which have been plagued by poor reproducibility across cohorts. We have now extended our previous work to include more datasets of GWAS, and more recent evidence from other lines of work. In essence our analysis is the most comprehensive integration of genetics and functional genomics to date in the field of bipolar disorder. Biological pathway analyses identified top canonical pathways, and epistatic interaction testing inside these pathways has identified genes that merit future follow-up as direct interactors (intra-pathway epistasis, INPEP). Moreover, we have put together a panel of best p-value Single Nucleotide Polymorphisms (SNPs), based on the top candidate genes we identified. We have developed a Genetic Risk Prediction Score (GRPS) based on our panel, and demonstrate how in two independent test cohorts the GRPS differentiates between subjects with bipolar disorder and normal controls, in both European-American and African-American subjects. Lastly, we describe a prototype of how such testing could be used to categorize disease risk in individuals and aid personalized medicine approaches, in psychiatry and beyond.

Introduction

As part of a Convergent Functional Genomics (CFG) strategy, expanding upon our earlier work(Le-Niculescu and others 2009b), we set out to comprehensively identify candidate genes for bipolar disorder, integrating available evidence in the field to date. We have used data from four publicly available genome-wide association studies (GWAS) datasets for bipolar disorder (2007),(Baum and others 2008),(Sklar and others 2008). We integrated those data with gene expression data - human postmortem brain gene expression data and human blood gene expression data published by others or us, as well as with relevant animal model brain and blood gene expression data generated by our group(Le-Niculescu and others 2007a; Le-Niculescu and others 2007b; Le-Niculescu and others 2008b; Niculescu and others 2000a; Ogden and others 2004). In addition, we have integrated as part of this comprehensive approach other genetic data- published human genetic (linkage or association) data for bipolar and related disorders to date, and relevant mouse genetic (QTL or transgenic) data (Figure 1).

Once the genes involved in a disorder are identified, and prioritized for likelihood of involvement, then an obvious next step is developing a way of applying that knowledge to genetic testing of individuals to determine risk for the disorder. Based on our comprehensive identification of top candidate genes described in this paper, we have chosen the best SNPs in those genes by their p-values in the GWAS datasets used, and assembled a Genetic Risk Prediction (GRP) panel out of those SNPs. We then developed a Genetic Risk Prediction Score (GRPS) for bipolar disorder based on the presence or absence of the alleles of the SNPs associated with the illness, and tested the GRPS in an independent study (GAIN-BP)(Smith and others 2009) for which we had both genotypic and clinical data available, comparing the bipolar subjects to demographically matched normal controls. Our results show that a relatively small size panel of genes identified by CFG analysis can differentiate very well between bipolar disorder subjects and controls at a population level, although at an individual level the margin is razor thin. The latter point suggests that the cumulative combinatorics of common variants plays a major role in risk for illness. Overall, our work sheds light on the genetic architecture and pathophysiology of bipolar disorder. In particular, it has implications for genetic testing to assess risk for illness before the illness manifests itself clinically.

Methods

Genome-Wide Association Studies (GWAS) data for bipolar disorder

Four bipolar GWAS were used for the expanded CFG discovery analysis. The GWAS data for the bipolar study from the Wellcome Trust Consortium (WTCC)(2007) is available at http://www.wtccc.org.uk/info/access_to_data_samples.shtml. The GWAS data from NIMH and German studies(Baum and others 2008) are available at http://mapgenetics.nimh.nih.gov/bp_pooling. The GWAS data from the STEP-BD study is available at http://pngu.mgh.harvard.edu/~purcell/bpwgas(Sklar and others 2008).

One independent study, GAIN-BP(Smith and others 2009), was used for testing the results of the discovery analyses. The GWAS data for GAIN-BP used for analyses described in this manuscript was obtained from the database of Genotype and Phenotype (dbGaP) found at www.ncbi.nlm.nih.gov through PHS project number 000017, data request numbers 2575-2, 2574-2, and 2573-2 provided to John I. Nurnberger, Jr.

The software package PLINK (http://pngu.mgh.harvard.edu/~purcell) was used to extract individual genotype information for each subject from the GAIN-BP GWAS data files. We used European Americans (EA), and separately, African American (AA), bipolar subjects and controls. Out of 1001 EA bipolar subjects in GAIN-BP, we used for our GRPS testing analyses only 407, from wave 5 of the NIMH Bipolar Genetics Consortium collection, to avoid any individual overlap (16%) or even pedigree overlap (57%) with probands from waves 1-4 that were also used in the NIMH(Baum and others 2008) study mentioned above. We also used 317 AA bipolar subjects from wave 5 of the NIMH Bipolar Genetics Consortium collection. Controls numbered 1034 for EA, and 671 for AA.

As a caveat, there was overlap in the control subjects within two of four discovery datasets (NIMH and STEP-BD), and between these two datasets and one of the datasets (GAIN-BP EA) used to test our results. However, as described below, multiple other studies and lines of evidence, human and animal model, are integrated in the CFG prioritization approach (Figure 1), which minimizes the relative contribution and impact of individual studies and the controls overlap in the discovery dataset. More importantly, there is no overlap at the bipolar subject level within discovery datasets, and between discovery datasets and the test dataset. This ensures that there is at least a degree of independence within discovery cohorts, and between discovery and test cohorts. Finally, the fact that the GRPS differentiates as well or better in the completely independent GAIN-BP AA cohort provides strong reassurance and confirmatory evidence for the method.

SNPs with a nominal genotypic p-value < 0.05 were selected for our analysis. No Bonferroni correction 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 CHIP Bioinformatics Tools 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 10cM (see (Niculescu and others 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, USA: 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 brain and human genetic literature to date on bipolar and related disorders(Niculescu and Le-Niculescu). These large databases have been used in our CFG cross-validation analyses.

Human blood gene expression data

For human blood gene expression evidence, we have used previously generated data from our group(Le-Niculescu and others 2009a) , as well as published data from the literature.

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 (Le-Niculescu and others 2007b; Le-Niculescu and others 2008c; Niculescu and others 2000a).

Mouse Genetic (QTL, transgenic) Convergence

To search for mouse genetic evidence- QTL (Quantitative Trait Loci) or transgenic -for our candidate genes, we utilized the MGI 3.54 - Mouse Genome Informatics (Jackson Laboratory) 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 10cM 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

We used two nominal p-value thresholds for scoring genes in the CFG analysis (see below) a lower stringency threshold ($p < 0.05$), and a higher stringency threshold ($p<0.001$). Genes from each GWAS data that had at least one SNP with p-value of <0.05 received 1 point; those that had at least one SNP with p-value of <0.001 received 1.5 points. 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; for human and mouse gene expression data, 1 point each for fresh brain or blood data, 0.5 points if it is from cells in culture/cell lines). Thus the maximum possible CFG score for each gene is 12 (6 =4 x 1.5 points from the four 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.

Pathway Analysis

Ingenuity 8.0 (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. The Ingenuity program generated the p-values assigned to the different pathways (Table 2).

Epistasis testing

The GAIN-BP case and control data were employed to test for epistatic interactions among SNPs from the GRPS panel in genes having a role in one or more of the top canonical biological pathways from our pathway analysis. These pathways, and the genes comprising each that were considered, are listed in Table 3. Within each pathway, SNPxSNP allelic epistasis was tested for each distinct pair of SNPs using the PLINK software package.

Genetic Risk Prediction Panel and Scoring

Out of our analysis, a panel of top genes prioritized by CFG scoring (Figure 1) can be chosen. We developed a GRP (Genetic Risk Prediction) panel, based on a list of top genes from Table 1 (n= 56, all the genes that had a CFG score better than 6, i.e. > than 50% of the maximum possible CFG score of 12). All the SNPs for these genes that had nominal p-values <0.05 in one or several of the four GWAS datasets (Wellcome, German, NIMH, STEP-BD) we used were identified. The best p-values SNPs in each study were assembled in a GRP panel (Table 1), and tested in the GAIN-BP data. As a caveat, not all the SNPs in our GRP panel had been genotyped in the GAIN-BP. Overall, out of 216 SNPs in our panel (4 SNPs x 56 genes= 224 SNPs theoretically, but some genes did not have a nominally significant SNPs in one or another of the 4 discovery GWAS), only 118 were tested in the GAIN-BP sample.

Each SNP has two alleles (represented by base letters at that position). One of them is associated with the illness (affected), the other not (non-affected). We assigned the affected allele a score of 1 and the non-affected allele a score of 0. A two-dimensional matrix of subjects by GRP panel alleles is generated, with the cells populated by 0 or 1 (Figure 3S). A SNP in a particular individual subject can have any permutation of 1 and 0 (1 and 1, 0 and 1, 1 and 0, 0 and 0). By adding these numbers, the minimum score for a SNP in an individual subject is 0, and the maximum score is 2. By adding the scores for all the alleles in the panel, averaging that, and multiplying by 100, we generate for each subject an average score corresponding to a genetic loading for disease, which we call Genetic Risk Predictive Score (GRPS). From lower to higher genetic risk, the GRPS has a minimum value of 0 and maximum value of 100. As a caveat, the assignments of 0 and 1 were made based on information for that allele in GAIN-BP for EA subjects, and separately for AA subjects, and rests on the assumption that the same alleles are associated with bipolar disorder in all subjects of the same ethnicity. However, the GAIN-BP test GWAS is not used to select the panel of genes and SNPs in the GRP panel, which is being derived completely independently from the CFG analysis of the four discovery GWAS.

The software package PLINK (http://pngu.mgh.harvard.edu/~purcell) was used to extract individual genotype information for each subject from the GAIN-BP GWAS data files. We analyzed separately EA (European-American) and African-American (AA) bipolar subjects and controls, to examine any potential ethnicity variability (Figure 3 a,b). To test for significance between bipolar and control subjects, a one-tailed t-test was performed between the bipolar subjects and the control subjects. We also analyzed males and females separately from each

other, to look at any gender-induced variability (Figure 3 c,d). Finally, we tested for the ability of the GRPS to distinguish between bipolar subjects based on an important clinical variable, episode frequency, which is the sum of all episodes of illness (depression and mania), divided by the number of years of illness. We compared the GRPS in subjects with the top 1/3 of episode frequency scores vs. subjects with the bottom 1/3 of episode frequency scores (Figure 3 e, f).

GRPS Prediction Testing

In a subsequent analysis, we used a split cohort design. We split the GAIN-BP samples for each ethnicity into a 2/3 cohort used for setting GRPS thresholds for bipolar and controls, and a 1/3 cohort used for testing the predictive value of these settings. Inside each ethnicity, the assignment to cohorts was matched for gender, but otherwise random (Table 1S).

The average GRPS score for bipolar subjects in the 2/3 cohort is used as a cut-off for bipolar in the test 1/3 cohort (i.e. being above that threshold), and the average GRPS score for controls in the 2/3 cohort is used as a cut-off for controls in the test 1/3 cohort (i.e. being below that threshold). The subjects who are in between these two thresholds are called undetermined. Furthermore, to stratify risk, we categorized subjects in the 1/3 testing cohort into Category 1 if they fall within one standard deviation above the bipolar threshold, and Category -1 if they fall within one standard deviation below the control threshold. Category 2 are between one and two standard deviations from the thresholds, Category 3 between two and three standard deviations, and Category 4 are those who fall beyond three standard deviations of the threshold. The positive predictive value (PPV) of the test was calculated for each of the categories (Figure 4).

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. We thus generated an initial list of 1657 unique genes with $p<0.05$ in at least one of the four 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 previous similar analysis by us using just three GWAS(Le-Niculescu and others 2009b) yielded 1529 unique genes, suggesting that: 1) with our genetic-genomic filtering of the 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, using our thresholds and minimal requirements, the number of genes potentially involved, directly or indirectly, in bipolar disorder may be indeed quite large, up to 10% of the genome (see also Supplementary Information- Figure 1S).

In order to minimize false positives, we then used a CFG analysis integrating multiple lines of evidence to prioritize this initial list of 1657 genes, and focused our subsequent analyses on only the top CFG scoring candidate genes. 56 genes had a CFG score of above 6 (> 50% of maximum possible score) (Table 1 and Figure 2).

As a way of testing the validity of our approach, we have examined whether our top findings were over-represented in an independent GWAS of bipolar disorder, the GAIN-BP study. 46 of the top 56 genes identified by our approach had a p- value of <0.05 in that independent study,

an estimated almost three-fold enrichment over what would be expected by chance alone in that study (see Table 1).

Candidate blood biomarkers

Of the top candidate genes from Table 1 (see also Figure 2), 22 out of 56 have prior blood gene expression evidence implicating them as potential blood biomarkers. The additional evidence provided by GWAS data suggests 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.

Biological Pathways

Ingenuity pathway analysis was carried out on the top 56 genes, revealing results similar to our previous work(Le-Niculescu and others 2009b). Notably, G-protein coupled receptor signaling, cAMP related signaling and synaptic long-term depression were the top canonical pathways over-represented in bipolar disorder, which is informative (and reassuring, as these pathways are highly druggable) for new drug discovery efforts by pharmaceutical companies.

Intra-pathway testing for epistasis (INPEP)

Epistatic interactions testing inside each of these pathways, using the independent GAIN-BP data, revealed some nominally significant pair-wise p-values (Table 3). For example, the possible interactions between CREBBP and GNAI1, and between NOS1 and GRM3 are non-obvious.

These prioritized pairs of genes inside each pathway may merit future hypothesis driven confirmatory genetic studies in independent cohorts, as well as testing for mechanistic interactions relevant to bipolar disorder pathophysiology in follow-up biological studies, such as transgenic mice studies.

Discussion:

Our CFG approach helped prioritize, as in our previous work(Le-Niculescu and others 2009b) and as expected, genes for which there was consistent evidence among the four discovery 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 very top of our list of candidate genes for bipolar disorder we have five genes: ARNTL, MBP, BDNF, NRG1 and RORB.

ARNTL (aryl hydrocarbon receptor nuclear translocator-like), a transcription factor, is a circadian clock gene. Another circadian top candidate genes identified by our analysis is RORB (Figure 2 and Table 1). RORB was also recently reported by us to be associated with bipolar disorder in an independent pediatric bipolar sample(McGrath and others 2009). 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 and others 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 in bipolar patients (Wirz-Justice and others 2004). We had previously described the identification of clock gene D-box binding protein (DBP) as a potential candidate gene for bipolar disorder(Niculescu and others 2000b), using a CFG approach. DBP was changed in expression by acute methamphetamine treatment in rat

pre-frontal cortex (PFC)(Niculescu and others 2000b), and mapped near a human genetic linkage locus for bipolar disorder(Morissette and others 1999) and for depression(Zubenko and others 2002) on chromosome 19q13. Subsequently, DBP was also reported changed in expression by acute and chronic amphetamine treatments in mice (Sokolov and others 2003). Moreover, DBP knock-out mice have abnormal circadian and homeostatic aspects of sleep regulation (Franken and others 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 and others 2008c), which is modulated by stress. Decreases in DBP expression have also been recently reported in fibroblasts from bipolar subjects(Yang and others 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, CSNK1Ds, and CCR4/nocturnin), as potential bipolar candidate genes(Ogden and others 2004). Following that, three independent reports have shown some suggestive association for ARNTL in human bipolar samples (Mansour and others 2006; Nievergelt and others 2006; Shi and others 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 and others 2006). An increase in ARNTL gene expression was reported in postmortem brains from bipolar subjects(Nakatani and others 2006). 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 and others 2003; Partonen and others 2007).. Overall, ARNTL, RORB, DBP and related circadian clock genes are compelling candidates for involvement in bipolar disorders, acting as rheostats as well as underlying the core clinical phenomenology of cycling and switching from depression to mania (Le-Niculescu and others 2008c; Niculescu and others 2000b),(Bunney and Bunney 2000),(Wager-Smith and Kay 2000),(Niculescu and Kelsoe 2001),(Kelsoe and Niculescu 2002),(Lenox and others 2002),(Hasler and others 2006),(McClung 2007; Wirz-Justice 2006).

MBP (myelin basic protein) is involved in white matter build-up and connectivity processes(Harauz and others 2009). Based on human postmortem and blood biomarker work, as well as animal models (see Table 1), it may be decreased in expression in the depressive phase of bipolar disorder, leading to a slowing of action potential transmission, potential disconnection between brain regions, and outward psychomotor retardation. The additional evidence provided by GWAS data indicates a genetic rather than purely environmental (medications , stress) basis for its alteration in disease, and its potential utility as trait marker for increased vulnerability. MBP alterations have also been reported in other neuropsychiatric disorders such as schizophrenia(Parlapani and others 2009), alcoholism(Lewohl and others 2005), multiple sclerosis(Zamvil and others 1985), as well as an animal models of stress reactivity(Le-Niculescu and others 2008c). Myelin-related genes may be a common if non-specific denominator of vulnerability to mental illness in response to stress(Le-Niculescu and others 2008c).

BDNF is a growth factor involved in neurotrophicity and synaptic transmission. Other growth factor top candidate genes identified by our analysis include NRG1 and PTN (Figure 2, and Table 1). BDNF has been previously implicated in a variety of neuropsychiatric disorders, by both animal model and human studies: depression(Pezawas and others 2008; Sen and others 2008), bipolar disorder(Ogden and others 2004), anxiety, alcoholism(Rodd and others 2007), and schizophrenia(Chao and others 2008; Le-Niculescu and others 2007a). Notably, there are several candidate gene association studies to date implicating BDNF in bipolar disorder(Fan and Sklar 2008),(Liu and others 2008).

APP (amyloid beta precursor protein), an Alzheimer Disease (AD) candidate gene, is among the top candidate gene for bipolar disorder (Table 1). Another key gene involved in AD, GSK3b, is also present on our list of top candidate genes. Previous epidemiological literature has pointed to increased AD in bipolar patients, and the prophylactic effect of the mood stabilizer lithium on the incidence of AD in bipolar patients(Nunes and others 2007). Notably, GSK3b is a target of lithium treatment(Beaulieu and others 2008a), as well as of serotonergic anti-depressants(Beaulieu and others 2008b). APP has recently been shown to have a neurotrophic role(Oh and others 2008), similar 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 and others 2004). It remains to be seen if APP's role in AD is pathogenic or is in fact a defense/compensatory mechanism to try to maintain neuronal survival(Rohn and others 2008). The possibility that drugs that regulate APP levels may have an impact on mood (i.e. downregulation of APP may be depressogenic) needs to be explored, given the prevalence of depression in the elderly in general(Alexopoulos and others 2005), and in AD patients in particular (Sun and others 2008). In any case, this is an intriguing example of potential genetic co-morbidity, overlap and interdependence between mood and cognition.

Genetic Risk Prediction

Once the genes involved in a disorder are identified, and prioritized for likelihood of involvement, then an obvious next step is developing a way of applying that knowledge to genetic testing of individuals to determine risk for the disorder. Based on our comprehensive identification of top candidate genes described above, we pursued a polygenic panel approach, with digitized binary digitization scoring for presence or absence, similar to the one we have devised and employed in the past for biomarkers(Le-Niculescu and others 2009a). Somewhat similar approaches, looking however at larger panels of markers without CFG prioritization, were subsequently also described by other groups(Purcell and others 2009).

We have chosen the best SNPs in our CFG prioritized genes by their p-values in the GWAS datasets used, and assembled a Genetic Risk Prediction (GRP) panel out of those SNPs (Table 1). We then developed a Genetic Risk Prediction Score (GRPS) for bipolar disorder based on the presence or absence of the alleles of the SNPs associated with the illness, and tested the GRPS in an independent study (GAIN-BP) for which we had both genotypic and clinical data available, comparing the bipolar subjects to demographically matched normal controls (Figure 3).

We demonstrate that in independent test cohorts, the GRPS differentiates between subjects with bipolar disorder and normal controls, in both European-American (EA) and African-American (AA) subjects (Figure 3 a, b). The GRPS also differentiates between high episode frequency and low episode frequency bipolar subjects in EA, but not AA subjects (Figure 3 e,f). Gender analyses exhibited slight trends towards higher GRPS in males than females in both ethnicities, that did not reach statistical significance (Figure 3 c, d). Lastly, we also describe a prototype of how such testing could be used at an individual rather than population level, to categorize individuals by risk and aid diagnostic and personalized medicine approaches (Figure 4).

Our results show that a relatively small size panel identified by CFG analysis can differentiate very well between bipolar disorder subjects and controls at a population level, although at an individual level the margin is razor thin (Figures 3 and 4). On average, a bipolar subject differs from a control subject by about 2 alleles out of 236 tested. The latter point suggests that the cumulative combinatorics of common gene variants plays a major role in

genetic risk for illness. Overall, our work sheds light on the genetic architecture and pathophysiology of bipolar disorder. In particular, it has implications for genetic testing to assess risk for illness. Our evaluation of the predictive value of the GRPS suggests some utility by itself at identifying risk for illness (Figure 4). More likely, such genetic information will have to be combined with family history and other clinical information (phenomics)(Niculescu and others 2006), as well as with blood biomarker testing(Le-Niculescu and others 2009a), to provide a comprehensive picture of risk of illness(Niculescu 2006; Niculescu and others 2009).

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 and others 2008). One would expect some noise due to gene size, as larger genes have more SNPs tested per gene. However, we did not observe a significant correlation between gene size and our top candidate gene prioritization using CFG (Supplementary Information- Figure 2S). 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 (Figure 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 intergenic or regulatory regions, such as promoter or enhancer regions. Moreover, genes where the illness 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 latter genes may be changed in expression as a consequence of distal regulatory SNPs or other genes in a network, an exciting area for future systems biology studies awaiting better bioinformatic tools and data analysis now on the horizon(Stumpf and others 2008). Our panel of genes prioritized by CFG is certainly not exhaustive, it is just an example of one approach. Some of the genes with strong published evidence of association, such as ANK3(Schulze and others 2009) (Ferreira and others 2008a) and CACNA1C(Ferreira and others 2008a), are not prioritized by our approach, (although related genes, ANK2 and CACNA1A, are) (Table 1). It may be that genes prioritized by p-values in genetic studies alone are the result of a *fit-to-cohort* phenomenon, resulting in poor reproducibility and predictive value in independent cohorts(Paynter and others) (Niculescu and Le-Niculescu 2010, in press). The few of them that are reproduced across studies may be more of a common denominator in bipolar patients (which tend to be heterogeneous), somewhat like housekeeping genes, but not necessarily more biologically relevant or important. CFG arguably identifies and prioritizes genes that have functional evidence and hence are more likely to be biologically relevant(Niculescu and Le-Niculescu). By being in essence a *fit-to-disease* approach, CFG also generates findings that are more reproducible and have predictive value in independent studies and cohorts, as we have demonstrated in our previous work on blood biomarkers(Kurian and others 2009; Le-Niculescu and others 2009a), and as we demonstrate in this current genetic work. That is the key litmus test, in our view.

Other animal models data could potentially be used for CFG cross-validation, in addition to the data from the pharmacogenomic (methamphetamine/valproate)(Ogden and others 2004)

and the genetic (DBP knock-out mouse)(Le-Niculescu and others 2008c) 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 likely not remove genes from our results, but rather move them up higher in the prioritization list/pyramid (Figure 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 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:

First, in spite of these 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 and others 2007) and transgenic animal work(Hikida and others 2007) (Le-Niculescu and others 2008c).

Second, our work provides additional integrated evidence focusing attention and prioritizing a number of genes as candidate blood biomarkers for bipolar disorder, with an inherited genetic basis (Table 1). 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.

Third, our work provides a proof how a combined approach, integrating functional and genotypic data, can be used for other complex disorders-psychiatric and non-psychiatric. What we are seeing 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 and others 2008). Using GWAS data in conjunction with gene expression data as part of CFG or integrative genomics(Degnan and others 2008) approaches, followed by pathway –level analysis of the prioritized candidate genes, can lead to the unraveling of the genetic code of complex disorders such as bipolar disorder.

Fourth, we have focused attention on key biological pathways in bipolar disorder, and used genetic epistatic testing to identify and prioritize molecular interactions inside those pathways. We believe that this intra-pathway epistasis testing approach (INPEP) may help with future work aimed at dissecting the molecular architecture of complex disorders.

Fifth, we have put together a panel of best p-value Single Nucleotide Polymorphisms (SNPs), based on the top candidate genes we identified. Such a panel could be used for genetic testing for bipolar disorder. To that end, we have developed a Genetic Risk Prediction Score (GRPS) based on our panel, and demonstrate how in independent cohorts, the GRPS differentiates between patients with bipolar disorder and normal controls. Based on the GRPS, we demonstrate a prototype of individual subject categorization for risk of illness. We anticipate that the GRPS approach will have utility for other complex disorders, psychiatric and non-psychiatric.

Lastly, while we cannot exclude that rare genetic variants with major effects may exist in some individuals and families, we propose a *cumulative combinatorics of common variants* genetic model for bipolar disorder based on our findings (Figure 5), to account for the razor thin genetic load margin between clinically ill subjects and normal controls, which leaves a major role to be played by the environment(Lahiri and others 2009; Niculescu and others 2009). A stressful/hostile environment may lead to sub-threshold illness even in normal genetic load individuals, whereas a favorable environment may lead to supra normative functioning in certain life areas for individuals who carry a higher genetic risk. From a speculative standpoint, this proposed flexible interplay between genetic load, environment and phenotype may permit evolution to engender diversity, select and conserve alleles, ultimately shaping population groups.

From a pragmatic utility standpoint, we would like to suggest that genetic testing with highly prioritized panels of best markers will have, by itself, a rather modest role in informing clinical decisions regarding early intervention and prevention efforts, for example before the illness fully manifests itself clinically, in young offspring from high-risk families. After the illness manifests itself, biomarker and phenomic testing approaches, including clinical data, may have higher yield than genetic testing, and a multi-modal integration of testing modalities may be optimal, as individual markers are likely to not be specific for a single disorder. The continuing re-evaluation in psychiatric nosology(Niculescu and others 2009) (O'Donovan and others 2009) brought about by recent advances will have to be taken into account as well for final interpretation of any such testing. Our emerging appreciation of the complexity, heterogeneity, overlap and interdependence of major psychiatric disorders as currently defined, and their building blocks/ Lego-like nature(Le-Niculescu and others 2007a), may make the development of tests for specific modular disease manifestations (mood, psychosis, anxiety)(Niculescu and others 2009) more useful and precise than those for broad diagnostic categories like bipolar disorder, schizophrenia or post-traumatic stress disorder.

Acknowledgements

This work was supported by funds from INGEN (Indiana Genomics Initiative of Indiana University), INBRAIN (Indiana Center for Biomarker Research In Neuropsychiatry), NARSAD Young Investigator Award and VA Merit Award to ABN, as well as NIMH R01 MH071912-01 to Ming Tsuang and ABN. ABN would like to thank Nicholas Schork for extensive discussions on genetic data analyses, Daniel Salomon, Sunil Kurian and Howard Edenberg for help and advice with microarray data analyses, Ming Tsuang and Steven Faraone for help and advice with translational studies, as well as Mariano Erpe, Joyti Gupta and Jesse Townes for their precise work with database maintenance and data analyses. Most importantly, we would like to thank our colleagues in the field whose painstaking work we have cited and integrated in our analyses, particularly the BiGS consortium (see Supplementary Information), as well as the subjects who participated in these studies, their families and their caregivers. Without their contribution, such work to advance the understanding of mental illness would not be possible. This work is, in essence, a field-wide collaboration.

Conflict of interest

ABN is a scientific co-founder of Mindscape Diagnostics.

Supplementary Information for this paper is available from the journal website. Additional information is available at www.neurophenomics.info

Table 1. Top candidate genes for bipolar disorder identified by Convergent Functional Genomics (CFG) of Genome-Wide Association studies (GWAS) data and replication of findings in an independent study. Top genes with a CFG score of 6.5 and above (n= 56) are shown. The complete list of genes (n= 1529) is available as Supplementary Information online. 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. 2009 are cited, the studies are in lymphoblastoid cell lines without correlation with mood state, I- increased; D- decreased). METH–methamphetamine, VPA-valproate. PFC - prefrontal cortex; AMY - amygdala; CP - caudate putamen; NAC - nucleus accumbens; VT - ventral tegmentum; DBP- DBP knock-out mice; NST-Non stressed; ST-Stressed; BP - bipolar disorder; BAD-Bipolar Affective Disorder; MDD-Major Depressive Disorder. TG- transgenic. QTL-quantitative trait locus. For additional human genetic evidence, Assoc- association evidence; where that is not mentioned, the evidence is linkage only. **Gene symbols underlined are blood biomarker candidate genes. P-values in bold are <0.001.** The column on the right of the bolded line depicts **replication of findings** in an independent bipolar GWAS (GAIN-BP). 46 of our top 56 genes had a p<0.05 in the GAIN-BP study. The p-value cited is the lowest for any SNP designated by SNPPER to be within the gene or flanking regions. As there were 6,041 genes at p<0.05 in that study, and the number of genes in the human genome is estimated at 20,500(Clamp and others 2007), the enrichment factor provided by our approach is (46/56)/(6041/20500)=2.8 fold. As a caveat, the GAIN-BP p-values are calculated for the whole cohort in that study, which contains some overlap with the cohort in the NIMH study (see Materials and Methods). In other words, the positive predictive value (PPV) of a GFG score greater than 6 (i.e. >50% maximum CFG score) for predicting possible involvement in bipolar disorder for a gene (p<0.05) is 46/56=82.1%. The negative predictive value (NPV) is (20500-6041-10)/ (20500-56) =70.7%. Such numbers compare favorably with detection modalities used in science in general, and medicine in particular.

Entrez ID	Gene Symbol/ Name	GWAS WTCC(2007) p-value	GWAS NIMH(Baum and others 2008) p-value	GWAS German(Baum and others 2008) p-value	GWAS Step-BD(Sklar and others 2008) p-value	Mouse Genetic Evidence (QTL, TG)	Mouse Models Brain Evidence (Ogden and others 2004),(Le-Niculescu and others 2008c)	Mouse Models Blood Evidence (Le-Niculescu and others 2008b)	Human Genetic Evidence (Linkage or Association)	Human Postmortem Brain Evidence	Human Blood/ Other Peripheral Tissue Evidence	CFG Score	GAIN-BP p-value
406	**ARNTL** aryl hydrocarbon receptor nuclear translocator-like	**7.71E-04** rs4757141	3.84E-02 rs4757138	3.72E-02 rs3816360	2.56E-02 rs11022781	Abnormal Sleep Pattern/ Circadian Rhythm(TG)	PFC (D) Cat IV-METH		11p15.2 BP (Mansour and others 2006; Nievergelt and others 2006; Partonen and others 2007) (Assoc)	I (BP) (Nakatani and others 2006)		8.5	4.87E-02
4155	**MBP** myelin basic protein		8.30E-03 rs470549	**8.19E-04** rs470821	1.17E-03 rs12967023		NST PFC (D) ST PFC (D) ST AMY (I)	BP Blood (I) Cat IV-Meth	18q23 BP (Potash and others 2008) (Assoc) BP (Schulze and others 2003), (Maziade and others 2005), (Freimer and others 1996)	D(BP) (Tkachev and others 2003) I (male BP) D (female BP) (Chambers and Perrone-Bizzozero 2004)	Mood (I) (Le-Niculescu and others 2008a)	8.5	3.14E-03

Entrez ID	Gene Symbol/ Name	GWAS WTCC(2007) p-value	GWAS NIMH(Baum and others 2008) p-value	GWAS German(Baum and others 2008) p-value	GWAS Step-BD(Sklar and others 2008) p-value	Mouse Genetic Evidence (QTL, TG)	Mouse Models Brain Evidence (Ogden and others 2004),(Le-Niculescu and others 2008c)	Mouse Models Blood Evidence (Le-Niculescu and others 2008b)	Human Genetic Evidence (Linkage or Association)	Human Postmortem Brain Evidence	Human Blood/ Other Peripheral Tissue Evidence	CFG Score	GAIN-BP p-value
627	**BDNF** brain derived neurotrophic factor	1.05E-02 rs16917234	3.76E-02 rs925946	1.91E-03 rs12291063		Abnormal emotion/affect behavior (TG)	PFC (D) Cat IV-METH		11p14.1 BP (Neves-Pereira and others 2002), (Liu and others 2008; Sklar and others 2002) (Assoc) BP (Detera-Wadleigh and others 1999), (McInnes and others 1996) Depression (Aguilera and others 2009) (Assoc) MDD (Licinio and others 2009) (Assoc)	D(BP) (Torrey and others 2005), (Pillai 2008), (Knable and others 2004) D(Depression)(Dumman and Monteggia 2006)	BP (D) (Karege and others 2004)	8.0	4.19E-02
3084	**NRG1** Neuregulin 1	**1.07E-05** rs7821190	2.19E-03 rs327380	4.51E-03 rs6468095	**8.81E-04** rs2466085				8p12 BP(Georgieva and others 2008; Green and others 2005; Thomson and others 2007; Walss-Bass and others 2006) (Assoc) BP (Park and others 2004),(Cichon and others 2001)	I (BP) (Tkachev and others 2003) D (Unipolar depression)(Bertram and others 2007)	BP(I) (Begemann and others 2008)	8.0	1.16E-02
6096	**RORB** RAR-related orphan receptor beta	1.29E-02 rs10869435	**5.88E-04** rs1327837	1.95E-02 rs1359073	**8.99E-04** rs10869435	Abnormal emotion/affect behavior (TG)	ST AMY (I) ST PFC (D)		9q21.13 BP (Macgregor and others 2004) BP (McGrath and others 2009) (Assoc)			8.0	9.38E-03
54715	**A2BP1** ataxin-2-binding protein 1	**3.42E-05** rs8046170	**4.23E-04** rs1818290	**1.59E-04** rs11077135	4.18E-03 rs7187986		VT (D) Cat III-VPA		16p13.2 BP (Baum and others 2008; Johnson and others 2009) (Assoc) BP (Ewald and others 2002)			7.5	1.11E-02
216	**ALDH1A1** aldehyde dehydrogenase family 1, subfamily A1	1.29E-02 rs348478	**1.58E-04** rs348458	3.34E-02 rs7873724		Abnormal sleep pattern/circadian rhythm (QTL)	NST PFC (D) ST AMY (I)	BP Blood (D) Cat IV-Meth	9q21.13 BP (Macgregor and others 2004)	I (BP)(Pennington and others 2007)		7.5	3.08E-02
27185	**DISC1** disrupted in schizophrenia 1	1.31E-02 rs6671423	2.99E-03 rs9431714	6.08E-03 rs7534681	8.61E-03 rs821577	Abnormal emotion/affect behavior (TG)			1q42.2 BP (Hodgkinson and others 2004; Maeda and others 2006; Thomson and others 2005),(Perlis and others 2008) (Assoc) MDD (Schosser and others 2009) (Assoc)	MDD (Sawamura and others 2005)	BP(D) (Maeda and others 2006)	7.5	2.73E-02
2890	**GRIA1** glutamate receptor, ionotropic, AMPA 1	1.47E-02 rs17096210	6.55E-03 rs4958667	9.19E-03 rs7719292	6.84E-03 rs1461232	Abnormal emotion/affect behavior (QTL)	VT (D) Cat IV-METH		5q33.2 BP (Kerner and others 2008) (Assoc) BP (Sklar and others 2004), (Morissette and others 1999)	I (BP),(MDD)(Choudary and others 2005)		7.5	**2.48E-04**

Entrez ID	Gene Symbol/ Name	GWAS WTCC(2007) p-value	GWAS NIMH(Baum and others 2008) p-value	GWAS German(Baum and others 2008) p-value	GWAS Step-BD(Sklar and others 2008) p-value	Mouse Genetic Evidence (QTL, TG)	Mouse Models Brain Evidence (Ogden and others 2004),(Le-Niculescu and others 2008c)	Mouse Models Blood Evidence (Le-Niculescu and others 2008b)	Human Genetic Evidence (Linkage or Association)	Human Postmortem Brain Evidence	Human Blood/ Other Peripheral Tissue Evidence	CFG Score	GAIN-BP p-value
3842	**NOS1** nitric oxide synthase 1, neuronal	1.72E-02 rs1607817	3.73E-02 rs2271987	4.56E-02 rs12811583	2.12E-02 rs10850803	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm (QTL)	NST AMY (D)		12q24.22 BP (Fallin and others 2005) (Assoc) BP (Chagnon and others 2004), (Morissette and others 1999)	I/D (BP) (Benes and others 2006)		7.5	1.13E-02
773	**CACNA1A** calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	2.99E-02 rs17777941	2.12E-02 rs10421810	**7.04E-04** rs10421810	2.70E-03 rs16016	Abnormal emotion/affect behavior (QTL)			19p13.13 BP (Ferreira and others 2008b) (Assoc) MDD (Zubenko and others 2003)	D (BP) (Iwamoto and others 2004)		7.0	5.67E-03
10659	**CUGBP2** CUG triplet repeat, RNA binding protein 2	**2.84E-05** rs682970	3.38E-03 rs932918	2.66E-02 rs2378991	9.51E-03 rs1990		ST PFC (I)		10p14 MDD (Zubenko and others 2003)		BP(I) (Matigian and others 2007)	7.0	1.59E-02
1826	**DSCAM** Down syndrome cell adhesion molecule like 1	1.39E-03 rs455304	**2.72E-04** rs8129283	**8.11E-04** rs7278073	1.51E-02 rs2837504				21q22.2 BP (Amano and others 2008) (Assoc)	I (BP) (Amano and others 2008)		7.0	1.66E-03
2913	**GRM3** glutamate receptor, metabotropic 3	3.43E-02 rs6955917	3.18E-03 rs10226401	7.36E-03 rs2237552	**2.22E-04** rs2237554		ST AMY (I)		7q21.12 BP (Lambert and others 2005), (Etain and others 2006)	D (MDD/ Suicide) (Klempan and others 2007) I (BP) (Choudary and others 2005)		7.0	5.69E-03
2932	**GSK3B** glycogen synthase kinase 3 beta	9.82E-03 rs17811013	1.62E-02 rs17810235	6.72E-03 rs6438552		Abnormal emotion/affect behavior (TG)	CP (D) Cat IV-VPA ST PFC (D) ST AMY (I) PFC (D) Cat IV-METH		3q13.33 BP (Lachman and others 2007; Szczepankiewicz and others 2006) (Assoc) BP (Bailer and others 2002; Benedetti and others 2004; Maziade and others 2005)	D (BP) (Nakatani and others 2006),(Vawter and others 2006) I (MDD) (Vawter and others 2006)		7.0	
3356	**HTR2A** 5-hydroxytryptamine (serotonin) receptor 2A	1.86E-02 rs2025296	4.52E-02 rs972979	1.65E-03 rs17288723	5.60E-03 rs977003	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm (TG)			13q14.2 BP (Arranz and others 1997; Lin and others 2003; McAuley and others 2009) (Assoc) BP (Chee and others 2001; Ranade and others 2003) (Assoc) BP (Badenhop and others 2002) Major Affective Disorders (Bonnier and others 2002)(Assoc) Mood Disorders (Brezo and others 2009)(Assoc) Response to Antidepressants (SSRI) (Uher and others 2009)(Assoc)	D (BP) (Torrey and others 2005),(Knable and others 2004) I (Suicide) (Klempan and others 2007)		7.0	3.19E-03

Entrez ID	Gene Symbol/ Name	GWAS WTCC(2007) p-value	GWAS NIMH(Baum and others 2008) p-value	GWAS German(Baum and others 2008) p-value	GWAS Step-BD(Sklar and others 2008) p-value	Mouse Genetic Evidence (QTL, TG)	Mouse Models Brain Evidence (Ogden and others 2004),(Le-Niculescu and others 2008c)	Mouse Models Blood Evidence (Le-Niculescu and others 2008b)	Human Genetic Evidence (Linkage or Association)	Human Postmortem Brain Evidence	Human Blood/ Other Peripheral Tissue Evidence	CFG Score	GAIN-BP p-value
2775	**KCNK1** potassium channel, subfamily K, member 1	1.89E-02 rs3843250	7.60E-03 rs4649240	**3.47E-04** rs701209	4.38E-02 rs4649343				1q42.2 BP (Curtis and others 2003; Macgregor and others 2004)	D (BP) (Jurata and others 2004)	BP (I) (Matigian and others 2007)	7.0	
11278	**KLF12** Kruppel-like factor 12	2.76E-03 rs4885151	**6.77E-04** rs9600160	**1.68E-04** rs9543443		Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm (QTL)	ST AMY (I) ST PFC (D)		13q22.1 BP (Potash and others 2003)		Mood (D)(Le-Niculescu and others 2008a)	7.0	**4.93E-04**
10150	**MBNL2** muscleblind-like 2	2.94E-03 rs6491345	4.64E-02 rs7318623	**4.02E-04** rs9584552	1.61E-02 rs16953952		AMY (D) Cat III-VPA	DBP NST Blood (D)	13q32.1 BP (Kelsoe and others 2001)			7.0	4.08E-02
89797	**NAV2** Neuron navigator 2	4.16E-03 rs2119981	**5.77E-04** rs1372797	2.04E-03 rs2218329	1.87E-03 rs10500860	Abnormal emotion/affect behavior (TG)			11p15.1 BP (Detera-Wadleigh and others 1999)	D, Bipolar Suicide(Kim and others 2007)		7.0	1.73E-03
4684	**NCAM1** neural cell adhesion molecule 1	2.77E-02 rs11214501	2.61E-02 rs586903	8.62E-03 rs12279261	1.75E-02 rs4366519				11q23.1 BP(Atz and others 2007) (Assoc) BP (Arai and others 2004) (Assoc)	D (BP) (Atz and others 2007) MDD (D) (Tochigi and others 2008)	BP (D) peripheral blood cells (Wakabayashi and others 2008)	7.0	
2908	**NR3C1** nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	4.03E-03 rs17209251	3.71E-02 rs10482672	2.96E-02 rs10482672	2.69E-02 rs2918417	Abnormal emotion/affect behavior (TG)			5q31.3 BP (Etain and others 2006) MDD (van West and others 2006) MDD (Wong and others 2008)(Assoc) Response to Antidepressants (SSRI) (Uher and others 2009)(Assoc)	D (BP) (Torrey and others 2005),(Knable and others 2004) I, MDD Suicide (Sequeira and others 2007)		7.0	7.54E-03
9988	**OPRM1** opioid receptor, mu 1	**7.82E-04** rs2010884	7.31E-03 rs650825	1.90E-03 rs7745499	2.11E-02 rs2141289	Abnormal emotion/affect behavior (TG)			6q25.2 BP (Cheng and others 2006)	I (BP) (Ryan and others 2006)		7.0	7.57E-03
5101	**PCDH9** protocadherin 9	9.77E-03 rs17082149	1.19E-03 rs9317626	**4.80E-04** rs7986387		Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm (QTL)	NST AMY (I)		13q21.32 BP (Potash and others 2003) MDD (Wong and others 2006)Assoc	D (MDD/Suicid) (Klempan and others 2007)		7.0	4.92E-03
5142	**PDE4B** phosphodiesterase 4B, cAMP-specific (phosphodiesterase E4 dunce homolog, Drosophila)	6.02E-03 rs6588190	1.60E-03 rs539322	1.41E-02 rs12021574	4.42E-02 rs17417507				1p31.2 BP(Millar and others 2007) (Assoc)	D (BP) (Fatemi and others 2008)	BP (I) (Padmos and others 2008) MDD (I), Leukocyte(Numata and others 2009)	7.0	1.54E-03
5581	**PRKCE** protein kinase C, epsilon	4.59E-03 rs2711293	**2.37E-04** rs2595221	1.20E-02 rs6748375	2.48E-02 rs4557033	Abnormal emotion/affect behavior (TG)			2p21 BP (Etain and others 2006)	D (BP) (Torrey and others 2005)		7.0	1.46E-03
5764	**PTN** pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	2.85E-02 rs6977819	1.90E-02 rs6977749	4.56E-03 rs320682	**8.78E-04** rs17169022		CP (I) Cat IV-METH		7q33 BP (Segurado and others 2003)	I (MDD)(Tochigi and others 2008)		7.0	1.03E-03

Entrez ID	Gene Symbol/ Name	GWAS WTCCC(2007) p-value	GWAS NIMH(Baum and others 2008) p-value	GWAS German(Baum and others 2008) p-value	GWAS Step-BD(Sklar and others 2008) p-value	Mouse Genetic Evidence (QTL, TG)	Mouse Models Brain Evidence (Ogden and others 2004),(Le-Niculescu and others 2008c)	Mouse Models Blood Evidence (Le-Niculescu and others 2008b)	Human Genetic Evidence (Linkage or Association)	Human Postmortem Brain Evidence	Human Blood/ Other Peripheral Tissue Evidence	CFG Score	GAIN-BP p-value
5797	**PTPM** protein tyrosine phosphatase, receptor type, M	1.74E-02 rs727951	1.10E-02 rs3786367	**2.41E-04** rs16952620	1.01E-02 rs4121619				18p11.23 BP (Segurado and others 2003)	I (BP) (Nakatani and others 2006)	Mood (D) (Le-Niculescu and others 2008a)	7.0	1.14E-03
4263	**RYR3** ryanodine receptor 3	1.21E-03 rs16957945	**2.89E-04** rs2596205	6.09E-03 rs2670955	8.07E-03 rs744776	Abnormal emotion/affect behavior (TG)	CP (I) Cat IV-VPA		15q13.3 Depression (Levinson and others 2007)			7.0	1.11E-03
9522	**SCAMP1** secretory carrier membrane protein 1	1.71E-02 rs1019803	1.31E-02 rs1968382	2.46E-03 rs16875382	2.25E-02 rs16875428		ST PFC (D)	DBP NST (D)	5q14.1		Mood (D) (Le-Niculescu and others 2008a)	7.0	4.14E-02
287	**ANK2** ankyrin 2, neuronal	**4.77E-04** rs17445459	1.34E-02 rs17590593	8.90E-03 rs10516593	5.18E-03 rs1351998	Abnormal emotion/affect behavior (QTL)	ST PFC (I)		4q25 BP (Lambert and others 2005)			6.5	**9.42E-05**
351	**APP** amyloid beta (A4) precursor protein	3.37E-02 rs3991	9.86E-03 rs2829984	7.81E-03 rs3787620	1.04E-02 rs2830048	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm (TG)			21q21.3 BP (Morissette and others 1999)	I (BP) (Jurata and others 2004)		6.5	
6310	**ATXN1** ataxin 1	1.11E-03 rs9370893	5.55E-03 rs2237198	6.58E-03 rs12198838	**3.96E-04** rs909786		ST PFC (D)		6p22.3		Mood (I)	6.5	1.12E-03
815	**CAMK2A** calcium/calmodulin-dependent protein kinase II alpha		1.76E-02 rs10515639	3.62E-02 rs3797617	2.30E-02 rs4958469	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm (TG)	NST AMY (I)		5q32 BP (Sklar and others 2004), (Etain and others 2006)	D (BP) (Xing and others 2002) I (MDD) (Tochigi and others 2008), (Novak and others 2006)		6.5	
960	**CD44** CD44 antigen	3.48E-02 rs16927100	3.94E-03 rs353615	1.06E-02 rs7115768			CP (I) Cat IV-METH	BP Blood (D) Cat IV-Meth	11p13 BP (McInnes and others 1996)		BP(I) (Middleton and others 2005)	6.5	**4.01E-04**
1012	**CDH13** cadherin 13	5.89E-03 rs1862682	2.50E-03 rs7198252	**9.08E-04** rs931408	8.01E-03 rs7197423	Abnormal emotion/affect behavior (QTL)	NST AMY (D)		16q23.3 BP (Etain and others 2006)			6.5	2.90E-03
1387	**CREBBP** CREB binding protein	5.02E-03 rs130036	1.39E-03 rs13332076	3.64E-03 rs129963	1.91E-02 rs11644593	Abnormal emotion/affect behavior (TG)	ST PFC (D)		16p13.3 BP (Ewald and others 2002)			6.5	1.37E-03
1612	**DAPK1** death-associated protein kinase 1	4.02E-02 rs11141909	**5.97E-05** rs10868644	4.04E-02 rs3124236	1.56E-03 rs3124236	Abnormal emotion/affect behavior (QTL)	AMY (D) Cat III-VPA		9q21.33 BP (Segurado and others 2003)			6.5	5.20E-03
4201	**DCLK1** doublecortin-like kinase 1	1.20E-02	2.36E-03	5.27E-03	2.59E-02		BP (D) Cat IV-VPA	DBP NST (D)	13q13.3 BP,SZ (Maziade and others 2005)			6.5	
1729	**DIAPH1** diaphanous (Drosophila, homolog) 1	2.62E-02 rs740474	4.70E-02 rs11954658	3.38E-03 rs397327	7.63E-03 rs3792896		CP (I) Cat III-VPA		5q31.3 BP (Etain and others 2006)		BP(I) (Matigian and others 2007)	6.5	
27086	**FOXP1** forkhead box P1	4.80E-03 rs950443	**9.66E-04** rs7640237	5.33E-03 rs3846031	**1.58E-04** rs17718783		NST AMY (D) ST PFC (D)		3p13 BP (McInnes and others 1996),(Etain and others 2006)			6.5	2.97E-03
2770	**GNAI1** guanine nucleotide binding protein, alpha inhibiting 1	4.98E-03 rs10429156	7.55E-03 rs6973616	1.55E-02 rs916905	3.71E-02 rs2523189		ST PFC (D)		7q21.11 BP (Lambert and others 2005)	D (BP) (Jurata and others 2004)		6.5	4.32E-02
2897	**GRIK1** glutamate receptor, ionotropic, kainate 1	**5.39E-04** rs2154490	2.79E-03 rs2832476	3.36E-02 rs464982	4.47E-02 rs467155	Abnormal emotion/affect behavior (QTL)			21q21.3 BP (Morissette and others 1999), (Detera-Wadleigh and others 1999)	D (BP) (Nakatani and others 2006), (Choudary and others 2005),(Iwamoto and others 2004) I (MDD) (Choudary and others 2005)		6.5	5.91E-03

Entrez ID	Gene Symbol/ Name	GWAS WTCC(2007) p-value	GWAS NIMH(Baum and others 2008) p-value	GWAS German(Baum and others 2008) p-value	GWAS Step-BD(Sklar and others 2008) p-value	Mouse Genetic Evidence (QTL, TG)	Mouse Models Brain Evidence (Ogden and others 2004),(Le-Niculescu and others 2008c)	Mouse Models Blood Evidence (Le-Niculescu and others 2008b)	Human Genetic Evidence (Linkage or Association)	Human Postmortem Brain Evidence	Human Blood/ Other Peripheral Tissue Evidence	CFG Score	GAIN-BP p-value
2939	**GSTA2** glutathione S-transferase, alpha 2 (Yc2)	1.14E-03 rs2207950	1.93E-03 rs2608632	1.89E-03 rs2224198	1.52E-02 rs2749010			BP (D) Cat III-Meth	6p12.2 BP (Lambert and others 2005)	I (BP)(Benes and others 2006)		6.5	
3751	**KCND2** potassium voltage-gated channel, Shal-related family, member 2	5.78E-03 rs10156125	4.08E-03 rs12538990	**5.24E-05** rs10268591	3.86E-02 rs2191736	Abnormal emotion/affect behavior(QTL)	ST PFC (D)		7q31.31 BP (Etain and others 2006)			6.5	
4008	**LMO7** LIM domain only 7	**6.62E-05** rs9530460	1.11E-02 rs9593132	8.17E-03 rs1570554	6.59E-03 rs9530460	Abnormal emotion/affect behavior Abnormal sleep pattern/circadian rhythm(QTL)			13q22.2 BP (Potash and others 2003)		Anti-depressant (D) Lymphocytes (Kalman and others 2005)	6.5	2.26E-02
23040	**MYT1L** myelin transcription factor 1-like	**2.25E-04** rs1991773	1.31E-02 rs1421614	1.25E-02 rs10519486	1.65E-02 rs17039396	Abnormal sleep pattern/circadian rhythm (QTL)	ST PFC (D)		2p25.3 BP (Detera-Wadleigh and others 1999)			6.5	5.83E-03
4720	**NDUFS2** NADH dehydrogenase (ubiquinone) Fe-S protein 2, 49kDa (NADH-coenzyme Q reductase)	4.27E-02 rs5085	1.08E-02 rs11421	4.67E-02 rs11421	3.61E-02 rs5085		BP (I) Cat III-VPA		1q23 BP (Fallin and others 2004)		BP(D) (Middleton and others 2005)	6.5	
4897	**NRCAM** neuronal cell adhesion molecule	1.63E-03 rs13227836	**5.94E-04** rs3763461	**8.60E-04** rs1548949	4.35E-02 rs11974528	Abnormal Sleep pattern/circadian rhythm (QTL)	NST AMY (I)		7q31.1			6.5	1.16E-03
10846	**PDE10A** phosphodiesterase 10A	1.50E-02 rs2983506	9.64E-03 rs12525763	1.50E-03 rs454165	3.40E-03 rs2983521	Abnormal emotion/affect behavior (TG)	NST AMY (D) ST PFC (D)		6q27 BP (Cheng and others 2006)			6.5	2.16E-02
5122	**PTPRT** protein tyrosine phosphatase, receptor type, T	6.27E-03 rs6030385	3.45E-03 rs2425478	1.12E-02 rs1016071	4.67E-03 rs1883842		ST AMY (I)		20q12 BP (Radhakrishna and others 2001)	I (MDD/Suicid) (Sequeira and others 2007) D (MDD) (Aston and others 2005)		6.5	1.20E-03
6546	**SLC8A1** solute carrier family 8 (sodium/calcium exchanger), member 1	4.57E-03 rs10490049	**2.77E-04** rs17025372	2.28E-02 rs381797	7.44E-03 rs12052585	Abnormal emotion/affect behavior (QTL)	ST AMY (I) ST PFC (D)		2p22.1 BP (Etain and others 2006)			6.5	1.30E-02
8224	**SYN3** synapsin III	**1.67E-04** rs11089599	4.94E-03 rs130301	4.17E-03 rs3788467	2.03E-02 rs933255				22q12.3 BP (Lachman and others 2006)(Assoc) BP (Kelsoe and others 2001), (Potash and others 2003), (Detera-Wadleigh and others 1999)	D(BP) (Vawter and others 2002)		6.5	7.97E-03
9074	**TIAM1** T-cell lymphoma invasion and metastasis 1	**7.39E-05** rs13340018	1.82E-03 rs12482796	2.65E-03 rs2257062	2.49E-03 rs845945	Abnormal emotion/affect behavior (QTL)			21q22.11 BP (Morissette and others 1999)	D(MDD) (Aston and others 2005)		6.5	3.31E-02
128553	**TSHZ2** Teashirt family zinc finger 2	1.98E-02 rs7263115	8.22E-03 rs2741356	**3.58E-04** rs169270	1.73E-02 rs6068531	Abnormal emotion/affect behavior(QTL)			20q13.2 BP (Radhakrishna and others 2001)		Mood (D) (Le-Niculescu and others 2008a)	6.5	8.16E-03
79683	**ZDHHC14** zinc finger, DHHC domain containing 14	4.09E-03 rs1885452	4.59E-03 rs596183	3.56E-02 rs16900254	4.89E-03 rs17297221		ST AMY (I)		6q25.3 BP (Cheng and others 2006)		Mood (D) (Le-Niculescu and others 2008a)	6.5	2.40E-02

Table 2: Biological Pathways. Ingenuity Pathway Analysis of the Top Candidate Genes from Table 1.

Top Networks	
Associated Network Functions	**Score**
1. Nervous System Development and Function, Neurological Disease, Genetic Disorder	38
2. Cellular Compromise, Neurological Disease, Drug metabolism	38
3. Cellular Assembly and Organization, Cardiovascular System Development and Function, Cellular Growth and Proliferation	24
4. Amino Acid Metabolism, Cancer, Cell Morphology	19

Top Bio Functions		
Diseases and Disorders	**p-value**	**# Molecules**
Genetic Disorder	1.52E-19 – 3.47E-03	53
Neurological Disease	1.52E-19 – 3.67E-03	47
Psychological Disorders	1.52E-19 – 1.95E-03	35
Endocrine System Disorders	4.63E-15 – 3.67E-03	38
Metabolic Disease	2.44E-14 – 1.05E-07	38
Molecular and Cellular Functions	**p-value**	**# Molecules**
Cellular Assembly and Organization	4.21E-08 – 3.67E-03	23
Cell-To-Cell Signaling and Interaction	8.46E-08 – 3.67E-03	26
Cellular Movement	2.87E-07 – 3.67E-03	15
Amino Acid Metabolism	1.68E-06 – 2.81E-03	15
Molecular Transport	1.68E-06 – 3.67E-03	18
Physiological System Development and Function	**p-value**	**# Molecules**
Behavior	4.22E-13 – 2.94E-03	19
Nervous System Development and Function	2.83E-11 – 3.67E-03	33
Organismal Functions	1.97E-10 – 1.45E-09	10
Tissue Morphology	2.27E-05 – 3.67E-03	17
Hematological System Development and Function	7.44E-05 – 3.67E-03	14

Top Canonical Pathways		
	p-value	**Ratio**
1. G-Protein Coupled Receptor Signaling	8.50E-07	8/218 (0.037)
2. CREB Signaling in Neurons	3.00E-06	7/194 (0.036)
3. Synaptic Long Term Depression	1.46E-05	6/164 (0.037)
4. cAMP-mediated Signaling	2.47E-05	6/164 (0.037)
5. Neuropathic Pain Signaling In Dorsal Horn Neurons	3.54E-05	5/104(0.048)

Table 3: Intra- Pathway Epistasis (INPEP) Testing Identifies Genes That May Work Together. Inside each of the top canonical pathways depicted in Table 2, we tested for epistatic interactions between genes in the pathway, in an independent dataset, the GAIN-BP, as a way of identyfing and prioritizing interactions. The top epistatic interactions in each pathway are depicted in bold. These genes merit future follow-up work to elucidate the biological and pathophysiological relevance of their interactions. As a caveat, the p-value was not corrected for multiple comparisons.

Ingenuity Top Canonical Pathways	Genes								Nominal Epistatic p-values
G-Protein Coupled Receptor Signaling	CAMK2A	GRM3	**PDE10A ***	OPRM1	GNAI1	PRKCE	**PDE4B***	HTR2A	*0.0133
CREB Signaling in Neurons	CAMK2A	GRM3	GRIA1	**CREBBP***	**GNAI1***	PRKCE	GRIK1		*0.0138
Synaptic Long Term Depression	**NOS1***	**GRM3***	GRIA1	RYR3	GNAI1	PRKCE			*0.0173
cAMP-mediated Signaling	CAMK2A	GRM3	**PDE10A ***	OPRM1	GNAI1	**PDE4B***			*0.0133
Neuropathic Pain Signaling In Dorsal Horn Neurons	CAMK2A	BDNF	**GRM3***	GRIA1	**PRKCE***				*0.0298

Figure legends:

Figure 1. Convergent Functional Genomics. Integration of multiple independent lines of evidence. The maximal possible score from GWAS data (6pt.) is equally weighed with the maximal possible score from other lines of evidence (other human and animal model gene expression and genetic data) (6 pt.).

Figure 2: Top Bipolar Candidate Genes. The lines of evidence (CFG scoring) is depicted on the right side of the pyramid.

Figure 3. The Genetic Risk Prediction Score (GRPS) for bipolar disorder differentiates between bipolar subjects and normal controls in an independent study, in two different ethnic groups. The GRPS is based on a panel of the best p-value SNPs (n=216) from the best top genes (n=56) for bipolar disorder identified by CFG of 4 GWAS for bipolar disorder (see Table 1). The GRPS shows statistically significant differences between subjects with bipolar disorder and normal controls, in European American (EA) **(a)** as well as in African Americans (AA) **(b),** in an independent GWAS study (GAIN-BP, Smith et. al. 2009). Out of 216 SNPs in our panel, 118 SNPs were genotyped in the GAIN-BP study. **Gender analyses** exhibited slight trends towards higher GRPS in males than females in both ethnicities, that did not reach statistical significance **(c,d). Episode frequency:** of note, the GRPS is able to differentiate between high episode frequency and low episode frequency bipolar subjects in EA **(e)**, but not AA subjects **(f)**. Episode frequency is a measure of clinical severity, tied to recurrence and to cycling between euthymia, depression and mania.

Figure 4. Prototype of how GRPS testing could be used at an individual rather than population level, to aid diagnostic and personalized medicine approaches. We split the GAIN-BP samples fro each ethnicity into a 2/3 cohort used for setting GRPS thresholds for bipolar and controls (a, c), and a 1/3 cohort used for testing the predictive value of these settings (b, d). The average GRPS score for bipolar subjects in the 2/3 cohort is used as a cut-off for bipolar in the test 1/3 cohort (i.e. being above that threshold), and the average GRPS score for controls in the 2/3 cohort is used as a cut-off for controls in the test 1/3 cohort (i.e. being below that threshold). The subjects who are in between these two thresholds are called undetermined. Furthermore, to stratify risk, we categorized subjects in the 1/3 testing cohort into Category 1 if they fall within one standard deviation above the bipolar threshold, and Category -1 if they fall within one standard deviation below the control threshold. Category 2 subjects are between one and two standard deviations from the thresholds, Category 3 between two and three standard deviations, and Category 4 are those who fall beyond three standard deviations of the threshold. The positive predictive value (PPV) of the tests increases in the higher categories, and the test is somewhat better at distinguishing controls (i.e., in a practical application, individuals that are lower risk of developing the illness) than bipolars (i.e., in a practical application, individuals that are higher risk of developing the illness).

Figure 5. The genetic architecture of bipolar disorders: Cummulative Combinatorics of Common Gene variants and Environment (CC xCGV xE) model. We proposed in our previous work(Le-Niculescu and others 2009b) that the repertoire of genes that may be involved directly or indirectly in bipolar disorders/mood regulation is large, up to 10% of the genes in the genome (*complexity*). Our current work suggests that different combinations of genes/alleles are found in different individuals (*heterogeneity*), and many alleles in these genes are shared between bipolars and controls (*overlap*). The environment may play a key interactive role in the trajectory from genetic risk to ultimate phenotype (*interdependence*), by modulating gene expression. For example, with the right environment a higher genetic load (GRPS score) individual may become normal or even a high performer. This shuffling of the genetic deck of cards and the interaction with the environment provide a basis for Darwinian adaptation and evolution of mood, a key bodily function synchronizing energy metabolism, trophicity and activity to external and internal milieu conditions(Le-Niculescu and others 2009a; Le-Niculescu and others 2009b) . Circadian clock molecular mechanisms, involving ARNTL, RORB, DBP and other molecules, may be essential mediators (Le-Niculescu and others 2008c; Niculescu and others 2000b; Ogden and others 2004; Takahashi and others 2008) (Zhang and others 2009). Geometric symbols in the figure depict different genes/alleles.

Literature cited:

2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447(7145):661-78.

Aguilera M, Arias B, Wichers M, Barrantes-Vidal N, Moya J, Villa H, van Os J, Ibanez MI, Ruiperez MA, Ortet G and others. 2009. Early adversity and 5-HTT/BDNF genes: new evidence of gene-environment interactions on depressive symptoms in a general population. Psychol Med:1-8.

Alexopoulos GS, Schultz SK, Lebowitz BD. 2005. Late-life depression: a model for medical classification. Biol Psychiatry 58(4):283-9.

Amano K, Yamada K, Iwayama Y, Detera-Wadleigh SD, Hattori E, Toyota T, Tokunaga K, Yoshikawa T, Yamakawa K. 2008. Association study between the Down syndrome cell adhesion molecule (DSCAM) gene and bipolar disorder. Psychiatr Genet 18(1):1-10.

Arai M, Itokawa M, Yamada K, Toyota T, Arai M, Haga S, Ujike H, Sora I, Ikeda K, Yoshikawa T. 2004. Association of neural cell adhesion molecule 1 gene polymorphisms with bipolar affective disorder in Japanese individuals. Biol Psychiatry 55(8):804-10.

Arranz MJ, Erdmann J, Kirov G, Rietschel M, Sodhi M, Albus M, Ball D, Maier W, Davies N, Franzek E and others. 1997. 5-HT2A receptor and bipolar affective disorder: association studies in affected patients. Neurosci Lett 224(2):95-8.

Aston C, Jiang L, Sokolov BP. 2005. Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. Mol Psychiatry 10(3):309-22.

Atz ME, Rollins B, Vawter MP. 2007. NCAM1 association study of bipolar disorder and schizophrenia: polymorphisms and alternatively spliced isoforms lead to similarities and differences. Psychiatr Genet 17(2):55-67.

Badenhop RF, Moses MJ, Scimone A, Mitchell PB, Ewen-White KR, Rosso A, Donald JA, Adams LJ, Schofield PR. 2002. A genome screen of 13 bipolar affective disorder pedigrees provides evidence for susceptibility loci on chromosome 3 as well as chromosomes 9, 13 and 19. Mol Psychiatry 7(8):851-9.

Bailer U, Leisch F, Meszaros K, Lenzinger E, Willinger U, Strobl R, Heiden A, Gebhardt C, Doge E, Fuchs K and others. 2002. Genome scan for susceptibility loci for schizophrenia and bipolar disorder. Biol Psychiatry 52(1):40-52.

Bauer M, Grof P, Rasgon N, Bschor T, Glenn T, Whybrow PC. 2006. Temporal relation between sleep and mood in patients with bipolar disorder. Bipolar Disord 8(2):160-7.

Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, Schulze TG, Cichon S, Rietschel M, Nothen MM and others. 2008. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. Mol Psychiatry 13(2):197-207.

Beaulieu JM, Marion S, Rodriguiz RM, Medvedev IO, Sotnikova TD, Ghisi V, Wetsel WC, Lefkowitz RJ, Gainetdinov RR, Caron MG. 2008a. A beta-arrestin 2 signaling complex mediates lithium action on behavior. Cell 132(1):125-36.

Beaulieu JM, Zhang X, Rodriguiz RM, Sotnikova TD, Cools MJ, Wetsel WC, Gainetdinov RR, Caron MG. 2008b. Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency. Proc Natl Acad Sci U S A 105(4):1333-8.

Begemann M, Sargin D, Rossner MJ, Bartels C, Theis F, Wichert SP, Stender N, Fischer B, Sperling S, Stawicki S and others. 2008. Episode-specific differential gene expression of peripheral blood mononuclear cells in rapid cycling supports novel treatment approaches. Mol Med 14(9-10):546-52.

Benedetti F, Bernasconi A, Lorenzi C, Pontiggia A, Serretti A, Colombo C, Smeraldi E. 2004. A single nucleotide polymorphism in glycogen synthase kinase 3-beta promoter gene influences onset of illness in patients affected by bipolar disorder. Neurosci Lett 355(1-2):37-40.

Benes FM, Matzilevich D, Burke RE, Walsh J. 2006. The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. Mol Psychiatry 11(3):241-51.

Bertram I, Bernstein HG, Lendeckel U, Bukowska A, Dobrowolny H, Keilhoff G, Kanakis D, Mawrin C, Bielau H, Falkai P and others. 2007. Immunohistochemical evidence for impaired neuregulin-1 signaling in the prefrontal cortex in schizophrenia and in unipolar depression. Ann N Y Acad Sci 1096:147-56.

Bonnier B, Gorwood P, Hamon M, Sarfati Y, Boni C, Hardy-Bayle MC. 2002. Association of 5-HT(2A) receptor gene polymorphism with major affective disorders: the case of a subgroup of bipolar disorder with low suicide risk. Biol Psychiatry 51(9):762-5.

Brezo J, Bureau A, Merette C, Jomphe V, Barker ED, Vitaro F, Hebert M, Carbonneau R, Tremblay RE, Turecki G. 2009. Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study. Mol Psychiatry.

Bunney WE, Bunney BG. 2000. Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. Neuropsychopharmacology 22(4):335-45.

Chagnon YC, Merette C, Bouchard RH, Emond C, Roy MA, Maziade M. 2004. A genome wide linkage study of obesity as secondary effect of antipsychotics in multigenerational families of eastern Quebec affected by psychoses. Mol Psychiatry 9(12):1067-74.

Chambers JS, Perrone-Bizzozero NI. 2004. Altered myelination of the hippocampal formation in subjects with schizophrenia and bipolar disorder. Neurochem Res 29(12):2293-302.

Chao HM, Kao HT, Porton B. 2008. BDNF Val66Met variant and age of onset in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 147B(4):505-6.

Chee IS, Lee SW, Kim JL, Wang SK, Shin YO, Shin SC, Lee YH, Hwang HM, Lim MR. 2001. 5-HT2A receptor gene promoter polymorphism -1438A/G and bipolar disorder. Psychiatr Genet 11(3):111-4.

Cheng R, Juo SH, Loth JE, Nee J, Iossifov I, Blumenthal R, Sharpe L, Kanyas K, Lerer B, Lilliston B and others. 2006. Genome-wide linkage scan in a large bipolar disorder sample from the National Institute of Mental Health genetics initiative suggests putative loci for bipolar disorder, psychosis, suicide, and panic disorder. Mol Psychiatry 11(3):252-60.

Choudary PV, Molnar M, Evans SJ, Tomita H, Li JZ, Vawter MP, Myers RM, Bunney WE, Jr., Akil H, Watson SJ and others. 2005. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. Proc Natl Acad Sci U S A 102(43):15653-8.

Cichon S, Schmidt-Wolf G, Schumacher J, Muller DJ, Hurter M, Schulze TG, Albus M, Borrmann-Hassenbach M, Franzek E, Lanczik M and others. 2001. A possible susceptibility locus for bipolar affective disorder in chromosomal region 10q25--q26. Mol Psychiatry 6(3):342-9.

Clamp M, Fry B, Kamal M, Xie X, Cuff J, Lin MF, Kellis M, Lindblad-Toh K, Lander ES. 2007. Distinguishing protein-coding and noncoding genes in the human genome. Proc Natl Acad Sci U S A 104(49):19428-33.

Curtis D, Kalsi G, Brynjolfsson J, McInnis M, O'Neill J, Smyth C, Moloney E, Murphy P, McQuillin A, Petursson H and others. 2003. Genome scan of pedigrees multiply affected with bipolar disorder provides further support for the presence of a susceptibility locus on chromosome 12q23-q24, and suggests the presence of additional loci on 1p and 1q. Psychiatr Genet 13(2):77-84.

Degnan JH, Lasky-Su J, Raby BA, Xu M, Molony C, Schadt EE, Lange C. 2008. Genomics and genome-wide association studies: An integrative approach to expression QTL mapping. Genomics.

Detera-Wadleigh SD, Badner JA, Berrettini WH, Yoshikawa T, Goldin LR, Turner G, Rollins DY, Moses T, Sanders AR, Karkera JD and others. 1999. A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. Proc Natl Acad Sci U S A 96(10):5604-9.

Duman RS, Monteggia LM. 2006. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59(12):1116-27.

Etain B, Mathieu F, Rietschel M, Maier W, Albus M, McKeon P, Roche S, Kealey C, Blackwood D, Muir W and others. 2006. Genome-wide scan for genes involved in bipolar affective disorder in 70 European families ascertained through a bipolar type I early-onset proband: supportive evidence for linkage at 3p14. Mol Psychiatry 11(7):685-94.

Ewald H, Flint T, Kruse TA, Mors O. 2002. A genome-wide scan shows significant linkage between bipolar disorder and chromosome 12q24.3 and suggestive linkage to chromosomes 1p22-21, 4p16, 6q14-22, 10q26 and 16p13.3. Mol Psychiatry 7(7):734-44.

Fallin MD, Lasseter VK, Avramopoulos D, Nicodemus KK, Wolyniec PS, McGrath JA, Steel G, Nestadt G, Liang KY, Huganir RL and others. 2005. 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 77(6):918-36.

Fallin MD, Lasseter VK, Wolyniec PS, McGrath JA, Nestadt G, Valle D, Liang KY, Pulver AE. 2004. Genomewide linkage scan for bipolar-disorder susceptibility loci among Ashkenazi Jewish families. Am J Hum Genet 75(2):204-19.

Fan J, Sklar P. 2008. Genetics of bipolar disorder: focus on BDNF Val66Met polymorphism. Novartis Found Symp 289:60-72; discussion 72-3, 87-93.

Fatemi SH, Reutiman TJ, Folsom TD, Lee S. 2008. Phosphodiesterase-4A expression is reduced in cerebella of patients with bipolar disorder. Psychiatr Genet 18(6):282-8.

Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, Fan J, Kirov G, Perlis RH, Green EK and others. 2008a. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 40(9):1056-8.

Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, Fan J, Kirov G, Perlis RH, Green EK and others. 2008b. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet.

Franken P, Lopez-Molina L, Marcacci L, Schibler U, Tafti M. 2000. The transcription factor DBP affects circadian sleep consolidation and rhythmic EEG activity. J Neurosci 20(2):617-25.

Freimer NB, Reus VI, Escamilla MA, McInnes LA, Spesny M, Leon P, Service SK, Smith LB, Silva S, Rojas E and others. 1996. Genetic mapping using haplotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22-q23. Nat Genet 12(4):436-41.

Georgieva L, Dimitrova A, Ivanov D, Nikolov I, Williams NM, Grozeva D, Zaharieva I, Toncheva D, Owen MJ, Kirov G and others. 2008. Support for Neuregulin 1 as a Susceptibility Gene for Bipolar Disorder and Schizophrenia. Biol Psychiatry.

Green EK, Raybould R, Macgregor S, Gordon-Smith K, Heron J, Hyde S, Grozeva D, Hamshere M, Williams N, Owen MJ and others. 2005. Operation of the schizophrenia susceptibility gene, neuregulin 1, across traditional diagnostic boundaries to increase risk for bipolar disorder. Arch Gen Psychiatry 62(6):642-8.

Harauz G, Ladizhansky V, Boggs JM. 2009. Structural polymorphism and multifunctionality of myelin basic protein. Biochemistry 48(34):8094-104.

Hasler G, Drevets WC, Gould TD, Gottesman, II, Manji HK. 2006. Toward Constructing an Endophenotype Strategy for Bipolar Disorders. Biol Psychiatry.

Hikida T, Jaaro-Peled H, Seshadri S, Oishi K, Hookway C, Kong S, Wu D, Xue R, Andrade M, Tankou S and others. 2007. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc Natl Acad Sci U S A 104(36):14501-6.

Hodgkinson CA, Goldman D, Jaeger J, Persaud S, Kane JM, Lipsky RH, Malhotra AK. 2004. Disrupted in schizophrenia 1 (DISC1): association with schizophrenia, schizoaffective disorder, and bipolar disorder. Am J Hum Genet 75(5):862-72.

Iwamoto K, Kakiuchi C, Bundo M, Ikeda K, Kato T. 2004. Molecular characterization of bipolar disorder by comparing gene expression profiles of postmortem brains of major mental disorders. Mol Psychiatry 9(4):406-16.

Johansson C, Willeit M, Smedh C, Ekholm J, Paunio T, Kieseppa T, Lichtermann D, Praschak-Rieder N, Neumeister A, Nilsson LG and others. 2003. Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. Neuropsychopharmacology 28(4):734-9.

Johnson C, Drgon T, McMahon FJ, Uhl GR. 2009. Convergent genome wide association results for bipolar disorder and substance dependence. Am J Med Genet B Neuropsychiatr Genet 150B(2):182-90.

Jurata LW, Bukhman YV, Charles V, Capriglione F, Bullard J, Lemire AL, Mohammed A, Pham Q, Laeng P, Brockman JA and others. 2004. Comparison of microarray-based mRNA profiling technologies for identification of psychiatric disease and drug signatures. J Neurosci Methods 138(1-2):173-88.

Kalman J, Palotas A, Juhasz A, Rimanoczy A, Hugyecz M, Kovacs Z, Galsi G, Szabo Z, Pakaski M, Feher LZ and others. 2005. Impact of venlafaxine on gene expression profile in lymphocytes of the elderly with major depression--evolution of antidepressants and the role of the "neuro-immune" system. Neurochem Res 30(11):1429-38.

Karege F, Schwald M, El Kouaissi R. 2004. Drug-induced decrease of protein kinase a activity reveals alteration in BDNF expression of bipolar affective disorder. Neuropsychopharmacology 29(4):805-12.

Kelsoe JR, Niculescu AB, 3rd. 2002. Finding genes for bipolar disorder in the functional genomics era: from convergent functional genomics to phenomics and back. CNS Spectr 7(3):215-26.

Kelsoe JR, Spence MA, Loetscher E, Foguet M, Sadovnick AD, Remick RA, Flodman P, Khristich J, Mroczkowski-Parker Z, Brown JL and others. 2001. A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. Proc Natl Acad Sci U S A 98(2):585-90.

Kerner B, Jasinska AJ, Deyoung J, Almonte M, Choi OW, Freimer NB. 2008. Polymorphisms in the GRIA1 gene region in psychotic bipolar disorder. Am J Med Genet B Neuropsychiatr Genet.

Kim S, Choi KH, Baykiz AF, Gershenfeld HK. 2007. Suicide candidate genes associated with bipolar disorder and schizophrenia: An exploratory gene expression profiling analysis of post-mortem prefrontal cortex. BMC Genomics 8(1):413.

Klempan TA, Sequeira A, Canetti L, Lalovic A, Ernst C, Ffrench-Mullen J, Turecki G. 2007. Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. Mol Psychiatry.

Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF. 2004. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. Mol Psychiatry 9(6):609-20, 544.

Kurian SM, Le-Niculescu H, Patel SD, Bertram D, Davis J, Dike C, Yehyawi N, Lysaker P, Dustin J, Caligiuri M and others. 2009. Identification of blood biomarkers for psychosis using convergent functional genomics. Mol Psychiatry.

Lachman HM, Pedrosa E, Petruolo OA, Cockerham M, Papolos A, Novak T, Papolos DF, Stopkova P. 2007. Increase in GSK3beta gene copy number variation in bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 144B(3):259-65.

Lachman HM, Stopkova P, Papolos DF, Pedrosa E, Margolis B, Aghalar MR, Saito T. 2006. Analysis of synapsin III-196 promoter mutation in schizophrenia and bipolar disorder. Neuropsychobiology 53(2):57-62.

Lahiri DK, Maloney B, Zawia NH. 2009. The LEARn model: an epigenetic explanation for idiopathic neurobiological diseases. Mol Psychiatry 14(11):992-1003.

Lambert D, Middle F, Hamshere ML, Segurado R, Raybould R, Corvin A, Green E, O'Mahony E, Nikolov I, Mulcahy T and others. 2005. Stage 2 of the Wellcome Trust

UK-Irish bipolar affective disorder sibling-pair genome screen: evidence for linkage on chromosomes 6q16-q21, 4q12-q21, 9p21, 10p14-p12 and 18q22. Mol Psychiatry 10(9):831-41.

Le-Niculescu H, Balaraman Y, Patel S, Tan J, Sidhu K, Jerome RE, Edenberg HJ, Kuczenski R, Geyer MA, Nurnberger JI, Jr. and others. 2007a. Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. Am J Med Genet B Neuropsychiatr Genet 144B(2):129-58.

Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ, Tsuang MT, Salomon DR, Nurnberger JI, Jr., Niculescu AB. 2008a. Identifying blood biomarkers for mood disorders using convergent functional genomics. Mol Psychiatry.

Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ, Tsuang MT, Salomon DR, Nurnberger JI, Jr., Niculescu AB. 2009a. Identifying blood biomarkers for mood disorders using convergent functional genomics. Mol Psychiatry 14(2):156-74.

Le-Niculescu H, McFarland MJ, Mamidipalli S, Ogden CA, Kuczenski R, Kurian SM, Salomon DR, Tsuang MT, Nurnberger JI, Jr., Niculescu AB. 2007b. Convergent Functional Genomics of bipolar disorder: from animal model pharmacogenomics to human genetics and biomarkers. Neurosci Biobehav Rev 31(6):897-903.

Le-Niculescu H, McFarland MJ, Ogden CA, Balaraman Y, Patel S, Tan J, Rodd ZA, Paulus M, Geyer MA, Edenberg HJ and others. 2008b. Phenomic, Convergent Functional Genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. Am J Med Genet B Neuropsychiatr Genet.

Le-Niculescu H, McFarland MJ, Ogden CA, Balaraman Y, Patel S, Tan J, Rodd ZA, Paulus M, Geyer MA, Edenberg HJ and others. 2008c. Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. Am J Med Genet B Neuropsychiatr Genet 147B(2):134-66.

Le-Niculescu H, Patel SD, Bhat M, Kuczenski R, Faraone SV, Tsuang MT, McMahon FJ, Schork NJ, Nurnberger JI, Jr., Niculescu AB, 3rd. 2009b. Convergent functional genomics of genome-wide association data for bipolar disorder: comprehensive identification of candidate genes, pathways and mechanisms. Am J Med Genet B Neuropsychiatr Genet 150B(2):155-81.

Lenox RH, Gould TD, Manji HK. 2002. Endophenotypes in bipolar disorder. Am J Med Genet 114(4):391-406.

Levinson DF, Evgrafov OV, Knowles JA, Potash JB, Weissman MM, Scheftner WA, Depaulo JR, Jr., Crowe RR, Murphy-Eberenz K, Marta DH and others. 2007. Genetics of recurrent early-onset major depression (GenRED): significant linkage on chromosome 15q25-q26 after fine mapping with single nucleotide polymorphism markers. Am J Psychiatry 164(2):259-64.

Lewohl JM, Wixey J, Harper CG, Dodd PR. 2005. Expression of MBP, PLP, MAG, CNP, and GFAP in the Human Alcoholic Brain. Alcohol Clin Exp Res 29(9):1698-705.

Licinio J, Dong C, Wong ML. 2009. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. Arch Gen Psychiatry 66(5):488-97.

Lin YM, Yang HC, Lai TJ, Fann CS, Sun HS. 2003. Receptor mediated effect of serotonergic transmission in patients with bipolar affective disorder. J Med Genet 40(10):781-6.

Liu L, Foroud T, Xuei X, Berrettini W, Byerley W, Coryell W, El-Mallakh R, Gershon ES, Kelsoe JR, Lawson WB and others. 2008. Evidence of association between brain-derived neurotrophic factor gene and bipolar disorder. Psychiatr Genet 18(6):267-74.

Macgregor S, Visscher PM, Knott SA, Thomson P, Porteous DJ, Millar JK, Devon RS, Blackwood D, Muir WJ. 2004. A genome scan and follow-up study identify a bipolar disorder susceptibility locus on chromosome 1q42. Mol Psychiatry 9(12):1083-90.

Maeda K, Nwulia E, Chang J, Balkissoon R, Ishizuka K, Chen H, Zandi P, McInnis MG, Sawa A. 2006. Differential expression of disrupted-in-schizophrenia (DISC1) in bipolar disorder. Biol Psychiatry 60(9):929-35.

Magnusson A, Partonen T. 2005. The diagnosis, symptomatology, and epidemiology of seasonal affective disorder. CNS Spectr 10(8):625-34; quiz 1-14.

Mansour HA, Wood J, Logue T, Chowdari KV, Dayal M, Kupfer DJ, Monk TH, Devlin B, Nimgaonkar VL. 2006. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. Genes Brain Behav 5(2):150-7.

Matigian N, Windus L, Smith H, Filippich C, Pantelis C, McGrath J, Mowry B, Hayward N. 2007. Expression profiling in monozygotic twins discordant for bipolar disorder reveals dysregulation of the WNT signalling pathway. Mol Psychiatry.

Maziade M, Roy MA, Chagnon YC, Cliche D, Fournier JP, Montgrain N, Dion C, Lavallee JC, Garneau Y, Gingras N and others. 2005. Shared and specific susceptibility loci for schizophrenia and bipolar disorder: a dense genome scan in Eastern Quebec families. Mol Psychiatry 10(5):486-99.

McAuley EZ, Fullerton JM, Blair IP, Donald JA, Mitchell PB, Schofield PR. 2009. Association between the serotonin 2A receptor gene and bipolar affective disorder in an Australian cohort. Psychiatr Genet.

McClung CA. 2007. Circadian genes, rhythms and the biology of mood disorders. Pharmacol Ther 114(2):222-32.

McGrath CL, Glatt SJ, Sklar P, Le-Niculescu H, Kuczenski R, Doyle AE, Biederman J, Mick E, Faraone SV, Niculescu AB and others. 2009. Evidence for genetic association of RORB with bipolar disorder. BMC Psychiatry 9:70.

McInnes LA, Escamilla MA, Service SK, Reus VI, Leon P, Silva S, Rojas E, Spesny M, Baharloo S, Blankenship K and others. 1996. A complete genome screen for genes predisposing to severe bipolar disorder in two Costa Rican pedigrees. Proc Natl Acad Sci U S A 93(23):13060-5.

Middleton FA, Pato CN, Gentile KL, McGann L, Brown AM, Trauzzi M, Diab H, Morley CP, Medeiros H, Macedo A and others. 2005. Gene expression analysis of peripheral blood leukocytes from discordant sib-pairs with schizophrenia and bipolar disorder reveals points of convergence between genetic and functional genomic approaches. Am J Med Genet B Neuropsychiatr Genet 136(1):12-25.

Millar JK, Mackie S, Clapcote SJ, Murdoch H, Pickard BS, Christie S, Muir WJ, Blackwood DH, Roder JC, Houslay MD and others. 2007. Disrupted in schizophrenia 1 and phosphodiesterase 4B: towards an understanding of psychiatric illness. J Physiol 584(Pt 2):401-5.

Morissette J, Villeneuve A, Bordeleau L, Rochette D, Laberge C, Gagne B, Laprise C, Bouchard G, Plante M, Gobeil L and others. 1999. Genome-wide search for linkage of bipolar affective disorders in a very large pedigree derived from a homogeneous population in quebec points to a locus of major effect on chromosome 12q23-q24. Am J Med Genet 88(5):567-87.

Nakatani N, Hattori E, Ohnishi T, Dean B, Iwayama Y, Matsumoto I, Kato T, Osumi N, Higuchi T, Niwa S and others. 2006. Genome-wide expression analysis detects eight genes with robust alterations specific to bipolar I disorder: relevance to neuronal network perturbation. Hum Mol Genet 15(12):1949-62.

Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL. 2002. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am J Hum Genet 71(3):651-5.

Niculescu A, Segal D, Kuczenski R, Barrett T, Hauger R, Kelsoe J. 2000a. Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. Physiological Genomics 4(1):83-91.

Niculescu AB, 3rd. 2006. Polypharmacy in oligopopulations: what psychiatric genetics can teach biological psychiatry. Psychiatr Genet 16(6):241-4.

Niculescu AB, 3rd, Kelsoe JR. 2001. Convergent functional genomics: application to bipolar disorder. Ann Med 33(4):263-71.

Niculescu AB, 3rd, Schork NJ, Salomon DR. 2009. Mindscape: A convergent perspective on life, mind, consciousness and happiness. J Affect Disord.

Niculescu AB, 3rd, Segal DS, Kuczenski R, Barrett T, Hauger RL, Kelsoe JR. 2000b. Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. Physiol Genomics 4(1):83-91.

Niculescu AB, Le-Niculescu H. Convergent Functional Genomics: what we have learned and can learn about genes, pathways, and mechanisms. Neuropsychopharmacology 35(1):355-6.

Niculescu AB, Lulow LL, Ogden CA, Le-Niculescu H, Salomon DR, Schork NJ, Caligiuri MP, Lohr JB. 2006. PhenoChipping of psychotic disorders: A novel approach for deconstructing and quantitating psychiatric phenotypes. Am J Med Genet B Neuropsychiatr Genet 141(6):653-62.

Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, McElroy SL, Keck PE, Jr., Schork NJ, Kelsoe JR. 2006. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 141(3):234-41.

Novak G, Seeman P, Tallerico T. 2006. Increased expression of calcium/calmodulin-dependent protein kinase IIbeta in frontal cortex in schizophrenia and depression. Synapse 59(1):61-8.

Numata S, Iga J, Nakataki M, Tayoshi S, Taniguchi K, Sumitani S, Tomotake M, Tanahashi T, Itakura M, Kamegaya Y and others. 2009. Gene expression and association analyses of the phosphodiesterase 4B (PDE4B) gene in major depressive

disorder in the Japanese population. Am J Med Genet B Neuropsychiatr Genet 150B(4):527-34.

Nunes PV, Forlenza OV, Gattaz WF. 2007. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. Br J Psychiatry 190:359-60.

O'Donovan MC, Craddock NJ, Owen MJ. 2009. Genetics of psychosis; insights from views across the genome. Hum Genet 126(1):3-12.

Ogden CA, Rich ME, Schork NJ, Paulus MP, Geyer MA, Lohr JB, Kuczenski R, Niculescu AB. 2004. Candidate genes, pathways and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. Mol Psychiatry 9(11):1007-29.

Oh ES, Savonenko AV, King JF, Fangmark Tucker SM, Rudow GL, Xu G, Borchelt DR, Troncoso JC. 2008. Amyloid precursor protein increases cortical neuron size in transgenic mice. Neurobiol Aging.

Padmos RC, Hillegers MH, Knijff EM, Vonk R, Bouvy A, Staal FJ, de Ridder D, Kupka RW, Nolen WA, Drexhage HA. 2008. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. Arch Gen Psychiatry 65(4):395-407.

Park N, Juo SH, Cheng R, Liu J, Loth JE, Lilliston B, Nee J, Grunn A, Kanyas K, Lerer B and others. 2004. Linkage analysis of psychosis in bipolar pedigrees suggests novel putative loci for bipolar disorder and shared susceptibility with schizophrenia. Mol Psychiatry 9(12):1091-9.

Parlapani E, Schmitt A, Erdmann A, Bernstein HG, Breunig B, Gruber O, Petroianu G, von Wilmsdorff M, Schneider-Axmann T, Honer W and others. 2009. Association between myelin basic protein expression and left entorhinal cortex pre-alpha cell layer disorganization in schizophrenia. Brain Res.

Partonen T, Treutlein J, Alpman A, Frank J, Johansson C, Depner M, Aron L, Rietschel M, Wellek S, Soronen P and others. 2007. Three circadian clock genes Per2, Arntl, and Npas2 contribute to winter depression. Ann Med 39(3):229-38.

Paynter NP, Chasman DI, Pare G, Buring JE, Cook NR, Miletich JP, Ridker PM. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA 303(7):631-7.

Pennington K, Beasley CL, Dicker P, Fagan A, English J, Pariante CM, Wait R, Dunn MJ, Cotter DR. 2007. Prominent synaptic and metabolic abnormalities revealed by proteomic analysis of the dorsolateral prefrontal cortex in schizophrenia and bipolar disorder. Mol Psychiatry.

Perlis RH, Purcell S, Fagerness J, Kirby A, Petryshen TL, Fan J, Sklar P. 2008. Family-based association study of lithium-related and other candidate genes in bipolar disorder. Arch Gen Psychiatry 65(1):53-61.

Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 2008. Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. Mol Psychiatry 13(7):654, 709-16.

Pillai A. 2008. Decreased expression of Sprouty2 in the dorsolateral prefrontal cortex in schizophrenia and bipolar disorder: a correlation with BDNF expression. PLoS ONE 3(3):e1784.

Pletnikov MV, Xu Y, Ovanesov MV, Kamiya A, Sawa A, Ross CA. 2007. PC12 cell model of inducible expression of mutant DISC1: new evidence for a dominant-negative mechanism of abnormal neuronal differentiation. Neurosci Res 58(3):234-44.

Potash JB, Buervenich S, Cox NJ, Zandi PP, Akula N, Steele J, Rathe JA, Avramopoulos D, Detera-Wadleigh SD, Gershon ES and others. 2008. Gene-based SNP mapping of a psychotic bipolar affective disorder linkage region on 22q12.3: association with HMG2L1 and TOM1. Am J Med Genet B Neuropsychiatr Genet 147B(1):59-67.

Potash JB, Zandi PP, Willour VL, Lan TH, Huo Y, Avramopoulos D, Shugart YY, MacKinnon DF, Simpson SG, McMahon FJ and others. 2003. Suggestive linkage to chromosomal regions 13q31 and 22q12 in families with psychotic bipolar disorder. Am J Psychiatry 160(4):680-6.

Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460(7256):748-52.

Radhakrishna U, Senol S, Herken H, Gucuyener K, Gehrig C, Blouin JL, Akarsu NA, Antonarakis SE. 2001. An apparently dominant bipolar affective disorder (BPAD) locus on chromosome 20p11.2-q11.2 in a large Turkish pedigree. Eur J Hum Genet 9(1):39-44.

Ranade SS, Mansour H, Wood J, Chowdari KV, Brar LK, Kupfer DJ, Nimgaonkar VL. 2003. Linkage and association between serotonin 2A receptor gene polymorphisms and bipolar I disorder. Am J Med Genet B Neuropsychiatr Genet 121B(1):28-34.

Rice TK, Schork NJ, Rao DC. 2008. Methods for handling multiple testing. Adv Genet 60:293-308.

Ripperger JA, Schibler U. 2006. Rhythmic CLOCK-BMAL1 binding to multiple E-box motifs drives circadian Dbp transcription and chromatin transitions. Nat Genet 38(3):369-74.

Rodd ZA, Bertsch BA, Strother WN, Le-Niculescu H, Balaraman Y, Hayden E, Jerome RE, Lumeng L, Nurnberger JI, Jr., Edenberg HJ and others. 2007. Candidate genes, pathways and mechanisms for alcoholism: an expanded convergent functional genomics approach. Pharmacogenomics J 7(4):222-56.

Rohn TT, Vyas V, Hernandez-Estrada T, Nichol KE, Christie LA, Head E. 2008. Lack of pathology in a triple transgenic mouse model of Alzheimer's disease after overexpression of the anti-apoptotic protein Bcl-2. J Neurosci 28(12):3051-9.

Ryan MM, Lockstone HE, Huffaker SJ, Wayland MT, Webster MJ, Bahn S. 2006. Gene expression analysis of bipolar disorder reveals downregulation of the ubiquitin cycle and alterations in synaptic genes. Mol Psychiatry 11(10):965-78.

Sawamura N, Sawamura-Yamamoto T, Ozeki Y, Ross CA, Sawa A. 2005. A form of DISC1 enriched in nucleus: altered subcellular distribution in orbitofrontal cortex in psychosis and substance/alcohol abuse. Proc Natl Acad Sci U S A 102(4):1187-92.

Schosser A, Gaysina D, Cohen-Woods S, Chow PC, Martucci L, Craddock N, Farmer A, Korszun A, Gunasinghe C, Gray J and others. 2009. Association of DISC1 and TSNAX genes and affective disorders in the depression case-control (DeCC) and bipolar affective case-control (BACCS) studies. Mol Psychiatry.

Schulze TG, Chen YS, Badner JA, McInnis MG, DePaulo JR, Jr., McMahon FJ. 2003. Additional, physically ordered markers increase linkage signal for bipolar disorder on chromosome 18q22. Biol Psychiatry 53(3):239-43.

Schulze TG, Detera-Wadleigh SD, Akula N, Gupta A, Kassem L, Steele J, Pearl J, Strohmaier J, Breuer R, Schwarz M and others. 2009. Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder. Mol Psychiatry 14(5):487-91.

Segurado R, Detera-Wadleigh SD, Levinson DF, Lewis CM, Gill M, Nurnberger JI, Jr., Craddock N, DePaulo JR, Baron M, Gershon ES and others. 2003. Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. Am J Hum Genet 73(1):49-62.

Sen S, Duman R, Sanacora G. 2008. Serum Brain-Derived Neurotrophic Factor, Depression, and Antidepressant Medications: Meta-Analyses and Implications. Biol Psychiatry.

Sequeira A, Klempan T, Canetti L, ffrench-Mullen J, Benkelfat C, Rouleau GA, Turecki G. 2007. Patterns of gene expression in the limbic system of suicides with and without major depression. Mol Psychiatry 12(7):640-55.

Shi J, Wittke-Thompson JK, Badner JA, Hattori E, Potash JB, Willour VL, McMahon FJ, Gershon ES, Liu C. 2008. Clock genes may influence bipolar disorder susceptibility and dysfunctional circadian rhythm. Am J Med Genet B Neuropsychiatr Genet.

Sklar P, Gabriel SB, McInnis MG, Bennett P, Lim YM, Tsan G, Schaffner S, Kirov G, Jones I, Owen M and others. 2002. Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. Mol Psychiatry 7(6):579-93.

Sklar P, Pato MT, Kirby A, Petryshen TL, Medeiros H, Carvalho C, Macedo A, Dourado A, Coelho I, Valente J and others. 2004. Genome-wide scan in Portuguese Island families identifies 5q31-5q35 as a susceptibility locus for schizophrenia and psychosis. Mol Psychiatry 9(2):213-8.

Sklar P, Smoller JW, Fan J, Ferreira MAR, Perlis RH, Chambert K, Nimgaonkar VL, McQueen MB, Faraone SV, Kirby A and others. 2008. Whole-genome association study of bipolar disorder. Molecular Psychiatry 13(6):558-569.

Smith EN, Bloss CS, Badner JA, Barrett T, Belmonte PL, Berrettini W, Byerley W, Coryell W, Craig D, Edenberg HJ and others. 2009. Genome-wide association study of bipolar disorder in European American and African American individuals. Mol Psychiatry 14(8):755-63.

Sokolov BP, Polesskaya OO, Uhl GR. 2003. Mouse brain gene expression changes after acute and chronic amphetamine. J Neurochem 84(2):244-52.

Stumpf MP, Thorne T, de Silva E, Stewart R, An HJ, Lappe M, Wiuf C. 2008. Estimating the size of the human interactome. Proc Natl Acad Sci U S A 105(19):6959-64.

Sun X, Steffens DC, Au R, Folstein M, Summergrad P, Yee J, Rosenberg I, Mwamburi DM, Qiu WQ. 2008. Amyloid-associated depression: a prodromal depression of Alzheimer disease? Arch Gen Psychiatry 65(5):542-50.

Szczepankiewicz A, Rybakowski JK, Suwalska A, Skibinska M, Leszczynska-Rodziewicz A, Dmitrzak-Weglarz M, Czerski PM, Hauser J. 2006. Association study of the

glycogen synthase kinase-3beta gene polymorphism with prophylactic lithium response in bipolar patients. World J Biol Psychiatry 7(3):158-61.

Takahashi JS, Shimomura K, Kumar V. 2008. Searching for genes underlying behavior: lessons from circadian rhythms. Science 322(5903):909-12.

Tan HY, Callicott JH, Weinberger DR. 2008. Intermediate phenotypes in schizophrenia genetics redux: is it a no brainer? Mol Psychiatry 13(3):233-8.

Thomson PA, Christoforou A, Morris SW, Adie E, Pickard BS, Porteous DJ, Muir WJ, Blackwood DH, Evans KL. 2007. Association of Neuregulin 1 with schizophrenia and bipolar disorder in a second cohort from the Scottish population. Mol Psychiatry 12(1):94-104.

Thomson PA, Wray NR, Millar JK, Evans KL, Hellard SL, Condie A, Muir WJ, Blackwood DH, Porteous DJ. 2005. Association between the TRAX/DISC locus and both bipolar disorder and schizophrenia in the Scottish population. Mol Psychiatry 10(7):657-68, 616.

Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, Starkey M, Webster MJ, Yolken RH, Bahn S. 2003. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 362(9386):798-805.

Tochigi M, Iwamoto K, Bundo M, Sasaki T, Kato N, Kato T. 2008. Gene expression profiling of major depression and suicide in the prefrontal cortex of postmortem brains. Neurosci Res 60(2):184-91.

Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB. 2005. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. Biol Psychiatry 57(3):252-60.

Uher R, Huezo-Diaz P, Perroud N, Smith R, Rietschel M, Mors O, Hauser J, Maier W, Kozel D, Henigsberg N and others. 2009. Genetic predictors of response to antidepressants in the GENDEP project. Pharmacogenomics J.

van der Veen DR, Minh NL, Gos P, Arneric M, Gerkema MP, Schibler U. 2006. Impact of behavior on central and peripheral circadian clocks in the common vole Microtus arvalis, a mammal with ultradian rhythms. Proc Natl Acad Sci U S A 103(9):3393-8.

van West D, Van Den Eede F, Del-Favero J, Souery D, Norrback KF, Van Duijn C, Sluijs S, Adolfsson R, Mendlewicz J, Deboutte D and others. 2006. Glucocorticoid receptor gene-based SNP analysis in patients with recurrent major depression. Neuropsychopharmacology 31(3):620-7.

Vawter MP, Thatcher L, Usen N, Hyde TM, Kleinman JE, Freed WJ. 2002. Reduction of synapsin in the hippocampus of patients with bipolar disorder and schizophrenia. Mol Psychiatry 7(6):571-8.

Vawter MP, Tomita H, Meng F, Bolstad B, Li J, Evans S, Choudary P, Atz M, Shao L, Neal C and others. 2006. Mitochondrial-related gene expression changes are sensitive to agonal-pH state: implications for brain disorders. Mol Psychiatry.

Wager-Smith K, Kay SA. 2000. Circadian rhythm genetics: from flies to mice to humans. Nat Genet 26(1):23-7.

Wakabayashi Y, Uchida S, Funato H, Matsubara T, Watanuki T, Otsuki K, Fujimoto M, Nishida A, Watanabe Y. 2008. State-dependent changes in the expression levels of NCAM-140 and L1 in the peripheral blood cells of bipolar disorders, but not in the

major depressive disorders. Prog Neuropsychopharmacol Biol Psychiatry 32(5):1199-205.

Walss-Bass C, Raventos H, Montero AP, Armas R, Dassori A, Contreras S, Liu W, Medina R, Levinson DF, Pereira M and others. 2006. Association analyses of the neuregulin 1 gene with schizophrenia and manic psychosis in a Hispanic population. Acta Psychiatr Scand 113(4):314-21.

Wirz-Justice A. 2006. Biological rhythm disturbances in mood disorders. Int Clin Psychopharmacol 21 Suppl 1:S11-5.

Wirz-Justice A, Terman M, Oren DA, Goodwin FK, Kripke DF, Whybrow PC, Wisner KL, Wu JC, Lam RW, Berger M and others. 2004. Brightening depression. Science 303(5657):467-9.

Wong ML, Dong C, Maestre-Mesa J, Licinio J. 2008. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. Mol Psychiatry 13(8):800-12.

Wong ML, Whelan F, Deloukas P, Whittaker P, Delgado M, Cantor RM, McCann SM, Licinio J. 2006. Phosphodiesterase genes are associated with susceptibility to major depression and antidepressant treatment response. Proc Natl Acad Sci U S A 103(41):15124-9.

Xing G, Russell S, Hough C, O'Grady J, Zhang L, Yang S, Zhang LX, Post R. 2002. Decreased prefrontal CaMKII alpha mRNA in bipolar illness. Neuroreport 13(4):501-5.

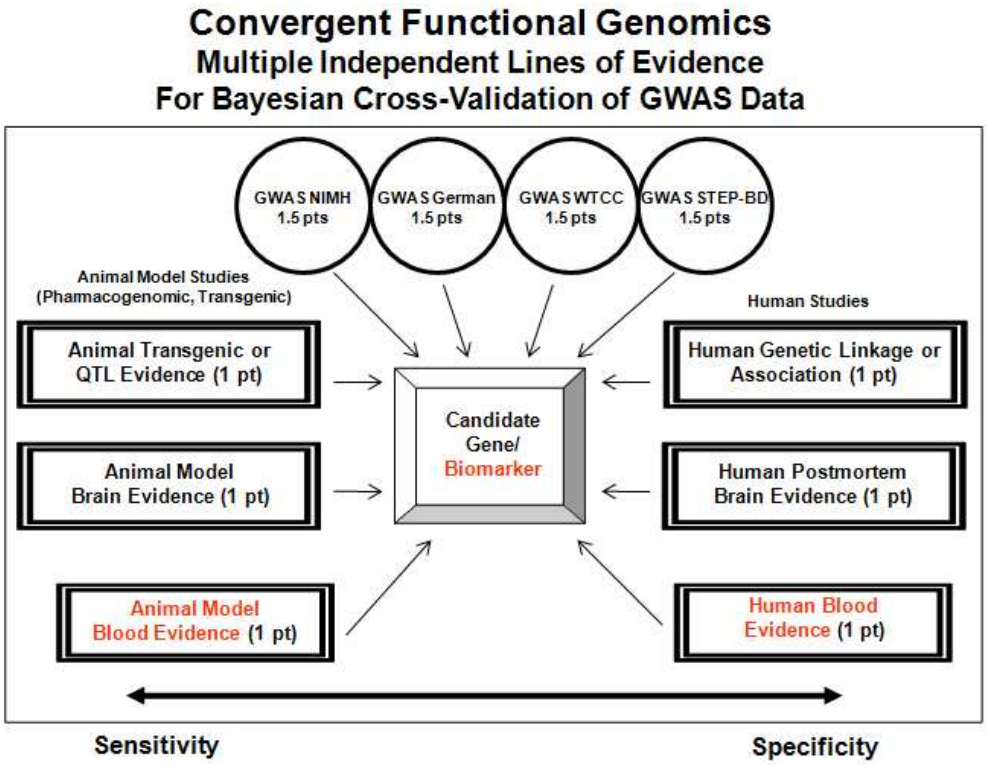
Yang S, Van Dongen HP, Wang K, Berrettini W, Bucan M. 2008. Assessment of circadian function in fibroblasts of patients with bipolar disorder. Mol Psychiatry.

Zamvil S, Nelson P, Trotter J, Mitchell D, Knobler R, Fritz R, Steinman L. 1985. T-cell clones specific for myelin basic protein induce chronic relapsing paralysis and demyelination. Nature 317(6035):355-8.

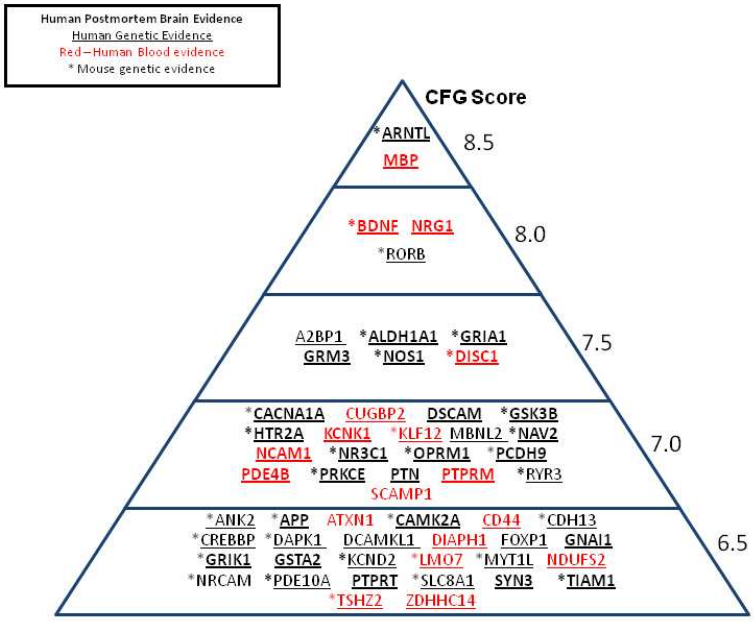
Zhang EE, Liu AC, Hirota T, Miraglia LJ, Welch G, Pongsawakul PY, Liu X, Atwood A, Huss JW, 3rd, Janes J and others. 2009. A genome-wide RNAi screen for modifiers of the circadian clock in human cells. Cell 139(1):199-210.

Zubenko GS, Hughes HB, Stiffler JS, Zubenko WN, Kaplan BB. 2002. Genome survey for susceptibility loci for recurrent, early-onset major depression: results at 10cM resolution. Am J Med Genet 114(4):413-22.

Zubenko GS, Maher B, Hughes HB, 3rd, Zubenko WN, Stiffler JS, Kaplan BB, Marazita ML. 2003. Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. Am J Med Genet B Neuropsychiatr Genet 123(1):1-18.

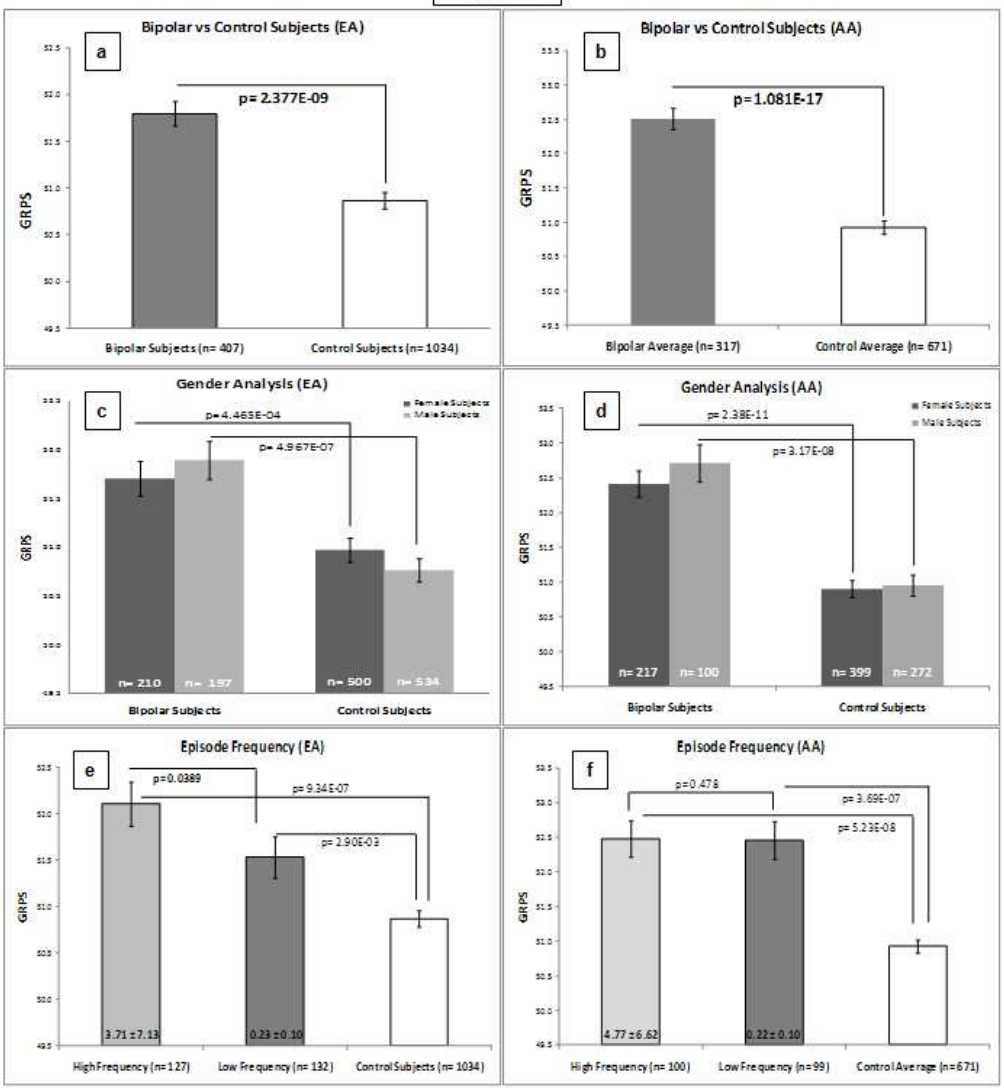


232x184mm (72 x 72 DPI)



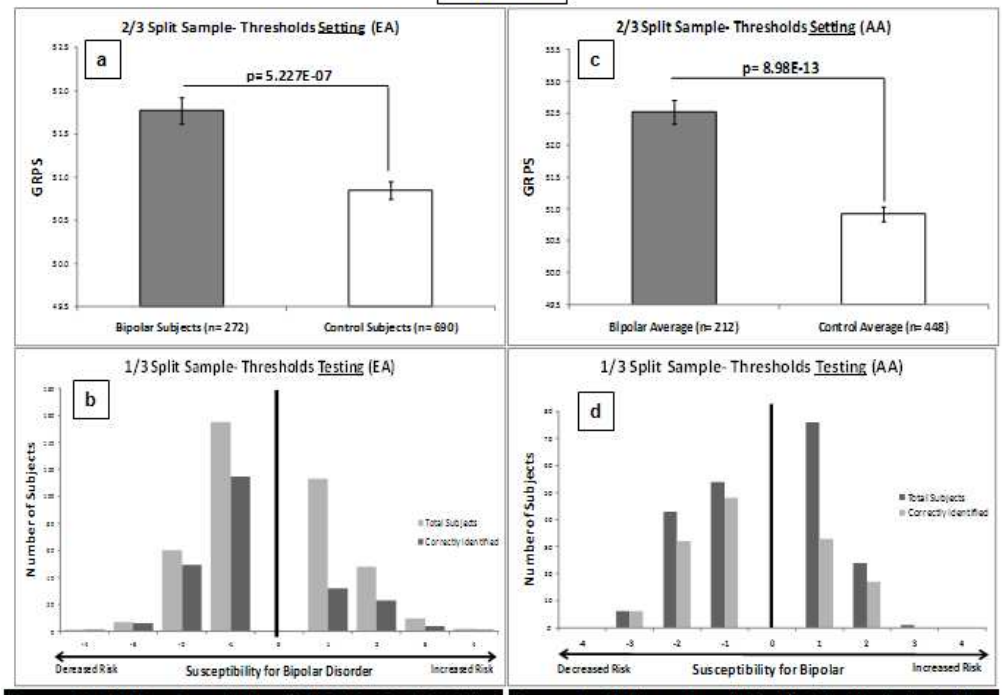
254x190mm (96 x 96 DPI)

Figure 3.



243x274mm (72 x 72 DPI)

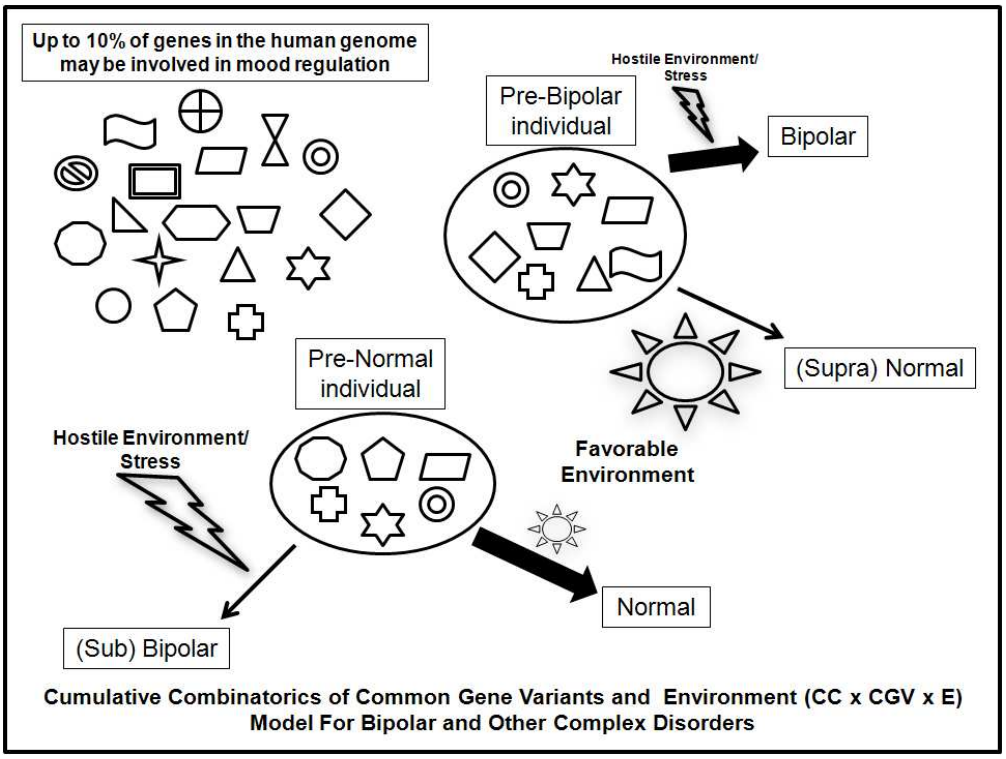
Figure 4.



Category	Total Subjects	Correctly Identified	Positive Predictive Value
-4	1	1	100.00%
-3	7	6	85.71%
-2	60	49	81.67%
-1	155	115	74.19%
0	83		
1	113	32	28.32%
2	48	23	47.92%
3	10	4	40.00%
4	2	1	50.00%

Category	Total Subjects	Correctly Identified	Positive Predictive Value
-4	0		
-3	6	6	100.00%
-2	43	32	74.42%
-1	54	48	88.89%
0	124		
1	76	33	43.42%
2	24	17	70.83%
3	1	0	0.00%
4	0		

240x229mm (72 x 72 DPI)



Cumulative Combinatorics of Common Gene Variants and Environment (CC x CGV x E) Model For Bipolar and Other Complex Disorders

340x256mm (72 x 72 DPI)

Supplementary Information

Figure 1S. CFG of GWAS for Bipolar Disorder -cross-matching genetic with gene expression data

3 GWAS (WTCC, NIMH, German)	1565 genes
+ Step-BD	+92 genes
+ GAIN-BP	+169 genes
Total	1826 genes

Up to 10% of the genome may be involved directly or indirectly in mood regulation

Figure 2S: Gene size vs. CFG score.

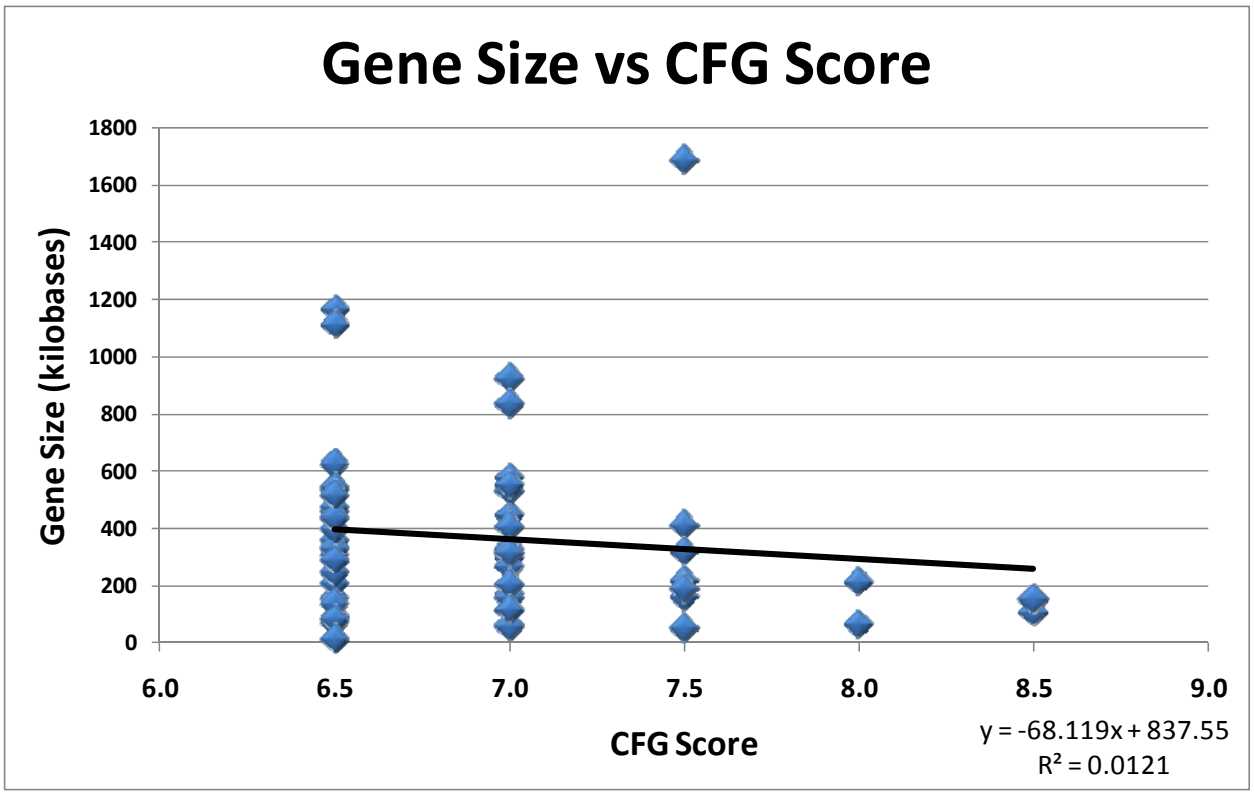


Figure 3S: Two-Dimensional Genetic Risk Prediction Matrix

Genetic Risk Prediction Panel																	
	Subject	Gene 1								--	--	--	Gene 56				Genetic Risk Prediction Score (0-100) (sum of allele scores/ number of alleles) x 100
		SNP1		SNP2		SNP3		SNP4		--	--	--	SNP1		SNP2		
		Allele 1	Allele 2	Allele 1	Allele 2	Allele 1	Allele 2	Allele 1	Allele 2	--	--	--	Allele 1	Allele 2	Allele 1	Allele 2	
Bipolar	1	1	1	1	0	1	0	0	1	--	--	--	0	1	1	0	51.709
	2	1	1	0	1	1	1	1	1	--	--	--	1	0	1	1	57.265
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	406	0	1	1	1	0	0	1	0	--	--	--	0	0	0	0	55.128
	407	1	0	0	1	1	1	1	1	--	--	--	1	0	1	1	55.508
Control	1	0	1	0	0	1	1	0	1	--	--	--	1	1	1	1	50.000
	2	1	0	0	1	1	0	0	0	--	--	--	1	0	1	0	47.863
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	1033	0	0	1	0	0	1	0	1	--	--	--	0	1	0	1	49.576
	1034	0	0	0	0	1	1	0	1	--	--	--	1	1	1	1	46.186

Table 1S. Demographics of the randomly split cohorts from GAIN-BP. NA- not available.

	European American (EA)				African American (AA)			
	2/3 Split Sample		1/3 Split Sample		2/3 Split Sample		1/3 Split Sample	
	Bipolar	Control	Bipolar	Control	Bipolar	Control	Bipolar	Control
Number of Subjects (males: females)	272 (133: 139)	690 (356: 334)	135 (64: 71)	344 (178: 166)	212 (67: 145)	448 (182: 266)	105 (33: 72)	223 (90: 133)
Age mean years (SD) range	43.32 (13.62) 20 to 82	51.41 (17.67) 18 to 90	43.19 (13.05) 21 to 77	53.94 (17.27) 18 to 84	42.92 (10.41) 17 to 70	NA	39.91 (10.83) 19 to 61	NA
Episode Frequency mean (SD) range	1.50 (5.04) 0.06 to 42.60	--	1.49 (2.20) 0.06 to 6.97	--	2.01 (4.94) 0.02 to 50.05	--	1.72 (2.65) 0.02 to 14.71	--

L. Suppl. Note. Members of the Bipolar Disorder Genetics (BiGS) Consortium

E N Smith[1,2,24], C S Bloss[1,3,24], J A Badner[4], T Barrett[5], P L Belmonte[6], W Berrettini[7], W Byerley[8], W Coryell[9], D Craig[10], H J Edenberg[11,12], E Eskin[13], T Foroud[12], E S Gershon[4], T A Greenwood[14], M Hipolito[15], D L Koller[16], W B Lawson[15], C Liu[4], F Lohoff[7], M G McInnis[17], F J McMahon[18], D B Mirel[19], S S Murray[1,2,3], C Nievergelt[14], J Nurnberger[16], E A Nwulia[15], J Paschall[20], J B Potash[6], J Rice[21], T G Schulze[18], W Scheftner[22], C Panganiban[10], N Zaitlen[13], P P Zandi[6], S Zöllner[17], N J Schork[1,2,3], J R Kelsoe[14,23]

[1]Scripps Genomic Medicine, Scripps Translational Science Institute, La Jolla, CA, USA; [2]Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, USA; [3]Scripps Health, La Jolla, CA, USA; [4]Department of Psychiatry, University of Chicago, Chicago, IL, USA; [5]Department of Psychiatry, Portland VA Medical Center, Portland, OR, USA; [6]Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD, USA; [7]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; [8]Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA; [9]Department of Psychiatry, University of Iowa, Iowa City, IA, USA; [10]Neurogenomics Division, The Translational Genomics Research Institute, Phoenix, AZ, USA; [11]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA; [12]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA; [13]Department of Computer Science, University of California, Los Angeles, Los Angeles, CA, USA; [14]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA; [15]Department of Psychiatry, Howard University, Washington, DC, USA; [16]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA;[17]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA; [18]Genetic Basis of Mood and Anxiety Disorders Unit, National Institute of Mental Health Intramural Research Program, National Institutes of Health, US Department of Health and Human Services, Bethesda, MD, USA; [19]Broad Institute of Harvard University and Massachusetts Institute of Technology, Cambridge, MA, USA; [20]National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD, USA; [21]Division of Biostatistics, Washington University, St Louis, MO, USA; [22]Department of Psychiatry, Rush University, Chicago, IL, USA; [23]Department of Psychiatry, VA San Diego Healthcare System, La Jolla, CA, USA