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Rapid Publication

Phenomic, Convergent Functional Genomic, and Biomarker Studies in a Stress-Reactive Genetic Animal Model of Bipolar Disorder and Co-Morbid Alcoholism

H. Le-Niculescu,[1,2,3] M.J. McFarland,[1,2,3] C.A. Ogden,[4] Y. Balaraman,[1,2,3] S. Patel,[1,3] J. Tan,[1,3] Z.A. Rodd,[3] M. Paulus,[4] M.A. Geyer,[4] H.J. Edenberg,[5] S.J. Glatt,[6] S.V. Faraone,[6] J.I. Nurnberger,[3] R. Kuczenski,[4] M.T. Tsuang,[4] and A.B. Niculescu[1,2,3]*

[1]*Laboratory of Neurophenomics, Indiana University School of Medicine, Indianapolis, Indiana*
[2]*INBRAIN, Indiana University School of Medicine, Indianapolis, Indiana*
[3]*Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, Indiana*
[4]*Department of Psychiatry, UC San Diego, La Jolla, California*
[5]*Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana*
[6]*Department of Psychiatry, SUNY Upstate Medical University, Syracuse, New York*

We had previously identified the clock gene D-box binding protein (Dbp) as a potential candidate gene for bipolar disorder and for alcoholism, using a Convergent Functional Genomics (CFG) approach. Here we report that mice with a homozygous deletion of DBP have lower locomotor activity, blunted responses to stimulants, and gain less weight over time. In response to a chronic stress paradigm, these mice exhibit a diametric switch in these phenotypes. DBP knockout mice are also activated by sleep deprivation, similar to bipolar patients, and that activation is prevented by treatment with the mood stabilizer drug valproate. Moreover, these mice show increased alcohol intake following exposure to stress. Microarray studies of brain and blood reveal a pattern of gene expression changes that may explain the observed phenotypes. CFG analysis of the gene expression changes identified a series of novel candidate genes and blood biomarkers for bipolar disorder, alcoholism, and stress reactivity.

KEY WORDS: clock gene; mouse; knockout; genomics; brain; biomarkers; stress; bipolar disorder; alcoholism

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INTRODUCTION

Circadian clock genes are compelling candidates for involvement in bipolar disorders, especially the core clinical phenomenology of cycling and switching from depression to mania [Bunney and Bunney, 2000; Niculescu et al., 2000; Wager-Smith and Kay, 2000; Niculescu and Kelsoe, 2001; Kelsoe and Niculescu, 2002; Lenox et al., 2002; Hasler et al., 2006; Wirz-Justice, 2006; McClung, 2007]. Circadian rhythm and sleep abnormalities have long been described in bipolar disorder-excessive sleep in the depressive phase, reduced need for sleep in the manic phase [Bauer et al., 2006]. Sleep deprivation is one of the more powerful and rapid acting treatment modalities for severe depression, and can lead to precipitation of manic episodes in bipolar patients [Wirz-Justice et al., 2004]. Clock genes expression levels (Per1, Per2, and Dbp) have been reported to be changed by sleep deprivation in rodents [Wisor et al., 2002]. Moreover, 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; association between polymorphisms in the clock genes Per2, Arntl and Npas2 and SAD have previously been reported [Johansson et al., 2003; Partonen et al., 2007]. Also, lithium, the gold standard treatment for bipolar disorder, has been implicated in the regulation of the circadian clock [Welsh and Moore-Ede, 1990; Yin et al., 2006]. Overall there is a convincing amount of evidence that circadian clock genes merit investigation for their potential role in bipolar disorder. Indeed, a recent elegant report describes lithium-sensitive, manic-like behavior in mice with a disrupted clock gene as compared to wild-type controls [Roybal et al., 2007].

We have previously described the identification of clock gene D-box binding protein (Dbp) as a potential candidate gene for bipolar disorder [Niculescu et al., 2000], using a Bayesian-like approach called Convergent Functional Genomics (CFG) [Niculescu et al., 2000; Ogden et al., 2004; Bertsch et al.,

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*Correspondence to: A.B. Niculescu, Institute of Psychiatric Research, 791 Union Drive, Indianapolis, IN 46202.
E-mail: anicules@iupui.edu

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2005; Rodd et al., 2007], that cross-matches animal model gene expression data with human genetic linkage/association data, as well as human tissue data. The integration of multiple independent lines of evidence, each by itself lacking sufficient discriminatory power, leads to the identification of high probability candidate genes, pathways and mechanisms for the disease of interest. In a model relevant to bipolar disorder, using a stimulant to mimic aspects of the illness, Dbp was changed in expression by acute methamphetamine treatment in rat pre-frontal cortex (PFC) [Niculescu et al., 2000], and mapped near a human genetic linkage locus for bipolar disorder [Morissette et al., 1999] and for depression [Zubenko et al., 2002] on chromosome 19q13. Subsequently, Dbp was also reported changed in expression by acute and chronic amphetamine treatments in mice [Sokolov et al., 2003b]. Moreover, DBP knockout (KO) mice have abnormal circadian and homeostatic aspects of sleep regulation [Franken et al., 2000]. Subsequent work carried out by us using an expanded CFG approach in a mouse pharmacogenomic model for bipolar disorder identified a series of other clock genes (Arntl/Bmal1, Cry2, Csnk1d, and Ccr4/nocturnin), as potential bipolar candidate genes [Ogden et al., 2004]. Recently, two reports have shown some suggestive association for one of these genes, Arntl/Bmal1, in human bipolar samples [Mansour et al., 2006; Nievergelt et al., 2006]. Arntl/Bmal1 is upstream of Dbp in the circadian clock intracellular molecular machinery, driving the transcription of Dbp [Ripperger and Schibler, 2006; van der Veen et al., 2006]. More recently, we have identified Dbp as a gene differentially expressed in alcohol-preferring (P) versus alcohol non-preferring (NP) rat strains [Rodd et al., 2007]. Dbp is increased in P rats vs. NP rats in the frontal cortex (FC), which suggests the hypothesis that lower levels or absence of Dbp, such as in DBP KO mice, might be associated with decreased consumption of alcohol. Of note, there is a high degree of co-morbidity of alcoholism with depression [Kuo et al., 2006a; Schuckit et al., 2006] as well as with bipolar disorder [Nurnberger et al., 2004].

As a way of further studying and validating Dbp as a potential molecular underpinning of bipolar and related disorders, we conducted behavioral and gene expression studies in mice with a constitutive homozygous deletion of Dbp (DBP KO mice). Moreover, we also conducted blood gene expression studies, to identify genes that change concomitantly in brain and blood, and thus may represent strong candidate biomarkers [Le-Niculescu et al., 2007b].

MATERIALS AND METHODS

Mouse Colony

The generation of transgenic mice carrying DBP KO has been described in detail previously [Lopez-Molina et al., 1997]. The 129/Ola *DBP* mice, carrying a null allele for the DBP gene, were received from the Schibler group (University of Geneva, Switzerland). The mice were re-derived on a C57/BL6 background at the UCSD Transgenic Mouse and Gene Targeting Core. Mice were subsequently maintained on this mixed background by heterozygote breeding, as described below, and not further back-crossed to C57/BL6. Storage and breeding of the mice took place at the San Diego VA Medical Center and subsequently at the Indiana University School of Medicine in Association for Assessment and Accreditation of Laboratory Animal Care-approved animal facilities, which met all state and federal requirements for animal care.

DBP (+/−) heterozygous (HET) mice were bred to obtain mixed littermate cohorts of wild-type (+/+) (WT), HET and DBP (−/−) KO mice. Mouse pups were weaned at 21 days and housed in groups of two to four (segregated by sex), in a temperature- and light-controlled colony on reverse cycle (lights on at 22:00 hr, lights off at 10:00 hr), with food and water available ad libitum. DNA for genotyping was extracted by tail digestion with a Qiagen Dneasy Tissue kit, following the protocol for animal tissue (Qiagen, Valencia, CA). We used the following three primers for genotyping by PCR:

Dbp forward: TTCTTTGGGCTTGCTGTTTCCCTGCAGA
Dbp reverse: GCAAAGCTCCTTTCTTTGCGAGAAGTGC (WT allele)
lacZ reverse: GTGCTGCAAGGCGATTAAGTTGGGTAAC (KO allele)

Only WT and KO's were used for experiments. Behavioral and gene expression experiments were carried out with mice 8–12 weeks of age.

Drugs

Mice were administered saline, valproate (200 mg/kg), or methamphetamine (10 mg/kg) acutely by intra-peritoneal injection.

Locomotor Pattern Testing

A SMART II Video Tracker (VT) system (San Diego Instruments, San Diego, CA) under normal light was used to track movement of mice immediately after drug administration and again 24 hr later. After injection, mice were placed in the lower-right-hand corner of one of four adjacent, $41 \times 41 \times 34$-cm^3 enclosures. Mice had no physical contact with other mice during testing. Each enclosure has nine pre-defined areas, that is, center area, corner area, and wall area. The movements of the mice were recorded for 30 min.

Measures of overall locomotor activity were obtained and represented by the total distance traveled within and between each of the nine regions of the enclosure. Two categories of behavior were obtained. First, the amount of locomotor activity was assessed by using the total distance traveled in the open field in a 30-min interval. Second, the spatial scaling exponent, d, or spatial D, was obtained. Spatial D is a quantified measure of the geometric patterns of locomotor activity, as described in detail elsewhere [Paulus and Geyer, 1993]. Briefly, spatial d is a measure of the non-linear nature of an animal's locomotor movement and is quantified on a scale from 1 to 2; with d=1 indicating extremely linear movement and d=2 representing highly non-linear locomotor movement.

Data and Statistical Analysis

Two-way analyses of variance (ANOVAs) were used to compare total distance traveled and spatial d. Genotype and/or drug treatment were between-subjects variables, and time was a within-subjects variable. All computations were conducted with SPSS statistical software (SPSS, Inc., Chicago, IL).

Non-Stress (NST) Versus Stress (ST) Experiments

For the non-stress (NST) experiments, mice were group housed. For the stress (ST) experiments, mice were subjected to a chronic stress paradigm consisting of isolation (single housing) for 1 month, with an acute stressor (behavioral challenge tests) in Week 3. The behavioral challenge tests consisted of sequential administration of the forced swim test, tail flick test and tail suspension test (data not shown). At 4 weeks, mice were injected with either saline or methamphetamine. Locomotor activity was measured immediately after drug administration and again 24 hr later, immediately after which the brains were harvested for microarray studies.

Sleep Deprivation Experiments

Sleep deprivation studies consisted of light cycle changes, with no handling of animals involved, to avoid inducing non-sleep related handling stress confounds. Male DBP KO mice were used in the sleep deprivation experiments as follows: sleep deprived (SD) animals were removed from the standard housing room with a 12 hr off/12 hr on (reverse) light cycle and kept in a dark room overnight the night before the experiment. Non-sleep deprived (NSD) animals were kept in the housing room with the standard light cycle the night before the experiment to allow for a normal night's sleep. On the day of the experiment, all mice were injected with saline (to keep conditions comparable to all of our other behavioral experiments) and locomotor activity was measured immediately afterward with video tracking software. Following the video tracking experiment, animals were sacrificed and the blood of each individual mouse was collected for future biomarker microarray studies. In another series of experiments, sleep deprivation studies were performed as described above, with the addition of a valproic acid injection (200 mg/kg) to both the SD and NSD animals 24 hr before video tracking.

Alcohol Consumption Experiments

To create an alcohol free-choice drinking paradigm, both male and female, wild-type and DBP KO mice were placed in individual cages with both a bottle of water and a bottle of 10% ethanol. Fluid consumption from both bottles was monitored for a period of 30 days with an acute stressor (as described in *Non-Stressed vs. Stressed Experiments* above) at the end of the third week. To determine consumption, the weight of each bottle was recorded every 3 days, at which time the place of the two bottles in each cage was switched. Following 30 days of free-choice drinking the animals were injected with saline and their locomotor activity was assessed with video tracking software. After video tracking we harvested the brain and the blood of each animal for use in future microarray studies.

Clustering Analysis of Behavioral Data

GeneSpring version 7.2 was used (Agilent Technologies, Palo Alto, CA). Unsupervised two-way hierarchical clustering of normalized (Z-scored) behavioral data from open-field video tracking was carried out, using methodology previously described [Niculescu et al., 2006]. Cohen's d effect size was used to standardize the locomotor behavior data for both non-stressed and stressed DBP KO mice: $(M_1-M_2)/\sigma_{pooled}$ (M_1 is the average value from the designated DBP KO group for the locomotor measurement of interest. M_2 is the average value from the wild-type group for that same locomotor measurement, and σ_{pooled} is the standard deviation of all the values that went into calculating both M_1 and M_2). Clustering of standardized scores was performed with GeneSpring 7.2 software (Fig. 2d). To do a clustering of the scores for individual subjects, we calculated a modified Z-score, in which Z-score $= (X_1-M_2)/\sigma_{pooled}$ (X_1 is the individual score for the locomotor measure of interest, M_2 is the average value from the wild-type group for that same locomotor measurement, and σ_{pooled} is the standard deviation of all the values that went into calculating both M_1 and M_2; Fig. 2e).

RNA Extraction and Microarray Work

Following the 24-hr time-point behavioral test, mice were sacrificed by cervical dislocation. Behavioral testing and tissue harvesting were done at the same time of day in all experiments described in this article. The brains of the mice were harvested, stereotactically sliced, and hand micro-dissected using Paxinos mouse anatomical atlas coordinates, to isolate anatomical regions of interest [Ogden et al., 2004; Le-Niculescu et al., 2007a]. Tissue was flash frozen in liquid nitrogen and stored at −80°C pending RNA extraction. Approximately 1 ml of blood/mouse was collected into a PAXgene blood RNA collection tubes, BD Diagnostic (VWR.com). The Paxgene blood vials were stored in −4°C overnight, and then at −80°C until future processing for RNA extraction.

Standard techniques were used to obtain total RNA (22 gauge syringe homogenization in RLT buffer) and to purify the RNA (RNeasy mini kit, Qiagen) from micro-dissected mouse brain regions. For the whole mouse blood RNA extraction, PAXgene blood RNA extraction kit (PreAnalytiX, a QIAGEN/BD Biosciences, San Jose, CA) was used, followed by GLOBINclear™–Human or GLOBINclear™–Mouse/Rat (Ambion/Applied Biosystems, Inc., Austin, TX) to remove the globin mRNA. All the methods and procedures were carried out as per manufacturer's instructions. The quality of the total RNA was confirmed using an Agilent 2100 Bioanalyzer (Agilent Technologies). The quantity and quality of total RNA was also independently assessed by 260 nm UV absorption and by 260/280 ratios, respectively (Nanodrop spectrophotometer). Starting material of total RNA labeling reactions was kept consistent within each independent microarray experiment.

For brain, equal amounts of total RNA extracted from brain tissue samples (PFC, amygdala) from individual mice was used for labeling and hybridization to Mouse Genome 430 2.0 arrays (Affymetrix, Santa Clara, CA). For blood, material from three mice was pooled for each experimental condition. The GeneChip Mouse Genome 430 2.0 Array contain over 45,000 probe sets that analyze the expression level of over 39,000 transcripts and variants from over 34,000 well-characterized mouse genes. Standard Affymetrix protocols were used to reverse transcribe the messenger RNA and generate biotinlylate cRNA (http://www.affymetrix.com/support/downloads/manuals/expression_s2_manual.pdf). The amount of cRNA used to prepare the hybridization cocktail was kept constant within each experiment. Samples were hybridized at 45°C for 17 hr under constant rotation. Arrays were washed and stained using the Affymetrix Fluidics Station 400 and scanned using the Affymetrix Model 3000 Scanner controlled by GCOS software. All sample labeling, hybridization, staining, and scanning procedures were carried out as per manufacturer's recommendations.

Quality Control

All arrays were scaled to a target intensity of 1000 using Affymetrix MASv 5.0 array analysis software. Quality control measures including 3′/5′ ratios for GAPDH and beta-actin, scaling factors, background, and Q values were within acceptable limits.

Microarray Data Analysis

Data analysis was performed using Affymetrix Microarray Suite 5.0 software (MAS v5.0). Default settings were used to define transcripts as present (P), marginal (M), or absent (A). For brain, a comparison analysis was performed for individual KO saline mouse, using individual WT saline mice as the baseline. "Signal," "Detection," "Signal Log Ratio," "Change," and "Change *P*-value," were obtained from this analysis. The *P*-value threshold for change was $P < 0.0025$. Only transcripts that were called Present in at least one of the two samples in a comparison pair, and that were reproducibly changed in the same direction in at least six out of nine comparisons, were analyzed further. For blood, a comparison analysis was performed for pooled ($n = 3$) KO saline mice blood, using pooled ($n = 3$) WT saline mice blood as the baseline, using the same criteria as described above. Only transcripts that were called Present in at least one of the two pooled samples in a

comparison pair (KO vs. WT), and that were reproducibly changed in the same direction in two independent biological experiments, were analyzed further.

Gene Identification

The identities of transcripts were established using NetAFFX (Affymetrix), and confirmed by cross-checking the target mRNA sequences that had been used for probe design in the Affymetrix Mouse Genome 430 2.0 arrays GeneChip® with the GenBank database. Where possible, identities of ESTs were established by BLAST searches of the nucleotide database. A National Center for Biotechnology Information (NCBI) (Bethesda, MD) BLAST analysis of the accession number of each probe-set was done to identify each gene name. BLAST analysis identified the closest known mouse gene existing in the database (the highest known mouse gene at the top of the BLAST list of homologues) which then could be used to search the GeneCards database (Weizmann Institute, Rehovot, Israel) to identify the human homologue. Probe-sets that did not have a known gene were labeled "EST" and their accession numbers kept as identifiers.

Human Genetic (Linkage, Association) Convergence

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

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, Bar Harbor, ME) and used the search menu for mouse phenotypes and mouse models of human disease/abnormal behaviors, using the following sub-categories: abnormal emotion/affect behavior, abnormal eating/drinking behavior, abnormal sleep pattern/circadian rhythm, and addiction/drug abuse. To designate convergence for a particular gene, the gene had to map within 10 cM of a QTL marker for the abnormal behavior, or a transgenic mouse of the gene itself displayed that behavior.

Human Tissue (Postmortem Brain, Blood) Convergence

Information about our candidate genes was obtained using GeneCards, 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, alcoholism, stress, anxiety, human, postmortem, brain, blood).

Gene Ontology (GO) Analysis

The NetAffx Gene Ontology Mining Tool (Affymetrix) was employed to categorize the genes in our datasets into functional categories, using the Biological Process ontology branch.

Ingenuity Pathway Analysis

Ingenuity 5.1 (Ingenuity Systems, Redwood City, CA) was employed to identify genes in our datasets that are the target of existing drugs, as well as used to analyze the direct interactions of top candidate genes resulting from our CFG analysis.

RESULTS

Phenomic Studies: Behavioral Phenotype, Response to Stress and Sleep Deprivation

At baseline, DBP KO (non-stressed, NST) mice exhibited an overall decrease in the distance traveled as compared to wild-type animals. Treatment with methamphetamine reversed this decrease (Fig. 1a). This observation of decreased locomotion in KO mice, along with reported sleep EEG abnormalities [Franken et al., 2000] suggest that the DBP KO mice at baseline have phenotypic similarities to the depressive phase of bipolar disorder. Of note, the KO mice treated with methamphetamine displayed, if anything, a reduction in stereotypy, as measured by spatial deviance [Ogden et al., 2004], whereas the WT mice exhibited a trend towards an increase in stereotypy (Fig. 1b), which likely accounts for their apparent lack of increased distance traveled. Stereotypy is associated with a strong response to methamphetamine. Thus, at similar doses, KO mice displayed a lower (blunted) response to methamphetamine compared to WT mice, consistent with a lower hedonic state.

Acute overwhelming stress (accidents, illness, loss of employment) on top of the chronic stress of social isolation often precede decompensation in human bipolar patients [Bunney et al., 1972]. With that in mind, we subjected mice to a chronic stress paradigm consisting of isolation (single housing) for 1 month, overlaid with an acute stressor (a series of behavioral challenge tests) at the end of the third week of isolation. When subjected to the chronic stress (ST) paradigm prior to the locomotor assessment, DBP KO ST mice display a change in their locomotor phenotype, becoming hyperlocomotive, while wild-type animals become hypolocomotive (Fig. 2b). This switch from a low level of locomotion to a high level of locomotion is analogous to the switch from a depressed phase to an activated (manic) phase of bipolar disorder [Post et al., 1977], and possibly to the activation triggered by stress in post-traumatic stress disorder (PTSD). Notably, there is a high rate of co-morbidity between PTSD and bipolar disorder [Otto et al., 2004].

An unsupervised two-way hierarchical clustering of the mouse locomotor behavioral data measures (phenes) [Niculescu et al., 2006] (Fig. 2d,e) using GeneSpring is illustrative in terms of the bipolar-like phenomenology and the switch from a depression-like state to a mania-like state in response to stress. First of all, the DBP KO NST mice and the DBP KO ST mice for the most part clustered into two distinct groups, illustrating the utility of our phenotypic battery of measures in distinguishing between the two groups (Fig. 2e). Second, the heat-plot shows that the phene that was most different in ST mice (decreased) and NST mice (increased) was Resting Time, which has strong analogies to behavioral correlates of mood (i.e., level of activity) in humans. Moreover, Center Time (time spent in the center quadrant of the open field), was increased in ST mice compared to NST mice. Increased Center Time may be a reflection of expansive, exploratory and risk-taking behavior, as mice tend to avoid the

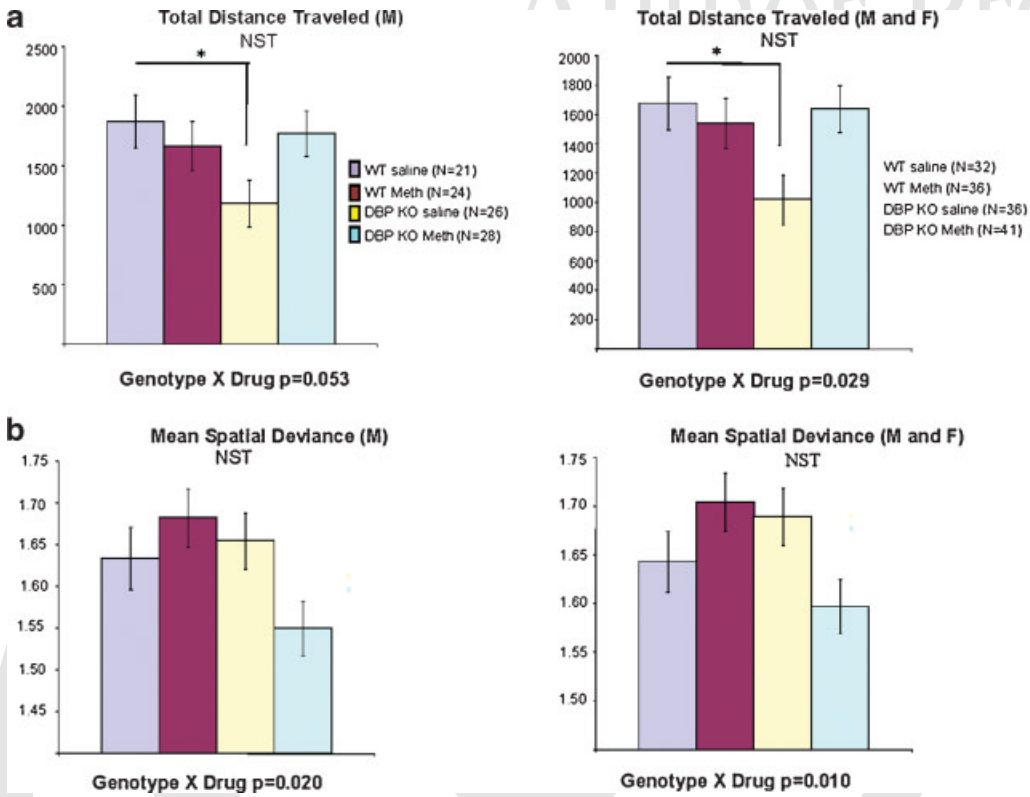

Fig. 1. Phenomics-locomotion at baseline in DBP KO NST mice. **a**: Total distance traveled (in centimeters); (**b**) mean spatial deviance. Error bars on histograms represent standard-error of mean (SEM). Graphs of data for males (M) and both genders combined (males and females—M and F) are shown. Genotypes × drug *P*-values are derived from two-way analyses of variance (ANOVAs), as described in Materials and Methods Section. *Individual comparison *P*-values derived from *t*-test. For males, $P = 0.0246$; for combined group, $P = 0.01$.

potentially dangerous center area of an open-field due to ancestral self-preservation mechanisms.

To further characterize the behavioral phenotype of the DBP KO strain, group-housed (NST) male DBP KO mice were subjected to sleep deprivation for a 24-hr period. Following sleep deprivation, sleep-deprived (SD) mice and control non-sleep-deprived (NSD) mice were monitored with video tracking software. SD DBP KO animals displayed a significant increase in the total distance traveled compared to the NSD animals (Fig. 2c). In a second sleep deprivation experiment, mice were pre-treated with an IP valproate injection (200 mg/kg) immediately prior to the sleep deprivation experiment. If the change in locomotor behavior that accompanies sleep-deprivation in the SD animals is representative of an endophenotype that is associated with bipolar disorder, then administration of the mood stabilizing agent valproate should counteract the behavioral response of DBP KO mice to sleep deprivation. Indeed, when valproate was administered prior to sleep deprivation there was no significant difference in the locomotor behavior of SD and NSD animals (Fig. 2c). Of note, valproate treatment did not have any significant effect on locomotion in NSD animals, as the NSD valproate treated animals displayed locomotion that was comparable to the NSD non-valproate treated animals.

Weight changes are a frequent clinical correlate of mood disorder episodes in humans. An actuarial tabulation of body weight in our male DBP KO mice colony revealed that the group housed non-stressed (NST) animals gained less weight over time compared to WT controls (Fig. 3a). This trend was switched in the single-housed stressed (ST) mice (Fig. 3b). As food is a hedonic stimulus, this weight trends may reflect an anhedonic state in the depressed-like KO NST mice compared to WT NST, and a relative hedonic state in the activated KO ST mice compared to WT ST. Of note, levels of activity and calorie burning are unlikely to be a direct confound for this weight phenomenon, quite the contrary. The KO NST mice, who gain less weight compared to WT NST mice, actually locomote less, whereas the more active KO ST mice gain more weight compared to WT ST mice.

Given the high degree of co-morbidity of alcoholism with depression [Schuckit et al., 1997; Nurnberger et al., 2004], as well as with bipolar disorder [Angst and Cassano, 2005; Strakowski et al., 2005b; Rodd et al., 2007], and the fact that DBP was also identified by us as a potential candidate gene for alcoholism using a CFG approach [Rodd et al., 2007], it was of interest to study the consumption of alcohol by DBP KO mice. DBP is increased in expression in alcohol preferring (P) rats versus alcohol non-preferring (NP) rats in the PFC, which suggests the hypothesis that lower levels or absence of DBP, such as in DBP KO mice, might be associated with decreased consumption of alcohol. However, this may only be applicable to DBP KO mice that are not stressed (NST), and are displaying a depressive-like phenotype. Conversely, DBP KO ST mice that exhibit an activated, manic-like behavior may display an elevated propensity to abuse hedonic substances such as alcohol compared to wild-type controls. Indeed, while the DBP KO mice consume at baseline (start of the stress paradigm) less alcohol than WT mice, they exhibited a switch in response to stress: DBP KO ST mice consumed more alcohol over a 30-day period as compared to ST WT mice (Fig. 4). No significant differences in water consumption were observed, except a trend to less water consumption in response to increased alcohol consumption (data not shown), making it unlikely that what we observe reflects a non-specific increase

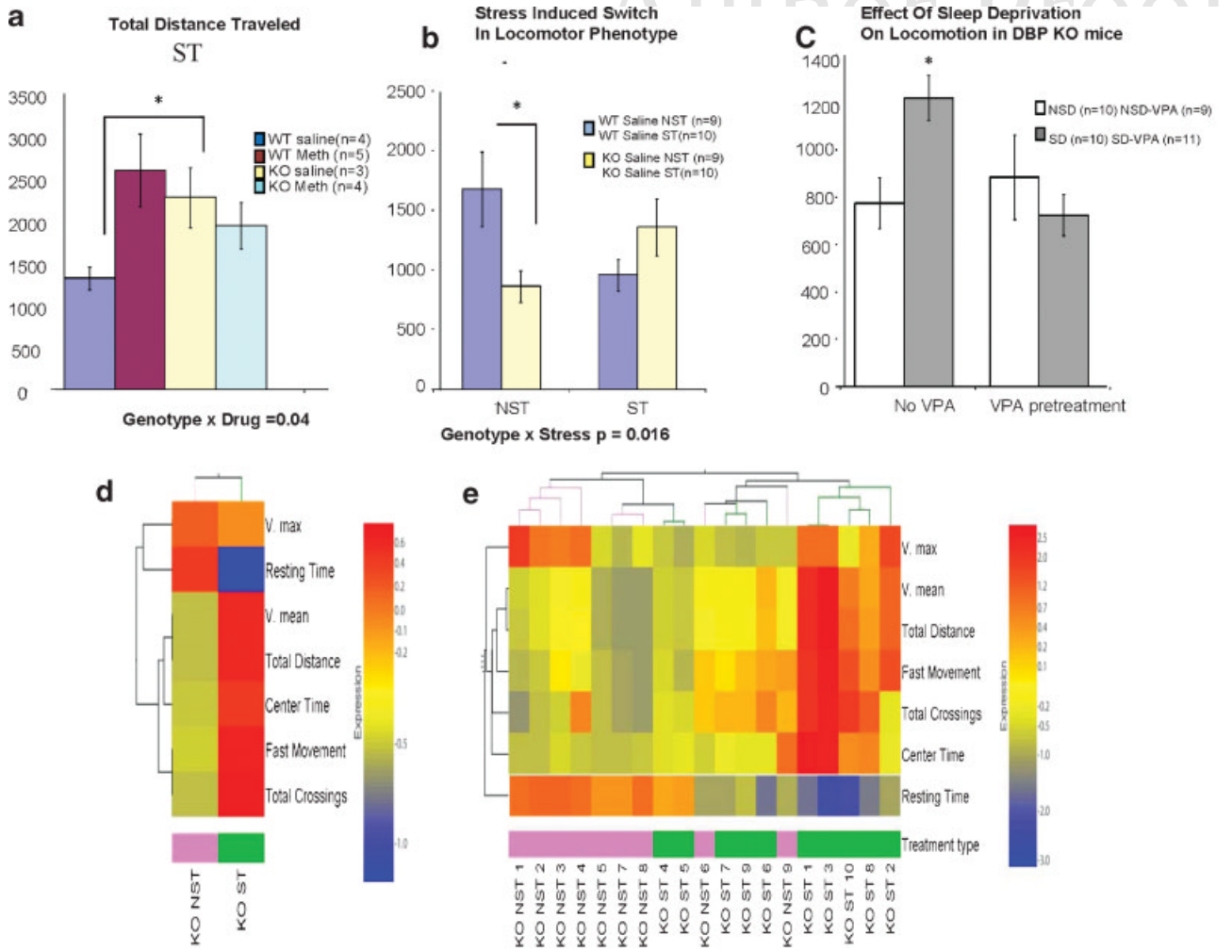

Fig. 2. Phenomics of DBP KO ST mice: locomotion, switch, sleep deprivation, clustering. **a**: After the 28-day stress (ST) paradigm video tracking software was used to measure the mean total distance traveled (in centimeters) during a 30-min period in both wild-type and knockout mice with and without methamphetamine treatment (*P-value = 0.0369); (**b**) stress-induced switch in total distance traveled comparing wild-type and knockout mice (*P-value = 0.01583); (**c**) sleep deprivation caused an increase in the total distance traveled by DBP KO mice. SD—sleep deprived, NSD—non-sleep deprived. This increase in locomotion is prevented by pretreatment with valproate (VPA; *P-value = 0.0068); (**d**) group, and (*P*) individual mice clustering of video tracker data using a PhenoChipping approach [Niculescu et al., 2006], as described in Materials and Methods Section. ST—stressed mice. NST—non-stressed mice. V. max—maximal velocity; V. mean—mean velocity. Red—increased; blue—decreased.

in fluid consumption as opposed to a preference for alcohol. Overall, this evidence, taken together with the gene expression evidence described below, strongly suggests that DBP KO mice may be a useful model for studying alcohol abuse co-morbidity with bipolar disorder, in relationship to the phases of the illness and response to stress.

Gene Expression Studies and Convergent Functional Genomics

To understand the molecular underpinnings of the observed phenomenology, we carried out brain gene expression profiling studies using microarrays. In order to identify new potential candidate genes for bipolar disorder, alcoholism and stress reactivity, we conducted an expanded CFG analysis (Fig. 5). Moreover, we extended our gene expression studies to blood, as a way of identifying potential candidate blood biomarkers (Table VI). Blood biomarkers—genes that change in expression in the blood in concordance with brain changes, are particularly interesting as a potential tool for diagnosis and for monitoring response to treatment [Le-Niculescu et al., 2007b].

Scoring the Independent Lines of Evidence

We used a CFG approach to interpret the data from a Bayesian perspective, assessing each gene's relevance based on animal model and human lines of evidence (Fig. 5). Internal lines of evidence reflect the new information generated by our series of experiments: being changed in expression by loss of the DBP gene in two key brain regions (PFC, AMY) and in blood. As external lines of evidence, we used public domain mouse QTL or transgenic data [Mulligan et al., 2006], human genetic linkage or association data, human postmortem brain data, and human blood (lymphocyte) data (Fig. 5). Each line of evidence received an empirical score of 1 if it was related to bipolar disorder, alcoholism or stress/anxiety, and 0.5 if it was related to other neuropsychiatric disorders. These external lines of evidence suffer from the obvious drawback of being constrained by what has been published so far, limiting novelty, and to the inherent biases and limitations of those particular lines of work. Moreover, these external criteria are arguably broad, and may benefit from future parsing. Including disorders other than bipolar disorder and alcoholism in our

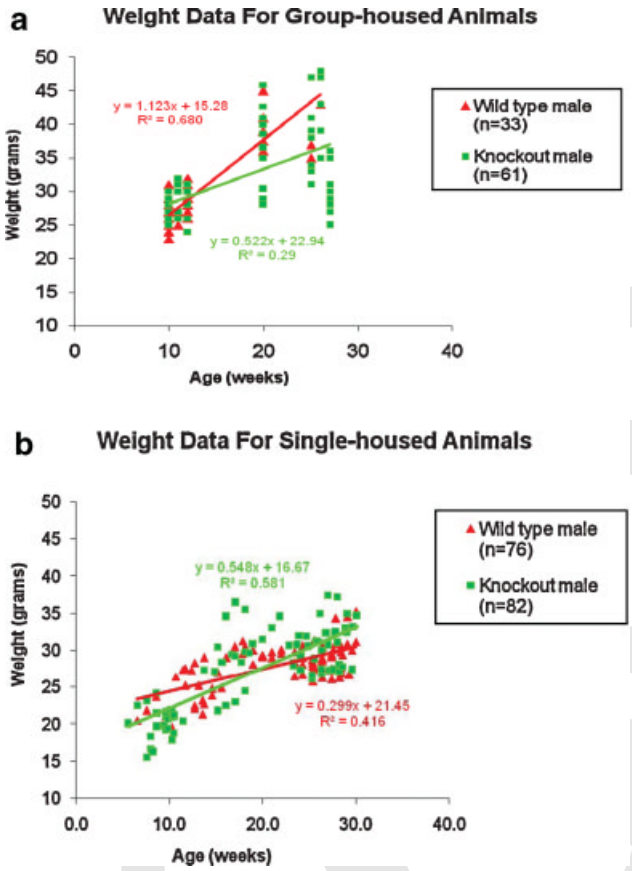

Fig. 3. Phenomics-weight (**a**) wild-type and DBP KO NST mice (group housed) (**b**) wild-type and DBP KO Stressed mice (single housed). Body weight measurements were taken at various time points. Data (n) is representative of a mixed population of repeated and individual measures of weight from animals at different time points. Scatter plots of data collected are shown. The best-fit line for each set of data was determined and is displayed along with the equation for the line and the R^2 value. R-Pearson correlation coefficient.

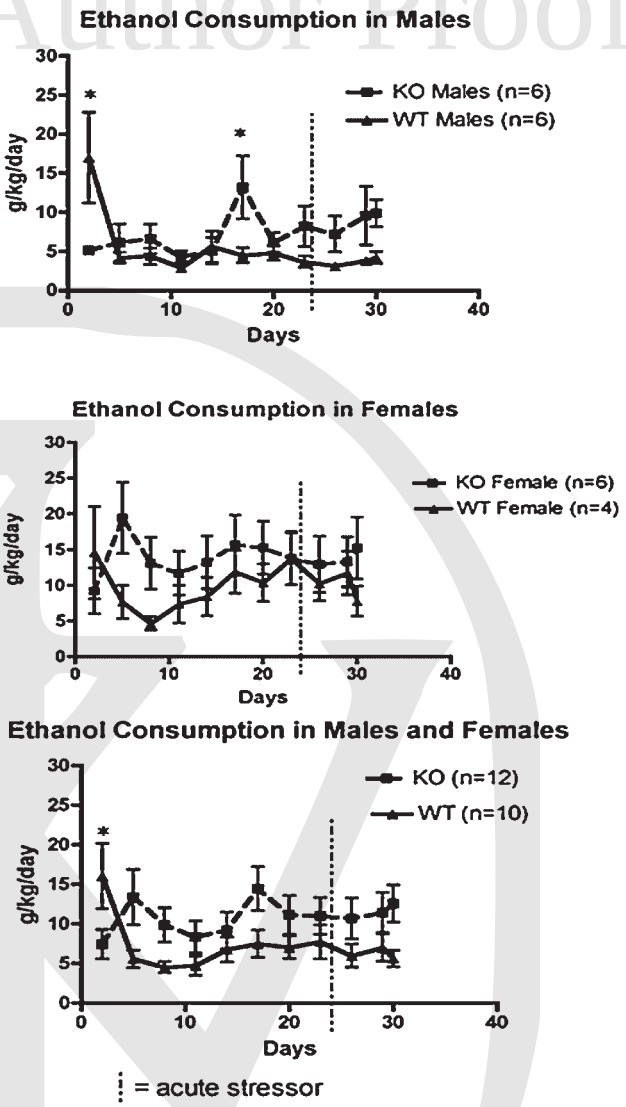

Fig. 4. Phenomics-ethanol consumption during the ST paradigm. Alcohol free-choice drinking paradigm, male and female, wild-type and DBP KO mice. Fluid consumption from both bottles was monitored for a period of 30 days with an acute stressor (dotted vertical line) at the end of the third week, as described in Materials and Methods Section. Two-way ANOVA were preformed on all data sets. *Significant $P < 0.05$ by ANOVA.

external lines of evidence arguably dilutes the specificity of our approach. We nevertheless decided to include them as a way of increasing sensitivity, based on the emerging clinical, neurobiological, and genetic evidence of substantial overlap between major neuropsychiatric disorders [Niculescu, 2006; Niculescu et al., 2006; Rodd et al., 2007; Le-Niculescu et al., 2007a] as well as the likelihood that published bipolar and alcoholism-related datasets to date are non-exhaustive. Totaling all the internal and external lines of evidence gives a maximum possible score of 6 points, with the animal model evidence and the human evidence weighted equally (Fig. 5).

While we cannot exclude that some of the candidate genes we have identified are false positives due to potential biological or technical limitations of the methodology and approach we and others have employed, the higher the number of independent lines of evidence, the lower the likelihood of that being the case. According to Bayesian theory, an optimal estimate results from combining prior information with new evidence [Bernardo and Smith, 1994]. Different ways of scoring the independent lines of evidence could be used, which might give somewhat different results in terms of the prioritization of the top candidate genes, if not in terms of the actual content of the list per se. However, our simple weighted scoring is arguably a reasonable compromise between specificity and sensitivity, between focus and broadness.

Overlap With Previous Findings

We examined the overlap of genes that showed changes in expression in the brain (PFC and AMY) of DBP KO NST and ST mice, with the genes that showed changes in expression, in the same brain regions, in two previous independent studies of ours: a bipolar pharmacogenomic discovery CFG model (Ogden et al., 2004; Table II), and an alcoholism CFG analysis of inbred alcohol preferring (iP) rat gene expression studies (Rodd et al., 2007; Table III).

For the bipolar comparison, our top candidate genes from the pharmacogenomic model (Ppp1r1b/Darpp-32, Penk, Tac1, Mef2c, Gpr88) were also changed in the genetic DBP KO model. This is an unexpectedly strong cross-validation between two independent and very different approaches, a genetic animal model and a pharmacogenomic animal model of bipolar disorder. The direction of change in the PFC (decreased in the DBP KO ST mice, increased in the pharmacogenomic

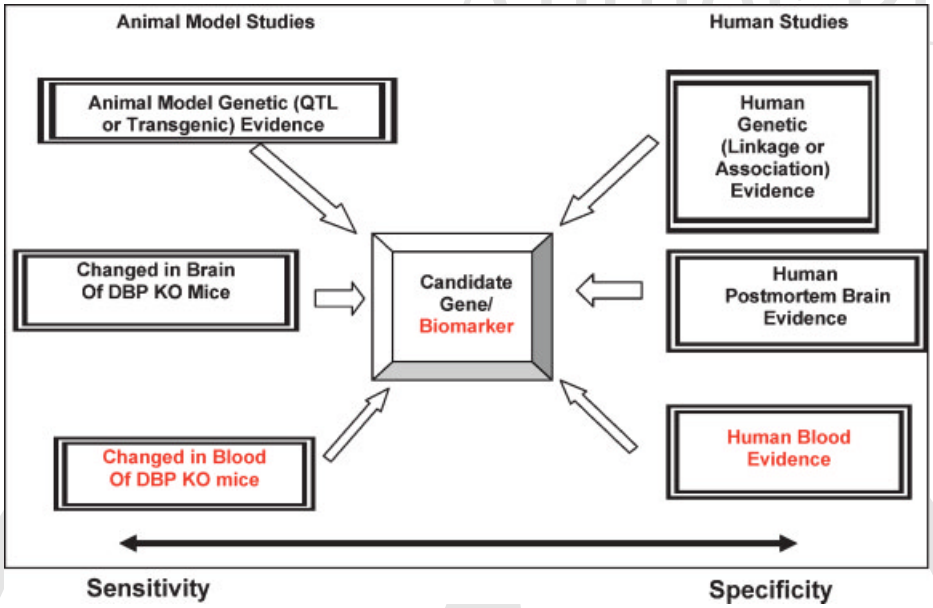

Fig. 5. Expanded Convergent Functional Genomics (CFG) analysis. Bayesian integration of multiple animal model and human lines of evidence.

model), is consistent with our interpretation of the behavioral data in the two studies—an activated phase in the DBP KO ST mice, and a depressed phase in the pharmacogenomic model, at the time of gene expression sampling [Ogden et al., 2004].

Darpp-32, Penk, and Tac1 each showed a remarkable opposite direction of change in the PFC and AMY of the DBP KO ST mice, being decreased in the PFC and increased in the AMY. This suggests that they may provide molecular underpinnings for the reciprocal cortical-limbic dysregulation seen in affective disorders by imaging studies [Strakowski et al., 2005a]. Moreover, Darpp-32 switched from being decreased in AMY in the DBP NST mice to being increased in AMY in the DBP ST mice. Darpp-32 has been previously described by us to be changed by separate methamphetamine and valproate treatment in the PFC of wild-type mice, and those changes are abolished by co-treatment with both drugs [Ogden et al., 2004]. It has been previously implicated as being at the crossroads of the mechanisms of action of various different psychotomimetic drugs [Svenningsson et al., 2003]. Darpp-32 also has been shown to mediate the stimulant actions of caffeine [Lindskog et al., 2002], the antidepressant fluoxetine (Prozac) [Svenningsson et al., 2002], possible tolerance to alcohol [Maldve et al., 2002], and progesterone-mediated sexual receptivity [Mani et al., 2000]. Transgenic mice lacking the Darpp-32 gene displayed deficits in their molecular, electrophysiological and behavioral responses to dopamine, drugs of abuse, and antipsychotic medications [Fienberg et al., 1998]. Moreover, Darpp-32 maps in the region of a linkage peak for bipolar disorder [Segurado et al., 2003] and conduct disorder [Stallings et al., 2005], and has been shown in postmortem studies to be decreased in the PFC of bipolar and schizophrenia subjects [Albert et al., 2002; Ishikawa et al., 2007].

Two other genes that show a flip in expression from NST to ST are Tmod2 and Gas5. Tmod2 (tropomodulin 2, neuronal) has been previously described by us as being decreased in expression by methamphetamine in the PFC of wild-type mice [Ogden et al., 2004]. Of note, Tmod2 is increased in the PFC of DBP KO NST mice and decreased in the PFC of DBP KO ST mice (Table II). This is strikingly consistent with previous studies that have shown that mice lacking Tmod2 show enhanced hyperactivity, long-term potentiation, and deficits in learning and memory [Cox et al., 2003]. Moreover, the opposite direction of change in DBP KO NST and DBP KO ST mice supports the possibility that Tmod2 may be a substrate for the observed behavioral changes induced by stress in our model.

Overlap With Human Postmortem Brain Findings (Table IS)

A number of the genes changed in DBP KO mice have also been reported changed in human postmortem brains from subjects with bipolar disorder, depression, alcoholism, as well as other related disorders (Table IS). This cross-validation, on one hand reinforces the validity of our approach, and on the other hand reduces the likelihood that those particular postmortem findings are methodological or gene–environment interactions artifacts of working with postmortem human tissue. Moreover, it illustrates at a genetic and neurobiological mechanism level the overlap among major neuropsychiatric disorders [Niculescu et al., 2006].

In particular, a group of glia/myelin related genes are decreased in both DBP KO NST and ST mice (Tables 1S and 2S), as well as in bipolar disorder (Mbp, Cldn11, Plp1, Mobp), depression (Cnp, Mog, Mal, Plp1), schizophrenia (Mbp, Cldn11, Plp1, Mobp, Cnp, Mal) and alcoholism (Mbp, Plp1, Mobp, Cnp, Mog, Mal) postmortem brains. Mag is decreased in DBP ST mice only, as well in bipolar, depression, schizophrenia, and alcohol brains. These data, on the one hand, point to the strong validity of our genetic mouse model, and on the other hand implicate glia/myelin pathology as integral to bipolar and related disorders. Indeed, the commonality of alterations in glia/myelin genes, namely a decrease in expression, across a spectrum of neuropsychiatric disorders suggests that hypofunction of glia/myelin systems may be a sensitive if not specific common denominator for mental illness, perhaps leading to hypofrontality and disregulated control of mood-similar to a loose switch. This may be the underlying neuroanatomical reason for the switch from a depressed to an activated (manic-like) phase in response to stress in our constitutive KO mice. Of note, omega-3 polyunsaturated fatty acids may directly target this glia/myelin abnormality [Salvati et al., 2004]. Omega-3 fatty acids have been reported to be clinically useful in the treatment of both mood [Parker et al., 2006] and psychotic

disorders [Peet and Stokes, 2005]. Deficits in omega-3 fatty acids have been linked to increased depression and aggression in both animal models [DeMar et al., 2006] and humans [Zanarini and Frankenburg, 2003]. Our animal model thus constitutes an interesting setting for future work examining the structural and behavioral effects of omega-3 fatty acids.

Other interesting examples of genes changed in our animal model for which there is postmortem evidence include Apod, Gsk3b, and Ptgs2. Apod (apolipoprotein D) is increased in postmortem brains from bipolar disorder and schizophrenia subjects [Thomas et al., 2001, 2003], and is decreased in brains from depression and alcoholism subjects. In DBP KO ST mice, Apod is increased in the amygdala and decreased in the PFC. Gsk3b (glycogen synthase kinase 3 beta) is a target of mood stabilizing drugs [Manji et al., 2000; Benedetti et al., 2005], as well as has been implicated in age of onset and response to sleep deprivation in bipolar patients [Benedetti et al., 2004]. It is decreased in postmortem brains from bipolar disorder and depression [Nakatani et al., 2006; Vawter et al., 2006]. In DBP KO ST mice, Gsk3b is increased in the amygdala and decreased in the PFC. Ptgs2 (prostaglandin synthase 2) is increased in DBP KO ST mice and in brains from schizophrenia, Alzheimer and multiple sclerosis subjects, suggesting an underlying inflammatory/neurodegenerative phenomenology that may tie in with the glia/myelin hypofunction and the therapeutic effects of omega-3 fatty acids, which also have anti-inflammatory properties. It may be of interest, then, to pursue inhibitors of Ptgs2 (COX2) as therapeutic options in mood disorders with a stress component (Table IIS). Of note, previous work has shown that chronic lithium treatment downregulates cyclooxygenase-2 activity in rat brain [Bosetti et al., 2002], and recently the COX2 inhibitor celecoxib was shown to have therapeutic effects in depression in a human clinical trial [Muller et al., 2006].

Stress-Induced Switch in Gene Expression Patterns

The genes changed in opposite directions in the DBP KO NST and DBP KO ST mice (Table I) are particularly interesting as potential candidate genes for bipolar disorder, as they show a diametric change in conjunction with the switch in phenotype.

PFC. Besides Tmod2, mentioned above, six other genes are increased in DBP KO NST mice and decreased in DBP KO ST mice: Kcnb1, Anp32a, Slc1a2, Fut9, Sdc4, and Fundc2. For example, Kcnb1 (voltage-gated potassium channel subunit

TABLE I. Genes Changed in DBP KO Mice

Region	DBP KO saline NST	DBP KO saline ST	Switched—changed in opposite directions in NST and ST Gene symbol (direction of change NST, ST)
PFC	65 Decreased 34 Increased	325 Decreased 102 Increased	Switched/increased by stress Gnb1 (D, I) Cdh11/2610005L07Rik /// LOC546041 (D, I) Rab39b (D, I) Switched/decreased by stress Anp32a (I, D) Fundc2 (I, D) Fut9 (I, D) Kcnb1 (I, D) Sdc4 (I, D) Tmod2 (I, D) Slc1a2 (I, D)
AMY	228 Decreased 206 Increased	147 Decreased 177 Increased	Switched/increased by stress Atp1a1 (D, I) Gpx3 (D, I) Irs4 (D, I) Kcna5 (D, I) Klhl13 (D, I) Lhx8 (D, I) LOC669637 (D, I) Pbx3 (D, I) Ppp1r1b (D, I) Ptov1 (D, I) Rasd2 (D, I) Slc32a1 (D, I) Vapb (D, I) Zic1 (D, I) Switched/decreased by stress Ap2b1 (I, D) C230078M08Rik (I, D) Eml2 (I, D) Gas5 (I, D) Nup62 (I, D) Pip5k1b (I, D) Rbbp4 (I, D) Rian (I, D) Sdc4 (I, D)
Blood	136 Decreased 9 Increased	28 Decreased 3 Increased	Switched/decreased by stress Crisp3 (I, D) Klk1b16 (I, D)

TABLE II. Overlap With Bipolar Pharmacogenomic Model CFG Analysis [Ogden et al., 2004]

Gene symbol—gene name	DBP NST	DBP ST	Bipolar CFG [Ogden et al., 2004]
Ppp1r1b/Darp32, protein phosphatase 1, regulatory (inhibitor) subunit 1B	AMY-D, PFC-D	**AMY-I, PFC-D**	PFC Cat I-Meth(I) VPA(I)
Ptov1, prostate tumor overexpressed gene 1	AMY-I	AMY-I	AMY Cat III-VPA(I)
Gnb1, guanine nucleotide binding protein (G protein), beta polypeptide 1	AMY-D, PFC-D	PFC-I	AMY Cat IV-Meth (I), CP Cat IV-VPA (D)
Gas5, growth arrest-specific 5	AMY-I	AMY-D	AMY Cat IV-Meth(I)
Actb, actin, beta	AMY-D	PFC-D	AMY Cat IV-VPA (I), PFC Cat IV-Meth (D)
Tmod2, tropomodulin 2	PFC-I	PFC-D	PFC Cat IV-METH (D)
Mef2a, MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A)	AMY-D, PFC-D	PFC-D	AMY Cat IV-Meth (D), CP Cat IV-VPA (I)
Ptpn5/Step, protein tyrosine phosphatase, non-receptor type 5	AMY-D	PFC-D	AMY Cat IV-VPA (I)
Timp2, tissue inhibitor of metalloproteinase 2	AMY-D	PFC-D	AMY Cat IV-VPA (D)
Penk1, preproenkephalin		**PFC-D, AMY-I**	PFC Cat I-Meth(I) VPA(I)
Tac1, tachykinin, precursor 1 (substance P)		**AMY-I, PFC-D**	PFC Cat I-Meth(I) VPA(I)
Gpr88, G-protein coupled receptor 88		PFC-D	PFC Cat I-Meth(I) VPA (I)
Mef2c, myocyte enhancer factor 2C		AMY-I	PFC Cat I-Meth(D) VPA(I), AMY Cat III-VPA(D)
Ckmt1, creatine kinase, mitochondrial 1 (ubiquitous)		AMY-D	AMY Cat III-Meth(I) VPA(I)
Sec24d, SEC24 related gene family, member D (*S. cerevisiae*)		AMY-D	AMY Cat III-Meth(I)
Alcam, activated leukocyte cell adhesion molecule		**AMY-I, PFC-D**	AMY Cat IV-VPA(D), PFC Cat III-Meth(D), VT Cat IV-Meth(D), CP Cat IV-VPA(D)
Gsk3b, glycogen synthase kinase 3 beta		**PFC-D, AMY-I**	PFC Cat IV-METH (D), CP IV-VPA (D)
Gng7, guanine nucleotide binding protein (G protein), gamma 7 subunit		PFC-D	PFC Cat III-Meth(I) VPA(I)
Ddx6, DEAD (Asp-Glu-Ala-Asp) box polypeptide 6		**AMY-I, PFC-D**	PFC Cat III-Meth (D), VT Cat IV-Meth (D)
Scn4b, sodium channel, type IV, beta polypeptide		**AMY-I, PFC-D**	PFC Cat III-Meth(I) VPA(I)
Hectd1, HECT domain containing 1		**AMY-I, PFC-D**	PFC Cat IV-Meth(D)
Peg3, paternally expressed 3		**AMY-I, PFC-D**	AMY Cat IV-VPA(D), PFC Cat IV-Meth(D)
Arhgap5, Rho GTPase activating protein 5		PFC-D	PFC Cat IV-Meth (I)
Gabra4, Gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 4		PFC-D	PFC Cat IV-METH (I)
Pten, phosphatase and tensin homolog		**AMY-I, PFC-D**	PFC Cat IV-Meth(D)
Atp8a1, ATPase, aminophospholipid transporter (APLT), Class I, type 8A, member 1		AMY-I	AMY Cat IV-VPA(D)
Cdk5r1, cyclin-dependent kinase 5, regulatory subunit (p35) 1	AMY-I		AMY Cat II-Meth(D), VPA(D) CP Cat III-VPA(I)
Cacnb2, calcium channel, voltage-dependent, beta 2 subunit	AMY-D		AMY Cat III-VPA(D), CP Cat IV-VPA(I)
Ids, iduronate 2-sulfatase	AMY-D		AMY Cat III-VPA(D), CP Cat IV-VPA(I)
Clasp2, CLIP associating protein 2	AMY-I, PFC-I		AMY Cat IV-VPA(D)
Sez6, seizure related gene 6	AMY-D		AMY Cat IV-VPA(I)
Ttr transthyretin	AMY-D		CP Cat IV-Meth(I)

I, increased in expression; D, decreased in expression; CP, caudate-putamen; VT, ventral tegmentum.
In bold, genes that show inverse PFC versus AMY expression.

Kv2.1) regulates neuronal excitability [Misonou et al., 2004], and has been implicated in protective mechanisms to suppress hyperexcitability [Misonou et al., 2005]. The increase in levels of Kcnb1 we see in the DBP NST mice may underlie neuronal hypoexcitability, and conversely the decrease in levels of KCNB1 in DBP ST mice may underlie neuronal hyperexcitability. This is remarkably congruent with the observed switch in their behavioral phenotype. Slc1a2 (Glt-1/ Eaat2, glial high affinity glutamate transporter) is involved in terminating the postsynaptic excitatory actions of glutamate by rapidly removing released glutamate from the synaptic cleft [Campbell and Hablitz, 2004]. Increased levels of GLT-1, as in the DBP KO NST mice, would lead to decreased excitability, and decreased levels of GLT-1, as in the DBP KO ST mice, would lead to increased excitability, consistent with the behavioral phenotype observed.

Three genes are decreased in DBP KO NST mice and increased in DBP KO ST mice: GNB1, Rab39b, and Cdh11. For example, Gnb1 (G protein beta 1 subunit gene) is upregulated by psychostimulants and may be involved in the initial behavioral activation response [Kitanaka et al., 2003]. Consistent with this, it is decreased in DBP KO NST mice, which show reduced locomotion, and increased in DBP KO ST mice, which show increased locomotion. Of note, Gnb1 is suppressed by experimental hyperthyroidism in mice [Haas et al., 2004], which is intriguing in view of the proposed use of thyroid hormone to treat rapid-cycling bipolar disorder in humans [Gyulai et al., 2003; Bauer et al., 2005].

TABLE III. Overlap With Alcohol CFG Analysis [Rodd et al., 2007]

Gene symbol	DBP NST	DBP ST	Alcohol CFG [Rodd et al., 2007]
Aldh1a1, aldehyde dehydrogenase family 1, subfamily A1	PFC-D	AMY-I	Category IIB-HIP(I), Category III-1 PFC(I)
Cnp, cyclic nucleotide phosphodiesterase 1	PFC-D	PFC-D	Category III-1 PFC(I)
Mal, myelin and lymphocyte protein, T-cell differentiation protein	PFC-D	PFC-D	Category III-1 PFC(I)
Mobp, myelin-associated oligodendrocyte basic protein	PFC-D	**AMY-I, PFC-D**	Category III-1 PFC(I)
Mog, myelin oligodendrocyte glycoprotein	AMY-D, PFC-D	PFC-D	Category III-1 PFC(I)
Plp1, proteolipid protein (myelin) 1	PFC-D	PFC-D	Category III-1 PFC(I)
Dbp, D site albumin promoter binding protein	PFC-D, AMY-D	AMY-D, PFC-D	Category III-1 PFC(I)
Hspb1, heat shock 27kDa protein 1		PFC-I	Category IIA-HIP(I), Category IIB-PFC(I)
Hnrpab, heterogeneous nuclear ribonucleoprotein A/B		AMY-I	Category IIA-AMY(D)
Tkt, transketolase		PFC-D	Category III-1 PFC(I)
Spr, sepiapterin reductase		PFC-D	Category III-1 PFC(D)
Apod, apolipoprotein D		**AMY-I, PFC-D**	Category III-1 PFC(I)

I, increased in expression; D, decreased in expression.
In bold, genes that show inverse PFC versus AMY expression.

A Broad/MIT Connectivity Map [Lamb et al., 2006] analysis of genes that show switch in response to stress in the PFC identified celecoxib, a COX2 inhibitor, as the drug most likely to produce a similar gene expression pattern, and valproate, a mood stabilizer, as one of the drugs most likely to produce an opposite pattern (Table VII). This is an unexpectedly strong independent corroboration of the validity of our genetic animal model, and reinforces the suggestion of exploring the use of anti-inflammatory agents in the treatment of mood disorders with a stress component, as discussed above.

AMY. Besides Gas5 mentioned earlier, seven other known genes are switched/decreased by stress: Ap2b1, Eml2, Nup62, Pip5k1b, Rbbp4, Rian, and Sdc4. For example, Pip5k1b (phosphatidylinositol-4-phosphate 5-kinase, type 1 beta) was independently identified as a gene downregulated in response to chronic stress in mice, consistent with our findings [Ejchel-Cohen et al., 2006].

Besides Ppp1r1b/Darpp-32 discussed above, 12 other genes are switched/increased by stress: Atp1a1, Gpx3, Irs4, Kcna5, Klhl13, Lhx8, Pbx3, Ptov1, Rasd2, Slc32a1, Vapb, and Zic1. For example, Irs4 (insulin receptor substrate 4) is involved in insulin and fibroblast growth factor receptor signaling [Hinsby et al., 2004]. Both the insulin growth factor system [Bezchlibnyk et al., 2007] and the fibroblast growth factor system [Evans et al., 2004] have been implicated in the pathogenesis of mood disorders [Niculescu, 2005].

Blood. Two genes were switched/decreased by stress: Crisp3 and Klk1b16. These two genes have no known brain functions to date, but may be interesting candidate blood biomarkers of response to stress and switching in bipolar disorder.

Genes in Gene Ontology (GO) Categories That Move Up in the Ranking Following Stress

Of note, a comparison between the biological role categories of DBP NST KO versus DBP ST KO mice revealed that the GO category of genes related to stress, behavior, and response to stimuli showed the most relative increase in prominence following stress, compared to other biological categories (Table VIIIa,b). This is remarkable concordance between molecular changes and behavioral data.

Top Candidate Genes and Biomarkers

Cnp (discussed above with other myelin genes), Clk1 and Drd2 are the top candidate genes for bipolar/depression identified by our CFG analysis in DBP KO NST mice (Fig. 6a). Clk1 (cdc2-like kinase 1) was increased in our DBP KO NST mice, and decreased in brain of mice exposed to psycho-physiological stress [Murata et al., 2005]. It was also reported to be decreased in lymphocytes from schizophrenia patients [Glatt et al., 2005]. Drd2 (dopamine receptor 2) was decreased in our DBP KO NST mice in the AMY, which may be consistent with a depressed state [Ginovart et al., 1999], and was decreased in expression in DBP KO ST mice in the PFC, which may be consistent with an activated, hyperdopaminergic state. It was also reported to be decreased in lymphocytes from schizophrenia patients [Zvara et al., 2005]. Other, novel candidates genes and biomarkers for bipolar/depression from the DBP KO NST mice include Itgav, Gls, Enah, Pctk1, Lpl, Gnb1, Kcnj4, Hnrpdl, Ywhaz, Clic4, Sgk, and Slc38a2 (Fig. 6, Tables IV and VI). Ywhaz (14-3-3 zeta) maps to a locus on chromosome 8q22.3 that has been implicated in autism [Ylisaukko-oja et al., 2006], as well as shows some association with schizophrenia [Wong et al., 2005]. Ywhaz has been reported increased in the PFC of subjects with bipolar disorder [Nakatani et al., 2006], consistent with the increase we see in DBP KO NST mice in brain (PFC, AMY) and blood. Clic4 (chloride intracellular channel 4), a mitochondrial gene, maps to a locus on chromosome 1p36.11 that has been implicated in bipolar disorder [Cichon et al., 2001] and schizophrenia [Straub et al., 2002b]. Clic4 has been reported increased in peripheral lymphocytes from bipolar subjects [Middleton et al., 2005], and we see a decrease in its expression in brains of DBP KO NST mice. Mitochondrial dysfunction has been implicated by various lines of evidence in the pathophysiology of bipolar disorder [Kato and Kato, 2000; Konradi et al., 2004; Iwamoto et al., 2005; Stork and Renshaw, 2005]. Of note, Clic4 is also a direct binding partner of Ywhaz (14-3-3 zeta) [Suginta et al., 2001]. Sgk (serum- and glucocorticoid-inducible kinase 1) maps to a locus on chromosome 6q23.2 that has been implicated in bipolar disorder [Ewald et al., 2002; Venken et al., 2005], as well as schizophrenia [Levi et al., 2005]. Sgk increases Slc1a2 (GLT-1/EAAT2) activity and plasma membrane expression and thus, may participate in the regulation of neuroexcitability [Boehmer et al., 2006]. We see a decrease in Sgk expression in brain and blood of DBP KO NST mice (Tables IV and VI), thus it is also a candidate blood biomarker. Consistent with our work and the depression-like phenotype of DBP NST KO mice, Sgk KO mice have been recently reported to exhibit decreased locomotion, reduced exploratory activity, and increased centre field avoidance in the open-field [Lang et al., 2006]. Conversely,

TABLE IV. Top DBP KO NST Genes

Gene Symbol—Description	Mouse Brain region(s)—Direction of change	Mouse Blood	Mouse Genetic/Evidence (QTL/transgenic)	Human Genetic Evidence	Human Postmortem Brain	Human Blood	CFGS core
Cnp, cyclic nucleotide phosphodiesterase 1	PFC-D	D	Chr 11, abnormal eating/drinking behavior, addiction/drug abuse	17q21.2, alcohol [Dick et al., 2006], autism [Cantor et al., 2005]	D depression [Aston et al., 2005], D alcohol [Lewohl et al., 2000; Liu et al., 2006], D SZ [Hakak et al., 2001; Davis et al., 2003; Flynn et al., 2003; Aston et al., 2004; Dracheva et al., 2005; McInnes and Lauriat, 2006; Peirce et al., 2006; McCullumsmith et al., 2007]		5.0
Drd2, dopamine receptor 2	AMY-D		Chr 9, abnormal eating/drinking behavior, abnormal emotion/affect behavior, addiction/drug abuse	11q23.92, alcohol [Sun et al., 1999]	I BP [Ryan et al., 2006], D depression [Torrey et al., 2005], D alcohol [Noble et al., 1991], D SZ [Seeman et al., 1997; Dean et al., 2004; Torrey et al., 2005], D Marijuana [Wang et al., 2004b], I Tourette Syndrome [Minzer et al., 2004]	I SZ [Zvara et al., 2005]	4.5
Clk1, CDC-like kinase 1	AMY-I		Chr 1, addiction/drug abuse	2q33.1, alcohol [Schuckit et al., 2001; Hill et al., 2004], SZ [Paunio et al., 2004; Takahashi et al., 2005], autism [Shao et al., 2002]	D alcohol [Lewohl et al., 2000]	D SZ [Glatt et al., 2005]	4.5
Itgav, integrin alpha V	AMY-I		Chr 2, addiction/drug abuse, abnormal eating/drinking behavior	2q32.1, BP [Cichon et al., 2001], alcohol [Schuckit et al., 2001], autism [Buxbaum et al., 2001; Shao et al., 2002; Vorstman et al., 2006]		I BP [Middleton et al., 2005]	4.0
Gls, glutaminase	AMY-I		Chr 1, addiction/drug abuse	2q32.2, BP [Cichon et al., 2001], alcohol [Schuckit et al., 2001; Hill et al., 2004], SZ [Takahashi et al., 2005], autism [Buxbaum et al., 2001; Shao et al., 2002; Vorstman et al., 2006]		D PTSD [Segman et al., 2005]	4.0
Scg2, secretogranin II	AMY-D		Chr 1, abnormal sleep pattern/circadian rhythm, addiction/drug abuse	2q36.1, alcohol [Valdes et al., 1999; Nurnberger et al., 2001; Schuckit et al., 2001], SZ [Cardno et al., 2001; Paunio et al., 2004]	I SZ [Hakak et al., 2001], D alcohol [Mayfield et al., 2002]		4.0
Avp, arginine vasopressin	AMY-D		Chr 2, addiction/drug abuse	20p13, BP [McQueen et al., 2005]	I depression [Meynen et al., 2007]		4.0
Nos1, Nitric oxide synthase 1, neuronal (Nos1), mRNA	AMY-D		Chr 5, abnormal emotion/affect behavior, abnormal sleep pattern/circadian rhythm	12q24.22, BP [Morissette et al., 1999; Chagnon et al., 2004], SZ [Fallin et al., 2003]	I BP [Benes et al., 2005]		4.0
Sparc, secreted acidic cysteine rich glycoprotein	AMY-D		Chr 11, abnormal emotion/affect behavior, abnormal eating/drinking behavior	5q33.1, BP [Sklar et al., 2004], Psychosis [Sklar et al., 2004], alcohol [Sun et al., 1999; Dick et al., 2002a], SZ [Gurling et al., 2001; Devlin et al., 2002; Suzuki et al., 2003; Sklar et al., 2004], Epilepsy [Chou et al., 2003]	I BP [Iwamoto et al., 2004] Tay-Sachs and Sandhoff diseases [Myerowitz et al., 2002]		4.0
Camk2a, calcium/calmodulin-dependent protein kinase II alpha	AMY-I		Chr 18, abnormal Sleep pattern/circadian rhythm, abnormal emotion/affect behavior, addiction/drug abuse, abnormal eating/drinking behavior	5q32, BP [Sklar et al., 2004], Psychosis [Sklar et al., 2004], alcohol [Sun et al., 1999], SZ [Devlin et al., 2002; Lewis et al., 2003; Sklar et al., 2004]	I BP [Molnar et al., 2003], D BP [Xing et al., 2002], I depression [Novak et al., 2006], I SZ [Novak et al., 2006]		4.0
Oprl1, opioid receptor-like 1	AMY-D		Chr 2, abnormal emotion/affect behavior, addiction/drug abuse	20q13.33, BP [Radhakrishna et al., 2001], SZ [Freedman et al., 2001], alcohol [Schuckit et al., 2001]	I BP [Ryan et al., 2006]		4.0
Timp3, tissue inhibitor of metalloproteinase 3	AMY-D		Chr 10, addiction/drug abuse	22q12.3, BP [Kelsoe et al., 2001; Potash et al., 2003], panic disorder [Hamilton et al., 2003]	I alcohol [Flatscher-Bader et al., 2005]		4.0

Gabrb3, gamma-aminobutyric acid (GABA-A) receptor, subunit beta 3	AMY-D, PFC-D		Chr 7, addiction/drug abuse	15q12, BP [Kerbeshian et al., 1990], SZ [Fallin et al., 2004; Maziade et al., 2005]	I alcohol [Mitsuyama et al., 1998], D epilepsy [Arion et al., 2006], D multiple sclerosis [Dutta et al., 2006]		4.0
Lmo2, LIM domain only 2	AMY-D		Chr 2, addiction/drug abuse	11p13, BP [McInnes et al., 1996; Detera-Wadleigh et al., 1999], autism [Yonan et al., 2003; Buxbaum et al., 2004; Vorstman et al., 2006]	D alcohol [Lewohl et al., 2000], D SZ [Arion et al., 2007]		4.0
Gad1, glutamic acid decarboxylase 1	AMY-D		Chr 2, Abnormal eating/drinking behavior, Addiction/drug abuse	2q31.1, BP [Cichon et al., 2001; Cheng et al., 2006], alcohol [Schuckit et al., 2001]	D BP [Konradi et al., 2004], I SZ (Straub et al., 2007), D epilepsy [Arion et al., 2006]		4.0
Apc, adenomatosis polyposis coli	AMY-I		Chr 18, abnormal eating/drinking behavior	5q22.2, alcohol [Hill et al., 2004]	D BP [Iwamoto et al., 2005], I alcohol [Sokolov et al., 2003a], I SZ [Glatt et al., 2005]		4.0
Dlx1, distal-less homeobox 1	AMY-D		Chr 2, abnormal eating/drinking behavior, Addiction/drug abuse	2q31.1, BP [Cichon et al., 2001], autism [Buxbaum et al., 2001], [Vorstman et al., 2006]	D BP [Kromkamp et al., 2003], D SZ [Kromkamp et al., 2003]		4.0
Mog, myelin oligodendrocyte glycoprotein	PFC-D, AMY-D		Chr 17, abnormal sleep pattern/circadian rhythm, Abnormal eating/drinking behavior	6p22.1, BP [Turecki et al., 2001; Schulze et al., 2004], Psychosis [Kohn et al., 2004], SZ [Straub et al., 2002b; Suarez et al., 2006], alcohol [Wyszynski et al., 2003]	D BP [Tkachev et al., 2003], D MDD [Aston et al., 2005], D alcohol [Lewohl et al., 2000], D SZ [Tkachev et al., 2003; McInnes and Lauriat, 2006], I Epilepsy [Arion et al., 2006]		4.0
Kcnab1, potassium voltage-gated channel, shaker-related subfamily, beta member 1	AMY-D		Chr 3, abnormal emotion/affect behavior	3q25.31, BP [Badenhop et al., 2002; Curtis et al., 2003], SZA [Badenhop et al., 2002], Simple Phobia [Gelernter et al., 2003], Agoraphobia [Gelernter et al., 2001]	D alcohol [Sokolov et al., 2003a]		4.0
Col4a1, procollagen, type IV, alpha 1	AMY-I		Chr 8, addiction/drug abuse	13q34, BP [Kelsoe et al., 2001], [Maziade et al., 2005]	D alcohol [Flatscher-Bader et al., 2005]		4.0
Hnrpdl, heterogeneous nuclear ribonucleoprotein D-like	AMY-I	D	Chr 5, abnormal emotion/affect behavior, addiction/drug abuse	4q21.22, BP [Curtis et al., 2003; Lambert et al., 2005], alcohol [Reich et al., 1998], SZ [Paunio et al., 2004]			4.0
Kcnj4, potassium inwardly-rectifying channel, subfamily J, member 4	AMY-I		Chr 15, abnormal sleep pattern/circadian rhythm, abnormal emotion/affect behavior, addiction/drug abuse	22q13.1, BP [Kelsoe et al., 2001; Potash et al., 2003], panic disorder [Hamilton et al., 2003]		I SZ [Zvara et al., 2005]	3.5
Gnb1, guanine nucleotide binding protein, beta 1	AMY-D, PFC-D		Chr 4, addiction/drug abuse	1p36.33	I SZ [Clark et al., 2006], D SZ [Hemby et al., 2002]	I BP [Middleton et al., 2005]	3.5
Enah, enabled homolog (Drosophila) (Enah), mRNA	AMY-I		Chr 1, abnormal sleep pattern/circadian rhythm, abnormal emotion/affect behavior, addiction/drug abuse	1q42.12, BP [Curtis et al., 2003; Macgregor et al., 2004], SZ [Hovatta et al., 1999; Blackwood et al., 2001; Ekelund et al., 2001; Paunio et al., 2004], autism [Buxbaum et al., 2004; Vorstman et al., 2006], panic disorder [Hamilton et al., 2003]	I SZ [Glatt et al., 2005]		3.5
Lpl, lipoprotein lipase	AMY-D		Chr 8, abnormal emotion/affect behavior	8p21.3, BP [Cheng et al., 2006], SZ [Kendler et al., 1996; Blouin et al., 1998; Brzustowicz et al., 1999; Brzustowicz et al., 2000; Pulver et al., 2000; Gurling et al., 2001; Chiu et al., 2002; Straub et al., 2002b; Straub et al., 2002b; Maziade et al., 2005; Maziade et al., 2005; Suarez et al., 2006]	I SZ [Glatt et al., 2005]		3.5
Clic4, chloride intracellular channel 4 (mitochondrial)	PFC-D			1p36.11, BP [Cichon et al., 2001], SZ [Straub et al., 2002b]		I BP [Middleton et al., 2005]	3.0
Ppp3cb, protein phosphatase 3, catalytic subunit, beta isoform	AMY-D			10q22.2, BP [Rice et al., 1997; Maziade et al., 2005], Alzheimers [Blacker et al., 2003]	I SZ [Hakak et al., 2001], I alcohol [Lewohl et al., 2000]		3.0

(*Continued*)

TABLE IV. (*Continued*)

Gene Symbol—Description	Mouse Brain region(s)—Direction of change	Mouse Blood	Mouse Genetic/Evidence (QTL/transgenic)	Human Genetic Evidence	Human Postmortem Brain	Human Blood	CFGS core
Ywhaz, tyrosine 3-monooxygenase/ tryptophan 5-monooxygenase activation protein, zeta polypeptide	AMY-I, PFC-I	I		8q22.3	I BP [Nakatani et al., 2006], D BP [Konradi et al., 2004], D SZ [Glatt et al., 2005], D alcohol [Flatscher-Bader et al., 2005]		3.0
Card10, caspase recruitment domain family, member 10	AMY-D			22q13.1, BP [Kelsoe et al., 2001; Potash et al., 2003], panic disorder [Hamilton et al., 2003]	I alcohol [Sokolov et al., 2003a]		3.0
Rims3, regulating synaptic membrane exocytosis 3	AMY-D			1p34.2, SZ [Fallin et al., 2003], anorexia nervosa [Grice et al., 2002]	I SZ [Weidenhofer et al., 2006], I alcohol [Lewohl et al., 2000]		3.0
Prpf4b, PRP4 pre-mRNA processing factor 4 homolog B (yeast)	AMY-I			6p25.2, SZ [Straub et al., 1995; Maziade et al., 1997], alcohol [Hill et al., 2004]	I BP, Major Depression, SZ [Iwamoto et al., 2004]		3.0
Cldn11, claudin 11 (oligodendrocyte transmembrane protein)	PFC-D, AMY-D			3q26.2, BP [Cichon et al., 2001], SZ [DeLisi et al., 2002]	D SZ [Tkachev et al., 2003; Dracheva et al., 2005; McInnes and Lauriat, 2006], D BP [Tkachev et al., 2003], I SZ [Weidenhofer et al., 2006]		3.0
Enpp2, ectonucleotide pyrophosphatase/ phosphodiesterase 2 (autotaxin)	PFC-D			8q24.12, BP [Cichon et al., 2001; Badenhop et al., 2002; Park et al., 2004], SZA [Badenhop et al., 2002], autism [Liu et al., 2001], [Ylisaukko-oja et al., 2006]	D MDD [Aston et al., 2005], D alcohol [Lewohl et al., 2000], [Liu et al., 2004], I alcohol [Mayfield et al., 2002]		3.0
Mapk8, mitogen activated protein kinase 8	AMY-I			10q11.22, BP [Rice et al., 1997], panic disorder [Hamilton et al., 2003], SZ [Straub et al., 1998], [Straub et al., 2002b]	D MDD [Aston et al., 2005]		3.0
Baiap3, BAI1-associated protein 3	AMY-D			16p13.3, BP [Ewald et al., 2002], alcohol [Foroud et al., 1998]	D BP [Nakatani et al., 2006]		3.0
Chn2, chimerin (chimaerin) 2	AMY-D			7p15.1, Neuroticism [Nash et al., 2004]	D alcohol [Flatscher-Bader et al., 2005]		3.0
Cntnap2, contactin associated protein-like 2	AMY-D			7q35, Unipolar [Curtis et al., 2003]	D alcohol [Flatscher-Bader et al., 2005]		3.0
Schip1, Schwannomin interacting protein 1	AMY-I			3q25.32, BP [Badenhop et al., 2002; Curtis et al., 2003], Simple Phobia [Gelernter et al., 2003], SZA [Badenhop et al., 2002]	D alcohol [Flatscher-Bader et al., 2005]		3.0
Mbp, myelin basic protein	PFC-D			18q23, BP [Coon et al., 1996; Freimer et al., 1996; Ewald et al., 1999; Schulze et al., 2003; Maziade et al., 2005], SZ [Straub et al., 2002b; Lewis et al., 2003]	D BP [Tkachev et al., 2003], D SZ [Tkachev et al., 2003], D alcohol [Lewohl et al., 2000], I alcohol [Liu et al., 2004], D Alzheimer [Wang et al., 2004a]		3.0
Rps6kb2, ribosomal protein S6 kinase, polypeptide 2	AMY-I			11q13.2, BP [Fallin et al., 2004], SZ [Yamada et al., 2004]	alcohol [Mayfield et al., 2002]		3.0
Sgk, serum/glucocorticoid regulated kinase	PFC-D	D		6q23.2, BP [Rice et al., 1997; Ewald et al., 2002], SZ [Kaufmann et al., 1998; Takahashi et al., 2005]			3.0
Slc38a2, solute carrier family 38, member 2	PFC-D	D		12q13.11, Neuroticism [Neale et al., 2005], SZ [Takahashi et al., 2005], panic disorder [Smoller et al., 2001; Fyer et al., 2006]			3.0
Gpm6b, glycoprotein M6B	AMY-I			Xp22.2	D alcohol [Lewohl et al., 2000], I alcohol [Mayfield et al., 2002], I SZ [Vawter et al., 2001]	D SZ [Middleton et al., 2005]	2.5
Calb2, calbindin 2	AMY-D			16q22.2, alcohol [Sheffield et al., 1999]	D SZ [Beasley et al., 2002], I SZ [Weidenhofer et al., 2006]		2.5
Pctk1, PCTAIRE-motif protein kinase 1	AMY-I			Xp11.3	I BP [Nakatani et al., 2006], D SZ [Glatt et al., 2005]		2.0
Abhd14a, abhydrolase domain containing 14A	AMY-D	D		3p21.2			2.0

Ap1s2, adaptor-related protein complex 1, sigma 2 subunit	AMY-D	D	Xp22.2			2.0
B230337E12Rik, RIKEN cDNA B230337E12 gene	AMY-I	D				2.0
Mal2 mal, T-cell differentiation protein 2	AMY-D PFC-D		8q23, BP [Cichon et al., 2001; Badenhop et al., 2002; Park et al., 2004], SZA [Badenhop et al., 2002], autism [Liu et al., 2001; Ylisaukko-oja et al., 2006]			2.0
Chrdl1, chordin-like 1	AMY-I		Xq23	I SZ [Glatt et al., 2005]		1.5
Hnrpa2b1, heterogeneous nuclear ribonucleoprotein A2/B1	AMY-I		7p15.2	D SZ [Glatt et al., 2005]		1.5
Igsf4c /// **Cadm4**, immunoglobulin superfamily, member 4B	AMY-I		1q23.2	D SZ [Glatt et al., 2005]		1.5

I, increased in expression; D, decreased in expression; Red, candidate blood biomarker genes; BP, bipolar; SZ, schizophrenia; SZA, schizoaffective; MDD, major depressive disorder; PTSD, post traumatic stress disorder.

antidepressant treatments increase Sgk levels in rats [Conti et al., 2007]. Consistent with that, we see Sgk increased in the AMY of the activated, DBK KO ST mice (Table IIS). Sgk has also been implicated in neuronal plasticity and long-term memory formation in rats [Lee et al., 2006]. Memory problems are a common clinical feature of depression in humans.

The top candidate genes/biomarkers for bipolar/activation identified by our CFG analysis in DBP KO ST mice (Fig. 6b) were Snca and Rxrg. Both were decreased in DBP KO ST mice (Fig. 6 and Table V), suggesting that they may play a protective role against activation. Snca (synuclein alpha) is an abundant and conserved pre-synaptic brain protein, implicated as a critical factor in several neurodegenerative diseases [Uversky, 2007]. Snca is decreased in both the brain (amygdala) and blood of DBP KO ST mice, thus being a candidate biomarker. Interestingly, it was also reported increased in lymphoblastoid cell lines of schizophrenia subjects compared to normal controls [Glatt et al., 2005]. Snca is also reported decreased in human postmortem brains from alcoholics [Mayfield et al., 2002; Lewohl et al., 2004], maps to a locus on chromosome 4q22.1 implicated in bipolar [Curtis et al., 2003], alcoholism [Reich et al., 1998], schizophrenia [Paunio et al., 2004], and autism [Buxbaum et al., 2004], as well as maps to a mouse QTL for addiction. Interestingly, Snca was recently shown in human genetic association studies to be associated with alcohol craving [Foroud et al., 2007] which is consistent with the increase in alcohol consumption we see in our DBP KO ST mice. The decreased levels of Snca we see in brain and blood in our mouse model, co-directional with the decrease reported in postmortem brains from alcoholics, suggests that it may have a protective role against alcoholism, and studying its' levels in human blood may be an interesting area for future research looking at potential biomarkers for alcoholism, cravings, and risk of relapse. Overall, the data on Snca is a remarkable example of translational convergence, and an unexpectedly strong validation of the relevance of our animal model. Rxrg (retinoid X receptor, gamma), a nuclear receptor member of the retinoid-signaling pathway, has been implicated in circadian and seasonal changes in energy metabolism and body weight [Ross et al., 2004]. Rxrg KO mice have been reported to have thyroid hormone resistance and increased metabolic rate [Brown et al., 2000]. This may be consistent with our finding of decreased Rxrg in the PFC of the activated DBP KO ST mice (Table V). RXRG has also been reported to be changed in lymphocytes from patients with PTSD [Segman et al., 2005], is decreased in postmortem brain from alcoholics [Lewohl et al., 2000], maps to a linkage locus on chromosome 1q23.3 for bipolar disorder [Fallin et al., 2004], alcoholism [Kuo et al., 2006b], schizophrenia [Gurling et al., 2001], and autism [Ylisaukko-oja et al., 2006], as well as maps to mouse QTL for addiction and for abnormal circadian and emotional behavior.

Other novel candidates genes/biomarkers for bipolar/activation from the DBP KO ST mice include Sfpq, Hspa1a, Fos, Mal, Drd2, Jak1, Egr1, Gnb1, and Lpl.

Biological Roles

An interrogation of our candidate genes from NST and ST mice, for classification in functional groups that had been previously implicated or hypothesized to have relevance to the pathophysiology of bipolar and related disorders, yielded genes related to glia/myelin function, GABA, glutamate, dopamine, circadian clocks, G-protein coupled receptors, signal transduction, transcription factors, neuropeptides, synaptic function, transporters, ion channels, and neuronal migration/neurite growth (Table IIS).

Our studies show gene expression changes in two key dopamine receptor genes. Drd1 and Drd2 are both decreased in the PFC of DBP KO ST mice. Human genetic association

TABLE V. Top DBP KO ST Genes

Gene Symbol—Description	Mouse Brain region(s)—Direction of change	Mouse Blood	Mouse Genetic/Evidence (QTL/transgenic)	Human Genetic Evidence	Human Postmortem Brain	Human blood	CFG Score
Snca, synuclein, alpha	AMY-D	D	Chr 6, addiction/drug abuse, abnormal eating/drinking behavior	4q22.1, BP [Curtis et al., 2003], alcohol [Reich et al., 1998; Williams et al., 1999; Wyszynski et al., 2003], SZ [Paunio et al., 2004], autism [Buxbaum et al., 2004; Vorstman et al., 2006]	D alcohol [Mayfield et al., 2002; Lewohl et al., 2004], I alcohol [Lewohl et al., 2000]	I SZ [Glatt et al., 2005]	5.5
Rxrg, retinoid X receptor gamma	PFC-D		Chr 1, abnormal sleep pattern/circadian rhythm, abnormal emotion/affect behavior, addiction/drug abuse	1q23.3, BP [Fallin et al., 2004], autism [Ylisaukko-oja et al., 2006], alcohol [Hill et al., 2004; Guerrini et al., 2005; Kuo et al., 2006b], SZ [Gurling et al., 2001]	D alcohol [Lewohl et al., 2000]	I PTSD [Segman et al., 2005]	5.0
Drd2, dopamine receptor 2	PFC-D		Chr 9, abnormal eating/drinking behavior, abnormal emotion/affect behavior, addiction/drug abuse	11q23.92, alcohol [Sun et al., 1999]	I BP [Ryan et al., 2006], D depression [Torrey et al., 2005], D alcohol [Noble et al., 1991], D SZ [Seeman et al., 1997; Dean et al., 2004; Torrey et al., 2005], I Tourette syndrome [Minzer et al., 2004], D Marijuana [Wang et al., 2004b]	I SZ [Zvara et al., 2005]	4.5
Hspa1a, heat shock protein 1A	PFC-I		Chr 17, abnormal sleep pattern/circadian rhythm, abnormal eating/drinking behavior	6p21.3, BP [Turecki et al., 2001], psychosis [Kohn et al., 2004], alcohol [Wyszynski et al., 2003], SZ [Lindholm et al., 2001; Straub et al., 2002a; Fallin et al., 2003; Suarez et al., 2006],	I SZ [Clark et al., 2006], D autism [Purcell et al., 2001]	I Stress [Ohmori et al., 2005]	4.5
Sfpq, splicing factor proline/glutamine rich (polypyrimidine tract binding protein associated)	AMY-I		Chr 4, abnormal emotion/affect behavior	1p34.3, SZ [Straub et al., 2002b], anorexia nervosa [Grice et al., 2002]	I BP [Nakatani et al., 2006]	D SZ [Glatt et al., 2005]	4.5
Cnp, cyclic nucleotide phosphodiesterase 1	PFC-D		Chr 11, abnormal eating/drinking behavior, addiction/drug abuse	17q21.2, BP [Segurado et al., 2003], alcohol [Dick et al., 2006], SZ [Lewis et al., 2003; Peirce et al., 2006], autism [Cantor et al., 2005]	D depression [Aston et al., 2005], D alcohol [Lewohl et al., 2000; Liu et al., 2006], D SZ [Hakak et al., 2001; Davis et al., 2003; Flynn et al., 2003; Aston et al., 2004; Dracheva et al., 2005; McInnes and Lauriat, 2006; Peirce et al., 2006; McCullumsmith et al., 2007]		4.0
Fos, FBJ osteosarcoma oncogene	AMY-I		Chr 12, abnormal sleep pattern/circadian rhythm, abnormal emotion/affect behavior, abnormal eating/drinking behavior, addiction/drug abuse	14q24.3, SZ [Takahashi et al., 2005], alcohol [Hill et al., 2004], simple phobia [Gelernter et al., 2003]		I PTSD [Segman et al., 2005]	4.0
Jak1, Janus kinase 1	AMY-D		Chr 4, abnormal sleep pattern/circadian rhythm, abnormal eating/drinking behavior, abnormal emotion/affect behavior, addiction/drug abuse	1p31.3, BP [Rice et al., 1997; Cichon et al., 2001], alcohol [Nurnberger et al., 2001; Schuckit et al., 2001], depression [Nurnberger et al., 2001]		I BP [Middleton et al., 2005]	4.0
Mal, myelin and lymphocyte protein, T-cell differentiation protein	PFC-D			2q11.1, alcohol [Reich et al., 1998; Foroud et al., 2000; Wyszynski et al., 2003], SZ [Chen et al., 1998; DeLisi et al., 2002; Straub et al., 2002b; Lewis et al., 2003]	D depression [Aston et al., 2005], D alcohol [Lewohl et al., 2000], D SZ [Hakak et al., 2001; Davis et al., 2003; McInnes and Lauriat, 2006]	D BP [Middleton et al., 2005], I BP [Matigian et al., 2007]	4.0

Rab5c, RAB5C, member RAS oncogene family	AMY-I	Chr 11, abnormal eating/ drinking behavior, addiction/drug abuse	17q21.2, alcohol [Dick et al., 2006], autism [Cantor et al., 2005]	Increase BP [Nakatani et al., 2006]	4.0
Gabra1, gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 1	PFC-D	Chr 11, abnormal emotion/ affect behavior, abnormal eating/drinking behavior, addiction/drug abuse	5q34-q35, alcohol [Dick et al., 2002a], BP [Morissette et al., 1999; Sklar et al., 2004], SZ [Sklar et al., 2004], psychosis [Sklar et al., 2004]	I SZ [Deng and Huang, 2006; Hakak et al., 2001], D multiple sclerosis [Dutta et al., 2006], I BP [Ishikawa et al., 2004], D suicide [Sequeira et al., 2007]	4.0
Rgs4, regulator of G-protein signalling 4	PFC-D	Chr 1, abnormal emotion/ affect behavior, abnormal sleep pattern/circadian rhythm, addiction/drug abuse	1q23.3, BP [Fallin et al., 2004; Fallin et al., 2005], alcohol [Hill et al., 2004; Guerrini et al., 2005; Kuo et al., 2006b], SZ [Brzustowicz et al., 2000; Gurling et al., 2001; Fallin et al., 2005], autism[Auranen et al., 2002; Vorstman et al., 2006; Ylisaukko-oja et al., 2006],	I alcohol [Lewohl et al., 2000], D SZ [Chowdari et al., 2002; Prasad et al., 2005; Erdely et al., 2006; Lipska et al., 2006; Arion et al., 2007], D Alzheimers [Emilsson et al., 2006]	4.0
Crym, crystallin, mu	AMY-D	Chr 7, abnormal eating/ drinking behavior, addiction/drug abuse	16p12.2, BP [Dick et al., 2002a; Maziade et al., 2005; Cheng et al., 2006], SZ [Maziade et al., 2005], panic disorder [Crowe et al., 2001]	D alcohol [Mayfield et al., 2002], D SZ [Arion et al., 2007], I SZ [Hakak et al., 2001], D Alzheimers [Emilsson et al., 2006]	4.0
Gfap, glial fibrillary acidic protein	AMY-I	Chr 11, abnormal emotion/ affect behavior, abnormal eating/drinking behavior, Addiction/drug abuse	17q21.31, alcohol [Dick et al., 2006], SZ [Lewis et al., 2003], SZA [Vincent et al., 1999], autism [Cantor et al., 2005]	D BP [Tkachev et al., 2003; Webster et al., 2005], D depression [Fatemi et al., 2004], D alcohol [Lewohl et al., 2000; Mayfield et al., 2002; Liu et al., 2004], I SZ [Tkachev et al., 2003], D SZ [Vawter et al., 2001; Webster et al., 2005; Clark et al., 2006], I autism [Purcell et al., 2001]	4.0
Pik3r1, phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	PFC-D	Chr 13, abnormal emotion/ affect behavior, abnormal eating/drinking behavior	5q13.1, psychosis [Kohn et al., 2004], alcohol [Hill et al., 2004], SZ [Suarez et al., 2006]	D MDD [Aston et al., 2005]	4.0
Ptprt, Protein tyrosine phosphatase, receptor type, T	AMY-I	Chr 2, abnormal eating/ drinking behavior, addiction/drug abuse	20q12, BP [Radhakrishna et al., 2001], alcohol [Hill et al., 2004]	D MDD [Aston et al., 2005]	4.0
Syt1, synaptotagmin I	PFC-D	Chr 10, abnormal eating/ drinking behavior, abnormal emotion/affect behavior	12q21.2, BP [Morissette et al., 1999]	D BP [Ryan et al., 2006], D alcohol [Flatscher-Bader et al., 2005], D heroin [Albertson et al., 2006], D SZ [Hemby et al., 2002], D SZ [Sokolov et al., 2000]	4.0
Gad1, glutamic acid decarboxylase 1	PFC-D	Chr 2, abnormal eating/ drinking behavior, addiction/drug abuse	2q31.1, BP [Cichon et al., 2001; Cheng et al., 2006], alcohol [Schuckit et al., 2001]	D epilepsy [Arion et al., 2006], D BP [Konradi et al., 2004]	4.0
Atn1, atrophin 1	PFC-I	Chr 6, abnormal emotion/ affect behavior, abnormal eating/drinking behavior, addiction/drug abuse	12p13.31, alcohol [Hill et al., 2004]	D BP [Nakatani et al., 2006]	4.0
Ckmt1, creatine kinase, mitochondrial 1 (ubiquitous)	AMY-D	Chr 2, abnormal emotion/ affect behavior	15q15.3, alcohol [Dick et al., 2002b], SZ [Stober et al., 2000; Freedman et al., 2001; Maziade et al., 2005]	D BP [Jurata et al., 2004]	4.0
Mog, myelin oligodendrocyte glycoprotein	PFC-D	Chr 17, abnormal sleep pattern/circadian rhythm, abnormal eating/drinking behavior	6p22.1, BP [Turecki et al., 2001; Schulze et al., 2004], alcohol [Wyszynski et al., 2003], psychosis [Kohn et al., 2004], SZ [Straub et al., 2002b; Suarez et al., 2006]	D BP [Tkachev et al., 2003], D depression [Aston et al., 2005], D alcohol [Lewohl et al., 2000], D SZ [Tkachev et al., 2003; McInnes and Lauriat, 2006], I epilepsy [Arion et al., 2006]	4.0
Kcnab1, potassium voltage-gated channel, shaker-related subfamily, beta member 1	PFC-D	Chr 3, abnormal emotion/ affect behavior	3q25.31, BP [Badenhop et al., 2002; Curtis et al., 2003], SZA [Badenhop et al., 2002], simple phobia [Gelernter et al., 2003], agoraphobia [Gelernter et al., 2001]	D alcohol [Sokolov et al., 2003a]	4.0

(*Continued*)

TABLE V. (*Continued*)

Gene Symbol—Description	Mouse Brain region(s)—Direction of change	Mouse Blood	Mouse Genetic/Evidence (QTL/transgenic)	Human Genetic Evidence	Human Postmortem Brain	Human blood	CFG Score
Spop, speckle-type POZ protein	PFC-D		Chr 11, abnormal eating/ drinking behavior, addiction/drug abuse	17q21.33, alcohol [Dick et al., 2006], autism [Cantor et al., 2005]	D alcohol [Sokolov et al., 2003a]		4.0
Ptprk, protein tyrosine phosphatase, receptor type, K	AMY-D		Chr 10, addiction/drug abuse, abnormal emotion/affect behavior	6q22.33, BP [Park et al., 2004], alcohol [Sun et al., 1999], SZ [Straub et al., 2002b]	D alcohol [Lewohl et al., 2000]		4.0
Col4a1, procollagen, type IV, alpha 1	PFC-I		Chr 8, addiction/drug abuse	13q34, BP [Kelsoe et al., 2001; Maziade et al., 2005]	D alcohol [Flatscher-Bader et al., 2005]		4.0
Timp2, tissue inhibitor of metalloproteinase 2	PFC-D		Chr 11, addiction/drug abuse, abnormal emotion/affect behavior	17q25, Unipolar [Curtis et al., 2003]	D alcohol [Flatscher-Bader et al., 2005], D alcohol [Liu et al., 2006]		4.0
Gsk3b, glycogen synthase kinase 3 beta	AMY-I PFC-D		Chr 16, abnormal emotion/ affect behavior	3q13.33, BP [Maziade et al., 2005]	D SZ [Kozlovsky et al., 2000; Torrey et al., 2005], D BP [Nakatani et al., 2006; Vawter et al., 2006], I MDD [Vawter et al., 2006]		4.0
Egr1, early growth response 1	AMY-I		Chr 18, abnormal emotion/ affect behavior, abnormal eating/drinking behavior	5q31.2, SZ [Straub et al., 1997; Devlin et al., 2002]	D SZ [Yamada et al., 2007]	I SZ [Middleton et al., 2005]	3.5
Gnb1, guanine nucleotide binding protein, beta 1	PFC-I		Chr 4, addiction/drug abuse	1p36.33	I SZ [Clark et al., 2006], D SZ [Hemby	I BP [Middleton et al., 2005]	3.5
Lpl, lipoprotein lipase	AMY-D, PFC-D		Chr 8, abnormal emotion/ affect behavior	8p21.3, BP [Cheng et al., 2006], SZ [Kendler et al., 1996; Blouin et al., 1998; Brzustowicz et al., 1999; Brzustowicz et al., 2000; Pulver et al., 2000; Gurling et al., 2001; Chiu et al., 2002; Straub et al., 2002b; Maziade et al., 2005; Cheng et al., 2006; Suarez et al., 2006]	I SZ [Glatt et al., 2005]		3.5
Gnai1, guanine nucleotide binding protein, alpha inhibiting 1	PFC-D			7q21.11, BP [Lambert et al., 2005], alcohol [Wang et al., 2005], panic disorder [Cheng et al., 2006], autism [Barrett et al., 1999; Liu et al., 2001; Vorstman et al., 2006]	D BP [Jurata et al., 2004]		3.0
Calb1, calbindin-28K	AMY-D			8q21.3, BP [Liu et al., 2003]	D BP, SZ [Torrey et al., 2005], BP [Shamir et al., 2005], I SZ [Iritani et al., 1999; Weidenhofer et al., 2006], Alzheimer [Ferrer et al., 1993]		3.0
Csrp1, cysteine and glycine-rich protein 1	PFC-D			1q32.1, alcohol [Sun et al., 1999], panic disorder [Smoller et al., 2001], anorexia nervosa [Devlin et al., 2002], SZ [Paunio et al., 2004]	D alcohol [Lewohl et al., 2000; Sokolov et al., 2003a], I epilepsy [Arion et al., 2006], D SZ [Hakak et al., 2001]		3.0
Rnf13, ring finger protein 13	PFC-D			3q25.1, BP [Badenhop et al., 2002; Curtis et al., 2003], SZA [Badenhop et al., 2002], simple phobia [Gelernter et al., 2003], agoraphobia [Gelernter et al., 2001]	I BP [Nakatani et al., 2006]		3.0
Tra1, tumor rejection antigen gp96	PFC-D			12q23.3, BP [Maziade et al., 2005], alcohol [Hill et al., 2004], SZ [Maziade et al., 2005]	I BP [Jurata et al., 2004]		3.0
Prpf4b, PRP4 pre-mRNA processing factor 4 homolog B (yeast)	PFC-I			6p25.2, alcohol [Hill et al., 2004], SZ [Straub et al., 1995; Maziade et al., 1997]	I BP [Iwamoto et al., 2004]		3.0
Prkacb, protein kinase, cAMP dependent, catalytic, beta	PFC-D			1p31.1, depression [Nurnberger et al., 2001], BP [Rice et al., 1997], alcohol [Reich et al., 1998; Peterson et al., 1999; Foroud et al., 2000; Nurnberger et al., 2001; Schuckit et al., 2001; Guerrini et al., 2005], SZ [Brzustowicz et al., 2000]	D alcohol [Lewohl et al., 2000], I Alzheimers [Emilsson et al., 2006]		3.0

Ptp4a2, protein tyrosine phosphatase 4a2	PFC-D		1p35.2, BP [Cichon et al., 2001], SZ [Straub et al., 2002b]	D MDD [Aston et al., 2005], I SZ [Vawter et al., 2004], I suicide [Sequeira et al., 2007]		3.0
Arpc3, actin related protein 2/3 complex, subunit 3	PFC-I		12q24.11, BP [Chagnon et al., 2004], alcohol [Hill et al., 2004], SZ [Fallin et al., 2003]	D BP [Konradi et al., 2004]		3.0
Dnm1l, dynamin 1-like	PFC-D		12p11.21, neuroticism [Neale et al., 2005], SZ [Takahashi et al., 2005], panic disorder [Smoller et al., 2001; Fyer et al., 2006]	D BP [Konradi et al., 2004]		3.0
Pja2, praja 2, RING-H2 motif containing	PFC-D		5q21.3, alcohol [Hill et al., 2004]	D BP [Ryan et al., 2006]		3.0
Cldn11, claudin 11 (oligodendrocyte transmembrane protein)	PFC-D		3q26.2, BP [Cichon et al., 2001], SZ [DeLisi et al., 2002]	D BP [Tkachev et al., 2003], D SZ [Tkachev et al., 2003; Dracheva et al., 2005; McInnes and Lauriat, 2006], I SZ [Weidenhofer et al., 2006]		3.0
Grm3, Glutamate receptor, metabotrophic 3	AMY-I		7q21.12, BP [Lambert et al., 2005], alcohol [Foroud et al., 2000; Wang et al., 2005], panic disorder [Cheng et al., 2006], autism [Barrett et al., 1999; Liu et al., 2001; Vorstman et al., 2006]	D BP [Choudary et al., 2005], SZ [Hemby et al., 2002]		3.0
Gsta4, glutathione S-transferase, alpha 4	AMY-D		6p12.1, BP [Lambert et al., 2005]	D BP [Benes et al., 2005], I BP [Nakatani et al., 2006]		3.0
Mobp, myelin-associated oligodendrocyte basic protein	AMY-I PFC-D	Chr 9, addiction/drug abuse	3p22.2	D BP, SZ [Tkachev et al., 2003], D MDD [Aston et al., 2005], D alcohol [Lewohl et al., 2000], I alcohol [Mayfield et al., 2002]		3.0
Nell2, nel-like 2 homolog (chicken)	PFC-I		12q12, neuroticism [Neale et al., 2005], SZ [Takahashi et al., 2005], panic disorder [Smoller et al., 2001; Fyer et al., 2006]	I alcohol [Lewohl et al., 2000], D Alzheimers [Emilsson et al., 2006], I SZ [Hakak et al., 2001]		3.0
Myt1l, myelin transcription factor 1-like	PFC-D		2p25.3, BP [Detera-Wadleigh et al., 1999], panic disorder [Hamilton et al., 2003], SZ [Cardno et al., 2001]	D alcohol [Liu et al., 2004]		3.0
Tkt, transketolase	PFC-D		3p21.1, alcohol [Foroud et al., 2000], SZ [Macgregor et al., 2004]	D alcohol [Liu et al., 2006]		3.0
Arf3, ADP-ribosylation factor 3	PFC-D		12q13.12, panic disorder [Smoller et al., 2001; Fyer et al., 2006]	D alcohol [Lewohl et al., 2000]		3.0
Mbp, myelin basic protein	PFC-D AMY-I		18q23, BP [Coon et al., 1996; Freimer et al., 1996; Ewald et al., 1999; Schulze et al., 2003; Maziade et al., 2005], SZ [Straub et al., 2002b; Lewis et al., 2003]	D BP [Tkachev et al., 2003], D alcohol [Lewohl et al., 2000], I alcohol [Liu et al., 2004], D SZ [Tkachev et al., 2003], D Alzheimer [Wang et al., 2004a]		3.0
Chn2, chimerin (chimaerin) 2	PFC-D		7p15.1, neuroticism [Nash et al., 2004]	D alcohol [Flatscher-Bader et al., 2005]		3.0
Prkaca, protein kinase, cAMP dependent, catalytic, alpha	PFC-I	Chr 8, addiction/drug abuse	19p13.12, SZA [Hamshere et al., 2005]	D SZ [Glatt et al., 2005]		3.0
Plp1, proteolipid protein (myelin) 1	PFC-D	Chr X, abnormal emotion/affect behavior	Xq22.2	D BP [Tkachev et al., 2003], D depression [Aston et al., 2005], D alcohol [Liu et al., 2006], D SZ [Pongrac et al., 2002; Tkachev et al., 2003; Aberg et al., 2006; McInnes and Lauriat, 2006]		3.0
Csda, cold shock domain protein A	AMY-I		12p13.2, alcohol [Hill et al., 2004]		I SZ [Glatt et al., 2005]	2.5
Mkrn1, makorin, ring finger protein, 1	AMY-I		7q34, Unipolar [Curtis et al., 2003]		I SZ [Glatt et al., 2005]	2.5
Smarce1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1	AMY-I		17q21.2, alcohol [Dick et al., 2006], autism [Cantor et al., 2005]		D SZ [Middleton et al., 2005]	2.5
Arhgap5, Rho GTPase activating protein 5	PFC-D		14q12, alcohol [Hill et al., 2004], SZ [Lerer et al., 2003]	I SZ [Glatt et al., 2005]		2.5

(*Continued*)

TABLE V. (*Continued*)

Gene Symbol—Description	Mouse Brain region(s)—Direction of change	Mouse Blood	Mouse Genetic/Evidence (QTL/transgenic)	Human Genetic Evidence	Human Postmortem Brain	Human blood	CFG Score
Camkk2, calcium/calmodulin-dependent protein kinase kinase 2, beta	PFC-D			12q24.31, SZ [Fallin et al., 2003], BP [Morissette et al., 1999; Chagnon et al., 2004], Unipolar [Curtis et al., 2003], alcohol [Hill et al., 2004]	D SZ [Glatt et al., 2005]		2.5
Calb2, calbindin 2	PFC-D			16q22.2, alcohol [Sheffield et al., 1999]	D SZ [Beasley et al., 2002], I SZ [Weidenhofer et al., 2006]		2.5
Nrip1, nuclear receptor interacting protein 1	PFC-D			21q11.2		D PTSD [Segman et al., 2005]	2.0
Nrip3, nuclear receptor interacting protein 3	PFC-D, AMY-D			11p15.3		D BP [Middleton et al., 2005]	2.0
Hnrpa2b1, heterogeneous nuclear ribonucleoprotein A2/B1	PFC-I			7p15.2		D SZ [Glatt et al., 2005]	1.5
Kctd12, potassium channel tetramerisation domain containing 12	AMY-D			13q22.3		D SZ [Glatt et al., 2005]	1.5
Scamp5, secretory carrier membrane protein 5	PFC-D			15q24.1	D SZ [Glatt et al., 2005]		1.5

I, increased in expression; D, decreased in expression; Red, candidate blood biomarker genes; BP, bipolar; SZ, schizophrenia; SZA, schizoaffective; MDD, major depressive disorder; PTSD, post traumatic stress disorder.

studies and postmortem work support a direct role of Drd1, and to a lesser extent Drd2, in bipolar disorder (see Table IIS). The receptor downregulation, together with their hyperlocomotor phenotype, suggests these mice may have chronic elevated extracellular dopamine levels, a likely feature of elevated mood states/mania [Niculescu et al., 2000; Ralph-Williams et al., 2003; Zarate et al., 2004; Brandish et al., 2005]. Interestingly, and consistent with our results, Drd2 has also been implicated in alcoholism and PTSD [Noble, 2003; Lawford et al., 2006].

In addition to DBP, which was constitutively knocked-out, and Rxrg mentioned above, we found four other clock-related genes, Csnk1e, Tef, Rora, and Rorb [Sato et al., 2004; Kamphuis et al., 2005] (Table IIS) to be changed in DBP KO mice. Csnk1e (casein kinase 1, epsilon) is a core component of the circadian clock. Animal models and human genetic association studies suggest that Csnk1e contributes to variability in stimulant (amphetamine) response [Veenstra-VanderWeele et al., 2006]. Interestingly, Csnk1e is a key component in the Darpp-32 (Dopamine-And-cAMP-Regulated-Phosphoprotein-32 kDa) second messenger pathway. Tef (thyrotrophic embryonic factor) is a transcription factor from the same PAR bZip family as DBP. It binds to and transactivates the Tshb promoter and Bnp promoter [Ma et al., 2005], among others—regulating thyroid hormone levels and fluid-electrolyte levels respectively. Both these activities are related to level of energy and physiological tonus. Consistent with this, Tef is decreased in PFC of DBP KO NST mice, which show a depression-like phenotype. Perhaps consistent with the increased excitability and reactivity to stress of our DBP KO mice, mice deficient for multiple PAR bZip proteins are highly susceptible to generalized spontaneous and audiogenic epilepsies [Gachon et al., 2004]. Both Rorb (RAR-related orphan receptor B) and Rora (RAR-related orphan receptor A) were increased in AMY and decreased in PFC in DBP KO NST mice. Perhaps consistent with our gene expression results and behavioral data, Rora sg/sg mutant mice, which lack Rora activity, exhibit an enhanced response to novel environment stress [Frederic et al., 2006], mediated through corticosterone circadian rhythm abnormalities. Of note, corticosterone abnormalities are prominent clinical findings in human affective disorders patients [Arana et al., 1985].

A number of potassium channel genes, such as Kcnb1 (discussed above), Kcnj10, Kcnv1 and others (Table IIS) are changed in the DBP KO mice. Potassium channels are modulated by anti-epileptic drugs, which are a mainstay of treatment in mood disorders [Amann and Grunze, 2005]. Kcnj10, for example, has been implicated as a susceptibility gene for seizure disorders [Buono et al., 2004], and maps to chromosome 1q23.2 in the vicinity of linkage peaks for bipolar disorder [Fallin et al., 2004] and schizophrenia [Brzustowicz et al., 2000]. Lack of Kcnj10 abolishes K+ buffering properties of astrocytes [Neusch et al., 2006]. We see Kcnj10 decreased in expression in both DBP KO NST and DBP KO ST mice. Taken together with our findings of decreases in glia/myelin related genes discussed above, our results are consistent with an overall glia hypofunction in DBP KO mice, in concordance with findings in human mood disorders and alcoholism patients [Ongur et al., 1998; Manji et al., 2000].

DISCUSSION

We have used phenomic studies and a comprehensive CFG approach in a KO mouse to pursue and biologically validate previous microarray-derived findings of a candidate gene for bipolar disorder and alcoholism. These studies revealed that knocking out DBP leads to a phenotype that is germane to bipolar disorder and alcoholism. Moreover, the phenotype is modulated by behavioral stress. Stress is a well-known major precipitant of bipolar disorder episodes in human patients

TABLE VI. DBP Mouse Brain-Blood Biomarkers

Gene Symbol—Description	NST DBP Blood	NST DBP PFC	NST DBP AMY	Mouse Genetic/Evidence (QTL/transgenic)	Human Genetic Evidence	Human Postmortem Brain	Human blood	CFG Score
Cnp, cyclic nucleotide phosphodiesterase 1	D	D		Chr 11, abnormal eating/drinking behavior, addiction/drug abuse	Alcohol [Dick et al., 2006], autism [Cantor et al., 2005]	D depression [Aston et al., 2005], D alcohol [Lewohl et al., 2000; Liu et al., 2006], D SZ [Davis et al., 2003; Flynn et al., 2003; Dracheva et al., 2005; Peirce et al., 2006]		5.0
Hnrpdl, heterogeneous nuclear ribonucleoprotein D-like	D		I	Chr 5, abnormal emotion/affect behavior, addiction/drug abuse	Alcohol [Reich et al., 1998], SZ [Paunio et al., 2004]			4.0
Ywhaz, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	I	I	I			I BP [Nakatani et al., 2006], D alcohol [Flatscher-Bader et al., 2005], D SZ [Glatt et al., 2005]		3.0
Sgk, serum/glucocorticoid regulated kinase	D	D			BP [Ewald et al., 2002; Venken et al., 2005], SZ [Takahashi et al., 2005]			3.0
Slc38a2, solute carrier family 38, member 2	D	D			Neuroticism [Neale et al., 2005], panic disorder [Fyer et al., 2006]			3.0
Abhd14a, abhydrolase domain containing 14A	D		D					2.0
Ap1s2, adaptor-related protein complex 1, sigma 2 subunit	D		D					2.0
B230337E12Rik, RIKEN cDNA B230337E12 gene	D		I					2.0
Gene Symbol—Description	ST DBP Blood	ST DBP PFC	ST DBP AMY	Mouse Genetic/Evidence (QTL/transgenic)	Human Genetic Evidence	Human Postmortem Brain	Human blood	CFG Score
Snca, synuclein, alpha	D		D	Chr 6, addiction/drug abuse, abnormal eating/drinking behavior	BP [Curtis et al., 2003], Alcohol [Reich et al., 1998; Williams et al., 1999; Foroud et al., 2007], SZ [Paunio et al., 2004], autism [Buxbaum et al., 2004]	D alcohol [Mayfield et al., 2002; Lewohl et al., 2004]	I SZ [Glatt et al., 2005]	5.5

I, increased in expression; D, decreased in expression; Red, candidate blood biomarker genes; BP, bipolar; SZ, schizophrenia; PFC, prefrontal cortex; AMY, amygdala.

TABLE VII. Broad/MIT Connectivity Map Results

Rank	cmap name	Dose	Cell line	Score
(a) PFC				
1	Celecoxib	10 ÂµM	PC3	1
2	Monorden	100 nM	PC3	0.998
452	Valproic acid	1 mM	PC3	−0.964
453	12,13-EODE	200 nM	MCF7	−1
(b) AMY				
1	Arachidonyltrifluoromethane	10 ÂµM	MCF7	1
2	15-Delta prostaglandin J2	10 ÂµM	MCF7	0.908
452	17-Allylamino-geldanamycin	1 ÂµM	SKMEL5	−0.949
453	Iloprost	1 ÂµM	MCF7	−1

Interogation with gene expression pattern of genes switched from NST to ST.

TABLE VIII. Gene Ontology (GO) Analysis

	Number of genes
a: GO analysis—biological processes NST data	
1. Cellular physiological process	315
2. Metabolism	217
3. Cell communication	156
4. Regulation of biological process	119
5. Localization	116
6. Organismal physiological process	81
7. Anatomical structure development	79
8. Response to stimulus	70
9. Death	30
10. Homeostasis	17
11. Cell adhesion	13
12. Locomotion	12
13. Cell recognition	7
13. Growth	7
14. Sexual reproduction	5
14. Pattern specification	5
14. Rhythmic process	5
15. Embryonic development	4
15. Extracellular structure organization and biogenesis	4
16. Reproductive physiological process	3
16. Developmental maturation	3
17. Lysogeny	2
17. Interaction between organisms	2
18. Physiological interaction between organisms	1
18. Pigmentation during development	1
18. postembryonic development	1
Response to stress	
Response to endogenous stimulus	
Behavior	
Response to chemical stimulus	
Response to external stimulus	
Defense response	
Response to abiotic stimulus	
Response to biotic stimulus	
Coagulation	
Segmentation	
b: GO analysis—biological processes ST data (rank of biological process category in DBP NST analysis)	
1. Cellular physiological process (1)	464
2. Cell communication (3)	186
4. Anatomical structure development (7)	127
5. Organismal physiological process (6)	105
3. Metabolism (2)	82
6. Regulation of biological process (4)	53
7. Localization (5)	42
8. Death (9)	38
9. Response to stress (unranked)	33
10. Behavior (unranked)	28
12. Embryonic development (15)	18
11. Response to endogenous stimulus (unranked)	16

(*Continued*)

TABLE VIII. (*Continued*)

	Number of genes
13. Response to external stimulus (unranked)	14
16. Homeostasis (10)	14
14. Sexual reproduction (14)	12
15. Defense response (unranked)	12
16. Pattern specification (14)	12
16. Response to abiotic Stimulus (unranked)	11
24. Extracellular structure organization and biogenesis (15)	7
19. Response to chemical stimulus (unranked)	6
22. Reproductive physiological process (16)	6
22. Response to biotic stimulus (unranked)	6
25. Interaction between organisms (17)	6
20. Growth (13)	5
20. Cell adhesion (11)	5
27. Rhythmic process (14)	5
25. Developmental maturation (16)	4
28. Physiological interaction between organisms (18)	2
29. Coagulation (unranked)	2
30. Segmentation (unranked)	2
31. Cell recognition (13)	1
31. Postembryonic development (18)	1
Response to stimulus (8)	
Lysogeny (17)	
Pigmentation during development (18)	
Locomotion (12)	

Genes changed in (a) DBP NST; (b) DBP ST.

[Ambelas, 1979], and increased alcohol consumption in alcoholics [Koob, 2006]. Microarray studies in the PFC and amygdala (AMY) of mice lacking DBP versus wild-type littermate control mice, with or without exposure to stress, revealed the underlying cascades of gene expression changes that, on the one hand reproduce some of the previous findings in the field by us and others using different approaches, and on the other hand may provide new candidate genes, pathways and mechanisms for bipolar, alcoholism, post-traumatic stress, and related disorders. Furthermore, blood gene expression studies in our animals identified genes that change concomitantly in brain and blood, and thus may represent candidate biomarkers.

Limitations and Confounds

The studies described have a series of potential caveats and limitations. First, the DBP KO mice are a constitutive KO, and there is always the possibility that compensatory changes can occur during development that may obscure the direct effects of DBP deletion. However, of note this is a very good equivalent of the human bipolar disorder genetic scenario, where most mutations are likely constitutive rather than acquired, as reflected in the familial inheritance of the disorder. Second, our mice colony is on a mixed genetic background, generated by heterozygote breeding, not on a back-crossed pure mouse-strain background. While this introduces epistatic variability, it is remarkable that the phenotype remains penetrant across generations and cohorts of mice. Again, however, this is a better model of the human condition, which occurs at a population level in a mixed genetic background, than deriving conclusions from a very particular strain of mice. Third, our behavioral cohorts were relatively small for some of the ST studies, and, while sufficient for locomotor behavior and alcohol consumption, they were probably underpowered to detect statistically significant effects as opposed to trends in some of the other behavioral measures that may be germane to mood disorders, such as sucrose consumption, forced-swim test and tail-suspension test (data not shown). Further studies are needed to more carefully evaluate the behavioral phenotype under a variety of tests and challenges, including pharmacological treatments. Our goal in this first report was to provide a preliminary ascertainment of key phenotypic features, and the gene expression changes underpinning them. Fourth, we have used predominantly male mice for the studies presented in this report. While in our preliminary work we have not observed significant differences at a behavioral level between male and female KO mice, this is an area that merits more careful exploration. Fifth, it is to be noted that our experimental approach for detecting gene expression changes relies on a single methodology, Affymetrix GeneChip oligonucleotide microarrays. It is possible that some of the gene expression changes detected from a single biological experiment, with a one-time assay with this technology, are biological or technical artifacts. With that in mind, we have designed our experiments to minimize the likelihood of having false positives, even at the expense of having false negatives. We compared microarray gene expression data from individual mice, from experiments performed at three different times, with different batches of mice (three mice per genotype per condition). We only considered the genes that were reproducibly changed in the same direction in at least six out of nine independent comparisons. This overall design is geared to factor out both biological and technical variability. It is to be noted that the concordance between reproducible microarray experiments using the latest generations of oligonucleotide microarrays and other methodologies such as quantitative PCR, with their own attendant technical limitations, is estimated to be over 90% [Quackenbush, 2003]. More importantly, our approach, as described above, is based on the concordance of multiple tissues (PFC, AMY, blood), each of which are independent microarray experiments, and has multiple additional external Bayesian cross-validators for each gene that is called reproducibly changed in the KO mice. Top candidate genes, for which there are multiple independent lines of evidence, are less likely to be false positives. The network of lines of evidence for each gene is resilient, even if one or another of the nodes (lines of evidence) is less than optimal. In the end, the results speak for themselves in terms of the ability of our CFG approach to extract signal and prioritize findings, similar to a Google PageRank algorithm [Morrison et al., 2005], from large and

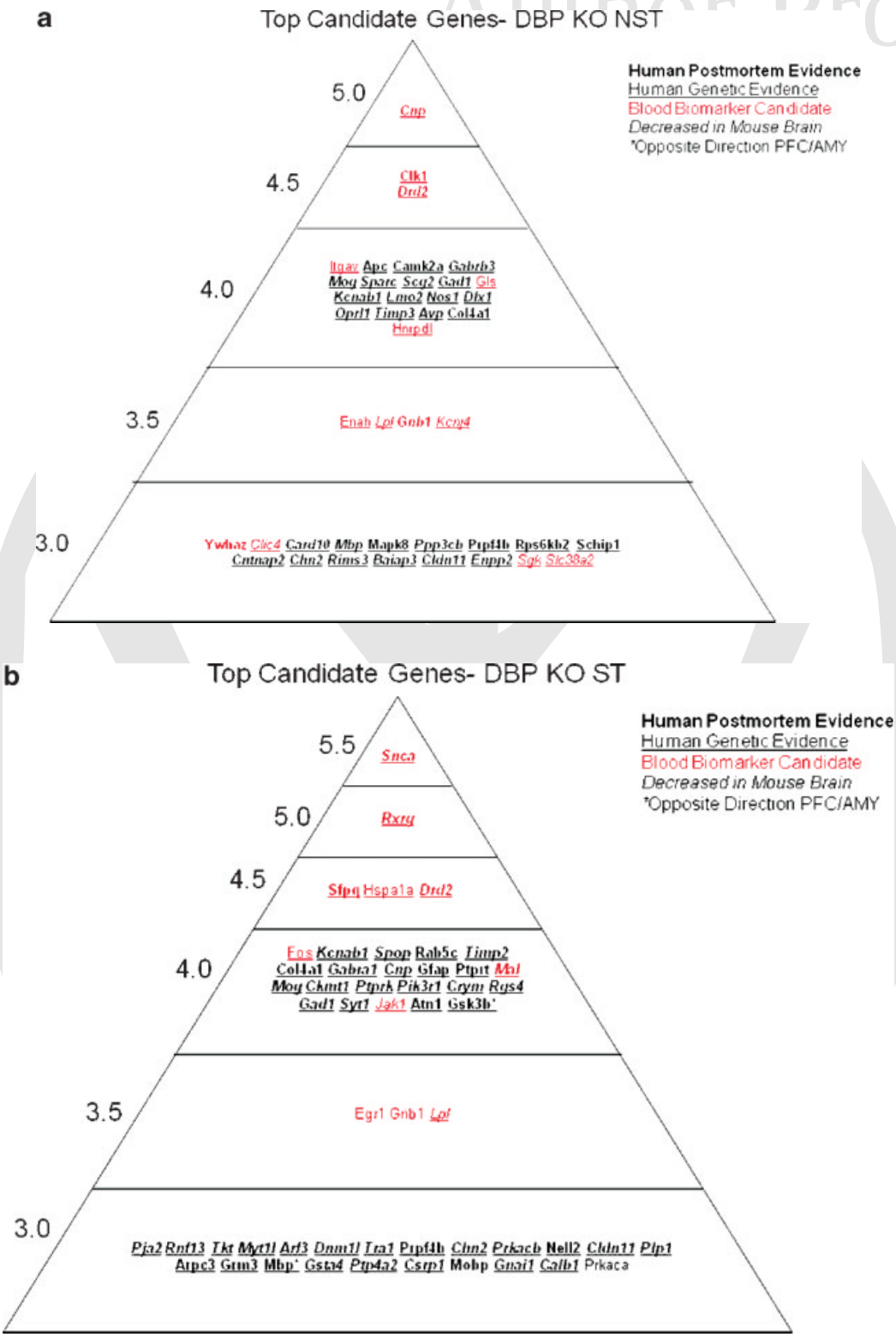

Fig. 6. Top candidate genes. **a**: DBP KO NST; (**b**) DBP KO ST. Scoring of lines of evidence depicted on the side of the pyramid. See Tables IV and V.

potentially noisy datasets (Fig. 5). It is remarkable, for example, that Snca, a gene associated with alcohol craving in humans [Foroud et al., 2007], comes up as the top candidate gene and blood biomarker in the activated, increased alcohol consuming DBP KO ST mice.

Conclusions and Future Directions

The results presented in this article have a series of direct implications. First, the behavioral phenomenology and inferences from molecular changes in the DBP KO mice bear

striking resemblances to DSM criteria for bipolar disorder. Moreover, their response to stress and switch in phenotype is a cardinal aspect of the human condition. As such, they are arguably among the first genetic animal models of bipolar disorder to be described, complementing earlier elegant pharmacological and genetic manipulations that mimic more restricted endophenotypic aspects of the disorder [Niculescu et al., 2000; Shaldubina et al., 2002; Einat et al., 2003; Gould et al., 2004; Ogden et al., 2004; Einat, 2006; Einat and Manji, 2006]. Of note, very recent work suggests that the amplitude of rhythmic expression for Dbp, and Dbp mRNA levels, are decreased in fibroblasts from bipolar subjects compared to healthy controls (Maja Bucan et al., personal communication). Second, our results show a remarkable overlap with top candidate gene findings by us and others using different approaches, specifically in our own previous work, a pharamcogenomic model of bipolar disorder [Ogden et al., 2004], and a rat genetic model of alcoholism [Rodd et al., 2007]. Third, other new potential candidate genes, pathways and mechanisms for bipolar and related disorders were uncovered, including additional clock genes. These prioritized candidates (Fig. 6, Tables IV and V, Table IIIS) are of high value for future hypothesis-driven studies, and extracting signal from whole-genome association studies. The fact that DBP is a transcription factor likely directly and indirectly regulating many other genes may explain the surprisingly comprehensive mimicry of a putative polygenic human disorder by a single gene ablation in mouse. Some of the genes identified may be directly regulated by DBP through promoter binding, while others may be regulated indirectly by a cascade of gene expression changes set in motion by DBP. Careful future bioinformatic and in vitro promoter-binding studies are warranted to elucidate these aspects. Genes that change together/co-acting gene expression groups may provide testable hypotheses for epistatic interactions [Bertsch et al., 2005]. Fourth, our work provides support for an underlying non-specific glia/myelin hypofunction and inflammatory/neurodegenerative phenomenology in bipolar and related disorders, both of which might contribute to a functional hypofrontality leading to affective and hedonic dysregulation. Fifth, our work is, to our knowledge, the first to comprehensively look at brain–blood correlations in an animal model, and integrate that with other multiple lines of evidence, as a way of identifying and prioritizing candidate blood biomarkers for psychiatric disorders [Le-Niculescu et al., 2007b]. Sixth, some of the candidate genes in our dataset encode for proteins that are modulated by existing pharmacological agents (Table IVS), which may suggest future avenues for rational polypharmacy using currently available agents. Seventh, in terms of drug development, DBP KO mice may serve a useful role for pre-clinical studies and validation of new candidate drugs for bipolar and related disorders. Lastly, the insights into overlapping phenomics, genomics and biomarkers among bipolar, alcoholism, stress and related disorders provided by this mouse model point in a translational fashion to the issue of heterogeneity, overlap and interdependence of major psychiatric syndromes as currently defined by DSM [Niculescu, 2006], and the need for a move towards comprehensive empirical profiling and away from categorical diagnostic classifications [Niculescu et al., 2006].

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