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Towards Understanding The Schizophrenia Code:
An Expanded Convergent Functional Genomics Approach

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Identifying genes for schizophrenia through classical genetic approaches has proven arduous. Here, we present a comprehensive convergent analysis that translationally integrates brain gene expression data from a relevant pharmacogenomic mouse model (involving treatments with a psychomimetic agent—phencyclidine (PCP), and an anti-psychotic—clozapine), with human genetic linkage data and human postmortem brain data, as a Bayesian strategy of cross validating findings. Topping the list of candidate genes, we have three genes involved in GABA neurotransmission (*GABRA1*, *GABBR1*, and *GAD2*), one gene involved in glutamate neurotransmission (*GRIA2*), one gene involved in neuropeptide signaling (*TAC1*), two genes involved in synaptic function (*SYN2* and *KCNJ4*), six genes involved in myelin/glial function (*CNP*, *MAL*, *MBP*, *PLP1*, *MOBP* and *GFAP*), and one gene involved in lipid metabolism (*LPL*). These data suggest that schizophrenia is primarily a disorder of brain functional and structural connectivity, with GABA neurotransmission playing a prominent role. These findings may explain the EEG gamma band abnormalities detected in schizophrenia. The analysis also revealed other high probability candidates genes (neurotransmitter signaling, other structural proteins, ion channels, signal transduction, regulatory enzymes, neuronal migration/neurite outgrowth, clock genes, transcription factors, RNA regulatory genes), pathways and mechanisms of likely importance in pathophysiology. Some of the pathways identified suggest possible avenues for augmentation pharmacotherapy of schizophrenia with other existing agents, such as benzodiazepines, anticonvulsants and lipid modulating agents. Other pathways are new potential targets for drug development. Lastly, a comparison with our earlier work on bipolar disorder illuminates the significant molecular overlap between schizophrenia and bipolar disorder.

KEY WORDS: schizophrenia; microarray; convergent functional genomics; phencyclidine (PCP); clozapine; brain

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INTRODUCTION

Schizophrenia is a heterogeneous syndrome characterized by perturbations of perception, attention, thinking, affect, volition, and social integration. Patients may present with positive symptoms (such as conceptual disorganization, delusions, and hallucinations) or negative symptoms (anhedonia, decreased emotional expression, decreased motivation, impaired concentration, and diminished social engagement), and must have at least two of these for a 1-month period and continuous signs for at least 6 months to meet formal diagnostic criteria. The genetic basis of schizophrenia is well documented, with an incidence of about 1% in the general population. Having a first-degree relative with the illness increases the likelihood of developing the illness by about 10-fold. Traditionally, linkage analysis and positional cloning approaches have been used to attempt to identify the genes involved. This has led to the identification of a series of loci in the genome that exhibit linkage with the illness. Several of these loci are identified in both schizophrenia and bipolar disorder studies, suggesting the possibility of shared genes between these disorders [Berrettini, 2000; Owen et al., 2004]. As these disorders are likely polygenic, non-Mendelian, with variable penetrance, and the clinical phenotypes are complex, there has been limited success so far in terms of reproducible findings, with some notable exceptions [Harrison and Weinberger, 2005; Petryshen et al., 2005a,b; Norton et al., 2006]. The linkage peaks supported by the most recent meta-analyses [Lewis et al., 2003] and genome scan data [Arinami, 2005] are fairly broad, with hundreds of genes in each peak. A method for prioritizing candidate genes for individual analysis of association with illness is critical. We have previously described one

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such approach, termed Convergent Functional Genomics, and its application to the study of bipolar disorders [Niculescu et al., 2000; Ogden et al., 2004; Bertsch et al., 2005], and more recently to alcoholism [Rodd et al., 2006]. The approach integrates gene expression data from a relevant animal model with human linkage data and human tissue data (postmortem brain, lymphocytes), as a way of cross-validating findings and coming up with a short list of high-probability candidate genes that deserve individual scrutiny in a prioritized manner. Here we apply our approach to schizophrenia, and report the first comprehensive analysis using an expanded convergent functional genomics approach as a way of unraveling the genetic code of schizophrenia and related disorders.

Single-dose phencyclidine (PCP) treatment in humans and animals mimics many of the behavioral signs and symptoms of schizophrenia-positive-like symptoms (hallucinations, delusions, bizarre behavior, and thought disorder), negative-like symptoms (affective flattening, alogia, apathy, and social interaction deficits), and disorganization [Jentsch and Roth, 1999; Abe et al., 2000; Turgeon and Case, 2001; Geyer and Ellenbroek, 2003; Morris et al., 2005; Ouchi et al., 2005] (Fig. 1a). Phencyclidine also produces a pattern of metabolic and neurochemical changes in the rodent brain that mirror those observed in the brains of schizophrenic patients [Morris et al., 2005]. PCP may act not only through NMDA receptor antagonism, but also through D2 receptor agonism, consistent with both hyperdopamine and hypoglutamate theories of psychosis [Seeman et al., 2005].

Clozapine, an atypical or second-generation antipsychotic, is currently the gold standard of treatment for schizophrenia [Tandon and Fleischhacker, 2005], and has been shown to interfere with and treat the development of both positive and negative symptoms. The spectrum of efficacy of clozapine is broader than for other antipsychotics, particularly for negative symptoms [Lindenmayer et al., 2004].

In essence, in our approach, we are using drug effects on gene expression as tools to tag genes that may have pathophysiological relevance. Changes in gene expression in response to each of the two drugs, PCP and clozapine, would be of interest in and of themselves, in terms of candidate gene generation

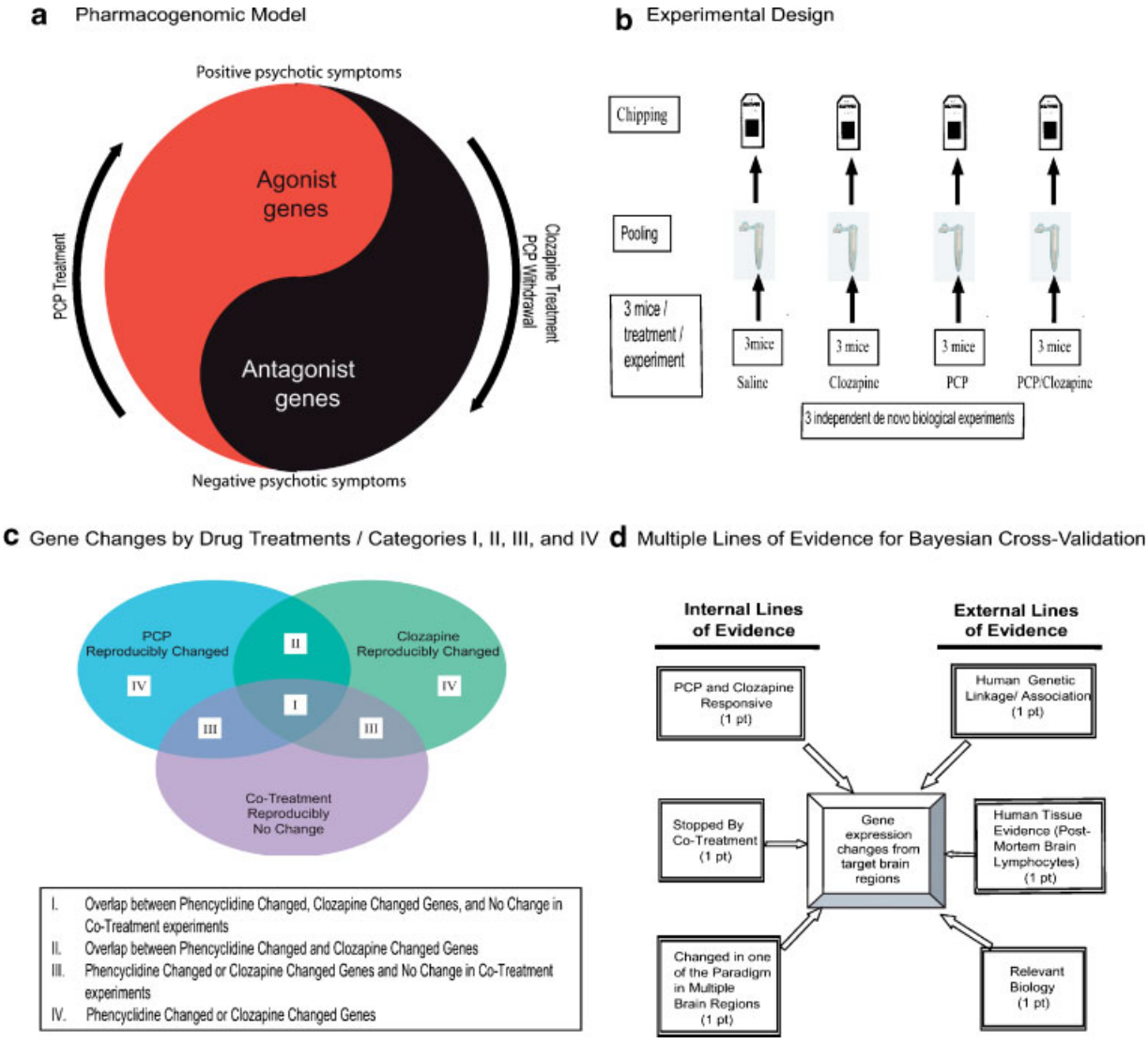
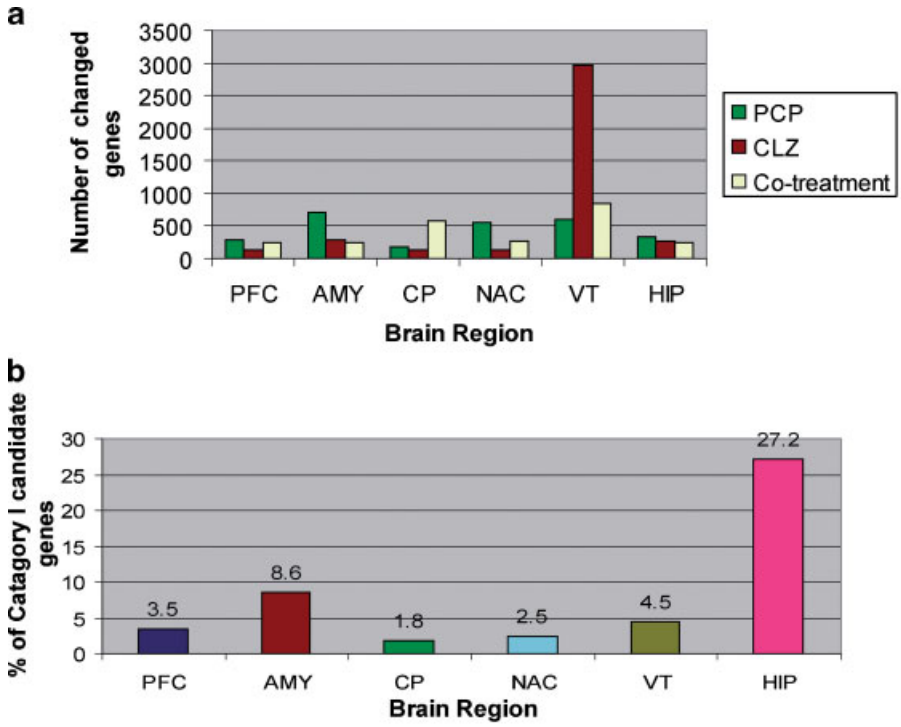


Fig. 1. Design of experiments and data analysis. **a**: Pharmacological treatment paradigm (**b**) Experimental design (**c**) Venn diagram categorizing genes changed by the various drug treatments, and their classification into Categories I, II, III, and IV (**d**) Multiple converging independent internal and external lines of evidence for cross—validation of findings.

and convergent functional genomics. However, not all genes that show changes in expression in response to either of the drugs are necessarily germane to the pathophysiology of schizophrenia and related disorders. It is likely that some of the gene expression changes have to do with other effects of the drugs, particularly their individual side-effects. We hence used three internal criteria for cross-validation. We reasoned, first, that genes that change in expression in response to both drugs are more likely to be involved in the core pathophysiology we are modeling, and are higher probability candidate genes. Second, co-treatment with the two drugs, one a schizophrenia inducing, and the other one a schizophrenia-treating drug, could arguably show interference effects (Figs. 1 and 2a), and some of the genes that would be changed by single drug treatment would be "nipped in the bud" and show no changes in expression in response to co-treatment. Those genes would also be deemed higher probability candidate genes than the genes that still change during co-treatment. Third, we comprehensively surveyed gene expression changes across six different brain regions (prefrontal cortex (PFC), amygdala (AMY), caudate putamen (CP), nucleus accumbens (NAC), ventral tegmentum (VT), and hippocampus (HIP)), that have shown evidence, in human imaging, human postmortem, or animal studies, of being potentially implicated in the pathophysiology of schizophrenia and related disorders [Galter et al., 2003; Aleman and Kahn, 2005; Lauer et al., 2005; Tamagaki et al., 2005; Snitz et al., 2005; Konopaske et al., 2006; Qiu et al., 2006; Shad et al., 2006; Vita et al., 2006]. We also reasoned that genes that had expression changes in more than one of the brain regions have a higher probability of being positive findings compared to genes that changed in a single region, at the very least for reproducibility reasons, as the assaying of different brain regions are essentially independent experiments.

As external cross-validators, we used three criteria in our expanded convergent functional genomics analysis [Ogden et al., 2004] (Fig. 1d). First, each gene was assessed to see if there was any published evidence of association with schizophrenia, or at least if it mapped to a linkage locus that had been implicated in schizophrenia. Our criterion was mapping within 10 centimorgans (cM) of a marker that has shown significant evidence of linkage [Niculescu et al., 2000] to schizophrenia, with a lod score >2 in at least one published study. We also looked more broadly at cross-matching with linkage data from other neuropsychiatric disorders (bipolar disorder, alcohol-



c

Brain Region \ Category	I	II	PCP III	CLZ III	PCP IV	CLZ IV	Total
Prefrontal Cortex	13	26	215	82	24	16	376
Amygdala	73	91	478	129	68	6	845
Caudate Putamen	5	19	114	47	39	53	277
Nucleus Accumbens	16	25	449	75	66	8	639
Ventral Tegmentum	145	165	227	2,423	58	225	3,243
Hippocampus	122	27	164	95	27	13	448

Fig. 2. Number of genes reproducibly changed. PCP—phencyclidine; CLZ-clozapine. (**a**) Comparative effects of Phencyclidine, clozapine and co-treatment with both drugs in different target brain regions, showing interference effects of co-treatment. **b**: Distribution of Category I candidate genes across brain regions—% of Category I genes out of total number of genes changed (Category I-IV). **c**: Number of reproducibly changed genes by Categories I–IV.

ism), based on the rationale that their clinical co-morbidity with schizophrenia may be due, at least in part, to genetic overlap [Nurnberger et al., 2004; Craddock et al., 2006]. Second, we searched to see if there was any human tissue data (postmortem brain, lymphocytes, fibroblasts) showing expression changes of the gene in patients that had schizophrenia or, more broadly, other neuropsychiatric disorders (bipolar disorder, major depression, anxiety, alcoholism, other substance dependence disorders, dementia, suicide). Third, we looked at the known biological functions associated with the gene and asked if they had any relevance to the pathophysiology of schizophrenia and/or other neuropsychiatric disorders. These external criteria 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 schizophrenia in our 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 these disorders and schizophrenia [Berrettini, 2000; Hyman and Fenton, 2003; Nurnberger et al., 2004; Brown, 2005; Craddock et al., 2006; Niculescu et al., 2006], and the likelihood that published schizophrenia related datasets to date are nonexhaustive. To address the issue of specificity for the external lines of evidence, we decided to differentially weight the significance of the evidence directly related to schizophrenia with a score of 1, and of the evidence only related to other neuropsychiatric disorders with a lesser score of 0.5.

For each gene in our datasets, using the three internal and three external cross-validators described above (Fig. 1d), we assigned a generic score of 1 for each internal criterion and a score of 1 or 0.5 for each external criterion, as a way of generating an empirical tabulation of the independent lines of evidence. According to Bayesian theory, an optimal estimate results from combining prior information with new evidence [Bernardo and Smith, 1994]. 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 employed, the higher the number of independent lines of evidence, the lower the likelihood of that being the case. Thus, totaling all the internal and external lines of evidence gives a maximum possible score of 6 points, with the internal evidence and the external evidence weighted equally.

It has not escaped our attention that 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.

Our approach identifies an extensive series of candidate genes, some of which have already been reported using various schizophrenia- related treatments or paradigms [Mirnics et al., 2001a; Iwamoto et al., 2004; Owen et al., 2004; Silverstone et al., 2004; Vawter et al., 2004; Wong et al., 2004; Katsel et al., 2005a; Talkowski et al., 2006], and thus in a sense serve as positive controls, as well as many which are novel. Moreover, the coalescence of the candidate genes into pathways and mechanisms is of particular importance and opens new directions. Last but not least, as per our earlier formulation that "genes that change together (may) act together" [Niculescu et al., 2000], the data we have generated showing genes expression changes in various brain regions (Tables I and II) offer testable hypotheses for transcriptional co-regulation, and for epistatic interactions among the corresponding loci.

MATERIALS AND METHODS

Phencyclidine (PCP) and Clozapine Treatments in Mice

All experiments were performed with male C57/BL6 mice, 8–12 weeks of age, obtained from Jackson Laboratories (Bar Harbor, ME), and acclimated for at least 2 weeks in our animal facility (IU School of Medicine LARC) prior to any experimental manipulation. Mice were treated by intraperitoneal injection with either single-dose saline, PCP (7.5 mg/kg), Clozapine (2.5 mg/kg), or a combination of PCP and Clozapine (7.5 and 2.5 mg/kg). Three independent de novo biological experiments were performed at different times. Each experiment consisted of three mice per treatment condition, for a total of nine mice per condition across the three experiments (Fig. 1b).

Behavioral Studies and Analysis

Locomotor activity was measured immediately after drug administration and again 24 hr later, using methodology previously described [Ogden et al., 2004]. At the beginning of the test session, each mouse was placed in an enclosure with pre-defined areas, that is, center area, corner area, and wall area. The movements of the mice were recorded for 30 min, with data being stored in six 5 min blocks.

Microdissection

Twenty-four hours after drug administration, following the 24 hr time-point behavioral test, the animals were sacrificed by decapitation. The brains of the mice were harvested and stereotactically sliced using a wire-slicer device, with wires spaced based on mouse brain atlas coordinates. Specific brain regions bilaterally -PFC, AMY, CP, NAC, VT, and HIP were hand micro-dissected on an ice-cold metal platform. Tissue samples were flash frozen in liquid nitrogen within 10 min of the animals being sacrificed, and stored in -80°C until future processing for RNA extraction and gene expression analysis.

Microarrays

We used Mouse Genome 430 2.0 arrays (Affymetrix, Santa Clara, CA). 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. Microarrays used in each independent experiment were derived from the same manufacturing lot.

Microarray Experiments

Standard techniques were used to obtain total RNA (22 gauge syringe homogenization in RLT buffer) and to purify the RNA (RNeasy mini kit, Qiagen, Valencia, CA) from microdissected mouse brain regions. The quality of the total RNA was confirmed using an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA). 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 each brain region, equal amounts of total RNA extracted from tissue samples was pooled within each biological experiment (3 mice per treatment group), and then used for labeling and microarray assays. The microarray assays for each of the three de novo biological animal experiments were conducted independently, at different times. Standard Affymetrix

TABLE I. Top Category I and II Genes

Gene Accession Number	Symbol - Description	CLZ Change	PCP Change	Stopped by Co-Treatment	Multiple Brain Regions	Human genetic linkage/ association	Relevant Biology	Human Tissue (Postmortem brain, blood)	Lines of evidence score
PREFRONTAL CORTEX									
Down									
NM_019439.2	**Gabbr1** gamma-aminobutyric acid (GABA-B) receptor, 1	D	D	Yes	**AMY** III-CLZ **NAC** III-PCP **VT** III-CLZ	6p22.1 SZ (Lewis et al 2003),(Hwu et al 2000),(Zai et al 2005),(Hisama et al 2001) BP (Turecki et al 2001),(Cichon et al 2001)	Yes	SZ and BP (Ishikawa et al 2005) SZ (Mizukami et al 2000)	**6**
AK019046	**Mal** myelin and lymphocyte protein, T-cell differentiation protein	D	D	Yes	**AMY** Cat **II** **VT** III-PCP **NAC**IV-PCP	2q11.1 SZ (Lewis et al 2003),(Straub et al 2002),(DeLisi et al 2002),(Chen et al 1998) (Faraone et al 2006a) Etoh (Wyszynski et al 2003)	Yes	SZ (Hakak et al 2001) MDD (Aston et al 2005) BP (Middleton et al 2005) Etoh (Lewohl et al 2000)	**6**
BB380620	**Arhgef9** Cdc42 guanine nucleotide exchange factor (GEF) 9	D	D	Yes	**NAC** Cat I **AMY** III-CLZ	Xq11.2 Unipolar Depression (Badenhop et al 2002)	Yes	SZ (Glatt et al 2005)	**5.5**
BB476448	**Camk2a** Calcium/Calmodulin-dependent protein kinase II-alpha	D	D	Yes	**AMY** Cat I **VT** Cat II **CP** III-CLZ **NAC** III-CLZ	5q32 SZ (Lewis et al 2003),(Devlin et al 2002) SZ,SZA (Sklar et al 2004) Etoh (Sun et al 1999)	Yes	BP (Molnar et al 2003) Depression (Novak et al 2006)	**5.5**
BG311385	**Adora2a** adenosine 2A receptor	D	D		**NAC** Cat II **AMY** III-PCP	22q11.23 SZ (Lewis et al 2003),(Takahashi et al 2003) BP (Detera-Wadleigh et al 1999)	Yes	SZ (Kurumaji and Toru 1998)	**5**
BE957273	**Drd1** dopamine receptor D1	D	D		**AMY** III-PCP	5q35.2 SZ (Rybakowski et al 2005),(Potkin et al 2003)	Yes	SZ and BP (Pantazopoulos et al 2004) SZ (Domyo et al 2001; Knable et al 1996)	**5**
NM_010077	**Drd2** dopamine receptor 2	D	D		**AMY** III-PCP	11q23.2 SZ (Lewis et al 2003),(Dubertret et al 2004; Golimbet et al 2003; Schindler et al 2002) Etoh (Sun et al 1999)	Yes	SZ (Dean et al 2004) SZ (Toru 1998),(Goldsmith et al 1997),(Seeman et al 1997) Tourette syndrome (Minzer et al 2004)	**5**
NM_009311.1	**Tac1** tachykinin, precursor 1 (substance K, substance P, neurokinin 1, neurokinin 2)	D	D		**VT** Cat I **AMY** III-PCP	7q21.3 SZ (Ekelund et al 2000),(Yan et al 2000) BP (Ogden et al 2004),(McInnis et al 2003) SZA (Yan et al 2000)	Yes	SZ (Tooney et al 2001) HD (Bird 1980) A (Rosler et al 2001)	**5**
AMYGDALA									
Up									
NM_009923.1	**Cnp** 2',3'-cyclic nucleotide 3' phosphodiesterase	I	I	Yes	**CP** Cat I **NAC** III-PCP **PFC** III-PCP **VT** III- CLZ	17q21.2 SZ (Lewis et al 2003),(Peirce et al 2006)	Yes	SZ (Hakak et al 2001; Peirce et al 2006),(Dracheva et al 2006),(Flynn et al 2003) MDD (Aston et al 2005), Etoh (Lewohl et al 2000)	**6**
NM_010250.1	**Gabra1** gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 1	I	I	Yes	**CP** III-PCP **NAC** III-PCP **VT** III-CLZ	5q34 SZ (Lewis et al 2003),(Sklar et al 2004) BP (Park et al 2004) Autism (Ma et al 2005)	Yes	SZ (Ishikawa et al 2004) (Impagnatiello et al 1998) Review (Costa et al 2005),(Lewis et al 2004) (Hakak et al 2001)	**6**
AF326550.1	**Gad2/Gad 65** glutamic acid decarboxylase 2	I	I	Yes	**NAC** III-PCP **VT** IV- CLZ	10p12.1 SZ, BP (Maziade et al 2005) SZ (Faraone et al 1998) BP (McInnis et al 2003)	Yes	SZ (Fatemi et al 2005c),(Dracheva et al 2004) ,(Todtenkopf and Benes 1998) SZ, BP (Heckers et al 2002)	**6**
BB183081	**Gfap** glial fibrillary acidic protein	I (MI)	I	Yes	**NAC** III-CLZ **PFC** IV- CLZ	17q21.31 SZ (Lewis et al 2003) Autism (Cantor et al 2005)	Yes	SZ, BP (Webster et al 2005),(Johnston-Wilson et al 2000) SZ (Rajkowska et al 2002) MDD (Fatemi et al 2004) Etoh (Lewohl et al 2000)	**6**
NM_010777.1	**Mbp** myelin basic protein	I	I	Yes	**PFC** III-PCP	18q23 SZ (Lewis et al 2003),(Straub et al 2002) BP (Schulze et al 2003)	Yes	SZ, BP (Chambers and Perrone-Bizzozero 2004),(Tkachev et al 2003), Etoh (Lewohl et al 2000) AD (Wang et al 2004) Cocaine Addiction (Bannon et al 2005)	**6**
M15442.1	**Plp1** proteolipid protein (myelin) 1	I	I	Yes	**PFC** III-PCP **VT** IV- CLZ	Xq22.2 SZ (Qin et al 2005c)	Yes	SZ (Aston et al 2004) SZ, BP (Tkachev et al 2003) MDD (Aston et al 2005) Etoh (Mayfield et al 2002) Cocaine Addiction (Bannon et al 2005)	**6**
BM899593	**Mobp** myelin-associated oligodendrocytic basic protein	I	I	Yes	**NAC** Cat II **PFC** III-PCP	3p22 SZ (Lewis et al 2003)	Yes	SZ,BP (Tkachev et al 2003) MDD (Aston et al 2005) Etoh (Mayfield et al 2002)	**6**
NM_013467.1	**Aldh1a1** aldehyde dehydrogenase family 1, subfamily A1	I	I	Yes	**NAC** Cat II	9q21.13 SZ (Hovatta et al 1999) BP (Macgregor et al 2004)	Yes	SZ (Galter et al 2003)	**5.5**
BB476448	**Camk2a** Calcium/Calmodulin-dependent protein kinase II-alpha	I	I	Yes	**PFC** Cat I **VT** Cat II **NAC** III-CLZ **CP** III-CLZ	5q32 SZ (Lewis et al 2003),(Devlin et al 2002) SZ and SZA (Sklar et al 2004) Etoh (Sun et al 1999)	Yes	BP (Molnar et al 2003) Depression (Novak et al 2006)	**5.5**
BC027019	**Syt2** Synaptotagmin 2	I	I	Yes	**CP** Cat II **VT** Cat II **NAC** III-PCP	1q32.1 SZ (Paunio et al 2004),(Hovatta et al 1999)	Yes	AD (Sze et al 2000)	**5.5**
NM_007470.1	**Apod** apolipoprotein D	I	I		**HIP** III-CLZ **PFC** III-CLZ **VT** III-PCP	3q26.2-qter SZ (Hansen et al 2006) BP (Cichon et al 2001)	Yes	SZ (Mahadik et al 2002) ,(Yao et al 2005) SZ, BP (Thomas et al 2003) ,(Thomas et al 2001)	**5**
NM_009871.1	**Cdk5r1** cyclin-dependent kinase 5, regulatory subunit (p35) 1	I	I	Yes	**CP** III-CLZ **NAC** III-PCP **PFC** III-PCP **VT** III-CLZ	17q11.2 Mental Retardation (Venturin et al 2006) Etoh (Hill et al 2004)	Yes	AD and Down syndrome (Swatton et al 2004)	**5**

(*Continued*)

TABLE I. (*Continued*)

Gene Accession Number	Symbol - Description	CLZ Change	PCP Change	Stopped by Co-Treatment	Multiple Brain Regions	Human genetic linkage/ association	Relevant Biology	Human Tissue (Postmortem brain, blood)	Lines of evidence score
AV322952	Foxp2 forkhead box P2	I	I	Yes	HIP cat II PFC III-PCP VT III-CLZ	7q31.1 SZ (Sanjuan et al 2006) BP (Detera-Wadleigh et al 1999) Autism (Gong et al 2004),(Muhle et al 2004)	Yes		5
NM_019691.2	Gria4 glutamate receptor, ionotropic, AMPA4	I (MI)	I	Yes		11q22.3 SZ (Lewis et al 2003),(Makino et al 2003)	Yes	SZ (Dracheva et al 2005)	5
AF109769.1	Mapk8ip1 mitogen activated protein kinase 8 interacting protein 1	I	I	Yes	NAC III-PCP PFC III-PCP	11p11.2 SZ (Yamada et al 2004)	Yes	AD (Helbecque et al 2003)	5
NM_011866.1	Pde10a phosphodiesterase 10A	I	I	Yes	PFC Cat II CP III-CLZ VT III-CLZ	6p27 SZ (Lindholm et al 2001)	Yes		5
NM_009062	Rgs4 regulator of G-protein signaling 4	I	I		VT Cat II HIP III-CLZ PFC III-CLZ	1q23.3 SZ (Lewis et al 2003),(Chen et al 2004a),(Chowdari et al 2002, Morris et al 2004)	Yes	SZ (Mirnics et al 2001b) ,(Mirnics et al 2001a)	5
NM_024226	Rtn4 reticulon 4/Nogo	I	I		PFC III-PCP	2p16.1 SZ (Tan et al 2005)	Yes	SZ and Nogo (Novak et al 2002) SZ (Bandlow et al 2004)	5
NM_080853	Slc17a6 solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), 6	I	I	Yes	NAC Cat II	11p14.3	Yes	SZ (Eastwood and Harrison 2005),(Harrison et al 2003),(Smith et al 2001)	5
Down									
NM_013681.1	Syn2 synapsin II	D	D	Yes	VT Cat I CP III-PCP	3p25.2 SZ (Paunio et al 2004),(Chen et al 2004b),(Lee et al 2005), (Chen et al 2004a)	Yes	SZ,BP (Vawter et al 2002b) SZ (Browning et al 1993) AD (Ho et al 2001)	6
AV152953	Ttr Transthyretin	D	D	Yes	CP Cat II NAC Cat II VT Cat II	18q21.1 SZ (Goodman 1998; Maziade et al 2005)	Yes	Depression (Sullivan et al 1999) Amyloid (Yoshinaga et al 2004)	5.5
BQ175227	Ywhab Tyrosine monooxygenase/ tryptophan 5monooxygenase activation protein, beta polypeptide/14-3-3 genes	D	D	Yes	NAC III-PCP PFC III-CLZ HIP IV-CLZ VT IV-CLZ	20q13.1 BP (Radhakrishna et al 2001)	Yes	SZ (Middleton et al 2005)	5.5
CAUDATE-PUTAMEN									
Down									
NM_009923.1	Cnp 2',3'-cyclic nucleotide 3' phosphodiesterase	D	D	Yes	AMY I NAC III-PCP PFC III-PCP VT III- CLZ	17q21.2 SZ (Lewis et al 2003), (Peirce et al 2006)	Yes	SZ (Hakak et al 2001; Peirce et al 2006),(Dracheva et al 2006),(Flynn et al 2003)	6
NUCLEUS ACCUMBENS									
Up									
U11075	Kcnj4/Kir2.3 potassium inwardly-rectifying channel, subfamily J, 4	I(MI)	I	Yes	PFC III-PCP	22q13.1 SZ (Cook et al 1994) BP (Kelsoe et al 2001)	Yes	SZ (Zvara et al 2005)	6
NM_008509.1	Lpl Lipoprotein lipase	I (MI)	I	Yes	HIP Cat I AMY III-CLZ	8p21.3 SZ (Lewis et al 2003),(Brzustowicz et al 2000; Straub et al 2002),(Chiu et al 2002)	Yes	SZ (Glatt et al 2005)	6
NM_013613	Nr4a2/ Nurr1 Nuclear receptor subfamily 4, group A, member 2	I	I	Yes	HIP Cat I VT Cat II AMY III-PCP PFC III-PCP	2q24.1 SZ, Suicidal Behavior (Cheng et al 2006) ADHD (Smith et al 2005)	Yes	Cocaine Abuser (Bannon et al 2002)	5.5
BM899593	Mobp myelin-associated oligodendrocytic basic protein	I	I		AMY Cat I PFC III-PCP	3p22 SZ (Lewis et al 2003)	Yes	SZ,BP (Tkachev et al 2003) MDD (Aston et al 2005) Etoh (Mayfield et al 2002)	5
NM_011361.1	Sgk serum/glucocorticoid regulated kinase	I	I	Yes	AMY Cat II VT Cat II	6q23.2 SZ (Levi et al 2005) BP (Venken et al 2005),(Ewald et al 2002)	Yes		5
AV031691	Zic1 Zinc finger protein of the cerebellum 1	I(MI)	I	Yes	AMY Cat II CP Cat II HIP Cat II PFC III-CLZ	3q24 SZ (Bulayeva et al 2005) BP, SZA (Badenhop et al 2002)	Yes		5
VENTRAL TEGMENTUM									
Up									
BB075797	Epha7 ephrin receptor A7	I	I(MI)	Yes	HIP Cat II	6q16.1 SZ (Lewis et al 2003),(Cao et al 1997) BP (Dick et al 2003)	Yes		5
BB549292	Maob monoamine oxidase B	I	I	Yes		Xp11.3 SZ (Dahl et al 1997)	Yes	SZ (Tachiki et al 1984)	5
NM_009062	Rgs4 regulator of G-protein signaling 4	I	I		AMY Cat II HIP III-CLZ PFC III-CLZ	1q23.3 SZ (Lewis et al 2003),(Chen et al 2004a),(Chowdari et al 2002; Morris et al 2004)	Yes	SZ (Mirnics et al 2001b) ,(Mirnics et al 2001a)	5
Down									
NM_013540.1	Gria2 glutamate receptor, ionotropic, AMPA 2	D(MD)	D(MD)	Yes		4q32.1 SZ (Hovatta et al 1999; Straub et al 2002) BP (Ekholm et al 2003; Segurado et al 2003; Williams et al 2003; Willour et al 2003)	Yes	SZ (Vawter et al 2002a)	6
NM_013681.1	Syn2 synapsin II	D	D	Yes	AMY Cat I CP III-PCP	3p25.2 SZ (Paunio et al 2004),(Chen et al 2004b),(Lee et al 2005), (Chen et al 2004a)	Yes	SZ,BP (Vawter et al 2002b) SZ (Browning et al 1993) AD (Ho et al 2001)	6
NM_009311.1	Tac1 tachykinin, precursor 1 (substance K, substance P, neurokinin 1, neurokinin 2)	D	D	Yes	PFC Cat II AMY III-PCP	7q21.3 SZ (Ekelund et al 2000),(Yan et al 2000) BP (Ogden et al 2004),(McInnis et al 2003) SZA (Yan et al 2000)	Yes	SZ (Tooney et al 2001) HD (Bird 1980) AD (Rosler et al 2001)	6
NM_009946.1	Cplx2 Complexin 2	D	D	Yes		5q35.2 SZ (Lee et al 2005)	Yes	SZ (Eastwood and Harrison 2005) (Eastwood et al 2003; Qin et al 2005c) HD (Morton and Edwardson 2001)	5

TABLE I. (*Continued*)

Gene Accession Number	Symbol - Description	CLZ Change	PCP Change	Stopped by Co-Treatment	Multiple Brain Regions	Human genetic linkage/ association	Relevant Biology	Human Tissue (Postmortem brain, blood)	Lines of evidence score
NM_008169	Grin1 glutamate receptor, ionotropic, N-methyl D-aspartate 1	D	D		NAC III-CLZ	9q34.3 SZ (Qin et al 2005b),(Marrocci et al 2003),(Begni et al 2003) BP (Faraone et al 2006b), (Mundo et al 2003)	Yes	Glutamate receptors (Stadler et al 2005)	5
NM_007863.1	Mpp3 membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)	D	D(MD)	Yes	HIP Cat I AMY III-CLZ NAC III-CLZ	17q21.31 BP(Segurado et al 2003) Etoh (Hill et al 2004)	Yes	SZ (Vawter et al 2004)	5
NM_011261.1	Reln reelin	D	D		PFC III-CLZ	7q22.1 SZ (Ekelund et al 2000)	Yes	SZ (Impagnatiello et al 1998), (Abdolmaleky et al 2005; Guidotti et al 2000) Autism (Fatemi et al 2005b)	5
HIPPOCAMPUS									
Up									
NM_007627.2	Cckbr cholecystokinin B receptor	I	I	Yes	NAC III-PCP VT III-CLZ CP IV-PCP	11p15.4 Parkinson(Weng et al 2003)	Yes	SZ (Zachrisson et al 1999)	5.5
NM_013613	Nr4a2/ Nurr1 Nuclear receptor subfamily 4, group A, member 2	I	I	Yes	NAC Cat I VT Cat II AMY III-PCP PFC III-PCP	2q24.1 SZ, Suicidal Behavior (Cheng et al 2006) ADHD (Smith et al 2005)	Yes	Cocaine Abuser (Bannon et al 2002)	5.5
NM_019789.2	Csen calsenilin, presenilin binding protein, EF hand transcription factor	I	I	Yes	VT III-CLZ CP IV-CLZ	2q11.1 SZ (Lewis et al 2003), (DeLisi et al 2002) ,(Straub et al 2002) Etoh (Wyszynski et al 2003)	Yes	AD (Jin et al 2005)	5
NM_008963.1	Ptgds prostaglandin D2 synthase 21kDa (brain)	I	I	Yes	VT Cat II AMY III-PCP CP III-PCP	9q34.3 SZ (Kaufmann et al 1998) BP (Faraone et al 2006b)	Yes	Neurological disorders, (Hiraoka et al 2001) (Harrington et al 2006)	5
Down									
NM_008509.1	Lpl Lipoprotein lipase	D	D	Yes	NAC Cat I AMY III-CLZ	8p21.3 SZ (Lewis et al 2003),(Brzustowicz et al 2000; Straub et al 2002),(Chiu et al 2002)	Yes	SZ (Glatt et al 2005)	6
NM_007863.1	Mpp3 membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)	D (MD)	D	Yes	VT Cat I Amy III-CLZ NAC III-CLZ	17q21.31 BP (Dahl et al 1997) EtoH (Hill et al 2004)	Yes	SZ (Dann et al 1997)	5

Category I and II genes with a minimum line of evidence score of 5.0 out of 6 are shown. I, increased; D, decreased; MI, moderately increased; MD, moderately decreased; PCP, Phencyclidine; CLZ, Clozapine; PFC, prefrontal cortex; AMY, amygdala; CP, caudate putamen; NAC, nucleus accumbens; VT, ventral tegmentum; HIP, hippocampus; SZ, schizophrenia; BP, bipolar disorder; MDD, major depressive disorder; Etoh, alcoholism; AD, Alzheimer; HD, Huntington disease. Roman numerals in the multiple brain region data column represent the Category of the gene.

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 intra-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. Data were extracted using the MicroArray Suite 5 (MAS5) algorithm. 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). A comparison analysis was performed for each drug treatment, using its corresponding saline treatment as the baseline. "Signal," "Detection," "Signal Log Ratio," "Change," and "Change *P*-value," were obtained from this analysis. Only transcripts that were called Present in at least one of the two samples (saline or drug) intra-experiment, and that were reproducibly changed in the same direction in at least two out of three independent 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 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.

Genetic Linkage Convergence

To designate convergence for a particular gene, the gene had to map within 10 cM of a microsatellite marker for which at least one published study showed evidence for linkage to schizophrenia, or another neuropsychiatric disorder. 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.

TABLE II. Genes that are Changed in Opposite Directions by PCP and CLZ

Gene Accession Number	Symbol - Description	CLZ Change	PCP Change	Stopped by Co-Treatment	Multiple Brain Regions	Human genetic linkage/ association	Relevant Biology	Human Tissue (Postmortem brain, blood)	Lines of evidence score
NUCLEUS ACCUMBENS Category I									
BB380620	Arhgef9 Cdc42 guanine nucleotide exchange factor (GEF) 9	D	I	Yes	PFC Cat I AMY III-CLZ	Xq11.2 Depression (Badenhop et al 2002)	Yes	SZ (Glatt et al 2005)	5.5
NM_010882.2	Ndn Necdin	I	D	Yes	AMY III-CLZ PFC III-PCP VT III- CLZ CP IV- CLZ	15q11.2 SZ (Fallin et al 2003)	Yes		5
NM_008142.2	Gnb1 Guanine nucleotide binding protein (G protein), beta polypeptide 1)	MI	D	Yes	AMY Cat II PFC III-PCP VT IV- CLZ	1p36.33 Neuroblastoma (Janoueix-Lerosey et al 2004)	Yes	BP (Middleton et al 2005)	4.5
NM_153529.1	Nrn1 Neuritin 1	D	I	Yes		6p25.1 SZ (Lewis et al 2003),(Maziade et al 1997) EtoH (Hill et al 2004)	Yes		4
VENTRAL TEGMENTUM Category I									
NM_009333.2	Tcf7l2 Transcription factor 7-like 2, T-cell specific, HMG-box	I	D	Yes	AMY III-PCP CP III- PCP NAC IVPCP	10q25.3 SZ (Lerer et al 2003) ;(Fallin et al 2003),(Faraone In Press)	Yes		5
NM_009723.1	Atp2b2 ATPase, Ca++ transporting, plasma membrane 2	I	D	Yes	NAC III- CLZ	3p25.3 SZ (Lewis et al 2003),(Paunio et al 2004)	Yes		5
NM_177343.2	Camk1d Calcium/calmodulin-dependent protein kinase ID	I	D	Yes		10p13 SZ (Freedman et al 2001; Paunio et al 2004),(Faraone et al 1998)	Yes	SZ (Vawter et al 2004)	4.5
NM_008124.2	Gjb1 Gap junction membrane channel protein beta 1	D	I	Yes	AMY III-PCP	Xq13.1 X-linked Charcot-Marie-Tooth disease (Vondracek et al 2005)	Yes		4
NM_008788.1	Pcolce Procollagen C-proteinase enhancer protein	D	I	Yes	HIP III- PCP NAC III- CLZ	7q22.1 SZ (Ekelund et al 2000) BP (Detera-Wadleigh et al 1997) EtoH (Foroud et al 2000)			4
BB649603	Rian RNA imprinted and accumulated in nucleus	D	I	Yes	AMY Cat I PFC III-PCP	n/a		SZ (Fatemi et al 2005a)	4
NM_130893.2	Scrt1 Scratch homolog 1, zinc finger protein (Drosophila)	I	D	Yes		8q24.3 BP (Segurado et al 2003)	Yes		3.5
NM_145978.1	Pdlim2 PDZ and LIM domain 2	D	I	Yes		8p21.2 SZ (Lewis et al 2003),(Straub et al 2002),(Brzustowicz et al 2000),(Blouin et al 1998),(Chiu et al 2002),(Brzustowicz et al 1999)			3
NM_011323.1	Scn8a Neuronal voltage-gated sodium channel alpha subunit (Scn8a)	I	D	Yes		12q13.13	Yes		3
AMYGDALA Category II									
BE859789	2900097C17Rik RIKEN cDNA 2900097C17 gene	D	I		NAC III-PCP VT IV- CLZ CP IV- CLZ				2
CAUDATE -PUTAMEN Category II									
NM_007428.2	Agt Angiotensinogen	I	D		NAC Cat II AMY III-PCP	1q42.2 SZ (Blackwood et al 2001; Ekelund et al 2001; Paunio et al 2004) BP (Macgregor et al 2004)	Yes	EtoH (Lewohl et al 2000)	4.5
NUCLEUS ACCUMBENS Category II									
NM_009630.1	Adora2a Adenosine A2a receptor	D	I		PFC Cat II AMY III-PCP	22q11.23 SZ (Lewis et al 2003),(Takahashi et al 2003) SZ, BP (Detera-Wadleigh et al 1999) BP (Kelsoe et al 2001)	Yes	SZ (Kurumaji and Toru 1998)	5
NM_027915.1	Ap2b1 Adaptor-related protein complex 2, beta 1 subunit	D	I		AMY III-CLZ VT IV- CLZ	17q12 BP (Dann et al 1997) EtoH (Hill et al 2004)	Yes		3.5
VENTRAL TEGMENTUM Category II									
NM_010597.2	Kcnab1 Potassium voltage-gated channel, shaker-related subfamily, beta member1	I	D		AMY III-PCP PFC III-PCP PFC IV- CLZ	3q25.31 BPA (Badenhop et al 2002)	Yes	SZ (Vawter et al 2004) EtoH (Sokolov et al 2003)	4.5
NM_010053.1	Dlx1 Distal-less homeobox 1	D	I		PFC III-CLZ AMY IVPCP	2q31.1	Yes	SZ, BP (Kromkamp et al 2003)	4
NM_024435.2	Nts Neurotensin	D	I		AMY III-PCP CP IV- CLZ PFC IV-PCP	12q21.31	Yes	SZ (Lahti et al 1998) (Wolf et al 1995)	4
NM_010714.1	Lhx9 LIM homeobox protein 9	I	MD		HIP Cat I	1q31.3 EtoH (Sun et al 1999),(Dick et al 2002b)	Yes		3
NM_013665.1	Shox2 Short stature homeobox 2	I	D			3q25.32 BP, SZA (Badenhop et al 2002)		SZ, BP (Kromkamp et al 2003)	3
AV337888	Pcp4l1 Purkinje cell protein 4-like 1	I	D		AMY Cat II PFC IV-PCP		Yes		3
BB041180	3110009O07Rik RIKEN cDNA 3110009O07 gene	I	D		HIP Cat I				2
NM_011406.1	Slc8a1 Solute carrier family 8 (sodium/calcium exchanger)1	I	D			2p22.1	Yes		2
NM_011618.1	Tnnt1 Troponin T1, skeletal, slow	I	D		NAC III-PCP	19q13.42			2

Category I and II genes changed in opposite directions in 2 out of 3 experiments in PCP and CLZ are shown. I, Increased; D, decreased; MI, moderately increased; MD, moderately decreased; PCP, phencyclidine; Up, upregulated; down, downregulated; PCP, phencyclidine; CLZ, clozapine; PFC, prefrontal cortex; AMY, amygdala; CP, caudate putamen; NAC, nucleus accumbens; VT, ventral tegmentum; SZ, schizophrenia; BP, bipolar disorder. Roman numerals in the multiple brain region data column represent the Category of the gene.

marshfieldclinic.org/genetics) was used with the NCBI Map Viewer web-site to evaluate linkage convergence.

Biological and Tissue (Postmortem Brain, Lymphocytes) 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: schizophrenia, psychosis, bipolar, depression, suicide, dementia, Alzheimer, alcoholism, opiates, cocaine, marijuana, hallucinogens, amphetamines, benzodiazepines, human, brain, postmortem, lymphocytes, fibroblasts). Genes were deemed to have biological convergence if their known biological function was relevant to the pathophysiology of schizophrenia and/or related disorders in human or animal models. Tissue convergence was deemed to occur for a gene if there were published reports of human postmortem brain data (or, rarely, lymphocytes and other tissue data) showing changes in expression of that gene in tissue from patients with schizophrenia and/or another neuropsychiatric disorder that impacts cognition.

GeneSpring Analysis

GeneSpring version 7.2 was used (Agilent Technologies). Unsupervised two-way hierarchical clustering of normalized (Cohen's D effect size) behavioral data [Niculescu et al., 2006] from open-field video-tracking was carried out.

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 Analysis

Ingenuity Pathway Analysis 3.1 (Ingenuity Systems, Redwood City, CA) was used to analyze the direct interactions of the top candidate genes resulting from our CFG analysis, as well as employed to identify genes in our datasets that are the target of existing drugs.

RESULTS

Based on the changes in response to single drug treatment and co-treatment, we divided our dataset of reproducibly changed genes into four categories (Figs. 1c and 2). Category I comprises genes that are changed by both PCP and clozapine, and the change is prevented (i.e., No Change) by co-treatment with both drugs. Category II comprises genes that are changed by both PCP and clozapine, but those changes are not prevented by co-treatment. Category III comprises genes that are changed by either PCP or clozapine, and the change is prevented (No Change) by co-treatment. Category IV comprises genes that are changed by one of the drugs only, and the changes are not prevented by co-treatment.

Number of Genes

PCP had the highest number of gene changes in the AMY. Clozapine had the highest number of genes changed in the VT. Nevertheless, a disproportionate number of higher-probability, category I genes were in the HIP, consistent with a likely central role of this region in the pathophysiology of schizophrenia and related disorders [Callicott et al., 2005; Gisabella et al., 2005; Holt et al., 2005; Katsel et al., 2005a,b; Benes et al., 2006; Kuroki et al., 2006; Olypher et al., 2006; Tanabe et al., 2006; Vita et al., 2006] (Fig. 2).

Top Findings

The top scoring genes in Categories I and II are shown in Table I. Figure 3 summarizes the assigned empirical probability score based on the multiple internal and external lines of evidence. At the top of our list, with 6 out of 6 lines of evidence, we have 14 genes: two from the PFC—GABBR1 (gamma-amynobutyric acid (GABA-B) receptor, 1)-located at 6p22.1 [Hwu et al., 2000; Hisama et al., 2001; Turecki et al., 2001; Schulze et al., 2004; Zai et al., 2005a,b]; and MAL (myelin and lymphocyte protein)-located at 2q11.1 [Chen et al., 1998; Hakak et al., 2001; DeLisi et al., 2002; Straub et al., 2002; Lewis et al., 2003; Aston et al., 2005; Middleton et al., 2005]; six from the AMY—gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 1 (GABRA1) located at 5q34 [Sklar et al., 2004; Petryshen et al., 2005a], glutamate decarboxylase 2 (GAD2) located at 10p12.1 [Maziade et al., 2001; McInnis et al., 2003], proteolipid protein (myelin) 1 (PLP1) located at Xq22.2 [Qin et al., 2005a], myelin basic protein (MBP)-located at 18q23 [Straub et al., 2002; Lewis et al., 2003], myelin-associated oligodendrocytic basic protein (MOBP) located at 3p22.2 [Lewis et al., 2003], and glial fibrillary acidic protein (GFAP)-located at 17q21.31 [Lewis et al., 2003]; one from the AMY and VT—SYN2 (synapisn II) located at 3p25.2 [Chen et al., 2004a; Paunio et al., 2004; Lee et al., 2005]; one from the AMY and CP—CNP (2′,3′-cyclic nucleotide 3′ phosphodiesterase) located at 17q21.2 [Lewis et al., 2003; Peirce et al., 2006]; one from the NAC—potassium inwardly-rectifying channel, subfamily J, member 4 (KCNJ4) located at 22q13.1 [Coon et al., 1994; Kelsoe et al., 2001]; one from the NAC and HIP—lipoprotein lipase (LPL) located at 8p21.3 [Brzustowicz et al., 2000; Chiu et al., 2002; Lewis et al., 2003; Straub et al., 2002]; and two from the VT—tachykinin, precursor 1 (TAC1) located at 7q21.3 [Ekelund et al., 2000; Yan et al., 2000; McInnis et al., 2003], and glutamate receptor, ionotropic, AMPA 2 (GRIA2) located at 4q32.1 [Hovatta et al., 1999; Straub et al., 2002; Ekholm et al., 2003; Willour et al., 2003].

Table II shows all the category I and II genes that are changed in opposite directions by PCP and clozapine. We reasoned that genes that are changed in opposite directions by a disease mimicking agent (PCP) and a disease treating agent (Clozapine) may be of particular interest, current external lines of evidence aside and total score notwithstanding.

Table III shows the categorization of the top candidate genes from Tables I and II into different biological roles categories of interest.

Other investigators have previously implicated a number of the above discussed genes, individually or as part of functional groups, in various biological and genetic contexts germane to the pathophysiology of schizophrenia and related disorders (Tables I and II) [Gisabella et al., 2005; Harrison and Weinberger, 2005; Torrey et al., 2005; Carlsson, 2006; Mirnics et al., 2006]. Our results, identifying these genes as top candidate genes, are thus a strong validation of the heuristic value and internal consistency of the approach we have used. Moreover, they outline networks of potentially co-acting genes (Fig. 5a), and support an important role for these pathways in schizophrenia and related disorders.

GABA Neurotransmission

Our work identified as top candidate genes for schizophrenia three genes involved in GABA neurotransmission: GABRA1, GABBR1, and GAD2 (Table I; Fig. 3). GABRA1 was previously

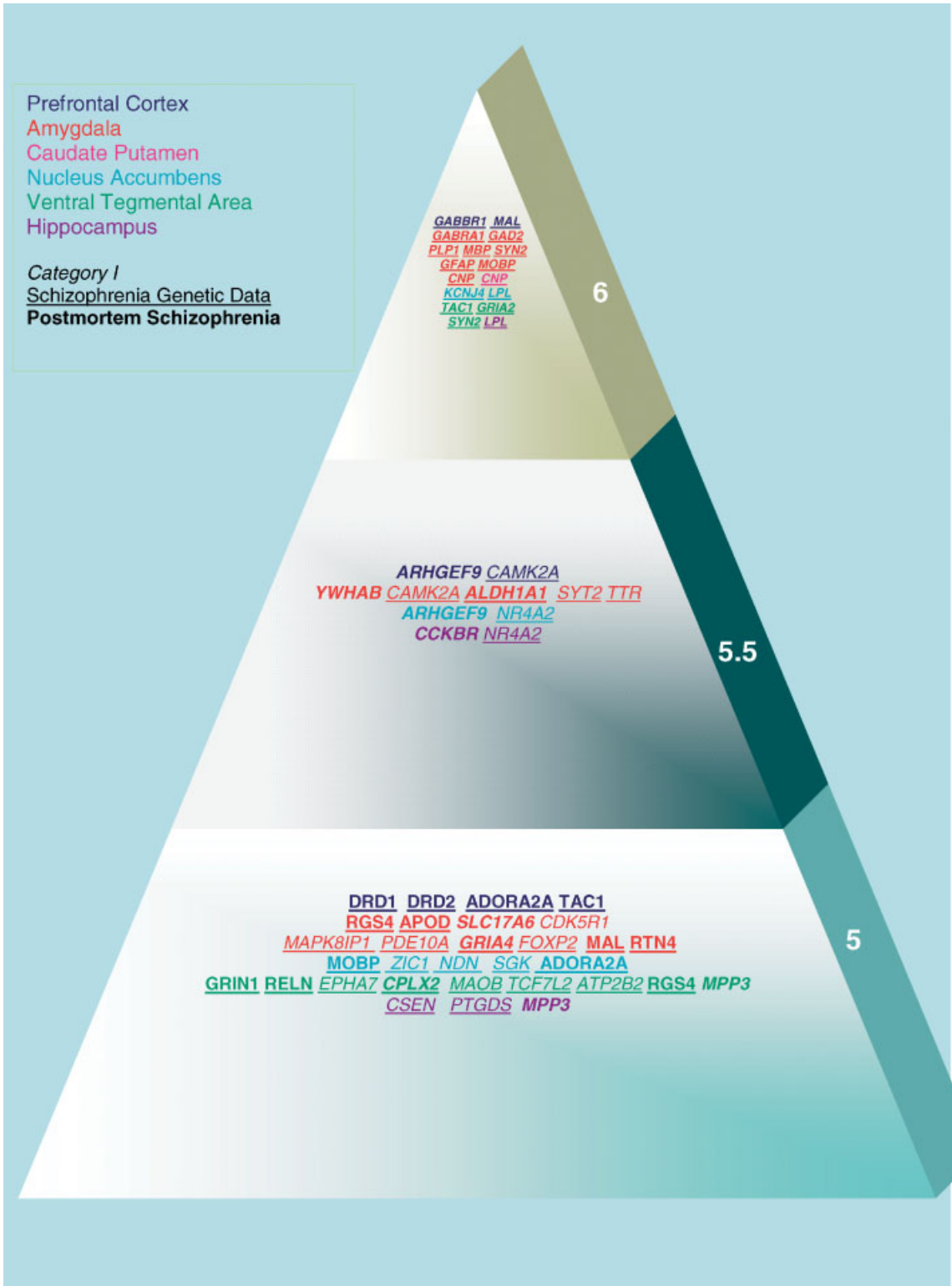


Fig. 3. Categories I and II candidate genes. Pyramid generated by the tabulation of independent converging lines of evidence. Italic—Category I genes. Underlined—schizophrenia genetic data. Bold—schizophrenia postmortem data. For full description of gene symbols see Table I.

reported to be increased in postmortem brains from schizophrenia patients [Ohnuma et al., 1999]. It has also recently been implicated in schizophrenia by human genetic linkage, association and preliminary gene expression studies in peripheral blood leukocytes [Petryshen et al., 2005a]. GABBR1 has been putatively implicated by human genetic association studies in both schizophrenia [Zai et al., 2005b] and obsessive-compulsive disorder [Zai et al., 2005a]. GAD2 (GAD65) was

TABLE III. Top Candidate Genes and Their Biological Roles

Gene Accession Numbers	Gene / Name	Brain Region (Drug-Category)
GABA related genes		
	Up	
NM_010250.1	GABRA1 gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 1 ■	AMY (I) / VT (CLZ-III) / NAC (PCP-III) / CP (PCP-III)
AF326550.1	GAD2 glutamic acid decarboxylase 2 ■	AMY (I) / NAC (PCP-III)
	Down	
NM_019439.1	GABBR1 gamma-aminobutyric acid (GABA-B) receptor, 1 ■	PFC (I) / AMY (CLZ-III) / NAC (PCP-III) / VT (CLZ-III)
BB380620	ARHGEF9 Cdc42 guanine nucleotide exchange factor (GEF) 9	PFC (I) / NAC (I)/ AMY(CLZ-III)
BQ175863	GABRA5 gamma-aminobutyric acid (GABA) A receptor, alpha 5 ■	VT (II) / HIP (PCP-III)
Glutamate related genes		
	Up	
NM_019691.1	GRIA4 glutamate receptor, ionotrophic, AMPA 4)	AMY (I) / NAC (II)
	Down	
NM_013540.1	GRIA2 glutamate receptor, ionotropic, AMPA 2 ■	AMY (I)
NM_008169	GRIN1 glutamate receptor, ionotropic, N-methyl D-aspartate 1	VT (I)
NM_008165	GRIA1 glutamate receptor, ionotropic, AMPA1 (alpha 1) ■	VT (II) / NAC (CLZ-III)
		AMY (II)
Other neurotransmitter related genes		
	Up	
BB549292	MAOB monoamine oxidase B ■	VT (I)
NM_007744	COMT catechol-O-methyltransferase	VT (CLZ-III)
	Down	
BG311385	ADORA2A adenosine A2a receptor ■	PFC(II) /NAC(II) /AMY(PCP-III)
BE957273	DRD1 dopamine receptor D1 ■	PFC (II) / AMY (PCP-III)
NM_010077	DRD2 dopamine receptor 2 ■	PFC (II) / AMY (PCP-III)
1420879_a_at	YWHAB tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	AMY (I) / NAC (PCP-III) / PFC (CLZ-III)
Signal transduction genes		
	Up	
BB476448	CAMK2A calcium/calmodulin-dependent protein kinase II alpha ■	AMY (I) / PFC (I) / VT (II) / NAC (CLZ-III) / CP (CLZ-III)
AF109769.1	MAPK8IP1 mitogen activated protein kinase 8 interacting protein 1 ■	AMY (I) / NAC (PCP-III) / PFC (PCP-III)
AW123977	PDE10A phosphodiesterase 10A ■	AMY (I) / PFC (II) / CP (CLZ-III) / VT (CLZ-III)
NM_009062	RGS4 regulator of G-protein signalling 4 ■	AMY (I) / VT (II) / HIP (CLZ-III) / PFC (CLZ-III)
	Up/down	
BG071068	GNB1 guanine nucleotide binding protein (G protein), beta polypeptide 1)	NAC (I) / AMY(II) / PFC (PCP-III)
BG071931	CAMK1D calcium/calmodulin-dependent protein kinase ID	VT (I)
Ion channels		
	Up	
U11075	KCNJ4 potassium inwardly-rectifying channel, subfamily J, member ■	NAC (I) / PFC (PCP-III)
	Up/down	
AV221826	SCN8A Neuronal voltage-gated sodium channel aplpha subunit (Scn8a)	VT (I)
1437675_at	SLC8A1 solute carrier family 8 (sodium/calcium exchanger), member 1	VT (II)
1448468_a_at	KCNAB1 potassium voltage-gated channel, shaker-related subfamily, beta member 1	VT (II)
Clock genes		
	Down	
U77967	NPAS1 neuronal PAS domain protein 1 ■	VT (I)
	Up	
NM_013646	RORA RAR-related orphan receptor alpha ■	AMY (I), VT (CLZ-III)

Gene Accession Numbers	Gene / Name	Brain Region (Drug-Category)
Glia/Myelin genes		
	Up	
NM_010777.1	MBP myelin basic protein ■	AMY (I) / PFC (PCP-III)
M15442.1	PLP1 proteolipid protein (myelin) ■	AMY (I) / PFC (PCP-III)
BB183081	GFAP glial fibrillary acidic protein ■	AMY (I) / NAC (CLZ-III)
NM_008885.1	PMP22 peripheral myelin protein ■	AMY (I)
NP_032640.1	MOBP myelin-essociated oligodendrocytic basic protein	AMY (I) / NAC (II) / PFC (PCP-III)
	Down	
NM_009923.1	CNP 2',3'-cyclic nucleotide 3' phosphodiesterase ■	CP (I) / NAC (PCP-III) /PFC (PCP-III) / VT (CLZ-III)
AK019046	MAL myelin and lymphocyte protein, T-cell differentiation protein ■ ■	PFC (I) / AMY (II) / VT (PCP-III)
Synaptic function genes		
	Down	
NM_013681.1	SYN2 synapsin II ■	AMY (I) / VT (I) / CP (PCP-III)
NM_009948.1	CPLX2 complexin 2 ■	VT (I)
1420418_at	SYT2 synaptotagmin 2	AMY (I) / CP (I) / VT (II) / NAC (PCP-III)
Neuronal migration/neurite growth		
	Up	
BB075797	EPHA7 EPH receptor A7 ■	VT (I) / HIP II
	Down	
NM_011261.1	RELN reelin ■	VT (II) / PFC (CLZ-III)
	Up/ Down	
BB074430	NDN necdin ■	NAC (I) / AMY (CLZ-III) / PFC (PCP-III) / VT (CLZ-III)
AK003046	NRN1 neuritin 1 ■	NAC (I)
BC026833.1	GJB1 gap junction membrane channel protein beta 1	VT (I) / AMY (PCP-III)
Transcription Factor		
	Up	
BB361162	ZIC1 Zinc finger protein of the cerebellum 1 ■	NAC (I) / AMY (II) / HIP (III)/ CP (III) / PFC (CLZ-III)
NM_013613 2	NR4A2/Nurr1 Nuclear receptor subfamily 4, group A, member	NAC (I) / HIP (I) / VT (II)/ PFC (PCP-III)
	Up/ Down	
NM_010053.1	DLX1 distal-less homeo box 1	VT (II) / PFC (CLZ-III)
NM_013665.1	SHOX2 short stature homeobox 2	VT (II)
BB175494	TCF7L2 transcription factor 7-like 2 (T-cell specific, HMG-box) ■	VT (I) / AMY (PCP-III) / CP (PCP-III)
BC024556.1	PDLIM2 PDZ and LIM domain 2	VT (I)
BE947440	SCRT1 scratch homolog 1, zinc finger protein (Drosophila)	VT (I)
1441313_x_at	LHX9 LIM homeobox protein 9	VT (II) / HIP (I)
Regulatory Enzymes /Carriers		
	Up	
NM_013467.1	ALDH1A1 aldehyde dehydrogenase family 1, subfamily A1 ■	AMY (I) / NAC (II)
1449129_a_at	CSEN calsenilin, presenilin binding protein, EF hand	HIP (I) / VT (CLZ-III)
NM_007470.1	APOD apolipoprotein D	AMY (II) /HIP (CLZ-III)/ PFC (CLZ-III) / VT (PCP-III)
NM_008509.1	LPL lipoprotein lipase	HIP (I) / NAC (I) / AMY (III-CLZ)
	Down	
AK018763	AGT angiotensinogen ■	CP (II) /NAC (II) /AMY(PCP-III)
1423860_at	PTGDS prostaglandin D2 synthase (brain)	HIP (I) / VT (II) / AMY (PCP-III) / CP (PCP-III)
	Up/ Down	
AV343478	ATP2B2 ATPase, Ca++ transporting, plasma membrane 2	VT (I) / NAC (CLZ-III)
BB250811	PCOLCE procollagen C-proteinase enhancer protein	VT (I) / HIP (PCP-III) / NAC (CLZ-III)
Regulatory RNAs		
	Up	
BB649603	RIAN RNA imprinted and accumulated in nucleus	AMY (I) / VT (I) / PFC (PCP-III) / CP (PCP-III)
AF224264	FUS fusion, derived from t(12;16) malignant liposercoma (human)	AMY (I) / PFC (I) / NAC (PCP-III)
AK013588.1	ELAVL4 ELAV (embryonic lethal, abnormal vision, Drosophila)- like 4 (Hu antigen D) ■	VT (I)
AK020483	MALAT1 Metastasis associated lung adenocarcinoma transcript 1 ■	PFC (I) / NAC (PCP-III) / VT (PCP-III)
AV015833	MEG3 Maternally expressed gene 3	PFC (I) / VT (II) / AMY (CLZ-III) / NAC (PCP-III)
AF022957.1	ANP32A acidic (leucine-rich) nuclear phosphoprotein 32 family, member ■	AMY (I) / PFC (II) / NAC (PCP-III)

Additional Evidence: ■ Linkage ■ Postmortem

Genes from Categories I and II were classified into biological groups of interest previously reported to have relevance to the pathophysiology of schizophrenia and related disorders. Up, upregulated; down, downregulated; PCP, phencyclidine; CLZ, clozapine; PFC, prefrontal cortex; AMY, amygdala; CP, caudate putamen; NAC, nucleus accumbens; VT, ventral tegmentum; HIP, hippocampus. Roman numerals in the brain region data column represent the Category of the gene.

reported elevated in the cortex of subjects with schizophrenia [Dracheva et al., 2004]. Other GABA related genes among our Category I and II genes include ARHGEF9 and GABRA5 (Table III), as well as GABRA3 and SLC6A13 (GABA transporter) (Table VII). Additional GABA related genes from our complete datasets include GABRA4, GABRB2, GABRB3, and GABRG2 (see supplementary online information).

Schizophrenia patients experience deficits in many aspects of cognition and perception. EEG studies suggest that abnormalities in gamma band activity may underlie some of these deficits [Symond et al., 2005; Wynn et al., 2005]. Networks of GABAergic neurons are key elements in the generation of gamma oscillations in the brain [Vida et al., 2006].

TABLE IV. Gene Ontology Analysis

GO ANALYSIS- BIOLOGICAL PROCESSES	Category I genes	Category II genes	Category III genes	Category IV genes
1. Cellular Physiological Process	176		1709	294
2. Cell Communication	83	88	872	
3. Metabolism	116		711	
4. Cellular Biological Process		160	488	
5. Development		58	260	94
6. Organismal Physiological Process	46		145	
7. Behavior		17	159	36
8. Cell Death	11	10	139	12
9. System Development	32		89	
10. Morphogenesis	27		96	
11. Organ Development	20		93	
12. Response to Biotic Stimulus	14	6	90	11
13. Embryonic Development	6		105	
14. Regulation of Biological Process	75			
15. Localization	59			
16. Sexual reproduction		2	83	1
17. Response to external stimulus	9	8	58	7
18. Response to Abiotic Stimulus	5	9	61	9
19. Homeostasis	4	8	61	14
20. Extracellular Structure Organization and Biogenesis	1	1	25	4
21. Rhythmic Process	3	2	13	3
22. Pattern Specification	5		12	
23. Locomotory Behavior	12			
24. Response to Endogenous Stimulus	3		12	
25. Response to Stress	8			
26. Coagulation		3	8	1
27. Tissue Development			11	
28. Growth	7			
29. Membrane Fusion	2	1	5	
30. Reproductive Physiological Process			8	2
31. Adult Behavior	4			
32. Sex Differentiation	1		4	
33. Appendage Development	1		3	
34. Post-embryonic Development	1		3	
35. Segmentation	1		3	
36. Lysogeny			3	1
37. Reproductive Process	2			
38. Tube Development			3	
39. Symbiosis, mutualism through parasitism			2	
40. Feeding behavior	1			
41. Mechanosensory Behavior	1			
42. Metamorphosis			1	
43. Pigmentation During Development			1	

Biological processes obtained from Gene Ontology analysis of our complete dataset. Genes from all the different brain regions and categories (Fig. 2c) were subjected to analysis.

Glutamate Neurotransmission

Our work has identified as a top candidate gene for schizophrenia GRIA2 (Table I and Fig. 3). GRIA2 levels were previously reported to be changed in postmortem brains from schizophrenia patients in microarray [Vawter et al., 2002a] and protein studies [Gupta et al., 2005]. Other glutamate related genes among our Category I and II genes include GRIA4, GRIN1 and GRIA1 (see Tables I and III). As such, in addition to the well known dopaminergic receptors (Table III), our work supports key molecular aspects underpinning the glutamatergic hypothesis of schizophrenia pathophysiology.

Myelin/Glia Related Genes

An emerging body of work over the last 5 years has implicated myelin/glia related dysfunction in schizophrenia [Hakak et al., 2001; Hof et al., 2002; Hof, 2003; Tkachev et al., 2003; Dracheva et al., 2004; Katsel et al., 2005a,b; Kubicki et al., 2005a,b; Aberg et al., 2006a,b; Georgieva et al., 2006; Peirce et al., 2006]. Our work has identified as top candidate genes for schizophrenia six genes involved in myelin/glia function -CNP, MAL, MBP, PLP1, MOBP, and GFAP (Table I and Fig. 3), and thus confirms and reinforces previous findings related to the role of white matter abnormalities in general, and of these genes in particular, in the pathophysiology of schizophrenia. Notably, some of the initial findings were reported primarily based on human postmortem brain studies, which face challenges such as genetic heterogeneity, variable environmentally induced changes, and potential aging related and agonally induced artifacts [Vawter et al., 2006]. Our acute treatment pharmacogenomic model in isogenic animals does not suffer from those caveats. It is thus reassuring that multiple approaches converge on the same genes. This convergence instills a high degree of confidence that these findings are not artifactual, but rather should be vigorously pursued as valid molecular underpinnings of the pathophysiology of schizophrenia.

Of note, these glia/myelin related genes are reported to be altered in expression also in bipolar disorder (MAL, MBP, PLP1, MOBP, GFAP), depression (CNP, MAL, PLP1, MOBP, GFAP), and alcoholism (CNP, MAL, MBP, PLP1, MOBP, and GFAP) postmortem brains. The commonality of alterations in glia/myelin genes, primarily 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. 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 psychotic disorders [Peet and Stokes, 2005] and mood disorders [Parker et al., 2006]. Deficits in omega-3 fatty acids have been linked to increased aggression and depression in both animal models [DeMar et al., 2006] and humans [Zanarini and Frankenburg, 2003].

Candidate Biomarker Genes

Our work has also identified two genes that were recently reported to be changed in both postmortem brain and lymphocytes from schizophrenia patients, BTG1 and SFRS1 [Glatt et al., 2005], as well as a gene reported changed in lymphocytes from a multiplex schizophrenia pedigree, GNAO1 [Vawter et al., 2004]. These three genes, in our dataset, were Category III genes changed in the VT by clozapine and showing no-change in PCP/clozapine co-treatment. Other candidate biomarker genes identified in those reports were not seen by us in the current analysis of brain microarray data. However, more extensive studies comparing brain and blood gene expression profiles in our animal model are warranted for definitive conclusions. While providing additional independent support for those three potential biomarker genes for schizophrenia, our work so far also points to the utility of cross-matching different lines of evidence with an approach such as Convergent Functional Genomics in order to pick and prioritize candidate gene results from potentially noisy human postmortem brain and lymphocyte datasets, for future pursuit and validation.

Behavioral Correlates of Gene Expression

We hypothesized a priori that genes that would be changed in expression by both PCP and clozapine single-drug treatment might show changes in opposite directions, that is, increased in one case, decreased in the other, and vice versa. This proved not to be the case for the majority of top scoring candidate genes. In retrospect, our hypothesis was simplistic. The behavioral data (Fig. 4) of the mice on PCP and the mice on clozapine is illustrative in this regard. Center Time (time spent in the center quadrant of the open filed), along with Total Crossings (from one quadrant to the other of the open field), were identified by a phenotypic clustering analysis of behavioral measures (PhenoChipping) [Niculescu et al., 2006] as being one of the measures changed initially in opposite directions the most by PCP and clozapine, with the co-treatment group showing an intermediary phenotype (Fig. 4a). Whereas Total Crossings may be a less specific reflection of the activating properties of PCP and tranquilizing properties of clozapine, perhaps germane to the overlap with bipolar phenomenology (see also below and Table VIII), Center Time may be a more specific reflection of disrupted cognition, as cognitively intact mice should avoid the potentially dangerous center area of an open-field due to ancestral self-preservation mechanisms. This result illustrates the power of our unbiased approach in identifying simple putative mouse behavioral correlates of disrupted cognition. While the treatment group phenotypes were clearly different in the initial assessment at 30 min following injection (Figs. 4a,b), showing the activating, psychomimetic effects of PCP and the tranquilizing, antipsychotic effects of clozapine, and with the co-treatment group displaying an intermediary phenotype, by 24 hr the behavioral parameters were more similar, pointing to the effects of clozapine having worn off and suggesting the possibility of a rebound change in levels in it is target genes (Fig. 4c). Nevertheless, more extensive time courses and gene expression-behavioral correlation work needs to be carried out, in both groups of animals [Whitfield et al., 2003] and individual animals, in order for a complete picture to emerge linking different behavioral parameters with changes in specific genes or groups of genes. It is to be noted that a number of Category I and II candidate genes do show opposite changes with PCP and clozapine, as captured by our 24 hr time point (Table II). The relative influence of gene expression kinetics in response to drug versus genuine biological relevance to schizophrenia remains to be determined, as few of them have multiple external lines of evidence supporting them so far, and thus score lower overall than the genes in Table I.

Gene Ontology Analysis Results

Gene Ontology analysis of the complete dataset—categories I, II, III, and IV (Table IV), revealed that the top 25 categories on the list, in that order, were genes having to do with: (1) brain cell functions (cellular physiological processes, metabolism, cellular biological processes, cell death), (2) communication between brain cells (cell communication), (3) brain development (development, system development, morphogenesis,

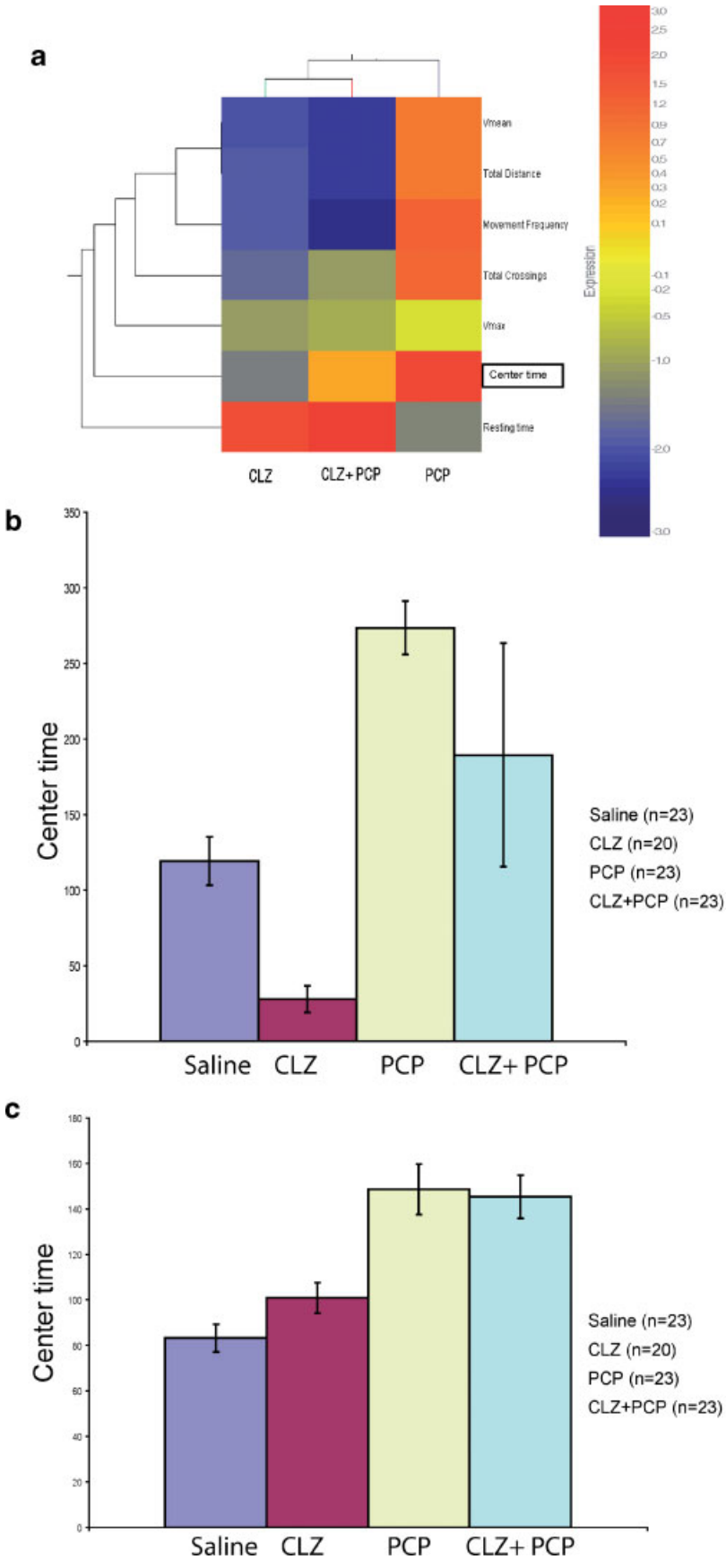

a
Vmean
Total Distance
Movement Frequency
Total Crossings
Vmax
Center time
Resting time
CLZ
CLZ+PCP
PCP
Expression
b
Center time
Saline
CLZ
PCP
CLZ+ PCP
Saline (n=23)
CLZ (n=20)
PCP (n=23)
CLZ+PCP (n=23)
c
Center time
Saline
CLZ
PCP
CLZ+ PCP
Saline (n=23)
CLZ (n=20)
PCP (n=23)
CLZ+PCP (n=23)

Fig. 4.

organ development, embryonic development, localization, extracellular structure organization, pattern specification), (4) integration of organismal physiological functions (organismal physiological processes, response to biotic stimuli, regulation of biological processes, response to abiotic stimuli, homeostasis, rhythmic processes, response to endogenous stimuli), (5) external behavioral responses (behavior, sexual reproduction, locomotor behavior), and (6) reactivity to the environment (response to external stimuli, response to stress). This is consistent with a model of schizophrenia as being primarily a disorder of brain cellular functioning and communication, with a strong developmental component, impacting the integration of organismal physiological functions, external behavioral responses, and, to a lesser extent, reactivity to the environment (Fig. 5b).

Our approach described thus far is to generate data in an appropriate discovery paradigm, and let the data coalesce into possible mechanistic interpretations. An opposite, hypothesis-driven approach for mining our dataset is to interrogate if genes related to known biological mechanisms of interest (Table III), linkage loci (Table V), or postmortem findings (Table VI) are present in it—spanning the spectrum from the more sensitive (biological) to the more specific (postmortem) external corroborative lines of evidence.

Biological Roles

An interrogation of our top candidate genes from Categories I and II, for classification in functional groups that had been previously implicated or hypothesized to have relevance to the pathophysiology of schizophrenia and related disorders, yielded genes related to GABA, glutamate, other neurotransmitters function (such as DRD1, DRD2, COMT), neuropeptides, glia/myelin function, synaptic function, ion channels, signal transduction (such as RGS4), regulatory enzymes, regulatory RNAs, neuronal migration/neurite growth (such as RELN/Reelin), transcription factors involved in brain development (such as NR4A2/Nurr1), and circadian clock genes (such as NPAS1 and RORA) (Table III).

Of note, circadian and sleep abnormalities are a common and relatively underappreciated feature of schizophrenia [Mattai et al., 2006]. NPAS1 has been implicated in mice in behavioral and neurochemical abnormalities (reduction in Reelin) consistent with schizophrenia [Erbel-Sieler et al., 2004]. RORA has been implicated in mice in regulating endocrine responses to stress and corticosterone circadian rhythms [Frederic et al., 2006]. Additionally, the circadian pacemaker gene PER1 has been reported to be altered in expression in postmortem brains of schizophrenics [Aston et al., 2004]. PER1 is one of the lower-priority genes in our dataset (in VT, Category IV—changed by clozapine only). Other lower priority clock genes in our dataset are CSNK1D (in VT, Category III—changed by clozapine, and the change is prevented by co-treatment with PCP), RORB (NAC, Category III—changed by PCP, and the change is prevented by co-treatment with clozapine; in VT, Category III—changed by clozapine, and the change is prevented by co-treatment with PCP), and DBP (in CP, Category IV-changed by PCP only).

Cross-Validation With Human Linkage Loci

Interrogating our dataset for genes that map to the linkage loci reported by recent meta-analyses for schizophrenia and bipolar disorder yielded a series of candidate genes at those loci (Table V) that may help prioritize future candidate gene research for each of the loci.

Cross-Validation With Human Postmortem Findings

Lastly, an interrogation of our dataset with genes that have previously been reported in the literature as altered in postmortem brains from patients with schizophrenia, as well as bipolar disorder, depression, and other brain disorders that affect cognition, confirmed in our dataset some of those earlier findings (Table VI). This cross-validation, on the one hand reinforces the validity of our approach, and on the other hand it reduces the likelihood that those particular postmortem findings are methodological or gene-environment interactions artifacts of working with post-mortem human tissue. Notably, we reproduce with our animal model data a series of genes recently reported by some of us to be changed in the dorsolateral PFC of schizophrenia subjects [Glatt et al., 2005] (such as ARHGEF9, LPL, LPHN1, FAIM2, RYR2—Table VI, as well as the brain-blood candidate biomarkers BTG1 and SFRS1 mentioned earlier).

DISCUSSION

We have used a comprehensive Convergent Functional Genomics approach for identifying high probability candidate genes, pathways and mechanisms for schizophrenia, and prioritizing them for future research, by the integration in a Bayesian fashion of multiple independent converging lines of evidence.

Limitations and Confounds

An acute treatment model like the one we are using is not necessarily inductive to assessing the long-term changes associated with schizophrenia, such as long-term cognitive changes as well as structural changes apparent on imaging. While we have no direct way of knowing if some of the genes we captured with our screen are involved or not in setting in motion such long term changes, it is to be noted that some of these gene changes have also been reported in postmortem brains of schizophrenia, bipolar disorder and dementia patients (Table VI), presumably affecting cognition. Moreover, we have candidate genes in our dataset with roles in brain infrastructure, including neurotrophic and myelin related genes (Table III). More chronic treatments should, nevertheless, be pursued to verify and expand the findings presented in this paper.

Different combinations of psychomimetic and anti-psychotic agents could be used in a comprehensive functional pharmacogenomic approach such as we have described. They could conceivably lead to different results, which would be interesting and welcome, since it is unlikely we are capturing with our model the full spectrum of gene expression changes and mechanisms involved in schizophrenia. However, if those drug combinations indeed mimic and modulate the same core phenomenology, the Venn diagrams of the overlap between different drug treatments will be of high interest in terms of identifying the key molecular players involved in the effects, as opposed to those involved in the (very different) side-effects of the individual drugs.

It is to be noted that our experimental approach for detecting gene expression changes relies on a single methodology,

Fig. 4. Behavioral correlates of phencyclidine and clozapine treatment. **a**: Clustering of mouse open field video-tracking behavioral phenotype data, in the first 30 min after injection. Normalized (Cohen's D effect size) behavioral data was imported into GeneSpring 7.2, where it was analyzed using standard unsupervised two-way hierarchical clustering algorithms. Red-increased, blue-decreased compared to saline controls. **b**: Center time data from video-tracking, first 30 min following injections. **c**: Center time data from video-tracking, 30 min interval at the 24 hr time point following injections, immediately prior to brain harvesting for gene expression studies.

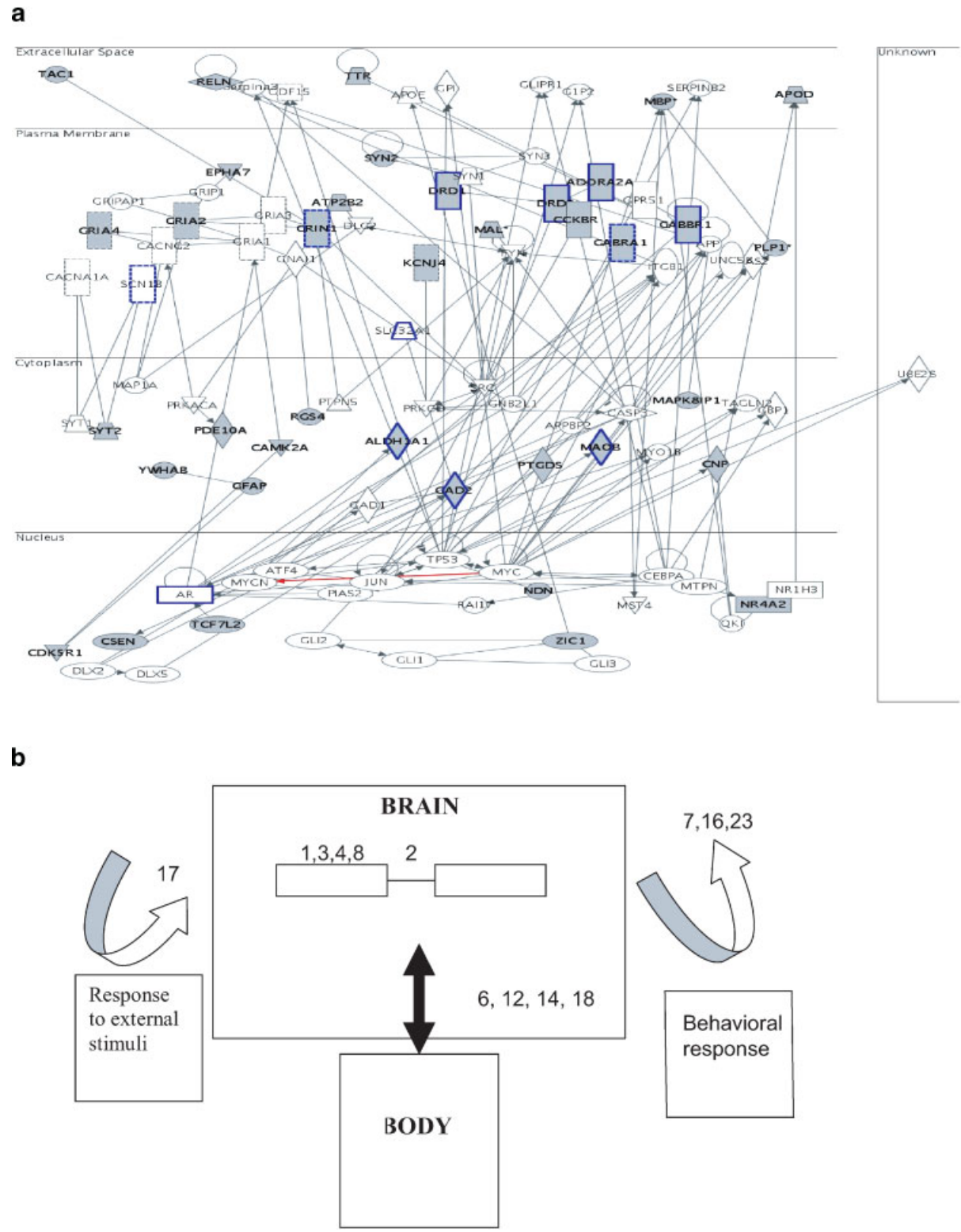


Fig. 5. Candidate genes, pathways and mechanisms. **a**: Top candidate genes and their relationships, using Ingenuity Pathway Analysis 3.1. Genes highlighted in grey are candidate genes from our dataset. Genes highlighted with blue are targets of existing drugs. **b**: Gene Ontology (GO) analysis-derived model of biological processes and mechanisms in schizophrenia. Numbered categories refer to GO analysis categories from Table IV.

TABLE V. Candidate Genes in our Dataset Mapping to Loci Identified by Meta-Analyses of Human Genetic Linkage Data

Schizophrenia		
Loci	**Symbol**	**Description**
1p13.3 - 1q23.3 Lewis et al;2003		
1p13	Ovgp1	oviductal glycoprotein 1
1p13.1	Atp1a1	ATPase, Na+/K+ transporting, alpha 1 polypeptide
1p13.1	Nhlh2	nescient helix loop helix 2
1p13.1	Tspan2	tetraspanin 2
1p13.3	Ampd2	adenosine monophosphate deaminase 2 (isoform L)
1p13.3	Kcna3	potassium voltage-gated channel, shaker-related subfamily, member 3
1p21.2	Gpr88	G-protein coupled receptor 88
1q21.2	Pip5k1a	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha
1q21.3	Rps27	ribosomal protein S27
1q23.1	Hapln2	hyaluronan and proteoglycan link protein 2
1q23.3	Rgs4	regulator of G-protein signaling 4
1q23.3	Rxrg	retinoid X receptor gamma
1q24.2	F5	coagulation factor V
1q25.3	Ier5	immediate early response 5
1q23.3	Olfml2b	olfactomedin-like 2B
2p12 - 2q22.1 Lewis et al;2003		
2p11.2	Tmsb10	thymosin, beta 10
2q11.1	Mal	myelin and lymphocyte protein, T-cell differentiation protein
2q11.1	Csen	calsenilin, presenilin binding protein, EF hand transcription factor
2q12.2	Ecrg4	Esophageal cancer related gene 4 protein
2q14.1	Dpp10	dipeptidylpeptidase 10
2q14.2	Inhbb	inhibin beta-B
2q22.1 - 2q23.3 Lewis et al;2003		
2q22.3	Zfhx1b	zinc finger homeobox 1b
2q23.3	Tnfaip6	tumor necrosis factor alpha induced protein 6
3p25.3 - 3p22.1 Lewis et al;2003		
3p22.2	MOBP	myelin-associated oligodendrocytic basic protein
3p22.3	Dcamkl3	doublecortin and CaM kinase-like 3
3p24.2	Rarb	retinoic acid receptor, beta
3p24.3	Satb1	special AT-rich sequence binding protein 1
3p25	Syn2	synapsin II
3p25.1	Sh3bp5	SH3-domain binding protein 5 (BTK-associated)
3p25.3	Atp2b2	ATPase, Ca++ transporting, plasma membrane 2
5q23.2 - 5q34 Lewis et al;2003		
5q23.3	8-Sep	septin 8
5q31.1	Hspa4	heat shock protein 4
5q31.2	Egr1	early growth response 1
5q32	Camk2a	calcium/calmodulin-dependent protein kinase II alpha
5q33.1	Sparc	secreted acidic cysteine rich glycoprotein
5q33.1	G3bp	Ras-GTPase-activating protein SH3-domain binding protein
5q33.2	Gria1	glutamate receptor, ionotropic, AMPA 1
5q34-q35	Gabra1	gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 1
6pter - 6q23.2 Lewis et al;2003		
6p21.31	Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)
6p22.1	Gabbr1	gamma-aminobutyric acid (GABA-B) receptor, 1
6p22.2	Hist1h1c	histone 1, H1c
6p23	Cd83	CD83 antigen
6p25.1	Nrn1	neuritin 1
6q15	Cnr1	Cannabinoid receptor 1 (brain)
6q16.1	Epha7	Eph receptor A7
6q16.1	Fut9	fucosyltransferase 9
6q21	Popdc3	popeye domain containing 3
6q21	Gpr6	G protein-coupled receptor 6
6q22.31	Fabp7	fatty acid binding protein 7, brain
6q23.2	Ctgf	connective tissue growth factor
8p22 - 8p21.1 Lewis et al;2003		
8p21	Nefl	neurofilament, light polypeptide
8p21.2	Pdlim2	PDZ and LIM domain 2
8p21.3	Lpl	lipoprotein lipase
10pter - 10p14 Lewis et al;2003		
10p15	Gata3	GATA binding protein 3
11q22.3 - 11q24.1 Lewis et al;2003		
11q22	Gria4	glutamate receptor, ionotrophic, AMPA 4)
11q23	Dscaml1	Down syndrome cell adhesion molecule-like 1
11q23.1	Cryab	crystallin, alpha B
11q23.2	Drd2	dopamine receptor 2
11q23.3	Tagln	transgelin
11q23.3	Scn4b	sodium channel, type IV, beta polypeptide
11q24	Eva1	epithelial V-like antigen 1
11q24.2	Nrgn	neurogranin
15q21.3 - 15q26.1 Lewis et al;2003		
15q21.1	Gatm	glycine amidinotransferase (L-arginine:glycine amidinotransferase)
15q21.2	Arpp19	cAMP-regulated phosphoprotein 19
15q21.3	Tcf12	transcription factor 12
15q21.3	Aldh1a2	aldehyde dehydrogenase family 1, subfamily A2
15q21-q22	Anxa2	annexin A2
15q21-q22	Rora	RAR-related orphan receptor alpha
15q22.2	Ca12	carbonic anyhydrase 12
15q22.3-q23	Anp32a	acidic (leucine-rich) nuclear phosphoprotein 32 family, member A
15q23	Calml4	calmodulin-like 4
15q24.1	Rpp25	ribonuclease P 25 subunit (human)
15q25.3	Akap13	A kinase (PRKA) anchor protein 13
16p13 - 16q12.2 Lewis et al;2003		
16p11.2	Doc2a	double C2, alpha
16p11.2	Fus	fusion, derived from t(12;16) malignant liposarcoma (human)
16p12.1	Hs3st2	heparan sulfate (glucosamine) 3-O-sulfotransferase 2
16p12.1	Ndufab1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1
16q12.1	Cbln1	cerebellin 1 precursor protein
16q12-q13	Adcy7	Adenylate cyclase 7
17q21.33 - 17q24.3 Lewis et al;2003		
17q21	Gfap	glial fibrillary acidic protein
17q21.2	Cnp	2',3'-cyclic-nucleotide 3'-phosphodiesterase (EC 3.1.4.37) (CNP) (CNPase).
17q21.2	Ramp2	receptor (calcitonin) activity modifying protein 2
17q12-q21	Mpp3	membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)
17q23.2	Sept4	septin 4
18q22.1 - 18qter Lewis et al;2003		
18q22.1	Cdh7	Cadherin 7, type 2
18q22.3	Neto1	neuropilin (NRP) and tolloid (TLL)-like 1
18q23	Mbp	myelin basic protein
20p12.3 - 20p11 Lewis et al;2003		
20p11	Flrt3	fibronectin leucine rich transmembrane protein 3
20p12	Thbd	thrombomodulin
22pter - 22q12.3 Lewis et al;2003		
22q11.1	Tuba8	tubulin, alpha 8
22q11.23	Adora2a	adenosine A2a receptor

(*Continued*)

TABLE V. (*Continued*)

Bipolar Disorder

Loci	Symbol	Description
1p32.1 - 1q32 Segurado2003		
1p22.3	Ddah1	dimethylarginine dimethylaminohydrolase 1
1p31.1	Lhx8	LIM homeobox protein 8
1p31.3	Cipp	channel-interacting PDZ domain protein
1p31.3	Ak3l1	adenylate kinase 3 alpha-like 1
1q31.3	Lhx9	LIM homeobox protein 9
1q32	Tnnt2	troponin T2, cardiac
1q32.1	Csrp1	cysteine and glycine-rich protein 1
1q32.1	Syt2	synaptotagmin 2
1q32.1	Fmod	fibromodulin
1q32.1	Nfasc	Neurofascin
1q32.1	Syt2	synaptotagmin 2
2q22.1 - 2q23.3 Segurado2003		
2q22.3	Zfhx1b	zinc finger homeobox 1b
2q23.3	Tnfaip6	tumor necrosis factor alpha induced protein 6
3q22.1 - 3q25.31 Segurado2003		
3q22.3	Sox14	SRY-box containing gene 14
3q24	Zic1	Zinc finger protein of the cerebellum 1
3q25.1	Rnf13	ring finger protein 13
3q25.31	Kcnab1	potassium voltage-gated channel, shaker-related subfamily, beta member 1
5pter - 5p15.1 Segurado2003		
5p15.3	Nkd2	naked cuticle 2 homolog (Drosophila)
8pter - 8qter Segurado2003		
8q24.3	Ndrg1	N-myc downstream regulated gene 1
8q24.3	Scrt1	scratch homolog 1, zinc finger protein (Drosophila)
9p22.3 - 9qter Segurado2003		
9p13	Ccl27	chemokine (C-C motif) ligand 27
9q21.13	Aldh1a1	aldehyde dehydrogenase family 1, subfamily A1
9q21.13	Gda	Guanine deaminase
10q11.21 - 10q22.1 Segurado2003		
10p11.22	Arhgap12	Rho GTPase activating protein 12
10q11.1	Cxcl12	chemokine (C-X-C motif) ligand 12
10q11.21	Asah2	N-acylsphingosine amidohydrolase 2
10q11.21	Rassf4	Ras association (RalGDS/AF-6) domain family 4
10q11.21	Rasgef1a	RasGEF domain family, member 1A
10q21.2	Arid5b	AT rich interactive domain 5B (Mrf1 like)
11p13 - 11q13.3 Segurado2003		
11p12-p11.2	Mapk8ip1	mitogen activated protein kinase 8 interacting protein 1
11q11	Slc22a8	solute carrier family 22(organic anion transporter),member 8
11q12.2	Fads2	fatty acid desaturase 2
11q12.3	Slc22a6	solute carrier family 22(organic anion transporter),member 6
11q13.1	Rasgrp2	RAS, guanyl releasing protein 2
11q13.1	Malat1	metastasis associated lung adenocarcinoma transcript 1 (non-coding RNA
12q15-12q23.2 Segurado2003		
12q21.31	Nts	neurotensin
12q21.33	Dcn	decorin
12q22	Socs2	suppressor of cytokine signaling 2
14q13.1 - 14q32.12 Segurado2003		
14q22.1	Pygl	liver glycogen phosphorylase
14q23.3	Max	Max protein
14q24.3	Fos	FBJ osteosarcoma oncogene
17p12 - 17q21.33 Segurado2003		
17p11.2	Rasd1	RAS, dexamethasone-induced 1
17p11.2	Specc1	spectrin domain with coiled-coils 1
17q11.1	Wsb1	WD repeat and SOCS box-containing 1
17q11.2	Evi2a	ecotropic viral integration site 2a
17q11.2	Cdk5r1	cyclin-dependent kinase 5, regulatory subunit (p35) 1
17q11.2	Ksr	kinase suppressor of ras
17q11.2	Vtn	vitronectin
17q12	Ap2b1	Adaptor-related protein complex 2, beta 1 subunit
17q12	Dusp14	dual specificity phosphatase 14
17q21.2	Cnp	2',3'-cyclic-nucleotide 3'-phosphodiesterase (EC 3.1.4.37) (CNP) (CNPase).
17q21.2	Ramp2	receptor (calcitonin) activity modifying protein 2
17q12-q21	Mpp3	membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)
17q21	Cnp	cyclic nucleotide phosphodiesterase 1
18pter - 18q12.3 Segurado2003		
18q11.2-q12.1	Aqp4	aquaporin 4
18q12.1	Ttr	transthyretin
18q12.2	Zfp191	Zinc finger protein 191
18q21.1	Myo5b	myosin Vb
19q13.33 - 19qter Segurado2003		
19q13.2-q13.3	Npas1	neuronal PAS domain protein 1
19q13.33	Dkkl1	dickkopf-like 1
19q13.42	Tnnt1	troponin T1, skeletal, slow
20pter - 20p12.3 Segurado2003		
20p13	Cds2	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 2
21q21.3 - 21qter Segurado2003		
21q22.11	Kcne2	potassium voltage-gated channel, Isk-related
21q22.12	Clic6	subfamily, gene 2
21q22.3	Col6a1	chloride intracellular channel 6
21q22.3	Rik/SH3bgr	RIKEN cDNA 5430437A18 gene

Genes from our complete dataset mapping to linkage loci identified in recent meta-analyses of schizophrenia [Lewis et al., 2003] and bipolar disorder [Segurado et al., 2003]. *average ranks with significant P_{AvgRnk} values <0.01 strongest linkages in the meta-analyses. The rest of the linkages loci have P_{AvgRnk} values <0.05. All genes listed were within at least 10 cM of the marker for the given chromosomal location.

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. Working with an isogenic mouse strain affords us an ideal control baseline of saline injected animals for our drug-injected animals. We performed three independent de novo biological experiments, at different times, with different batches of mice (Fig. 1b). We have pooled material from three mice in each experiment, and carried out microarray studies. The pooling process introduces a built in averaging of signal. We used a Venn diagram approach and only considered the genes that were reproducibly changed in the same direction in at least two out of three independent experiments. 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]. Moreover, our approach, as described above, is predicated on the existence of three internal cross-validators for each gene that is called reproducibly changed: (1) is it changed by the other drug also, (2) is the change prevented by co-treatment with both drugs, and (3) is it changed in multiple brain regions, all of which are independent microarray experiments.

While we reproduced a majority of previous findings, we did not see in the mouse work described in this report some of the changes that had previously reported in rats by others using

TABLE VI. Top Candidate Genes and Human Postmortem Data

Genes from our dataset (Categories I-II) with human postmortem brain changes	Brain region, Category, Drug treatment
SCHIZOPHRENIA	
- **Adora2a** - adenosine A2a receptor	**NAC** II, **PFC** II, **AMY** III-PCP
- **Aldh1a1** - aldehyde dehydrogenase family 1, subfamily A1	**AMY** I, **NAC** II
- **Apod** - apolipoprotein D	**AMY** II, **HIP** III- CLZ, **PFC** III-CLZ, **VT** III-PCP
- **Arhgef9**- Cdc42 guanine nucleotide exchange factor (GEF) 9	**NAC** I, **PFC** I , **AMY** III- CLZ
- **Calb1**- calbindin 1	**VT** II, **VT** III-CLZ
- **Calb2**- calbindin 2	**CP** II, **PFC** IV-CLZ
- **Cckbr**- cholecystokinin B receptor	**HIP** I, **NAC** III-PCP, **VT** III-CLZ, **CP** IV- PCP
- **Cplx2** - complexin 2	**VT** I
- **Cnp**- 2',3'-cyclic nucleotide 3' phosphodiesterase	**AMY** I, **CP** I , **NAC** III-PCP, **PFC** III-PCP, **PFC** IV-PCP, **VT** III-CLZ
- **Dlx1**- distal-less homeo box 1	**VT** II, **PFC** III-CLZ, **AMY** IV- PCP
- **Drd1**- dopamine receptor D1	**PFC** II, **AMY** III-PCP
- **Drd2** - dopamine receptor D2	**PFC** II, **AMY** III- PCP
- **Faim2** - Fas apoptotic inhibitory molecule 2	**HIP** I, **VT** I, **PFC** III- PCP
- **Fos**- v-fos	**HIP** I, **AMY** III-CLZ, **NAC** III-CLZ
- **Gabra1** - gamma-aminobutyric acid (GABA-A) receptor, subunit alpha	**AMY** I, **AMY** III-CLZ, **CP** III-PCP, **NAC** III-PCP, **VT** III-CLZ, **VT** IV-CLZ
- **Gabbr1**- gamma-aminobutyric acid (GABA-B) receptor, 1	**AMY** I , **PFC** I , **AMY** III- CLZ, **NAC** III-PCP, **VT** III-CLZ, **VT** IV-CLZ
- **Gad2** - glutamic acid decarboxylase 2	**AMY** I, **NAC** III-PCP, **VT** IV-CLZ
- **Gfap** - glial fibrillary acidic protein	**AMY** I, **NAC** III-CLZ, **PFC** IV-CLZ
- **Gria1**- glutamate receptor, ionotropic, AMPA1 (alpha 1)	**AMY** II
- **Gria2** - glutamate receptor, ionotropic, AMPA 2	**VT** I, **VT** III-PCP
- **Gria4**- glutamate receptor, ionotrophic, AMPA 4	**AMY** I
- **Grin1 (Nmda-1)** - glutamate receptor, ionotropic, N-methyl D-aspartate 1	**VT** II, **NAC** III-CLZ
- **Kcnj4/Kir2.3**-potassium inwardly-rectifying channel, subfamily J, member 4	**NAC** I, **PFC** III-PCP
- **Lphn1** - latrophilin 1	**PFC** I, **VT** II, **CP** III-PCP
- **Lpl**-Lipoprotein Lipase	**NAC** I, **HIP** I, **AMY** III-CLZ
- **Mal**-myelin and lymphocyte protein, T-cell differentiation protein	**PFC** I, **AMY** II, **VT** III-PCP, **NAC** IV-PCP
- **Mag** - myelin associated glycoprotein	**AMY** II, **PFC** III-PCP, **VT** III-PCP, **NAC** IV-CLZ
- **Maob**-monoamine oxidase B	**VT** I
- **Mbp** - myelin basic protein	**AMY** I, **PFC** III-PCP
- **Mobp**- myelin-associated oligodendrocytic basic protein	**AMY** II, **NAC** III-CLZ, **PFC** III-PCP, **NAC** IV-PCP, **VT** IV- CLZ
- **Mpp3**- membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)	**HIP** I, **VT** I, **AMY** III-CLZ, **NAC** III-CLZ
- **Neurod1**- neurogenic differentiation 1	**AMY** II, **AMY** III-PCP, **NAC** III-PCP, **PFC** III-PCP, **VT** III-CLZ
- **Npas1**- neuronal PAS domain protein 1	**VT** I
- **Plp1** - proteolipid protein (myelin)	**AMY** I, **PFC** III-PCP, **VT** IV-CLZ
- **Pmp22**- peripheral myelin protein	**AMY** I
- **Pvalb**- parvalbumin	**AMY** II
- **Rarb** - retinoic acid receptor, beta	**PFC** II, **AMY** III-PCP
- **Reln** - reelin	**VT** II, **PFC** III-CLZ
- **Rgs4** - regulator of G-protein signalling 4	**AMY** II, **VT** II, **HIP** III-CLZ, **PFC** III-CLZ, **AMY** IV-CLZ, **HIP** IV-CLZ, **VT** IV-CLZ
- **Rtn4/Nogo** - neurite growth inhibitor reticulon 4	**AMY** II, **PFC** III-PCP
- **Ryr2** -ryanodine receptor 2	**VT** II
- **Sema3a**- semaphorin 3A	**HIP** I
- **Shox2**- short stature homeobox 2	**VT** II, **VT** III-CLZ, **VT** III-PCP
- **Slc17a6/Dnpl**-solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 6	**AMY** I , **NAC** Cat II
- **Syn2**- synapsin II	**AMY** I, **VT** I, **AMY** III-PCP, **CP** III-PCP
- **Tac1** - Tachykinin 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma)	**VT** I, **PFC** II, **AMY** III-PCP
- **Trf** - transferrin	**AMY** II, **PFC** III-PCP, **VT** III-PCP
- **Trhr**- thyrotropin releasing hormone receptor	**AMY** II, **VT** IV-CLZ
- **Ywhab**-tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide/14-3-3 genes	**AMY** I, **HIP** IV-CLZ, **NAC** III-PCP, **PFC** III-CLZ, **VT** IV-CLZ
BIPOLAR DISORDER	
- **Aldh1a1** - aldehyde dehydrogenase family 1, subfamily A1	**AMY** I, **NAC** II, **HIP** III-CLZ, **PFC** III-CLZ, **VT** III-PCP
- **Apod** - apolipoprotein D	**AMY** II, **HIP** III- CLZ, **PFC** III-CLZ, **VT** III-PCP
- **Calb1**- calbindin 1	**VT** II, **VT** III-CLZ
- **Calb2**- calbindin 2	**CP** II, **PFC** IV-CLZ
- **Camk2a** - Calcium/Calmodulin-dependent protein kinase II-alpha	**AMY** I, **PFC** I, **VT** II, **CP** III-CLZ, **NAC** III-CLZ, **PFC** III-PCP, **AMY** IV-PCP
- **Dlx1**- distal-less homeo box 1	**VT** II, **PFC** III-CLZ, **AMY** IV- PCP
- **Gabbr1**- gamma-aminobutyric acid (GABA-B) receptor, 1	**PFC** I, **AMY** III- CLZ, **NAC** III-PCP, **VT** III-CLZ
- **Gabra1** - gamma-aminobutyric acid (GABA-A) receptor, subunit alpha	**AMY** I, **AMY** III-CLZ, **CP** III-PCP, **NAC** III-PCP, **VT** III-CLZ, **VT** IV-CLZ,
- **Gad2** - glutamic acid decarboxylase 2	**AMY** I, **NAC** III-PCP, **VT** IV-CLZ
- **Gfap** - glial fibrillary acidic protein	**AMY** I, **NAC** III-CLZ, **PFC** IV-CLZ
- **Mbp** - myelin basic protein	**AMY** I, **PFC** III-PCP
- **Plp1** - proteolipid protein (myelin)	**AMY** I, **PFC** III-PCP, **VT** IV-CLZ
- **Pmp22**- peripheral myelin protein	**AMY** I
- **Pvalb**- parvalbumin	**AMY** II
- **Shox2**- short stature homeobox 2	**PFC** II, **AMY** III-PCP
- **Syn2**- synapsin II	**AMY** I, **VT** I, **CP** III-PCP

(*Continued*)

TABLE VI. (*Continued*)

- **Tac1** - Tachykinin 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma) ■	**VT** I, **PFC** II, **AMY** III-PCP
DEPRESSION	
- **Cnp**- 2',3'-cyclic nucleotide 3' phosphodiesterase ■	**AMY** I, **CP** I , **NAC** III-PCP, **PFC** III-PCP, **VT** III-CLZ, **PFC** IV-PCP
- **Mag** - myelin associated glycoprotein ■	**AMY** II, **PFC** III-PCP, **VT** III-PCP, **NAC** IV-CLZ
- **Mal**- myelin and lymphocyte protein, T-cell differentiation protein ■	**PFC** I, **AMY** II, **VT** III-PCP, **NAC** IV-PCP
- **Mobp**- myelin-associated oligodendrocytic basic protein ■	**AMY** II, **NAC** III-CLZ, **PFC** III-PCP, **NAC** IV-PCP, **VT** IV- CLZ
- **Plp1** - proteolipid protein (myelin) ■	**AMY** I, **PFC** III-PCP, **VT** IV-CLZ
- **Pmp22**- peripheral myelin protein ■	**AMY** I
- **Pvalb**- parvalbumin ■	**AMY** II
ALCOHOLISM	
- **Agt** - angiotensinogen ■	**CP** II, **NAC** II, **AMY** III-PCP
- **Apod** - apolipoprotein D ■	**AMY** II, **HIP** III-CLZ, **PFC** III-CLZ, **VT** III-PCP
- **Cnp**- 2',3'-cyclic nucleotide 3' phosphodiesterase ■	**AMY** I, **CP** I , **NAC** III-PCP, **PFC** III-PCP, **VT** III-CLZ, **PFC** IV-PCP
- **Cryab**- crystallin, alpha B ■	**AMY** II, **AMY** III-PCP, **CP**-III-CLZ, **VT** III-CLZ
- **Fn1**- fibronectin 1 ■	**VT** II
- **Gfap** - glial fibrillary acidic protein ■	**AMY** I, **NAC** III-CLZ, **PFC** IV-CLZ
- **Mal**- myelin and lymphocyte protein, T-cell differentiation protein ■	**PFC** I, **AMY** II, **VT** III-PCP, **NAC** IV-PCP
- **Mbp** - myelin basic protein ■	**AMY** I, **PFC** III-PCP
- **Mobp**- myelin-associated oligodendrocytic basic protein ■	**AMY** II, **NAC** III-CLZ, **PFC** III-PCP, **NAC** IV-PCP, **VT** IV- CLZ
- **Plp1** - proteolipid protein (myelin) ■	**AMY** I, **PFC** III-PCP, **VT** IV-CLZ
- **Syn2**- synapsin II ■	**AMY** I, **VT** I, **AMY** III-PCP, **CP** III-PCP
ALZHEIMER	
- **Apod** - apolipoprotein D ■	**AMY** II, **HIP** III-CLZ, **PFC** III-CLZ, **VT** III-PCP
- **Calb1**- calbindin 1	**VT** II, **VT** III-CLZ
- **Calb2**- calbindin 2	**CP** II, **PFC** IV-CLZ
- **Cdk5r1**- cyclin-dependent kinase 5, regulatory subunit (p35) 1	**AMY** I, **CP** III-CLZ, **NAC** III-PCP, **PFC** III-PCP, **VT** III-CLZ
- **Cnp**- 2',3'-cyclic nucleotide 3' phosphodiesterase ■	**AMY** I, **CP** I, **NAC** III-PCP, **PFC** III-PCP, **VT** III-CLZ, **PFC** IV-PCP
- **Gabbr1**- gamma-aminobutyric acid (GABA-B) receptor, 1 ■	**PFC** I, **AMY** III- CLZ, **NAC** III-PCP, **VT** III-CLZ
- **Mal**- myelin and lymphocyte protein, T-cell differentiation protein ■	**PFC** I , **AMY** II, **VT** III-PCP, **NAC** IV-PCP
- **Mbp** - myelin basic protein ■	**AMY** I, **AMY** II, **PFC** III-PCP
- **Pvalb**- parvalbumin ■	**AMY** II
- **Rgs4** - regulator of G-protein signalling 4 ■	**AMY** II, **VT** II, **HIP** III-CLZ, **PFC** III-CLZ, **AMY** IV-CLZ, **HIP** IV-CLZ, **VT** IV-CLZ
- **Sema3a**- semaphorin 3A	**HIP** I
- **Tac1** - Tachykinin 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma) ■	**VT** I, **PFC** II, **AMY** III-PCP
- **Trhr**- thyrotropin releasing hormone receptor	**AMY** II, **VT** IV-CLZ
EPILEPSY	
- **Csen**- calsenilin ■	**HIP** I, **HIP** III-PCP, **VT** III-CLZ, **CP** IV-CLZ
- **Gabbr1**- gamma-aminobutyric acid (GABA-B) receptor, 1 ■	**PFC** I, **AMY** III- CLZ, **NAC** III-PCP, **VT** III-CLZ
- **Rtn4/NoGo** - neurite growth inhibitor reticulon 4 ■	**AMY** II, **PFC** III-PCP
- **Tac1** - Tachykinin 1 (substance K, substance P, neurokinin 1, neurokinin 2, neuromedin L, neurokinin alpha, neuropeptide K, neuropeptide gamma) ■	**VT** I, **PFC** II, **AMY** III-PCP
OTHER DISORDERS	
PARKINSON	
- **Pvalb**- parvalbumin ■	**AMY** II
COCAINE ADDICTION	
- **Mbp** - myelin basic protein ■	**AMY** I, **PFC** III-PCP
- **Plp1** - proteolipid protein (myelin) ■	**AMY** I, **PFC** III-PCP, **VT** IV-CLZ

Additional Evidence: ■ Linkage

Category I and II genes in our dataset for which there are published reports of alterations in mRNA or protein levels in postmortem brains from individuals with schizophrenia, bipolar disorder, or other brain disorders that impact cognition. PCP, phencyclidine; CLZ, clozapine; PFC, prefrontal cortex; AMY, amygdala; CP, caudate putamen; NAC, nucleus accumbens; VT, ventral tegmentum; HIP, Hippocampus. Roman numerals in the brain region data column represent the Category of the gene.

PCP only, or clozapine only, treatment paradigms [Kaiser et al., 2004; Ouchi et al., 2005]. While some of this may be technical, that is, whole brain versus microdissected brain regions, cDNA microarrays or older generation oligonucleotide microarrays that did not have probe sets for some of our top findings in the current report, there are genes that are present in both the rat and mouse microarrays used. While clearly technical (experimental methodology, drug doses, pharmacokinetics) and biological (inter-strain, inter-species) differences remain open questions deserving of future extensive comparative work, it is likely that in similar paradigms across different species, it is pathways and mechanisms rather than individual genes that are more conserved. That would in turn imply that a convergent functional genomics approach such as ours, where one cross-matches animal gene expression changes with human linkage data at an individual gene level, productive as it may be, could miss many things. An arguably better approach, awaiting more complete datasets as well as more sophisticated bioinformatics tools now emerging, would be to do such a cross matching at a pathway and mechanism level.

Intergenic regions of DNA that are not transcribed, have indirect regulatory roles and give strong linkage and association data would not have a direct cross-matching with gene expression datasets, and would thus not be directly identified, validated and prioritized by our Convergent Functional Genomics approach. However the downstream effector genes whose expression is regulated by these regions would likely be captured by an approach such as ours.

TABLE VII. Top Candidate Genes in our Datasets Encoding Targets of Existing Pharmacological Agents

Gene Symbol -Description	Brain Region/ Category	Drugs
ALDH1A1 aldehyde dehydrogenase 1 family, member A1	AMY Cat I NAC Cat II	Disulfiram
GABBR1 gamma-aminobutyric acid (GABA) B receptor, 1	PFC Cat I AMY III-CLZ NAC III-PCP	Baclofen
GABRA1 gamma-aminobutyric acid (GABA) A receptor, alpha 1	AMY Cat I VT IV-CLZ CP III-PCP	amobarbital, atropine/hyoscyamine/phenobarbital/scopolamine, butabarbital, chlordiazepoxide, clonazepam, clorazepate, desflurane, diazepam, enflurane
GAD2 glutamate decarboxylase 2 (pancreatic islets and brain, 65kDa)	AMY Cat I NAC III-PCP VT IV-CLZ	valproic acid
LPL lipoprotein lipase	HIP Cat I NAC Cat I AMY III-CLZ	gemfibrozil, lovastatin/niacin, nicotinic acid, topiramate
MAOB monoamine oxidase B	VT Cat I	isocarboxazid, phenelzine, selegiline, tranylcypromine
SLC1A6 solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	VT Cat I	Riluzole
TUBA8 tubulin, alpha 8	HIP Cat I	colchicine, docetaxel, podophyllotoxin, taxol, vinblastine, vincristine, vinorelbine ditartrate
ADORA2A adenosine A2a receptor	NAC Cat II PFC Cat II AMY III-PCP	aminophylline, caffeine, fioricet, theophylline
DRD2 dopamine receptor D2	PFC Cat II AMY III-PCP	apomorphine, aripiprazole, bromocriptine, buspirone, cabergoline, chloropromazine, clozapine, dihydroergotamine, dopamine, droperidol, olanzapine, fluphenazine,
F5 coagulation factor V (proaccelerin, labile factor)	AMY Cat II	drotrecogin alfa
GABRA3 gamma-aminobutyric acid (GABA) A receptor, alpha 3	PFC Cat II AMY III-CLZ CP III-CLZ NAC III-CLZ	amitriptyline/chlordiazepoxide, amobarbital, butabarbital, chlordiazepoxide, clonazepam, clorazepate, desflurane, diazepam, enflurane,
GABRA5 gamma-aminobutyric acid (GABA) A receptor, alpha 5	VT Cat II HIP III-PCP	acetaminophen/butalbital, acetaminophen/butalbital/caffeine/codeine, amitriptyline/chlordiazepoxide, amobarbital, atropine/hyoscyamine/phenobarbital/scopolamine, butabarbital, chlordiazepoxide, clonazepam, clorazepate, desflurane, diazepam, enflurane, est
KCNE2 potassium voltage-gated channel, Isk-related family, member 2	AMY Cat II	amiodarone, Nicorandil
NR3C2 nuclear receptor subfamily 3, group C, member 2	HIP Cat II	epoxymexrenone, fludrocortisone acetate, hydrochlorothiazide/spironolactone, Spironolactone
RARB retinoic acid receptor, beta	PFC Cat II AMY III-PCP	13-cis-Retinoic acid, 9-cis-retinoic acid, acitretin, adapalene, retinoic acid, tazarotene
RXRG retinoid X receptor, gamma	PFC Cat II AMY III-PCP	9-cis-retinoic acid, retinoic acid
SLC6A13 solute carrier family 6 (neurotransmitter transporter, GABA), member 13	VT CAT II	Tiagabine

Ingenuity Pathway Analysis (Ingenuity) was used to identify genes in our datasets that are targets of existing pharmacological agents. PCP, phencyclidine; CLZ, clozapine; PFC, prefrontal cortex; AMY, amygdala; CP, caudate putamen; NAC, nucleus accumbens; VT, ventral tegmentum; HIP, hippocampus. Roman numerals in the brain region data column represent the Category of the gene.

Lastly, it is notable that we do not identify with our approach some of the genes implicated by recent work in the field-NRG1 [Thomson et al., 2006], DNTBP1 [Donohoe et al., 2006], and DAOA [Goldberg et al., 2006]. However, levels of NRG1, for example, do not reportedly differ between schizophrenics and controls, and a related signaling abnormality has been proposed [Hahn et al., 2006]. Thus, our approach may miss genes where the regulation of expression level is not the primary driving force for their implication in disease pathophysiology.

CONCLUSIONS AND FUTURE DIRECTIONS

The results presented in this paper have a series of direct implications. First, our work identifies, cross-validates and prioritizes for future research (candidate gene association studies-including epistatic interactions, neurobiological studies in transgenic mice, and new drug development) a series of known as well as novel candidate genes, pathways and mechanisms for schizophrenia. Figure 3, in particular, summarizes our prioritizing of candidate genes for future follow-up work, and Table V informs prioritization of genes in loci identified by large-scale meta-analysis work [Lewis et al., 2003].

Second, in terms of pharmacotherapy and drug development, some of the candidate genes in our dataset encode for proteins that are modulated by existing pharmacological agents (Table VII), which may suggest future avenues for rational polypharmacy using currently available agents.

TABLE VIII. Top Candidate Genes Overlap Between Our CFG Schizophrenia Dataset and Our CFG Bipolar Dataset [Ogden et al., 2004]

Gene Symbol Description	Schizophrenia CFG	Bipolar CFG (Ogden et al.2004)	Chromosomal location Human linkage/ association
MEF2C myocyte enhancer factor 2C	**AMY** Cat I **HIP** Cat I **VT III**-CLZ **CP** III-PCP **NAC** III-PCP	**PFC** Cat I **AMY** III-VPA	5q14.3 Etoh (Hill et al 2004)
CDK5R1 cyclin-dependent kinase 5, regulatory subunit (p35) 1	**AMY** Cat I **CP** III-CLZ **NAC** III-PCP **PFC III**-PCP **VT III**-CLZ	**AMY** Cat II **CP** III-VPA	17q11.2 Mental Retardation (Venturin et al 2006) Etoh (Hill et al 2004)
GPR88 G-protein coupled receptor 88	**AMY** Cat II **PFC** Cat II **VT** III-CLZ	**PFC** Cat I	1p21.2 SZ (Brzustowicz et al 2000),(Faraone et al 2006a) BP (Numberger et al 2001) Etoh (Foroud et al 2000), (Nurnberger et al 2001), (Lappalainen et al 2004), (Reich et al 1998),(Schuckit et al 2001)
TAC1 tachykinin 1	**VT** Cat I **PFC** Cat II **AMY** III-PCP	**PFC** Cat I	7q21.3 SZ (Ekelund et al 2000),(Yan et al 2000) BP (McInnis et al 2003),(Ogden et al 2004)
COPG2AS2 coatomer protein complex, subunit gamma 2, antisense 2	**HIP** Cat I **PFC** III-CLZ **VT III**-PCP	**PFC** III-Meth	7q32
FREQ frequenin homolog (Drosophila)	**AMY** Cat I **VT** IV-CLZ	**AMY** III-VPA	9q34.11 SZ (Kamnasaran et al 2003)
NPY2R neuropeptide Y receptor Y2	**HIP** Cat I **NAC** IV-PCP	**NAC III**-Meth	4q32.1
PTGDS prostaglandin D2 synthase (brain)	**HIP** Cat I **VT** Cat II **AMY** III-PCP **CP** III-PCP	**AMY** III-Meth	9q34.3 SZ (Kaufmann et al 1998) BP (McInnis et al 2003)
RFX3 Regulatory factor X, 3 (influences HLA class II expression)	**AMY** Cat I	**PFC** III-VPA	9p24.2
CLDN11 claudin 11	**AMY** Cat II	**CP** Cat II	3q26.2 BP (Cichon et al 2001) Epilepsy (Sander et al 2000)
MOBP myelin-associated oligodendrocytic basic protein	**AMY** Cat I **NAC** Cat II **PFC III**-PCP **VT** IV-CLZ	**CP** Cat II **VT** IV-VPA	3p22.2 SZ, BP, Autism (Kleiderlein et al 1998),(Lewis et al 2003) SZ (Macgregor et al 2004),(Combi et al 2005)
NPTX1 neuronal pentraxin 1	**VT** Cat II **CP** III-PCP **HIP** III-PCP **NAC** III-PCP	**CP** Cat II	17q25.3 BP (Dick et al 2003) Etoh (Hill et al 2004)
PPP1R1B/DARPP-32 protein phosphatase 1, regulatory (inhibitor) subunit 1B	**AMY** III-PCP, **PFC** IV-PCP	**PFC** Cat I	17q12
ANXA2 annexin A2	**VT** Cat I	**CP** IV-Meth	15q22.2 SZ (Paunio et al 2004)
FUT9 fucosyltransferase 9	**HIP** Cat I **CP** III-PCP **VT** III-CLZ	**CP** IV-Meth	6q16 SZ (Cao et al 1997) BP (Dick et al 2003)
GFAP glial fibrillary acidic protein	**AMY** Cat I **NAC** III-CLZ **PFC** IV-CLZ	**CP** IV-Meth **NAC** IV-Meth	17q21.31 SZ (Lewis et al 2003) Autism (Cantor et al 2005)
GNB1 guanine nucleotide binding protein, beta 1	**NAC** cat I **AMY** Cat II **PFC** III-PCP **VT** IV-CLZ	**AMY** IV-VPA **CP** IV-VPA	1p36.33 Neuroblastoma (Vincent et al 2000)
HNRPDL heterogeneous nuclear ribonucleoprotein D-like	**VT** Cat I	**CP** IV-Meth	4q13-q21 SZ (Paunio et al 2004) Etoh (Reich et al 1998),(Wyszynski et al 2003)
NRN1 neuritin 1	**NAC** cat I	**CP** IV-VPA	6p25.1 SZ (Lewis et al 2003),(Maziade et al 1997) Etoh (Hill et al 2004)

(*Continued*)

TABLE VIII. (*Continued*)

PMP22 peripheral myelin protein	**AMY** Cat I	**CP** IV-Meth	17p12 SZ, BP (Park et al 2004) BP (Liu et al 2003)
RPS27 ribosomal protein S27 Rps27	**HIP** Cat I	**AMY** IV-VPA	1q21.3 SZ (Brzustowicz et al 2000)
SATB1 special AT-rich sequence binding protein 1	**HIP** Cat I	**CP** IV-VPA	3p24.3 SZ (Lewis et al 2003)
SGK serum/glucocorticoid regulated kinase	**NAC** Cat I **AMY** Cat II **VT** Cat II **CP** III-PCP **HIP** Cat III-PCP **PFC** IV-PCP	**VT** IV-VPA	6q23.2 SZ (Levi et al 2005) BP (Venken et al 2005)
SOX11 SRY-box containing gene 11	**Amy** Cat I	**NAC** IV-Meth	2p25.2 SZ (Brzustowicz et al 2000)
TTR transthyretin	**AMY** Cat I **CP** Cat II **NAC** Cat II **VT** Cat II	**CP** IV-Meth	18q21.1 SZ (Goodman 1998; Maziade et al 2005)
ZIC1 Zinc finger protein of the cerebellum 1 (Zic1), mRNA	**NAC** Cat I **AMY** Cat II **CP** Cat II **HIP** Cat II **PFC** III-CLZ	**VT** IV-VPA	3q24 SZ (Bulayeva et al 2005) BP,SZA (Badenhop et al 2002)
AQP4 aquaporin 4	**AMY** Cat I	**AMY** IV-VPA **CP** IV-Meth **PFC** IV-Meth	18q11.2 BP (Detera-Wadleigh et al 1999) Etoh (Hill et al 2004)
ATP1B2 ATPase, Na+/K+ transporting, beta 2	**NAC** cat I	**CP** IV-VPA	17p13.1
SEPT8 septin 8	**AMY** Cat II	**CP** III VPA	5q23.3 SZ (Straub et al 1997)
AGT angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	**CP** Cat II **NAC** Cat II **AMY** III-PCP	**NAC** III-Meth	1q42.2 SZ (Ekelund et al 2001), (Paunio et al 2004),(Blackwood et al 2001), (Paunio et al 2004) BP(Macgregor et al 2004)
GNG7 guanine nucleotide binding protein (G protein), gamma 7 subunit	**PFC** Cat II	**PFC** III-Meth	19p13.3 SZ, BP (Kleiderlein et al 1998)
PLP1 proteolipid protein (myelin) 1	**AMY** Cat II **PFC** III-PCP **VT** IV-CLZ	**AMY** III-VPA **CP** IV-VPA,	Xq22.2 SZ (Qin et al 2005c)
SCN4B sodium channel, type IV, beta	**AMY** Cat II **PFC** Cat II **VT** IV-PCP	**PFC** III-Meth	11q23.3 SZ (Gurling et al 2001),(Demirhan and Tastemir 2003), (Golimbet et al 2003) Etoh (Wyszynski et al 2003), (Sun et al 1999)
SPARC secreted acidic cysteine rich glycoprotein	**NAC** Cat II **AMY** III-PCP	**NAC** III-Meth	5q33.1 SZ, BP, Psychosis (Sklar et al 2004) SZ (Devlin et al 2002), (Gurling et al 2001) (Suzuki et al 2003) Epilepsy (Chou et al 2003) Etoh (Dick et al 2002a), (Sun et al 1999)
BTBD3 BTB (POZ) domain containing 3	**AMY** III-PCP **VT** III-CLZ **CP** IV-CLZ	**CP** Cat II **AMY** III-VPA **PFC** IV-VPA	20p12.2
CCK cholecystokinin	**AMY** III-PCP **NAC** IV-PCP	**CP** Cat II **NAC** IV-Meth	3p22.1
CNOT7 CCR4-NOT transcription complex, subunit 7	**AMY** III-PCP	**CP** Cat II	8p22
GORASP2 golgi reassembly stacking protein 2	**VT** III-CLZ	**AMY** Cat II	2q31.1
HRMT1L2 heterogeneous nuclear ribonucleoproteins methyltransferase-like 2	**AMY** III-CLZ **PFC** III-PCP **VT** III-CLZ	**NAC** Cat II	19q13.33
NCALD neurocalcin delta	**AMY** III-PCP	**CP** Cat II **AMY** IV-VPA	8q22.3
PITPNB phosphatidylinositol transfer protein, beta	**AMY** III-PCP **VT** III-CLZ	**CP** Cat II	22q12.1
PSME1 proteasome (prosome, macropain) 28 subunit, alpha	**VT** III-CLZ	**AMY** Cat II	14q11.2
SYT1 synaptotagmin I	**AMY** III-PCP **CP** III-PCP **VT** III-CLZ	**CP** Cat II **AMY** IV-VPA **VT** IV-VPA	12q21.2
TBR1 T-box brain gene 1	**HIP** Cat III-PCP **NAC** III-PCP **CP** IV-PCP	**CP** Cat II **NAC** IV-VPA	2q24.2
CAMKK2 calcium/calmodulin-dependent protein kinase kinase 2, beta	**PFC** IV-PCP	**CP** Cat I	12q24.31 BP (Barden et al 2006)

PCP, phencyclidine; CLZ, clozapine; PFC, prefrontal cortex; AMY, amygdala; CP, caudate putamen; NAC, nucleus accumbens; VT, ventral tegmentum; SZ, schizophrenia; BP, bipolar disorder; MDD, major depressive disorder; AD, Alzheimer; HD, Huntington Disease. Roman numerals in the multiple brain region data column represent the Category of the gene.

Notably, existing drugs approved for other indications, such as disulfiram, baclofen, benzodiazepines, anticonvulsants (divalproex, topiramate), and lipid lowering agents (gemfibrozil, nicotinic acid) are potential augmentation options for existing first-line anti-psychotics and merit careful exploration as such. Moreover, our datasets of the effects of PCP and clozapine on gene expression in different key brain regions (Tables I–III) may be used as a source of new targets for drug development. Individual genes involved in the response to PCP could be of relevance for developing faster acting antipsychotic agents, in addition to agents for the treatment of hallucinogenic drug abuse. Individual genes involved in the response to clozapine may be of relevance for developing next generation antipsychotic agents as well as in pharmacogenetic and pharmacoimaging testing of responders versus non-responders.

Third, our work documents an apparent overlap between candidate genes for schizophrenia and candidate genes for bipolar disorder identified through Convergent Functional Genomics (Tables V and VIII) [Ogden et al., 2004]. This has been a topic of ongoing interest and debate in the field [Berrettini, 2000; Craddock et al., 2006]. A recent study by us has shown significant heterogeneity and overlap of phenotypic aspects of schizophrenia and bipolar disorder [Niculescu et al., 2006]. Moreover, the clinical literature has long abounded in examples of mood symptoms in schizophrenia patients, and the use of antidepressants and anticonvulsant mood stabilizers for symptom improvement in schizophrenia has been explored in both human studies [Kremer et al., 2004] and pre-clinical models [Ong et al., 2005]. It seems possible that nature has recruited more primitive mechanisms related to mood regulation for participation in higher functions such as cognition [Eisenberger et al., 2003]. The utility of regulating mood in relationship to cognition is of speculative evolutionary interest, and of pragmatic clinical importance. Specifically, treating schizophrenia proactively with mood regulating agents, and mood disorders with cognition modulating agents, warrants pursuit at the level of both drug development and clinical trials. Of note, we also see overlap with a recently published Convergent Functional Genomics dataset for alcoholism [Rodd et al., 2006] (data not shown)—see also Table VI, which may point to a more general issue of shared genes between major psychiatric disorders, including substance abuse disorders, perhaps in a Lego-like fashion [Niculescu et al., 2006].

Fourth, the model that emerges out of the Gene Ontology analysis of our data is that of schizophrenia as a disorder of disrupted connectivity: primary brain cellular malfunctioning and altered intercellular communication, of a developmental origin, impacting the brains' ability to integrate organismal physiology, have appropriate external behavior responses, and react appropriately to environmental stimuli (Fig. 5b). The cybernetic-like simplicity of the model should not overshadow the important fact that it is the result of the empirical coalescence of data in a non-hypothesis driven, discovery type approach. The implications for understanding the pathophysiology and treatment of schizophrenia and related disorders are profound. One needs to correct brain cell functioning and communication, body physiology, behavioral output, and reactivity to the environment, in the treatment of these disorders. It is a place where psychopharmacology, management of medical problems, behavioral therapy and social rehabilitation can and should go hand in hand. Moreover, the strong developmental component indicates a critical need for early intervention to prevent difficult to reverse, full-blown brain infrastructure changes and mitigate the course of the illness.

In conclusion, we propose that our comprehensive Convergent Functional Genomics approach is a useful starting point in helping unravel the genetic code and neurobiology of schizophrenia and related disorders, and generates a series of leads for both future research and clinical practice.

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