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Review

Convergent Functional Genomics of bipolar disorder: From animal model pharmacogenomics to human genetics and biomarkers

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Abstract

Progress in understanding the genetic and neurobiological basis of bipolar disorder(s) has come from both human studies and animal model studies. Until recently, the lack of concerted integration between the two approaches has been hindering the pace of discovery, or more exactly, constituted a missed opportunity to accelerate our understanding of this complex and heterogeneous group of disorders. Our group has helped overcome this "lost in translation" barrier by developing an approach called convergent functional genomics (CFG). The approach integrates animal model gene expression data with human genetic linkage/association data, as well as human tissue (postmortem brain, blood) data. This Bayesian strategy for cross-validating findings extracts meaning from large datasets, and prioritizes candidate genes, pathways and mechanisms for subsequent targeted, hypothesis-driven research. The CFG approach may also be particularly useful for identification of blood biomarkers of the illness.

Keywords: Microarray; Animal model; Convergent functional genomics; Bipolar; Genes; Brain; Blood; Biomarkers

Contents

1. Introduction

Identifying genes for bipolar disorder through classic human genetic studies has proven arduous, despite some recent successes (as reviewed in Hayden and Nurnberger,

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2006; Kato, 2007). There are at least three possible reasons for this relatively slow pace of discovery. First, bipolar disorder, like other neuropsychiatric disorders, is in all likelihood a complex polygenic disorder, with variable penetrance. Moreover, some (if not all) true illness-causing mutations may be deleterious to reproductive potential and thus be evolutionarily selected against, resulting in minor-frequency alleles that require sample sizes beyond those used to date in order to be able to unequivocally establish statistical association with illness. Second, the phenotypic heterogeneity, overlap and interdependence with other neuropsychiatric disorders (Niculescu et al., 2006; Niculescu, 2006) is not fully explored or built into the genetics work carried out so far, including the more recent whole-genome association (WGA) efforts. Third, gene–environment interactions and the effect of environmental factors (epigenetic modifications, effects of stress, infections, drugs, medications) on the expression of the phenotype are not fully factored in human genetic linkage studies to date (Tsuang et al., 2004; Abdolmaleky et al., 2004; Crow, 2007).

Possible solutions to the above three problems are the following: (1) carrying out association studies with groups of genes that may work together, rather than with individual genes; (2) analysis of association with discrete quantitative endophenotypes (Hasler et al., 2006; Niculescu et al., 2006) rather than broad DSM diagnostic classifications; and (3) use of gene expression studies (in human blood, postmortem brain or animal models), which are a direct reflection of gene–environment interactions, in conjunction with classic genetic studies.

Animal models can provide help with these three potential solutions encountered by classic human genetic research: (1) gene expression studies in animal models can identify groups of genes that change together, and thus may work together, on a homogeneous genetic background, with the signal not masked by the noise generated from the variable genetic background present in human studies; (2) endophenotypes of the disorder can be deliberately mimicked in animal models with pharmacological approaches (Ogden et al., 2004), or fortuitously observed in genetic mutants (Roybal et al., 2007) and (3) gene–environment interactions are minimized, well defined and well controlled in animal model studies as opposed to human studies.

Our expanded convergent functional genomics (CFG) approach (Ogden et al., 2004; Bertsch et al., 2005; Rodd et al., 2006; Le-Niculescu et al., 2007) embodies an appreciation of the strengths and limitations of animal model data and human data (potential lack of specificity for animal model data, potential lack of sensitivity for human data). It relies on the integration of multiple independent lines of evidence. Each of the lines of evidence is potentially vulnerable to type I or type II errors, but taken together in a Bayesian fashion (Bernardo and Smith, 1994), they are less likely to provide false positives or false negatives. By putting together carefully designed animal model experimental data with human genetic and human tissue expression data, the CFG approach provides a comprehensive solution to the challenge of identifying candidate genes, pathways and mechanisms for neuropsychiatric disorders. It has been applied with some success to bipolar disorder (Niculescu et al., 2000; Ogden et al., 2004), and more recently to alcoholism (Rodd et al., 2006) and schizophrenia (Le-Niculescu et al., 2007). Approaches similar to ours (named, alternately, as *integrative genomics*) have started to be applied widely in various fields of biomedicine (Mootha et al., 2003; Schadt, 2006; Zhu et al., 2007).

2. Convergent Functional Genomics

The CFG approach was developed initially to integrate gene expression data from a relevant animal model with data from human linkage analyses as a way of cross-validating findings and deriving a short list of high-probability candidate genes that deserve individual scrutiny in a prioritized fashion (Niculescu et al., 2000) (Fig. 1). For bipolar disorder, one relevant animal model involves the administration of a single dose of methamphetamine. Methamphetamine administration mimics in human and rodents some of the behavioral signs and symptoms of bipolar disorder including manic-like features in the activation phase and depressive-like features in the withdrawal phase. With more chronic escalating dose binge treatments of methamphetamine, a more complex picture akin to psychosis emerges (Fig. 2).

Candidate genes emerging from our initial application of this strategy have since been actively investigated for a role in bipolar disorder, with some genes such as DBP (which codes for albumin D-box-binding protein) (Sokolov et al., 2003; McFarland et al., 2007) and GRK3 (which codes for G-protein-coupled receptor kinase 3) (Barrett et al., 2003; Shaltiel et al., 2006) yielding additional evidence for involvement in the disorder that may, upon further

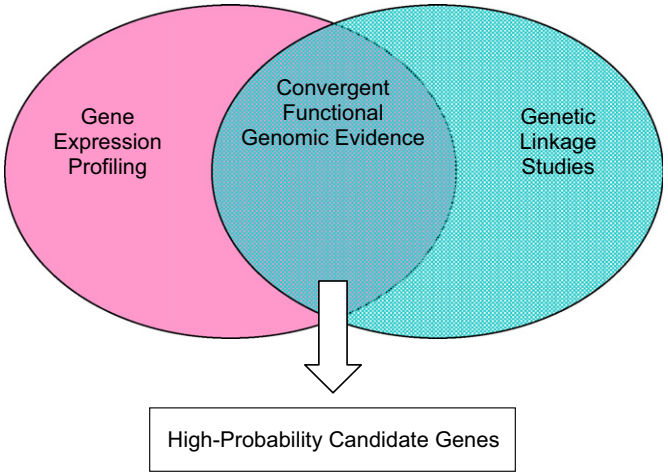

Fig. 1. Initial iteration of Convergent Functional Genomics.

replication, warrant distinction as "risk genes" for bipolar disorder.

More recently, we have expanded the CFG approach to look at the effects of two opposing pharmacological manipulations in mice, using both an agonist of the illness/bipolar disorder-mimicking drug (methamphetamine) and an antagonist of the illness/ bipolar disorder-treating drug (valproate) (Ogden et al., 2004). In essence, the pharmacogenomic approach is a tool for tagging genes that may have pathophysiological relevance. Additionally, we have extended the convergent cross-validation beyond genetic linkage results to data on biological relevance of genes and postmortem brain changes (Ogden et al., 2004). In this application of the CFG paradigm, mice received either (1) the bipolar disorder-mimicking agent methamphetamine; (2) the bipolar disorder-relieving agent valproate; or (3) co-treatment with both drugs.

Comprehensive gene expression analysis of specific target brain regions that have previously been implicated in bipolar disorder (including prefrontal cortex, amygdala, nucleus accumbens, ventral tegmentum and caudate-putamen) with oligonucleotide microarrays was carried out in parallel with behavioral studies. As internal cross-validation, genes that were changed by both methamphetamine and valproate were deemed to be higher-probability candidate genes than genes changed by either drug alone (Fig. 3A, Categories I and II). Genes that were changed by individual drug treatments but were "nipped in the bud" (showed no change) by co-treatment were also deemed to be of higher probability (Fig. 3A, Category III). Lastly, genes that were changed in multiple target brain regions were deemed to be of higher probability as well, from a detection standpoint if not necessarily from an etiopathological one. As external cross-validation, gene expression data was cross-referenced to linked loci from human genetic studies of bipolar and related disorders, reports from the literature regarding the biological role of these genes and reports of changes in postmortem brain tissue from patients (Fig. 3B).

By integrating multiple internal and external lines of evidence, a prioritized list of candidate genes was generated. Functionally relevant genes represented in this dataset, for some of whom additional evidence has accumulated in the field since our publication (Ogden et al., 2004), include DARPP-32 pathway genes (Meyer-Lindenberg et al., 2007), pain-related genes (such as TAC1-substance P (Carletti et al., 2005), PENK- preproenkephalin (Nieto et al., 2005)), circadian clock genes (such as ARNTL1/BMAL1 (Nievergelt et al., 2006; Mansour et al., 2006)), apoptosis-related genes (such as BAD (Laeng et al., 2004)), G-protein-coupled receptor signaling genes (such as GPR88 (Brandish et al., 2005; Conti et al., 2007)), intracellular signaling genes (such as GSK3b (Gould et al., 2006)), glutamate neurotransmission (such as

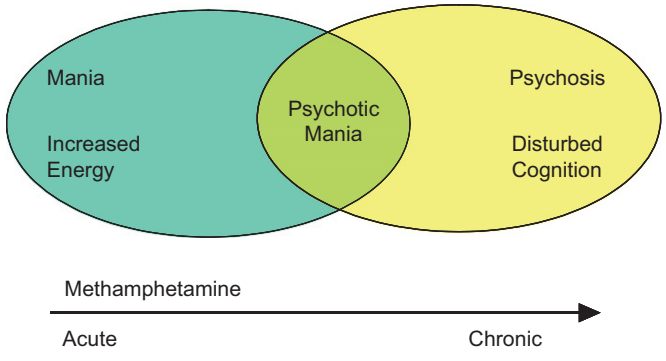

Fig. 2. Effects of methamphetamine.

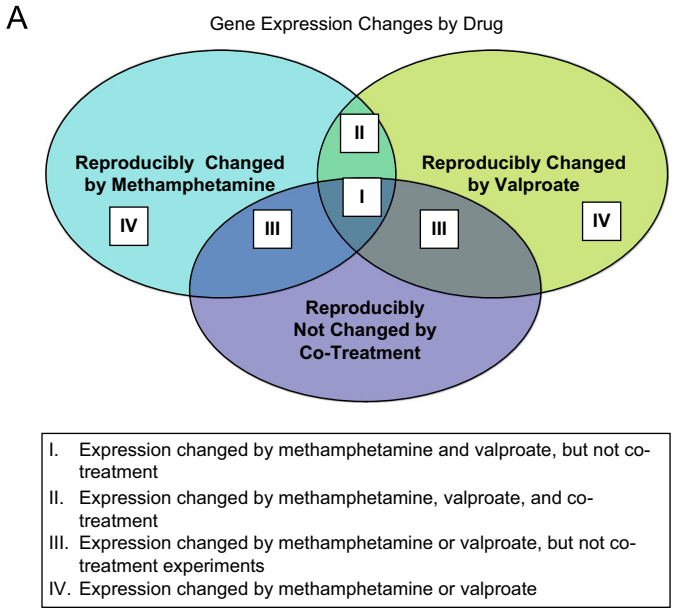

Fig. 3. Expanded Convergent Functional Genomics approach to identifying candidate genes involved in bipolar disorder and related disorders.

GRM3 (Fallin et al., 2005) transporters (such as DAT1-dopamine transporter (Greenwood et al., 2006), neurotrophic/neuronal survival factor genes (such as BDNF—brain-derived neurotrophic factor (Muller et al., 2006) and glia/myelin-related genes (such as MOBP, PLP1, CLDN11, PMP22, MAG, GFAP, GMFB). The glia/myelin story is particularly interesting, as similar findings are reported by others (Davis et al., 2003; Tkachev et al., 2003; Haroutunian et al., 2007) and us (Le-Niculescu et al., 2007) in schizophrenia, and alcoholism (Lewohl et al., 2005; Rodd et al., 2006). These findings point to the issue of overlap among genes involved in major neuropsychiatric disorders (Niculescu, 2006; Le-Niculescu et al., 2007). Moreover, hypomyelination of frontal lobe regions may reflect the incomplete development of brain regions involved in the process of executive control and motivation (Volkow and Li, 2005; Bartzokis, 2006; Sokolov, 2007), potentially resulting in cognitive, affective and hedonic dysregulation. As such, this neurobiological abnormality could be a sensitive but nonspecific common denominator of mental illness, and an explanation for what are clinically called dual-diagnosis disorders (substance abuse and another psychiatric disorder).

Our dataset also identified candidate genes mapping to linkage loci identified by large-scale meta-analyses for bipolar disorder (McQueen et al., 2005; Segurado et al., 2003) and schizophrenia (Lewis et al., 2003), cross-validated these candidates with human postmortem findings and revealed other novel genes (Fig. 4), pathways and mechanisms that may be of importance in the pathophysiology of bipolar disorder (Ogden et al., 2004). These findings are prime starting points for subsequent hypothesis-driven work, such as candidate gene association studies, epistatic interactions testing and transgenic mouse models generation. Moreover, they provide insights for new pharmacotherapeutic approaches to bipolar disorder.

3. Future directions: blood gene expression profiling and biomarker research

Objective biomarkers of illness and treatment response would make a significant difference in our ability to diagnose and treat patients with psychiatric disorders, eliminating subjectivity and our reliance on patient's self-report of symptoms. Lymphocyte gene expression profiling has emerged as a particularly interesting area of research in the search for peripheral biomarkers (Vawter et al., 2004; Tsuang et al., 2005; Segman et al., 2005; Glatt et al., 2005; Middleton et al., 2005; Sullivan et al., 2006; Naydenov et al., 2007). Most of the studies to date have focused on human blood gene expression profiling, comparison between illness groups and normal controls, and cross-matching with human postmortem brain gene expression data. They suffer from one or both of the following caveats. The first is the widespread use of lymphoblastoid cell lines in lieu of fresh blood. Fresh blood, with quantitative phenotypic state measures gathered at time of harvesting, may be more informative than immortalized

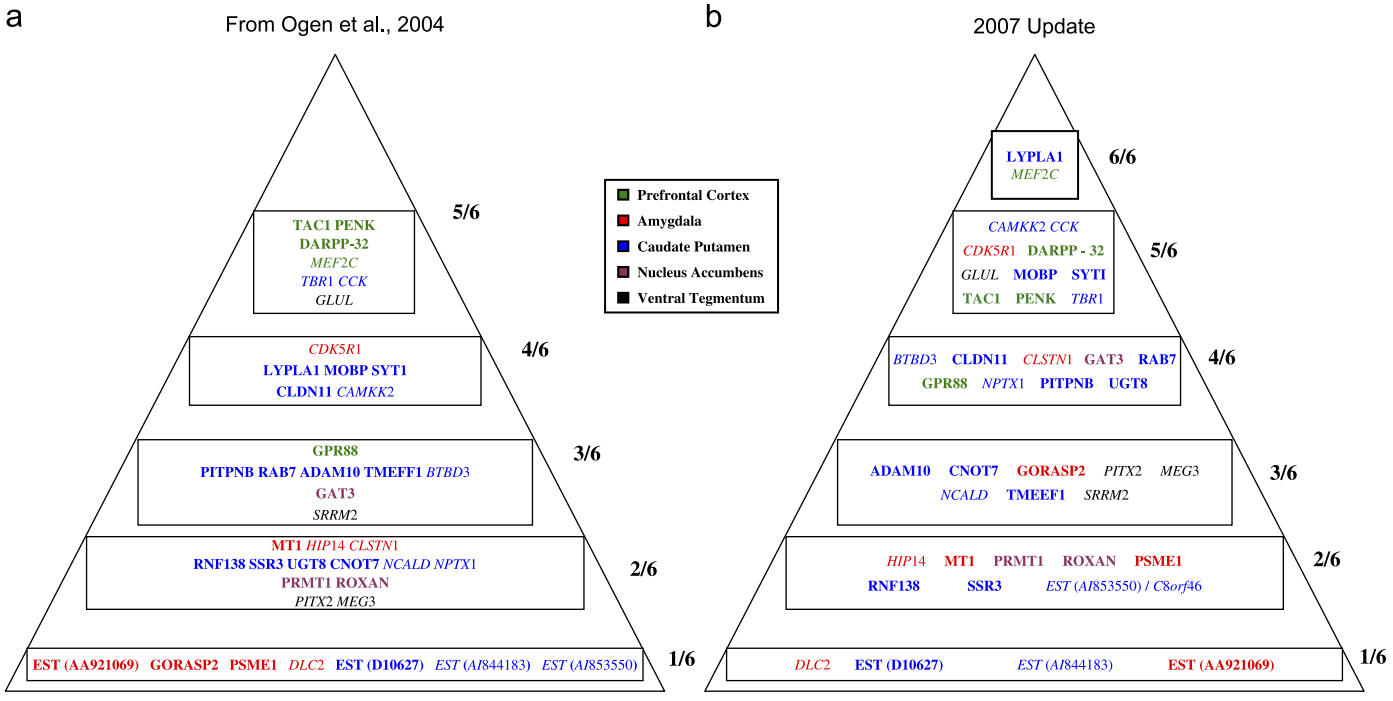

Fig. 4. Top candidate genes for bipolar disorder(s). Probability pyramid generated by the tabulation of independent convergent lines of evidence (as shown in Fig. 3B). Plain text—increased by methamphetamine. Italics—decreased by methamphetamine. Color coding—different target brain regions in our animal model. (a) From Ogden et al. (2004). (b) Updated 2007 with new external lines of evidence published in the field since 2004. Once a gene is on the pyramid, it can only move up in priority as new evidence emerges over time. On the sides of the pyramids is depicted the scoring based on number of lines of evidence.

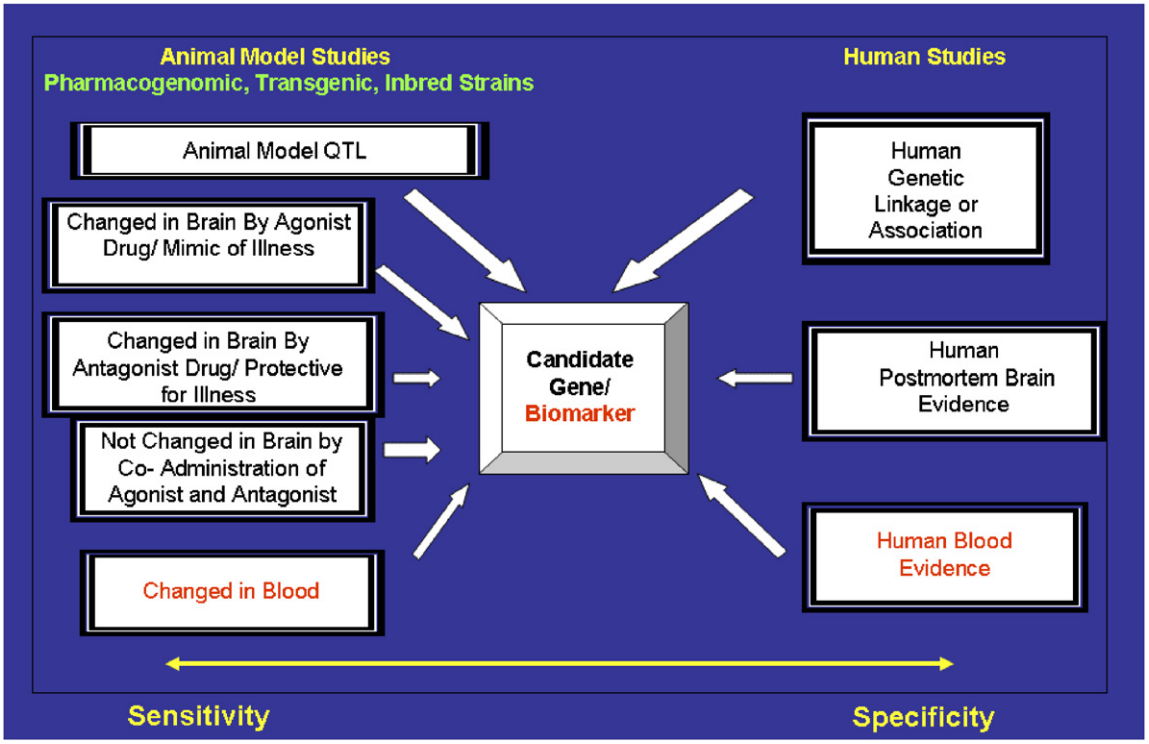

Fig. 5. Expanded Convergent Functional Genomics (2007): multiple independent lines of evidence for Bayesian cross-validation.

lymphocytes, and avoid some of the caveats of Epstein–Barr virus immortalization and cell culture passaging. The second potential caveat is that human tissue gene expression studies are susceptible to the issue of being underpowered, due to genetic heterogeneity, the effect of variable environmental exposure (including medications and drugs of abuse) on gene expression and difficulty of accrual of large sample cohorts, particularly fresh blood samples with state phenotypic information. It is questionable if, by themselves, such studies have sufficient power to identify all the bona fide biomarkers out of large and noisy human blood gene expression datasets, despite a variety of sophisticated statistical methodologies (Glatt et al., 2005; McClintick and Edenberg, 2006; Zapala and Schork, 2006; Li and Horvath, 2007) that can be employed.

4. Summary

The current state of our understanding of the genetic and neurobiological basis for bipolar disorder in general and of peripheral molecular biomarkers of the illness in particular is still inadequate. Most of the fundamental genetic, environmental and biological elements needed to delineate the etiology and pathophysiology of bipolar disorder are yet to be completely identified, understood and validated. A rate-limiting step, which we are helping overcome, has been the lack of concerted integration across disciplines and methodologies. The use of a multidisciplinary, integrative research framework such as CFG should lead to a reduction in the historically high rate of inferential errors committed in studies of complex diseases like bipolar disorder. Currently emerging WGA studies will provide a wealth of information to be mined, made sense of and prioritized with approaches such as ours.

An interesting area of future research is in regard to peripheral biomarkers of the illness. To our knowledge, no one has reported, at the time of writing of this review (early 2007), a comprehensive investigation of blood gene expression profiling in conjunction with brain gene expression studies in an animal model presenting features of bipolar disorder, and cross-validated that data with comprehensive human fresh blood gene expression studies tied to illness state as well as integrated the findings in the context of the available human genetic linkage/association data, postmortem brain data and information on biological pathways. We suggest that such an expanded CFG approach (Fig. 5) may be particularly fruitful for biomarker discovery, and overcome the caveats mentioned above. These studies are underway in our laboratories. We anticipate that panels of biomarkers, rather than single biomarkers, are going to emerge as clinically useful tools.

Acknowledgments

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