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Convergent integration of animal model and human studies of bipolar disorder (manic-depressive illness)

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Animal models and human studies of bipolar disorder and other psychiatric disorders are becoming increasingly integrated, prompted by recent successes. Particularly for genomics, the convergence and integration of data across species, experimental modalities and technical platforms is providing a fit-to-disease way of extracting reproducible and biologically important signal, in sharp contrast to the fit-to-cohort effect, disappointing findings to date, and limited reproducibility of human genetic analyses alone. Such work in psychiatry can provide an example of how to address other genetically complex disorders, and in turn will benefit by incorporating concepts from other areas, such as cancer biology and diabetes.

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Introduction

Psychiatric disorders are phenotypically and biologically complex, heterogeneous, overlapping and interdependent [1–3]. Unraveling their genetic basis by human genetic studies has proven arduous. The combination of complex genetics with imprecise clinical nosology and lack of objective laboratory tests has made this one of the truly difficult challenges in science. Given that the rewards of a better understanding range from alleviating mental illness and suffering to improved brain performance and understanding how the mind works, the prize is commensurate with the degree of difficulty. Recent breakthroughs give reason for optimism. We will focus in this review paper on advances in bipolar disorder, specifically on the high yield of integrating animal model and human studies.

Animal models of bipolar disorder (manic-depressive illness)

Animal models are developed and used for two main reasons: a better understanding of the disorder (including at a gene expression level), and the testing of new drugs. Animal models of bipolar disorder can broadly be classified into genetic and environmentally induced. We will confine our discussion to rodent models, which are much more experimentally tractable and widely used than those of other species (Table 1). The genetic models arise from naturally occurring or inbred strains, or more often from transgenic manipulation (genetic engineering) of candidate genes hypothesized to be involved in bipolar disorder. For the environmentally induced models, pharmacological manipulation and different stress-related paradigms are used to mimic different aspects of bipolar disorder. Usually, the animal model recapitulates features of one or the other of the two antithetical phases of the illness — mania *vs.* depression. It is important to note that while there is a nosological distinction between depression and bipolar disorder, the genetics, biology and clinical symptomatology involved are likely part of a continuum-spectrum [4••,5].

The most widespread pharmacological model to date involves the use of stimulants (amphetamines and methamphetamine) to mimic the manic phase of bipolar disorder [6]. Withdrawal from the stimulant can also mimic the depressive phase of the disorder. Sometimes, an anxiolytic agent is added, on the premise that mitigating the anxiogenic side-effects of stimulants leads to modeling of euphoric mania [7•]. However, that approach is questionable, as human bipolar patients naturalistically often display co-morbid anxiety and/or irritability as part of their bipolar clinical picture.

A more systematic pharmacogenomic approach used a comparison of the gene expression effects of a disease-mimicking stimulant (methamphetamine) and a disease-treating mood stabilizing agent (valproate) [8••], as a way of prioritizing genes that are affected by both treatments, especially the genes that are changed in opposite directions by the disease agonist and the disease antagonist. Moreover, gene expression effects were mapped in key disease-relevant brain regions, not in the whole brain [8••]. That work was subsequently extended to look at the gene expression changes in blood from the animals on the different treatments, as a way of identifying brain–blood biomarkers [9].

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Table 1

Animal models for bipolar disorder: recent and/or key studies.

Genetically engineered	Naturally occurring/inbred strains	Pharmacological models	Other environmental manipulations
DBP [10••]	Nile grass rat [38]	Methamphetamine [6]	Learned helplessness [39]
CLOCK [11,12•]	Flinders Sensitive Line (FSL) rats [40]	Metamphetanine/valproate [8••]	Isolation housing [10••]
CTNNB1 [41]	Wistar Kyoto (WKY) rats [40,42]	Amphetamine–chlordiazepoxide [7]	Forced swim test [10••]
POLG [19••,20•]		Lithium [43–45]	Tail suspension test [10••]
HINT1 [15]		Other mood stabilizers: lamotrigene [46], topiramate [47]	Restraint stress [45,48]
GRIN2A [14]		Ouabain [49]	Shock-induced aggression [44]
WFS1 [50]		GBR [51••]	
DAT [13]			
ERK1 [16]			
GRIK2 [17,18••]			

Only one genetic model to date, the DBP (D-box binding protein) knock-out mouse, has been shown to mimic both phases of the illness, using clinically relevant environmental manipulations [10••]. DBP is a circadian clock gene candidate for bipolar disorder that was identified in earlier gene expression studies [6] in pharmacogenomic models and maps to a locus implicated in bipolar disorder in humans. At baseline, the knock-out animals are depressed compared to wild-type controls. During exposure to chronic stress (isolation housing) and acute stress (experimental handling), the mice exhibit a switch in phenotype to a manic-like phase, characterized by increased activity and increased hedonic behavior. This two hit paradigm (genetic vulnerability, followed by environmental stressors) mimics very well the human condition. The fact that a single gene constitutive knock-out has such a broad phenotype exceeded a priori expectations. It may be due in part to the fact that the gene knocked-out is a transcription factor, responsible for setting in motion a cascade of other changes, and also due to the fact that it is a circadian clock gene, which are emerging as key molecular underpinnings of mood disorders. Comprehensive gene expression studies in brain and blood, with and without exposure to stress, were carried out in this animal model, generating additional candidate genes and blood biomarkers for bipolar disorder [10••].

Another genetic model, a knock-out of the circadian clock gene CLOCK, has been originally described to have a phenotype that mimics only the manic side of the illness [11]. More recent work with it involving brain region-specific manipulation of gene expression has revealed a mixed mood phenotype [12•]. Other recently described genetically engineered models for manic-like behavior involve manipulation of the genes DAT (dopamine transporter) [13], GRIN2A (NMDA receptor subunit 2A) [14], HINT1 (protein kinase C interacting protein) [15], ERK1 (extracellular signal regulated kinase 1) [16], and GRIK2 (metabotropic glutamate receptor 6) [17,18••].

An interesting model, supportive of a role for mitochondrial involvement in bipolar disorder, is that of POLG1 (mitochondrial DNA polymerase) transgenic mice, where mutant POLG1 is expressed in a neuron-specific manner. These mice exhibit periodic activity changes and altered circadian rhythm, similar to bipolar cycling [19••]. Subsequent studies comparing gene expression changes in these mutant mice to human postmortem brain gene expression changes in bipolar subjects identified two overlapping genes [20•]. One of them, SFPQ (splicing factor proline/glutamine rich), is also a top candidate gene for bipolar disorder from the DBP KO mouse model described above, where it is increased in expression in the amygdala, the activated (manic) phase. The second gene, PPIF, encodes cyclophilin D, a component of the mitochondrial permeability transition pore. A blood–brain barrier permeable cyclophilin D inhibitor improved the abnormal behavior of the POLG1 mice, suggesting a potential lead for new drug discovery efforts.

Human genetic and genomic studies of bipolar disorder

Over the last few years, in concert with other fields, genetic studies for bipolar disorder have been dominated by genome-wide association (GWAS) studies [21–24,25••], and to a lesser extent copy-number variants (CNV) studies [26,27]. GWAS studies to date have identified few polymorphisms that meet the genome-wide statistical threshold for significance (Table 2). Those few findings in turn are not reproduced as statistically significant in independent GWAS, although some show additional evidence in meta-analyses [28–31]. Moreover, they tend to be in obscure, housekeeping-type genes (ANK3, CACNA1C, and ZNF804A), in

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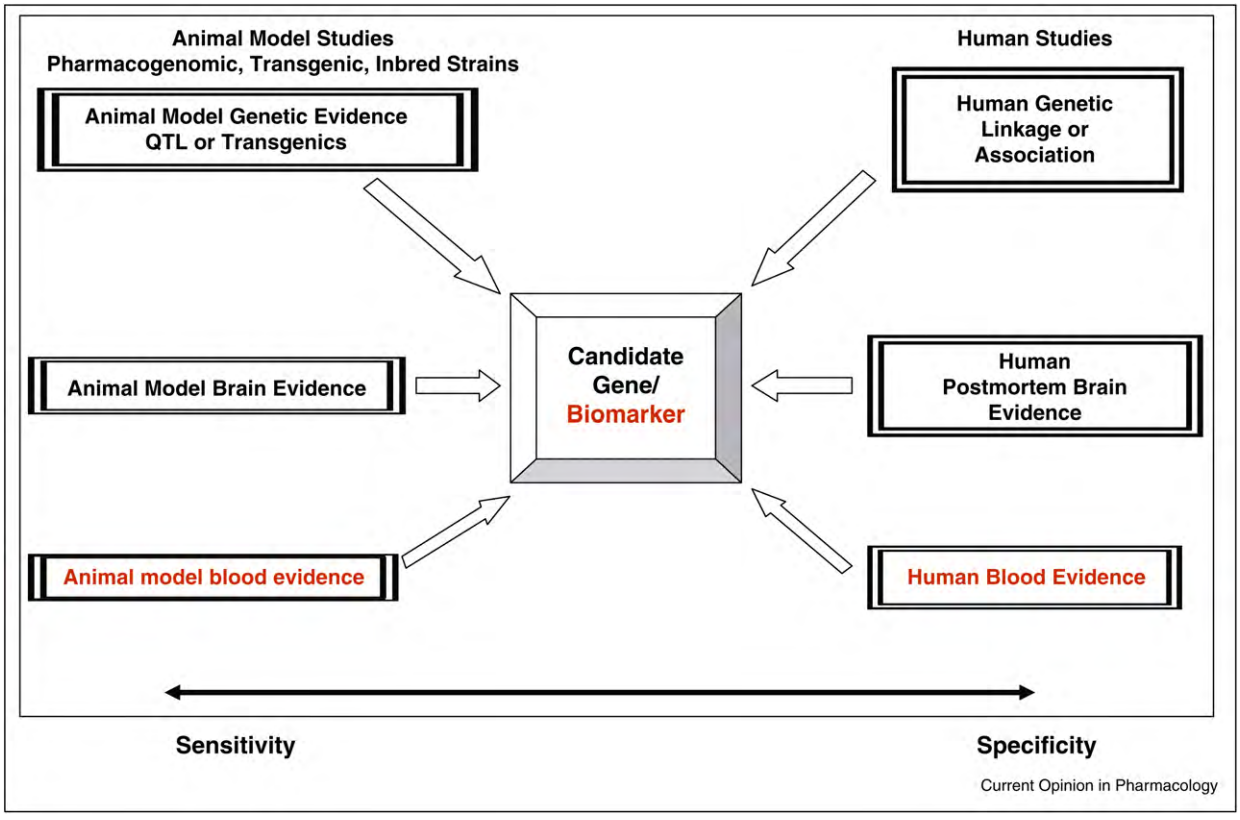
Table 2

GWAS of bipolar disorder: recent and/or key studies and analyses.

GWAS	Meta-analyses of GWAS	Mega-analyses of GWAS and gene expression
Wellcome Trust Consortium [25••]	Ferreira *et al.* [28]	Le-Niculescu *et al.* [33••]
rs420259-PALB2	rs10994336-ANK3 rs1006737-CACNA1C	ARNTL, ALDH1A1, BDNF, KLF12, A2BP1, MBP, etc.
Baum *et al.* [21] rs1012053-DGKH	Schulze *et al.* [29] rs10994336-ANK3	Patel *et al.* [34••] ARNTL, MBP, BDNF, DISC1, RORB, etc.
Sklar *et al.* [22] rs4939921-MYO5B	Liu *et al.* [30] rs10994336-ANK3 rs10994338-ANK3 rs1006737-CACNA1C rs7297582-CACNA1C	
Scott *et al.* [24] rs17418283-MCTP1	Williams *et al.* [31] rs1344706-ZNF804A	
Smith *et al.* [23] rs2111504-DPY19L3 rs2769605-NTRK2 rs5907577-Intergenic rs10193871-NAP5(NCKAP5)		

contrast to the more biologically interesting genes implicated by gene expression studies in animal models and in human postmortem brain from subjects with bipolar and related disorders. A discussion of the reasons for this limited success of GWAS is ongoing in the field [32], but an emerging explanation is that genetic heterogeneity at the SNP level is a contributory factor. As such, gene-level analyses are more likely to be reproducible, in addition to permitting cross-platforms, cross-methodologies and cross-species integration [33••,34••], particu-

Figure 1



Convergent Functional Genomics: multiple independent lines of evidence for Bayesian cross-validation.

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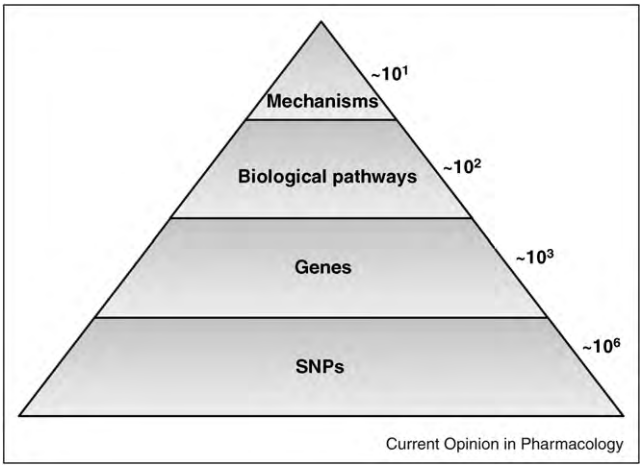
larly with animal models and gene expression studies (Figure 1).

Synergies from integration

The integration of animal model and human studies has occurred either as hypothesis-driven validation, or as discovery-driven convergent integration of datasets.

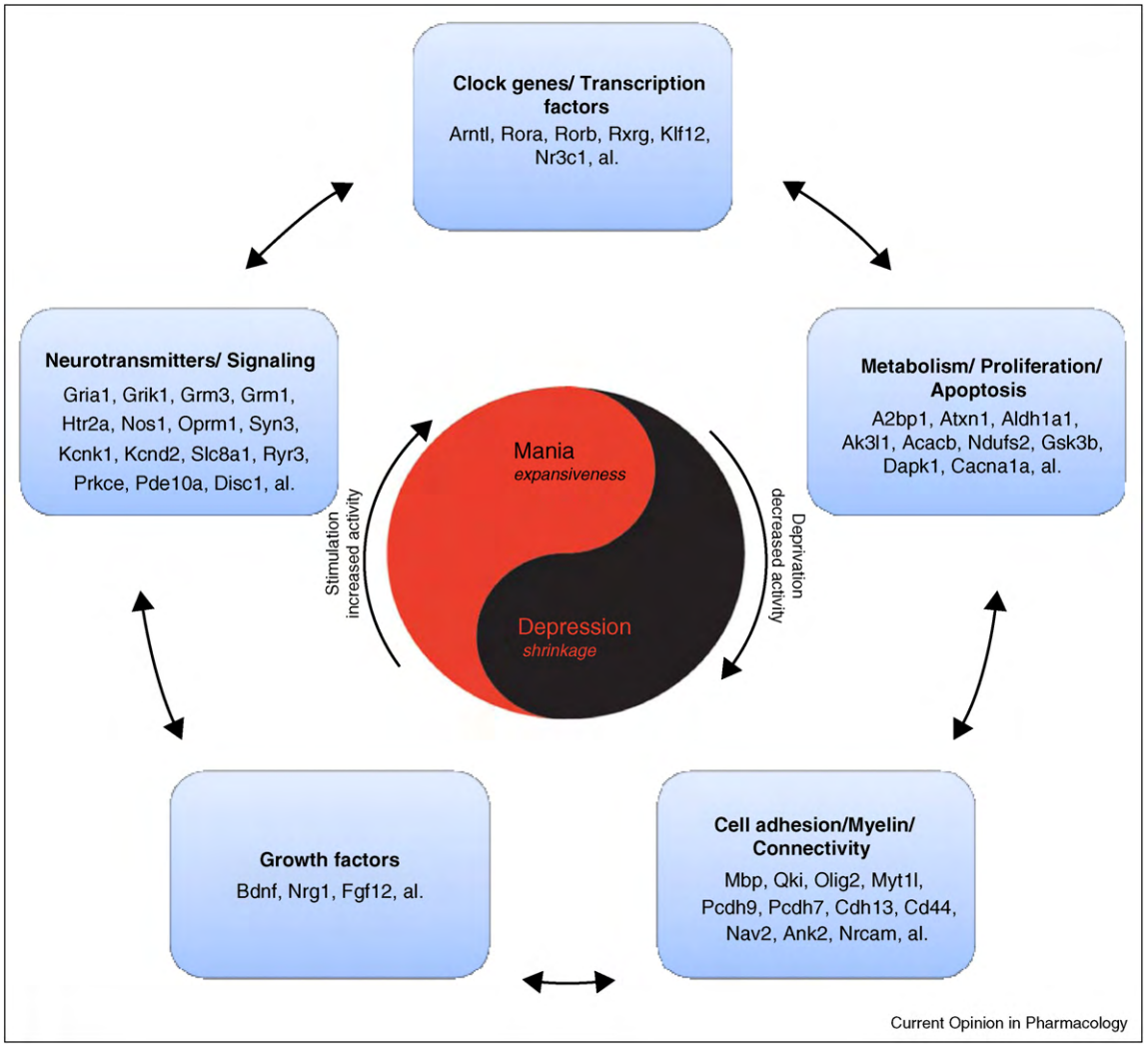
The first approach takes a finding from one line of work, and studies it in the other. For example, genetically engineered mice of human candidate genes for mood disorders have been generated (DBP, CLOCK, and others), as described above, and are proving to be useful animal models for the disorder. Conversely, a gene expression finding from animal model studies is pursued in candidate gene association studies in human populations. One such recent successful example is that of RORB (RAR-related orphan receptor beta), another circadian clock gene. RORB

Figure 2



Reducing heterogeneity of bipolar disorder by higher level analyses.

Figure 3



A comprehensive model of bipolar disorder pathophysiology.Adapted from Ref. [33••].

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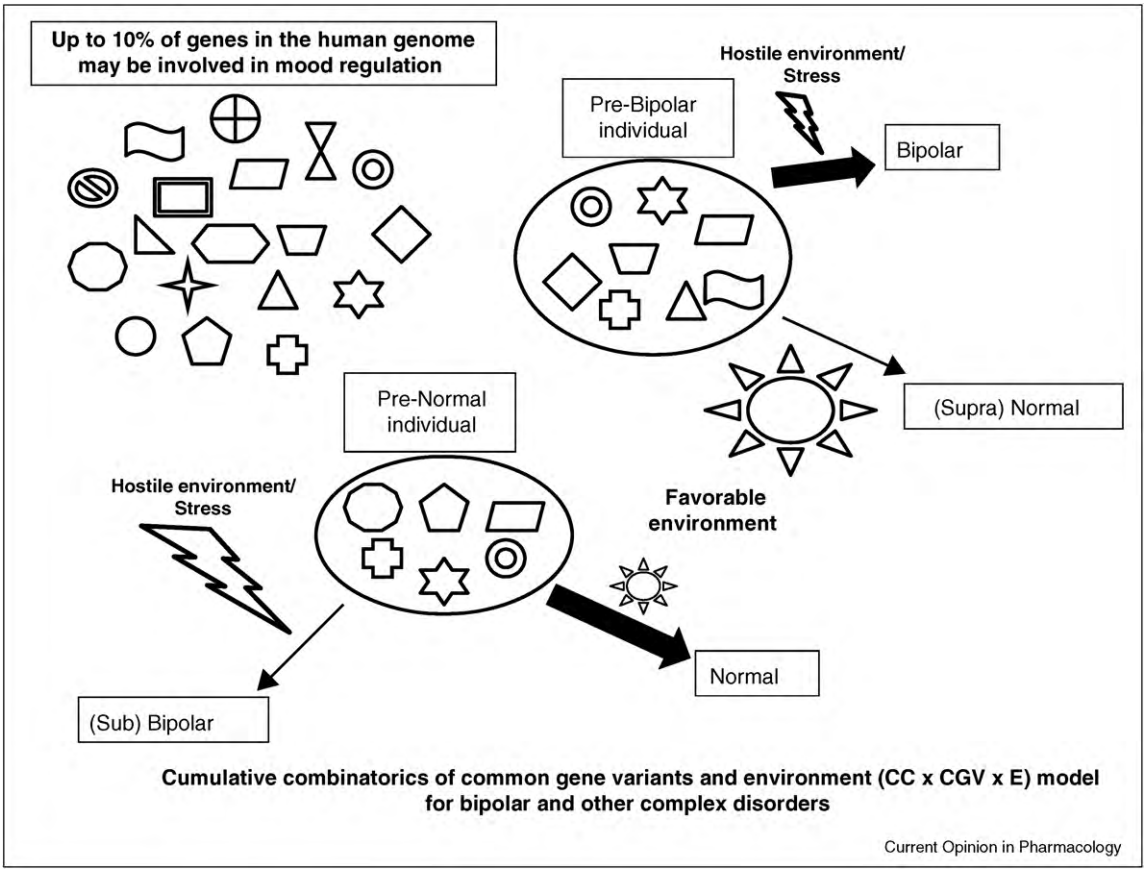
was identified as changed in expression in the brain of DBP KO mice [10••]. It was then tested and shown to have genetic association with bipolar disorder in a human pediatric bipolar population [35]. The rationale for studying a pediatric bipolar population was that pediatric bipolar subjects exhibit more rapid cycling and changes in mood state (switching), which are likely underpinned at a molecular level by circadian clock genes.

The second approach, the discovery-based integration of animal model and human data, has had its most systematic embodiment to date through Convergent Functional Genomics (CFG) (Figure 1). The approach is predicated on using large datasets as well as manually curated databases of the published literature to date [1,36]. Each individual line of work has had its strengths and limitations. Animal model data can provide sensitivity and ability to conduct experimental manipulations not feasible in humans. Human data provide more specificity and relevance to the human disease. Using a set of mouse experiments as a driving force [8••,10••], or using human blood biomarker [9] or GWAS data [33••,34••] as a driving force, such studies have identified and prioritized candidate genes and biomarkers for bipolar disorder that show good reproducibility as well as predictive ability in independent cohorts [9,34••].

The mining of GWAS data for bipolar disorder with a CFG approach was particularly successful [33••,34••], and holds generalizable lessons. The integration of GWAS data had as a first step the selection of SNPs. A nominal p-value threshold, not a genome-wide significance threshold, was used to select the positive SNPs from each GWAS, as it was assumed that most SNPs make only a small contribution to the disorder at a population level, and the work relied on the subsequent integration with other lines of evidence to identify and prioritize true positives. The second step is the conversion of SNPs into genes. From then on, all lines of evidence are tabulated at a gene level. The more lines of evidence, i.e. the more times a gene shows up as positive finding across independent studies, platforms, methodologies and species, the higher its CFG score (Figure 1). This is very similar conceptually to a Google PageRank algorithm, in which the more links to a page, the higher it comes up on the search prioritization list. Human and animal models, genetic and gene expression, datasets were integrated and tabulated. The top candidate genes were then assembled in a panel composed of their component

Figure 4



Cumulative combinatorics of common gene variants and environment.Adapted from Ref. [34••].

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SNPs, and tested in independent cohorts. Each subject in an independent cohort has a genetic risk prediction score (GRPS) based on how many of the SNPs in the panel it was positive for. Using such an approach, a panel of 56 top candidate genes for bipolar disorder, mined from GWAS using CFG, showed good predictive ability to differentiate, in independent cohorts, between bipolar and controls, as well as between less severe and more severe forms of bipolar disorder [34••]. As an added feature, this approach identified top candidate genes that have a lot of prior biological evidence and disease relevance, as opposed to the mundane top findings from GWAS alone. For example, at the very top of the candidate gene list for bipolar disorder generated by this mega-analysis is ARNTL [34••], another circadian clock gene also recently implicated in diabetes [37••]. The top candidate genes for bipolar were then analyzed in terms of distribution in biological pathways and mechanisms, levels of analysis where there is less heterogeneity and a clearer picture emerges (Figure 2). The analysis resulted in the first comprehensive empirically derived model of bipolar disorder pathophysiology to date [33••] (Figure 3). This led to a proposed understanding of mood as related to cellular and organismal energy, activity and trophicity, as an adaptive clock-gene-mediated synchronization to a favorable or hostile environment [5,33••]. Excessive, discordant or variable reactivity to environmental stimuli leads to clinical illness (depression in a favorable environment, mania in a hostile environment, cycling and switching from one mood state to the other that is not warranted by adaptation to the environment).

Future directions

The advances described in this review have opened the door to a better understanding of the genetics, biology, diagnosis and ultimately treatment of bipolar and related mood disorders, paving the way in the near future for individualized/personalized medicine. It is clear that such convergent strategies should continue to be employed and refined for bipolar disorder, in other psychiatric disorders, and in complex medical disorders in general. Psychiatric disorders share similarity at a genetic level with cancer and diabetes in terms of complex genetics, and even in terms of some of the molecular pathways involved [5,9]. Paradigms from cancer could be borrowed in psychiatric research, particularly the classification of genetic variants into risk genes (similar to oncogenes) and protective genes (similar to tumor-suppressor genes). An early proposal for such a classification used the terms psychogenes and psychosis-suppressor genes [6]. The complexity of these broad groups of disorders however is such that simple binary classifications may be insufficient, and only the complete understanding of the cumulative combinatorics of common gene variants, development and environment may yield the ultimate answer [34••] (Figure 4).

Conflict of interest statement

There are no conflicts of interest related to this work.

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- •• of outstanding interest

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