Published in final edited form as:
Psychiatr Clin North Am. 2010 March ; 33(1): 67–82. doi:10.1016/j.psc.2009.10.005.

Genetic research into bipolar disorder: the need for a research framework that integrates sophisticated molecular biology and clinically-informed phenotype characterization

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Abstract

Research into the genetic basis of bipolar disorder (BD) has reached a turning point. Genome-wide association studies (GWAS), encompassing several thousands of samples, have produced replicated evidence for some novel susceptibility genes; however, the genetic variants implicated so far account for only a fraction of disease liability, a phenomenon not limited to psychiatric phenotypes but characteristic of all complex genetic traits studied to date. It appears that pure genomic approaches such as GWAS alone will not suffice to unravel the genetic basis of a complex illness like BD. Genomic approaches will need to be complemented by a variety of strategies including phenomics, epigenomics, pharmacogenomics, and neurobiology, as well as the study of environmental factors. This review will highlight the most promising findings from recent GWAS and candidate gene studies in BD. It will furthermore sketch out a potential research framework integrating various lines of research into the molecular biological basis of BD.

Keywords

manic-depressive illness; schizophrenia; depression; classification; linkage; association

Introductory remarks

This review of the basic principles and recent advances in genetic research into bipolar disorder (BD) can take advantage of a large, already extant body of work reviewing the evolution of findings from early family, twin, and adoption studies to linkage and association studies in BD [1–16]. Rather than reviewing these findings again in a chronological and detailed manner, this review will sketch where we have come from, where we stand right now, how we can use the

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Disclosure: This work was supported by the Intramural Research Program of the National Institute of Mental Health. Dr. Schulze reports no conflicts of interest or other sources of funding.

knowledge gleaned over the course of nearly a century, and how we can incorporate novel molecular and analytical techniques into our quest to unravel the genetics of BD.

Formal genetics, linkage, and association studies

To summarize some well-known facts, BD is a highly heritable disorder. Early 20th century family and twin studies had already observed that BD and other mental disorders aggregate in families, and that they have a heritable basis17¯19. Whereas the lifetime prevalence of BD in the general population is around 1–2%, multiple studies have reported that the lifetime morbidity risk for BD in a first-degree relative of an individual with BD lies between 10 to 20% 13. Furthermore, twin studies have repeatedly cemented the heritable component of BD, with heritability estimates ranging between 80 and 90%, and adoption studies similarly support the notion that genetic factors contribute substantially more to the etiology of BD than environmental factors (for a comprehensive review of family, twin, and adoption studies, see 13).

This large body of evidence, established over the course of several decades, across changing diagnostic concepts of BD, and in populations of varying ethnic backgrounds, laid the foundation for gene mapping via linkage and association studies. The early days of this molecular era of genetic research into BD could be frustrating [20], as most linkage findings were not supported by subsequent studies [11]. Problems associated with these early linkage studies were manifold: limited sample sizes, sparse genetic maps, and the use of the standard parametric *logarithm of the odds* (LOD) score method; in this method, originally designed for Mendelian disorders with monogenic inheritance, parameters such as mode of inheritance, penetrance, or the clinically unaffected status of probands' relatives need to be specified, which is not possible for complex phenotypes.

With the advent of larger, multi-center studies, the availability of denser maps, and the use of non-parametric linkage algorithms (e.g., affected sib pair design), many of these early problems could be alleviated. Half a decade ago, we argued that large-scale linkage studies would in the end succeed in gene-identification, or at least serve as the starting point for systematic molecular genetic research in BD 11. Since then, however, even the largest studies or meta-analyses have left us with a void. Some consistencies of linkage findings hold up in large meta-analyses (e.g. for chromosomes 6q and 8q 21), but most of the reported linkages on virtually every chromosome remain isolated findings. The impact of this lack of replicability on our thinking is significant. For instance, does it imply that the linkage findings are false? If so, linkage analysis as a tool to pinpoint susceptibility genes might be considered a thing of the past. The genetic (or locus) heterogeneity of BD may be so high that we are not able to dissect it by means of linkage analysis (alone), even with very large sample sizes. Nevertheless, incorporating the information gained from linkage studies into future analyses, as well as continuing to collect exact phenotype data of families might still be very valuable and should not be dismissed 22.

As with linkage analysis, positional cloning efforts by means of candidate-gene association mapping have not lived up to their promise. Although several studies, particularly systematic linkage disequilibrium (LD) mapping in linkage regions, have identified potential susceptibility genes for BD 3, 7¯9, these findings have been difficult to replicate. While replication at the gene level has been reached for some of these genes, replications at the allelic level—i.e. association with the identical allele of a particular single nucleotide polymorphism (SNP) across studies—are rare 23 (Table 1).

Genome-wide association studies of bipolar disorder

Despite these rather disheartening experiences, researchers in the field of complex genetics entered the 21st century with great aspirations based on an ever-advancing technology that made genome-wide association studies (GWAS) a practical reality. The first two chapters of this special issue will present this method in detail. GWAS have been performed in the study of several complex disease and physiological trait phenotypes, including type I and type II diabetes [24–28], lung cancer [29–31], body-mass-index and obesity [32–35], coronary heart disease [24, 36, 37], hypertension [24], rheumatoid arthritis [24], age-related macular degeneration [38, 39], Crohn's disease [24, 40, 41], prostate cancer [42, 43], height [44–47], and pigmentation and hair color[48–50]. Thus, the study of GWAS in complex disorders has successfully identified and replicated several susceptibility genes [51].

With regards to GWAS of BD, several studies have been published or are in the pipeline [24, 52–56]. These have highlighted several novel susceptibility genes. Among these, the genes *DGKH*, *CACNA1C*, and *ANK3* have been found at robust levels of genome-wide significance and have notably been replicated across samples [52–58; Table 1). *DGKH* is located within the BD linkage region on chromosome 13q14, and encodes diacylglycerol kinase eta, a key protein in the lithium-sensitive phosphatidyl inositol pathway. The *CACNA1C* gene encodes an alpha-1 subunit of a voltage-dependent calcium channel. The *ANK3* gene encodes ankyrin-G, a large protein whose neural-specific isoforms, localized at the axonal initial segment and nodes of Ranvier, may help maintain ion channels and cell adhesion molecules.

GWAS in BD have taught us several important lessons, and these lessons can be easily generalized to genetic research into other complex psychiatric or somatic disorders:

- BD is a polygenic disorder. That means that the contribution of each locus to risk of disease is modest, that cases carry significantly more risk alleles than controls, and that disease risk increases substantially with the total burden of risk alleles carried.
- The best findings from GWAS do not necessarily fall within those genes that have previously been widely studied. These "usual suspects" typically included candidate genes studied on the basis of either hypothetical reasoning concerning neurotransmission or linkage findings.
- Pursuing a "top-hits-only" strategy may prevent us from understanding the genetic complexity of BD and polygenic disorders in general. Stringent levels of statistical significance such as genome-wide significance are indispensible for confirming any risk gene or polymorphism identified through a GWAS. However, meta-analyses may reveal several points of agreement between independent studies and highlight genes that do not make it to the p-value-defined top of an individual study. A detailed consideration of the wider distribution of association signals across studies may thus prove to be a valuable strategy in complex genetics [59].
- Allelic heterogeneity may be an important factor in complex disorders such as BD. Allelic heterogeneity means that a phenotype can be caused by different alleles within a gene; this phenomenon has been extensively observed in monogenic disorders such as cystic fibrosis [60], as well as in *BRCA1/2*-associated breast cancer [61]. In the case of *ANK3* and BD, various alleles and haplotypes appear to be independent risk factors [56, 58].
- Finally, as with other complex phenotypes, GWAS in BD have brought to light the fact that the identified variants only account for a small fraction of genetic variability. This phenomenon has become known as the "case of the missing heritability" [62].

Consequences for future approaches in the genetics of BD

The information detailed above might lead one to believe that GWAS have failed, and that the genetics of a complex disorder such as BD may be too complex to ever be understood. However, in the scientific community there is broad consensus that GWAS results are only a starting point rather than an end point, that many more steps need to be taken in order to put the pieces together, and that GWAS need to be embedded in a framework of complementary approaches [63–65]. These include studies focusing on genomic, epigenomic, phenomic, neurobiological, and environmental aspects (Figure 1).

Genomics and epigenomics

Most of the world's largest data collections of individuals with BD and controls have already been analyzed by GWAS, and the results published. Compared to many GWAS of non-psychiatric phenotypes, sample sizes in psychiatric GWAS—usually totaling around two to four thousand cases and controls—are still not large enough to detect risk variants with small effect sizes. Thus, the psychiatric genetic research community has embraced the idea of bringing together all available samples for joint mega- and meta-analyses through a collaborative effort known as the *Psychiatric GWAS Consortium* (*PGC*) [66]. While this will most certainly help to identify further common vulnerability variants, validate existing findings, and allow the study of allelic heterogeneity and gene-gene interaction, increasing sample size is only one of many necessary steps.

Such collaborative GWAS focusing on common SNP variations (i.e., GWAS to date have typically studied HapMap-SNPs (http://www.hapmap.org/) with a minor allele frequency above 5%) will need to be complemented by studies investigating uncommon (i.e. in the 1–5% range) and rare (i.e. <1%) genetic variations. This includes the genome-wide study of copy number variants (CNVs) presenting with deletions or duplication of variably-sized segments of DNA. The study of CNVs has proven pivotal for identifying structural chromosomal variation as rare sources of genetic susceptibility to psychiatric disorders [67] such as schizophrenia [68, 69] and autism [70–72]. With regards to BD, it was recently shown that singleton deletions—deletions that appear only once in the dataset of more than 100 kb in length—were present in 16.2% of BD cases in contrast to 12.3% of controls, and that this effect was more pronounced in patients with an age at onset of mania at or below 18 years of age. This suggests that BD can result from the effects of multiple rare structural variants [73].

The notion that current GWAS designs fail to assess the impact of uncommon or rare variations has led to the development of several resequencing strategies. In contrast to GWAS approaches that use SNP markers derived from HapMap and thus miss rare or idiosyncratic variations, resequencing determines an individual's DNA sequence. Large-scale international resequencing projects such as the 1,000 Genomes Project (www.1000genomes.org) or the ClinSeq project [74] are well under way. While the latter study focuses on disease traits, it is hoped that both will contribute to the hunt for the lost heritability.

The field of pharmacogenomics may also emerge as an important part of the process of discovery in bipolar disorder, and especially the discovery of genetic variation that is relevant to the management of patients. While the high heritability of psychiatric disorders is well-known, evidence for the heritability of response or side-effect susceptibility to psychiatric medications is less well established; systematic formal genetic studies such as twin studies have not been performed [75]. However, in addition to clinical observations supporting the notion that response to treatment is familial, ample justification exists for pursuing pharmacogenetic studies in psychiatry, as reviewed by Peter Zandi in this special issue. Over the last decades, progress has been made in understanding the genetics of pharmacokinetics—broadly defined as mechanisms regarding the blood and tissue concentrations of a drug. As a result, quantitative

dose adjustments based on genotype can be calculated for many medications, including antidepressants and antipsychotics. In marked contrast, translation of genetic findings on pharmacodynamic phenotypes (i.e. drug effects) into psychiatric clinical practice is still not feasible [76, 77]. However, recent findings on the genetics of response or susceptibility to adverse events to pharmacotherapy in depression have yielded relatively large effect sizes, illustrating that the availability of large and adequately characterized samples will be key to success in this line of research [75, 78–85].

Overall, little research has been done on the genetics of response or susceptibility to adverse events in the treatment of BD. Despite lithium's proven efficacy, and evidence suggesting that there is a genetic basis of response to lithium treatment [86], pharmacogenetic studies in this area have so far been confined to small sample sizes and varying phenotype definitions [87]. Using data from the STEP-BD study sample and collaborators from the UK, Perlis and colleagues [88] performed a GWAS on lithium response that included more than 800 lithium-treated patients. They identified multiple regions of interest but none met the threshold for genome-wide significance [88]. Recently, researchers from the *International Study Group of Lithium Treated Patients* (*IGSLI*; www.igsli.org) and the National Institute of Mental Health (NIMH) spearheaded the creation of the *Consortium on Lithium Genetics* (*ConLiGen*; www.ConLiGen.org). *ConLiGen* is a worldwide effort to harmonize phenotype definition of response to lithium treatment and to perform GWAS of response and adverse events to lithium in adequately sized samples [89]. Efforts like this will be needed to move towards a personalized medicine approach in the treatment of BD. The potential pharmacogenetic target phenotypes are plentiful: acute depressive and manic episodes, prophylaxis, characteristic acute and long-term side effects of mood stabilizers, etc.

The field of epigenomics has recently drawn increased attention, given ample evidence for the involvement of epigenetic mechanisms and of their interplay with environmental factors in the etiology of somatic disorders such as cancer [90]. With regards to mental illness, postmortem studies suggest that epigenetic factors play a role in the etiology of schizophrenia and BD [91, 92]. Stress-induced imbalances of histone acetylation may also be involved in the transition from acute adaptive response to chronic psychiatric illness [93].

Phenomics

To date, psychiatric genetic studies, including GWAS, have mainly focused on categorical diagnoses such as BD for phenotype definitions. While the use of diagnostic systems such as the DSM-IV has increased diagnostic reliability, categorical diagnoses are by definition artificial constructs. The psychiatric genetic community has thus embraced the idea of thorough genotype-phenotype studies. Here, investigators hope that focusing on phenotypic dissection will help decrease phenotypic—and hence genotypic—heterogeneity; this would allow the delineation of characteristic genotype-phenotype signatures [94–98]. Thorough genotype-phenotype studies may also deliver clues in dissecting the phenotypic and genotypic overlap between schizophrenia and BD.

Subphenotype approaches have proven successful in elucidating the genetics of breast cancer 99 and non-syndromal deafness [100]. Thus, they may prove valuable in psychiatric genetics. To avoid an insurmountable multiple testing problem, investigators should carefully choose the subphenotypes to be studied out of the plethora of phenotypic variables potentially amenable to phenotypic dissection approaches. This could be done by focusing on well-formulated hypotheses, or by concentrating on variables that show some evidence of heritability or at least familiality. As regards BD, considerable research has established the familiality of clinical variables for subphenotypic analyses. For instance, the following familial phenotypic characteristics have been identified: episode frequency, comorbid panic disorder, comorbid obsessive compulsive disorder (OCD), comorbid anorexia nervosa, comorbid substance abuse,

comorbid alcoholism, psychosis, a history of suicide attempts, a history of missed work, a history of psychiatric hospitalizations, (early) age of onset, polarity of onset, puerperal trigger of onset, temperament, rapid cycling, and level of social functioning [97, 101–108]. For some of these, heritability has also been established. Most of these variables are currently being used in subphenotype analyses of large GWAS datasets.

One major motivation behind these analyses is the notion that subphenotyping may help define more homogenous subgroups of the disorder, and that this increased homogeneity will improve chances of identifying susceptibility genes. Furthermore, both case-control and cases- only strategies can be pursued in these subphenotype analyses. In the case-control design, cases with (or without) a specific subphenotype are compared to control individuals. In the cases-only design, cases with a specific subphenotype are compared to cases without this subphenotype. These different strategies are believed capable of better disentangling the underlying genetic architecture, as they may help to differentiate between factors such as genetic heterogeneity (e.g., gene A may increase the risk of developing BD with psychosis while gene B may increase the risk of developing BD without psychosis) as well as modifier genes (e.g., gene A may increase risk of developing BD only in the presence of gene B, which by itself confers no risk for BD).

Reverse phenotyping, originally proposed by Schulze & McMahon (2004), is a particular form of subphenotyping [19]. Here, genetic marker data are used to drive, or form, the basis of new phenotype definitions. In the case of association studies, reverse phenotyping aims to define phenotypic groupings that are distinguished by more deviant allele frequencies than are seen in traditional diagnostic categories. For instance, we demonstrated that the association between a haplotype in the gene *G72* and BD in a large German and Polish sample was driven by an association with the subphenotype "history of persecutory delusions" [98]. Furthermore, in the Polish sample, the association was only revealed through this approach, as the overall sample of BD patients showed no association. Thus, the subphenotype "history of persecutory delusions" helped to homogenize the samples. Reverse phenotyping has now also been successfully applied to research in non-mental illnesses [110].

As outlined below, applying phenotypic dissection approaches such as reverse phenotyping to the study of the longitudinal course of psychiatric illness might be another fruitful—though so far largely untraveled—road in psychiatric genetics. To fully understand the phenomic expression of genetic liability to disease, phenomic studies should include the study of endophenotypes, comprising neurophysiological, biochemical, endocrine, neuroanatomical, cognitive, or neuropsychological measurements. The joint consideration of endophenotypes and genetic factors may hold promise for understanding the actual mechanisms leading from genetic variation to phenotypic expression [112]. The prerequisite for phenomic studies is the availability of large and adequately characterized samples, as well as sophisticated data management strategies [107, 113].

For decades, biological psychiatric research, in particular psychiatric genetics, has been based on cross-sectional datasets but has not paid much attention to a phenotype that is of utmost relevance to the clinician, the patient, and the patient's family: the longitudinal course. In the case of schizophrenia, epidemiological studies have shown that there are characteristic subtypes of longitudinal courses in schizophrenia [114], and that these are defined by both relapse pattern and level of impairment. In BD, there is broad consensus that BD is a severe, usually lifelong, chronic condition, as suggested by longitudinal studies like the McLean-Harvard First Episode Project [115–117]. According to these data, full recovery from initial episodes is uncommon. When full symptomatic recovery does happen, it occurs much more slowly than early syndromal recovery. Furthermore, initial depression or mixed states predict more depressive episodes and overall morbidity during later stages of the disorder, while initial mania

or psychotic features predict more manic episodes and a better prognosis. Characteristic polymorphic patterns with mood-dominated, schizo-affective-dominated and schizo-dominated course have also been described for BD [118]. Again, switching between mania and depression within one episode has been suggested to predict poor prognosis [119], and rapid cycling is associated with substantial depressive morbidity and high risk for serious suicide attempts [120]. Nevertheless, data are still lacking on the course of BD across the life cycle, encompassing aspects of phenomenology, severity, and impairment [121].

In their recent review on the course and outcome of BD, Treuer & Tohen (2009) urged more research to establish better and more reliable course predictors for individual patients [122]. This need is reflected by current efforts for a paradigmatic change in the upcoming DSM-V and the ICD-11; notably, measures of longitudinal course along with dimensional aspects will be core elements of the new classification systems 123. Surprisingly, integrating longitudinal aspects into future classification systems has not yet been paralleled by a similar move in the field of biological, mainly genetic research in psychiatry; rather, current efforts focus on increasing sample sizes of cross-sectional diagnoses, not establishing longitudinal cohorts. In the future, genetic studies of BD and other psychiatric disorders should target the longitudinal course of the illness as an important phenotype of interest. This, of course, will require patience as well as a trained clinician's eye. Such efforts will have to be paralleled by the establishment of phenotypic databases such as the Bipolar Phenome Project 107, as well as by the development of mathematical algorithms that allow for the robust delineation of phenomic profiles and their genomic signatures. Finally, it is important to note that these genomic, epigenomic, and phenomic approaches outlined above need to be embedded in a framework of "neurobiological vetting", and that environmental influences must also be modeled.

Neurobiology

Once genetic susceptibility to psychiatric disorders has been identified and, more crucially, robustly replicated, the variants in question become prime targets for focused neurobiological studies to further elucidate their relevance to the mode of action in the pathway leading up to disease presentation [124–127]. Such studies should include gene-expression studies and the development and testing of animal models. Ideally, phenotype and endophenotype studies in humans (e.g. brain imaging) can be paralleled with identical approaches in animals (e.g. brain imaging in animals).

Study of environment

As noted previously, classic formal genetic studies demonstrated that heritability estimates in BD range up to 80–90%. Given this high heritability, it is easy to forget that non-genetic factors are also part of the equation describing phenotypic variance. Psychiatric geneticists have long wanted to study the complex interplay between genes and environment. The crucial question, however, has always been how best to do it. A recent, large-scale, meta-analysis of the widely-reported interaction between variation in the serotonin transporter gene and stressful life events [128] found little substance to this finding. Inconsistency of study designs, measures, and analyses proved to be main explanatory factors in this sobering but much-needed finding. Therefore, the question remains whether we will ever be able to account for environmental factors in a robust way. Plugging in retrospectively collected environmental data as covariates into an analysis may prove to be a futile endeavor. Instead, prospective studies may be key to success in this area. Furthermore, we may see a renaissance of studies targeting multiply-affected families, this time not to conduct linkage studies but rather for in-depth sequencing within the framework of longitudinal observation. Families from populations with similarly shared patterns of idiosyncratic environmental exposures (e.g. Amish or Hutterite communities in the Americas) might prove ideal for gene-environment studies.

Concluding remarks

Over the last decade, the psychiatric genetics research community has made considerable progress, and has learned much. Indeed, our most important lesson has been that the complexity of a complex disorder like BD is always a little more complex than we think. As our technological advances become progressively more sophisticated, new layers of complexity will undoubtedly arise; this is, in essence, the nature of science. That said, we should not shy away from these new challenges because we *have* made some headway. Our research efforts have demonstrated that BD is a truly polygenic disorder and have revealed potential mechanisms beyond those traditionally-hypothesized pathophysiological pathways, as illustrated by replicated GWAS findings of susceptibility genes involved in the architecture of calcium and sodium channels. Furthermore, we now know that we will not find *the gene* or *the genes* for BD; in fact we may have to settle for a scenario where we can only sufficiently characterize the joint effect of several hundreds or even thousands of genes on disease presentation. However, the fact that recent replicated findings only explain a fraction of phenotypic variability should serve as a stimulus to think ahead rather than give up. After all, GWAS in somatic phenotypes may have produced smaller p-values, but they do not fare better in terms of explaining. Thus, many areas of research still need to be explored. If explored systematically and in a harmonized way, they will shed more light on the genetics of disorders such as BD.

Acknowledgments

The author is greatly indebted to Francis J. McMahon for highly inspirational discussions and gratefully acknowledges the support of the Intramural Research Program of the National Institute of Mental Health. Ioline Henter provided outstanding editorial assistance. The author gratefully acknowledges Daniela Reich-Erkelenz for assistance in designing graphical presentations.

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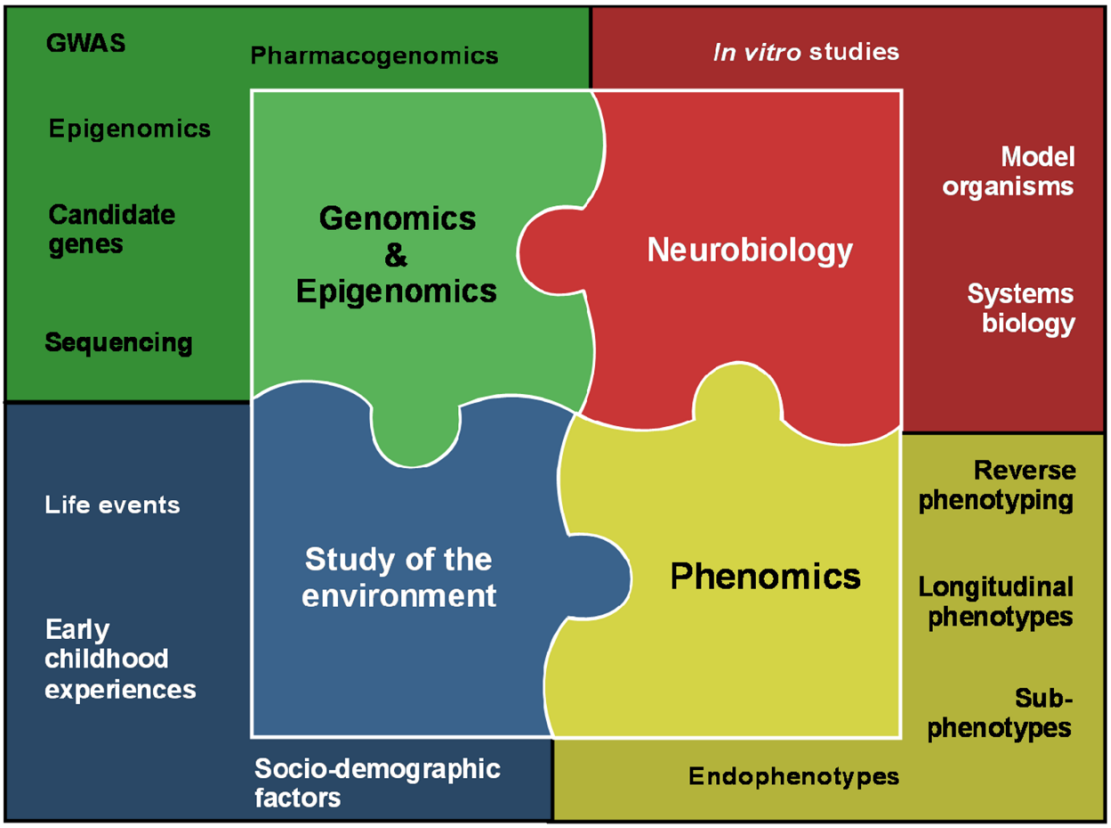

Figure 1.
Conceptual framework for future genetic research into bipolar disorder

Table 1

Potential susceptibility genes for bipolar disorder

Gene	Symbol	Individual study or meta-analysis (MA)	Evidence
Candidate gene association studies			
Serotonin Transporter	*SLC6A3*	Anguelova et al. 2003 (MA)	+++
D-amino acid oxidase activator (G72)	*DAOA*	Detera-Wadleigh & McMahon 2006 (MA)	+++
Brain-derived neurotrophic factor	*BDNF*	Kanazawa et al. 2007 (MA); Fan & Sklar 2008 (MA)	+++
Disrupted-in-schizophrenia-1	*DISC1*	Hodgkinson et al. 2004; Thomson et al. 2005 ; WTCCC 2007 ; Perlis et al. 2008	++
Tryptophan hydroxilase 2	*TPH2*	Harvey et al. 2004 ; Van den Bogaert et al. 2006 ; Lopez et al. 2007 ; Harvey et al. 2007; Cichon et al. 2007	++
Aryl hydrocarbon receptor nuclear translocator-like	*ARNTL/CLOCK*	Mansour et al. 2006 ; Nievergelt et al. 2006	+
Cadherin gene (homolog of the Drosophila tumor suppressor gene *fat*)	*FAT*	Blair et al. 2006 ; Abou Jamra et al. 2008	+
Genome-wide association studies			
Diacylglycerol kinase eta	*DGKH*	Baum et al. 2008a	++++
alpha-1 subunit of a voltage-dependent calcium channel	*CACNA1C*	Sklar et al. 2008; Ferreira et al. 2008	++++
Ankyrin 3	*ANK3*	Baum et al. 2008a; Ferreira et al. 2008; Smith et al. 2009; Scott et al. 2009	++++

+ supported by 2 studies

++ supported by several studies

+++ supported by meta-analysis of 3 or more samples

++++ genome-wide level of significance (in at least one of the studies)