

Genetics of Bipolar Disorder

Jens R. Wendland and Francis J. McMahon

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Abstract In this chapter, we will attempt to outline the current state of genetic knowledge for bipolar disorder and briefly summarize the main findings from genetic epidemiology studies. We then review the most recent original literature, based largely on genome-wide association study methods. We conclude with some ideas about future directions.

1 Introduction

There is a broad consensus that the etiology of bipolar disorder (BPD) has a genetic basis. This consensus rests substantially on genetic epidemiology studies that have demonstrated the high familiarity and heritability of BPD. The identification of

J.R. Wendland (✉) and F.J. McMahon
Genetic Basis of Mood and Anxiety Disorders Section, National Institute of Mental Health,
National Institutes of Health, US Department of Health and Human Services, Bethesda, MD, USA
e-mail: wendlandj@mail.nih.gov, mcmahonf@intra.nimh.nih.gov

specific genes involved in BPD has therefore been a high priority. Such genes, or their associated cellular mechanisms, should provide insight into the molecular etiology of BPD, but might also serve as novel targets for prevention, diagnosis, or treatment.

Below, we outline the current state of genetic knowledge for BPD and briefly summarize the main findings from genetic epidemiology studies. We also review the most recent studies, which are based predominantly on genome-wide association study (GWAS) methods. Although some GWAS are still ongoing and it may be too early to reach definitive conclusions, it is already becoming clear that the GWAS method does identify markers that can be consistently replicated across studies. However, as with other common diseases, the markers identified so far seem to confer very modest risk for BPD, and it now seems clear that there are no common variants of major effect size for BPD. Also, as with other common diseases, the genes implicated so far were largely unexpected and would not have been predicted on the basis of current pharmacological or neurobiological theories. As the GWAS era winds down, new strategies for BPD genetics research are being explored. These new strategies involve, among others, redefinition and dissection of the BPD phenotype, novel molecular methods such as next-generation sequencing, and new bioinformatics approaches aimed at integrating genetic findings with neurobiology.

2 Genetic Epidemiology of BPD

Most lifetime prevalence estimates for BPD range between 1 and 2% in the general population. It has long been recognized that BPD runs in families, leading to a number of family and twin studies. Among common complex genetic disorders, BPD is one of the most highly heritable, with about 80% of the phenotypic variation attributable to genetic effects.

The familial aggregation of BPD has been demonstrated in controlled systematic studies. Close relatives of probands with BPD have about a five- to tenfold higher risk of BPD, and a 10- to 15-fold higher risk of major depression, compared to close relatives of healthy individuals [reviewed in (Smoller and Finn 2003)].

2.1 Twin Studies

Twin studies have been used to investigate the amount of familial aggregation associated with BPD that is explicable by genes. Dizygotic (DZ) twins share about half of their genes, while monozygotic (MZ) twins inherit identical genes, even though both kinds of twins share similar environments. Thus, comparing

MZ and DZ twins can parse environmental and genetic contributions to a phenotype. For BPD, it has been consistently observed that MZ twins have a much higher concordance for BPD than dizygotic twins. This difference in concordance leads to heritability estimates from large twin studies in the range of 59–87% (Bertelsen et al. 1977; Cardno et al. 1999; Edvardsen et al. 2008; Kendler 1993, 2001).

2.2 *Family Studies*

Family studies have also helped define the range of clinical phenotypes present in the relatives of people with BPD. In the most informative family studies, so-called controlled family studies, case, and healthy control participants are typically ascertained regardless of family history, and their relatives are then systematically evaluated for phenotypes of interest. Several large BPD family studies were published in the 1980s (Weissman et al. 1984). These studies have shown that relatives of probands with BPD are also at increased risk for other mood and anxiety disorders, as well as alcohol and substance-related disorders. Some studies also found a modestly increased risk of schizophrenia. This idea was supported by a recent large study that joined relatives based on registry data and clinical diagnoses (Berrettini 2000; Lichtenstein et al. 2009).

Family studies can also be used to help determine the way in which an illness is inherited. The formal fitting of inheritance models to family data is known as segregation analysis. Segregation analysis has been largely unsuccessful for BPD, since most studies have been unable to distinguish between polygenic, multifactorial, and major locus models of inheritance. This probably reflects the limited ability of segregation analysis to cope with heterogeneity and the assortative mating, parent-of-origin effects, and other nonstandard inheritance patterns that have often been observed in BPD (McInnis et al. 1993; McMahon et al. 1995; Stine et al. 1995).

3 Molecular Genetics

3.1 *Genetic Linkage and Candidate Gene Studies*

Numerous linkage and candidate gene studies have been conducted in BPD. In general, they have not yielded widely accepted findings. Therefore, we will not review these studies here and instead refer the interested reader to several excellent published reviews (Barnett and Smoller 2009; Burmeister et al. 2008; Craddock and Sklar 2009).

3.2 *Genome-Wide Association Studies*

GWAS use common genetic markers that are spread across the entire genome to test for associations between individual marker alleles and disease. Thanks to high-throughput technology, hundreds of thousands to millions of markers can be assayed in a single experiment. In this section, we will first describe the basic concepts of GWAS and some of the challenges associated with the analysis of such large datasets. We will then review GWAS in BPD and discuss the results and implications for BPD genetics research.

The central methodological feature of GWAS is the highly parallel, simultaneous determination of many genotypes for single nucleotide polymorphism (SNP) markers located throughout the genome. Initial arrays were only capable of interrogating a few hundred SNPs in a single experiment (Wang et al. 1998), but within less than a decade, this number was scaled up by three orders of magnitude. Such high-density arrays are designed on the basis of HapMap data (International HapMap Consortium 2003), so that each marker actually samples not just a single base pair but also nearby regions that may be hundreds or thousands of base pairs in size. Modern SNP arrays provide nearly complete coverage of common genetic variation, at least in populations of non-African ancestry (Barrett and Cardon 2006). After raw data cleaning and quality control procedures (which are very important), GWAS data are typically analyzed using one marker at a time. This introduces a considerable multiple hypothesis testing problem. To minimize type I error, most researchers have accepted a p value threshold of $\sim 10^{-8}$ (Dudbridge and Gusnanto 2008) for samples of European ancestry. Such a threshold means that GWAS are underpowered to detect small effects unless sample sizes are very large (greater than 1,000 cases and 1,000 controls).

As of early 2010, no single BPD sample has yielded a p value below this threshold in a GWAS (Wellcome Trust Case Control Consortium 2007; Baum et al. 2008; Ferreira et al. 2008; Hattori et al. 2009; Scott et al. 2009; Sklar et al. 2008; Smith et al. 2009). Some signals have been identified in studies that combined more than one BPD sample in joint or meta-analyses (Fig. 1). The first of these (Baum et al. 2008) implicated the gene diacylglycerol kinase ϵ (DGKH), which is known to be involved in pathways sensitive to lithium, a mood stabilizer frequently used to treat BPD. Subsequent studies (Ferreira et al. 2008; O'Donovan et al. 2008) have implicated novel genes (*ANK3*, *CACNA1C*, and *ZNF804A*) that suggest novel biological pathways. Reminiscent of the family studies that found increased rates of major depression among the relatives of individuals with BPD, one study found a locus that may be involved in both disorders (McMahon et al. 2010).

Taken together, these studies can be regarded as a “successful start to a long journey” (Craddock and Sklar 2009), but it is important to realize that the effect sizes are very small. This means that although the identified genetic markers are associated with BPD at genome-wide significance thresholds, their individual contribution to the genetic risk of BPD is very modest. For example, an individual who carries one of the identified markers might have a 1.1–1.3-fold increased risk

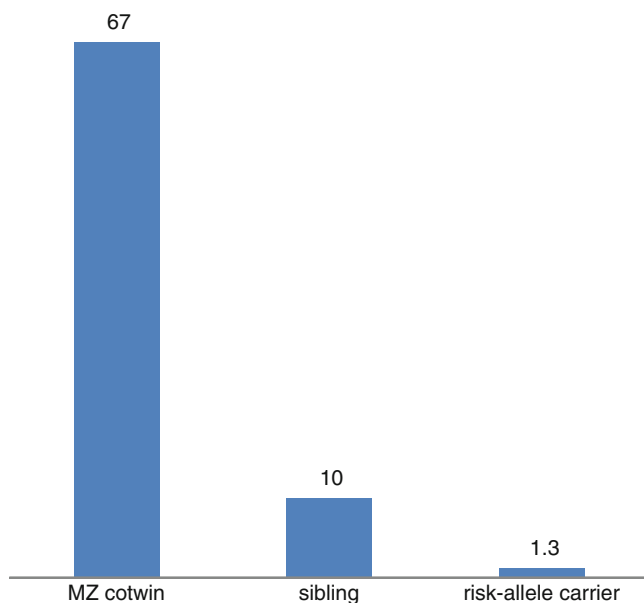


Fig. 1 The “missing heritability” of bipolar disorder (BPD). Twin studies show that the monozygotic (MZ) co-twin of a person with BPD has 60 to 80-fold increased risk of BPD, while a sibling has about a tenfold increased risk. In contrast, a carrier of a typical “risk-allele” identified by a genome-wide association study has only a 1.3-fold increased risk. It would take over 50 such risk alleles to fully account for the risk observed in MZ twins

of the illness, compared to a 60–80-fold increased risk for an identical twin or a tenfold increased risk for a sibling of someone with BPD (Fig. 2). Clearly, additional genes are yet to be found. Still, the current findings might shed some light on the biology of BPD [see (Maher 2008) for a general review on small effect sizes and GWAS].

In summary, several GWAS have been completed so far in BPD. A few markers hold up to stringent statistical thresholds, but their effects on BPD risk are quite small. The lack of common variants that confer substantial risk for BPD leaves considerable room for novel strategies in future research, some of which we will discuss below.

4 New Strategies in BPD Genetics Research

4.1 *Redefining the Phenotype*

The genetic studies we have reviewed so far rely on standard clinical definitions of BPD. While such definitions can be quite reliable, it is unknown how closely they correspond to a shared underlying biology. Indeed, BPD is actually a quite

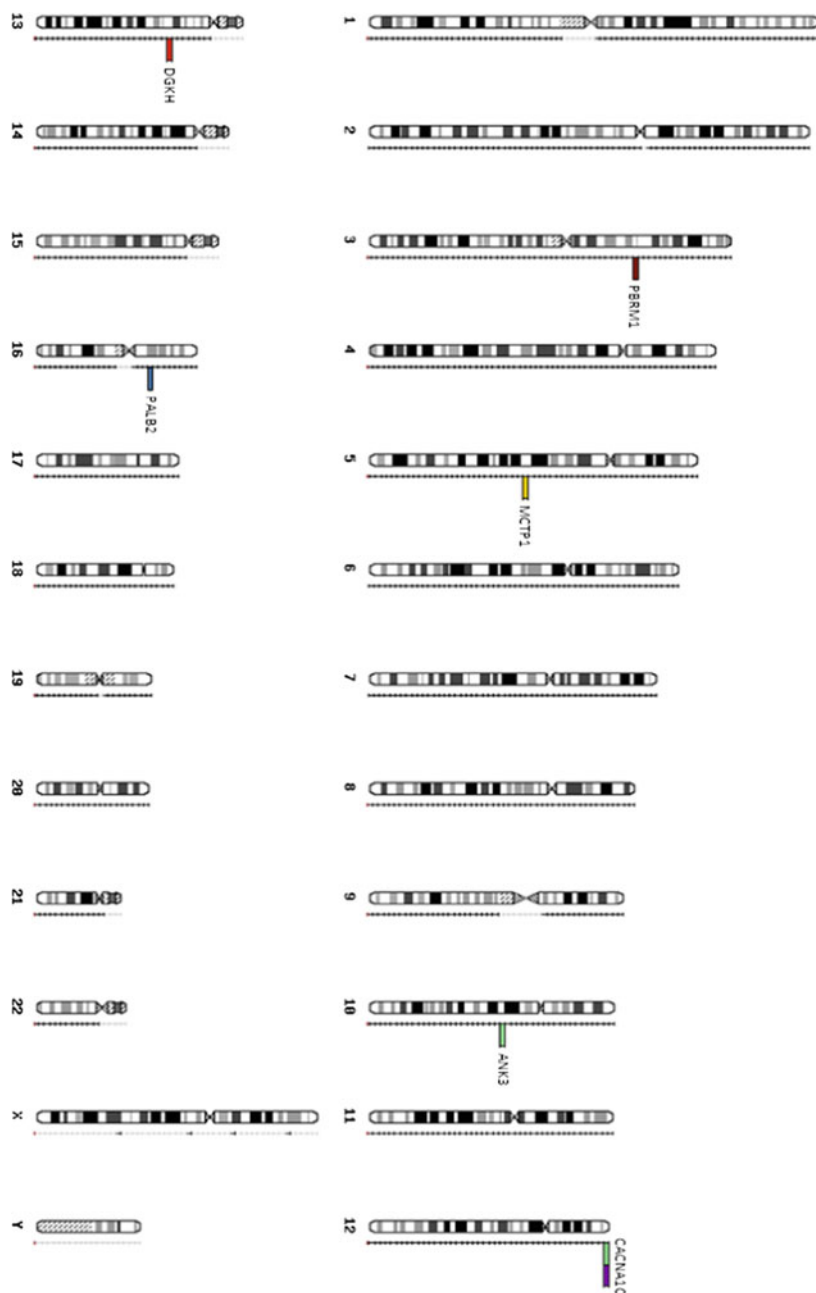


Fig. 2 Key genome-wide association findings in bipolar disorder (BPD) samples as of June 2010. Each finding is indicated by a box drawn near the chromosomal location of the associated marker(s) and annotated with the name of the nearest gene(s). Each study is assigned a unique color, but many of the samples reported to date contain overlapping individuals. Figure drawn using HGVbaseG2P at www.hgvbaseg2p.org

heterogeneous entity at the clinical level, and it seems likely that at least several conditions, with distinct etiologies, comprise what we call BPD. Some studies, based on GWAS data, have even suggested overlap in genetic risk factors between BPD and schizophrenia, despite markedly different clinical courses and treatments (Purcell et al. 2009). Two commonly used scientific approaches to address these phenotype limitations are the search for subphenotypes and intermediate or endophenotypes. Both of these approaches have been applied to BPD, but comprehensive genetic studies are still underway.

Subphenotype studies usually aim at dissecting current case definitions into several *phenomenologically* more “pure” phenotypes, based on clinical or other data. This can be as straightforward as dividing cases into groups based on a particular clinical feature, such as age of onset. More complex studies use methods such as cluster or factor analyses to try to discern the best set of cases or clinical features that can then be tested for association with genetic variants. These strategies have been used in BPD primarily on a candidate gene basis, with some success (Craddock et al. 2010; Schulze et al. 2005), but the overall results have been mixed. It is possible that applying subphenotype methods to samples that were collected under standard case definitions leads to biased ascertainment with a consequent loss of statistical power. Perhaps the studies to date, which have focused on common genetic variants, have missed effects that will only be evident when it becomes possible to study less common variants. It is also possible that the key assumption underlying subphenotype analyses – that phenotypic homogeneity reflects biological and genetic homogeneity – may not be correct for something as complex as BPD. Thus, it remains an open question whether subphenotype approaches will prove valuable in genetic studies of BPD.

Intermediate and endophenotype approaches are intended to use biologically valid and easily measurable phenomena related to the phenotype of interest as biomarkers for some underlying genetic vulnerability. In BPD studies, such biomarkers can be derived from data obtained in brain imaging, biochemical measures of blood or cerebrospinal fluid, or EEG wave patterns, just to name a few. The key assumption in these kinds of studies is that biomarkers are a more stable indicator of underlying biological dysfunction. Like subphenotypes, this approach has had some success in genetic studies (Dick et al. 2006; Hariri et al. 2005), but it is not clear how useful it will be in the longer term. Endophenotype approaches to nonpsychiatric disorders have generally not proven to be more powerful than clinical diagnoses for GWAS, but might perform better in studies of less common variation. A major problem with this strategy is that the initial identification of biomarkers generally depends on a statistical correlation with psychiatric phenotypes, with attendant problems distinguishing between state and trait, cause and consequence. The usefulness of biomarkers for BPD genetics research, particularly in GWAS, remains to be fully tested.

4.2 *Novel Molecular Tools*

The SNP arrays used so far for GWAS capture only a small subset of human genetic variation, namely, that which is represented by common SNPs. Some platforms are also designed to include monomorphic SNPs that can be used to identify known chromosomal regions that are commonly deleted or duplicated (so-called copy-number variants, or CNVs), but much copy-number variation cannot be measured in this way (Kidd et al. 2010). Some of the newest platforms also include less common SNPs identified by research, such as the Thousand Genomes Project, which aims to fully sequence hundreds of unrelated people. However, a full understanding of the inherited risk for BPD and other complex genetic diseases will probably require information on the full range of genetic variation present in our genomes. Epigenetic variation, which includes several kinds of inherited variation not reflected in the DNA sequence, such as histone modifications, may prove to be quite important (Petronis 2010). Genetic variation that arises spontaneously from one generation to the next, so-called *de novo* variation, is often deleterious and can generally not be captured by standard SNP arrays. Such *de novo* variation can work at the cytogenetic level, or can lead to smaller CNVs, insertion/deletion mutations, or mutations affecting single nucleotides.

Several large studies are currently underway that use next-generation sequencing (NGS) methodology to identify rare genetic variants. NGS uses new molecular and computing technology to generate large amounts of DNA sequences at high accuracy and at a fraction of the cost of previous sequencing methods. Although this is still a relatively young technology, NGS has already begun to provide a new understanding of human genetic variation. For example, we now know that rare variants, each of which may occur in one or a few individuals out of thousands studied, appear to be more common than previously recognized. Initial studies identified over three million such variants per individual (Lupski et al. 2010; Roach et al. 2010), at least 10,000 of which are predicted to be functional based on our current understanding of gene regulation. Surprisingly, everyone seems to carry several rare variants that would previously have been considered sufficient to cause disease, such as variants that change a conserved amino acid or create a premature stop codon, both of which typically lead to major changes in the functions of the encoded protein. Clearly, we have a lot to learn about the range of genetic variation that is compatible with health before we can fully appreciate how genes cause disease.

In the field of common disease genetics, NGS is driving a shift away from the common variant/common disease hypothesis toward a model that postulates multiple, unrelated mutations in genes (or regulatory regions) that may be variably deleterious but result in a common phenotype. The many rare variants that will be found will pose an even greater multiple hypothesis testing problem than that posed by GWAS, and new analytical strategies will need to be developed. One such approach focuses on the joint analysis of all variants detected in a gene or gene

family (the “mutational load”) (Li and Leal 2008), but additional analytic tools will clearly be needed.

4.3 *Novel Analytical Tools*

Another major challenge for genetic studies of BPD and other complex genetic disorders is the limited availability of tools to identify nonadditive genetic interactions. Given the lack of common loci in the genome of major effect size, it seems reasonable to postulate that several or many genes interact in a manner whereby each gene has little or no effect *itself* (no marginal effect), but can explain more of the phenotype when tested in the context of other interacting genes. Such epistatic effects, however, still await computationally efficient detection strategies and powerful statistical procedures for clear interpretability [for review, see (Cordell 2009)]. This is a heavily researched field and a number of such analyses of BPD can be expected in the near future.

5 Summary

The strong familiarity and heritability of BPD remain some of the best clues to its etiology. After a long period of slow progress, individual genes that contribute to the risk of BPD are finally beginning to be identified. As the pace of discovery quickens, we can expect that the identified genes will allow us to piece together a much more coherent understanding of the biological underpinnings of BPD. We hope that such an understanding will drive new discoveries in diagnosis and treatment that will ultimately benefit patients and their families.

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