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The Genetics of Bipolar Disorder

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Abstract

Bipolar disorder is a mood disorder characterized by impairing episodes of mania and depression. Twin studies have established that bipolar disorder is among the most heritable of medical disorders and efforts to identify specific susceptibility genes have intensified over the past two decades. The search for genes influencing bipolar disorder has been complicated by a paucity of animal models, limited understanding of pathogenesis, and the genetic and phenotypic complexity of the syndrome. Linkage studies have implicated several chromosomal regions as harboring relevant genes, but results have been inconsistent. It is now widely accepted that the genetic liability to bipolar disorder reflects the action of many genes of individually small effect, a scenario for which linkage studies are poorly suited. Thus, association studies, which are more powerful for the detection of modest effect loci, have become the focus of gene-finding research. A large number of candidate genes, including biological candidates derived from hypotheses about the pathogenesis of the disorder and positional candidates derived from linkage and cytogenetic studies, have been evaluated. Several of these genes have been associated with the disorder in independent studies (including *BDNF*, *DAOA*, *DISC1*, *GRIK4*, *SLC6A4*, and *TPH2*), but none has been established. The clinical heterogeneity of bipolar disorder and its phenotypic and genetic overlap with other disorders (especially schizophrenia, schizoaffective disorder, and major depressive disorder) has raised questions about the optimal phenotype definition for genetic studies. Nevertheless, genomewide association analysis, which has successfully identified susceptibility genes for a variety of complex disorders, has begun to implicate specific genes for bipolar disorder (*DGKH*, *CACNA1C*, *ANKK1*). The polygenicity of the disorder means that very large samples will be needed to detect the modest effect loci that likely contribute to bipolar disorder. Detailed genetic dissection of the disorder may provide novel targets (both pharmacologic and psychosocial) for intervention.

Bipolar disorder (BPD) is a common and serious mental disorder characterized by severe mood symptoms, including episodes of mania or hypomania and depression, occurring with a typically cyclical course. Lifetime risk for BPD has typically been reported to be approximately 1%, though recent estimates are as high as 4%. (Kessler et al., 2005). The personal and societal costs of BPD are enormous: even among adequately-treated individuals, relapse is common and the disorder can be profoundly disabling, resulting in serious economic burden (Kessler et al., 2006) and a lifetime risk of suicide as high as 20%

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(Goldberg and Harrow, 2004). A range of genetic methods have confirmed that BPD is highly heritable, with genetic influences explaining 60–85% of risk (Smoller and Finn, 2003). In this article we review the epidemiological evidence for the heritability of BPD, describe prior and current attempts to find genes responsible for BPD, and discuss the implications that new genetic knowledge has for our understanding of BPD.

The Clinical Spectrum of Bipolar Disorder

The diagnosis of BPD has evolved from Emil Kraepelin's description as manic depressive insanity more than 100 years ago (Kraepelin, 1907). In the late 1950s and early 1960s, Leonhard and others proposed the division of affective disorders into bipolar and unipolar disorders (UPD) (Leonhard, 1959). The defining feature of BPD is the manic episode, characterized by at least one week of markedly elated or irritable mood that is accompanied by at least three of the following (or four, if mood is only irritable): rapid or pressured speech, marked distractibility, racing thoughts, increased goal-directed activity or agitation, an impulsive or high-risk behaviors such as reckless spending and hypersexuality. To qualify as a manic episode, the symptoms must result in marked impairment of social or occupational functioning, psychosis, or hospitalization. Most individuals with BPD experience episodes of major depression, though this is not required for the diagnosis. In the 1970s, a further distinction was made between bipolar I disorder (characterized by manic episodes) from bipolar II disorder (characterized by hypomania and recurrent depressive episodes) (Dunner et al., 1976). Hypomania is a milder form of mania requiring a minimum of four days of symptoms with an observable, uncharacteristic change in function but not marked impairment, psychosis, or need for hospitalization. Mood episodes in which criteria are met for both a manic episode and a major depressive episode are referred to as mixed episodes. Finally, rapid-cycling BPD is diagnosed when four or more mood episodes (mania, hypomania, depression, or mixed) occur within a 12 month period and episodes are demarcated either by partial or full remission for at least 2 months or a switch to an episode of opposite polarity.

Recent data from the population-based National Comorbidity Survey Replication (Merikangas et al., 2007) indicate that the lifetime prevalence of bipolar I disorder is 1%, with an additional 1.1% prevalence of bipolar II disorder. A larger proportion of the population (2.4%) exhibit subthreshold forms of BPD (Merikangas et al., 2007). Males and females are approximately equally at risk, and the mean age of onset is 18 years for bipolar I and 20 years for bipolar II (Merikangas et al., 2007). Other diagnoses in the DSM-IV bipolar spectrum include cyclothymia, characterized by at least two years of hypomanic and depressive symptoms that do not meet criteria for a manic or depressive episode, and bipolar disorder not otherwise specified, which includes disorders with bipolar features that do not meet criteria for bipolar I or II disorder.

The Genetic Epidemiology Of BPD

Family Studies

A large number of family studies have consistently documented that BPD aggregates in families. Studies published since 1960 suggest that the recurrence risk for BPD in first-degree relatives of BPD patients is approximately 9% (Smoller and Finn, 2003), nearly ten times that of the general population (Tsuang and Faraone, 1990, Kessler et al., 1997) (Table 1). Relatives of probands with BPD are also at increased risk (approximately 3-fold) of unipolar major depressive disorder (MDD) compared to relatives of unaffected controls. In fact, because the base rate of MDD is greater than that of BPD, relatives of individuals with BPD are more likely to be affected with MDD than BPD (Smoller and Finn, 2003). Family studies also suggest that bipolar I and II are at least partly genetically distinct: the risk of

bipolar II disorder is higher among relatives of patients with bipolar II than among relatives of patients with bipolar I disorder (Gershon et al., 1982, Andreasen et al., 1987, Heun and Maier, 1993), although in some studies risk of bipolar I is also elevated in relatives of bipolar II probands, suggesting that these mood disorders are not completely etiologically distinct (Smoller and Finn, 2003). Taken together, the data suggest that bipolar II is a heterogeneous entity in which some cases are more closely related to bipolar I, some to MDD, and others may represent a genetically distinct disorder that breeds true (Smoller and Finn, 2003).

Other phenotypic subtypes appear to influence familial risk of BPD. For example, early-onset BPD has been associated with greater familial risk of mood disorder in numerous studies (Pauls et al., 1992) (James, 1977, Taylor and Abrams, 1981, Grigoriu-Serbanescu et al., 2001, Somanath et al., 2002). In particular, prepubertal-onset BPD may represent a distinct form of the disorder that is genetically related to disruptive behavior disorders, particularly attention-deficit/hyperactivity disorder (Spencer et al., 2001). In one controlled family study (Geller et al., 2006), the prevalence of either bipolar I disorder or recurrent MDD was as high as 46.5% among first-degree relatives of prepubertal/early-adolescent onset BPD probands. In addition, relatives with ADHD were at increased risk of BPD; this is consistent with other studies suggesting that comorbid BPD and ADHD is a familial phenotype (Faraone et al., 2003). In addition to age of onset, other phenotypic features of BPD that have been reported to aggregate in families include polarity of illness onset (mania vs. depression) (Kassem et al., 2006), mood episode frequency (Fisfalen et al., 2005), psychosis (Potash et al., 2003, Saunders et al., 2007) and lithium-responsiveness (Grof et al., 2002), suicidality (Saunders et al., 2007), rapid-cycling (Saunders et al., 2007), and comorbid alcohol use disorders and panic disorder (Saunders et al., 2007).

The familial nature of BPD does not in itself establish that genes contribute since both genes and environmental factors could cause familial aggregation. Two methods which do allow genetic effects to be teased apart from environmental ones are adoption studies and twin studies. Adoption studies of BPD have been small and inconclusive. (Smoller and Finn, 2003). On the other hand, twin studies have clearly established that the familiarity of BPD is predominantly due to genetic influences. These studies have documented that the concordance rate for BPD is significantly greater among monozygotic or MZ twin pairs (who are genetically identical) than among dizygotic or DZ twin pairs (who share, on average, half their genes). The three largest recent twin studies have reported a concordance rate of 38.5–43% for MZ twins compared with 4.5 – 5.6% for DZ twins (Kendler et al., 1995, McGuffin et al., 2003, Kieseppa et al., 2004). These studies estimated the heritability (proportion of disorder risk in the population attributable to genetic variation) of BPD to be 79 – 93%, substantially higher than even medical disorders such as breast cancer for which specific susceptibility genes have been identified.

Molecular Genetic Studies Of BPD

Since concordance in MZ twins is not 100%, genes cannot be ‘sufficient’ causes for BPD, though they may be ‘necessary’. The aetiology of BPD is complex, probably involving multiple genetic and environmental influences, which may vary widely between affected individuals. There are no known single gene mutations which produce a syndrome we recognize as BPD, implying that no one gene can produce BPD in a deterministic fashion. Instead, genetic factors are assumed to increase risk probabilistically. As with other psychiatric disorders, unaffected relatives of patients with BPD probably carry risk alleles, and pass on an increased risk for disorder (Gottesman and Bertelsen, 1989).

Research into the genetic basis of BPD has thus developed into a search for the specific genes that confer risk for BPD. Our understanding of the likely genetic architecture of BPD has been partially driven by technological changes that have allowed us to test different types of genetic hypothesis. These technological transformations have pushed the field of psychiatric genetics from linkage to association methodologies, and from candidate gene to genome-wide approaches. Here we summarize the current knowledge derived from each of these approaches.

Linkage

Linkage studies use information from family members who are affected and unaffected with the disorder. The method typically examines a few hundred or thousand markers spread across the genome to determine the chromosomal regions where susceptibility genes are located, by examining which markers (and hence regions) appear to be co-inherited with disease within the family. More than 40 linkage scans for BPD, including three meta-analyses, have been published, implicating many areas of the genome but with little consistency between studies (Badner and Gershon, 2002, Segurado et al., 2003, McQueen et al., 2005b). The most comprehensive meta-analysis, which combined original data from the 11 largest linkage studies, found evidence for linkage on chromosomes 6q (for bipolar I disorder) and 8q (for bipolar I + bipolar II disorder) that met statistical criteria for genome-wide significance (McQueen et al., 2005a). As yet, the genes responsible for these linkage signals have not been identified.

Linkage has proved extremely successful in determining the genetic causes of single-gene Mendelian disorders such as Huntington disease (dominant inheritance) or cystic fibrosis (a recessive disorder) but its success in psychiatric genetics, including BPD, has been limited. Linkage analysis works best where genetic risk is conferred by a relatively small number of genes, each of which has a relatively large effect on disease risk. The limited success of linkage studies in psychiatric genetics is therefore taken as evidence that such genes do not underlie risk for BPD. Alternatively, such genes may exist, but may be specific to particular families or populations, explaining why they fail to replicate in other samples. Either way, it is clear that the genetic architecture of BPD is probably more similar to genetically complex diseases such as type II diabetes than it is to Huntington disease. As such, much of the focus of psychiatric genetic research has shifted towards association studies, which are more suitable for detecting susceptibility variants that are relatively common in the population, and which confer a relatively modest increase in risk for disease (Risch and Merikangas, 1996).

Candidate gene association studies

Over the past decade much research effort has focused on genetic association studies which examine whether specific alleles are more common in affected individuals than in matched controls (case-control studies) or whether specific variants are transmitted from parents to affected individuals more often than expected by chance (family-based studies). The markers are selected from genes that are candidate susceptibility genes, based on positional evidence from linkage studies, or from hypotheses about the underlying neurobiology of the disorder. Individuals can be related or unrelated, making larger sample sizes easier to accrue than the pedigrees required for linkage studies, and the genetic markers can include a number of different types of variation, including single nucleotide polymorphisms (SNPs) and repeat polymorphisms.

Candidate gene studies have provided tantalizing glimpses into the possible genetic aetiology of BPD but few, if any genes are universally accepted (Smoller and Gardner-Schuster, 2007, Burmeister et al., 2008). Of those genes which have been reasonably well-

studied, many are putative candidates because of their central role in neurotransmitter pathways, particularly the dopamine, serotonin and glutamate systems. Several specific genes have been associated with BPD in independent samples or meta-analyses including Disrupted in schizophrenia 1 (*DISC1*), the dopamine transporter (*SLC6A3*), brain-derived neurotrophic factor (*BDNF*), the NMDA glutamate receptor, subunit 2B (*GRIN2B*), d-amino acid oxidase activator (*DAOA*, aka *G72*), peroxisome proliferators-activated receptor delta (*PPARD*), neuregulin1 (*NRG1*), the serotonin transporter (*SLC6A4*), tryptophan hydroxylase-2 (*TPH2*) and catechol-o-methyl transferase (*COMT*) (De Luca et al., 2005, Fallin et al., 2005, Green et al., 2005, Craddock and Forty, 2006, Martucci et al., 2006, Van Den Bogaert et al., 2006, Thomson et al., 2007, Georgieva et al., 2008, Zandi et al., 2008) (Chen et al., 2008) (Lasky-Su et al., 2005) (Fan and Sklar, 2008). However, to date, none of these has been established as a BPD susceptibility gene.

Recent evidence has suggested a protective effect of variation in the kainate class ionotropic glutamate receptor gene *GRIK4* (Pickard et al., 2006, Pickard et al., 2008b). After detecting a complex chromosomal translocation in a patient with schizophrenia and learning disability, Pickard and colleagues (Pickard et al., 2006) noted that one of the genes disrupted by the translocation was *GRIK4* on chromosome 11. They subsequently showed that a 14 base-pair insertion/deletion polymorphism in the 3' UTR of the gene was strongly associated with a reduced risk of BPD ($p = 1.9 \times 10^{-7}$) in a case-control study and found supportive evidence in a second case-control sample ($p = .011$) (Pickard et al., 2008b). The protective (deletion) allele was also associated with increased expression of *GRIK4* transcripts *in vitro* and in postmortem brain (especially in the hippocampus).

Another class of candidates of particular interest in BPD are genes involved in circadian rhythms. Abnormalities of circadian rhythm may underlie aspects of BPD (McClung, 2007, Harvey, 2008) and it has been known for 30 years that sleep deprivation can be effective in alleviating depression and regulating mood in BPD (Larsen et al., 1976, Fahndrich, 1981, Wehr et al., 1982). Interestingly, effective pharmaceutical treatments for BPD including lithium and valproate, also produce alterations in circadian rhythm in humans and other species (Johnsson et al., 1983, Hafen and Wollnik, 1994, Dokucu et al., 2005), suggesting that circadian rhythm regulation may be a common pathway for stabilizing mood. Mice with an inactivating mutation of the *Clock* gene, a key regulator of circadian rhythmicity, have a behavioral profile resembling human mania that is largely reversed by chronic lithium treatment (Roybal et al., 2007). Genetic studies in BPD have found some modest evidence for association between BPD and SNPs in the genes that control human circadian rhythms, including the *CLOCK* and *BMAL1* genes (Benedetti et al., 2003, Serretti et al., 2003, Serretti et al., 2005, Mansour et al., 2006, Shi et al., 2008). These genes control the primary molecular clock, located in the suprachiasmatic nucleus of the hypothalamus: the *CLOCK* and *BMAL1* proteins together form a dimer that activates a transcriptional feedback loop, driving circadian rhythm by cycling over a 24-hour period (Ko and Takahashi, 2006).

Selecting genes as candidates because of the known or, (more often), hypothesized biology of BPD depends crucially on the accuracy of prior knowledge about the etiology of the disorder. In many cases, despite good biological plausibility and initially-promising associations with BPD, candidate genes which have been arrived at in this hypothesis-driven manner have failed to replicate in subsequent studies. There are clear methodological explanations for this, including the low prior probability that any particular gene from the very large number of possible candidates will turn out to be truly associated with disorder, and the perennial problem of 'winner's curse' (Zollner and Pritchard, 2007), which dictates that the initial report of a genetic association is likely to be an over-estimate of the true effect size. Two more manageable challenges have been controlling the likelihood of type I error, through stringent correction for multiple genetic and phenotypic comparisons, and of

type II error, by conducting studies with adequate statistical power to detect a realistic effect size. The use of meta-analysis can help overcome both of these problems (Munafo and Flint, 2004), but it nonetheless remains likely that the majority of published psychiatric genetic associations are in fact false (Ioannidis, 2005, Sullivan, 2007).

Genome-wide association studies (GWAS)

Genome-wide association studies offer a new way of finding susceptibility genes: instead of requiring researchers to pick candidates based on imperfect hypotheses, GWAS can agnostically generate new hypotheses, implicating novel biological systems, which would then be the basis for further research in BPD and, eventually, novel drug targets. This promise has become a reality in the past two years, as statistical and technological advances made large-scale GWAS feasible for the first time (see Table 2). Using DNA microarrays (“gene chip” technology), one can now survey common genetic variation across the entire genome by simultaneously assaying up to 1 million or more SNPs that directly or indirectly capture the full complement of common variants. This approach has already proven successful in identifying susceptibility alleles for a broad range of common complex disorders including diabetes, cardiovascular disease, inflammatory bowel disease, prostate and breast cancer, and growing list of others. While only a handful of risk alleles for complex disorders had been found prior to 2006, the tally of confirmed findings by late 2008 has already exceeded 100. The application of GWAS technology to BPD emerged in 2007 and has begun to bear fruit.

The first wave of BPD GWAS studies implicated several novel loci but did not achieve genomewide statistical significance (a threshold of $p < 5 \times 10^{-8}$ is often used to account for the fact that surveying common variants represents approximately 1 million independent tests). Baum and colleagues (Baum et al., 2008a) used pooled DNA in cases and controls of European descent to screen >550,000 SNPs, and then individually genotyped in a German replication sample only those SNPs which appeared promising in the first, pooled, analysis. Their top hit was for SNP rs1012053 in the first intron of *DGKH*, the gene encoding diacylglycerol kinase etc. In the combined test and replication samples the p-value for this SNP was 1.5×10^{-8} , with an allelic OR of 1.59. The *DGKH* gene is of interest because its product is involved in the phosphatidyl inositol pathway through which lithium may exert some of its mood stabilizing effects.

Another, larger GWAS for BPD was conducted as part of the UK Wellcome Trust Case Control Consortium (WTCCC) (2007) in a report on seven major diseases. In a sample of nearly 2000 cases and 3000 controls, the strongest result in the primary analysis was for a SNP (rs420259) on chromosome 16p12 which gave a genotypic p value of 6.3×10^{-8} , exceeding the pre-specified significance threshold of 5×10^{-7} , and an odds ratio of approximately 2.1 for both heterozygotes and homozygotes. This SNP falls in a region near several genes that might be plausible candidates for BPD including *PALB2* (involved in the stability of key nuclear structures including chromatin), *NDUFAB1* (which encodes a component of the mitochondrial respiratory chain), and *DCTN5* (which interacts with *DISC1*).

A third BPD GWAS included nearly 1500 cases (drawn from the multicenter STEP-BD study of BPD treatment and a sample from the University College London) and 2000 controls of European ancestry, testing approximately 370,000 SNPs (Sklar et al., 2008). None of the top hits from this STEP-UCL analysis were replicated in an independent family-based sample, though combining results with the WTCCC data yielded promising evidence for association with SNP rs1006737 in the third intron of *CACNA1C* on 12p13, which encodes the alpha-1C subunit of the L-type voltage-gated calcium channel.

Combining p-values or, better still, pooling raw genotypes across multiple samples has proven extremely powerful in detecting novel genetic associations in complex disease such as type II diabetes (Zeggini et al., 2008). Since it is likely that true positive findings have only a small chance of falling into the top p-values in a given GWAS, even when there is adequate power to detect them (Zaykin and Zhivotovsky, 2005), combined datasets may provide a more powerful way of homing in on disease genes. A meta-analysis combining data from the WTCCC (Wellcome Trust Case Control Consortium, 2007) and Baum et al. (Baum et al., 2008a) analyses, provided evidence implicating two additional genes, *JAM3* and *SLC39A3* (Baum et al., 2008b). The most robust statistical evidence thus far for BPD susceptibility variants emerged from a meta-analysis of the STEP-UCL and WTCCC GWAS studies. An additional 1098 cases and 1267 controls were added from the STEP-BD sample and samples from the University of Edinburgh and Trinity College Dublin (Ferreira et al., 2008). This combined dataset, comprising 4387 cases and 6209 controls, provided far greater statistical power than the previous studies, and was able to detect two association signals that meet conventional genome-wide criteria. Evidence for the *CACNA1C* gene, mentioned before, was strengthened, with the rs1006737 SNP now reaching genomewide levels of statistical significance ($p = 7 \times 10^{-8}$). A second, even stronger genomewide significant signal emerged for an intronic SNP (rs10994336) in the *ANKK3* gene on 10q21. *ANKK3* encodes the Ankyrin-G protein, a neuronal adaptor protein that regulates the assembly of voltage-gated sodium channels. The relevance of *CACNA1C* and *ANKK3* to BPD is supported by evidence that both are downregulated in mouse brain in response to lithium (McQuillin et al., 2007). These findings may represent the first unequivocal successes for GWAS in BPD. Much work is now necessary to move from these association signals to an understanding of the function and regulation of these genes, and more still, in turning that basic biological knowledge into targets for pharmaceutical or other intervention. In the meantime, further large datasets are being collected and genotyped and new BPD studies, with ever-larger samples and ever-improved statistical power are expected in the near future. A collaborative consortium, the Psychiatric GWAS Consortium (2008), has been formed in order to best use the large amounts of GWAS data currently being generated for BPD and other disorders, using methods including meta-analysis and cross-disease analysis.

At this point, however, two themes have already emerged from GWAS studies of BPD. First, the effect sizes of variants that demonstrate some degree of association are modest (with odds ratios < 1.4), suggesting that the genetic basis of BPD is likely to reflect polygenic effects of many genes of small effect. The highly polygenic nature of BPD means that identifying loci that account for the full heritable component of BPD will require extremely large sample sizes and may, in the limit, be unfeasible. Second, none of the traditional candidate genes nominated by prior biological hypotheses or by positional findings from linkage studies have demonstrated strong evidence of association in hypothesis-free genomewide studies. This phenomenon is not unique to BPD: confirmed loci emerging from GWAS studies of other medical disorders (including diabetes, autoimmune diseases, neoplastic diseases, and cardiovascular disease) have rarely included genes that were previously identified as candidates. Although this might seem discouraging, it underscores the power of the GWAS method to reveal novel pathogenic loci and biological pathways. Indeed, the two loci most strongly associated with BPD to date—*CACNA1C* and *ANKK3*—suggest the intriguing possibility that BPD is in part an ion channelopathy. This is not to say that GWAS studies have disproven a role for previous candidate genes. Given the growing evidence that BPD is highly polygenic, the “top hits” from a GWAS will not include all of the relevant loci. A larger set of variants (possibly including traditional candidates) may be contributing to disease risk despite falling below genomewide significance thresholds in a given GWAS.

Like other genetic designs, GWAS are suited to detecting a particular type of genetic effect, namely effects that are modest in size but where the risk allele is relatively common in the general population (Newton-Cheh and Hirschhorn, 2005). Compared with its success in other complex diseases, GWAS has not provided a panacea for psychiatric genetics, and the vast majority of genetic risk in BPD is yet to be explained. GWAS studies are designed only to detect the effects of common SNPs; it is likely that other types of genetic variation may provide complementary sources of information about genetic risk in BPD (Burmeister et al., 2008). Moreover, establishing an association is only the first step, and translating this knowledge into something of tangible benefit for patients the ultimate goal. As technological advance continues, methods such as large-scale genomic sequencing are becoming more widely available and affordable. Sequencing may prove extremely useful both as means of discovering new disease associations, especially those involving rare mutations, or areas of the genome not well covered by commercial microarrays, and also as a way of establishing or better characterizing the causative allele in a known association signal. Once a causative allele is established, the mechanism of the pathway from gene to disease can be explored using a variety of in vitro and in vivo techniques, including transgenic animal models.

Structural Variants: Another Source of Genetic Risk Factors for BPD?

Cytogenetic changes, large-scale chromosomal abnormalities including translocations, duplications and deletions, have identified a number of risk loci for serious psychiatric disorder. A balanced (1:11) chromosomal translocation which segregated in a Scottish family with schizophrenia and mood disorders led to the identification of DISC1 as a susceptibility gene for major mental illness (St Clair et al., 1990, Millar et al., 2000). Subsequent association studies have implicated a variety of markers on the DISC1 gene with schizophrenia and BPD (Hodgkinson et al., 2004, Palo et al., 2007, Hennah et al., 2008). Other translocations segregating with bipolar or psychotic illness have implicated additional genes including *GRIK4* and *NPAS3* (Pickard et al., 2006, Pickard et al., 2008a).

Deletions or duplications of a small part of a chromosome (in the range of 1 kb to several megabases (Mb)), may also play an important role in the aetiology of psychiatric disorder. These copy number variants (CNVs) include the well-known 1.5–3 Mb deletion on 22q11 that produces velo-cardio-facial syndrome (VCFS), one expression of which is a 25–30-fold increased risk for psychotic disorders (Murphy, 2002).

While the association between VCFS and disorders including schizophrenia and BPD has been long-established, very recent evidence has suggested at least two other regions (on chromosome 15q13 and 1q21) strongly implicated in schizophrenia (Stone et al., 2008). These results add to accruing evidence that CNVs that disrupt genes may be more common in individuals with schizophrenia than controls (Walsh et al., 2008), and that some of them are new mutations seen in the DNA of the affected individual but not in either parent (Xu et al., 2008). As yet there have been no large-scale scans on CNVs in BPD, and little is yet known about the role that individual CNVs may play (Wilson et al., 2006, Lachman et al., 2007, Lachman et al., 2008). It is plausible that CNV effects will be less important in BPD than in disorders with an established neurodevelopmental component, such as schizophrenia, and autism (Sebat et al., 2007, Weiss et al., 2008). On the other hand, recent evidence has indicated that advanced paternal age, a risk factor for de novo structural mutations, is associated with BPD risk (Frans et al., 2008). In a large population-based Swedish registry study, the risk of BPD was 37% higher among offspring of fathers 55 years and older compared to offspring of men age 20–24. The risk was particularly pronounced for early-onset BPD (onset age < 20 years) (OR = 2.63; 95%CI 1.19–5.81) (Frans et al., 2008).

Alternative Strategies for Identifying Genetic Risk Factors

How to take forward the search for genetic influences on BPD is a perennial question that continues to attract controversy. In common with other psychiatric disorders, there are no clinical diagnostic tests for BPD; as such it is likely that the phenotype of BPD is more heterogeneous and less accurately measured than medical disorders where biomarkers can be objectively measured and monitored. Some researchers argue that additional strategies will be needed to capture genetic influences on BPD (see Table 3).

A notable trend in psychiatric genetics has been the increasing use of intermediate, (or endo-) phenotypes; traits that are more proximal to the genetic substrate than are complex diagnostic categories. (Gottesman and Gould, 2003). Proposed endophenotypes in BPD include measures of cognitive function, personality, brain structure and function, neurophysiological parameters, circadian rhythm, and response to pharmacological challenge (Sobczak et al., 2002, Chiaroni et al., 2005, Hasler et al., 2006, Savitz and Ramesar, 2006, Arts et al., 2008, Thaker, 2008). These traits typically show lower heritabilities than the diagnosis of BPD, but might still prove useful in identifying susceptibility genes if they have a simpler genetic architecture that is more amenable to genetic dissection. So far no endophenotype studies have led to the unequivocal identification of susceptibility genes in BPD, but some successes in other psychiatric disorders (e.g. Leonard et al., 1998) suggest that the approach is promising.

One possible model for the genetic influences on BPD is that individual variants only affect risk if they occur in combination with other genetic or environmental risk factors. Gene-gene interactions (epistasis) may play a major role in the aetiology of complex human diseases, and some argue that attempts to unravel the genetic basis of such disorders will fail if epistasis is ignored (Frankel & Schork, 1996). Searching for epistatic effects at a genome-wide level is an ambitious goal that has so far met with limited success in BPD (Abou Jamra et al., 2007, Ferreira et al., 2008). In contrast, a burgeoning literature now exists suggesting possible gene-environment effects in psychiatric disorders (Caspi et al., 2002, Caspi et al., 2003). While these have not been universally replicated (Kim-Cohen et al., 2006, Zammit and Owen, 2006) such interactions allow testing of more plausible models of causation than those provided by single genes alone.

One environmental exposure which may of particular importance in BPD and other psychiatric disorders is illicit drug use. Drug use is itself subject to genetic influences (Tsuang et al., 1996, Kendler and Prescott, 1998), and exposure to alcohol, cannabis and other drugs is extremely common among patients with some psychiatric disorders (Regier et al., 1990, Barnett et al., 2007). A heated debate has surrounded the possible effects of cannabis on risk for schizophrenia (Arseneault et al., 2004) and though less is known about the effects of cannabis on risk for BPD (Henquet et al., 2006), drug use may an important source of environmental risk and gene-environment interactions for many disorders. For example, in one study, (Roiser et al., 2005), individuals with the short allele of the 5HTTP who were habitual 3,4-methylenedioxymethamphetamine (Ecstasy) users showed abnormal emotional processing and a tendency towards higher depression scores, when compared with other genotypes and with individuals who had not used Ecstasy.

Environmental risk factors may exert their effects at a molecular level through epigenetic modification of DNA or chromatin (Tsankova et al., 2007). Epigenetic mechanisms are stable and potentially heritable effects that do not involve a change in DNA sequence but can affect gene expression. Modification of gene expression by epigenetic mechanisms plays a crucial role in human brain development (Keverne et al., 1996) and may therefore be important in the genesis of many psychiatric disorders. Variations in DNA methylation have

been reported in post-mortem brains from patients with both schizophrenia and BPD (Benes et al., 2007, Mill et al., 2008), with some evidence for differentiation between the two disorders (Veldic et al., 2007). The association between advanced paternal age and BPD could be mediated in part by epigenetic mechanisms (Frans et al., 2008).

Genetics and the Definition of Bipolar Disorder

As noted at the start of this review, the history of genetic studies of BPD partly reflects the history of the diagnosis itself. The genetic studies described above largely relied on an evolving but categorical definition of BPD in order to test and generate hypotheses about its genetic basis. It may be worth considering the opposite question however: what can genetic studies us about the definition of BPD? Two obvious possibilities are that genetic studies may help us understand where the boundaries of BPD lie with respect to other psychiatric diseases, and that they may help us understand whether what we currently think of as BPD is indeed a single entity, or a collection of related disorders.

BPD has symptom overlap and substantial comorbidity with a range of other DSM-IV Axis I diagnoses, most notably other mood disorders such as major depressive disorder, and psychotic disorders such as schizophrenia and schizoaffective disorder. Family and twin studies on the whole support the hypothesis that there is overlap in genetic liability among these disorders. The first-degree relatives of individuals with BPD show not only increased risk for BPD, but also increased risk for unipolar depression (Gershon et al., 1975, Maier et al., 1993). Smoller & Finn (2003) estimate that the recurrence risk ratio for BPD in relatives of bipolar probands is around 4 (with an absolute risk of approximately 9%), while the recurrence risk ratio for unipolar depression among the relatives of bipolar probands is around 2 (and an absolute risk of approximately 15%). In contrast, the relative risk for BPD does not seem to be substantially elevated among relatives of individuals with unipolar depression (Smoller and Finn, 2003), though individual studies have varied somewhat in this respect. The overall picture is thus that some, but all, genetic influences appeared to be shared between unipolar and BPDs.

There is also increasing evidence of genetic overlap between BPD and schizophrenia (Bramon and Sham, 2001, Craddock et al., 2005, Lin and Mitchell, 2008). Increased rates of schizophrenia are seen among relatives of people with BPD (Valles et al., 2000, Mortensen et al., 2003), and increased risk for schizoaffective disorder is found among relatives of both schizophrenia and bipolar patients (Kendler and Gardner, 1997, Cardno et al., 2002, Mortensen et al., 2003). Several authors have highlighted regions which have shown linkage to both BPD and schizophrenia, including 6q21–25, 10p14, 13q32–34, 18p11 and 22q11–13 (Berrettini, 2000, Bramon and Sham, 2001, Smoller and Gardner-Schuster, 2007) although it is possible that these shared peaks are due to entirely separate genes, or indeed, just coincidence (Kendler, 2006). Similarly, several candidate genes have been associated with both schizophrenia and bipolar diagnoses (e.g. Hodgkinson et al., 2004, Funke et al., 2005, Green et al., 2005, Williams et al., 2006, Palo et al., 2007), leading some authors to suggest that psychosis may be a better phenotype for genetic studies than DSM diagnosis (Craddock and Owen, 2005, Owen et al., 2007).

Kendler (2006) warns against adopting a gene-centric view of psychiatric nosology, arguing that the effect sizes of individual genes are currently too modest to justify overthrowing other ways of defining the boundaries between disorders. Nevertheless, identifying genetic variants that have pleiotropic effects across disorders may reveal fundamental biologic mechanisms that could provide targets for novel and more broad-spectrum interventions. Genetic studies may also clarify whether DSM-IV BPD is a single entity. Family studies suggest that BPII disorder is somewhat genetically distinct from BPI: risks of BPII are

higher in relatives of BPII patients than in relatives of patients with BPI or unipolar depression (Gershon et al., 1982, Andreasen et al., 1987, Heun and Maier, 1993). Similarly, pediatric BPD may represent a genetically-distinct subtype that shares genetic risk with ADHD (Spencer et al., 2001), while genetic risk for BPD appears generally higher in families with earlier onset (Smoller and Finn, 2003).

Summary

BPD is one of the most highly heritable medical disorders. As such, it is clear that genetic variation accounts for most of the population risk of illness. However, it is also clear that the genetic etiology of BPD is complex and multifactorial. Until recently, efforts to identify specific susceptibility variants have been restricted to studies of biological and positional candidate genes. Given our incomplete understanding of the biological basis of BPD and the inconsistency of findings from linkage studies, it is not surprising that these studies have had limited success. Within the past 2 years, however, unbiased genomewide association analyses have been applied to increasingly large samples with promising results. Early findings have implicated previously unsuspected genes and biologic pathways (e.g. genes involved in neuronal ion channel function). The successful identification of risk loci for a growing range of medical disorders using GWAS methods justifies optimism that common risk variants for BPD will emerge in the near future. However, given that the disorder appears to be highly polygenic, success will require much larger samples than have typically been studied to date. In addition, because SNP-based GWAS methods are designed to detect common risk alleles, other methods (e.g. DNA sequencing to detect rare variants and genomewide analyses for rare CNVs) will be needed to account for susceptibility variants not well captured by GWAS. The recent formation of large international collaborative consortia should make these goals feasible. The dividend of such efforts is likely to be substantial. Currently available pharmacologic therapies for BPD are based on a small set of targets that were identified decades ago. The genetic dissection of BPD should permit the development of more specific and effective treatment options for this devastating disorder.

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Table 1

Summary of the Genetics of Bipolar Disorder

Population Risk	1–2%
Risk for 1 st degree relatives	9%
Recurrence Risk Ratio	7 - 10
MZ twin concordance	40–45%
Heritability	80–85%
Cytogenetic/CNV-associated region	22q11 *
Leading Linked Regions	6q, 8q, 13q, 22q
Leading Candidate Genes [#]	<i>BDNF, DAOA, DISC1, TPH2, SLC6A4</i>
Genes Implicated by GWAS	<i>DGKH, CACNA1C, ANK3</i>

* Velocardiofacial/DiGeorge syndrome microdeletion

[#] supported in independent studies or meta-analysis

CNV: Copy number variation

GWAS: Genomewide association studies

Table 2

Summary of results from individual GWAS and meta-analyses in bipolar disorder

Year	1 st author	Sample origin	Diagnostic Criteria	Genotyping Platform	Cases (n)	Controls (n)	Top SNP	Nearest gene	Chr	p
2007	WTCCC	UK	RDC BPD I, BPD II, schizoaffective bipolar type, manic disorder	Affymetrix 500K	1868	2938	rs420259	PALB2	16	6.3×10^{-8}
2008	Baum	US/Germany	DSM-IV BPD I	Illumina 550(pooled genotypes)	1233	1439	rs1012053	DGKH	13	1.5×10^{-8}
2008	Sklar	US/UK	DSM-IV/ICD-10 BPD I	Affymetrix 500K or 5.0	1461	2008	rs4939921	MYO3B	18	1.7×10^{-7}
2008	Ferreira	US/UK/Ireland	BPD I, BPD II	Affymetrix 5.0 or 6.0	1098	1267	rs7221510	SKAP1	17	1.4×10^{-6}
2008	Baum	Meta-analysis combining WTCCC & Baum (a) (individually genotyped SNPs)			3101	4377	rs10791345	JAM3	11	1×10^{-6}
							rs4806874	SLC39A3	19	5×10^{-6}
2008	Ferreira	Meta-analysis combining WTCCC, Sklar and Ferreira samples			4387	6209	rs10994336	ANK3	10	9.1×10^{-9}
							rs1006737	CACNA1C	12	7.0×10^{-8}

WTCCC: Wellcome Trust Case-Control Consortium; RDC: Research Diagnostic Criteria; BPD I: bipolar I disorder; BPD II: bipolar II disorder

Table 3**Strategies for Gene Discovery and Characterization**

Strategy	Hypothesis	Examples	Challenges
Collecting larger samples and meta-analysis	Increasing sample size will enable detection of many more genuine risk alleles	Psychiatric GWAS Consortium (PGC): international effort to combine GWAS datasets including more than 7000 BPD cases and 10,000 controls (2008).	# of samples in the world is limited; meta-analysis may increase genetic and phenotypic heterogeneity
Endophenotypes	Genetic effects on intermediate phenotypes may be larger, or simpler, than those on clinically-diagnosed disorders.	Neurophysiologic abnormalities (e.g. P50, P300 event-related potentials in psychotic bipolar disorder (Hall et al., 2009))	Often more complex and costly to phenotype; few validated endophenotypes for BD exist
Phenotypic subtyping	Subtypes of DSM-IV BPD may be more genetically homogenous	Putative subtypes include: psychotic BPD, early-onset, lithium-responsive, rapid-cycling and others	Splitting sample may compromise power
Explore phenotype spectrum	Effects of risk alleles may transcend diagnostic categories	Meta-analysis indicates <i>ZNF804A</i> influences broad phenotype encompassing schizophrenia and BPD (O'Donovan et al., 2008)	Increasing phenotypic heterogeneity may add noise
Studying structural variation	Structural variants, including CNVs, may contribute to genetic basis of BPD	Rare CNVs implicated in autism (Weiss et al., 2008) and schizophrenia (Stone et al., 2008); recent evidence suggests increased CNV burden in BPD (Zhang et al., 2008)	Very large samples required to detect rare structural variants
Deep resequencing	Genetic risk for BPD may involve rare mutations or SNPs not covered by commercial microarrays	None to date	Costly at present; technology still developing
Epigenetic analyses	Genetic risk may involve epigenetic modulation of gene expression	DNA methylation changes observed in postmortem frontal cortex from patients with schizophrenia and BPD (Mill et al., 2008)	Availability of relevant brain tissue; methods for epigenomic profiling not yet mature
Functional genomics	Phenotypic effects may reflect altered transcription, translation, or protein-protein interactions	Preliminary results now emerging (Le-Niculescu et al., 2009)	Availability of relevant tissues; replicability of gene and protein expression profiles
Animal Models	Characterization of risk genes can be facilitated by experimental animal models	<i>Clock</i> mutant mice exhibit mania-like phenotype (Roybal et al., 2007)	Modeling complex BPD phenotype is difficult in animals