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Genetic approaches to a better understanding of bipolar disorder

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ABSTRACT

Bipolar disorder is a disease which causes major disability. The disease has both a manic and depressive component. Current standard of care consists of atypical antipsychotics for the treatment of mania, antidepressants for the treatment of depression, and mood stabilizers for the maintenance of euthymia. The molecular mechanisms which cause the disease are not well understood. Genome wide association studies have provided a set of genes which are linked to the disease. These genes show linkage to physiological and neuroanatomical alterations which are also seen in bipolar disorder.

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1. Introduction

Many of the recent advances in understanding bipolar disorder have come from the intersection of medicine with molecular genetics and the human genome project. Work has begun to define the genetic basis for the disorder, and which genes are associated with the disease. This work will help to define the molecular mechanisms that underlie bipolar disorder, and help to provide new therapeutics for the disease. This review will discuss recent results in genome-wide association studies (GWAS) of bipolar disease, and how the relevant findings may be related to human physiology.

Bipolar disorder is an affective disease in which the patient cycles between bouts of mania and depression. The disease manifests in a patient's late teens to twenties, and most patients present in the depressed state (Goodwin & Jamison, 2007).

The disease is often misdiagnosed as unipolar depression. In order to be diagnosed as bipolar disease, a patient must have a history of at least one episode of mania. The prevalence of the disease is thought to be around 1% of the population, though due to the problem of misdiagnosis, the prevalence may be higher (Hirschfeld & Vornik, 2005; Perlis, 2005; Goodwin & Jamison, 2007; Angst et al., 2010).

Longitudinal studies show that the depressed phase is the preponderant one (Judd et al., 2002). Since depressed patients generally seek treatment for depression, they are often prescribed antidepressants which may be ineffective. When a patient develops mania, a diagnosis of bipolar disease is made, and treatment is adjusted (Goodwin and Jamison, 2007).

Treatment of bipolar disease can be complicated. Atypical antipsychotics are used to treat mania, both mild and severe (Perlis et al., 2006; Goodwin & Jamison, 2007). Antidepressants are of questionable utility, but are often prescribed (Gijsman et al., 2004; Sachs et al., 2007). There is a general reluctance to treat bipolar patients with antidepressants due to the perception that antidepressants can switch depressed patients into a manic episode, though there is a considerable controversy around this point (Gijsman et al., 2004; Post et al., 2006; Grunze, 2008; Perlis et al., 2010). Atypical antipsychotics like quetiapine are beginning to be used for bipolar depression (Tohen et al., 2003; Gao et al., 2005).

Mood stabilizers are compounds which are used to maintain euthymia in patients by preventing patients from entering a manic

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or depressed state (Muzina et al., 2005). Mood stabilizers are often prescribed along with antidepressants to prevent switching.

Mood stabilizers come from different classes of compounds, but fall into a couple of classes. Anticonvulsants such as lamotrigine, carbamazepine, or valproic acid are often used (Muzina et al., 2005). There are some data that indicate that lamotrigine has antidepressant activities, but this is not clear (Calabrese et al., 2008; Geddes et al., 2009). Lithium has been used as a mood stabilizer since the late 1940s, and is very effective. Due to lithium having a therapeutic index very close to 1, lithium is very difficult to use (Goodwin & Jamison, 2007). Because of its unique efficacy in bipolar disease, and the fact that the mechanism whereby it exerts its effect is unknown, several different activities of the drug are being studied in an effort to use those activities to better understand bipolar disease (Rapoport et al., 2009; Squassina et al., 2010).

2. Genetic results in bipolar disease

While bipolar disease is currently served by a wide number of different drugs, including atypical antipsychotics, antidepressants, and mood stabilizers, there is a high unmet medical need in this disease. Drugs currently used for treatment were developed for other indications and do not treat the entire set of domains of the disease (mania, depression, mood stability). Thus, there has been active research in the area of bipolar disease over the last 10 years to identify more efficacious treatment with a better side-effect profile. However, in the absence of an understanding of the etiology of the disease, the progress has been slow. Recent work in the genetics of bipolar disease is beginning to provide insights into molecular mechanisms and is providing exciting prospects for understanding the disease and developing new therapeutics.

Heritability in bipolar disease is high. In a study of monozygotic and dizygotic twins, there is a very high concordance for bipolar disorder in monozygotic twins (75%), and a lower concordance for dizygotic twins (10.5%) (Kieseppa et al., 2004). This compares with an earlier study showing 67% concordance in monozygotic twins and 19% in dizygotic twins (McGuffin et al., 2003) and both of these studies looked at a relatively small number of patients. The Maudsley Twin study broke patients out into mania, hypomania, and depressive psychosis. For each of these, concordance rates were higher for monozygotic twins (44% for mania and hypomania), and a lower concordance of 9.1% in dizygotic twins (Cardno et al., 1999). This difference in concordance between monozygotic twins, which share identical genomes, and dizygotic twins is strong evidence of genetic links (Table 1).

That the concordance between monozygotic twins is not 100% is an indication that the phenotype being studied (bipolar disease) is not exclusively determined genetically. The disease has components which are not dependent on the genetic makeup of the individual patient, but is also contributed to by other factors such as environment (Boomsma et al., 2002).

There have been many attempts to identify genes linked to bipolar disease using standard linkage analysis and association studies (Law et al., 1992; De bruyn et al., 1996). While genes have been identified using this approach, the linkage is generally not a strong one and few of these studies have been replicated using independent groups of patients, nor are the study sizes large enough to provide the statistical power to detect low abundance alleles that might be linked to bipolar disorder.

Table 1
Concordance of bipolar disease in monozygotic and dizygotic twin pairs.

Study	Monozygotic concordance	Dizygotic concordance
McGuffin et al., 2003	67%	19%
Kieseppa et al., 2004	75%	10.5%
Cardno et al., 1999	44%	9.1%

3. GWAS to the rescue

Human genetic techniques have become much more powerful with the determination of the sequence of the human genome (T. I. H. Consortium, 2003). Sequencing of the genome allowed the identification of common single nucleotide polymorphisms (SNPs) in humans. The HapMap project used these data to identify sets of SNPs that could be used to genotype humans and generate high-resolution maps, (T. I. H. Consortium, 2003) making it possible to put together genetic maps for human traits. Alongside these developments came the ability to perform high throughput, high speed genotyping, which made it possible to fully genotype patients, with coverage across the entire genome, and to do this quickly. This allowed large sample sizes to be analyzed, and ushered in the era of the Genome Wide Association Study (GWAS) (Corvin et al., 2010).

A complete description of GWAS is beyond the scope of this review. However, there have been several recent reviews that discuss this technology, including some that focus on the utility of GWAS in understanding psychiatric disease (Committee, 2008; Corvin et al., 2010). High throughput genotyping on large numbers of patients is expensive, and so large consortia have been formed to provide funding, and also to provide the large number of patient samples needed to achieve the appropriate power. These consortia also allow comparisons between different disease populations, providing insights into possible commonalities between different psychiatric conditions including depression, bipolar disease, and schizophrenia (Committee, 2008). The number of different SNPs that are associated with a disease also provides information on how polygenic a disease may be (T. I. S. Consortium, 2009).

Success in GWAS is based on the common variant, common disease hypothesis (Goldstein, 2009; Manolio, 2010). This hypothesis asserts that in a patient population, if a disease has a genetic component, there will be common variant alleles among individuals in that population. In other words, if allele X is associated with a disease in many individuals, it will also be associated with the disease in a given individual patient. Some of these variants will be causative for the disease. Each of these variants is thought to contribute small effects, but in combination with other genes there will be a large effect seen. In general, given current technologies and sample sizes, psychiatric GWAS are powered to detect variant alleles that are present at 5% to 10% (Goldstein, 2009).

There are technical and statistical issues that need to be considered when interpreting GWAS results. The first consideration is understanding when a result is significant. With up to a million SNPs being analyzed in a GWAS, multiple testing correction is very important. This presents interesting challenges, but in general a SNP is considered to be significantly associated with a disease with a $\underline{p}$ value $< 1 \times 10^{-8}$. GWAS studies are done as case control studies in which a patient population is compared with a control population (Corvin et al., 2010). Due to the difficulty of identifying psychiatric patients compared with individuals with easily observable traits such as obesity or height, the results from psychiatric GWAS require much larger sample sizes.

4. Results from Bipolar Disorder GWAS identify CACNA1C, ANK3 and ZNF804A as containing alleles associated with a risk of psychotic disease

In an early bipolar disease GWAS, a set of 461 bipolar I patients of European Caucasian background was used. These were obtained from NIMH (Baum et al., 2007). The control set consisted of 563 healthy volunteers. A replication sample was assembled from 772 bipolar I patients in Germany who had been hospitalized, matched with 876 control samples. All patients met DSMIV criteria for bipolar I. In order to lower the cost of genotyping, DNA samples from both patients and controls were pooled. The pools consisted of 50–80 individuals. For the NIMH samples, 7 case pools and 9 control pools were generated. Each pool was genotyped with slightly over 500,000 SNPs. For the replication samples, 13 case pools and 10 control pools were generated, each