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The genetic basis of bipolar disorder

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Abstract

Bipolar disorder has long been known to have a strong genetic component, with heritability estimates ranging between 80–90%. However, major breakthroughs on the molecular genetic level have remained elusive. Linkage and candidate gene association studies produced a host of reports, but failed to deliver consistently replicable results. This may in part be attributed to limited sample sizes and high degrees of phenotypic and genotypic heterogeneity. The advent of genome-wide association studies (GWAS) has spurred new hopes for the identification of true susceptibility genes. After close to a century of genetic studies, bipolar disorder is emerging as a complex (non-Mendelian) disorder with a polygenic etiology. The search for common genetic variants with small effects by GWAS will probably have to be complemented by approaches that can detect rare genetic variations with larger effects, such as copy number variants. Progress would be much enhanced by improved phenotype definitions that reduce genetic heterogeneity.

Introduction

In this chapter, we attempt to review some of the basic principles underlying advances in our understanding of the genetic basis of bipolar disorder. We take advantage of a large body of published work that has already thoroughly reviewed family, twin, and adoption studies as well as genetic linkage and candidate gene-association studies of bipolar disorder and related conditions [1–15]. Interested readers are referred to these reviews for many of the details that we will merely summarize here. Our main goal is to broadly describe the progress of this field, and how we can use the knowledge gained over the course of the past century of research as the field attempts to master novel molecular and analytical techniques in the quest to unravel the genetic basis of bipolar disorder.

Genetic epidemiology: The first 100 years

Bipolar disorder is a highly heritable illness. This means that the majority of the individual variation in risk can be explained by genes. This has been a very

consistent finding over more than a century of research, despite differences in study populations, case definitions, and analysis methods (for review see [16]).

Early 20th century research demonstrated through systematic studies that bipolar disorder (and other mental illnesses) aggregates in families (reviewed in [17, 18]). Whereas the lifetime prevalence in the general population is around 1–2% (or higher, depending on whether broad or narrow phenotype definitions are used), multiple studies have reported that the lifetime risk for bipolar disorder in first-degree relatives of a patient with the illness is increased 10 to 20-fold.

Twin studies, published between 1930 and 2003 [19–22] have consistently supported the high heritability of bipolar disorder. Heritability estimates for bipolar disorder range between 80–90%. Two systematic adoption studies in bipolar disorder [23, 24], while performed in comparatively small samples, further support the notion that genetic factors contribute substantially more to the etiology of bipolar disorder than environmental factors.

Family studies are also an excellent way to define the range of clinical manifestations of underlying risk genotypes. Classically, probands are ascertained and diagnosed without regard to family history, and then their first- and (if available) second-degree relatives are systematically assessed for the presence of traits of interest. The best-known such studies in bipolar disorder were published in the 1980s [25, 26]. These studies showed that bipolar disorder, as well as unipolar (major depressive) disorder, dysthymia, cyclothymia, schizoaffective bipolar disorder, alcoholism, and anxiety disorders, were all increased among the first-degree relatives of probands with bipolar disorder. On the other hand, schizophrenia and other non-affective psychotic illnesses were not found to be increased in most studies. These data are generally interpreted as supporting the existence of a spectrum of bipolar-related conditions that are distinct from schizophrenia; however, some have challenged this conclusion [27].

The clear findings from classical family studies have not been matched by similarly clear findings in studies of the patterns of disease transmission in families. While some segregation analyses have supported a single major locus (Mendelian) model, most studies have been unable to exclude polygenic or multifactorial models. This probably reflects inherent limitations of the methods of segregation analysis to handle heterogeneity and complex modes of inheritance. This is further complicated by evidence that families of probands with bipolar disorder are characterized by assortative mating [28], genetic anticipation [29], and parent of origin effects that may reflect genomic imprinting [30], mitochondrial inheritance [31], or other factors.

Gene mapping

Genetic epidemiology provided compelling evidence that genetic factors play the major role in the etiology of bipolar disorder, and laid the foundation for

future studies. However, the methods of genetic epidemiology cannot identify the genes involved or pinpoint the genetic variation that explains the high heritability of bipolar disorder. This task requires a method of genetic mapping, and the advent of genetic linkage studies in humans seemed to fit the bill.

The phenomenon of genetic linkage was first described by Thomas Hunt Morgan in his studies of fruit flies. He found that certain traits, such as eye color and wing shape, did not assort independently, in apparent violation of Mendel's Second Law. Instead, they tended to be inherited together from generation to generation in a probabilistic fashion. Morgan's insight was that this apparent linkage between traits actually reflected a physical proximity of the responsible genes on the same chromosome. The further apart that two genes lie on a chromosome, the more likely they are to be separated by recombination during meiosis. In fact, despite conformational forces that make two recombination events on the same chromosome arm very unlikely, the relative position of two genes on a chromosome can be reliably inferred by the frequency with which traits encoded by those genes run together across the generations. To this day, the Morgan (and its 100th part, the centimorgan) remains the standard unit of genetic distance, in honor of Morgan's seminal work.

At first, the application of Morgan's principles to humans proved challenging. Outward traits can be difficult to measure, and the limited observational space of human pedigrees made linkage difficult to establish, except in unusual situations such as chromosome X-linked traits. Not long after the Nobel prize-winning discovery of restriction enzymes by Arber, Nathans and Smith in 1978, it was discovered that these DNA-slicing proteins sometimes failed to make the cut, reflecting single base-pair differences in the DNA sequence, and resulting in DNA restriction fragments that varied in size between individuals. The era of the restriction fragment-length polymorphism (RFLP) was thus born. In 1980, Botstein and colleagues proposed that RFLPs could be used to map genes by linkage even in the human genome [32]. Their prediction was soon proven true, with the mapping of markers linked to cystic fibrosis [33, 34], Huntington's Disease [35], and bipolar disorder [36].

The former two genetic linkages were quickly confirmed, and disease-causing mutations identified. But the latter was not, and was soon retracted [37]. This false start foretold much of what would follow in the ensuing decade of genetic linkage studies of bipolar disorder. It also embodied many of the difficulties – genetic heterogeneity, small effect sizes, and non-Mendelian inheritance patterns – that would by the 1990s come to be seen as the key characteristics of all complex genetic conditions like bipolar disorder, type II diabetes, and cardiovascular disease.

In the early days of this molecular era of bipolar genetic research, researchers' moods would very often switch between exuberance and disappointment as linkage findings were reported – sometimes with great fanfare – only to fail to find support in subsequent studies [38]. The problems that these early linkage studies had to confront were manifold: small sample sizes, par-

tially informative sets of genetic markers, and statistical methods that were originally designed for Mendelian disorders with monogenic inheritance, where the mode of inheritance, penetrance, and the clinically unaffected status of probands' relatives can be specified reliably. With the advent of larger, multi-center studies, the availability of denser sets of more informative markers, and the use of non-parametric linkage algorithms (e.g., affected sib pair design), many of these problems could be alleviated.

Yet, robust linkage findings remained elusive. 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 bipolar disorder [39]. Since then, many genetic linkage signals have been detected, several of which – one on essentially every chromosome but Y – have been identified by more than one study. Yet definitive findings have remained elusive. Three meta-analyses of linkage studies of bipolar disorder have been published [40–42]. While providing support for loci on chromosomes 6q, 8q, 13q, 18q, and 22q, each study tended to highlight non-overlapping sets of loci. In 2003, during a meeting celebrating the 50th anniversary of the discovery of the double helix, Eric Lander lamented that linkage studies had become "mumbo jumbo". We were thus stating the obvious when we wrote in early 2007 that "the passing of the linkage era would not be widely mourned" [43].

Linkage analysis is now no longer seen as a powerful tool to pinpoint susceptibility genes for complex traits and diseases. While many of the reported linkage regions may ultimately be found to harbor risk alleles, the genetic (or locus) heterogeneity of bipolar disorder may be so high that it defeats the ability of linkage analysis to separate true findings from a large number of false positives, even with very large sample sizes. Nevertheless, incorporating the information gained from linkage studies into future analyses and continuing to collect and phenotypically characterize multiply-affected families might still prove very valuable [44, 45].

Positional cloning efforts by means of candidate-gene association mapping have made some headway, but with little consensus around the main findings. Several studies, in particular systematic linkage disequilibrium mapping (LD) in linkage regions and large-scale candidate gene studies, have identified potential susceptibility genes for bipolar disorder [3, 6, 7, 15], but results remain inconsistent across studies. While corroboration at the gene level has been reached for some of these genes (Tab. 1), replications at the allelic level, i.e., association with the identical allele of a particular single nucleotide polymorphism (SNP) across studies, are rare [46].

Moving into the next 100 years

As with genetic research in other complex disorders, the genetics of bipolar disorder entered the 21st century against the backdrop of important developments in human genetics. These included the publication of the sequence of

Table 1 Promising candidate genes for bipolar disorder

Gene	Symbol	Key polymorphisms	Individual association studies or meta-analyses (MA)	Evidence
Serotonin transporter	*SLC6A3*	LPR	Anguelova et al 2003 (MA) [101]	+++
D-amino acid oxidase activator (G72)	*DAOA*	Various	Detera-Wadleigh and McMahon 2006 (MA) [46]	+++
Disrupted-in-schizophrenia-1	*DISC1*	Various	Hodgkinson et al. 2004; Thomson et al. 2005; WTCCC 2007; Perlis et al. 2008 [53, 104–106]	++
Tryptophan hydroxilase 2	*TPH2*	Various	Harvey et al. 2004; Van den Bogaert et al. 2006; Lopez et al. 2007; Harvey et al. 2007; Cichon et al. 2007 [107–111]	++
Brain-derived neurotrophic factor	*BDNF*	Val/Met	Kanazawa et al 2007 (MA); Fan and Sklar 2008 (MA) [102, 103]	+
Aryl hydrocarbon receptor nuclear translocator-like	*ARNTL (heterodimer with CLOCK)*	Various	Mansour et al. 2006; Nievergelt et al. 2006 [112, 113]	+
Cadherin gene (homolog of the Drosophila tumor suppressor gene *fat*)	*FAT*	Various	Blair et al. 2006; Abou Jamra et al. 2008 [114, 115]	+

+ supported by 2 studies or evidence quite mixed
++ supported by several studies
+++ supported by meta-analysis of three or more samples

the human genome [47, 48], the completion of the HapMap project (www.hapmap.org; [49]), and the advent of DNA microchip technology. These landmark developments have virtually eradicated one major impediment in complex genetic research: technical feasibility. Now, financial resources allowing, several thousand samples can be genotyped with several hundred thousand genetic markers or sequenced over hundreds of megbases in a small fraction of the time that such an endeavor would have taken just a few years ago. Genome-wide association studies (GWAS), large-scale surveys of copy number variation, and large-scale resequencing studies are all early products of these technological developments. Although it is impossible to predict the future, it is already clear that GWAS have opened new windows into the genetic architecture of common complex disorders such as age-related macular degeneration, type II diabetes, and cardiovascular disease.

Genome-wide association studies

There are probably about 10,000,000 SNPs in the human genome. Previous case-control association studies could assay only a fraction of this important source of genetic variation. In a GWAS, several hundred thousand SNPs are rapidly scanned across the complete genome of a large number of case and control individuals (or, less commonly, case-parent trios). SNPs are selected on the basis of informativeness, without a specific prior hypothesis of etiological involvement in disease; thus GWAS are commonly referred to as 'hypothesis-free' studies.

GWAS have now been performed for several complex phenotypes, such as type I and type II diabetes [50–53], obesity [54], coronary heart disease [53, 55, 56], hypertension [53], rheumatoid arthritis [53], age-related macular degeneration [57, 58], Crohn's disease [53, 59, 60], prostate cancer [61, 62], and bipolar disorder [53, 63, 64]. At the time of this writing, within the Genetic Association Information Network (GAIN), further large-scale studies on kidney disease in type I diabetes, psoriasis, attention deficit/hyperactivity disorder, schizophrenia, and bipolar disorder are underway (http://www.fnih.org/GAIN2/home_new.shtml).

Although these GWAS cover a wide range of disease phenotypes, some overall conclusions can be drawn (for a review, see [65]). First, and most importantly, GWAS methods can re-energize gene-mapping efforts even in diseases that have suffered long stretches of stalled progress. This may best be illustrated by the case for Type II diabetes, where several novel and some previously implicated genes could be detected and unambiguously replicated at the allele level across several samples [66]. Second, the implicated genes often challenge our limited etio-pathological reasoning by implicating novel pathways to disease. For example, the identification of *ATG16L1* (a gene involved in the autophagosome pathway processing intracellular bacteria) as a susceptibility gene for Crohn's disease, offers intriguing fresh insights into the pathophysiological mechanisms of this disorder. Third, GWAS may point to variation lying in 'gene deserts' that would never have been considered by candidate gene studies, but that evidently play an important regulatory role. This is illustrated by chromosome 9p's association with cardiovascular disease. Fourth, GWAS have revealed that many complex disorders, while highly heritable, are actually the product of many genes with small individual effects that, together, increase risk of disease, similar to the classical polygenic threshold model [67].

At the time of this writing, three GWAS of bipolar disorder have been published. Although robust, unambiguously replicated findings have yet to emerge at this early stage, it seems clear that at least a part of the common genetic architecture of bipolar disorder will ultimately be revealed by GWAS methods. Some of the key bipolar disorder GWAS findings to date are summarized in Table 2.

However, in the same way that many psychiatric disorders have been more difficult to explore via linkage and candidate gene association studies than

Table 2 Published genome-wide association studies of bipolar disorder

Study	Cases : controls	Internal replication	Platform	Key findings	Gene overlaps	References
Baum et al. 2007	1233 : 1439	Yes	Illumina HumanHap550	DGKH ($p < 10–7$), among 88 replicated associations in 80 distinct genes	DFNB31 (WTCCC & Sklar); GRM7, JAM3, SLC39A3 (WTCCC); ANK3 (Sklar)	[63, 116]
WTCCC 2007	1838 : 2938	No	Affymetrix 500K	16p12, KCNC2, DFNB31, GABRB1, GRM7, among 14 hits at the $p < 10–5$ level	DFNB31 (Baum & Sklar); GRM7, JAM3, SLC39A3 (Baum); CACNA1A (Sklar)	[53]
Sklar et al. 2008	1000 : 1000	No	Affymetrix 500K	CACNA1A, TMEM, among 6 hits at the $p < 10–5$ level	DFNB31 (Baum, WTCCC); ANK3 (Baum); CACNA1A (WTCCC)	[64]

somatic disorders, bipolar disorder may hold some unique challenges for the GWAS approach. GWAS methods are not well-powered to detect uncommon alleles, and rare alleles may be missed entirely, unless they confer a very large risk of disease. Furthermore, some common disorders are related to many hundreds of alleles, each of small effect. GWAS methods alone cannot tell the whole story of truly polygenic disorders, because effect sizes much below 5% of the variance cannot be detected one locus at a time, even if the alleles are common.

Reconciling the polygenic nature of bipolar disorder and family recurrence risks: filling the risk gap

While it can be difficult to *dis*prove, the polygenic threshold model still offers the best overall fit to the existing family, linkage, and association findings for bipolar disorder. Polygenic disorders cluster in families and may be highly heritable, but in contrast to monogenic disorders do not show simple inheritance patterns. Classically, risk for disease is spread over many dozens – or hundreds – of distinct genes, each of which confers only a small part of the total risk for disease. Each person's disease risk is influenced by the total burden of risk alleles they carry, with fewer alleles conferring lower, and more alleles conferring greater, risk. Disease occurs when the allele burden crosses some threshold, although the exact disease threshold for a given person may be influenced by non-genetic factors.

The common disease/common variant (CDCV) hypothesis is a more modern theory than the polygenic threshold model, but the models have many similarities. Under the CDCV, human genetic variation is assumed to be relatively simple and finite, with only a few common haplotypes at each locus maintained in the population at one time. Risk for common diseases is postulated to result from common alleles and haplotypes at one or more loci.

While compelling and supported by findings in some common diseases, the CDCV hypothesis has repeatedly been challenged by an alternative theory whereby a large set of individually rare, high-risk alleles – each present in one or a few individuals – are thought to play the major role in risk for disease [68–71]. Individually rare, these alleles are proposed to occur in so many different genes that they can, together, account even for a common disease. Early results from studies of autism [45, 72] and schizophrenia [73, 74] suggest that the rare allele model may indeed have some explanatory power in the genetic basis of mental illness, but compelling rare-allele findings have not yet appeared for bipolar disorder.

Existing findings in bipolar disorder seem to point toward many alleles of small effect. But if this were the whole story, it is not clear how the relatively high recurrence rates in first-degree relatives (on the order of 10–15% [25]) could be explained. The true genetic architecture of common diseases like bipolar disorder probably encompasses both common alleles that alone confer

small risk (odds ratios 1.1–1.5), and uncommon or rare alleles (including copy number variants) that confer larger risks in a few people or families. From this perspective, it also seems likely that alleles will be found that shape the clinical picture and response to treatment. This idea will be developed further in the next section.

Alleles that shape the clinical picture: the bipolar phenome

Bipolar disorder as currently defined in the standard diagnostic manuals (DSM-IV and ICD 10) is a highly reliable but clinically variable entity. Most of the genetic work in bipolar disorder has focused on genes that contribute to the broader phenotype, but is not clear that such genes, if found, will be able to explain the clinical variability in terms of age at onset, symptoms, chronicity, co-morbidity, and treatment response that is a hallmark of the bipolar diagnosis. Without an operational diagnosis, large collaborative linkage and association studies of bipolar disorder would not have been possible, since case definitions would have varied too much from center to center. Diagnostic entities in psychiatry are still mainly constructs, without a well-defined shared biology. Correspondences between genotype and phenotype, when they finally emerge in psychiatry, are unlikely to show a close resemblance to our current diagnostic systems.

For example, several recent findings suggest a genetic overlap between schizophrenia and bipolar disorder [75, 76]. If true, these findings would challenge the assumption that the century-old Kraepelinian dichotomy between schizophrenia and mood disorders has a solid genetic basis. Indeed, some have called for abandoning this dichotomy in favor of an approach based on severity and course of illness, which accounts for developmental aspects that may better correspond to the underlying biology [77]. On the other hand, there are many examples of diseases with distinct symptoms, course, and treatment that share genetic risk factors. The B27 haplotype of the human leukocyte antigen (HLA) locus is a very strong risk factor for ankylosing spondylitis, anterior uveitis, and Reiter Syndrome, but each of these autoimmune diseases affects a different organ system, produces specific signs and symptoms, and responds best to specific treatments (reviewed in [78]). It is possible that alleles exist that increase risk for psychopathology in a fairly general way, with other alleles or non-genetic factors influencing precise clinical presentation.

Some studies have indeed found evidence of specific loci influencing symptomatology [75, 79–81], age at onset [82, 83], and clinical course [84] in bipolar disorder. If verified, such loci may help explain the variable clinical picture of bipolar disorder. More importantly, they may reveal aspects of pathophysiology that are good targets for novel treatments or preventive therapies.

If alleles exist that influence the clinical picture of bipolar disorder, how can we find them? Genetic linkage and candidate gene studies are two approaches, but still have the same limitations discussed above. GWAS data may be a

particularly good source of candidate alleles, but the problems of sample size, multiple testing, heterogeneity, and ascertainment bias inherent to all GWAS are that much more acute when the focus is on individual elements of the clinical picture. One approach is to use genetic markers to define phenotypic groupings that are distinguished by higher rates of allele-sharing (linkage data) or more deviant allele frequencies (association data) than are seen in traditional diagnostic categories (Fig. 1). We have called this approach 'reverse phenotyping' [14]. While replication testing is vital, reverse phenotyping has already shown promise as an approach to elucidating the genetics of bipolar disorder [75, 80, 85] and other complex phenotypes [86].

In addition to replication, a key issue in reverse phenotyping is the careful selection of traits to be studied. Many researchers favor traits that have shown a high degree of heritability or familiality. In bipolar disorder, this list includes several variables. Among these, psychosis, history of suicide attempts, alcoholism, substance abuse, OCD, level of social functioning, missing work due to mood disorder, number of manic episodes, episode frequency, and polarity of onset have all been the subjects of recent interest [79, 84, 87, 88].

Effective reverse phenotyping also requires access to large, well-characterized samples. While these are far from abundant, the field now has more suitable samples available than ever before. For example, the *Bipolar Phenome Database* [87] contains 197 clinical variables on 5,721 subjects in 1,177 families; DNA is available for 5,373 subjects. The Wellcome Trust Case Control

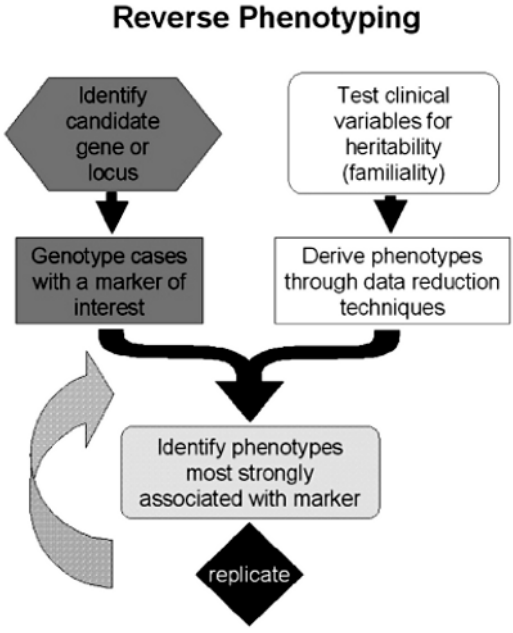

Figure 1. Reverse phenotyping.

Consortium (WTCCC) [53] and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) collaboration each have over 1,000 well-characterized cases with DNA, most of which is available to the public upon approval of a simple application form.

One fundamental question concerns the subphenotype structure (Fig. 2) we expect to find. Does bipolar disorder actually consist of subphenotypes that neatly present as clusters with only marginal overlap between them and other disorders? Or does the polygenic nature of bipolar disorder create an ill-defined multidimensional distribution of phenotypes – a 'phene space' – that cannot be easily cut into clusters but rather presents with poles enriched for specific phenotypic features? The statistical tools we want to use for pheno-

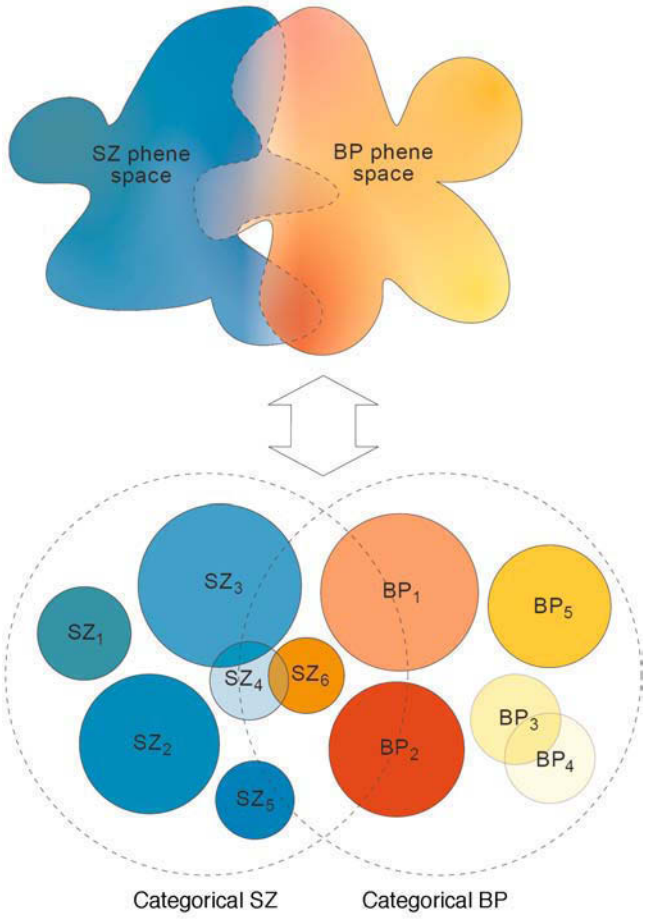

Figure 2. The subphenotype concept of psychiatric disorders. Schizophrenia (SZ) and bipolar disorder (BP) may comprise neatly clustering subphenotypes (indicated by circles and subscripts), or represent different points on an ill-defined multidimenisonal distribution of phenotypes, enriched for specific clinical features (indicated by smooth transitions of colors).

type refinement in bipolar disorder will need to be able to accommodate these different scenarios and modifications.

The field of pharmacogenetics has evolved within the past 40 years from a niche discipline to a major driving force in clinical pharmacology, and it is currently one of the most actively pursued disciplines in applied biomedical research in general, as Brockmöller and Tzvetkov put it [89]. Whereas genetic information may already be useful in identifying individual cases of poor or fast metabolism, the use of pharmacogenetic knowledge to predict actual outcome and truly individualize treatment is only just becoming feasible [90]. Recently, genetic studies from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) cohort on major depression have highlighted several markers associated with outcome and adverse events with citalopram treatment [91–94]. If replicated, findings such as these may ultimately prove to have considerable clinical utility.

In future phenotype refinement strategies, measures of treatment response and adverse events should be included alongside other variables. In bipolar disorder for instance, lithium response may be considered a prime phenotype [95, 96]. Sample size, however, will be the crucial issue. So far, pharmacogenetic studies of lithium response are characterized by small samples with a corresponding lack of statistical power [97–100]. International consortia and standardized phenotype characterization across centers are clearly needed for pharmacogenetic studies of lithium response or other measures of outcome in bipolar disorder.

Future frontiers

As we begin to accumulate data that may clarify genetic risk factors for bipolar disorder, questions have begun to accumulate. How much of a role will epigenetic factors play? How does SNP or CNV variation affect gene function? How do we best translate from a genetic association finding to a deeper understanding of disease biology and treatment? These questions are top priorities for the field of research into the genetic underpinnings of bipolar disorder, and will undoubtedly be addressed in the coming years.

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