Response to treatment in bipolar disorder

Cristiana Cruceanu^a, Martin Alda^b, Guy Rouleau^c, and Gustavo Turecki^a

^aMcGill Group for Suicide Studies, Douglas Hospital, McGill University, Montreal, Quebec

^bDepartment of Psychiatry, Dalhousie University, Halifax, Nova Scotia

^cDepartment of Medicine, Université de Montréal, Montreal, Quebec, Canada

Abstract

Purpose of review—Bipolar disorder is a complex psychiatric condition that has been shown to carry a great degree of genetic loading. This review addresses current research in the genetics of treatment response in bipolar disorder, with a focus on findings that have shaped our understanding of the changing direction of this field in light of recent technological advancements.

Recent findings—The recent publications in bipolar disorder treatment response have helped consolidate or improve upon knowledge of susceptibility loci and genes in the field. There seems to be an increasing trend toward functionally assessing the role played by putative candidate genes and molecular factors modulating expression in bipolar disorder, as well as a movement toward more global, pathway and genome-wide-oriented research.

Summary—Genetic and molecular research to date in bipolar disorder treatment response has not completely answered all the lingering questions in the field, but has contributed to the development of a more patient-based understanding of treatment. In order to apply these findings at a clinical level, more comprehensive treatment response studies are imperative, combining recent advances in high-throughput genomics with functional molecular research.

Keywords

bipolar disorder; genetics; GWAS; lithium

Introduction

Bipolar disorder is a psychiatric condition characterized by abnormal shifts in energy, activity levels, and mood. Given its debilitating nature, lifetime occurrence, and relatively high prevalence in the general population (1–2%), bipolar disorder represents a major public health problem and an important topic in health research [1*,2,3]. Bipolar disorder has been shown to have a relatively high genetic risk component, with estimates ranging from 60 to 85% [1*]. However, bipolar disorder is a complex genetic condition, a fact made evident by the limited consensus findings from the linkage and association studies thus far [4*,5].

Correspondence to Gustavo Turecki, MD, PhD, McGill Group for Suicide Studies, 6875 LaSalle Blvd Verdun, QC H4H 1R3, Canada, Tel: +1 514 761 6131x2369; fax: +1 514 762 3023; gustavo.turecki@mcgill.ca.

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Among the treatment options available, lithium (Li) salts are the most commonly prescribed, and are considered as the first-line mood stabilizer [6]. Other highly prescribed medications for bipolar disorder include, among others, valproate, carbamazepine, and lamotrigine [1*,6]. Studies have shown that response to Li treatment runs in families, indicating a significant genetic component. Accordingly, if heritable factors are found to accurately predict response to treatment, these could be used as guidelines when prescribing bipolar disorder medication in order to increase the likelihood of treatment success.

The scope of this review is to outline the recent publications in the genetics of bipolar disorder with reference to response to treatment. It addresses research ranging from candidate gene studies to more comprehensive genome-wide approaches, as well as the functional and expression-related research that goes hand in hand with the identification of susceptibility factors for the disorder.

Genetic studies

Family history is an important factor associated with treatment response in bipolar disorder, as was shown primarily for Li as well as other treatments. Bipolar disorder patients who respond well to Li have shown higher genetic liability, which led to a variety of studies focusing on the families of these patients, and most of these studies have confirmed an increased frequency of bipolar disorder among relatives [2,3,7–9]. These studies have also revealed very low rates of other psychiatric disorders, like schizophrenia, among relatives of Li-responder patients [7,10,11], as well as familial clustering [8]. Studies investigating family histories of patients who respond to other drugs such as lamotrigine and divalproex [10,12] suggest that these different treatments may be most effective in patients who are clinically and biologically distinct from Li responders – possibly with distinct genetic profiles.

Previous work in bipolar disorder genetics focused on linkage and association. Linkage work has identified over 40 chromosomal susceptibility regions [2], and several meta-analyses have been performed in an effort to compare these, but no significant genome-wide support was found for any loci [13,14]. Since sample heterogeneity is a major factor in the disagreement between studies, more homogenous phenotypes have been used in linkage studies. Our group has been focusing on Li response, finding interesting results for chromosomes 3, 14, 18, 15, and 7 [11,15,16**]. To complement linkage findings, association studies have been performed to test individual candidate genes in relation to response to Li [17–21]. Some of the most promising findings from other research groups looking at treatment response involve a promoter polymorphism in the serotonin transporter gene (SLC6A4) [22], a promoter variant in the glycogen synthase kinase 3 β (GSK3- β) gene [23], and the inositol monophosphatase gene (IMPA2) on chromosome 18 [24].

Candidate gene studies

The genetic studies in bipolar disorder published in the past year have focused in large part on individual bipolar disorder candidate genes, such as serotonin, dopamine or glutamate-related genes, as well as genes in the GSK3- β pathway [1*,25]. Others have pursued genes identified by the recent genome-wide association studies (GWAS) in bipolar disorder [26–

28]. A few of the recent studies have taken a broader approach to look for associations with genome-wide effect.

Campos-de-Sousa *et al.* [29] investigated the Rev-erb- α gene – nuclear receptor subfamily 1, group D, member 1 (NR1D1) – for single-nucleotide polymorphism (SNP) associations with Li therapy in a sample of 170 bipolar disorder patients followed for up to 27 years. The authors found no significant association with Li response, but the nonresponder group showed a significant increase in T-allele frequency at rs2314339 [29].

Manchia *et al.* [30] reported efforts to validate genes associated with bipolar disorder with regard to Li response by looking for associations between polymorphisms in the dopamine receptors D1, D2 and D3 (DRD1, DRD2, DRD3 respectively), LIM domain only 3 (rhombotin-like 2) (LMO3 a.k.a. DAT1), the serotonin neurotransporter (5-HTTLPR), and the serotonin receptor 2A (HTR2A) and response to Li prophylaxis in a Sardinian sample of 155 unrelated bipolar disorder probands. The same authors also queried the association and interaction effect of the NR1D1 gene and the diacylglycerol kinase, beta (DGKH) gene with response to Li prophylaxis in a sample of 199 Sardinian Li-responsive bipolar disorder patients [31]. Overall, the results from these two studies showed no significant associations with Li response, which corroborates previous findings for these genes.

Szczepankiewicz *et al.* [32] investigated the role of glutamatergic neurotransmission in Li response by investigating SNPs in the N-methyl D-aspartate (NMDA) receptor 2B subunit gene (GRIN2B) in a sample of 105 bipolar disorder patients treated with Li for at least 5 years and assessed for positive response. The gene was a promising candidate based on its chromosomal location (12p12) and evidence of altered protein expression in bipolar disorder; however, no significant associations were found [32]. In a different study published recently, the same authors found a putative association with two SNPs of the glutamatergic FYN oncogene related to SRC, FGR, YES (FYN) with bipolar disorder in a cohort of 425 bipolar disorder patients and 518 controls [33]. This protein kinase is functionally related to NMDA receptors involved in signal transduction mediation in the brain-derived neurotrophic factor (BDNF)/neurotrophic tyrosine kinase, receptor, type 2 (TrkB) pathway commonly altered in bipolar disorder [34]. When analyzing specifically Li prophylaxis in a follow-up study of the same SNPs, the group found no association with the rs6916861 SNPs and only a marginal association with rs3730353 [35].

Whereas the studies discussed above focused on response to Li, recent work has also investigated response to other drugs prescribed for bipolar disorder, and some interesting significant associations have been described. Polymorphisms in the X-box binding protein 1 (XBP1), a gene involved in endoplasmic reticulum stress response, have previously been described as risk factors for bipolar disorder [1*]. Kim *et al.* [36] looked at the XBP1-116C/G SNP in relation to prophylactic treatment response to valproate in 51 bipolar disorder patients. They showed that patients with the G-allele of XBP1-116C/G had better response to prophylactic valproate treatment compared with C-allele carriers, which is in accordance with in-vitro data showing that the drug ameliorates the endoplasmic reticulum stress response compromised in G-allele carriers [36]. In a randomized, double-blind study of 88 bipolar type I patients treated with an olanzapine/fluoxetine combination (OFC) and

85 patients treated with lamotrigine, Perlis *et al.* [37] genotyped 19 genes. SNPs within the dopamine D3 receptor (DRD3) and histamine H1 receptor (HRH1) genes were significantly associated with response to OFC. SNPs within the dopamine D2 receptor (DRD2), histamine receptor H1 (HRH1), dopamine β -hydroxylase (DBH), glucocorticoid receptor, and melanocortin 2 receptor (MC2R) genes were significantly associated with response to lamotrigine [37].

Genome-wide association studies

Over the past few years, researchers have moved toward a more comprehensive approach when investigating the role of genetic variation on bipolar disorder susceptibility and drug response, using GWAS designs. Several GWAS have been published to date focusing on bipolar disorder in general [26–28] but few loci have reached statistical significance, and overlap between findings has been minimal. One of the most interesting findings was the genome-wide association found by Baum *et al.* [27] between bipolar disorder and the DGKH gene, which encodes a key protein in the Li-sensitive phosphatidylinositol pathway. An attempt to replicate this result was reported by Squassina *et al.* [38] in a Sardinian sample of 197 bipolar disorder patients, of whom 97 were characterized as Li responders. However, neither the associations found by Baum *et al.* nor the expected association with Li response in bipolar disorder could be validated [38].

One issue with large-scale GWAS is the high degree of phenotypic and genotypic heterogeneity among the bipolar disorder patients, resulting from the large sample sizes required for sufficient statistical power. To address this problem, Perlis *et al.* used treatment response to classify patients in a more homogenous, though smaller, subgroup. They performed a GWAS in 1177 bipolar disorder patients from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort, of whom 458 were Li-treated, as well as an additional replication cohort of 359 Li-responsive bipolar disorder patients [39^{**}]. Though no SNP passed the significance threshold for genome-wide association, the study pointed to several candidate genes. Of note was the gene for the glutamate/alpha-amino-3-hydroxy-5-methyl-4-isoxazol-propionate (AMPA) receptor subunit 2 (GRIA2) [39^{**}], which has been shown to be down-regulated by chronic Li treatment in a human neuronal cell line [40].

Candidate gene study results showing association of particular genetic variants with treatment response suggest that eventually genetic markers may be used when selecting pharmacologic treatments for bipolar disorder. However, more research is imperative in order to identify valid markers of response and comprehend the complexity of the various response pathways. For this reason, the Consortium on Lithium Genetics (ConLiGen) was formed to bring together Li researchers from around the world to establish the largest sample to date for genome-wide studies of Li response. The group's collaborative effort boasts more than 1200 patients characterized for response under a very stringent phenotype definition. In a publication released earlier this year, the consortium extended an invitation to all Li researchers to join in this effort [41^{**}].

Functional studies

It has been well demonstrated through a wealth of genetic epidemiological studies that the susceptibility to develop bipolar disorder is strongly influenced by genetic factors. However, it is clear that bipolar disorder is a complex disorder and the genetic studies completed to date have provided little insight into the underlying molecular pathology. In order to fully understand the nature of bipolar disorder, it is essential to elucidate the pathways that are influenced by genetic variants, and the functional effects these have at the cell and organism levels leading to the clinical presentation. With this aim in mind, in a recently published study our group combined linkage with gene expression strategies [16**]. We initially performed a linkage study in 36 families (275 individuals, of whom 132 were affected) ascertained through long-term Li-responsive bipolar disorder probands. We found genome-wide linkage significance at three chromosomal regions (3p25, 3p14 and 14q11), and pursued these findings with a study of the brain expression of all the genes mapping to these regions in a separate cohort of postmortem bipolar disorder and control brains. Our findings point to an altered synaptic and mitochondrial functional profile in bipolar disorder, with some of the most interesting genes being synapsin II (SYN2) and mitochondrial ribosomal protein subunit 25 (MRPS25) [16**].

Expression studies

A recent effort to extend genetic susceptibility knowledge into a more global functional analysis was reported by Pedrosa *et al.* [42], who attempted to identify genes of interest in the GSK3- β pathway – a well established Li target [1*]. To achieve this goal they used a chromatin immunoprecipitation (ChIP)-chip approach in fetal brains to capture all annotated human promoters bound by β -catenin, a transcription factor that is directly regulated by GSK3- β . They identified 640 genes, which included several genes of interest to bipolar disorder: calcium channel, voltage-dependent, N type, alpha 1B subunit (CACNA1B), neurogranin (NRGN), synaptosomal-associated protein, 29 kDa (SNAP29), fibroblast growth factor receptor 1 (FGFR1), and protocadherin 9 (PCDH9). Many of the other genes identified correlate with previous findings in schizophrenia and related psychiatric disorders [42]. Thus, Pedrosa *et al.* showed that a significant number of bipolar disorder candidate genes fit into a molecular pathway revolving around GSK3- β signaling.

In another pathway analysis approach, King *et al.* [43] undertook a genetic screen for Li resistance in the social amoeba *Dictyostelium* in hopes of deciphering the molecular basis for Li's effectiveness as a mood stabilizer. Prolyl oligopeptidase – an enzyme altered in bipolar disorder patients – is a modulator of Li sensitivity and a negative regulator of inositol(1,4,5)trisphosphate (IP3) synthesis, a Li-sensitive intracellular signal. The authors showed that in *Dictyostelium*, as well as in cultured human cells, prolyl oligopeptidase acts via multiple inositol polyphosphate phosphatase (Mipp1) to modulate Li sensitivity through a gene-regulatory network that converges on inositol metabolism [43]. Kubota *et al.* took a similar approach to the King *et al.* study by comparing gene expression data from brains of bipolar disorder-like transgenic mice – the phenotype includes periodic activity change and altered circadian rhythm – with expression data obtained from post-mortem brains of bipolar disorder patients to identify relevant biological pathways [44*]. They identified several genes

differentially expressed in the brains of both species; however, only one gene was consistently down-regulated in both humans and mice: PPIF. Since this gene encodes cyclophilin D (CypD), a component of the mitochondrial permeability transition pore, the authors continued by showing that a CypD inhibitor was effective in treating the bipolar-like behavior in their mouse model, thus pointing to a potential treatment avenue involving CypD inhibition [44*].

Post-transcriptional regulation

Other levels of regulation – such as microRNA (miRNAs) post-transcriptional interference – have been shown to be relevant in psychiatric disorders and, though there have been limited studies thus far, it is important to incorporate these into treatment-responsive pathways. Zhou *et al.* [45*] have recently investigated miRNAs and their predicted effectors as targets for the long-term actions of mood stabilizers. They screened miRNA levels in Li or valproate-treated rat hippocampi and showed altered levels for several miRNAs suspected to modulate the expression of brain-specific genes. Additionally, they identified miRNA target sequences amongst bipolar disorder-risk genes such as dipeptidyl-peptidase 10, metabotropic glutamate receptor 7 (GRM7). Changes in expression of this gene were correlated with changes in miR-34a in primary cultures under Li or valproate treatment, confirming that miR-34a contributes to the effects of Li and valproate on GRM7 [45*].

In a similar approach in humans, Chen *et al.* [46] queried the expression patterns of 13 miRNAs in 20 lymphoblastoid cell lines (from 10 bipolar disorder patients and 10 corresponding discordant unaffected siblings) with or without Li treatment in culture. Seven miRNAs showed significant changes after treatment [46]. Interestingly, miR-221 and miR-34a had also been identified by Zhou *et al.* in rat hippocampi, although expression was altered in the opposite direction. Another human study by Rong *et al.* [47] took a candidate approach by focusing on one miRNA of interest: miRNA-134, a potential regulator of dendritic spine volume and synapse formation. In a sample of 21 bipolar type I manic patients and matched controls they found that plasma miR-134 levels in drug-free, 2-week medicated, and 4-week medicated bipolar disorder patients were significantly decreased when compared with controls before treatment, and the level was increased following treatment [47]. These results suggest that miR-134 may be a peripheral marker of mania and response to mood stabilizers in bipolar disorder.

Conclusion

Response to treatment in bipolar disorder has a significant genetic component, as primarily shown for Li [1*,48]. Factors such as clinical presentation, family history, genetic variants or biomarkers that reliably predict response could be used to make decisions on course of treatment in order to enhance long-term treatment success. There has been a great deal of interest in finding predictive factors with potential use at the clinical level; however, more work is called for. The recent research presented in this review has contributed to the field by providing more information on potential molecular mechanisms involved in bipolar disorder or on underlying neurobiological processes associated with drug response, as well the mechanisms by which they influence gene expression and molecular pathways. These

findings can be incorporated into a strategy for improving treatment, but do not completely answer the lingering questions regarding the cause of bipolar disorder and treatment response.

More comprehensive treatment response studies need to be conducted combining high-throughput genomics in the form of treatment-specific GWAS and large-scale re-sequencing, as well as assessments of the precise molecular functions of the genetic factors identified. The latter is essential since, as was seen from the wealth of genetic studies thus far, bipolar disorder is a very complex disorder and the combined action of various relatively rare susceptibility factors likely results in this phenotype.

Acknowledgments

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