

Analysis of Biological Pathways Involved in the Pathogenesis of Bipolar Disorder

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DOI: 10.29322/IJSRP.11.02.2021.p11052
<http://dx.doi.org/10.29322/IJSRP.11.02.2021.p11052>

Abstract- Bipolar disorder (BD) is a mental health condition that affects approximately 1% of the global population. It is characterized by extreme euphoric mood swings and depressive and manic episodes. Despite the increasing number of patients world-wide, there are very few viable treatments that have proven efficacy for treating bipolar disorder. A challenge for the development of novel treatment options, is a relative lack of understanding into the causes and biological mechanisms driving BD onset. Recent research has consistently found a high degree of heritability of BD, with estimates between 60% to 80% and many genes playing a factor in the development of the disorder [1][7]. To better define genes and pathways that could potentially play a role in BD onset, we completed an analysis of human genetic data. Through the EMBL-EBI GWAS catalog, we analyzed the top 10 SNPs and genes with the strongest connection to BD. Using the EMBL-EBI GWAS Catalog to determine a list of genes significant to the cause of BD, a pathway analysis was conducted using the Database for Annotation, Visualization and Integrated Discovery (DAVID) to find the most significant pathways. As a result, it was found that alternative splicing is the most significant pathway in Bipolar disorder, alongside phosphoprotein, postsynaptic density, and immunoglobulin I-set. Multiple approaches of targeting bipolar disorder through these pathways were highlighted like usage of alternatively spliced genes as novel biomarkers. Thus, these pathways could be novel potential therapeutic targets for bipolar disorder in the future.

Index Terms- Bipolar disorder, Genetic Pathways, Single nucleotide polymorphisms

I. INTRODUCTION

Bipolar disorder, previously known as manic depressive disorder, is a chronic psychiatric disorder, which is typically characterized with episodes of mania, hypomania, and alternating episodes of depression [5]. While mania means the state of excessive energy, associated with euphoria, impulsivity, and psychosis, depression leads to non-reactive mood, disruption of sleep, eating routines, feelings of guilt and worthlessness. As of the latest estimates, nearly 1-2% of the world population is affected by bipolar disorder [2]. Despite the significant healthcare burden, there are only limited treatments available for bipolar disorder.

Here, we expand on previous research to characterize both known and novel biological pathways involved in the pathogenesis of BD. Using the EMBL-EBI GWAS catalog, we analyzed more than 1200 single nucleotide polymorphisms (SNPs) that have previously been associated with BD. Based on nearest genes, we next performed a pathway analysis using the Database for Annotation, Visualization and Integrated Discovery (DAVID) [4]. We found that individual SNPs for the nearest genes within the pathways caused a dysregulation that was linked with Bipolar Disorder. This research shows the linkage between the dysregulation caused by SNPs and Bipolar Disorder, and highlights both known and novel genes and pathways that should be further investigated for their role(s) in BD.

II. IDENTIFY, RESEARCH AND COLLECT IDEA

Prior research suggests that there is no single factor or gene that causes BD but rather a multitude of factors that contribute to the pathogenesis of bipolar disorder (National Institute of Mental Health, 2018). Research has shown that BD is a heritable disease, with a concordance rate for identical twins averaging 67% and heritability estimates of 85% [1][7]. Heritability of BD, combined with environmental factors, including trauma or stress, have contributed to the prevalence of BD [12]. Because of this genetic contribution towards BD risk, researchers have devoted the last 25 years to the search for specific genetic factors that may influence disease development.

Previous meta-analysis of pathways has shown that BD is highly correlated with glutamate receptor signaling, PLC signaling, CRH signaling, endothelin 1 signaling, cardiac beta-adrenergic signaling and cardiac hypertrophy signaling. Earlier examples cite the PKC and glycogen synthase kinase 3 β (GSK3 β) signaling pathways as correlated with BD [9].

III. WRITE DOWN YOUR STUDIES AND FINDINGS

A. Bits and Pieces together

SNP	P Value	Ranking of Risk	Scores	Peaks	Gene	Function of Gene	Reported Trait(s)
rs13217619	1 x 10 ⁻²⁷	5	0.58955	5	ZSCAN31	Responsible for nucleic acid binding and DNA-binding transcription factor activity	Schizophrenia, major depressive disorder, anorexia nervosa, OCD, Bipolar Disorder
rs1516725	1 x 10 ⁻²⁴	5	0.70952	4	ETV5	Responsible for DNA-binding transcription factor activity and transcription regulatory region DNA binding	BMI, hip/waist circumference in men and women
rs3888190	1 x 10 ⁻²⁴	1f	0.55436	28	ATP2A1	Responsible for calcium ion binding and nucleotide binding; instructions for the SERCA1 enzyme, regulating levels of calcium ions	BMI, specifically in relation to smoking
rs12552	1 x 10 ⁻²³	5	0.14427	3	OLFM4	Responsible for protein homodimerization activity and cadherin binding; facilitates cell adhesion	Bipolar Disorder, autism, MDD, intelligence
rs34706883	7 x 10 ⁻²⁰	3a	0.47482	1078	H2BC15	Responsible for transcription regulation, DNA repair, DNA replication and chromosomal stability	Schizophrenia, Bipolar Disorder
rs4298967	8 x 10 ⁻²⁰	5	0.05	18	CACNA1C	Regulates intracellular processes such as contraction, secretion, neurotransmission and gene expression; instructions for calcium channels and electrical signals	anorexia nervosa, attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depression, obsessive-compulsive disorder, schizophrenia, or Tourette syndrome (pleiotropy)
rs151181	3 x 10 ⁻¹⁹	1f	0.24002	14	CLN3	Mediates microtubule-dependent, anterograde transport connecting the Golgi network, endosomes, autophagosomes, lysosomes and plasma	Core binding factor acute myeloid leukemia, bipolar disorder or body mass index, Crohn's disease
rs75782365	3 x 10 ⁻¹⁸	5	1	6	BTN3A1	Plays a role in T-cell activation and in the adaptive immune response.	Autism spectrum disorder or schizophrenia, depression (broad), Help-seeking from a GP, bipolar disorder (MTAG), schizophrenia (MTAG)
rs4481150	5 x 10 ⁻¹⁷	1f	0.11	21	ITIH3	Stabilizes the extracellular matrix through its ability to bind hyaluronic acid	anorexia nervosa, attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depression, obsessive-compulsive disorder, schizophrenia, or Tourette syndrome (pleiotropy), Serum 25-Hydroxyvitamin D levels, red blood cell count
rs4298967	3 x 10 ⁻¹⁶	5	0.05	18	CACNA1C	Regulates intracellular processes such as contraction, secretion, neurotransmission and gene expression.	anorexia nervosa, attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depression, obsessive-compulsive disorder, schizophrenia, or Tourette syndrome (pleiotropy)

Figure 1

To begin to understand how genetic factors may influence biological mechanisms leading to BD, we started by analyzing the full repertoire of SNPs that had previously been associated with the disease. We used the EMBL-EBI GWAS catalog [6] to identify SNPs and their nearest genes that had previously reached genome-wide significance in 104 genome wide association studies. Approximately 1,200 SNPs were identified. The top SNPs with the most significant p-values are represented in **Figure 1**, with rs13217619, rs1516725, and rs3888190 among the top 3. Rs13217619, has been linked with a wide variety of mental disorders, including Schizophrenia, bipolar disorder, and Obsessive-Compulsive Disorder. rs1516725 and rs3888190, however, have both been associated with body mass index. Rs151181 is linked to bipolar disorder as well as Crohn's disease and rs4481150 is linked with multiple mental disorders, including bipolar disorder [6].

Since the top SNPs are in non-coding regions of the genome, we next asked if any SNPs might increase risk for BD by acting via gene regulatory element. We utilized RegulomeDB [3] which predicts the likelihood of genetic variants falling within and interrupting known or predicted enhancer elements. Each SNP receives a rank and a probability score from 0 to 1 based on the number of published genome-wide ChIP-seq peaks that the SNPs lie within in multiple different cell lines (**Figure 2**). The majority of our lead BD-associated SNPs have low RegulomeDB rank scores, signaling a high probability that they fall within and may interrupt gene regulation. SNPs rs3888190, rs151181, and rs4481150 have rankings of 1f, which is the RegulomeDB score computation based on multiple high throughput datasets [3] (**Figure 1**).

In order to better understand the genes that are nearest to the BD-associated SNPs. By analyzing the functions of those genes and the biological pathways that they act within, we reasoned that we could identify known and novel mechanisms that may lead to disease. We utilized the Database for Annotation, Visualization and Integrated Discovery (DAVID) [4] to derive a list of pathways related to approximately 1250 genes nearest the BD-associated SNPs (**Figure 2**).

Pathway Name	P Value	Number of BD Associated Genes in the Pathway	Percentage of BD Associated Genes in the Pathway	Category
Alternative Splicing	6.20E-21	411	0.50%	UP_KEYWORDS
Splice Variant	2.80E-20	334	0.40%	UP_SEQ_FEATURE
Phosphoprotein	6.10E-12	316	0.30%	UP_KEYWORDS
Postsynaptic Density	3.30E-08	23	0.00%	GOTERM_CC_DIRECT
Immunoglobulin I-Set	4.10E-08	20	0.00%	INTERPRO
Dendritic Spine	4.20E-08	17	0.00%	GOTERM_CC_DIRECT
Calcium Signaling Pathway	1.30E-06	20	0.00%	KEGG_PATHWAY
Immunoglobulin subtype 2	1.80E-06	24	0.00%	INTERPRO
Intracellular Signal Transduction	4.70E-06	31	0.00%	GOTERM_BP_DIRECT
Calcium	5.50E-06	50	0.10%	UP_KEYWORDS
Membrane	6.90E-06	265	0.30%	UP_KEYWORDS
Polymorphism	7.70E-06	394	0.40%	UP_KEYWORDS
Coiled Coil	8.30E-06	126	0.10%	UP_KEYWORDS
Magnesium Ion Homeostasis	1.10E-05	5	0.00%	GOTERM_BP_DIRECT

Figure 2

B. Use of Simulation software

EMBL-EBI GWAS-based SNP detection

The EMBL-EBI GWAS Catalog [6], a catalog of human genome-wide association studies, was used to identify 1264 SNPs previously found to be associated with BD. BD-associated genes were identified based on the gene nearest to each SNP. The top ten SNPs were identified based on the EMBL-EBI GWAS catalog-reported p-values.

RegulomeDB analysis

RegulomeDB [3] analysis was completed by entering the top ten SNPs (by p-value) into the RegulomeDB tool. Rank and probability scores were used to determine the likelihood of each SNP influencing a genetic regulatory element. The RegulomeDB Probability Score ranged from 0 to 1 and referred to the probability of the SNP being a variant. The RegulomeDB Rank ranged from 1a to 7 and it referred to the amount of evidence available for a variant to be located in a functional region, with 1a having the most evidence. In total, the data consisted of the genes, SNPs of each gene, and the probability scores and probability rankings of each SNP, allowing for a meta-analysis of these significant genes and SNPs.

DAVID pathway analysis

The genes nearest to BD-associated SNPs were used to analyze biological pathways using the Database for Annotation, Visualization and Integrated Discovery (DAVID) [4]. Specifically, after analyzing the genes and SNPs given by EMBL-EBI GWAS, DAVID provided a list of pathways that the specific genes fall into. Based on the analysis of the P-values, percentage of BD-associated genes in the pathway, as well as by building upon the foundation from the SNPs data, an understanding of how each pathway plays a role on BD were made.

IV. CONCLUSION

Complex genetic diseases like bipolar disorder are caused by the contribution of many different variants, genes, and pathways, combined with environmental influences. To identify novel genes and biological functions involved in BD, we performed a thorough analysis of SNPs previously associated with disease. We found several SNPs with known links to mental disorders, and SNPs that have not been extensively studied and could be promising targets for future studies. Several of the top SNPs are predicted to fall within gene regulatory elements, suggesting crucial functions of those SNPs in regulating genes involved are involved with bipolar disorder. Moreover, analysis of biological pathways encompassing genes nearest the top SNPs, showed enrichment of alternative splicing, which can result in undesired variation of gene expression and faulty genomic instruction in functional protein, leading to multiple physiological diseases. These results highlight both known and novel biological mechanisms that should be included as targets for future investigation.

Alternative Splicing

Our results found that the first most significant pathway related to BD-associated genes is alternative splicing. Alternative splicing is the process by which mRNA can be stitched together in different ways such that multiple protein isoforms can be encoded by a single gene. SNPs can impact alternative splicing, resulting in unintended variation in gene expression [10]. Previous research has linked splicing variants with psychiatric disorders [11]. Others have suggested that alternatively spliced genes could be utilized as novel biomarkers for BD [14]. Through further focusing on alternative splicing and its risk variants, new therapeutic treatments can be discovered for bipolar disorder and related mental illnesses.

Synaptic Function Pathways

Our results found that the second most significant pathway related to BD-associated genes was postsynaptic density, which is essential for regulating developmental and structural aspects of the nervous system. Genes in this pathway function to localize glutamate receptors and position neurotransmitter receptors [15]. We also identified the dendritic spine pathway, which is related to the small protrusions from neuronal dendrites that form the post-synaptic component of most excitatory synapses in the brain. Glutamatergic excitatory synapses along this pathway are responsible for the maintenance of these synapses as they play an important role in plasticity [15].

The mechanism of action between ion channels, specifically lithium and calcium are significant. It was found that such ions can stimulate various receptors and neurotransmitters; this can account for the balance of connection between excitatory synapses, neuronal cells, and generally throughout the nervous system -- as well as modulating glutamate / synapses. When this balance is essentially destroyed, this can lead to Bipolar Disorder as certain neurotransmitters and signaling enzymes can lead to limitations of synaptic transmission.

As for bipolar disorder, the genes involved in this pathway include FXR1, DGKI, SHANK2 and MOB4. FXR1: The FXR1 genes have been implicated to cause dysregulation of dopamine receptor signaling. Since dopamine receptors signaling is one of the main known causes of BD, FXR1 theoretically plays a main role. Furthermore, the DGKI gene has shown high correlation with bipolar disorder, as the η isozyme of diacylglycerol kinase (DGK) is highly expressed in the hippocampus and Purkinje cells in the central nervous system. Recently, several genome-wide association studies have implicated DGK η in the etiology of bipolar disorder (BD).

Golgi Organization

The Golgi organization pathway has not been connected to Bipolar Disorder in any prior research making this connection a novel finding. The Golgi organization pathway was found to include many of the BD-linked genes, including ATP8B3, CLASP1, LMAN2L, MYO28A, PRKD1, SYNE1, and ASAP2. The Golgi is an organelle that is directly involved in the packaging of proteins into vesicles before transportation. ASAP2 is known to activate small GTPases, including ARF1, regulate the formation of post-Golgi

vesicles and modulate constitutive secretion. This connection should be explored further as this variant plays a huge role in bipolar disorder.

Relationships with other Neurological Disorders

Our results from the DAVID functional analysis tool found that bipolar disorder shares several pathways and genes with schizophrenia, narcolepsy, Parkinson's disease, schizophrenia, and major depressive disorder. In recent years, researchers have investigated the relationship between narcolepsy and bipolar disorder which report conflicting results. The AKAP6 gene functions in the sarcoplasmic reticulum of skeletal muscle cells and is a candidate loci for narcolepsy [13]. The involvement of genes which function in skeletal muscle cells in bipolar disorder coupled with the genetic/symptomatic associations with narcolepsy suggest another possible shared pathophysiology between the two disorders which may warrant further investigation. Parkinson's disease has been previously connected to mitochondrial dysfunction and the PRKN gene is known to cause mitochondrial impairment. Mitochondrial impairment will result in apoptosis if the mitochondrial impairment is at a significantly severe level. Mitochondrial dysfunction is an important part of the organelle organization pathway, which is a significant pathway in BD. However, more valuable research is to be done within these sectors to fully defend these conclusions made. The intracellular signal transduction is a significant pathway in bipolar disorder, connecting the cell surface to the nucleus, and targeting many hormones altering hormonal levels for many mood disorders. Kinase-mediated signaling events are important in schizophrenia as imbalances in kinase activity caused by intracellular signaling contributes to many of the observed deficits in schizophrenia.

The integration of genome wide expression or EMBL-EBI GWAS data with pathways and networks is very promising, but it can be improved by considering other information, such as epigenetics. However, the field is still far from maturity due to incomplete pathway knowledge. Furthermore, pathway analysis is currently coding gene-centered; non-protein coding elements (noncoding RNA, non-transcribed regions and epigenetic marks) have not been sufficiently integrated in the analysis. Moreover, research can be done on a larger sample of relevant SNPs, as a contrast to just the top 10 SNPs, to gain a more accurate understanding of these factors. These topics also warrant further, more holistic, research that investigates pathways and networks in relation to bipolar disorder, with the integration of novel factors such as non-protein coding elements, epigenetics, and more thorough analysis of pathways. All these findings show great promise to lead to future research in bipolar disorder and its relation to pathways and genome wide expression.

There is difficulty in understanding disease risk associated with non coding SNPs, and EMBL-EBI GWAS-identified SNPs, as they only serve as representatives for all SNPs in the same haplotype block. SNPs often do not cause changes in protein function but cause changes in gene expression instead. Unlike cystic fibrosis that is caused by mutations in the coding region of a gene, most disease associated SNPs are located in noncoding regions of the genome, which is why we focused on genetic pathways in our paper. Furthermore, SNPs cannot be used to find specific genes that affect the disease, as SNPs often affect many genes.

ACKNOWLEDGMENT

Thank you to Postdoctoral Scientist at AbbVie Genomics Research Center, Lindsay Stolzenburg, for thorough guidance throughout our work research and more.

Thank you to Nicholas Canaday Spitzer, Professor in the Division of Biological Sciences at the University of California, San Diego for guidance through our research.

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