Article

A Genome-Wide Association Study and Complex Network Identify Four Core Hub Genes in Bipolar Disorder

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Abstract: Bipolar disorder is a common and severe mental illness with unsolved pathophysiology. A genome-wide association study (GWAS) has been used to find a number of risk genes, but it is difficult for a GWAS to find genes indirectly associated with a disease. To find core hub genes, we introduce a network analysis after the GWAS was conducted. Six thousand four hundred fifty eight single nucleotide polymorphisms (SNPs) with $p < 0.01$ were sifted out from Wellcome Trust Case Control Consortium (WTCCC) dataset and mapped to 2045 genes, which are then compared with the protein–protein network. One hundred twelve genes with a degree >17 were chosen as hub genes from which five significant modules and four core hub genes (*FBXL13*, *WDFY2*, *bFGF*, and *MTHFD1L*) were found. These core hub genes have not been reported to be directly associated with BD but may function by interacting with genes directly related to BD. Our method engenders new thoughts on finding genes indirectly associated with, but important for, complex diseases.

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1. Introduction

Bipolar disorder (BD) is a common and severe mental disorder characterized by alternative episodes of mania/hypomania and depression [1]. It affects 1–5% of the world's population [2–4]. Genetic studies have shown that bipolar disorder is a complex genetic disease that involves the interaction of multiple genes and the environment. Genetic factors can account for up to 60–85% of the risk [5–8]. The strong genetic basis of BD inspires plenty of research focused on finding candidate genes or single nucleotide polymorphisms (SNPs) associated with this disease.

Over the past few decades, traditional family-based linkage analysis and population-based case–control association analysis have been common means of identifying bipolar disorder susceptibility genes. With the advent of the third-generation polymorphism genetic marker SNPs, genome-wide association studies (GWASs) have also been applied to large-scale scanning of new BD susceptibility gene loci and a number of genes, such as *CACAN1C* [9,10], *ANK3* [10,11], *SYNE1* [12], *CSMD1* [12], *ITIH1* [11], *KIT* [11], and *DGKH* [13], have been found.

GWASs have proven to be useful in finding susceptibility genes of diseases. However, when used alone, it is difficult to determine genes that have relatively high GWAS p-values but may play a role through interaction with the genes directly associated with BD. The complexity of the disease makes it even more difficult to elucidate its molecular mechanism. Therefore, although the previous study has found a lot of genetic factors with significant effects on BD, its molecular mechanism remains unresolved. In this case, a comprehensive analysis focusing on gene interactions and biological functions will provide valuable information to explore the pathogenesis of BD. It has been found that

the distribution of genetic marker loci on chromosomes and the interaction between SNPs are one of the major genetic basis for complex diseases [14]. The gene network is often used to reveal complex relationships among genes.

Considering that complex mental phenotypes may be affected by many genes with small or mild effects rather than one or two genes with a major impact [15], a comprehensive analysis of the underlying genes in the pathway or network framework may provide more insights into its molecular mechanism. It will be more efficient to understand the role of genes in complex diseases using network study. Some methods have been developed in this area, but the problem is far from being solved. There is scarce known molecular interaction mechanism and systematic gene network analysis for BD. Construction of a gene interaction network can be used to explore the synergistic effect of multiple genes on BD.

In this study, we performed a GWAS to obtain BD-related genes and confirmed their function by functional enrichment analysis. To further explore the association between these genes and BD, a network was constructed using a human protein–protein interaction database, and the BD-risk genes identified in the GWAS were mapped onto the network to find core hub genes. This will provide more insight into the molecular mechanisms of BD by determining the core hub genes of the network.

2. Results

2.1. GWAS Results

A total of 482,247 SNPs located on 22 chromosomes of 1868 BD cases and 2938 controls satisfies the quality control. The number of SNPs decreases to 354,282 after the Hardy–Weinberg equilibrium test. Finally, a total of 6458 SNPs is qualified in the GWAS where $p < 0.01$ and used for further analysis. The result is shown in Figure 1.
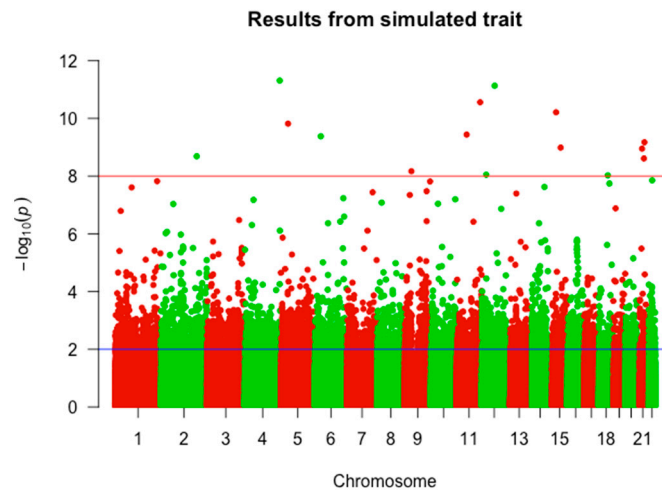

Figure 1. Results of the genome wide association study (GWAS). The horizontal axis represents 22 chromosomes and the vertical axis represents the negative logarithm with base 10 of GWAS *p*-value for each SNP. Red line: canonical 5×10^{-8} cutoff. Blue line: 0.01 cutoff used in this study.

2.2. Gene Functional Analysis

A total of 2045 risk genes was obtained after mapping the 6458 SNPs onto human genes. These genes were then classified into three Gene Ontology (GO) sections: cellular components, molecular functions, and biological processes. The first 10 GO items ($p < 0.01$) are shown in Tables 1–3. Genes with transferase and kinase function dominate in molecular functions. In cellular components, most gene products are located in the nervous system. This coordinates with the biological process result in which most genes are involved in nervous system development.

Table 1. Molecular functions (GO).

Name	FDR	Gene Count
transferase activity, transferring phosphorus-containing groups	5.67×10^{-5}	118
kinase activity	5.67×10^{-5}	103
phosphotransferase activity, alcohol group as acceptor	5.67×10^{-5}	96
protein serine/threonine kinase activity	1.03×10^{-4}	63
protein kinase activity	1.90×10^{-4}	81
GTPase regulator activity	2.61×10^{-4}	47
signal transducer activity, downstream of receptor	2.61×10^{-4}	33
GTPase activator activity	4.57×10^{-4}	43
adenyl ribonucleotide binding	7.16×10^{-4}	154

Table 2. Cellular components (GO).

Name	FDR	Gene Count
synapse	5.23×10^{-14}	131
postsynapse	1.68×10^{-13}	83
synapse part	7.30×10^{-13}	110
synaptic membrane	1.89×10^{-12}	62
cell junction	9.04×10^{-10}	149
postsynaptic embrane	1.91×10^{-9}	47
neuron part	2.94×10^{-9}	178
excitatory synapse	7.86×10^{-9}	49
plasma membrane region	8.87×10^{-9}	130
neuron projection	8.89×10^{-9}	144

Table 3. Biological processes (GO).

Name	FDR	Gene Count
neurogenesis	1.28×10^{-7}	186
cell morphogenesis	1.28×10^{-7}	159
generation of neurons	1.28×10^{-7}	176
regulation of nervous system development	1.28×10^{-7}	116
neuron differentiation	3.55×10^{-7}	162
neuron development	3.55×10^{-7}	136
cell projection morphogenesis	3.61×10^{-7}	116
cellular component morphogenesis	4.18×10^{-7}	164
cell projection organization	4.63×10^{-7}	163
neuron projection morphogenesis	6.25×10^{-7}	88

2.3. Overlapped Genes in Different Mental Illnesses

We enriched these candidate genes in BD and other three mental illnesses: schizophrenia, intellectual disability, and autistic disorder. In the total 2045 risk genes, the numbers of genes associated with schizophrenia, intellectual disability, autism, and bipolar disorder are 151, 123, 84, and 84, respectively. A Venn map of the overlap genes of these four diseases shows that, out of the 84 genes associated with bipolar disorder, 55 genes are in common with schizophrenia, 17 with intellectual disorder, and 28 with autism (Figure 2).
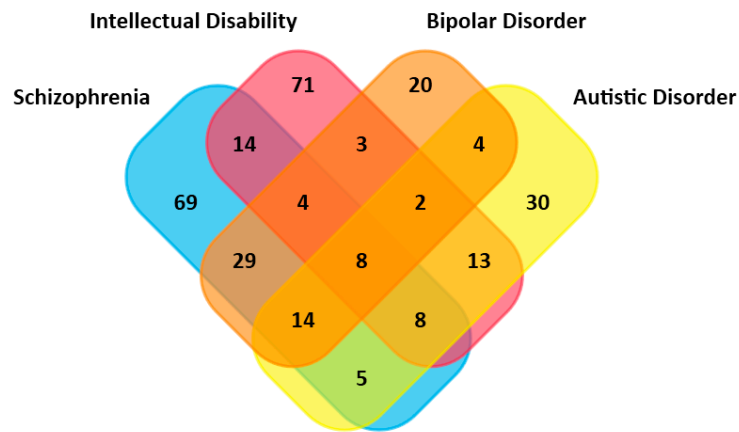
Figure 2. Overlapped genes associated with four mental illnesses.

2.4. Protein Interaction Network

The 2045 genes from the GWAS result are mapped onto the protein–protein interaction network constructed using data from the STRING database (Figure 3).
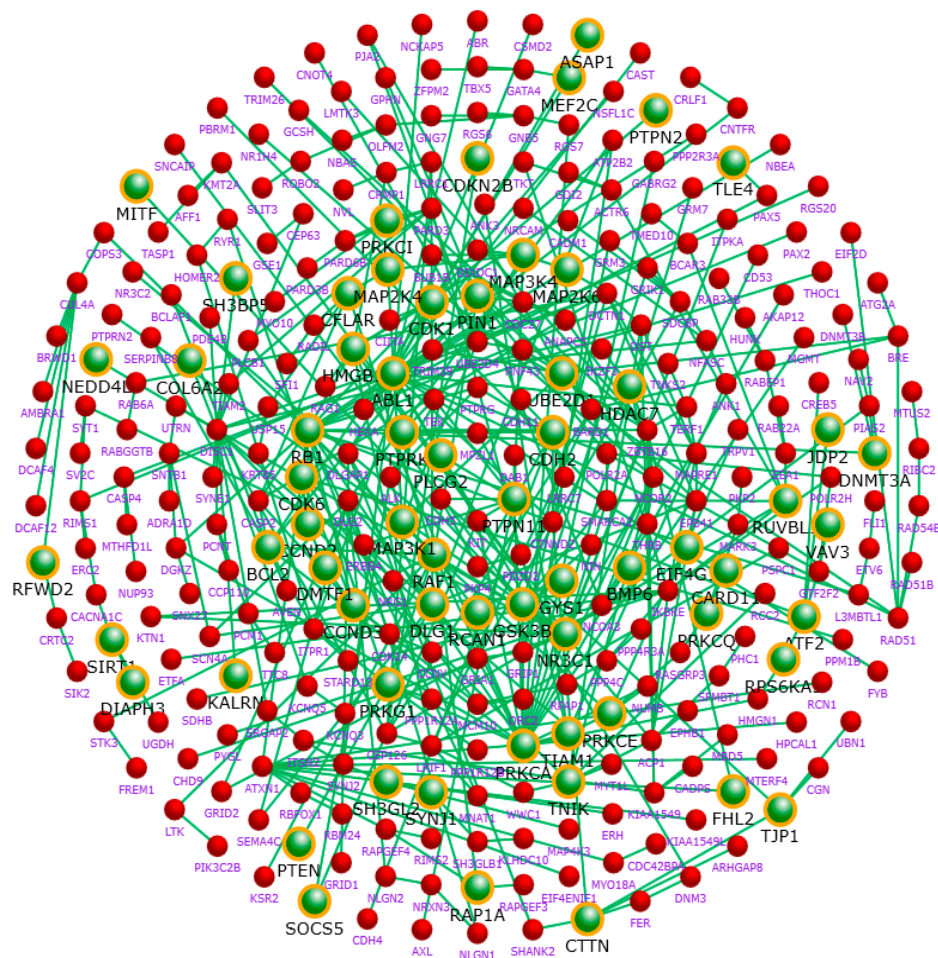

Figure 3. BD risk gene interaction network. Only the nodes with a degree ≥ 4 are shown. Green balls are BD risk genes identified in the GWAS with $p < 0.01$.

There are 1083 nodes in the network. The average node degree of the network is 7.555. The clustering coefficient is 0.232, and the characteristic path length is 3.393. The properties of the network are further analyzed and the results are shown in Figure 4. The connectivity of the network exhibits characteristic power distribution. Figure 4b shows that the shortest path with the highest frequency among the candidate genes of BD is between 3 and 4, indicating that the network is not a stochastic network but a complex network with characteristics of biological molecular network. The number of neighbors shared by the network nodes has a significant inverse relationship with its topological coefficients (Figure 4c), but shows a positive correlation with the node's identity (Figure 4d).
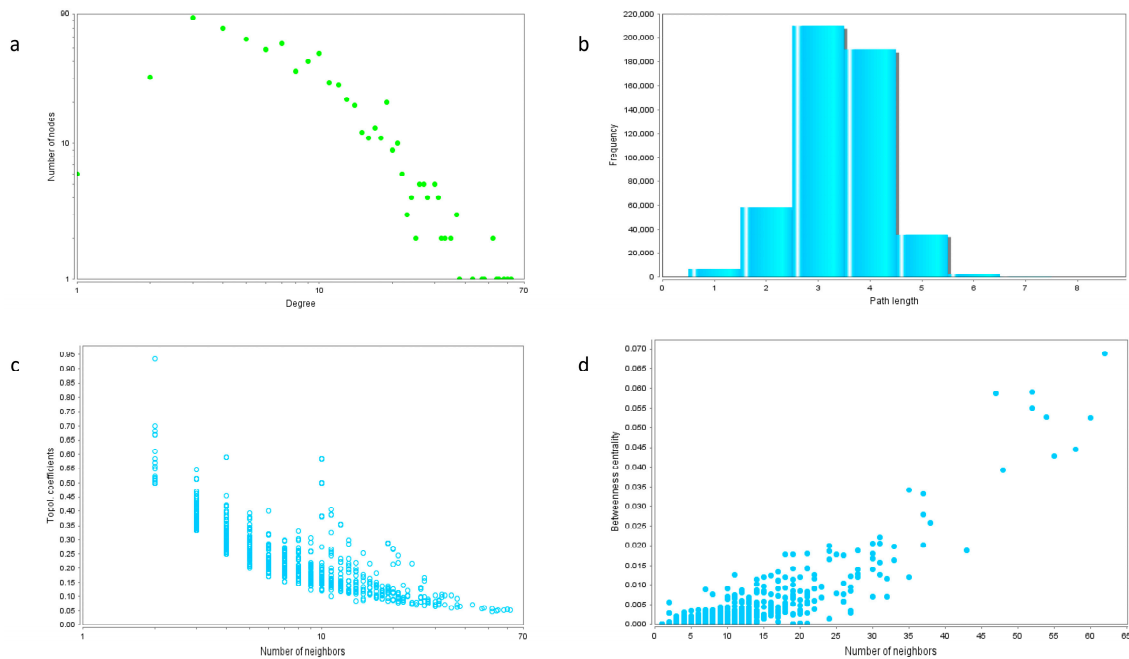

Figure 4. The topology properties of the network. (**a**) The distribution of number of nodes with different degrees. (**b**) Frequency distribution of shortest paths. (**c**) The relationship between topological coefficients and the number of node neighbors. (**d**) The relationship between betweenness and the number of node neighbors.

2.5. Hub Genes of the Network

One hundred twelve gene nodes with a degree >17 is chosen as hub genes from the network for further analysis (Tables 4 and A1).

Table 4. The gene nodes with a network degree >17.

Hub Gene	Degree	Hub Gene	Degree	Hub Gene	Degree
CDK1	62	PNPLA6 [16]	27	FARS2	20
PTEN [17,18]	61	SYNJ2	27	FBXO22	20
BCL2 [19]	60	UBE2R2 [20]	27	FLT3	20
POLR2A [21]	55	CACNA1D [22–24]	26	GATA4 [25] *	20
SMARCA2 [26,27]	55	CDK6 [28]	26	ITSN2 [29]	20
GSK3B [30–33]	54	CHRM2 [34]	26	KIF18A	20
ABL1 [35–37]	53	MTHFD1L [38] **	26	LONRF1	20
PRKCA [39,40]	50	GRIA1 [41]	25	NCOA3	20
bFGF [42] **	48	POLR2H	25	PCNT [43]	20
RB1 [44] *	45	TJP1 [45] *	25	PJA2	20
KIT [11]	40	MAPRE1 [46] *	24	SYT1 [47]	20
RAD51 *	38	RUNX1 [48]	24	TRIM39	20
SIRT1 [49–51]	38	UBE2D4	24	WDFY2 [52] **	20
UBE2D1 [53,54]	37	EHHADH	23	AK4	19

Table 4. *Cont.*

Hub Gene	Degree	Hub Gene	Degree	Hub Gene	Degree
DLG1 [55,56]	36	*IQCB1*	23	*ASB15*	19
CDC27 [57]	35	*PPM1B* [58]	23	*ATF2* [29]	19
NEDD4L [59]	35	*PPP4C* [60] *	23	*BUB1B*	19
PRKG1 [61] *	35	*RAD50*	23	*DHX15*	19
RAP1A	34	*SH3GL2*	23	*DNM3* [62] *	19
CDH2 [63] *	33	*DCTN1*	22	*ETV6*	19
GNB5 [64] *	33	*ERBB4* [65,66]	22	*FBXL13* [67,68] **	19
MAPK6 [69]	33	*FBXO32*	22	*HECW2*	19
GNG7 [70]	32	*ITPR1* [71] *	22	*MEF2C* [72] *	19
PTPN11 [73] *	32	*MLL* [74]	22	*NR3C1* [75]	19
ZBTB16 [76]	32	*NCOR2* [77]	22	*BDE4D*	19
ADCY2 [78]	31	*PRKCE* [79]	22	*RNF19B*	19
DICER1 [80,81]	31	*RAD51B*	22	*RNF217*	19
SYNJ1 [82–85]	31	*ACTN4*	21	*RXFP2*	19
CACNA1C [9,52,86,87]	30	*CCND2* [88,89]	21	*RYR1*	19
CTTN	30	*CDH5*	21	*THBS2*	19
DLG2 [90,91]	30	*CUL4A* [92] *	21	*AKT3* [93] *	18
MAP3K1 [94] *	30	*EFCAB13*	21	*BARD1*	18
RIT2 [95]	30	*LMO7*	21	*CTNNA2* [11,96]	18
ANAPC5 [28]	28	*MITF*	21	*HDAC7*	18
PLCB1 [97–99]	28	*TRIM9* [100]	21	*ITGAV*	18
RAF1 [101] *	28	*CCND3*	20	*PARD3* [102] *	18
PARK2 [61] *	27	*EPHB1* [103] *	20	*PCSK2*	18
PLCG2 [13,39]	27				

* associated with other mental illness ** core hub genes.

Of these 112 hub genes, 45 were reported associated with BD in previous studies. Another 24 were reported associated with other mental illnesses. Gene nodes with higher degrees have a higher ratio of genes being reported associated with BD. Only five genes with a degree >23 (51 genes) are not reported associated with BD or other mental illnesses, while 24 with a degree ≤23 (61 genes) are not found reported directly associated to any mental illnesses. Obviously, risk genes with more degrees have a closer connection to BD than those with fewer degrees.

2.6. Significant Modules of the Network and Core Hub Genes

Five significant gene modules are found in the network containing 112 hub genes with Cytoscape. Four core hub genes are found in these modules: *FBXL13*, *WDFY2*, *bFGF* (*FGF2*), and *MTHFD1L*. No core hub gene is found for one module (Cluster 4) (Table 5, Figure 5).

Table 5. Significant risk gene modules.

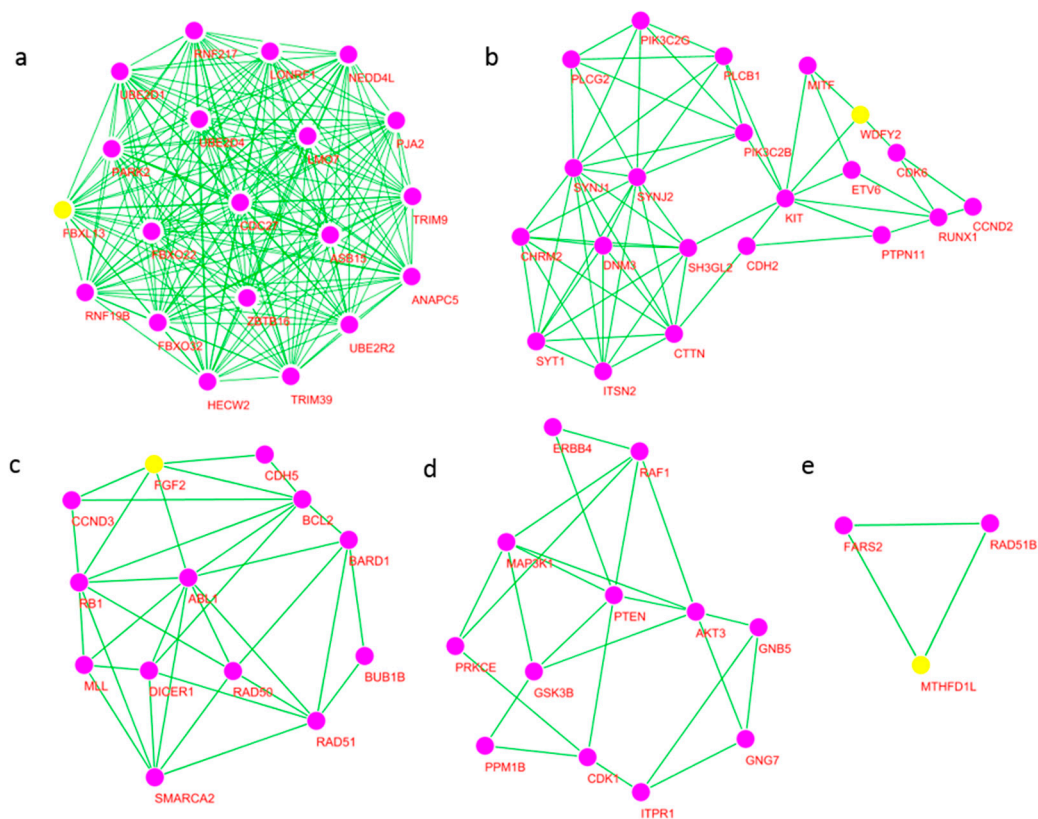| Cluster	Score	Nodes	Edges	Node IDs
1	20	20	190	*ASB15, HECW2, UBE2D1, NEDD4L, ANAPC5, PJA2 TRIM39, UBE2R2, UBE2D4, CDC27, TRIM9, ZBTB16 LONRF1, PARK2, FBXL13 *, FBXO22, RNF19B, LMO7 RNF217, FBXO32*
2	6.1	21	61	*SYNJ1, KIT, PIK3C2G, PTPN11, PIK3C2B, SYNJ2 RUNX1, ITSN2, PLCB1, CDH2, DNM3, SYT1, CTTN WDFY2 *, CHRM2, CCND2, MITF, PLCG2, CDK6, ETV6, SH3GL2*
3	5.5	13	33	*MLL, bFGF(FGF2) *, BUB1B, BARD1, RB1, DICER1, RAD50, RAD51, BCL2, CDH5, SMARCA2, ABL1, CCND3*
4	4.182	12	23	*AKT3, PTEN, ITPR1, PRKCE, GNB5, CDK1 ERBB4, GNG7, RAF1, GSK3B, PPM1B, MAP3K1*
5	3	3	3	*FARS2, RAD51B, MTHFD1L **

* core hub genes.

Figure 5. Gene clusters identified with Cytoscape. Yellow nodes are core hub genes. No core hub gene is found in Cluster 4 (**d**). (**a**) Cluster 1; (**b**) Cluster 2; (**c**) Cluster 3; (**d**) Cluster 4; (**e**) Cluster 5.

3. Discussion

3.1. Most BD Risk Gene Products Are Located in the Nervous System

Our gene functional analysis of 2045 BD risk genes shows that most of their products are located in the nervous system, such as synapse and postsynapse. The result of GO biological process analysis shows most genes are involved in nervous system development. These two results verify each other and are consistent with previous studies [104]. BD risk genes may affect patients in two aspects: short-term and permanent. Environmental or internal factors may cause ectopic expression of some of the risk genes, which in turn cause episodes of BD. Some genes may work in the development of the nervous system and have a permanent effect on patients. This may explain why 60% patients will relapse into depression or mania within two years after treatment [105].

3.2. Intense Overlappings of Genes Associated with BD and Other Mental Disorders

Many symptoms and signs overlap between different mental disorders and patients often present with features of more than one disorder [106]. This may be caused by underlying genetic reasons. We compared BD risk genes with those of three other mental disorders and found intense overlaps. Similar results were also reported in other studies [28,52,86,89,106,107].

Schizophrenia and BD share the most associated genes. Previous work also found a significant correlation between a BP polygenic risk score and the clinical dimension of mania in schizophrenia patients [86]. *PRKG1* was reported to be significantly associated with schizophrenia. In this study, we also find it is a hub gene in the network of BD risk genes. This gene encodes a cGMP-dependent protein kinase which acts as key mediator of the nitric oxide (NO)/cGMP signaling pathway. Another gene, *SMARCA2*, was also found to play a role in the pathophysiology of schizophrenia [27]. Its product is a transcription activator and involved in neuron differentiation. Many other risk genes

are also found involved in signal transduction and nervous system development. This suggests that these two diseases may share some common underlying pathways.

3.3. Core Hub Genes Give New Insights of BD

We combined protein–protein network and genome wide association analysis in this study and found four core hub genes. Although genes with higher degrees are more frequently reported to be associated with BD, two core hub genes (*WDFY2* and *FBXL13*) have relatively low degrees (20 and 19, respectively).

bFGF has not been reported to be associated with BD before, but is usually used for treatment of neurodegenerative diseases such as Alzheimer's disease [42]. It plays an essential role in regulation of cell proliferation, differentiation, and migration. *bFGF* is found as a core hub gene implies the abnormal nervous development of BD patients.

There is no obvious evidence for another core hub gene, *MTHFD1L*, to be associated with BD, but it is thought to have an important effect on the pathophysiology of depression through rumination, and maybe via this cognitive intermediate phenotype on other mental and physical disorders [38].

WDFY2 is not directly associated with BD, but its product interacts with *AKT1* [108], which has been found involved in BD and schizophrenia [109]. This result suggests that the pathophysiology of BD is even more complicated than we thought. Some genes may play a role through its interaction with genes directly associated with BD.

FBXL13 functions in the maturation of human dendritic cells [68] which are key regulators in the immune system and show mild aberrancies in bipolar disorder that can be fully restored to even activation after in vivo lithium treatment [67].

Interestingly, all the four core hub genes are not directly associated with BD. Although the role of these genes in the pathophysiology of BD requires further investigation, our method inspires new initiatives to find those genes that are important for BD but overlooked by studies using GWAS alone.

3.4. Effectiveness of GWAS Followed by Gene Network Analysis

GWAS is a successful tool for identifying human disease-associated genes. However, results of different studies often vary due to sampling even when a strict significant *p*-value of 5×10^{-8} is used [110]. In this study, a loose *p*-value threshold of 0.01 was used for the GWAS, and a gene network analysis was then used to find BD-associated genes in the GWAS result. Many resulted genes with high network degrees but relatively high GWAS *p*-values are reported to be associated with BD and/or other mental illnesses (Table 4), which suggests that the combination of the two methods is efficient in finding disease-related genes. It is necessary to use a loose *p*-value threshold in the first step to provide enough input genes for the following network analysis. A second screening using network degrees can help to make the final result more reliable.

Sklar et al. conducted a combined GWAS with 7481 BD cases and 9250 controls and identified *CACNA1C* and a miRNA located in the first intron of *ODZ4* as BD-associated genes [87]. The calcium channel subunit coding gene *CACNA1C* has also been found to be associated with BD in previous studies [9,52,86] and is confirmed with a relatively high degree (30) in our results. However, the miRNA is not detected in this study, probably due to our relatively smaller sample size.

4. Materials and Methods

4.1. Bipolar Disorder Datasets

The dataset is from a study published by Wellcome Trust Case Control Consortium (WTCCC), which conducted a genome-wide scan of all SNPs of 17,000 British Caucasian loci by human SNPs genotyping chips. This dataset includes 14,000 disease samples from seven common complex diseases: bipolar disorder, bipolar depression, Crohn's disease, hypertension, rheumatoid arthritis, type 1 diabetes, type 2 diabetes, and 3000 healthy control samples, which has been completed by more than 50 research teams [111]. The dataset is downloaded from WTCCC website [112]. This study

uses the BD part of the dataset. Human SNP annotation data and human reference sequence data are downloaded from NCBI (https://www.ncbi.nlm.nih.gov/), which contain 336,843,011 SNPs on 24 human chromosomes and the start and end of genes in which they are located [113].

4.2. Screening of Risk SNPs

SNP sites that do not meet one of the following criteria are excluded for quality control: Hardy–Weinberg equilibrium test (Bonferroni corrected $p < 5 \times 10^{-7}$), missingness >5%, minor allele frequency <5%, and odds ratio $R^2 > 0.8$. Risk SNPs are screened under $p < 0.01$. Quality control and risk gene screening are finished with Plink software [114].

4.3. Mapping Significant Risk SNPs to Genes

Risk SNPs are mapped onto human genes by comparing them with transcription start sites and stop sites. An SNP will be mapped onto its nearest gene within 5 kb if it is not located within any gene. SNPs located outside of the 5 kb of genes are removed.

4.4. Gene Function and Disease Enrichment Analysis

FunRich [115] software is used to carry out gene enrichment analysis with $p < 0.01$. Results are reversely ordered by FDR-values, and only the first 10 results are listed in each GO section. ToppGene [116] is used to enrich genes in four different mental illnesses.

4.5. Protein Network Analysis

STRING database [117] is used to find a protein–protein relationship and FunRich is then used to map BD risk genes to the protein–protein network. Those protein (gene) nodes with degree >17 are sifted out as hub genes, which are further analyzed with the MCODE plugin [118] of Cytoscape [119] to find out network clusters (modules) and core hub genes. The node gene with the highest MCODE node score in a cluster is designated as its core hub gene, which is crucial for the cluster.

The topological properties of a gene cluster include [120,121] the following: (1) degree, the number of genes directly connected to a gene, (2) the cluster coefficient (CC), the coincidence of the common regulatory genes between two adjacent genes, defined as

$$\text{CC} = \frac{2n_i}{k_i(k_i - 1)} \tag{1}$$

where n_i represents the number of edges of the k_i neighbors that connect to node i—the mean of the clustering coefficients of all nodes is designated as the clustering coefficient of the network—(3) the shortest path, the path with the least edges between two nodes, and (4) betweenness (B(v)), the sum of the ratios of number of shortest paths connecting to a node to that of all shortest paths in a network

$$\text{B}(v) = \sum_{s \neq v, s \neq t, v \neq t \in v} \frac{\delta_{st}(v)}{\delta_{st}} \tag{2}$$

where δ_{st} is total number of shortest paths from node s to t, and $\delta_{st}(v)$ is the number of those paths that pass through v.

Author Contributions: Zengyan Xie contributed literature search, study design, data interpretation, and wrote the paper and provided study supervision. Xianyan Yang contributed literature search, figures, study design, data collection, data analysis, data interpretation and wrote the paper. Xiaoya Deng contributed literature search and data checking. Mingyue Ma contributed paper revising. Kunxian Shu contributed study design and provided study supervision.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

BD	bipolar disorder
GWAS	genome-wide association study
SNP	single nucleotide polymorphism
WTCCC	the World Healthcare Case Control Association

Appendix A

Table A1. Gene information of the nodes with a network degree greater than 17.

GENE	Degree	Ensembl	UniProtKB
CDK1	62	ENSG00000170312	P06493
PTEN	61	ENSG00000171862	P60484
BCL2	60	ENSG00000171791	P10415
POLR2A	55	ENSG00000181222	P24928
SMARCA2	55	ENSG00000080503	P5153
GSK3B	54	ENSG00000082701	P49841
ABL1	53	ENSG00000097007	P00519
PRKCA	50	ENSG00000154229	P17252
FGF2	48	ENSG00000138685	P09038
RB1	45	ENSG00000139687	P06400
KIT	40	ENSG00000157404	P10721
RAD51	38	ENSG00000051180	Q06609
SIRT1	38	ENSG00000096717	Q96EB6
UBE2D1	37	ENSG00000072401	P51668
DLG1	36	ENSG00000075711	Q12959
CDC27	35	ENSG00000004897	P30260
NEDD4L	35	ENSG00000049759	Q96PU5
PRKG1	35	ENSG00000185532	Q13976
RAP1A	34	ENSG00000116473	P62834
CDH2	33	ENSG00000170558	P19022
GNB5	33	ENSG00000069966	O14775
MAPK6	33	ENSG00000069956	Q16659
GNG7	32	ENSG00000176533	O60262
PTPN11	32	ENSG00000179295	Q06124
ZBTB16	32	ENSG00000109906	Q05516
ADCY8	31	ENSG00000155897	P40145
DICER1	31	ENSG00000100697	Q9UPY3
SYNJ1	31	ENSG00000159082	O43426
CACNA1C	30	ENSG00000151067	Q13936
CTTN	30	ENSG00000085733	Q14247
DLG2	30	ENSG00000150672	Q15700
MAP3K1	30	ENSG00000095015	Q13233
RIT2	30	ENSG00000152214	Q99578
ANAPC5	28	ENSG00000089053	Q9UJX4
PLCB1	28	ENSG00000182621	Q9NQ66
RAF1	28	ENSG00000132155	P04049
PARK2	27	ENSG00000185345	O60260
PLCG2	27	ENSG00000197943	P16885
PNPLA6	27	ENSG00000032444	Q8IY17
SYNJ2	27	ENSG00000078269	O15056
UBE2R2	27	ENSG00000107341	Q712K3
CACNA1D	26	ENSG00000157388	Q01668
CDK6	26	ENSG00000105810	Q00534
CHRM2	26	ENSG00000181072	P08172

Table A1. *Cont.*

GENE	Degree	Ensembl	UniProtKB
MTHFD1L	26	ENSG00000120254	Q6UB35
GRIA1	25	ENSG00000155511	P42261
POLR2H	25	ENSG00000163882	P52434
TJP1	25	ENSG00000104067	Q07157
MAPRE1	24	ENSG00000101367	Q15691
RUNX1	24	ENSG00000159216	Q01196
UBE2D4	24	ENSG00000078967	Q9Y2X8
EHHADH	23	ENSG00000113790	Q08426
IQCB1	23	ENSG00000173226	Q15051
PPM1B	23	ENSG00000138032	O75688
PPP4C	23	ENSG00000149923	P60510
RAD50	23	ENSG00000113522	Q92878
SH3GL2	23	ENSG00000107295	Q99962
DCTN1	22	ENSG00000204843	Q14203
ERBB4	22	ENSG00000178568	Q15303
FBXO32	22	ENSG00000156804	Q969P5
ITPR1	22	ENSG00000150995	Q14643
MLL	22	ENSG00000118058	Q03164
NCOR2	22	ENSG00000196498	Q9Y618
PRKCE	22	ENSG00000171132	Q02156
RAD51B	22	ENSG00000182185	O15315
ACTN4	21	ENSG00000130402	O43707
CCND2	21	ENSG00000118971	P30279
CDH5	21	ENSG00000179776	P33151
CUL4A	21	ENSG00000139842	Q13619
EFCAB13	21	ENSG00000178852	Q8IY85
LMO7	21	ENSG00000136153	Q8WWI1
MITF	21	ENSG00000187098	O75030
TRIM9	21	ENSG00000100505	Q9C026
CCND3	20	ENSG00000112576	P30281
EPHB1	20	ENSG00000154928	P54762
FARS2	20	ENSG00000145982	O95363
FBXO22	20	ENSG00000167196	Q8NEZ5
FLT3	20	ENSG00000122025	P36888
GATA4	20	ENSG00000136574	P43694
ITSN2	20	ENSG00000198399	Q9NZM3
KIF18A	20	ENSG00000121621	Q8NI77
LONRF1	20	ENSG00000154359	Q17RB8
NCOA3	20	ENSG00000124151	Q9Y6Q9
PCNT	20	ENSG00000160299	O95613
PJA2	20	ENSG00000198961	O43164
SYT1	20	ENSG00000067715	P21579
TRIM39	20	ENSG00000204599	Q9HCM9
WDFY2	20	ENSG00000139668	Q96P53
AK4	19	ENSG00000162433	P27144
ASB15	19	ENSG00000146809	Q8WXK1
ATF2	19	ENSG00000115966	P15336
BUB1B	19	ENSG00000156970	O60566
DHX15	19	ENSG00000109606	O43143
DNM3	19	ENSG00000197959	Q9UQ16
ETV6	19	ENSG00000139083	P41212
FBXL13	19	ENSG00000161040	Q8NEE6
HECW2	19	ENSG00000138411	Q9P2P5
MEF2C	19	ENSG00000081189	Q06413
NR3C1	19	ENSG00000113580	P04150
PDE4D	19	ENSG00000113448	Q08499
RNF19B	19	ENSG00000116514	Q6ZMZ0

Table A1. *Cont.*

GENE	Degree	Ensembl	UniProtKB
RNF217	19	ENSG00000146373	Q8TC41
RXFP2	19	ENSG00000133105	Q8WXD0
RYR1	19	ENSG00000196218	P21817
THBS2	19	ENSG00000186340	P35442
AKT3	18	ENSG00000117020	Q9Y243
BARD1	18	ENSG00000138376	Q99728
CTNNA2	18	ENSG00000066032	P26232
HDAC7	18	ENSG00000061273	Q8WUI4
ITGAV	18	ENSG00000138448	P06756
PARD3	18	ENSG00000148498	Q8TEW0
PCSK2	18	ENSG00000125851	P16519
PIK3C2B	18	ENSG00000133056	O00750
PIK3C2G	18	ENSG00000139144	O75747
UBQLN1	18	ENSG00000135018	Q9UMX0

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