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Interactome Analyses implicated *CAMK2A* in the genetic predisposition and pharmacological mechanism of Bipolar Disorder

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ABSTRACT

Bipolar disorder (BPD) is a severe mental illness characterized by fluctuations in mood states, behaviors and energy levels. Growing evidence suggests that genes associated with specific illnesses tend to interact together and encode a tight protein-protein interaction (PPI) network, providing valuable information for understanding their pathogenesis. To gain insights into the genetic and physiological foundation of BPD, we conduct the physical PPI analysis of 184 BPD risk genes distilled from genome-wide association studies and exome sequencing studies. We have identified several hub genes (*CAMK2A*, *HSP90AA1* and *PLCG1*) among those risk genes, and observed significant enrichment of the BPD risk genes in certain pathways such as calcium signaling, oxytocin signaling and circadian entrainment. Furthermore, while none of the 184 genetic risk genes are "well established" BPD drug targets, our PPI analysis showed that αCaMKII (encoded by *CAMK2A*) had direct physical PPIs with targets (*HRH1*, *SCN5A* and *CACNA1E*) of clinically used anti-manic BPD drugs, such as carbamazepine. We thus speculated that αCaMKII might be involved in the cellular pharmacological actions of those drugs. Using cultured rat primary cortical neurons, we found that carbamazepine treatment induced phosphorylation of αCaMKII in dose-dependent manners. Intriguingly, previous study showed that *CAMK2A* heterozygous knockout (*CAMK2A*$^{+/-}$) mice exhibited infradian oscillation of locomotor activities that can be rescued by carbamazepine. Our data, in combination with previous studies, provide convergent evidence for the involvement of *CAMK2A* in the risk of BPD.

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1. Introduction

Bipolar disorder (BPD) is a common mental illness characterized by recurrent manic and depressive episodes, and affects about 1% of the global populations (Grande et al., 2016; Vieta et al., 2018). Patients with BPD usually exhibit swings in emotions and behaviors, as well as dysregulations in circadian rhythm (Alloy et al., 2017; Harvey, 2008). Although previous basic and clinical studies have suggested dysfunctions in certain subcortical brain regions of BPD patients, including aberrant synaptic development, plasticity and transmission (Forrest et al., 2018; Harrison et al., 2018; Penzes et al., 2011), the pathological mechanisms are yet to be fully characterized. BPD is considered to be a highly heritable psychiatric disorder, whose heritability was estimated to be more than 70% (Craddock and Sklar, 2013). To date, studies have confirmed substantial contributions from genetic risk factors to BPD, which are built by both common and rare genetic variations (Craddock and Sklar, 2013; Sullivan et al., 2012). Indeed, accumulating genetic risk factors for BPD have been identified through genome-wide association studies (GWAS) and exome sequencing studies (ESS). For example, 30 BPD risk loci in European subjects were reported by the PGC Bipolar Disorder Working Group in a GWAS of 29,764 cases and 169,118 controls (Stahl et al., 2019). In this study, multiple risk genes for BPD were confirmed or highlighted, such as *CACNA1C*, *ANK3*, *TRANK1* and *NCAN etc.* (Stahl et al., 2019). Meanwhile, ESS have also identified a number of BPD genetic risk factors, of which some are overlapped with those found in GWAS studies. For instance, Kataoka et al. (2016) has reported numerous *de novo* mutations by trio-based exome sequencing. In sum, GWAS (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Nurnberger et al., 2014; Ryu et al., 2017; Stahl et al., 2019) and ESS (Ament et al., 2015; Goes et al., 2016; Kataoka et al., 2016; Rao et al., 2017) have implicated more than one hundred potential risk genes of BPD (Table S1).

While the genes identified through GWAS and ESS likely account for a considerable genetic liability to BPD susceptibility, the whole genetic architecture of BPD remains largely unclear. Investigations using increased sample size and/or different methodologies are called up for characterizing additional unknown risk factors. Convergent functional genomics (CFG), which have identified susceptibility genes for BPD with robust evidence (Le-Niculescu et al., 2007; Niculescu and Le-Niculescu, 2010), are thought to be plausible approaches for this purpose. Also, previous studies found that interconnected protein-protein interaction (PPI) networks (Lage et al., 2007; Lim et al., 2006; Rossin et al., 2011) are usually formed by physical interaction between proteins encoded by genes associated with specific illnesses, e.g., schizophrenia (Liu et al., 2018). This is likely explained by the fact that genes/proteins in shared biological processes usually interact with each other to exert functions in these diseases together (Liu et al., 2018). There are currently several types of PPIs, among which physical PPI network is one of the most common interactome networks (Huttlin et al., 2017; Vidal et al., 2011) that are utilized in the prioritization and discovery of novel risk candidates for psychiatric diseases (Sun et al., 2010). We therefore sought to investigate whether BPD susceptibility genes/proteins encoded a densely physical PPI network and converged on common molecular pathways, and whether physical PPI analysis could aid in identifying novel risk genes for this illness.

The results of the current study might also help to identify the pathogenesis of BPD and to develop better clinical management strategies (Nelson et al., 2015; Sanseau et al., 2012). Several studies have shown that identification of risk genes for psychiatric disorders might benefit the drug repositioning of psychiatric disorders including BPD (Lencz and Malhotra, 2015; So et al., 2016; So and Wong, 2019). Comparison between GWAS imputed transcriptome of psychiatric disorders and drug expression profiling from the Connectivity Map (Lamb et al., 2006) allowed successful drug repositioning and even novel drug candidates identification, demonstrating the value of genetic data in guiding drug discoveries (So et al., 2016). Meanwhile, Cao et al. (2014) also showed that GWAS approach might only detect a small fraction of existing drug targets. Therefore, genetic risk genes may be directly translated into novel drug targets, or their protein products may interact with existing drug targets and exert impact on the effects of current medications. According to Vieta et al. (2018) review, 13 drugs have been approved by the US FDA for treatment of acute bipolar mania, bipolar depression and maintenance, among which four are mood stabilizers and nine are antipsychotics. Although these drugs are clinically effective, the biological mechanisms underlying their effects are poorly understood, limiting the development of novel drugs and the improvement of their existing applications. We believe that understanding the overlaps and/or interactions between proteins encoded by BPD risk genes and targets of these drugs will provide essential information regarding their actions and optimal usage.

Here, we conducted physical PPI analysis of 184 BPD risk genes distilled from GWAS and ESS, and found that these BPD risk genes/proteins tended to form a larger and more densely interconnected disease module compared to random genes, and several hub genes (*CAMK2A, PLCG1* and *GRIN2A*) in the PPI network were identified. Though none of the risk proteins have been reported as direct BPD drug targets of known pharmacological actions, five (*ANK3*, *GRIN2A*, *CAMK2A*, *DNAH9* and *MEF2C*) showed direct PPIs with these drug targets. Notably, the protein αCaMKII encoded by BPD risk gene *CAMK2A* directly interacted with three of BPD drug targets (*HRH1*, *SCN5A* and *CACNA1E*). To test whether αCaMKII participated in the cellular process of existing BPD drugs, we treated neurons with two BPD drugs (carbamazepine and chlorpromazine) and measured the protein levels of total and phosphorylated αCaMKII. We observed that both drugs increased the phosphorylation of αCaMKII (at residue Thr286) in dose-dependent manners.

2. Experimental procedures

The study protocol was approved by the institutional review board of the Kunming Institute of Zoology, Chinese Academy of Sciences. All participants provided written informed consents.

2.1. Data collection

BPD risk genes The BPD risk genes were extracted primarily according to two criteria: ① they were located in or adjacent to the regions showing genome-wide significance ($p < 5.00 \times 10^{-8}$) in recent GWAS (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Nurnberger et al., 2014; Stahl et al., 2019), or ② they contained rare (exonic or regulatory) mutations that were enriched in BPD patients compared with normal controls in recent ESS (Ament et al., 2015; Goes et al., 2016; Kataoka et al., 2016; Rao et al., 2017), and the gene names were extracted from the main text or supplementary materials of those previous studies. Finally, a total of 184 non-overlapping BPD risk protein-coding genes were selected for the subsequent analysis (Table S1). The impacts of the risk variants/mutations on gene expression or protein function were not assessed in the present study, and the criteria of candidate gene selection was primarily according to genomic coordinates and linkage disequilibrium (LD) status.

PPIs resources For PPIs analyses, we utilized six well-characterized PPIs datasets, including CORUM (Ruepp et al., 2010), BioPlex (Huttlin et al., 2015), CCSB (Rolland et al., 2014), IntAct (Orchard et al., 2014), BioGRID (Chatr-Aryamontri et al., 2017), and GeneMANIA (Zuberi et al., 2013). All physical PPIs extracted from these six databases were merged, and 471,449 non-duplicated PPIs were assembled. Detailed information are shown in Supplements.

BPD drugs and drug targets A recent review listed 13 drugs approved by the US FDA for treatment of BPD (Vieta et al., 2018). The DrugBank database (version 5.1.1) presents basic information of drugs

and their possible targets (Wishart et al., 2018). When the therapeutic action of a certain drug is driven by its activity towards a particular target, the pharmacological action tag for this drug-target pair will show "Yes"; when the activity of a drug towards its known target is not related to its therapeutic activity, the respective pharmacological tag will be "No"; in the event that such correlation has not been established or denied, the pharmacological tag will be "Unknown". In the DrugBank database, the 13 selected BPD drugs have 13 targets with the pharmacological action tagged "Yes", and 75 additional drug targets with pharmacological action tagged "Unknown" (detailed information of the 13 BPD drugs and drug targets is shown in Table S2).

2.2. Calculation of PPIs network parameters among BPD risk genes

Physical PPIs among BPD risk genes were constructed using CytoScape (Shannon et al., 2003). We downloaded the version 27 of the human gene annotation file from the GENCODE website (Harrow et al., 2012). There are 19,802 protein-coding genes extracted from gene annotation file. To investigate whether BPD risk genes were significantly interconnected in the PPI network, we performed a permutation test by randomly selecting 184 genes (which is equal to the number of BPD risk genes) from 19,802 protein-coding genes for 10,000-times and generated 10,000 random PPI networks. We then obtained the distribution of the number of total connections and the number of genes included in the largest PPI subnetwork in 10, 000 random PPI networks (Gursoy et al., 2008). We assessed whether these PPI parameters of BPD risk genes ranked top 5% among the distribution of 10,000 random PPI networks using one-tailed test.

To prioritize the importance of each BPD risk gene/protein (as node) in PPI network, we calculated topological parameters of each node, including degree, betweenness centrality, and other components using NetworkAnalyzer v2.7 (Assenov et al., 2008; Gao et al., 2018). We defined genes/protein with degree > 10 and betweenness centrality > 0.1 as hub genes (Gao et al., 2018; Nair et al., 2014), and we also calculated kleinberg's hub centrality scores of each node using igraph package (http://igraph.org/) in R.

2.3. Functional annotation analyses of BPD risk genes

We performed functional annotation analyses (with KEGG pathway annotation and Gene Ontology (GO) annotation) to investigate whether the BPD risk genes in the PPI subnetwork were enriched for specific functional categories using R package clusterProfiler (Yu et al., 2012). GO terms included biological process (BP). KEGG pathways and GO BP terms with less than five genes were excluded, and significantly enriched KEGG pathways and GO BP terms were defined as having FDR-corrected p-values less than 0.01.

2.4. Identification of novel candidate risk genes through PPI analysis

As mentioned above, protein products of genes associated with specific illnesses tend to physically interact with each other. Alternatively, if the protein encoded by a specific gene (not from the 184 BPD risk gene list) was found physically interacting with those encoded by BPD risk genes in the PPI analysis, it might also be potentially involved in the risk of BPD, although such genes/protein may not show genome-wide associations in the recent GWAS or ESS. Such genes were concluded and then further investigated to examine whether they showed associations in genetic samples or whether their expression levels were altered in BPD patients compared with controls.

2.5. PPI analysis between BPD genetic risk genes and targets of BPD drugs

As mentioned in a previous study (Cao and Moult, 2014), genetic analyses may only detect a tiny portion of existing drug targets, and the authors also proposed that genetic risk proteins may physically interact with existing drug targets rather than themselves. Based on this contention, we further hypothesized that the more PPIs observed between a genetic risk gene/protein with drug targets, the more likely that this risk gene/protein is a key molecule in the cellular processes involved in the action of the drug. To test this hypothesis, we analyzed the PPI network formed by BPD genetic risk genes/proteins and targets of BPD drugs extracted from DrugBank.

2.6. Cortical neuronal cultures and drug treatment

Dissociated cortical neurons were prepared from Sprague Dawley rat at E18–E19 days of gestation. The 6-well culture-plates were coated with poly-D-lysine (10 μg ml^{-1}) for 12 h at 37 °C, and neurons were then seeded to a density of 1×10^6 viable cells/well. Neurons were cultured in the Neurobasal medium with 2% B27 (Invitrogen), 2.0 mM glutamax, and 2.5% fetal bovine serum. Neurons were treated with drugs at 6 days *in vitro* (DIV), and treatments were performed with two BPD drugs: carbamazepine (1 μM, 5 μM, 10 μM, 50 μM, 100 μM) and chlorpromazine (0.1 μM, 1 μM, 2 μM, 3 μM, 5 μM), no-drug controls were performed at each time of experiment. The concentrations of drugs used in treatment were determined according to previous studies (Niespodziany et al., 2015; Shi et al., 1989) and our pilot experiments. The drugs were purchased from TargetMol (carbamazepine, catalog number T0943, molecular formula C15H12N2O; chlorpromazine hydrochloride, catalog number T1384, molecular formula C17H19CIN2S•HCL). The rat neurons were treated with these drugs for 48 h, and then proceeded to protein extraction. All experiments were replicated at least three times.

2.7. Western blots

Anti-αCaMKII (#50049, diluted at 1:1000) and anti-phospho-CaMKII (at residue Thr286 of αCaMKII, diluted at 1:1000) (#12716) antibodies were purchased from Cell Signaling Technology, and anti-alpha-tubulin (#sc-8035, diluted at 1:1000) antibody was purchased from Santa Cruz Biotechnologies. The protocol of Western blot was similar to a previous study (Chang et al., 2016). In brief, after 48 h of drug treatment, rat neurons were rinsed with cold PBS and lyses were prepared using RIPA lysis buffer containing protease and phosphatase inhibitors. The protein were quantified using the BCA kit (Thermo Scientific). The cell lysates containing denatured proteins were separated on an 8% SDS-PAGE gel and then wet transferred to polyvinylidene fluoride (PVDF) membranes, which were then blocked using 5% non-fat milk for detection of total proteins or 5% bovine serum albumin for detection of phosphorylated proteins. The membranes were then incubated with primary antibodies at 4 °C overnight, followed by rinsing 3 times with Tris-buffered saline solution containing 0.2% Tween 20, and then incubated with peroxidase-linked secondary antibodies for 60 min at room temperature. Finally, the membranes were incubated with SuperSignal West FemtoChemiluminescent Substrate (Thermo Scientific) for detection of HRP in dark chamber and images were captured by Tanon 5200 imaging system (Tanon).

3. Results

3.1. Overview of study design and research logic

An overview of the strategy for the current hypothesis-driven analyses and experiments, from PPI analysis of proteins encoded by BPD risk genes as well as their interactions with BPD drug targets, to the total levels and phosphorylation statuses of BPD risk associated proteins induced by BPD drugs, is summarized in Fig. 1.

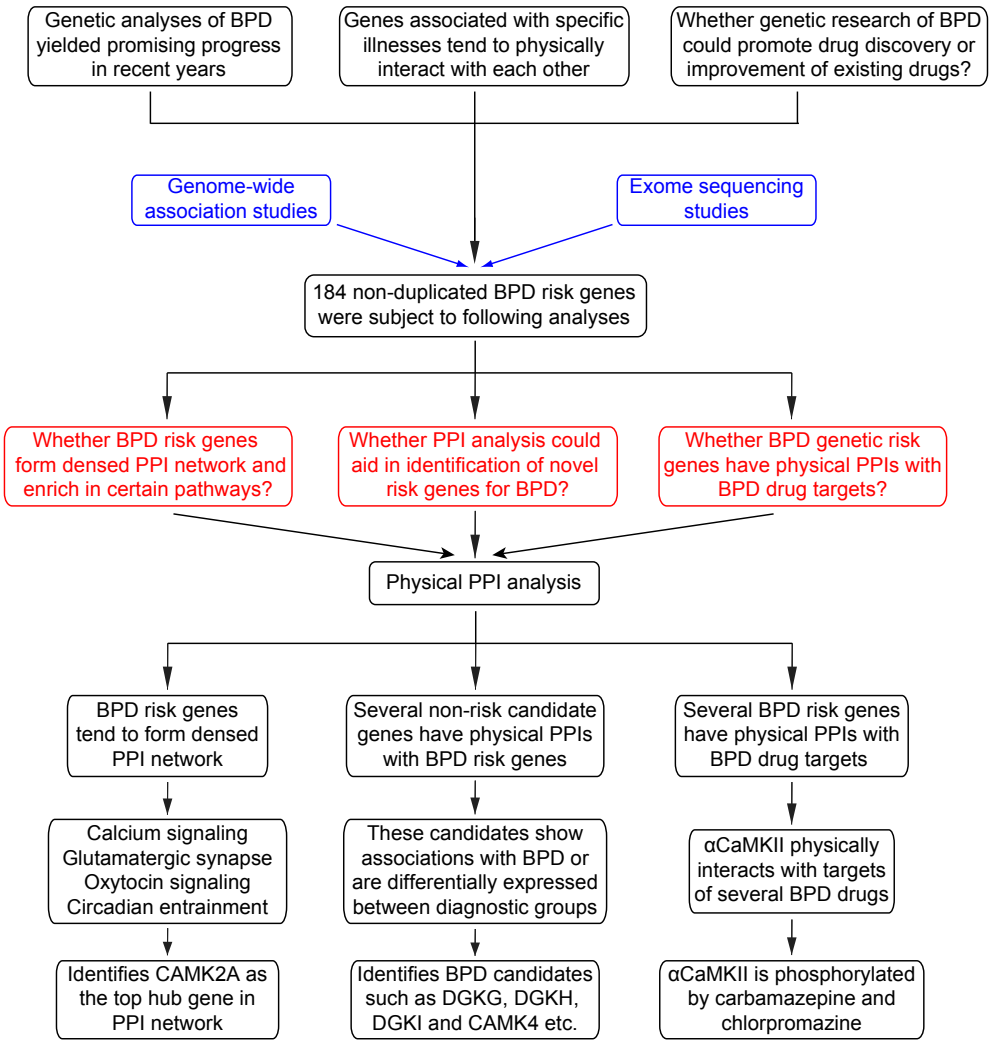

Fig. 1. Overview of study design and research logic.

3.2. BPD risk genes encoded an interconnected PPI network and identified a hub gene CAMK2A

During the PPI analysis, we found that among the 184 BPD risk genes/proteins, 95 of them have direct physical PPIs with other protein products of BPD risk genes, yielding a total of 119 PPI connections among them (Fig. 2A). The largest PPI subnetwork constructed by BPD risk genes/proteins has 80 nodes and 110 edges (i.e., interactions). To assess if the interactions observed between proteins encoded by these BPD risk genes were due to random effect, we performed a simulation by generating 10,000 PPI networks using 184 genes randomly selected from the genome. The number of nodes and edges in the largest PPI subnetwork were compared to those in the BPD risk genes/proteins PPI analyses by permutation test. We found that the number of physical PPIs between proteins encoded by BPD risk genes were significantly larger than that of interactions randomly generated ($p = 0.0066$ for number of edges, and $p = 0.0095$ for number of nodes in the largest subnetwork; Fig. 2B and C), suggesting that BPD risk genes/proteins likely exhibit more physical PPIs between each other.

To further characterize of the PPI network constructed by protein products of the BPD risk genes, we further collected and examined multiple network parameters, including degree, betweenness centrality and other components, and thereby identified 3 hub genes including *CAMK2A*, *HSP90AA1* and *PLCG1* (Table 1). We also calculated the kleinberg's hub centrality scores of each node (gene) and found that *CAMK2A* had the highest score among all the risk genes in the PPI network (Table 1). At the genome-wide level, *CAMK2A* has PPIs with 241 genes/proteins in the full PPI network (Figure S1), among which 15 are BPD risk genes and seven encode BPD drug targets. *CAMK2A* was reported to be significantly associated with BPD in a recent ESS, and its rare regulatory variants were found significantly enriched in BPD patients than controls (Ament et al., 2015). In addition, a CFG analysis that integrated genetic and functional studies of BPD in human and animal models also identified *CAMK2A* as a leading candidate gene for this illness (Le-Niculescu et al., 2009). More intriguingly, a previous study reported that *CAMK2A* heterozygous knockout (*CAMK2A*$^{+/-}$) mice exhibited infradian oscillation of locomotor activity, deficits in cognitive memory, and abnormalities in the maturation of granule cells in the hippocampal dentate gyrus (Yamasaki et al., 2008), which is in proxy to the phenotypes frequently observed in patients with BPD (Alloy et al., 2017; Arts et al., 2008; Glahn et al., 2010; Walton et al., 2012). Furthermore, the authors found that many circadian genes were related to the infradian rhythm behavior in the *CAMK2A* heterozygous knockout mice (Hagihara et al., 2016). These lines of evidence converged together with our PPI analysis and highlighted the essential roles of *CAMK2A* in the genetic risk and pathogenesis of BPD.

3.3. BPD risk genes are enriched in oxytocin signaling pathway and circadian entrainment

Our PPI analysis showed that proteins encoded by 80 BPD risk genes encoded a densely PPI network (Fig. 2A). To further explore whether

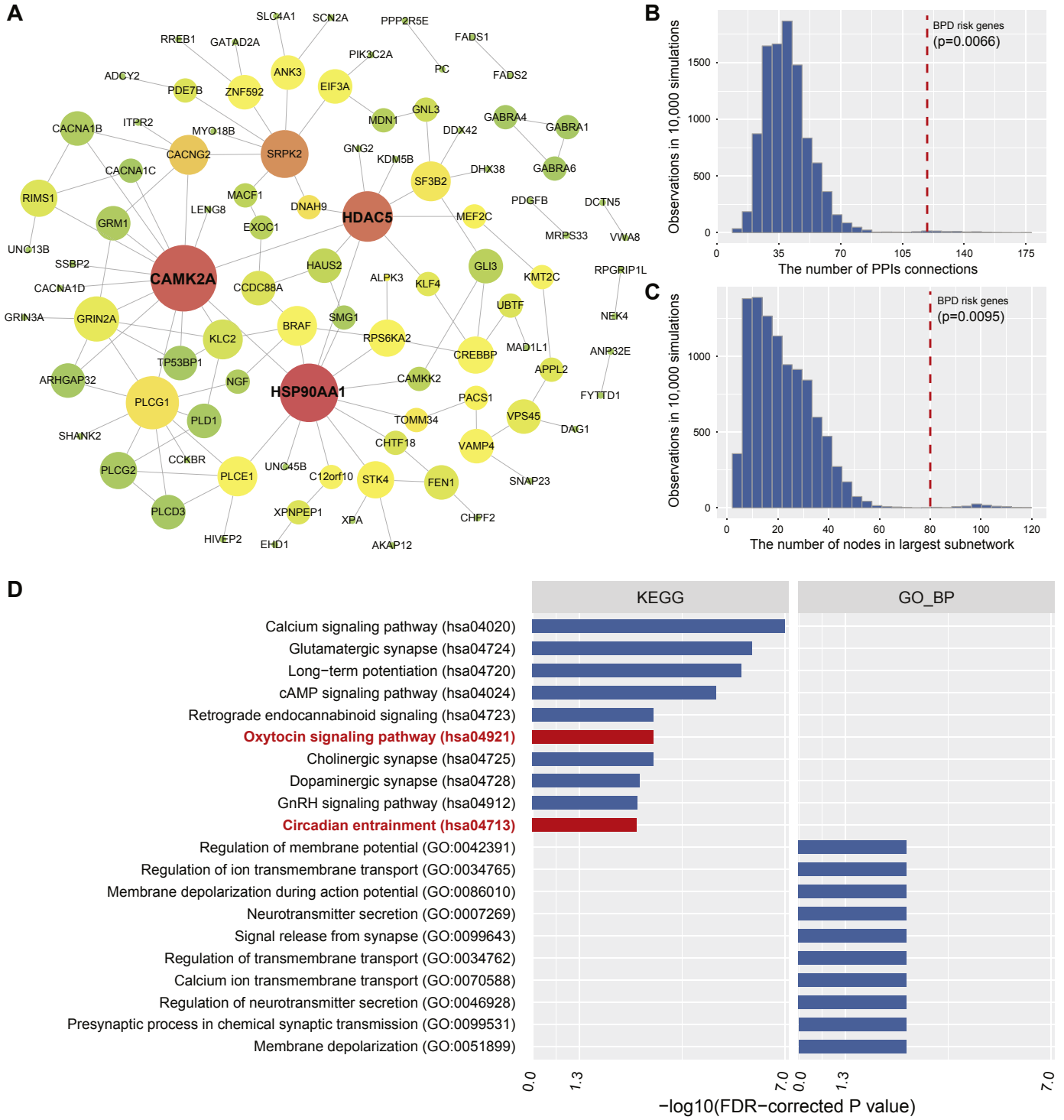

Fig. 2. Physical PPI and pathway analyses of BPD risk genes. (A) Among the 184 BPD risk genes, 95 have direct physical PPIs with other BPD risk genes and there are 119 PPI connections among them. The largest PPI subnetwork includes 80 nodes and 110 edges. In this PPIs network, *CAMK2A* is the most vital gene. **(B)** Among the 10,000 simulations of PPI analysis of randomly selected genes, we observed 66 times that the number of PPI connections constructed by random genes are larger than 119 (which is the number of PPI connections constructed by the 184 BPD risk genes). **(C)** Among the 10,000 simulations of PPI analysis of randomly selected genes, we observed 95 times that the number of nodes in the largest subnetwork PPI constructed by random genes are more than 80 (which is the number of nodes in the largest subnetwork PPI constructed by the 184 BPD risk genes). **(D)** BPD risk genes in the largest PPI subnetwork (N = 80) are significantly enriched in 25 KEGG pathways and 24 GO BP terms. We show top 10 terms among these pathways, and detailed results can be found in Table S3.

these 80 BPD genes/proteins converge on certain molecular pathways, we conducted KEGG and GO pathway analysis using clusterProfiler (Yu et al., 2012). Consistent with the results of previous studies (Ament et al., 2015; Khanzada et al., 2017), our KEGG and GO BP terms analysis revealed significant enrichment of calcium signaling pathway (hsa04020), glutamatergic synapse signaling pathway (hsa04724), regulation of membrane potential (GO:0042391), neurotransmitter secretion (GO:0007269) and others among the BPD risk genes/proteins in the densely PPI network (Fig. 2D, Table S3). Additionally, we also identified intriguing new pathways in the risk of BPD, such as oxytocin

Table 1
We identified 3 hub genes including *CAMK2A*, *HSP90AA1* and *PLCG1* in the PPI network. The topological parameters of top 10 genes sorted by degree are shown in the table.

Genes	Degree	Betweenness Centrality	Closeness Centrality	Clustering Coefficient	Eccentricity	Neighborhood Connectivity	Radiality	Stress	Topological Coefficient	Hub scores#
CAMK2A	15	0.40	0.39	0.11	6	4.60	0.83	3736	0.11	1.00
HSP90AA1	12	0.44	0.39	0.03	5	4.42	0.82	4382	0.10	0.52
PLCG1	10	0.11	0.31	0.16	7	4.40	0.75	1108	0.19	0.63
HDAC5	9	0.34	0.39	0.03	5	4.78	0.83	2906	0.12	0.38
SRPK2	8	0.28	0.29	0	7	2.63	0.73	2644	0.13	0.10
GRIN2A	7	0.03	0.30	0.33	7	5.71	0.74	286	0.24	0.61
CACNG2	5	0.16	0.32	0.2	7	6.00	0.77	1644	0.25	0.33
BRAF	5	0.05	0.31	0.1	6	5.20	0.75	592	0.23	0.25
KLC2	5	0.02	0.30	0.3	7	6.60	0.74	358	0.31	0.46
PLCE1	5	0.06	0.30	0.3	6	6.00	0.74	686	0.28	0.31

Note: we defined genes that the degree of which more than 10 and betweenness centrality more than 0.1 as hub genes.
#Hub scores: Kleinberg's hub centrality scores.

signaling pathway (hsa04921) and circadian entrainment (hsa04713). These discoveries provide valuable insights into the neurobiological basis of BPD. Indeed, oxytocin has been proven crucial for social cognition and adaptation (Kirsch et al., 2005), and BPD patients usually exhibit abnormalities in these functions (Mercedes Perez-Rodriguez et al., 2015). Moreover, dysfunctions in oxytocin signaling have been reported in psychotic and affective disorders (Rubin et al., 2014), and oxytocin has thus been proposed to be a potential trait marker for BPD (Turan et al., 2013). Besides, it is well known that one of the typical symptoms for BPD is circadian rhythm dysregulation (Harvey, 2008; Murray and Harvey, 2010; Wehr, 2018), and a recent review summarized that aberrant biological clock pace-making and circadian entrainment caused by internal and external factors likely contribute to BPD (Alloy et al., 2017). These results and our data also support the previous finding that mice with heterozygous knockout of *CAMK2A*, the hub gene for BPD, exhibited infradian oscillation of mood (Hagihara et al., 2016; Yamasaki et al., 2008).

3.4. Identification of novel candidates using physical PPIs followed by genetic and expression analyses

As stated above, there are likely additional genetic risk factors for BPD to be identified, and PPI based analysis might be a plausible method to discover novel risk genes. We here hypothesized that novel candidate risk genes/proteins for BPD, like the other BPD risk genes/proteins, tend to form a large physical PPI network with each other, and higher degree of PPIs between a specific protein-coding gene and the known 184 BPD risk genes/proteins suggests that this gene is likely a BPD risk factor. We developed a simple and straightforward method accordingly to define the candidate genes: if the number of PPIs between the specific gene (randomly selected from the genome) and 184 known BPD risk genes accounts for more than 10% of all known PPIs for this gene in the whole genome, it is considered a potential BPD risk gene. Using this approach, we found that 27 genes (not from the 184 BPD risk gene list) are closely linked to the BPD risk genes, and the degree of PPIs between each of these 27 genes and 184 known BPD risk genes accounts for more than 10% of all known PPIs in the genome (Table S4).

As proposed by CFG analysis, if a specific gene is a true risk factor for BPD, it may show associations with the illness in many aspects, such as genetic predispositions, expression profiling and functionality, as well as disease related intermediate phenotypes. We therefore examined expression alternations of the 27 candidate genes in the brains between BPD patients and healthy controls by re-analyzing the public RNA-seq data (GSE53239) (Akula et al., 2014) and results of a recent independent study (Cruceanu et al., 2015). In GSE53239 dataset, the expression of many genes (such as *DGKH*, *DGKI*, *CAMK4, RIT2* and *DGKB*) were significantly or marginally lower in the DLPFC of 11 BPD patients compared with that in the 11 healthy controls (*DGKH*, logFC = −0.264, p = 0.0593; *DGKI*, logFC = −0.573, p = 0.0111; *CAMK4*, logFC = −0.677, p = 0.00749; *RIT2*, logFC = −0.467, p = 0.0608; *DGKB*, logFC = −0.473, p = 0.0539; Table S5). In addition, in the independent RNA-seq analysis of anterior cingulate tissues from 13 BPD patients and 13 controls (Cruceanu et al., 2015), the authors observed significant reduction of the expression levels of *DGKH*, *DGKI*, *CAMK4, RIT2* and *CACNB3* in BPD patients compared with healthy controls (*DGKH*, logFC = −0.4431, p = 0.00802; *DGKI*, logFC = −0.4314, p = 0.0101; *CAMK4*, logFC = −0.5924, p = 0.0205; *RIT2*, logFC = −0.6483, p = 0.0108; *CACNB3*, logFC = −0.8146, p = 0.019; Table S5 of our supplementary material and Table S4 in their study (Cruceanu et al., 2015)).

We also chose several genes (*DGKH*, *DGKI*, *CAMK4*, *CACNB3*, *DGKG*, *DGKB* and *RIT2*) among the top of the 27 candidate genes and examined their associations with BPD in a GWAS from European populations (Psychiatric Gwas Consortium Bipolar Disorder Working Group, 2011). Although these genes did not show genome-wide significance in this GWAS sample (Psychiatric Gwas Consortium Bipolar Disorder Working Group, 2011), there were SNPs that survived gene-wide multiple corrections according to the number of tested SNPs in each gene (Figure S2). For example, a SNP rs3819863 in *DGKG* showed nominal significance in this European GWAS ($p = 6.71 \times 10^{-4}$, OR = 1.098, a total of 7481 cases and 9250 controls) (Psychiatric Gwas Consortium Bipolar Disorder Working Group, 2011). Although not reached genome-wide significance, this result could be caused by the moderate sample size. In fact, in a later larger European BPD GWAS (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018) which had substantial overlap with the above-mentioned GWAS (Psychiatric Gwas Consortium Bipolar Disorder Working Group, 2011), rs3819863 showed a stronger association with BPD ($p = 4.55 \times 10^{-4}$, OR = 1.056, a total of 20,129 patients and 21,524 controls). To replicate the associations, we conducted association analyses in an independent case-control sample collected from Han Chinese populations (1315 cases and 1956 controls), and found that rs3819863 was again nominally associated with BPD in the same directions ($p = 7.42 \times 10^{-3}$, OR = 1.147, Table S6). Meta-analysis combining the two samples observed a stronger association ($p = 2.04 \times 10^{-5}$, OR = 1.109, Table S6). In addition, a SNP rs2593116 in *DGKH* was also associated with BPD in the meta-analysis of the two samples surviving gene-wide corrections ($p = 1.30 \times 10^{-3}$, OR = 1.075, Table S6). Notably, although *DGKH* has not been included into our 184 BPD gene list, this gene has been identified in a previous small European GWAS of BPD and follow-up replications (Baum et al., 2008; Zeng et al., 2011).

Therefore, although these genes (e.g., *DGKG*, *DGKH*, *CAMK4* and *DGKI*) were not highlighted in recent GWAS or ESS, our results suggest that they are likely BPD risk factors and deserve further investigations.

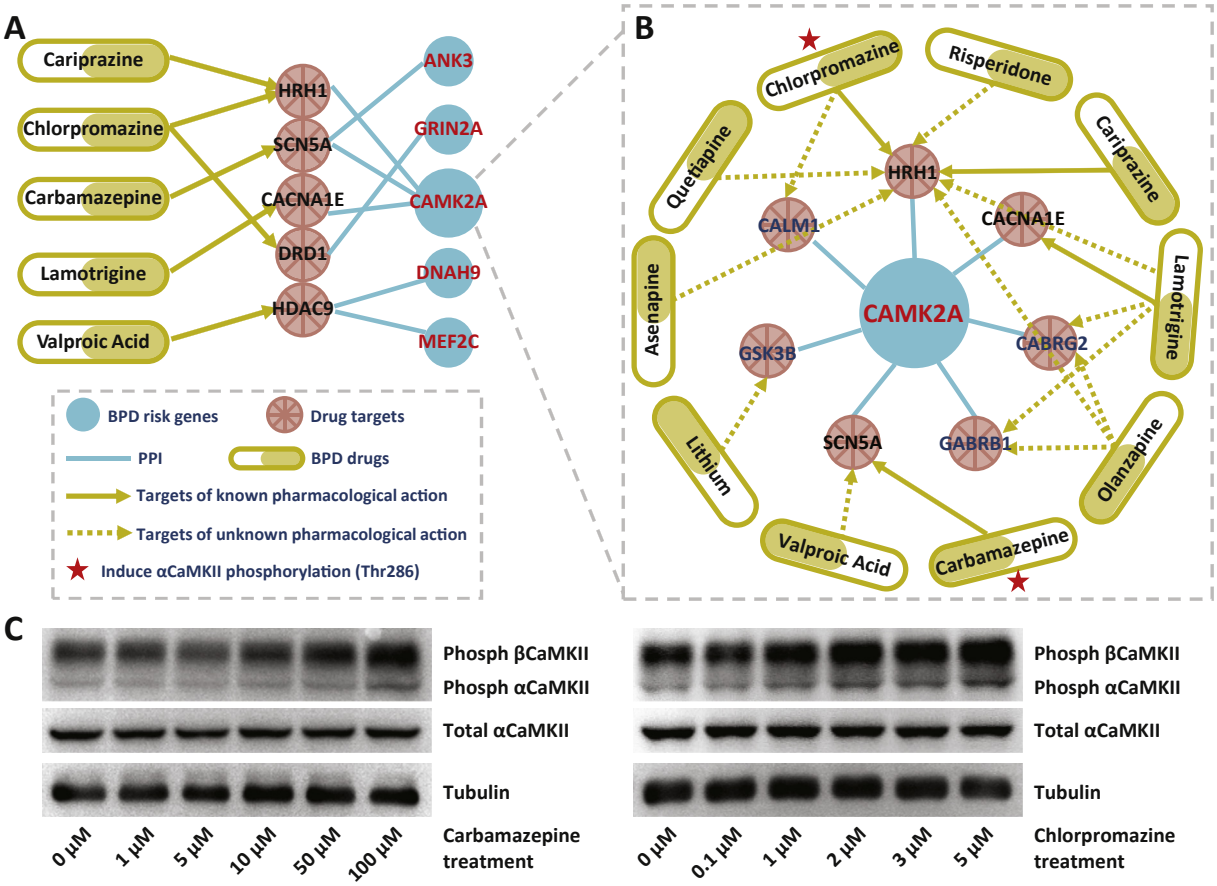

Fig. 3. Physical PPI analyses between BPD risk genes and drug targets, and Western blot of αCaMKII followed by treatment of carbamazepine and chlorpromazine. (A) Five risk genes have direct PPIs with five BPD drug targets of known pharmacological action. Among these five risk genes, *CAMK2A* interacts with three BPD drug targets. **(B)** In addition to the three targets of known pharmacological action, *CAMK2A* also directly interacted with four additional BPD drug targets of unknown pharmacological action: *GSK3B*, *CALM1*, *GABRB1* and *GABRG2*. **(C)** Carbamazepine and chlorpromazine induced phosphorylation of αCaMKII in rat primary cultured neurons. The full-scaled gel plot of Western blot is shown in Figure S4.

3.5. *CAMK2A is a hub molecule in the PPI network constructed by BPD risk genes and drug targets*

A recent review listed 13 drug entries that recorded to manage BPD (Table S2) (Vieta et al., 2018). As stated in the method section, these 13 BPD drugs have 13 targets proven to facilitate their respective clinical therapeutic actions (pharmacological action labeled as "yes"), as well as 75 additional targets with pharmacological action labeled as "Unknown". We firstly extracted the 13 targets with pharmacological action labeled as "Yes" (i.e., *HDAC9*, *ABAT*, *CACNA1E*, *SCN5A*, *DRD2*, *DRD1*, *HTR2A*, *HTR1A*, *ADRA1A*, *ADRA1B*, *HRH1*, *DRD3* and *HTR2B*) from the DrugBank database (Table S2). None of these drug targets were included in the 184 BPD risk genes identified by genetic analyses. However, when we performed the physical PPI analysis between the 184 BPD risk genes and these 13 drug targets with "Yes" pharmacological action label, we found that five risk genes (*ANK3*, *GRIN2A*, *CAMK2A*, *DNAH9* and *MEF2C*) had direct physical PPIs with five drug targets (*HRH1*, *SCN5A, CACNA1E, DRD1, HDAC9*) (Fig. 3A). Among those five risk genes/proteins, four of them (*ANK3*, *GRIN2A*, *DNAH9* and *MEF2C*) were predicted to interact with only one of the drug targets, while *CAMK2A* had direct PPIs with three BPD drug targets (*HRH1*, *SCN5A* and *CACNA1E*), which were proven to be targeted by 4 BPD drugs: carbamazepine, lamotrigine, cariprazine and chlorpromazine (Fig. 3A). We therefore hypothesized that *CAMK2A* might be involved in the action and effects of these drugs, providing potential opportunities for clinical applications. To test this hypothesis, we first performed subsequent expanded PPI analyses using drug targets labeled both "Yes" and "Unknown", and found that in addition to the three drug targets of known pharmacological action, the protein encoded by *CAMK2A* (αCaMKII) also has direct PPIs with four additional BPD drug targets of "Unknown" pharmacological action, such as *GSK3B*, *CALM1*, *GABRB1* and *CABRG2* (Fig. 3B).

3.6. *αCaMKII is phosphorylated after treatment with "anti-manic" BPD drugs carbamazepine and chlorpromazine*

αCaMKII is a primary isoform belonging to Ca^{2+}/calmodulin dependent protein kinase-II (CaMKII). αCaMKII plays a vital role in the glutamatergic synaptic plasticity and is crucial for cognition and memory in humans and other animals (Hudmon and Schulman, 2002; Robison, 2014). αCaMKII can be activated through the binding of Ca^{2+}/CaM followed by auto-phosphorylation of its residue threonine 286 (Thr286), leading to a persistent activity of CaMKII (Buard et al., 2010; Coultrap and Bayer, 2012; Erickson et al., 2008; Rellos et al., 2010), which is necessary for long-term potentiation and learning and memory (Fukunaga et al., 1993; Giese et al., 1998). As shown in Fig. 3A, there are 4 BPD drugs (carbamazepine, lamotrigine, cariprazine and chlorpromazine) targeting the three proteins (*HRH1, SCN5A* and *CACNA1E*) that have direct PPIs with αCaMKII. Intriguingly, in a previous study (Hagihara et al., 2016), carbamazepine was used to treat the mice with heterozygous knockout of *CAMK2A*, and rescued the impaired infradian oscillatory locomotor activities. Their results were considered direct demonstration of the anti-manic effects clinically observed in carbamazepine treatment of BPD patients (Okuma et al.,

1979; Weisler et al., 2005).

Based on these *prior* evidence as well as the physical interactions between αCaMKII and multiple BPD drug targets in our PPI analysis, we speculated that αCaMKII might participate in molecular pathways related to the mechanisms of action of those drugs. We first examined whether αCaMKII was modulated by carbamazepine in cultured primary neurons. As stated above, phosphorylation of Thr286 on αCaMKII is an important index for the activities and function of this protein, and we analyzed the phosphorylation status of this residue in rat neurons treated with carbamazepine. Briefly, cortical neurons dissociated from E17 rat embryos were cultured for 6 days, and then treated with different concentrations of carbamazepine for 48 h. Western blot analysis of lysates from these cells were performed, and we observed that endogenous αCaMKII phosphorylation at the residue Thr286 was significantly higher in cells treated with carbamazepine compared with vehicle controls (Fig. 3C). The total αCaMKII level was not altered by this drug.

We also examined the effects of chlorpromazine on αCaMKII. Chlorpromazine is one of the first antipsychotic reagents used clinically for the treatment of manic phase of BPD (Ban, 2007; Lopez-Munoz et al., 2005). Although a previous study showed that chlorpromazine is less effective than carbamazepine in the clinical management of manic state in BPD (Okuma et al., 1979), our results showed that chlorpromazine could also phosphorylate αCaMKII in a dose-dependent manner in rat neurons (Fig. 3C). Although the cellular mechanisms underlying the pharmacological actions of carbamazepine and chlorpromazine are not fully understood, our results and previous studies (Hagihara et al., 2016; Yamasaki et al., 2008) suggested potential involvement of αCaMKII in the therapeutic effects of mood stabilizers and major antipsychotics against mania.

4. Discussion

Previous studies showed that susceptibility genes/proteins of psychiatric disorders tend to enrich in particular molecular pathways, such as histone methylation, inflammatory responses, neuronal processes, *etc.* (Network Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015), suggesting that the risk genes might contribute to disease susceptibility in an aggregated manner rather than acting individually (Liu et al., 2018). We herein conducted the PPI and pathway analysis of 184 BPD risk genes identified by recent GWAS and ESS, and as expectedly, found that 80 of them formed a significantly densely PPI network, and enriched in several specific biological pathways. Taken one step further, we attempted to identify novel candidate risk genes for BPD using the PPI analysis, and we found several genes with more frequent physical interactions with the BPD susceptibility genes than random genes across genome (e.g., *DGKG* and *DGKH*). These genes failed to show genome-wide associations with BPD in recent GWAS (Stahl et al., 2019). However, previous studies have presented multiple cases in which early stages of GWAS failed to identify bona-fide genome-wide significant risk genes due to the limited sample size, and emerging risk genes were progressively highlighted when the sample size increased to more than 100,000 individuals (Schizophrenia Working Group of the Psychiatric Genomics, 2014). For example, *DRD2* and *GRM3*, which have been widely recognized in the candidate gene era due to their pivotal roles in the pathology of schizophrenia (Egan et al., 2004; Glatt et al., 2003, 2009), were only found genome-wide significantly associated with this illness in recent GWAS of large sample pools (Schizophrenia Working Group of the Psychiatric Genomics, 2014). To this end, we conducted independent genetic analyses and differential expression analyses of the potential candidate genes in the PPI network, and found that even they did not show genome-wide significant associations in previous studies, they showed dysregulated expression in BPD cases compared to normal controls, and displayed consistent nominal significant associations in independent samples. Therefore, these convergent evidence suggest potential roles of those genes in the risk of BPD.

Results of the current study suggest involvement of *CAMK2A* in the risk of BPD, which is intriguing and yet not unexpected. Although none of the common SNPs in this gene showed genome-wide significance in recent BPD GWAS (Stahl et al., 2019), ESS found that rare variations in the regulatory regions of *CAMK2A* were significantly enriched in BPD patients compared with controls (Ament et al., 2015). This result is also in concordant with the long-term hypothesis that genetic risk of complex psychiatric disorders is involved with both common and rare variations (Sullivan et al., 2012). αCaMKII is brain-specifically expressed and acts as a key regulator during memory and learning processes (Erondu and Kennedy, 1985; Miller and Kennedy, 1986), which is found essential in the induction of hippocampal long-term potentiation and synaptic plasticity (Coultrap and Bayer, 2012; Silva et al., 1992). Not surprisingly, *CAMK2A* is identified as the top candidate gene in a recent CFG study of BPD (Le-Niculescu et al., 2009). In addition, decreased mRNA expression of *CAMK2A* has also been reported in the brains of BPD patients compared with healthy controls (Xing et al., 2002). In our re-analysis of existing RNA-seq datasets (Akula et al., 2014), expression of *CAMK2A* was also marginally down-regulated ($\log FC = -0.327$, $p = 0.090$). In addition, we also identified two candidate risk genes (*BSN* and *FAM171A1*) that showing PPI interactions with *CAMK2A*, and both of them showed significant down-regulation in the BPD patients versus controls (Table S5). These data confirmed the feasibility of the current PPI analyses and such strategy for identifying BPD risk factors.

One of the primary goals of genetic studies of complex diseases is to develop new therapeutic approaches. Several previous studies have attempted to identify novel drug targets for psychiatric disorders using GWAS data (Docherty et al., 2017; Gaspar and Breen, 2016; Lencz and Malhotra, 2015; So et al., 2016, 2017; So and Wong, 2019; Zhao and So, 2019), and gained valuable insights as schizophrenia GWAS results showed increased enrichment for antipsychotic drugs. (Lencz and Malhotra, 2015). However, most of these previous studies mainly focused on schizophrenia and major depressive disorder. We herein explored the targets of approved BPD treatment drugs for BPD susceptibility genes, and found that none of the risk genes reported by genetic studies were direct targets of known pharmacological action. As proposed in a previous study (Cao and Moult, 2014), protein interactions might be a good option to identify novel drug target, we again performed the PPI analysis using BPD risk genes and BPD drug targets. Our results showed that five risk genes had direct PPIs with five BPD drug targets. Among those five risk genes, *CAMK2A* interacted with three BPD drug targets with known pharmacological action. Additionally, the phosphorylation of αCaMKII in rat neurons was also increased after treatment with carbamazepine and chlorpromazine in a dose-dependent manner, suggesting participation of this protein in the signaling pathway induced by these drugs. Although the evidence is still preliminary, our results might provide an intriguing example that the hub genes of PPI networks constructed by genetic risk genes and drug targets are potential novel drug targets that worth further investigations.

Besides the intriguing findings present in the current study, there are however limitations to acknowledge. First, while our data strongly suggests that carbamazepine and chlorpromazine likely induce phosphorylation of αCaMKII at Thr268, the precise molecular mechanisms regarding how αCaMKII is phosphorylated are not clear. To gain some insights into the interaction between αCaMKII and carbamazepine or chlorpromazine, we used AutoDock Vina (Trott and Olson, 2010) to predict the binding affinity between these two drugs and the ATP binding pocket of αCaMKII (Figure S3). Table S7 showed that these two drugs had a lower docking energy score than ATP, the natural substrate of αCaMKII, suggesting that these two drugs might directly bind to this protein, resulting in alteration of its phosphorylation status. However, αCaMKII is a central molecule and could be phosphorylated by many other kinases, so there is also the possibility that carbamazepine and chlorpromazine might act on other molecules upstream of αCaMKII to

result in the observed increase of phosphorylation at Thr268. Further studies are needed to test either hypothesis. Second, although αCaMKII has been highlighted for its essential roles in the long-term potentiation and relevant memory functions, whether the mood stabilizer (e.g., carbamazepine) resulted phosphorylation status change is related to such function of αCaMKII remains to be elucidated. As shown in a previous study (Hagihara et al., 2016), mice with heterogeneous knockout of *CAMK2A* displayed aberrant emotional phenotypes and infradian rhythm behaviors, and carbamazepine could partially rescue these deficits. Since the cellular pathways affected by carbamazepine is not fully characterized, αCaMKII might be an interesting target to investigate the pharmacological action of carbamazepine. Future studies analyzing the relevance between the phosphorylation alterations in αCaMKII and cognitive or emotional functions may even promote our understanding of the major endophenotypes (e.g., synaptic plasticity) of these neurological processes.

In summary, using PPI analysis of BPD genetic risk genes identified by GWAS and ESS, we show that proteins encoded by these genes physically interact with each other and converge on several major biological pathways likely related to the pathogenesis of BPD. We have also highlighted several hub genes in the genetic risk of BPD, in which one of them, *CAMK2A*, is likely an important player in the action of major anti-BPD medications. Further investigations dissecting the mechanisms by which this gene and its protein product participate in BPD may provide valuable information for understanding and clinical management of this illness.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Contributors

Authors ML, HL and LG designed the study. Authors HL, DSZ and HC generated the primary data. Authors LW and WL conducted the neuron culture. Author XX performed the drug treatment. Author SXD assisted the drug-gene interaction prediction. Authors DSZ, CZ, JC, WL, XL, WF, WT, WT, FL, YH and YB collected the clinical samples. Author ZH contributed to the functional experiments. Authors ML, XX and HL wrote the paper. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

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