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ARTICLE

Genome-wide Mendelian randomization identifies actionable novel drug targets for psychiatric disorders

Jiewei Liu[1], Yuqi Cheng[2], Ming Li[1], Zhijun Zhang[3,4], Tao Li[5] and Xiong-Jian Luo[3,4]✉

Psychiatric disorders impose tremendous economic burden on society and are leading causes of disability worldwide. However, only limited drugs are available for psychiatric disorders and the efficacy of most currently used drugs is poor for many patients. To identify novel therapeutic targets for psychiatric disorders, we performed genome-wide Mendelian randomization analyses by integrating brain-derived molecular quantitative trait loci (mRNA expression and protein abundance quantitative trait loci) of 1263 actionable proteins (targeted by approved drugs or drugs in clinical phase of development) and genetic findings from large-scale genome-wide association studies (GWASs). Using transcriptome data, we identified 25 potential drug targets for psychiatric disorders, including 12 genes for schizophrenia, 7 for bipolar disorder, 7 for depression, and 1 (*TIE1*) for attention deficit and hyperactivity. We also identified 10 actionable drug targets by using brain proteome data, including 4 (HLA-DRB1, CAMKK2, P2RX7, and MAPK3) for schizophrenia, 1 (PRKCB) for bipolar disorder, 6 (PSMB4, IMPDH2, SERPINC1, GRIA1, P2RX7 and TAOK3) for depression. Of note, MAPK3 and HLA-DRB1 were supported by both transcriptome and proteome-wide MR analyses, suggesting that these two proteins are promising therapeutic targets for schizophrenia. Our study shows the power of integrating large-scale GWAS findings and transcriptomic and proteomic data in identifying actionable drug targets. Besides, our findings prioritize actionable novel drug targets for development of new therapeutics and provide critical drug-repurposing opportunities for psychiatric disorders.

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INTRODUCTION

Psychiatric disorders (including schizophrenia, bipolar disorder (BP), depression and attention deficit and hyperactivity (ADHD)) impose enormous economic burden on society and are a major global public health threat [1, 2]. Due to the high prevalence, substantial mortality and morbidity, psychiatric disorders contributed about 14% of global burden of disease [1, 2]. Mental disorders affect about 18% population of the worldwide [3] and the global costs of mental disorders were estimated about 2.5 trillion US dollars in 2010 [4]. The COVID-19 pandemic further exacerbates the threat of psychiatric disorders [5]. There is a pressing need for efficient intervention and treatment of mental disorders.

So far, treatment of psychiatric disorders remains a major challenge. First, only limited drugs are available for psychiatric disorders [6–12]. Second, most of the approved drugs exert their therapeutic effects by targeting a small number of specific molecular targets. For example, almost all antipsychotics exert their therapeutic effects by antagonizing type 2 dopaminergic receptor (DRD2) [13–15], and most antidepressants targeting monoaminergic systems (including dopaminergic, noradrenergic and serotonergic systems) [16–18]. Third, in addition to beneficial therapeutic effects, antipsychotics and antidepressants also bring considerable side effects [19–27], including hyperlipidemia, myocarditis, weight gain, sexual side effects, type II diabetes mellitus, etc. Fourth, many drugs take effect slowly (about several weeks). Finally, many patients do not respond to pharmacological treatment (i.e., treatment resistant) [28–34]. These challenges account for a large proportion of the enormous costs of psychiatric disorders.

Despite the fact that psychiatric disorders impose tremendous economic burden on society and are a major global public health threat, drugs discovery for psychiatric disorders gained little progress for decades [35–38]. Therapeutic stasis is mainly attributable to the unknown pathophysiology of psychiatric disorders. The rapid progress of genome-wide association studies (GWASs) provides an unprecedented opportunity for development of novel drugs for many complex diseases [39]. In the past two decades, GWASs have identified numerous risk variants and genes for many human complex diseases and traits, including psychiatric disorders such as schizophrenia [40–43], depression [44, 45], BP [46] and ADHD [47]. GWASs have also revealed important biological insights into psychiatric disorders [40], which will facilitate to the identification of new drugs targets and

[1]Key Laboratory of Animal Models and Human Disease Mechanisms of the Chinese Academy of Sciences & Yunnan Province, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan 650223, China. [2]Department of Psychiatry, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032, China. [3]Zhongda Hospital, School of Life Sciences and Technology, Advanced Institute for Life and Health, Southeast University, Nanjing 210096, China. [4]Department of neurology, affiliated Zhongda Hospital, Southeast University, Nanjing 210096, China. [5]Affiliated Mental Health Center & Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. ✉email: luoxiongjian@seu.edu.cn

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development of new treatments. Nelson et al. showed that selecting genetically supported target genes (as therapeutic targets) could greatly increase the success rate of drug development [48], indicating the pivotal role of human genetic studies in drug discovery [49]. In fact, several new drugs have been successfully developed based on human genetic studies, including *PCSK9* [50] and *CCR5* [51].

Considering the huge time and economic costs of development of new drugs, integrating GWAS findings and approved drugs provides a unique opportunity for quick discovery of novel targets (drug repurposing or repositioning). Most of risk variants for complex diseases are though to exert their biological effects by affecting gene expression [52], thus, integration of GWAS and expression quantitative trait loci data (e.g., transcriptome-wide association study [53], TWAS) will help to identify the potential risk genes. Recently, Mendelian randomization (MR) has been widely used to infer if the altered gene expression acts as a causal factor for many diseases [54–59]. By using eQTL and GWAS data, the main purpose of two sample MR is to test if a genetic variant (or combination of several variants) mediates its effect on disease through affecting gene expression. As many drugs exert their therapeutic effects by down-regulating or up-regulating targeting proteins, associations between the disease-associated risk genetic variants (derived from GWAS) and gene or protein expression provide a useful opportunity for drug repurposing. Risk genetic variants that mimic the therapeutic effects of approved drugs can inform drug development. Focusing on actionable proteins (targeted by approved drugs or drugs in clinical phase of development) provide a rapid and efficient approach for drug repurposing as the safety and dose of the approved drugs have been well-established.

To identify new drug targets and to seek potential drug repurposing opportunities for psychiatric disorders, we performed MR by integrating GWAS findings from large-scale human genetic studies and brain-derived molecular quantitative trait loci (mRNA expression and protein abundance quantitative trait loci) of 1,263 actionable proteins (targeted by approved drugs or drugs in clinical phase of development). We identified promising actionable novel drug targets for psychiatric disorders, including TIE1, AKT3, HLA-DRB1, P2RX7, PSMA4, MAPK3, CACNA1C, PRKCB, PSMB4, IMPDH2, GRIA1 and TAOK3.

MATERIALS AND METHODS

Actionable drug targets

We used 1263 actionable drug targets (approved drugs or drugs in clinical phase of development) curated by Gaziano et al. [60] as potential candidates in this study. To identify drug repurposing opportunity for COVID-19, Gaziano et al. [60] curated 1263 actionable proteins targeted by approved drugs (or drugs in clinical phase of development) using the ChEMBL database [60, 61]. Among these 1263 proteins, 531 proteins are therapeutic targets of approved drugs, 381 proteins are under clinical trial evaluation and 351 proteins are potential drug targets of the approved drugs. More detailed information about these actionable drug targets have been described in study by Gaziano et al. [60].

QTL datasets used for genetic instrumental variables selection

We used 3 QTL datasets to derive genetic instrumental variables. The first dataset is the expression quantitative trait loci (eQTL) data from The Genotype-Tissue Expression (GTEx) [62], the second dataset is the PsychENCODE eQTL [63], and the last dataset is ROSMAP protein abundance quantitative trait loci (pQTL) [64].

GTEx eQTL. We downloaded GTEx eQTL data [62] using the MRInstruments R package (https://github.com/mrcieu/mrinstruments). As we focused on psychiatric disorders, we firstly extracted brain eQTL from all the GTEx results and obtained 35,673 conditionally independent *cis* SNPs that were associated with gene expression. We further investigated if genes whose expression were associated with these SNPs were included in the 1263 actionable drug targets. Genetic variants associated with expression of actionable drug targets (eQTL $P < 1 \times 10^{-04}$) were selected for subsequent analysis, as described in recent studies [65, 66]. As MRInstruments R package uses top eQTL hit of each gene across 44 tissues of GTEx (i.e. one gene corresponds one instrument, and the selected instrument shows the most significant association with the gene in the GTEx eQTL summary statistics), LD clumping is not applicable for this dataset [67]. Finally, we selected 1433 LD independent top eQTL SNPs as the MR instrumental variables.

PsychENCODE eQTL. The PsychENCODE eQTL were generated using brain tissues (the prefrontal cortex) of 1,378 human individuals [63]. The PsychENCODE eQTL summary data were downloaded from the SMR website (https://cnsgenomics.com/software/smr/#eQTLsummarydata) [68]. eQTL Summary data corrected for 50 PEER factors were used. A total of 2,542,908 SNP-gene expression pairs were included in PsychENCODE dataset. SNPs were retained if the target genes (i.e., genes whose expression were associated with these SNPs) of these SNPs were included in the 1263 drug targets. For each gene, only SNPs with eQTL *P* values less than 1×10^{-04} were included. We performed LD clumping by using clump_data() function in TwoSampleMR R package (https://mrcieu.github.io/TwoSampleMR/reference/clump_data.html) [67], with the use of default LD clumping parameters, i.e., the clumping r^2 cutoff was set to 0.001 and "EUR" was selected as LD reference panel. The LD reference panel of the European (EUR) population was obtained from the 1000 Genomes project provided by OpenGWAS API (https://gwas-api.mrcieu.ac.uk/) [69, 70]. A total of 926 LD independent eQTL SNPs were finally included as instrumental variables in the MR analysis. Please refer to the original paper for further details about the PsychENCODE eQTL data [63]. For genes with two or more independent instrumental variables, we performed heterogeneity test by using the mr_heterogeneity() function implemented in the TwosampleMR R package [67].

ROSMAP pQTL. The protein QTL (pQTL) data were from a recent study by Wingo et al. [64]. Briefly, Wingo et al. performed a pQTL analysis in the prefrontal cortex to identify genetic variants associated with protein abundance in the human brain. We downloaded the pQTL summary statistics (ROSMAP, $n = 376$) generated by Wingo et al. from Synapse (https://doi.org/10.7303/syn23627957). A total of 912,253 SNP-protein expression pairs were included in the ROSMAP pQTL dataset and SNPs were extracted if they showed significant associations with expression of actionable proteins (pQTL $P < 0.05$). LD clumping was conducted as described in above PsychENCODE eQTL dataset. We finally selected 626 pQTL SNPs for 445 drug target proteins as MR instrumental variables. Further information about ROSMAP pQTL data, please refer to the original publication [64]. Heterogeneity test was also performed as described in above PsychENCODE eQTL dataset when more than two instruments are available for a protein [67].

GWAS summary statistics used in this study

We used genome-wide summary statistics of four common psychiatric disorders [41, 45–47], including schizophrenia, BP, depression and ADHD. The GWAS summary statistics were downloaded from the PGC website (https://www.med.unc.edu/pgc/download-results/). The GWAS results were used as outcome data in MR analysis.

For schizophrenia, we used GWAS results of European populations (33,640 SCZ cases and 43,456 controls) reported by Lam et al. [41]. For BP, we used the largest GWAS (41,917 BP cases and 371,549 controls) reported by Mullins et al. [46]. The depression GWAS summary statistics were from a large-scale GWAS study (170,756 cases, 329,443 controls) by Howard et al. [45]. The ADHD GWAS were performed in 20,183 ADHD cases and 35,191 controls [47].

Mendelian randomization

The TwoSampleMR R package (version 0.5.6, https://mrcieu.github.io/TwoSampleMR/) were used to perform two sample MR analysis [67]. The two-sample MR framework requires two datasets to conduct MR analysis. In this study, the *cis* eQTL and pQTL data were used as genetic proposed instruments (exposure), and the GWASs were used as the outcome trait data. MR tests the relationship between gene expression and diseases (or traits) by using genetic variants associated with gene expression (exposure) as instrumental variables and GWAS as outcomes. MR could investigate if change of gene expression has causal effects on diseases or traits. For proposed instruments with one SNP, Wald ratio was used. For proposed instruments containing more than one SNP, fixed-effects,

inverse-variance-weighted MR were conducted. As we only performed MR analysis for the 1263 drug targets, the multiple correction level for MR analysis result was set at $P < 3.60 \times 10^{-06}$ (Bonferroni corrected $P = 3.96 \times 10^{-05}$ (0.05/1263). We further corrected the 11 eQTL panels used in this study, including 10 GTEx eQTL panels and PsychENCODE eQTL panel, obtaining the final Bonferroni correction threshold: (3.96×10^{-05})/$11 = 3.60 \times 10^{-06}$)) for eQTL MR analysis. For pQTL panel we used a relatively relaxed correction threshold ($0.05/445 = 1.12 \times 10^{-04}$, 445 is the number of actionable drug targets that had instruments included in the pQTL data). No further correction was applied for pQTL MR analysis as only one pQTL panel was included in this study.

Consistency analysis between transcriptomic and proteomic associations

To investigate whether there is a consistency between transcriptomic and proteomic associations, we performed a correlation analysis on MR effect (odds ratio, OR) between transcriptomic and proteomic associations as described in a recently published study [71]. In brief, we select $P = 1 \times 10^{-04}$ as the threshold for QTL instrumental variables for PsychENCODE eQTL and ROSMAP pQTL datasets. SCZ genome-wide summary statistics from European ancestry (33,640 cases and 43,456 controls) were used as outcomes. R function cor() was used to perform Pearson correlation analysis of the MR effect of PsychENCODE eQTL and ROSMAP pQTL MR analyses results.

Genome-wide Mendelian randomization by including all proteins

In addition to the actionable druggable targets, we also performed a genome-wide Mendelian randomization by including pQTL of all proteins. The selection of instrumental variables was the same as described in above PsychENCODE eQTL dataset. In total, we selected 1357 LD-independent pQTL instruments of 1295 proteins. The multiple correction level was set at $P < 3.86 \times 10^{-05}$ (Bonferroni correction 0.05/1295).

Protein-protein interaction (PPI) analysis

We performed protein-protein interaction (PPI) analysis to investigate the PPI of the significant MR drug targets. The PPIs were retrieved from our previous study which includes 517,927 high-confidence (i.e., experimentally validated) non-overlapping PPIs [72]. Please refer to the original paper for further information about the PPI datasets. Visualization of the PPI network was performed in Cytoscape platform (https://cytoscape.org/) [73].

Expression analysis of the identified genes in different cell types of the human brain and protein expression pattern analysis

We utilized the Cortical Development Expression Viewer (CoDEx) data portal to explore the expression pattern of the MR significant genes at the single cell level. The CoDex database includes expression profile (measured by RNA sequencing) of approximately 40,000 single cell from the developing human cortex. Detailed information about the CoDex database and the single cell data can be found in the original paper [74] and the CoDex website (http://solo.bmap.ucla.edu/shiny/webapp/).

We also performed protein expression analysis of the identified drug targets using The Human Protein Atlas (proteinatlas.org) database [75]. The Human protein atlas includes protein expression data of 44 human tissues, more details about human protein atlas is available in the original publication and the website (https://www.proteinatlas.org/about/publications) [75].

RESULTS

MR analysis identifies 12 actionable therapeutic targets for SCZ

MR analysis could make causal inference to investigate if gene or protein expression change causes disease. Thus, the significant genes or proteins identified by MR can be used as potential therapeutic targets. Using *cis* eQTL SNPs from GTEx as genetic instruments, we identified 8 actionable drug targets for schizophrenia (MR $P < 3.60 \times 10^{-06}$) (Fig. 1a). These potential actionable drug targets include *HLA-DRB1, BRD2, CHRNA2, RORB, CACNA1C, MAPK3, PTK6* and *CYP2D6* (Fig. 1a, Table 1). Of note, *CACNA1C* had the most significant MR result ($P = 3.23 \times 10^{-15}$, OR [95%CI] = 0.85 [0.81, 0.88]). *HLA-DRB1* is supported by genetic instruments from three different brain regions. *BRD2* and *HLA-DRB1* are located in the major histocompatibility complex (MHC) region, which contains the most significant genetic association signals for SCZ [40]. We identified 3 significant associations (*AKT3, PSMA4* and *PTK6*) when using *cis* eQTL SNPs from PsychENCODE as genetic instruments (Fig. 1b, Table 1). Interestingly, *PTK6* was supported by both GTEx ($P = 1.53 \times 10^{-06}$, OR [95%CI] = 0.90 [0.86, 0.94]) and PsychENCODE ($P = 2.31 \times 10^{-06}$, OR [95%CI] = 0.49 [0.37, 0.66]) eQTL datasets. We also identified significant MR results for 4 proteins (HLA-DRB1, CAMKK2, P2RX7 and MAPK3), suggesting that abundance change of these 4 proteins have a causal role in SCZ (Fig. 1c, Table 1). Of note, three independent instruments were included for CAMKK2 ($P = 9.68 \times 10^{-06}$, OR [95%CI] = 0.32 [0.19, 0.53], heterogeneity test $P = 0.52$) (Fig. 1c, Table 1). Intriguingly, two genes (*MAPK3* and *HLA-DRB1*) were supported by both gene expression-based MR analysis and protein abundance-based MR, strongly suggesting that these two genes might have a causal role in SCZ (Fig. 1a, c). Compared with the original GWAS results, 9 genes (*HLA-DRB1, BRD2, AKT3, CHRNA2, CACNA1C, MAPK3, PSMA4, CAMKK2* and *P2RX7*) were located in the genome-wide significant (GWS) risk loci. Considering that the analyzed genes or proteins are therapeutic targets for approved drugs or drugs in clinical phase of development, out results not only provide an effective approach to identify novel therapeutic targets for psychiatric disorders, but also provide drug-repurposing opportunities to explore the repositioning of licensed drugs in psychiatric disorders.

In addition, we conducted a correlation analysis to test whether there is a consistency between transcriptomic and proteomic MR associations of SCZ. Our results showed that the correlation of MR effect between transcriptomic and proteomic associations is moderate (Pearson correlation R = 0.35, Fig. S1).

MR analysis identifies 7 actionable drug targets for bipolar disorder

We identified 7 actionable targets for BP. *CACNA1C* was identified by using GTEx eQTL as genetic instruments, and 5 genes (*DCLK3, SRPK2, DAGLA, PSMD3 and STK4*) were identified by using PsychENCODE eQTL. We also identified significant MR results for 1 protein (PRKCB) (Fig. 2, Table S1). Five genes (*CACNA1C, DAGLA, SRPK2, PSMD3* and *STK4*) were nominated by the BP GWAS. No overlapping genes were observed in the 3 QTL panels (Fig. 2). However, we found overlapping MR results between SCZ and BP (Figs. 1, 2). The *CACNA1C* gene is the top MR hit for BP (GTEx eQTL) (Fig. 2a, $P = 3.31 \times 10^{-11}$, OR [95%CI] = 0.89 [0.85, 0.92]) and SCZ (GTEx eQTL) (Fig. 1a). In addition, we noticed that two independent instruments (rs75968099, rs56131451) were included for *DCLK3* gene (Table S1. MR $P = 6.05 \times 10^{-13}$, OR [95%CI] = 0.51 [0.42, 0.61], heterogeneity test $P = 0.79$) in our MR result.

Identification of 7 actionable therapeutic targets for depression

We identified a total of 7 actionable targets for depression (Fig. 3, Table S1), including 1 gene *STK24* (MR $P = 1.29 \times 10^{-06}$, OR [95% CI] = 1.05 [1.03, 1.07]) from GTEx eQTL dataset (Fig. 3a) and 6 proteins from ROSMAP pQTL (PSMB4, SERPINC1, IMPDH2, GRIA1, TAOK3 and P2RX7) (Fig. 3c). Of note, 3 genes (*STK24, IMPDH2* and *P2RX7*) were nominated as risk genes in the original depression GWAS.

We observed protein-protein interactions between the significant MR proteins. For example, PSMB4 interacts with PSMA4 and PSMD3 (Fig. S2), and GRIA1 interacts with PRKCB (Fig. S2). These results suggest the physical interactions between the nominated risk proteins.

Identification of TIE1 as a potential drug target for ADHD

Only one significant MR result (*TIE1*) was identified for ADHD (Fig. 4b, $P = 2.12 \times 10^{-07}$, OR [95%CI] = 1.56 [1.32, 1.85]). Interestingly, *TIE1* is

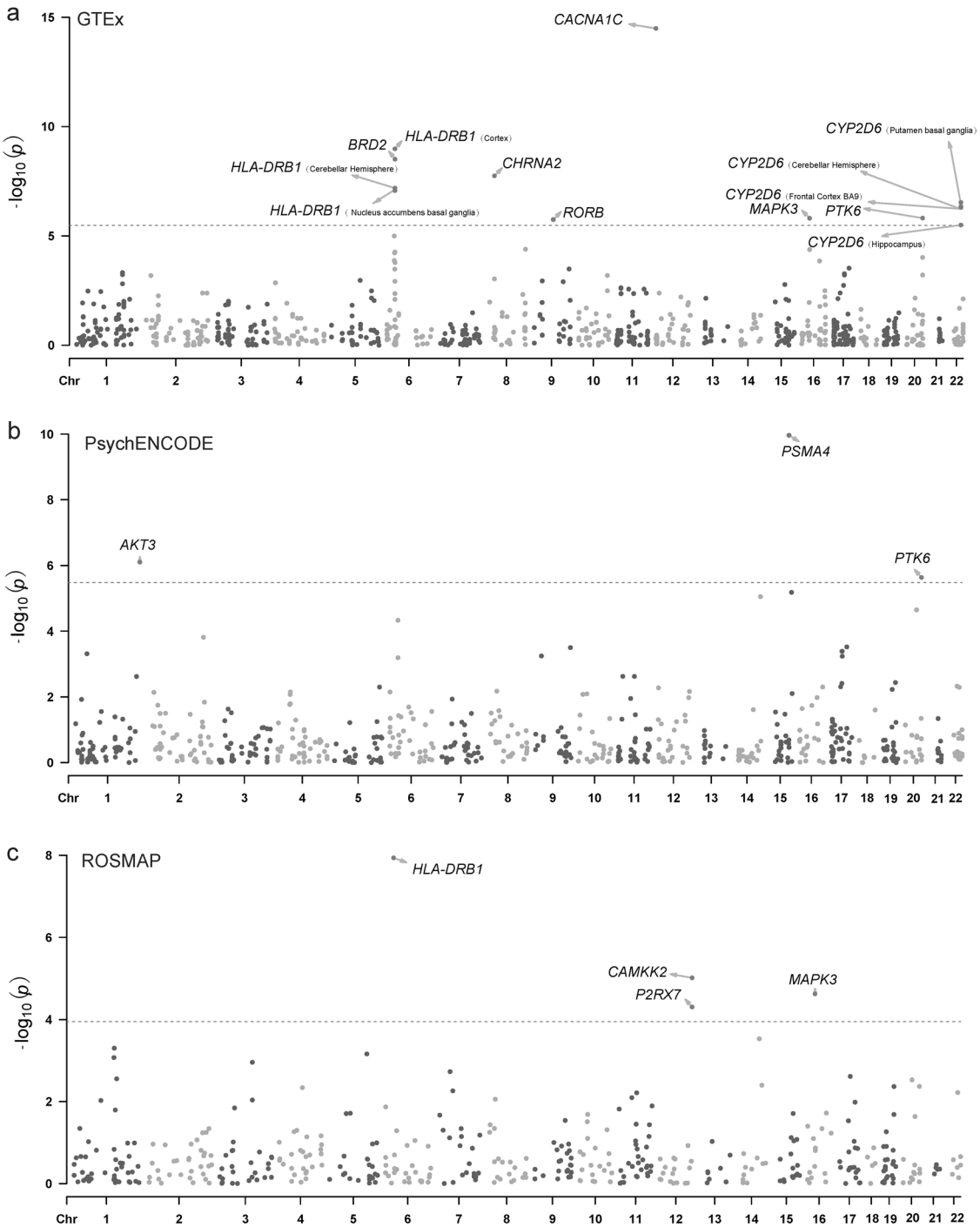

Fig. 1 The Manhattan plots of MR analysis results using QTLs and SCZ GWAS summary statistics (33,640 SCZ cases and 43,456 controls). The red dashed line is the Bonferroni corrected significant level. **a** The MR result using GTEx brain eQTL as instruments. **b** The MR result using PsychENCODE eQTL as instruments. **c** The MR result using ROSMAP pQTL as instruments.

not nominated by the original ADHD GWAS. No significant MR results were identified in GTEx eQTL and ROSMAP pQTL panels. The top finding in GTEx eQTL panel (Fig. 4a, *CD40*) and ROSMAP pQTL (Fig. 4c, *ITGA5*) were marked in Fig. 4.

Expression of the identified genes in different cell types of the human brain

We explored the expression pattern of the prioritized genes using the single cell RNA sequencing data. Among genes associated with SCZ, *AKT3, BRD2, CAMKK2, PSMA4 and RORB*, are widely expressed in different brain cell types at relatively high level (Figs. S3–S6). RORB, MAPK3 and AKT3 are highly expressed in human brain tissues, while PSMA4, CACNA1C and PTK6 show moderate expression (Figs. S11–S14). For BP, *DCLK3, PSMD3, SRPK2*, and *STK4* are widely expressed in different brain cell types (Figs. S7, S8). However, *PRKCB* is specifically expressed in excitatory deep layer 1 (Fig. S7b). SRPK2 and PSMD3 proteins are highly expressed in human brain tissues (Fig. S15). For depression, *GRIA1, IMPDH2, PSMB4, STK24* and *TAOK3*, are widely expressed in different brain cell types (Figs. S8–S10). STK24, IMPDH2 and

Table 1. The Mendelian Randomization results of brain QTL datasets (GTEx eQTL, PsychENCODE eQTL and ROSMAP pQTL) and schizophrenia GWAS.

Gene	Instruments	Method	Instruments dataset	MR *P* value	Beta	OR [95% CI]
HLA-DRB1	rs926961	Wald ratio	GTEx (Brain Cortex)	1.04×10^{-09}	0.059	1.06 [1.04, 1.08]
BRD2	rs209474	Wald ratio	GTEx (Brain Cerebellum)	3.08×10^{-09}	−0.17	0.84 [0.80,0.89]
HLA-DRB1	rs9270692	Wald ratio	GTEx (Brain Cerebellar Hemisphere)	6.47×10^{-08}	0.055	1.06 [1.04, 1.08]
HLA-DRB1	rs9281938	Wald ratio	GTEx (Brain Nucleus accumbens basal ganglia)	8.41×10^{-08}	0.046	1.05 [1.03, 1.06]
CHRNA2	rs11783093	Wald ratio	GTEx (Brain Cerebellum)	1.78×10^{-08}	−0.085	0.92 [0.89, 0.95]
RORB	rs11144082	Wald ratio	GTEx (Brain Cerebellum)	1.78×10^{-06}	0.16	1.17 [1.10, 1.25]
CACNA1C	rs7297582	Wald ratio	GTEx (Brain Cerebellum)	3.23×10^{-15}	−0.17	0.85 [0.81, 0.88]
MAPK3	rs28529403	Wald ratio	GTEx (Brain Frontal Cortex BA9)	1.55×10^{-06}	0.13	1.14 [1.08, 1.20]
CYP2D6	rs2142694	Wald ratio	GTEx (Brain Putamen basal ganglia)	2.92×10^{-07}	−0.066	0.94 [0.91, 0.96]
CYP2D6	rs2267448	Wald ratio	GTEx (Brain Cerebellar Hemisphere)	4.52×10^{-07}	−0.053	0.95 [0.93, 0.97]
PTK6	rs139707650	Wald ratio	GTEx (Brain Cerebellar Hemisphere)	1.53×10^{-06}	−0.10	0.90 [0.86, 0.94]
CYP2D6	rs2743451	Wald ratio	GTEx (Brain Frontal Cortex BA9)	4.97×10^{-07}	−0.066	0.94 [0.91, 0.96]
CYP2D6	rs2284087	Wald ratio	GTEx (Brain Hippocampus)	3.16×10^{-06}	−0.064	0.94 [0.91, 0.96]
AKT3	rs3008660	Wald ratio	PsychENCODE	7.82×10^{-07}	−1.29	0.28 [0.17. 0.46]
PSMA4	rs28498264	Wald ratio	PsychENCODE	1.09×10^{-10}	1.70	5.48 [3.27, 9.19]
PTK6	rs2150808	Wald ratio	PsychENCODE	2.31×10^{-06}	−0.71	0.49 [0.37, 0.66]
HLA-DRB1	rs502771	Wald ratio	ROSMAP	1.15×10^{-08}	0.50	1.65 [1.39, 1.96]
CAMKK2	rs3794207; rs12825611; rs792600	Inverse variance weighted	ROSMAP	9.68×10^{-06}	−1.15	0.32 [0.19, 0.53]
P2RX7	rs3751143	Wald ratio	ROSMAP	5.00×10^{-05}	−0.15	0.86 [0.80, 0.93]
MAPK3	rs11865086	Wald ratio	ROSMAP	2.38×10^{-05}	1.93	6.91 [2.82, 16.93]

TAOK3 show moderate protein abundance in the human brain tissue (Figs. S16, S17).

Genome-wide MR analysis using all pQTL identified additional candidate risk proteins

In addition to the actionable proteins, we also performed a genome-wide Mendelian randomization by including pQTLs of all proteins. We identified 25, 15, 10, and 1 risk proteins for SCZ, BP, depression and ADHD, respectively (Table S2, Figs. S18–S21). Notably, CNNM2 (MR $P = 2.52 \times 10^{-15}$) was the top risk protein for SCZ, which is consistent with our previous findings (Fig. S18) [76]. NEK4 (MR $P = 5.05 \times 10^{-09}$) represents the most significant MR result for BP (Fig. S19) and this protein was also nominated by SCZ MR analysis (Fig. S18). Interestingly, CNNM2 (MR $P = 2.49 \times 10^{-06}$) was also identified by pQTL MR analysis for depression (Fig. S20). GMPPB showed association with both depression and ADHD (Figs. S20, S21). These results nominated additional risk proteins for psychiatric disorders.

DISCUSSION

Development of novel therapeutic drugs for psychiatric disorders has been proved to be extreme challenging. A major reason for this plight is the unknown pathophysiology of psychiatric disorders. In the past decade, large-scale genetic studies have identified multiple risk variants for psychiatric disorders. These GWASs have provided important biological insights into psychiatric disorders. In fact, human genetics could provide important information to inform drug development and a recent study by Nelson et al. showed that selecting genetically supported target genes (as therapeutic targets) could increase the success rate of drug development substantially [48]. Thus, leveraging GWASs may provide new opportunities to develop drugs for psychiatric disorders. In this study, we conducted comprehensive MR analyses to identify potential causal genes for psychiatric disorders. By focusing on druggable genes or proteins, we prioritized 46 actionable drug targets for four common psychiatric disorders (schizophrenia, BP, depression and ADHD). Our results provide actionable promising candidates for drug repurposing for psychiatric disorders. *CACNA1C* had the most significant MR results among the prioritized targets for SCZ, strongly suggesting that this gene represents a promising drug target for SCZ. *CACNA1C* encodes the alpha-1 (Cav1.2) subunit of a voltage-dependent calcium channel, which mediates the influx of calcium ions into the cell [77]. CACNA1C regulates gene expression and synaptic plasticity by initiating downstream signaling cascades [78]. Genetic variants in *CACNA1C* showed robust associations with SCZ and BP [78], and mouse models also revealed psychiatric-like and mood phenotypes in *Cacna1c* heterozygous deletion mice [78]. These lines of convergent evidence indicate the pivotal role of *CACNA1C* in psychiatric disorders. Of note, dihydropyridine could inhibits CACNA1C. Thus, this gene is a promising drug target for SCZ and BP. We checked the ChEMBL database (https://www.ebi.ac.uk/chembl/) and found that DRONEDARONE (CHEMBL184412), which was approved by Food and Drug Administration (FDA), could target voltage-gated L-type calcium channel proteins (including CACNA1C, CACNA1D, CACNA1S and CACNA1F), suggesting the therapeutic potential of DRONEDARONE for SCZ and BP.

Other interesting candidate targets for SCZ include MAPK3 and PSMA4. MR analysis indicated that MAPK3 showed significant associations with SCZ in both eQTL and pQTL datasets, implying

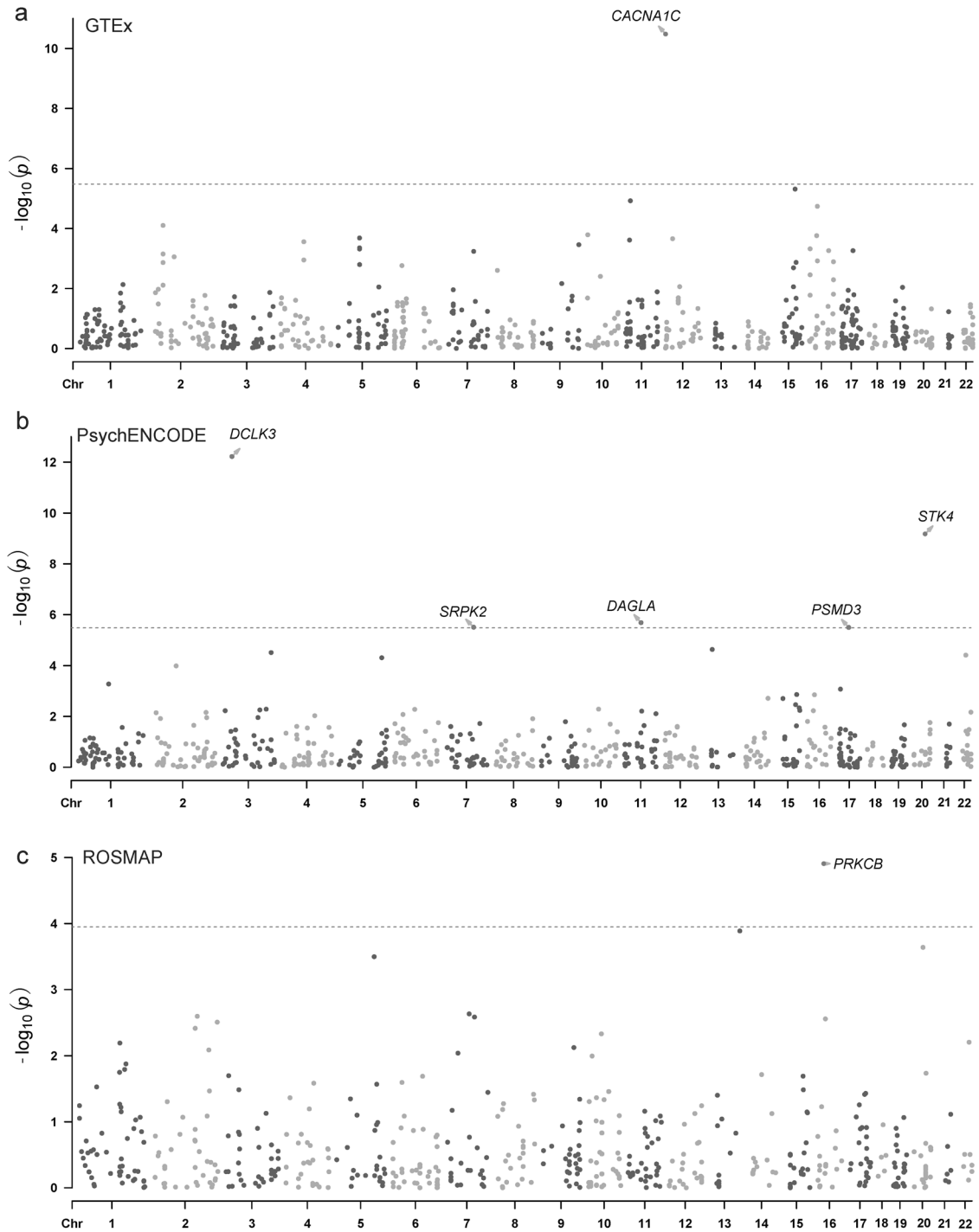

Fig. 2 The Manhattan plot of MR analysis using QTLs and BP GWAS summary statistics (41,917 BP cases and 371,549 controls). The red dashed line is the Bonferroni corrected significant level. **a** The MR result using GTEx brain eQTL as genetic instruments. **b** The MR result using PsychENCODE eQTL as genetic instruments. **c** The MR result using ROSMAP pQTL as genetic instruments.

the causal effects of expression change of these two genes in SCZ. Many studies, including genetic study [40], transcriptome and proteome profiling [79], integrative analysis [80], network-based prioritization [81] and functional genomics study [82], have showed the pivotal role of *MAPK3* in SCZ. For example, MAPK3 has been reported to be dysregulated in schizophrenia cases compared with healthy controls ($P = 0.0001$) [79]. The potential role of *PSMA4* in SCZ was also supported by large-scale GWAS [40] and a recent prioritization study [81]. These results highlight the pivotal role of *MAPK3* and *PSMA4* in SCZ. Thus, these two genes may be served as promising therapeutic targets for SCZ treatment. MAPK3 is a potential target of SORAFENIB (CHEMBL1336), and PSMA4 (20 S proteasome subunit alpha-3) is a potential target of CARFILZOMIB (CHEMBL451887, targeting 26 S proteasome). Our MR analysis suggested that SORAFENIB and CARFILZOMIB may be repositioned for schizophrenia treatment. However, further clinical trials are needed.

For depression, interesting protein candidates include PSMB4, GRIA1 and TAOK3. Interestingly, a previous study also has revealed the potential role of *PSMB4* in depression [83]. Glutamate

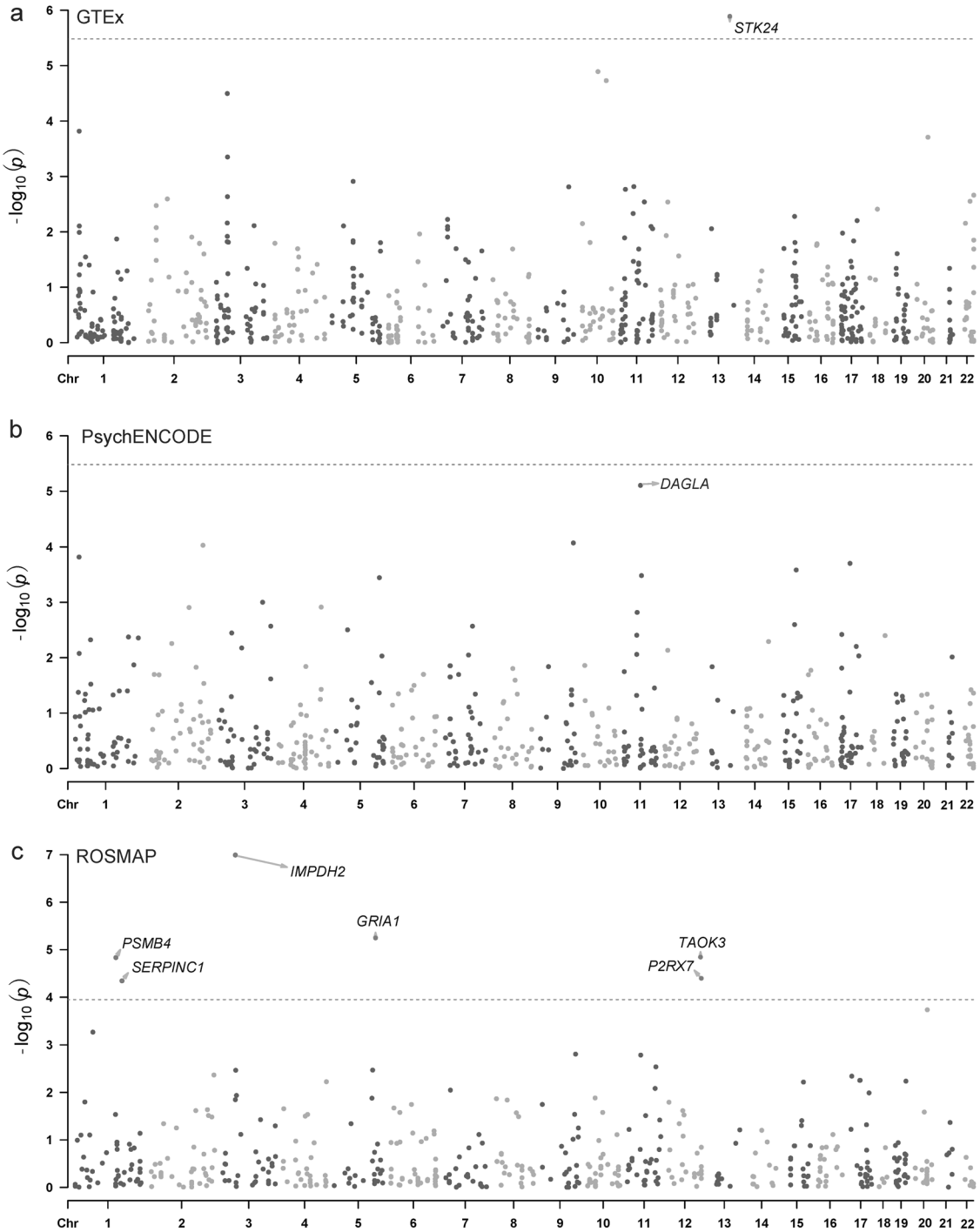

Fig. 3 The Manhattan plot of MR analysis result using QTLs and depression GWAS summary statistics (170,756 cases, 329,443 controls). The red dashed line is the Bonferroni corrected significant level. **a** The MR result using GTEx brain eQTL as instruments. **b** The MR result using PsychENCODE eQTL as instruments. **c** The MR result using ROSMAP pQTL as instruments.

ionotropic receptor AMPA type subunit 1 (GRIA1) has a critical role in glutamate-mediated neurotransmission and synaptic plasticity. In fact, the rapid antidepressant ketamine is an inhibitor of N-methyl D-aspartate (NMDA) receptors, indicating the crucial role of glutamate signaling in depression. TAOK3 is a serine/threonine protein kinase that regulates the p38/MAPK14 stress-activated MAPK cascade and the MAPK8/JNK cascade [84, 85]. Interestingly, previous studies have reported the crucial role of MAPK signaling in depression [86–89]. These lines of evidence support that TAOK3 and MAPK signaling pathway may be a promising target for depression treatment.

Only *TIE1* gene is significant in our MR analysis for ADHD. *TIE1* encodes a transmembrane tyrosine-protein kinase. *TIE1* has been reported as one of the significant genes in a Transcriptome-wide association study (TWAS) of ADHD [90], suggesting that the expression level change of *TIE1* gene may have a role in ADHD etiology. These evidence supported that TIE1 may be served as a promising therapeutic drug target for ADHD.

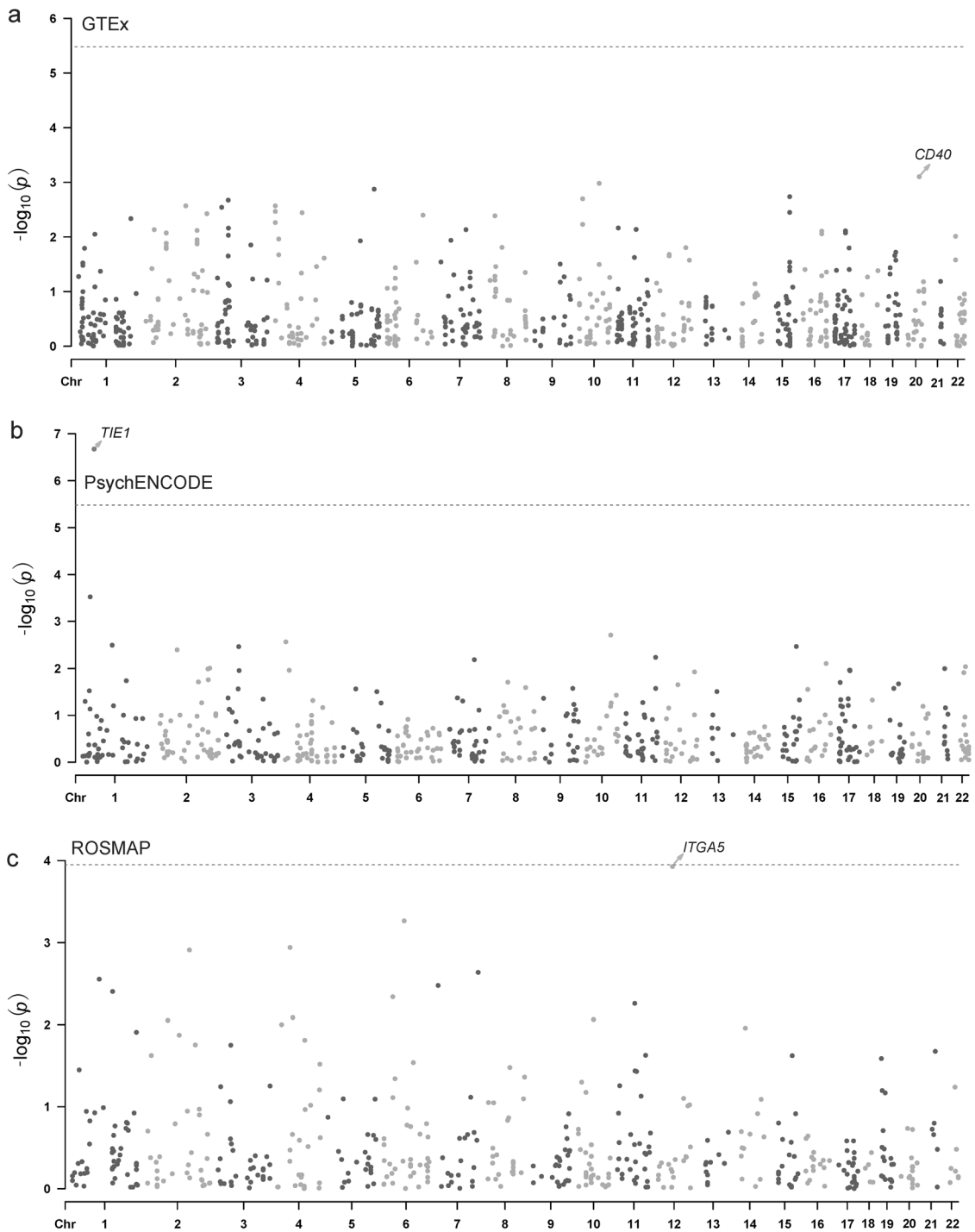

Fig. 4 The Manhattan plot of MR analysis result using QTLs and ADHD GWAS summary statistics (20,183 cases, 35,191 controls). The red dashed line is the Bonferroni corrected significant level. **a** The MR result using GTEx brain eQTL as genetic instruments. **b** The MR result using PsychENCODE eQTL as genetic instruments. **c** The MR result using ROSMAP pQTL as genetic instruments.

The candidate genes identified by MR varied across the 4 psychiatry disorders (e.g., 12 for SCZ, and only 7 for depression and 1 for ADHD, respectively). Following reasons may lead to this result: First, the sample size included in the original genome-wide association studies (GWASs) of different psychiatric disorders were different. For example, the SCZ GWAS included 33,640 cases and 43,456 controls. However, the sample size included in the ADHD GWAS was smaller (20,183 ADHD patients and 35,191 controls). The larger sample size, the higher power to detect the associations between common variations and diseases. Second, the heritability of these psychiatric disorders are different [91–94]. The heritability of depression (about 30–40%) is much smaller than other psychiatric disorders [91–94]. Accordingly, the number of identified candidate genes for depression is less than SCZ. In addition, our significant MR analysis findings were not supported by both eQTL and pQTL MR analysis. The potential reasons may due to the weak correlation between mRNA expression level and protein level as previously [95] reported. Besides, the number of instruments and sample size of pQTL panel is smaller than eQTL panels, leading to less proteins were included in MR.

It should be noted that many genes identified in this study have been reported in previous studies [45, 76, 90, 96–102]. However, the key purpose of our study is to prioritize the actionable novel drug targets for psychiatric disorders (which is different from previous studies as the main goal of these studies is to identify risk genes). We thus believe that our findings provide critical drug-repurposing opportunities for psychiatric disorders.

In summary, we identified actionable new drugs targets for psychiatric disorders. As these proteins are targets of approved drugs or drugs in clinical phase of development, our findings prioritize actionable novel drug targets for development of new therapeutics and provide critical drug-repurposing opportunities for psychiatric disorders.

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AUTHOR CONTRIBUTIONS

XJL conceived, designed and supervised the whole study. JWL performed the analyses. XJL, JWL, QYC, ML, ZJZ and TL wrote the manuscript. All authors provided critical comments and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Xiong-Jian Luo.

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