

# Mendelian Randomization Using the Druggable Genome Reveals Genetically Supported Drug Targets for Psychiatric Disorders

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**Background and hypothesis:** Psychiatric disorders impose a huge health and economic burden on modern society. However, there is currently no proven completely effective treatment available, partly owing to the inefficiency of drug target identification and validation. We aim to identify therapeutic targets relevant to psychiatric disorders by conducting Mendelian randomization (MR) analysis. **Study design:** We performed genome-wide MR analysis by integrating expression quantitative trait loci (eQTL) of 4479 actionable genes that encode druggable proteins and genetic summary statistics from genome-wide association studies of psychiatric disorders. After conducting colocalization analysis on the brain MR findings, we employed protein quantitative trait loci (pQTL) data as genetic proposed instruments for intersecting the colocalized genes to provide further genetic evidence. **Study results:** By performing MR and colocalization analysis with eQTL genetic instruments, we obtained 31 promising drug targets for psychiatric disorders, including 21 significant genes for schizophrenia, 7 for bipolar disorder, 2 for depression, 1 for attention deficit and hyperactivity (ADHD) and none for autism spectrum disorder. Combining MR results using pQTL genetic instruments, we finally proposed 8 drug-targeting genes supported by the strongest MR evidence, including gene *ACE*, *BTN3A3*, *HAPLN4*, *MAPK3* and *NEK4* for schizophrenia, gene *NEK4* and *HAPLN4* for bipolar disorder, and gene *TIE1* for ADHD. **Conclusions:** Our findings with genetic support were more likely to be to succeed in clinical trials. In addition, our study prioritizes approved drug targets for the development of new therapies and provides critical drug reuse opportunities for psychiatric disorders.

**Key words:** drug targets/Mendelian randomization/psychiatric disorders/GWAS/eQTL/pQTL

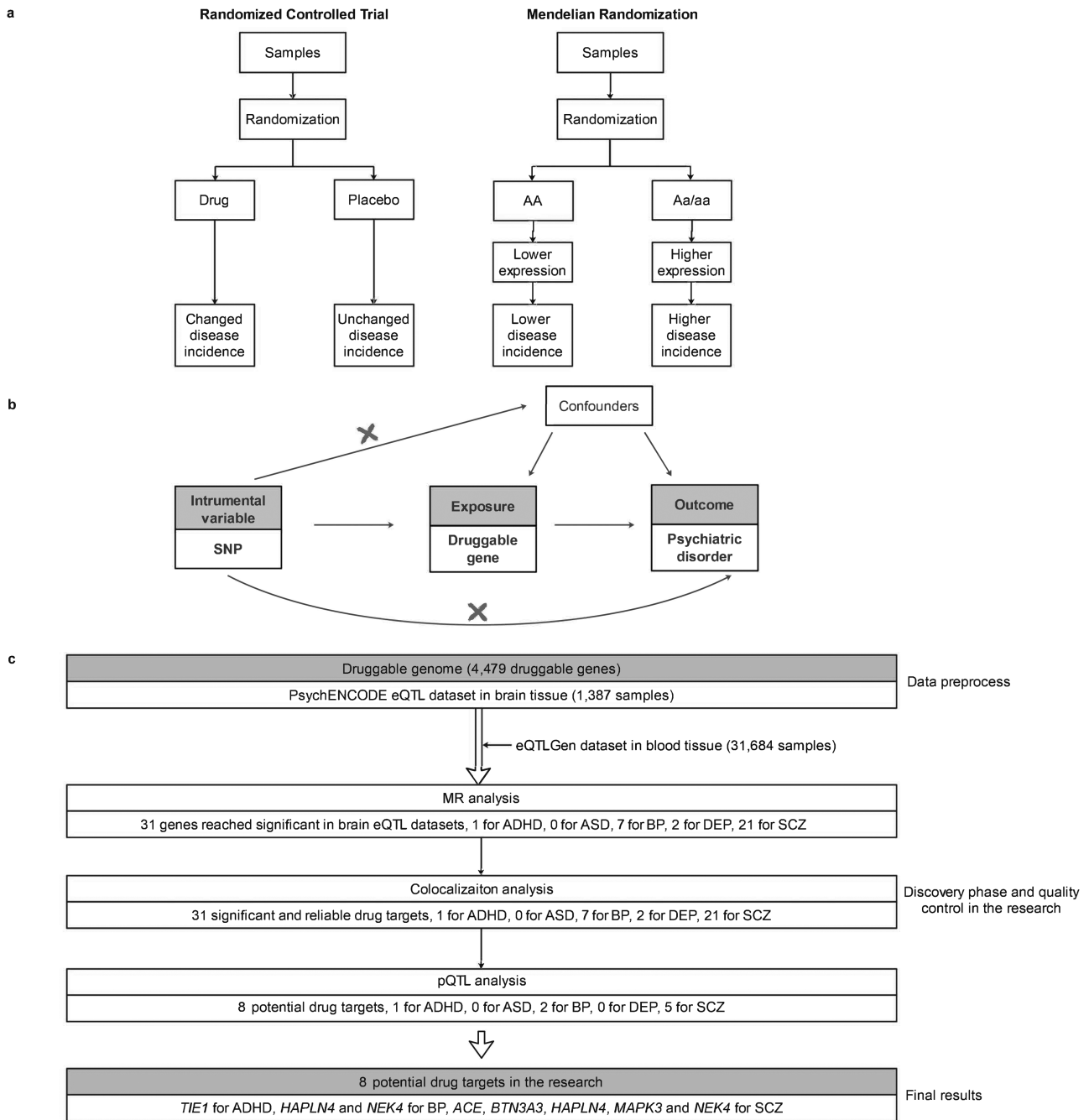
## Introduction

Psychiatric disorders are one of the leading causes of disability worldwide and impose an enormous health and economic burden on human society.<sup>1,2</sup> Emerging evidence suggests that the current coronavirus disease 2019 (COVID-19) pandemic is worsening the prevalence of psychiatric disorders globally.<sup>3,4</sup> To date, no effective treatments able to prevent the recurrence of psychiatric disorder symptoms are available, although available therapies offer symptomatic relief. In spite of considerable efforts in drug discovery and development, over 90% of proposed therapeutics fail in the course of clinical trials due to poor therapeutic efficacy and unacceptable safety.<sup>5,6</sup> This contributes to the costs for the development of a novel drug and bringing it to the market can be ranging from \$314 million to \$2.8 billion.<sup>7</sup> There is a compelling need for the discovery of novel drugs for the management of psychiatric disorders, which is time-consuming and expensive.

Human genetic studies are now widely adopted in drug development for many complex diseases. Drug target pairs supported by human genetic evidence are more likely to be clinically successful.<sup>8</sup> For example, genetic loci identified in genome-wide association studies (GWASs) of type 2 diabetes, which contain genes encoding targets for the sulphonylurea and glitazone drug classes, have been used to treat diabetes.<sup>9,10</sup> In the past decade, GWASs have identified multiple genetic loci harboring associated single nucleotide polymorphisms (SNPs) for psychiatric disorders. Nevertheless, the genetic associations from GWAS cannot reliably pinpoint causal genes and directly inform future drug design and development efforts for disease.

Well-designed randomized clinical trials (RCTs) are generally accepted as the gold standard approaches for assessing whether drug treatment is efficacious (figure 1).<sup>11,12</sup> However, RCTs are expensive to undertake and not always feasible.<sup>13</sup> Mendelian randomization (MR) is now widely used to infer causal relationships between exposures and outcomes by using genetic factors as instrumental variables,<sup>14-18</sup> providing opportunities for informing therapeutic targeting. Specifically, genetic

variants acting in “cis” and “trans” on the druggable gene (ie, gene encoding the approved and clinical-phase drugs target proteins or drug-like small-molecule binding partners as annotated by Finan et al.<sup>10</sup>) expression, also referred to as expression quantitative trait loci (eQTL), can be used as MR instruments for drug exposure. The association between the same genetic variants and complex disease (ie, the outcome) can then be derived from GWAS for the outcome. Thus, integration of GWAS (ie,



**Fig. 1.** Overview of MR and the study design. (a) The comparison between MR and randomized controlled trial. MR is similar to the randomized controlled trial. (b) Diagram of MR analysis and assumptions. (c) Workflow and statistical results of this research. MR: Mendelian randomization.

SNP-disease associations) and eQTL data (ie, SNP-gene-expression) using MR will help to infer the causal effect of the exposure on the outcome (ie, identifying the potentially druggable genes), as they mimic the on-target beneficial or harmful effects observed by pharmacological modification. Recent studies have adopted such an approach through a combination of 2 sample MR analysis<sup>19</sup> to investigate the association between druggable gene expression and disease outcomes including Parkinson's disease<sup>20</sup> and COVID-19.<sup>21</sup>

In this study, to identify the most promising drug targets and to seek drug repurposing candidates for psychiatric disorders, we performed a 2 sample MR analysis by integrating summary statistics from the most recent and largest GWAS of psychiatric disorders (including schizophrenia (SCZ), bipolar disorder (BP), depression (DEP), autism spectrum disorder (ASD), and attention deficit and hyperactivity (ADHD)) and publicly available eQTL data in brain and blood tissue of 4479 actionable druggable genes (including protein targets or drug-like small-molecule binding partners that encode approved) (figure 1). By combining evidence of colocalization of effects, we identified 31 promising drug targets for psychiatric disorders. Of these, we proposed 8 genetically supported promising actionable novel drug targets with strong evidence for psychiatric disorders by protein quantitative trait loci (pQTL) verification, including gene *ACE*, *BTN3A3*, *HAPLN4*, *MAPK3* and *NEK4* for SCZ, gene *NEK4* and *HAPLN4* for BP, and gene *TIE1* for ADHD but no drug-targeting gene with DEP and ASD. Our analysis provides a road map for the identification of potential therapeutic targets with genetically supported evidence in psychiatric disorders.

## Materials and Methods

### *Genome-Wide Association Studies Summary Statistics Used in This Study*

To incorporate human genetic studies in drug discovery and development, the most recent and largest-scale GWASs summary statistics that identified the genetic risk variants across various psychiatric disorders, including SCZ, BP, DEP, ASD, and ADHD, were used in this study. For SCZ, we used transancestry SCZ meta-analysis results (67 390 cases and 94 015 controls) reported by Trubetskoy et al.<sup>22</sup> For BP, we used meta-analysis results of Europe, North America and Australia cohorts (41 917 cases and 371 549 controls) reported by Mullins et al.<sup>23</sup> For DEP, we used meta-analysis results (246 363 cases and 561 190 controls) reported by Howard et al. which samples collected from the 3 largest GWAS of depression.<sup>24</sup> For ASD, we used meta-analysis results from the Danish population (18 381 cases and 27 969 controls) reported by Grove et al.<sup>25</sup> For ADHD, we used ADHD meta-analysis results on samples from multi cohorts (20 183 cases and 35 191 controls) reported by Demontis et

al.<sup>26</sup> We obtained these GWAS summary datasets from the Psychiatric Genomics Consortium (PGC) (<https://www.med.unc.edu/pgc/>). Details on the processing of these GWAS summary statistics are provided in the original publications.

### *Quantitative Trait Loci Datasets Used for Genetic Instrumental Variables Selection*

The eQTL dataset has been extensively utilized for identifying genetic variants that regulate gene expression.<sup>27</sup> The eQTL data can be an indispensable connection between instrumental variables and exposures in MR analysis. Therefore, eQTL datasets from brain and blood tissues were included in the MR analysis. We downloaded publicly available data from the PsychENCODE Consortium (<http://resource.psychencode.org/>) as eQTL data for brain tissue (1387 samples, mostly from European cohorts) which results reached significant FDR < 0.05.<sup>28</sup> Moreover, we obtained publicly available eQTL data for blood tissues (31 684 samples, mostly from European cohorts) from the eQTLGen consortium (<https://eqtlgen.org/>) selecting those that reached significance with false discovery rate (FDR) < 0.05.<sup>29</sup> The detailed descriptions of these eQTL datasets can be found in the original publications.

### *Actionable Drug Targets*

In order to ensure that final experimental results are usable and reliable for drug target genes, the dataset of druggable genes required a stringent verification process. The druggable genome dataset in the public [supplementary materials](#) of the original publication<sup>10</sup> was downloaded to ensure that the results of our experiments were corresponding to drug targets. This druggable genome dataset is straight set into diverse classes for different stages of the drug development procedure. It includes the approved and clinical-phase drugs target proteins, proteins analogous to approved drug targets and proteins accessible to drug-like small molecules. See the [Supplementary Methods](#) for details.<sup>10</sup> We took the intersection of the druggable genome and eQTL datasets on the gene level and then obtained the input dataset of druggable genes with corresponding SNPs as exposures and instrumental variables. After potential drug targets were inferred, the drug information can be retrieved through DrugBank,<sup>30</sup> with the purpose of highlighting novel repurposing opportunities for existing drugs.

### *Mendelian Randomization*

GWAS has identified a large number of risk SNPs associated with diseases.<sup>31</sup> However, GWAS cannot be utilized directly for drug discovery and development because druggable genes encode proteins rather than SNPs. MR analysis used genetic variants as instrumental variables to

assess whether an association between an exposure and an outcome is consistent with a causal effect.<sup>32,33</sup> This is because the natural, random assortment of genetic variants during meiosis yields a random distribution of genetic variants in a population<sup>32,34</sup> (figure 1a). Two-sample MR analysis is a function based on MR analysis which is used to estimate the causal effect of an exposure on an outcome<sup>35</sup> (figure 1b). Two-sample MR analysis could be conducted with the R package TwoSampleMR (version 0.5.4) (<https://mrcieu.github.io/TwoSampleMR/>). Different in-built functions were integrated when we performed a 2 sample MR analysis through the R package. If the druggable gene only contained 1 available SNP after the data processing, the Wald ratio was used to estimate the causal effect between druggable genes and diseases. Inverse-Variance Weighted (IVW) was utilized to assess the effect between the druggable gene with 2 available SNPs and psychiatric disorders. Moreover, a weighted median was conducted in the analysis as well for druggable genes with the number of available SNPs > 2. More specifically, IVW combines the Wald ratio estimates of each of the instrumental variables (ie, SNP) into one causal estimate for each risk factor. The weighted median estimate is the median of the weighted empirical distribution function of individual SNP Wald ratio estimates.

Details on data preprocessing before MR analysis are provided in the [Supplementary Methods](#). By conducting a 2 sample MR analysis, the effect of druggable genes on psychiatric disorders can be estimated to predict the efficient drug targets for diseases. The MR analysis calculated the *P*-value of each druggable gene which indicated the probability of causal association between druggable gene and psychiatric disorder. To avoid the type 1 error, Bonferroni correction for multiple testing (ie, Bonferroni-corrected *P*-value cutoff of 0.05/27 421 total significant eQTLs in brain and blood =  $1.82 \times 10^{-6}$ ) was used to identify significant associations.<sup>36</sup>

### Colocalization Analysis

For 2 sample MR analysis, SNP-druggable gene association and SNP-psychiatric disorder association should be rooted in the shared SNP. However, there were certain occasions when 2 different SNPs can influence druggable genes and psychiatric disorders independently. To estimate whether the druggable gene and psychiatric disorder association are consistent with an overlap causal variant, we conducted the colocalization analysis (based on the Bayesian framework<sup>37</sup>) to adjust such spurious results and posterior probabilities (PP) for 5 hypotheses (H0, H1, H2, H3, and H4) were calculated. Specifically, H4 indicates that one shared SNP associates with the druggable genes and the psychiatric disorders. The correct hypothesis above is H4 and the PP of H4 approximately probes the probability of one shared causal variant influencing

druggable gene and psychiatric disorder. SNPs with strong evidence (PP.H4 > 0.8) and their corresponding genes were kept. Those druggable genes that reached significance in MR analysis and pass colocalization analysis were more likely to be drug targets for the corresponding psychiatric disorders.<sup>17</sup> The R package coloc (Version 5.1.0) was used to conduct the colocalization analysis (<https://www.rdocumentation.org/packages/coloc/versions/5.1.0>).

### Protein Quantitative Trait Loci Analysis

The pQTL study has identified genetic variants that regulate protein expression in various tissues. The proteins play an indispensable role in disease pathogenesis<sup>38</sup> and drug target genes are based on protein. The pQTL dataset was selected based on 2 criteria, namely that the pQTL should be significant and provide all the information required for 2 sample MR analysis. Therefore, we obtained 4 public pQTL datasets in blood tissues<sup>39-42</sup> (see the [Supplementary Methods](#) for details) and performed MR analysis on each pQTL dataset. We then conducted MR analysis again with pQTLs and GWASs of 5 psychiatric disorders. If druggable genes remained significant and reliable in a series of experiments of pQTL, we considered that these druggable genes were more likely to be drug targets for the corresponding diseases.

### Mendelian Randomization Analysis in Non-European Study Participants

We further examined whether our MR findings are informative for non-European study populations using eQTL and GWAS data of non-European populations. By searching the PGC website for GWAS statistics in 5 psychiatric disorders, we found that the publicly downloadable non-European GWAS on the PGC website were only from East Asian (EAS) populations, including schizophrenia,<sup>43</sup> and depression.<sup>44</sup> Because there is no publicly available EAS brain eQTL data available for analysis, we used EAS blood eQTL data ( $N = 162$ ) from Stranger et al.<sup>45</sup> for MR analysis of non-European (ie, EAS) participants. The threshold for significant associations with MR evidence was set at  $P < 1.12 \times 10^{-5}$  (ie, Bonferroni-corrected *P*-value cutoff of 0.05/ 4479 druggable gene). See [Supplementary Material](#) for details.

## Results

### Genetic Proposed Instruments for Actionable Druggable Genes

To identify potential drug repurposing opportunities for psychiatric disorders, we collected the most comprehensive druggable genome library to date from Finan et al.,<sup>10</sup> covering a total of 4479 human genes that encode druggable proteins ([Supplementary table 1](#)). Furthermore,

we identified all significant *cis*-eQTLs with  $FDR < 0.05$  in the brain (1387 prefrontal cortex samples of mostly European ancestry from PsychENCODE Consortium), which acted in *cis* within 5 kb on either side of that encoded druggable gene and blood (31 684 samples from eQTLGen, mostly European ancestry individuals), which acted in *cis* within 5 kb either side of that encoded druggable gene. Moreover, only autosomal genes were kept for further research. Eventually, eQTL data for 2300 and 2580 druggable genes in brain and blood tissue entered the further MR analyses, respectively. For all selected druggable genes, we kept eQTLs after clumping at  $r^2 = 0.001$  based on the 1000 genomes European reference panel to avoid LD bias.

### *Mendelian Randomization Identifies Potential Drug Targets for Psychiatric Disease*

Using brain and blood eQTL proposed instruments, we performed 2 sample MR analysis<sup>19</sup> on summary statistics from the 5 largest-scale GWAS published to date for psychiatric diseases (including SCZ, BP, DEP, ASD, and ADHD) (**figure 1**). The threshold for significant associations with MR evidence was set at  $P < 1.82 \times 10^{-6}$  (ie, 0.05 Bonferroni-corrected for 27 421 total significant eQTLs of brain and blood) and full significant MR results are shown in **Supplementary table 2**. Using *cis*-eQTLs from PsychENCODE dataset as proposed instruments, we identified a significant relationship between 21 genes and SCZ, 7 genes and BP, 2 genes and DEP, and a single gene for ADHD. Using *cis*-eQTLs from the eQTLGen dataset as proposed instruments, we discovered a significant relationship between 33 genes and SCZ, 15 genes and BP, 7 genes and DEP, 3 genes and ADHD, and none of the genes associated with ASD risk. Among these significant genes, the treatment of the target gene may be associated with disease risk because it has an odds ratio (OR) of greater than 1.00 (ie,  $OR > 1.00$  indicates a relationship between increased gene expression and increased disease risk).

Furthermore, we found that a set of replicated genes reached significance in both 2 eQTL datasets (**Supplementary table 3**), including 11 genes for SCZ, 3 genes for BP, and 1 gene for DEP and ADHD. However, 12 of the 16 replicated genes had different directions of the MR effect between tissues (**Supplementary figure 1** and **Supplementary table 3**). For example, genetically raised gene *BTN3A2* expression was associated with reduced DEP risk in brain tissue ( $OR = 0.95$ ; 95% CI, 0.94–0.97;  $P = 1.65 \times 10^{-12}$ ) and increased DEP risk in blood tissue ( $OR = 1.06$ ; 95% CI, 1.03–1.08;  $P = 5.09 \times 10^{-7}$ ), and this pattern was consistent with SCZ. Caution is required in interpreting MR results with opposite directions of effect.

Taking into account the priority given to brain tissue probably most relevant to psychiatric disorders and the

different directions of the MR effect between tissues, we adapted a potentially useful approach to screening for potentially druggable genes as follows: prioritizing genes associated with brain eQTL, even if they are not in the blood. Therefore, a total of 31 significant genes identified in MR analysis might be used as potential drug targets for psychiatric disease. Twenty-six of these 31 potential targets identified were nominated by the psychiatric disease GWAS previously and the rest five additional potential targets were reported here, which suggests that integrating eQTL evidence may help substantiate GWAS findings. Intriguingly, we found that several candidate genes with consistent directions of effect in the brain and blood, including one SCZ gene (*FURIN*), 2 BP genes (*FURIN*, *MCHRI*) and 1 ADHD gene (*TIE1*), strongly suggest that these genes represent potential drug targets for brain disorders (**Supplementary figure 1**). Moreover, we examined whether the significant MR results were overrepresented in a particular tier (**Supplementary figure 2**). Chi-squared tests assessed differences between the groups (ie, tiers) and we founded no significant relationship between any of the significant MR results and particular tier ( $P > 0.05$ , chi-squared test, **Supplementary table 4**).

### *Mendelian Randomization Quality Control Further Identifies That Promising Drug Targets Have the Most Robust Mendelian Randomization Evidence for Psychiatric Disease Risk*

Given the low number of instruments used in this study ( $N = 1-3$ , **Supplementary Tables**), MR–Egger and heterogeneity analyses may be less reliable, thus we did not perform sensitivity analyses. For potential associations that reached the significance threshold in brain MR analysis, we undertook an important quality control step to prioritize the MR significant results: colocalization analysis (**Online Methods**). Due to the presence of LD, there may be 2 distinct pathogenic SNPs in the association region of SNP exposure and SNP outcome, resulting in a spurious MR result.<sup>46</sup> To further investigate whether the genetic associations with both gene expression and disease trait shared the same causal variant in the region, we performed colocalization analysis on MR preliminary results of the brain (**Supplementary table 2**) for psychiatric diseases. As summarized in **Supplementary table 5**, all of these 31 signals showed strong evidence of colocalization between gene expression and disease (posterior probability of shared causal variant across 2 traits, hypothesis 4 (PP.H4)  $> 0.8$ ), indicating that both eQTL instrument (ie, gene expression) and outcome (ie, disease trait) are associated with the same region and share a same causal variant. Evidence shows that genes with strong evidence of MR and colocalization are more likely to become promising drug targets.<sup>17</sup> In total, we prioritized 31 significant genes as promising drug targets for psychiatric disorders

after MR quality control, including 21 significant genes for SCZ, 7 significant genes for BP, 2 significant genes for DEP and 1 significant gene for ADHD (**figure 2** and **Supplementary table 5**).

#### *Protein Quantitative Trait Loci Data Provide Further Genetic Evidence for Identifying Actionable Therapeutic Targets for Psychiatric Disorders*

Considering that most clinical use of proteins as drug targets rather than gene expression and the nonlinear relationship between protein and mRNA levels,<sup>47</sup> it is necessary and important to utilize pQTLs to model drug target effects (ie, defined as MR instruments for drug exposure).<sup>48</sup> Using pQTLs in the MR analyses for the 31 proposed targets (**figure 2**), we identified 8 protein-trait associations (**figure 3** and **Supplementary table 6**) on three diseases with strong evidence of MR ( $P < 1.12 \times 10^{-5}$  at a Bonferroni-corrected threshold; after applying colocalization), including 5 (*ACE*, *NEK4*, *BTN3A3*, *HAPLN4*, and *MAPK3*) significant proteins for SCZ, 2 (*NEK4* and *HAPLN4*) significant protein for BP and 1 (*TIE1*) significant protein for ADHD. By integrating drug-target information from the DrugBank database,<sup>30</sup> 4 of the 8 significant genes mentioned above encode targets of approved or clinical-phase drugs, presenting a possible repurposing opportunity: *NEK4*, *MAPK3*, *ACE*, and *TIE1* (**table 1**). If the drug target is used as an inhibitor, there would need to be an OR > 1 in the MR, otherwise, it could be a safety concern and may not be a good drug target. For instance, by integrating summary data from brain eQTL/blood pQTL and SCZ GWAS in the MR analysis, we found that *ACE* with OR > 1 in both datasets (**Supplementary table 2** and **figure 3**), indicating that a higher gene *ACE* expression level corresponded to a higher risk of SCZ. As shown in **Table 1**, perindopril is an *ACE* inhibitor prodrug with an appropriate direction of effect, possibly representing a repurposing opportunity. In addition, we observed that several identified potential druggable genes corresponding to the same drug (ie, fostamatinib), including *TIE1* and *NEK4* (**table 1**). Interestingly, another *MARK3* gene that was significant only in brain tissue MR analysis also corresponded to the fostamatinib drug (**Supplementary table 7**). We found that the direction of effect of the fostamatinib (action as inhibition) on *MARK3* expression was consistent with the effect seen in MR Analysis (*MARK3* with OR > 1 in brain MR results, **Supplementary table 2**) and inconsistent with the other 2 gene effects (*TIE1* and *NEK4* with OR < 1 in brain MR results, **Supplementary table 2**), thus warranting further safety investigation in follow-up studies. Similar to the above, *MAPK3*, encodes the target of an approved-phase medication (ie, Arsenic trioxide) with an appropriate direction of effect (ie, inducer with negative MR effect), possibly representing an actionable therapeutic target for SCZ in future clinical studies (**table 1**).

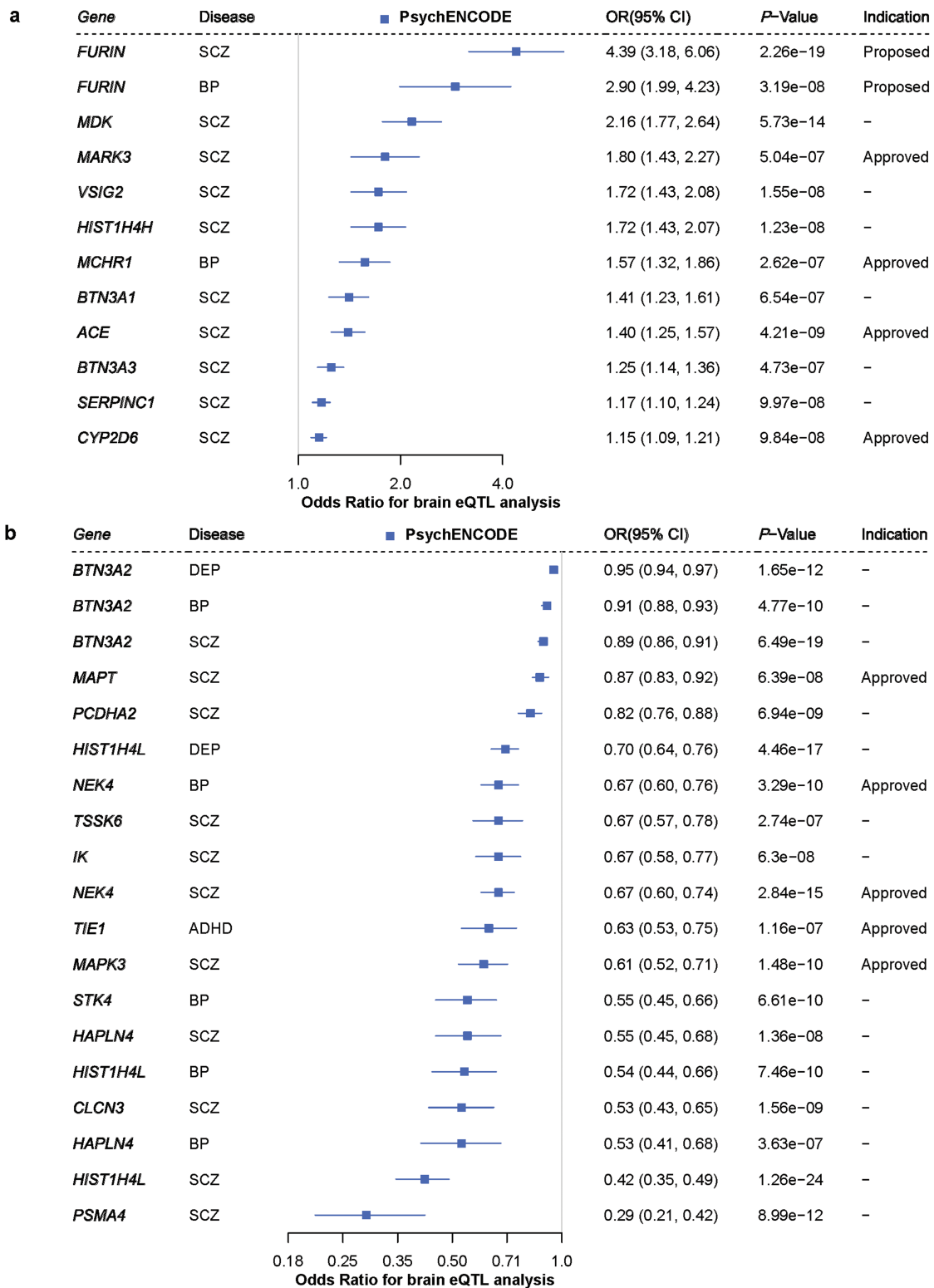
## Discussion

To identify drug repurposing opportunities and find novel drug targets for psychiatric disorders (including SCZ, BP, DEP, ASD, and ADHD), we undertook a large-scale 2 sample MR analysis by integrating eQTL/pQTL datasets for druggable genes with genetic summary statistics from the largest currently available GWAS datasets. By performing a colocalization analysis of the MR significant results in the brain, we further identified 31 promising drug targets with robust evidence (**figure 2** and **Supplementary table 5**). By combining pQTL MR results, we proposed 8 drug targets with the strongest MR evidence. Among them, 4 of which (*ACE*, *MAPK3*, *NEK4*, and *TIE1*) offer possible drug repurposing opportunities as clinical drug candidates for psychiatric disorders (**table 1**). The potential contributions of the above 4 drug-target genes to psychiatric disorders are discussed in detail in the **Supplementary Discussion**. Overall, we highlight the importance and opportunities of eQTL MR analyses for drug repositioning and emphasize the key analytical methods to support such inference.

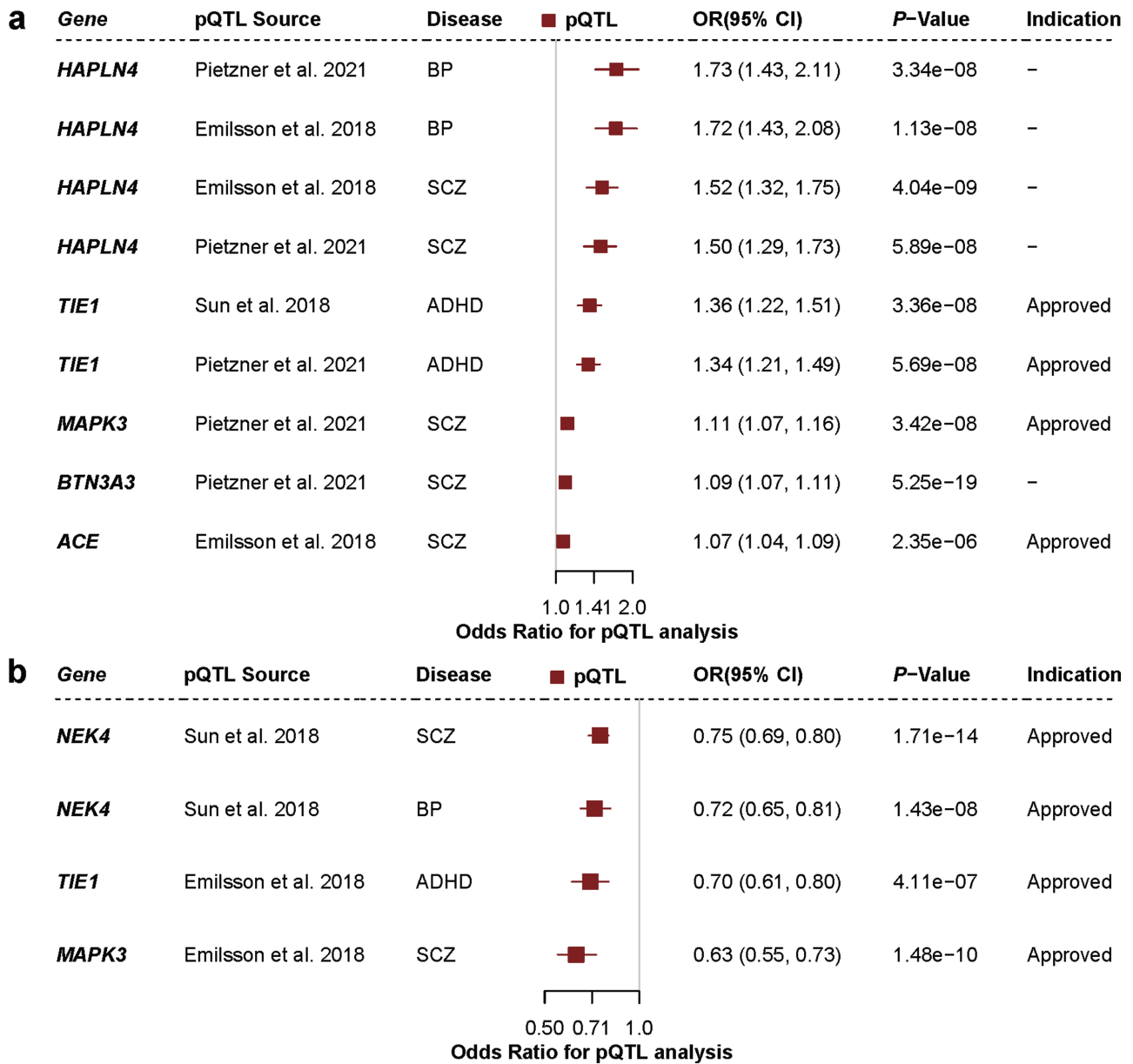
Several previous similar MR studies<sup>49,50</sup> have been performed to provide valuable information for brain-related traits by integrating eQTL and GWAS from multiple sources. Detailed discussions on comparison with previous similar MR studies are provided in the **Supplementary Discussion**.

Due to the relatively small number of non-European study participants in the psychiatric GWASs and eQTL dataset, it is uncertain whether the MR results from this study are applicable to other non-European study populations. Therefore, we performed MR analysis using blood eQTL and GWAS data of schizophrenia and depression in EAS populations and full significant MR results are shown in **Supplementary table 8**. Considering that differences in LD patterns between populations tend to affect the MR and colocalization results, we have repeated the MR analysis using brain eQTL data and European-specific GWAS summary statistics of SCZ (including 53 386 cases and 77 258 controls) to compare the EAS MR results (the detailed European-specific MR results are summarized in **Supplementary table 9**). Using *cis*-eQTL SNPs from the blood eQTL dataset of the EAS population as genetic instruments, we identified 3 significant drug targets for schizophrenia (including *MAPK3*, *BTN3A2*, and *ITIH4*) but no significant drug-targeting gene with depression. Of note, we noticed that *MAPK3* and *BTN3A2* also showed significant associations in the European-specific MR study (**Supplementary table 2**). However, we found that both 2 significant genes (*MAPK3* and *BTN3A2*) had different directions of effect between tissues, possibly due to the discrepancy in effect direction and the heterogeneity of different eQTL tissues.

There are also several potential limitations to this study. First, although we used SNP instruments derived



**Fig. 2.** Thirty-one promising drug targets were proposed for psychiatric disorders. (a) Forest plots showing the results that drug targets as an antagonist reached significance and pass stringent quality tests in the brain eQTL dataset (blue =PsychENCODE). (b) Forest plots showing the results that drug targets as an agonist reached significance and pass stringent quality tests in the brain eQTL dataset (blue =PsychENCODE). The “Indication” column indicates whether the corresponding drug is approved or proposed (the drug information can be retrieved through DrugBank). The term “NA” used in the plot represents encoded druggable genes that have not been included in the DrugBank. Replicated significant genes with concordant effect direction between blood and brain tissues are distinguished and bolded. Additionally, we calculated a 95% CI for the OR. SCZ: schizophrenia, BP: bipolar disorder, DEP: depressive disorder, ADHD: attention deficit hyperactivity disorder.



**Fig. 3.** Protein quantitative trait loci in blood provide further genetic evidence. (a) Forest plots showing the results that all proteins as an antagonist and outcomes where a pQTL was available. (b) Forest plots showing the results that all proteins as an agonist and outcomes where a pQTL was available. The term “NA” used in the plot represents encoded druggable genes that have not been included in the DrugBank. The “pQTL Source” column indicates which pQTL study the SNPs were derived from. The “Indication” column indicates whether the corresponding drug is approved or proposed (the drug information can be retrieved through DrugBank). 95% CI, OR, SCZ: schizophrenia, BP: bipolar disorder, ADHD: attention deficit hyperactivity disorder.

from different data sources in MR analysis, they still limit the generalizability of the results because the genetic instruments obtained did not cover the whole actionable druggable genome. Second, most previous GWAS and eQTL studies of psychiatric disorders have used data from individuals of European descent. This limits the understanding of the underlying biology of psychiatric disorders and raises questions about the transferability of findings between populations. Our study also suggests ancestry-specific MR findings diverge and converge across modalities in schizophrenia

and depression. Third, we mainly focused on the effect of SNPs (ie, variants) on gene expression and protein levels. This work did not take into account other factors that may affect disease, including chromatin accessibility, histone modification, and DNA methylation. Also, we overlooked the effect of variants on expression levels of gene isoforms. Finally, MR cannot fully reproduce clinical trials (ie, the MR results do not yet directly reflect the practical effect size) and does not perfectly predict a drug effect, considering that standard MR studies typically determine lifespan and low-dose



**Table 1.** Four Potential Drug Targets Offer Possible Drug Repurposing Opportunities as Clinical Drug Candidates for Psychiatric Disorders

Gene	Outcome	Drug	Clinical phase	Action	Indication
<i>ACE</i>	SCZ	Perindopril	Approved	Inhibitor	Perindopril is an ACE inhibitor prodrug used to treat hypertension, mild to moderate congestive heart failure, and to reduce cardiovascular risk in patients with hypertension or postmyocardial infarction.
<i>MAPK3</i>	SCZ	Arsenic trioxide	Approved	Inducer	Arsenic trioxide is a chemotherapeutic agent used in the treatment of refractory or relapsed acute Promyelocytic leukemia in patients with prior retinoid and anthracycline chemotherapy.
<i>NEK4</i>	SCZ	Fostamatinib	Approved	Inhibitor	Fostamatinib is a spleen tyrosine kinase inhibitor used to treat chronic immune Thrombocytopenia after attempting one other treatment.
<i>NEK4</i>	BP	Fostamatinib	Approved	Inhibitor	Fostamatinib is a spleen tyrosine kinase inhibitor used to treat chronic immune Thrombocytopenia after attempting one other treatment.
<i>TIE1</i>	ADHD	Fostamatinib	Approved	Inhibitor	Fostamatinib is a spleen tyrosine kinase inhibitor used to treat chronic immune Thrombocytopenia after attempting one other treatment.

*Note:* These drugs are approved, clinical phase, and drug indication based on <https://go.drugbank.com>.

Gene: The name of the drug target gene.

Outcome: The psychiatric disorder in which the drug target gene associates.

Drug: The name of the drug to the corresponding disorder.

Clinical phase: The phase of drug discovery procession.

Action: Pharmacological action of the drug.

Indication: Brief introduction to the drug.

exposure, whereas RCTs only report the effects of relatively shorter and high-dose exposures.

In conclusion, we performed comprehensive 2 sample MR analyses covering all actionable druggable genes to identify potentially causal genes for psychiatric disorders. By focusing on brain eQTL to mimic exposure to medications, we prioritized 31 promising causal genes based on genetic data (**Supplementary table 10**). Eight of these genes with the strongest pQTL MR evidence served as actionable drug targets for common psychiatric disorders (**figure 2**). Our work provides both an analytical framework for prioritizing potential new targets and provides actionable and promising drug candidates for drug repurposing in psychiatric disorders. The strategies proposed in this study can also be applied to other complex diseases, like cancer, that have extensive eQTL data available but still have many cases without well-defined, therapeutic targets with genetically supported evidence.

### Supplementary Material

Supplementary material is available at <https://academic.oup.com/schizophreniabulletin/>.

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