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RESEARCH

Novel Insights into Schizophrenia Treatment: Comprehensive Analysis Unveiling FGFR1 as a Promising Druggable Gene

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Abstract

Schizophrenia (SCZ) is a chronic, relapsing mental disorder with a complex and poorly understood etiology. Identifying novel therapeutic targets is essential for advancing treatment options. Druggable genes were sourced from the eQTLGen consortium and integrated with SCZ-related GWAS data. Two-sample Mendelian randomization (MR) and co-localization analyses assessed the likelihood of shared pathogenic variants between the expression quantitative trait loci (eQTL) of these genes and SCZ. Positive results were further validated using Summary-based MR (SMR). Phenome-wide association studies, drug prediction, and molecular docking analyses were also conducted to identify potential therapeutic targets among these genes. SMR analysis revealed six druggable genes significantly associated with SCZ: NMB, IK, FGFR1, SERPING1, EDEM2, and CTSS. Molecular docking studies demonstrated favorable binding energies for PD 173074-FGFR1 (−8.1407 kcal/mol), WZ-7043-FGFR1 (−7.8027 kcal/mol), and lenvatinib-FGFR1 (−7.3075 kcal/mol). Single-cell expression analysis further indicated that FGFR1 is predominantly expressed in mural cells, suggesting its potential role in SCZ pathogenesis. This study identifies six druggable genes as potential therapeutic targets for SCZ, with FGFR1 emerging as a particularly promising candidate. These findings provide valuable insights for SCZ treatment development and position FGFR1 as a viable target for future therapeutic strategies.

Keywords Schizophrenia · Druggable genes · Mendelian randomization · SMR · Colocalization analyses

Introduction

Schizophrenia (SCZ) is a chronic, progressive mental disorder marked by symptoms such as hallucinations, delusions, disorganized thinking, and deficits in emotional and social functioning [1]. Despite extensive research, the exact etiology and pathogenesis of SCZ remain unclear. Identified risk factors include genetic predisposition, environmental stressors, neurobiological and immunological dysregulation, and neurodevelopmental abnormalities [2, 3]. Current guideline-based antipsychotic treatments focus on symptom management; however, sustained symptom relief and improved quality of life remain difficult to achieve [4, 5]. Consequently, identifying novel therapeutic targets to prevent SCZ onset or mitigate its progression is critical.

Recent research has explored innovative SCZ treatment strategies, including drugs targeting specific neurotransmitter receptors and those designed based on underlying pathophysiological mechanisms [6, 7]. Notably, collaborative efforts have led to the development of novel antipsychotic compounds aimed at selectively improving positive,

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negative, and cognitive symptoms by targeting specific receptors [8, 9]. Additionally, the neurodevelopmental hypothesis of SCZ has gained traction, with treatment strategies based on this model showing promise in targeted interventions [10].

Mendelian randomization (MR) is a statistical method that utilizes genetic variations associated with an exposure of interest as instrumental variables to assess causal relationships between the exposure and an outcome [11]. MR offers statistical power comparable to randomized controlled trials (RCTs) while reducing bias and eliminating reverse causation [12]. Drug-target MR specifically uses single nucleotide polymorphisms (SNPs) linked to gene expression levels, particularly those of cis-eQTLs near the target genes, to investigate the impact of bioactive genes [13].

In this study, an MR approach was employed to identify potential drug target genes for SCZ therapy. Following initial MR analysis, colocalization analysis was used to identify genes mediating interactions between prospective therapeutic targets and SCZ risk. Further screening of potential therapeutic genes was performed using summary-data-based MR (SMR) analysis, and PheWAS was applied to assess associations between these targets and other phenotypes. Finally, molecular docking and drug prediction analyses were conducted to evaluate the therapeutic potential of the identified targets.

Materials and Methods

Study Design

Data sources and prior studies on target genes were first evaluated, with a particular focus on blood regulatory regions. Positive MR data were then used to screen druggable genes, followed by co-localization analysis for further refinement. SMR analysis subsequently validated the co-localization of these druggable genes. Candidate genes and potential drug targets were further explored through PheWAS analysis, drug prediction models, and molecular docking of validated genes. This integrated approach highlighted the significance of six potential drug target genes in SCZ development and their therapeutic potential. The study design is illustrated in Fig. 1.

Druggable Genes

Druggable genomes refer to genes encoding proteins that can potentially be targeted by drugs. The present study utilized druggable gene data from Finan et al., who identified a total of 4479 druggable genes [14] (Supplement Table 1). The gene list included 1427 genes encoding approved or clinical-stage drug targets, 682 genes encoding proteins with known drug-binding affinity or structural similarity to approved drug targets, and 2370 genes that belong to key druggable families or encode proteins closely related to established drug targets.

eQTL Datasets

Blood eQTL data were sourced from the eQTLGen consortium, available at https://eqtlgen.org/. The consortium consists of 37 datasets, encompassing a total of 31,684 individuals and 16,987 genes [15]. The analysis excluded linkage disequilibrium and provided cis-eQTL data for 2525 of the 4479 druggable genes in blood (Supplement Table 1).

GWAS Dataset for SCZ

The present study utilized summary data from the 2022 SCZ GWAS meta-analysis conducted by the Psychiatric Genomics Consortium (PGC) [16]. The combined dataset included 320,404 individuals of European, East Asian, African American, and Latino descent, comprising 76,755 cases and 243,649 controls.

Mendelian Randomization Analysis

MR analyses were performed using the "TwoSampleMR" package in R (version 0.5.4). eQTLs from the pharmacogenome were selected as representation data for exposure. The instrumental variable (IV) was constructed from SNPs in the cis-eQTL data, with inclusion limited to SNPs exhibiting p-values below the 5.0×10^{-8} genome-wide significance threshold. SNPs of treatment-relevant genes were clustered using the European samples from the 1000 Genomes Project. A linkage disequilibrium (LD) window of 10,000 kb was set with an r^2 threshold of < 0.1 [17] (Supplement Table 2). MR analysis was conducted on the screening SNPs, with the Wald ratio method applied when a single SNP was present in the IV. When multiple SNPs were available for IV analysis, MR was performed using five approaches: inverse variance weighting (IVW), MR-Egger, weighted median, simple mode, and weighted mode. The pleiotropic effects between SNPs and response variables were assessed using the MR Egger intercept.

Colocalization Analysis

Colocalization analysis was performed to validate potential shared causative genetic variations between SCZ and eQTL regions. Colocalization studies were conducted using the "coloc" R package (version 5.2.3) for druggable genes with significant MR responses [18]. Default values were set for all probabilities: $P1 = 1.0 \times 10^{-4}$, $P2 = 1.0 \times 10^{-4}$, and $P12 = 1.0 \times 10^{-5}$. The posterior

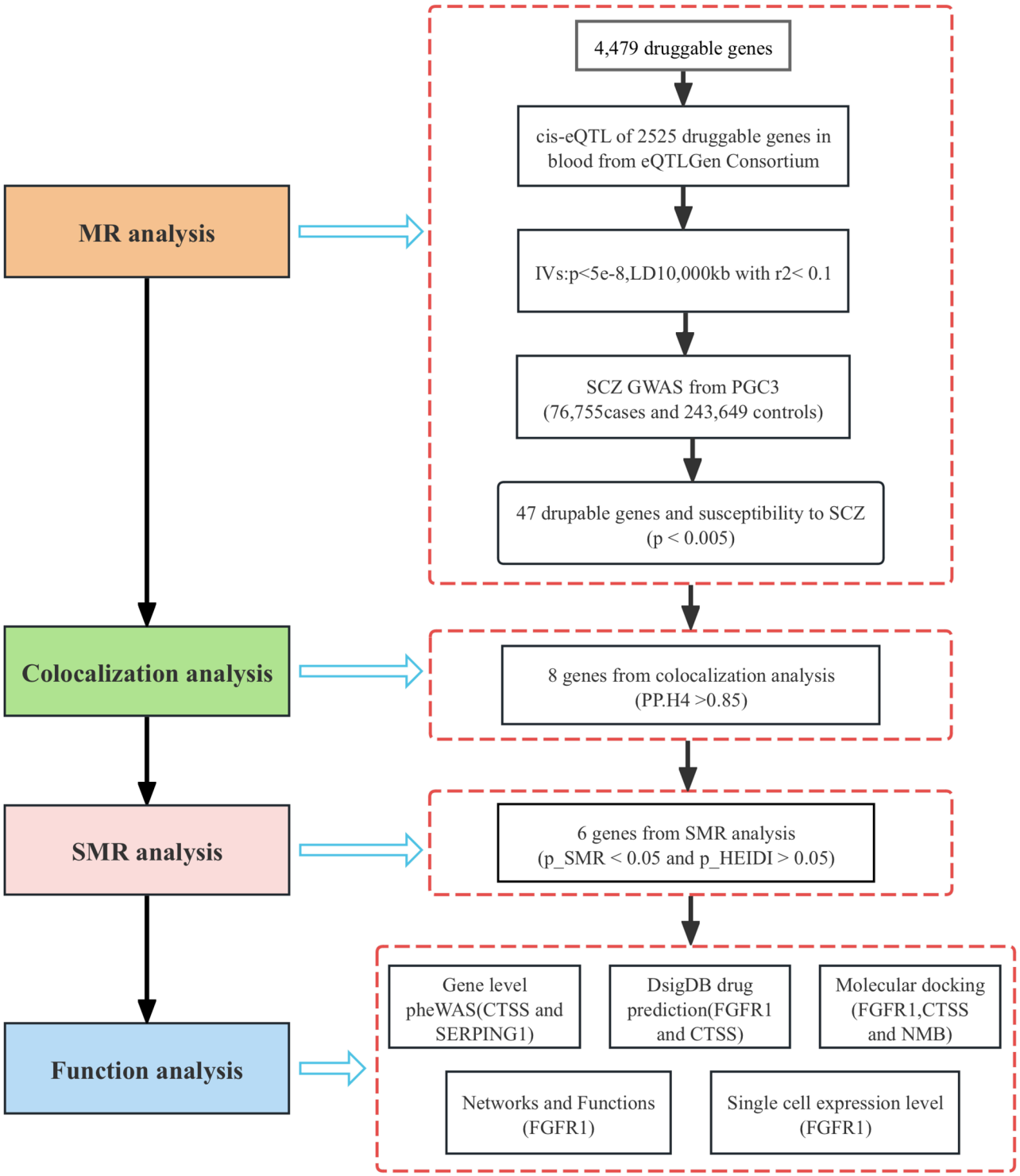

Fig. 1 The flow chart of the study design

probability (PP) was used to quantify the support for all hypotheses, ranging from PPH0 to PPH4. A PPH4 > 0.85 was considered strong evidence of colocalization, indicating a shared causal relationship between SCZ risk and gene expression.

SMR Analysis

SMR analysis was further conducted to validate the causal relationship between target genes and SCZ. The SMR tool (version 1.3.1) is available for download at https://yangl

ab.westlake.edu.cn/[19]. To assess whether the observed effects were due to common genetic variation rather than genetic linkage, the Heterogeneity in Dependent Instruments (HEIDI) test was applied to SNPs with a minimum of three instances. Statistical significance for the SMR analysis was set at $p < 0.05$, with a p-value greater than 0.05 in the HEIDI test indicating that linkage disequilibrium did not significantly affect the causal association between exposure and outcome. A Manhattan plot was generated using the CMplot (version 4.5.1) R tool to visualize the positive SMR results.

PheWAS Analysis

Phenome-wide association studies (PheWAS) were employed to assess the pleiotropic effects and potential adverse consequences of prospective drug targets. The PheWAS portal developed by AstraZeneca (https://azphewas.com/) provides extensive data on genotype–phenotype correlations [20]. These statistics were derived from a subgroup of approximately 450,000 individuals who underwent exome sequencing, with data made available through the UK Biobank. The dataset includes approximately 155,000 binary and 15,000 continuous phenotypic records. After thorough data evaluation and adjustments, a stringent criterion ($p < 5e-9$) was established to minimize the risk of false positives. This comprehensive PheWAS analysis offers valuable insights into the genetic underpinnings of complex traits and evaluates the safety and efficacy of pharmacological targets.

Drug Candidate Prediction

A thorough assessment of protein-drug interactions is essential for identifying promising therapeutic targets. The drug characteristics database (DSigDB, http://dsigdb.tanlab.org/DSigDBv1.0/) contains 22,527 gene sets, 19,531 genes, and 17,389 distinct compounds [21]. To predict potential drug targets, the target genes were uploaded to the Enrichr gene enrichment analysis tool suite (https://maayanlab.cloud/modEnrichr/).

Molecular Docking

To evaluate the impact of potential medications on target genes and their potency, molecular docking at the atomic level was employed to assess target-drug binding. The PubChem database (http://pubchem.ncbi.nlm.nih.gov/) provided the 2D structures of small molecule ligands [22], which were subsequently converted into 3D structures (mol2 files) using Chem Office 20.0. Following protein target selection, the RCSB PDB database (http://www.rcsb.org/) was consulted to identify high-resolution crystal structures, which were used as molecular docking receptors. The PyMOL2.6.0 software was applied to remove water and phosphate groups from the protein structure, which was then saved in a PDB format. Autodock4.2 was used to perform semi-flexible docking simulations with docking times set to 10 [23]. The Molecular Operating Environment (MOE) 2019 software optimized compound energy, preprocessed target proteins, and identified active binding pockets. A total of 50 docking simulations were performed using the MOE 2019 program and the highest 1% of the compounds with docking scores was set to ≤ -7 [24]. Binding potency was evaluated by measuring binding energy, with results visualized using PyMOL2.6.0 and MOE 2019.

Networks and Function Analysis

Gene functions and interaction networks for FGFR1 were analyzed using GeneMANIA (https://genemania.org/). GeneMANIA constructs networks by integrating data from various sources, including gene co-expression, protein–protein interactions, genetic interactions, co-pathways, and physical interactions, identifying genes with potentially shared functions.

Validation of Single-Cell Expression Levels

Single-cell sequencing technology provides insights into cellular heterogeneity, cell differentiation, development, and disease. A comprehensive understanding of cellular gene expression was gained by analyzing single-cell expression data from key druggable genes. Data from the 3D brain organoids of GSE184878 were downloaded, which included samples from three individuals with SCZ and four healthy controls. Primary cell types were annotated using the SingleR v1.4.116 tool.

Results

MR Analysis: Identification and Association of Druggable Genes

Using data from the eQTLGen Consortium, 40,356 SNPs within 2525 druggable genes were identified as instrumental variables (IVs) by intersecting druggable gene lists with significant cis-eQTLs (Supplemental Table 2). Significant cis-eQTLs for 40,356 SNPs in 2,525 druggable genes were identified as IVs in this analysis (Supplemental Table 3). Additionally, applying the IVW method, a significant association between the expression of 47 druggable genes and SCZ susceptibility was revealed ($p < 0.005$) (Fig. 2; Supplemental Table 4). MR-Egger regression analysis confirmed the absence of pleiotropy in these genes, validating the selected IVs as specific genetic instruments. These results suggest a

potential causal relationship between the expression of these druggable genes and SCZ susceptibility, warranting further investigation.

Colocalization Analysis: Key SCZ Target Genes with Shared Causal Variants

To refine our therapeutic candidate selection based on significant MR results, colocalization analysis was conducted to assess the likelihood of shared causal variants between cis-eQTLs and SCZ-associated markers. This analysis identified eight key genes—CYP21A2, IK, SERPING1, EDEM2, CACNB3, FGFR1, CTSS, and NMB—with strong evidence of shared causal variants (PP.H4 > 0.85) (Table 1; Supplemental Table 5). These shared variants suggest a pivotal role for these genes in SCZ pathogenesis, positioning them as promising targets for therapeutic intervention.

SMR Validation: Robust Confirmation of SCZ Target Genes

To further validate the impact of these druggable target genes on SCZ susceptibility, SMR analysis coupled with the HEIDI test was performed, corroborating findings from the MR and colocalization analyses (Supplemental Table 6). Of the eight genes, six (NMB, IK, FGFR1, SERPING1, EDEM2, and CTSS) showed significant associations in the SMR analysis (p_SMR < 0.05) and passed the HEIDI test (p_HEIDI > 0.05), confirming a lack of heterogeneity (Table 2; Fig. 3). These validated genes exhibit strong associations with SCZ risk, highlighting their potential as druggable targets for future therapeutic strategies.

PheWAS Analysis: Assessing Potential Side Effects of Target Genes

Through PheWAS analysis using the PheWAS Portal and PheWeb databases, potential side effects associated with targeting these six key genes were assessed. No significant associations between the six protein targets and other phenotypes were identified ($p < 5e-9$) in the PheWeb database (Table 3) or the PheWAS Portal (Fig. 4a, b). These findings suggest a minimal likelihood of adverse effects from targeting these genes, underscoring their favorable safety profile as therapeutic targets for SCZ.

Table 2 The results of SMR and HEIDI test

Gene	Probe-Chr	b_SMR	se_SMR	p_SMR	p_HEIDI
NMB	15	0.308703	0.069839	$9.86e-06$	0.287
IK	5	0.294094	0.074541	$7.97e-05$	0.163
FGFR1	8	0.065376	0.017231	0.000148	0.245
SERPING1	11	0.263910	0.071835	0.000239	0.635
EDEM2	20	−0.296048	0.084939	0.000491	0.311
CTSS	1	0.259385	0.077649	0.000836	0.667

Drug Candidate Prediction: Identification of Potential Therapeutic Compounds

Potential drug candidates were predicted using the DSigDB database, ranking the top ten compounds by p-value (Supplemental Table 7). Notably, 2-Nonenal-4-hydroxy-(2E,4R) (CTD 00001295) demonstrated a significant association with NMB and FGFR1, while GLYOXAL (CTD 00006046) and methylglyoxal (CTD 00006677) were linked to CTSS. PD 173074 (TTD 00010068) exhibited a strong association with FGFR1 (Table 4). These findings suggest that targeting these interactions with specific compounds may offer therapeutic potential for mitigating SCZ-related pathology.

Molecular Docking: Evaluation of Compound-Target Binding Affinities

Molecular docking analysis was conducted using MOE 2019 software to investigate the interactions between small compounds and protein targets. Binding energies for the docking interactions ranged from − 3.6453 to − 8.1407 kcal/mol (Supplemental Table 8). Binding energies below − 4.25 kcal/mol suggest specific binding activity, those below − 5.0 kcal/mol

Table 1 Colocalization results of eQTLs for 8 genes with SCZ-associated SNPs

Gene	No. of SNPs	PP.H0.abf	PP.H1.abf	PP.H2.abf	PP.H3.abf	PP.H4.abf
CYP21A2	6	0.000	0.000	0.000	0.000	1.000
IK	7	0.000	0.000	0.000	0.000	1.000
SERPING1	11	0.000	0.002	0.000	0.000	0.998
EDEM2	5	0.000	0.086	0.000	0.000	0.914
CACNB3	5	0.000	0.088	0.000	0.000	0.912
FGFR1	5	0.000	0.090	0.000	0.000	0.910
CTSS	6	0.000	0.096	0.000	0.000	0.904
NMB	10	0.000	0.148	0.000	0.000	0.852

Table 3 Significantly continuous trait PheWAS association with CTSS and SERPING1

Gene	Phenotype	Collapsing model	*p*-value	No. of samples	Effect size
CTSS	Neurology	Flexdmg	$1.28e-13$	35,547	−1.24
CTSS	Neurology	Ptvraredmg	$1.97e-12$	35,547	−1.39
CTSS	Neurology	Flexnonsynmtr	$4e-11$	35,547	−1.42
CTSS	Neurology	Raredmg	$1.09e-10$	35,547	−1.27
SERPING1	InflammationII	Flexdmg	$1.77e-11$	45,606	−0.61
SERPING1	SHBG	Ptv5pcnt	$4.51e-9$	362,988	−2.37

indicate satisfactory binding, and energies below −7.0 kcal/mol reflect robust binding activity. Docking analysis revealed that four compound-protein pairs exhibited significant binding activity, with two showing satisfactory binding, while the other two demonstrated no binding activity. PD 173074-FGFR1 (−8.1407 kcal/mol), WZ-7043-FGFR1 (−7.8027 kcal/mol), and lenvatinib-FGFR1 (−7.3075 kcal/mol) exhibited particularly low binding energies, indicating strong and stable binding interactions (Fig. 5a–c). These results suggest that these compounds could effectively bind to FGFR1, supporting their potential as therapeutic agents. However, Docking scores are predictive and need to be validated by experimental or multimethod pathways [25].

Networks Analysis: FGFR1 Functional Pathways and Therapeutic Implications

To further explore FGFR1's therapeutic potential, its network profile was expanded using the GeneMANIA database (Fig. 6). The functional network of FGFR1 highlighted significant enrichment in pathways involved in cellular response to fibroblast growth factor stimuli, regulation of protein kinase B signaling, endothelial cell chemotaxis, phospholipase C activity, neurotrophin receptor binding, and neuron projection guidance. This network analysis reinforces FGFR1's role in processes crucial to SCZ pathophysiology, highlighting its potential as a therapeutic target.

Single-Cell Expression: FGFR1 Distribution in Brain Cell Clusters

Single-cell RNA sequencing data were analyzed using Seurat, identifying ten distinct cell clusters, including macrophages, oligodendrocytes, endothelial cells, neurons, and mural cells (Fig. 7). FGFR1 expression was most pronounced in the mural cell cluster. Mural cells, essential components of the cerebrovascular system, contribute to blood–brain barrier (BBB) formation. FGFR1's involvement in cerebrovascular network dysfunction could influence SCZ pathogenesis, underscoring its potential role in cerebrovascular integrity and SCZ-related mechanisms.

Discussion

Schizophrenia, a mental disorder, affecting over 1% of the global population, is characterized by cognitive impairment, emotional flattening, social dysfunction, and positive symptoms such as hallucinations and delusions [26–28]. Current treatments mainly target positive symptoms; however, no effective therapies exist for negative symptoms and cognitive impairments, which significantly impact patients' long-term social functioning and quality of life [29]. Despite targeting several receptors, including dopamine, 5-HT, Glu, cannabis, and sigma receptors [30], anti-SCZ drug development faces challenges such as low cure rates, high relapse rates, and the emergence of new adverse effects [31]. Therefore, exploring novel drug targets and mechanisms is critical.

In this study, MR, co-localization, and SMR analyses were performed to identify potential therapeutic targets for SCZ. This represents the first application of MR in this context, utilizing the largest publicly available GWAS dataset for SCZ risk. To enhance statistical rigor, genes were required to demonstrate significance in both GWAS cohorts, minimizing the risk of false positives. The therapeutic potential of these genes was further demonstrated through drug prediction and molecular docking, which revealed strong binding interactions, supporting their viability as targets for pharmaceutical intervention. Through the application of IVW, MR-Egger regression, co-localization analysis, SMR analysis, PheWAS, drug prediction, and molecular docking, six genes (IK, SERPING1, EDEM2, FGFR1, CTSS, and NMB) were identified as the most promising therapeutic targets for SCZ. Notably, FGFR1 exhibited stable binding interactions in molecular docking, and network analysis highlighted its regulation of endothelial cell chemotaxis, phospholipase C activity, neurotrophin receptor binding, and neuron projection guidance—processes that may be linked to neurodevelopmental abnormalities in SCZ. Additionally, single-cell analysis revealed that FGFR1 expression was most prominent in mural cells, which are integral to the BBB, suggesting a potential role for FGFR1 in cerebrovascular dysfunction contributing to the pathophysiology of SCZ.

FGFR1, a member of the fibroblast growth factor receptor (FGFR) family, features a ligand-binding extracellular

Gene	Pvalue	or(95%CI)
CYP21A2	<0.001	0.749(0.703−0.797)
BTN3A2	<0.001	1.104(1.078−1.130)
SERPING1	<0.001	1.148(1.099−1.199)
EDEM2	<0.001	0.890(0.851−0.930)
CACNB3	<0.001	1.109(1.062−1.158)
TXNRD1	<0.001	0.774(0.694−0.862)
CTSS	<0.001	1.115(1.064−1.169)
KLHL8	<0.001	0.766(0.682−0.861)
PCSK6	<0.001	1.464(1.228−1.746)
DARC	<0.001	0.901(0.859−0.946)
NMB	<0.001	1.208(1.104−1.322)
C4B	<0.001	0.918(0.881−0.957)
HLA−C	<0.001	0.928(0.893−0.964)
SRD5A1	<0.001	0.929(0.894−0.965)
CSNK1G1	<0.001	1.195(1.089−1.310)
VCP	<0.001	1.089(1.042−1.139)
PARP1	<0.001	1.061(1.027−1.095)
NMT1	<0.001	1.153(1.066−1.246)
CD53	<0.001	1.233(1.098−1.385)
IGFBP4	<0.001	1.117(1.050−1.187)
FGFR1	<0.001	1.088(1.038−1.140)
PTK2B	<0.001	1.081(1.035−1.130)
CD40	<0.001	0.925(0.885−0.966)
DPEP2	<0.001	1.083(1.035−1.132)
PLBD1	<0.001	0.900(0.847−0.955)
HEBP1	<0.001	0.916(0.870−0.965)
TPP1	0.001	1.059(1.023−1.096)
QDPR	0.001	1.026(1.010−1.042)
EFTUD1	0.001	0.821(0.727−0.926)
MMP24	0.002	0.878(0.810−0.951)
IK	0.002	1.182(1.066−1.311)
OPN3	0.002	1.054(1.020−1.090)
PIP4K2B	0.002	1.241(1.084−1.422)
SIGLEC11	0.002	0.956(0.929−0.984)
KAT2B	0.002	0.908(0.854−0.967)
FST	0.003	1.107(1.035−1.183)
NAGA	0.003	1.233(1.075−1.416)
ICAM1	0.003	1.234(1.074−1.418)
MAP4K5	0.003	1.175(1.056−1.308)
PRKCE	0.003	1.292(1.088−1.533)
PLA2G6	0.004	0.881(0.809−0.960)
SOAT1	0.004	1.039(1.012−1.066)
ECE1	0.004	1.078(1.024−1.135)
CPA3	0.005	1.126(1.037−1.222)
AKT1	0.005	0.873(0.794−0.959)
TLR6	0.005	0.908(0.850−0.971)
SIRPG	0.005	0.921(0.870−0.975)

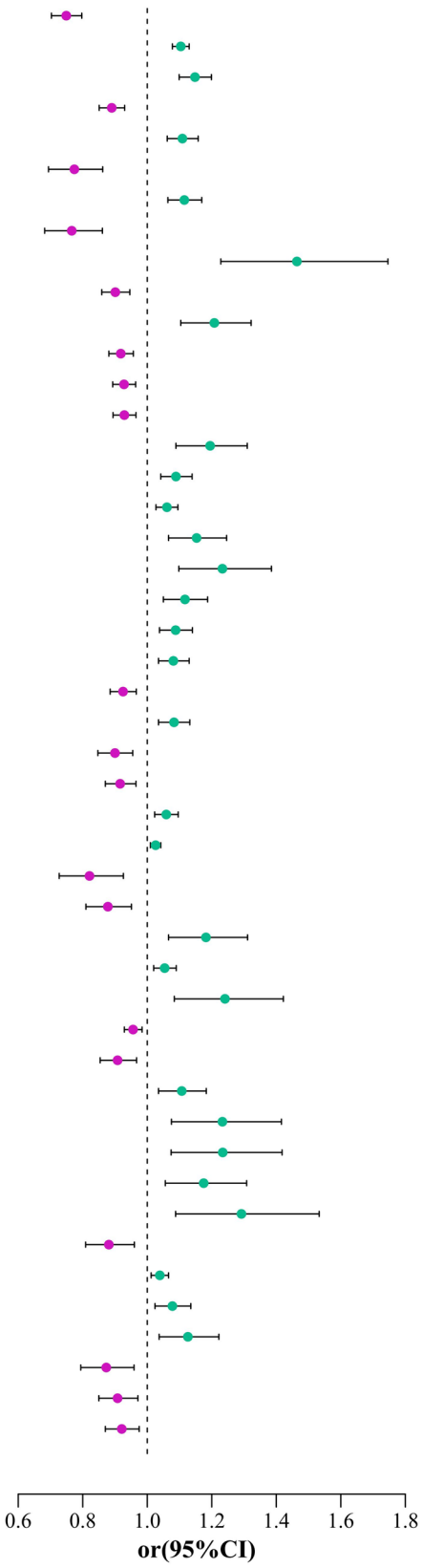

Fig. 2 Forest plots displaying the findings from the MR for 47 significant genes

Table 4 Candidate drug predicted using DSigDB

Drug names	*p*-value	Odds ratio	Combined score	Genes
Nonenal-4-hydroxy-(2E,4R) CTD 00001295	0.0027	36.25	214.35	NMB; FGFR1
GLYOXAL CTD 00006046	0.0032	399.68	2284.21	CTSS
Ro-4396686 TTD 00010666	0.0035	363.32	2044.88	FGFR1
Urea CTD 00006965	0.0038	333.03	1847.76	FGFR1
Methylglyoxal CTD 00006677	0.0041	307.40	1682.80	CTSS
PD 173074 TTD 00010068	0.0050	249.72	1318.67	FGFR1
Fucose TTD 00008125	0.0053	235.02	1227.64	CTSS
Kinome 511 Roche	0.0059	210.26	1076.20	FGFR1
WZ-7043 LINCS	0.0059	210.26	1076.20	FGFR1
Lenvatinib FDA	0.0062	199.74	1012.62	FGFR1

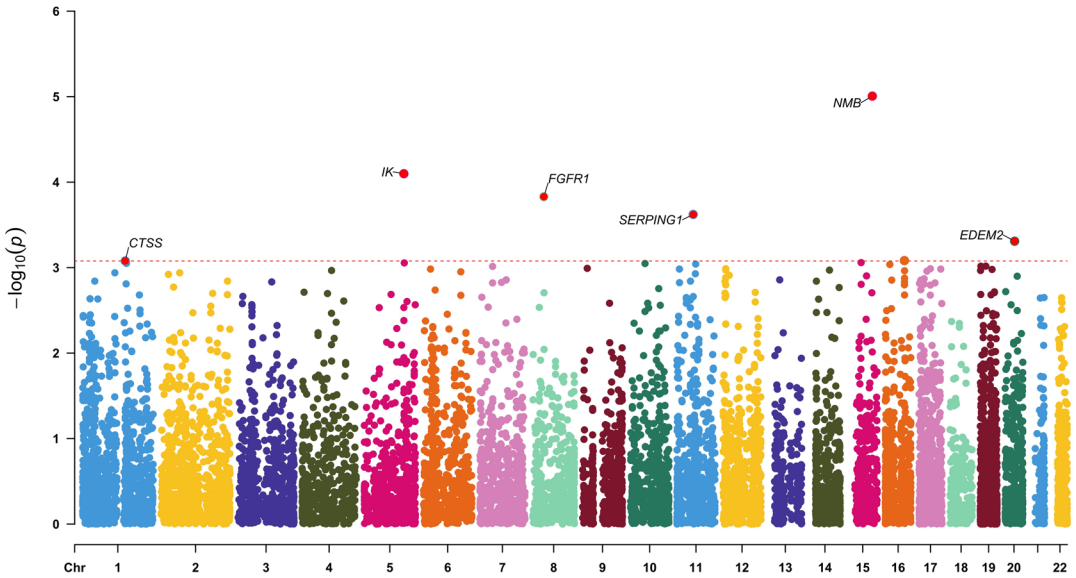

Fig. 3 Manhattan plot of SMR analysis. Significant genes were labelled and highlighted in red

domain, a transmembrane domain, and an intracellular receptor phosphorylation domain [32]. It forms a ternary complex with 18 distinct fibroblast growth factors (FGF), triggering various signaling pathways involved in cell growth, metastasis, immune regulation, and angiogenesis [33]. Several FGFR1-targeting drugs, including small molecule inhibitors and monoclonal antibodies, have been developed. Pemigatinib, an inhibitor targeting FGFR1-3, is approved for cholangiocarcinoma treatment and has shown efficacy in other cancers, such as urothelial carcinoma, breast cancer, endometrial cancer, and squamous cell carcinoma [34, 35]. The role of FGFR1 in psychiatric and neurological disorders is an emerging area of research, with recent studies highlighting FGFR1 signaling as crucial for neurodevelopment and neural function [36]. Our findings of elevated FGFR1 expression in SCZ-associated monomembranous cell clusters align with previous research linking FGF/FGFR and VEGF/VEGFR signaling pathways to angiogenesis and cell proliferation, suggesting that FGFR1 inhibitors could have therapeutic potential in neuropsychiatric conditions. FGF21, through FGFR1 activation, has been shown to reduce inflammation-induced depressive behaviors and promote neuronal recovery after hypoxic-ischemic injury [37]. Moreover, FGF21 may prevent neuronal ferroptosis following spinal cord injury by activating the FGFR1/β-Klotho pathway [38]. Ferroptosis has been implicated in SCZ pathology in our previous study [39]. Further research is required to explore how FGFR1 activation may modulate ferroptosis-related neurodegeneration and influence SCZ symptoms. Furthermore, FGF21 promotes functional recovery following hypoxic-ischemic brain damage in neonatal rats by activating the PI3K/Akt signaling pathway through the FGFR1/β-Klotho complex [40]. Moreover, docking is a valuable in silico tool that allows us to computationally

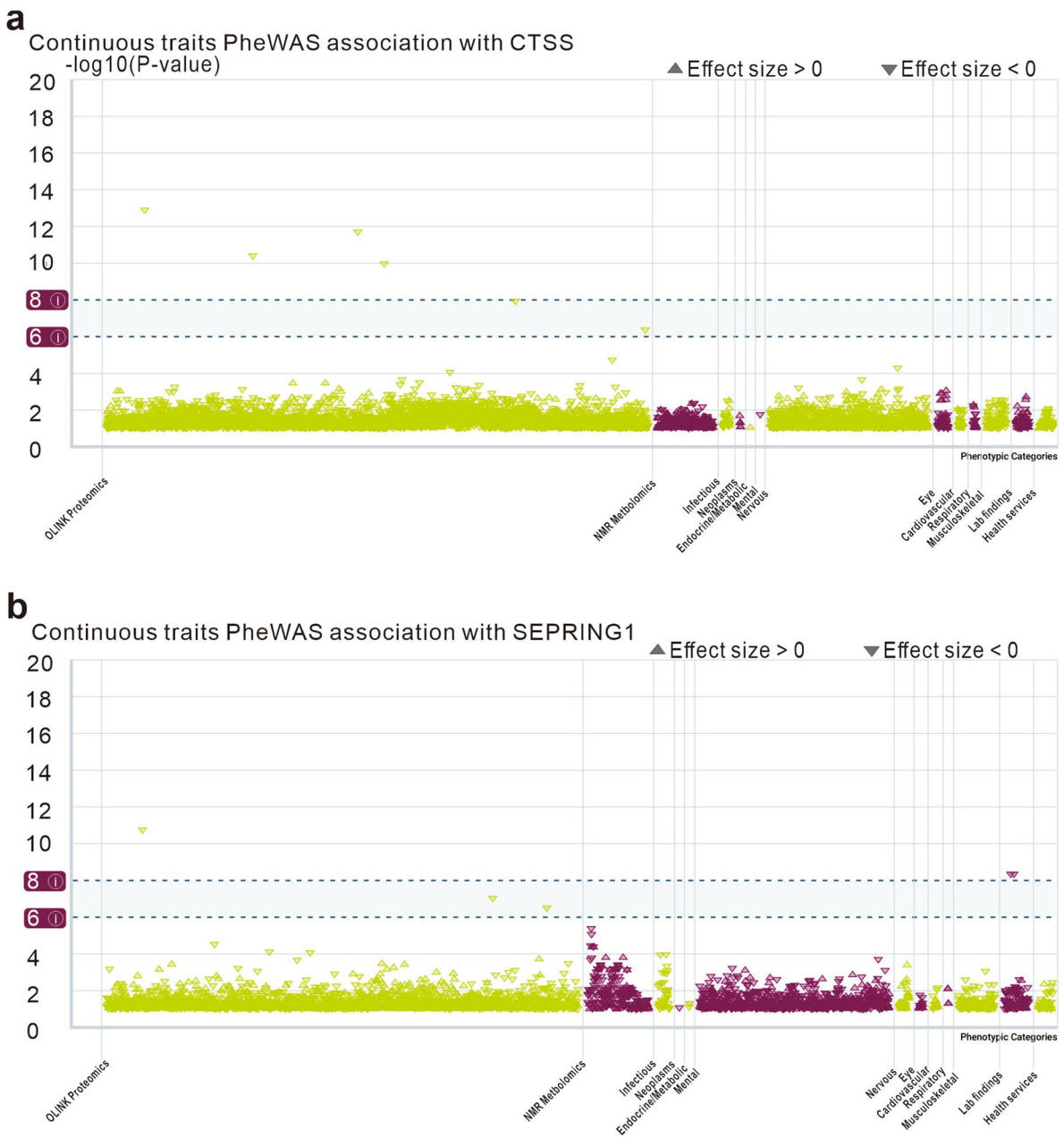

Fig. 4 Continuous trait PheWAS association with CTSS and SERPING1

predict how a small molecule might interact with a target protein at the atomic level, and FGFR1 indicates a strong binding affinity in this regard. However, we fully acknowledge that these in silico findings are only the first step in exploring potential therapeutic candidates. There are potential limitations of molecular docking, such as force field inaccuracies and static binding mode assumptions, which will affect the evaluation of docking scores [23–25]. As research advances, clinical trials will be essential to evaluate the efficacy and safety of FGFR1 inhibitors in these contexts.

We further identified a potential link between FGFR1, mural cells, and schizophrenia pathophysiology. Cytokines secreted by adherent cells such as CXCL12 regulate the behavior of microglia and astrocytes [41]. Dysregulated FGFR1 signaling can disrupt this interaction, leading to uninhibited microglial activation and the release of pro-inflammatory cytokines such as IL-6, TNF-α, which are elevated in SCZ patients and animal models [42]. Second, similar to SCZ behavioral defects [43], FGFR1 inhibition in parietal cells aggravated neuroinflammation following systemic immune challenge in preclinical models. Alternatively,

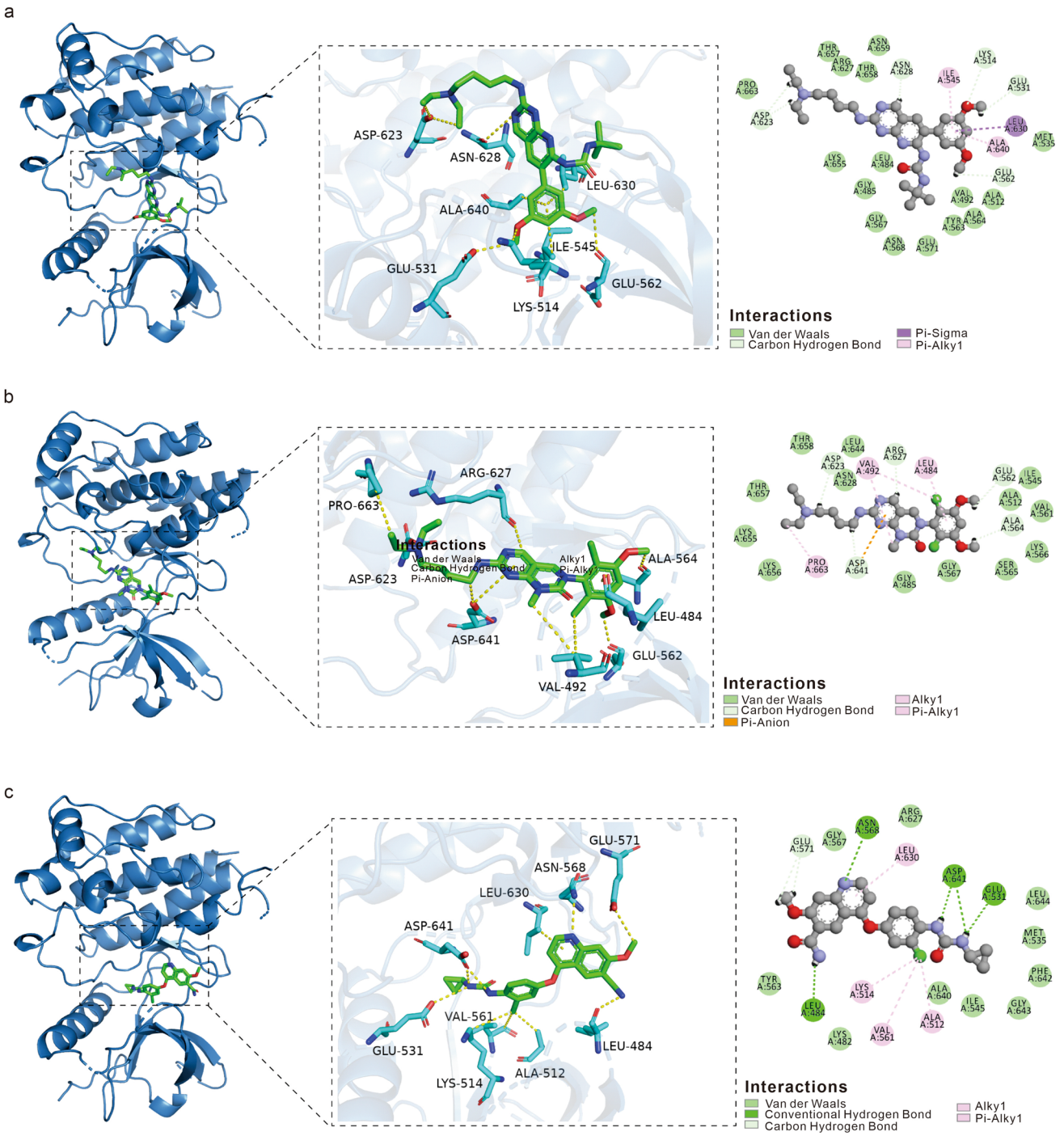

Fig. 5 Docking results of available proteins small molecules. **a** FGFR1 docking PD 173074; **b** FGFR1 docking WZ-7043; **c** FGFR1 docking Lenvatinib

parietal cells mediate neurovascular coupling, linking neuronal activity to blood flow. FGFR1 signaling in these cells may affect synaptic pruning and plasticity. FGFR1 promotes pericyte mediated excessive synaptic phagocytosis during brain development [44]. Parietal cells regulate the release of brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF2), which are required for dendritic spine maturation [45]. Although the results of our analysis suggest that parietal cell FGFR1 plays a meaningful role in SCZ, direct evidence from human brain tissue is lacking. In the future, we will integrate multi-omics approaches

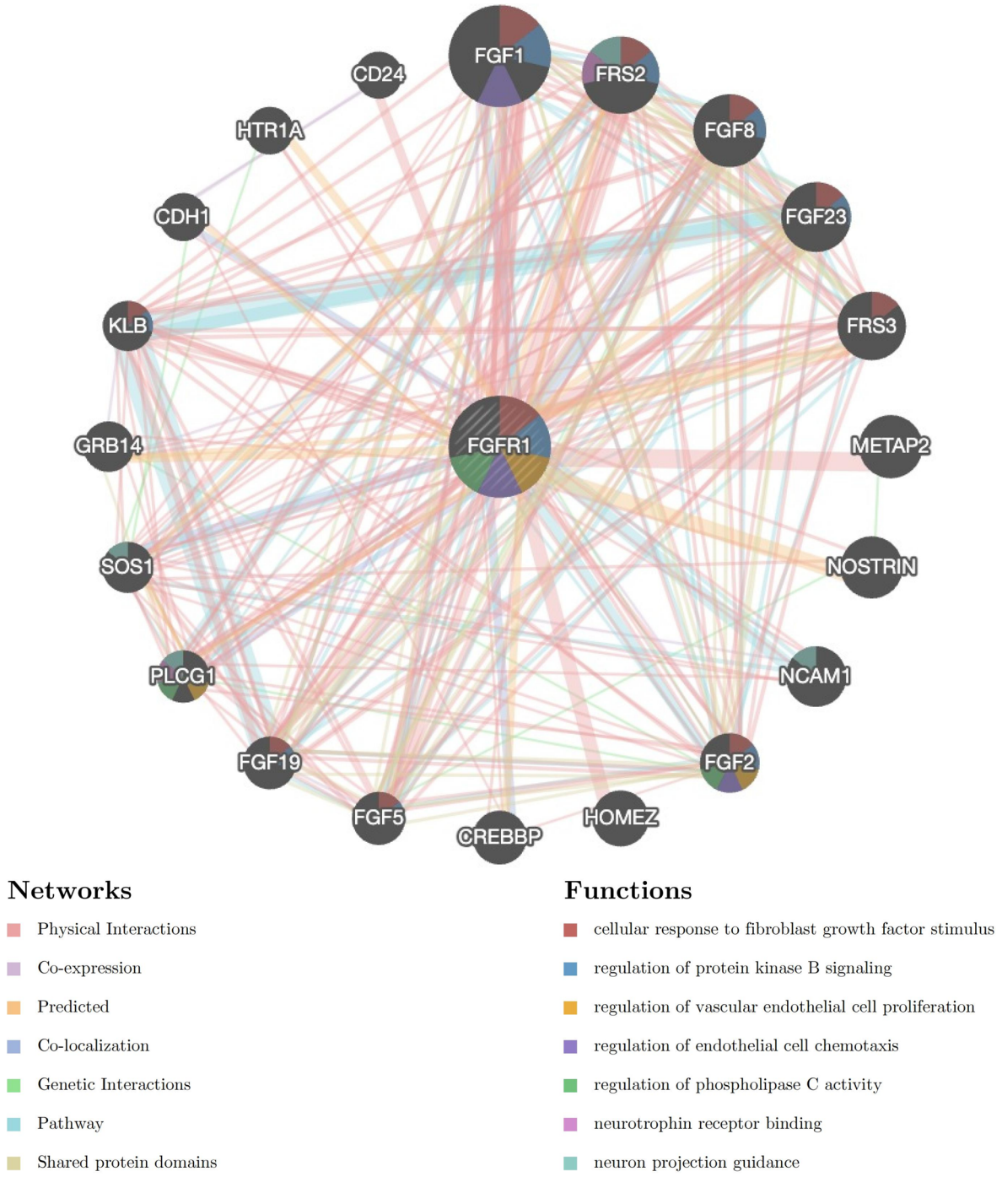

Fig. 6 The network of FGFR1 using automatically selected weighting method

combining single-cell RNA sequencing and spatial transcriptomics to map FGFR1 signaling pathway in neural vessels.

IK is associated with the NF-κB signaling pathway, a key regulator of immune responses and cellular stress responses. Aberrant activation of NF-κB signaling has been linked to the inflammatory hypothesis of SCZ, suggesting that IK may influence SCZ pathology by modulating inflammation [46]. Endoplasmic reticulum degradation-enhancing α-mannosidase 2 (EDEM2), an endoplasmic reticulum-associated deubiquitinating enzyme, plays a critical role in protein folding, quality control, and degradation [47]. Abnormal protein homeostasis in SCZ could lead to misfolded or aggregated proteins in the brain,

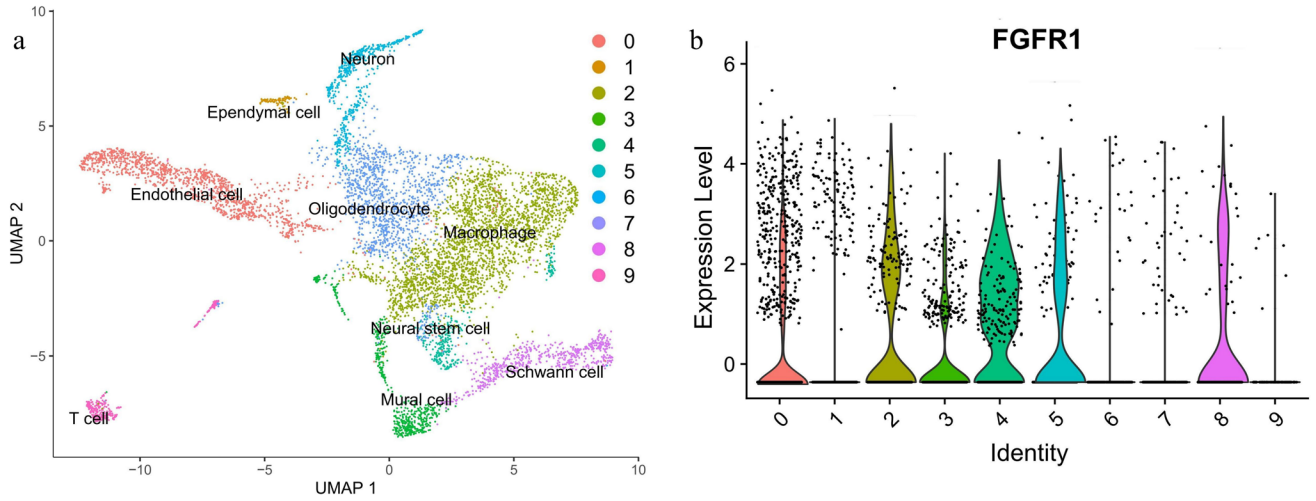

Fig. 7 Results of single-cell RNA sequencing data analysis. **a** The single-cell clustering results identified UMAP maps of 10 cell clusters. **b** Expression level of FGFR1 in 10 cell clusters

implicating EDEM2 in the disease process [48]. SERPING1 encodes C1 inhibitor, a serine protease inhibitor that regulates the complement system, and has been linked to various neurological disorders, including SCZ. Targeting SERPING1 or its regulatory pathways could potentially modulate inflammatory responses in SCZ [49, 50]. CTSS, a cysteine protease primarily active in lysosomes, plays a role in antigen processing and presentation and may affect inflammatory pathways relevant to SCZ. Its abnormal expression could contribute to neuroinflammation and cell death, hallmark features of SCZ [51–53]. Neuropeptide B (NMB), involved in appetite regulation, energy balance, immune responses, neuroendocrine regulation, and behavioral responses, may help modulate chronic inflammation in SCZ by reducing neuroinflammation [54, 55].

This study has several limitations. While MR offers causal insights, it cannot substitute for clinical trials, and the predicted drug effects in MR models may not accurately reflect clinical outcomes, potentially overestimating or underestimating their impact. The reliance on blood eQTLs in MR testing complicates the identification of the most relevant tissues for treatment, as different organs have distinct genetic regulatory systems. Additionally, the focus on cis-eQTLs may have overlooked other environmental and regulatory factors contributing to SCZ. Validation of these therapeutic targets through clinical studies and experimental models is crucial to confirm their potential for SCZ treatment. In future studies, we will use CRISPR/Cas9 gene editing technology combined with scRNA-seq to verify the specific expression of FGFR1 in parietal cells and its regulatory effect on BBB genes. Furthermore, molecular dynamics was used to predict the ability of FGFR1 as druggable target for uptake, distribution, metabolism, and metabolic processes.

Conclusion

In conclusion, this study utilized MR analysis to identify potential pharmacological targets for SCZ. Colocalization analysis confirmed six key targets across cohorts, emphasizing genes involved in immune function and neuroplasticity—critical pathways in SCZ pathogenesis and promising targets for therapeutic intervention. Drug prediction and molecular docking analyses further supported the therapeutic potential of these targets. Ongoing research and clinical validation will be necessary to establish these targets as effective therapeutic options for SCZ.

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Data Availability Data is provided within the manuscript or supplementary information files.

Declarations

Ethics Approval Ethical approval was obtained for the data used in this study.

Consent to Participate Informed consent was obtained from the original study participants.

Conflict of interest The authors declare no competing interests.

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