Genetics based putative drug targets of several brain diseases

Motivation & Background

Brain diseases such as schizophrenia (SPR), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD) pose significant therapeutic challenges, making it essential to identify effective drug targets and repurposing opportunities. In our study, we utilize Two-sample Mendelian randomization [1, 2], which leverages summary statistics from independent genome-wide association studies (GWAS) [3], to examine both qualitative and quantitative traits related to the diseases, including gene expression (eQTL) [4,5]. Additionally, we employ MetaXcan to predict gene expression effects in disease-relevant tissues using GWAS and eQTL data, thereby linking disease-associated gene expression patterns to functional outcomes (Table 1) [6]. By integrating these approaches, we aim to accelerate drug target discovery and repurposing by linking genetically driven expression changes to therapeutic potentials in human brain disorders.

Table 1. Information About the Dataset Used

Disease	GWAS Dataset	eQTL Dataset
SPR	ieu-b-5099	GTEx eQTL (49 tissues)
ALS	ieu-a-1085	
AD	ukb-b-14699	

Method

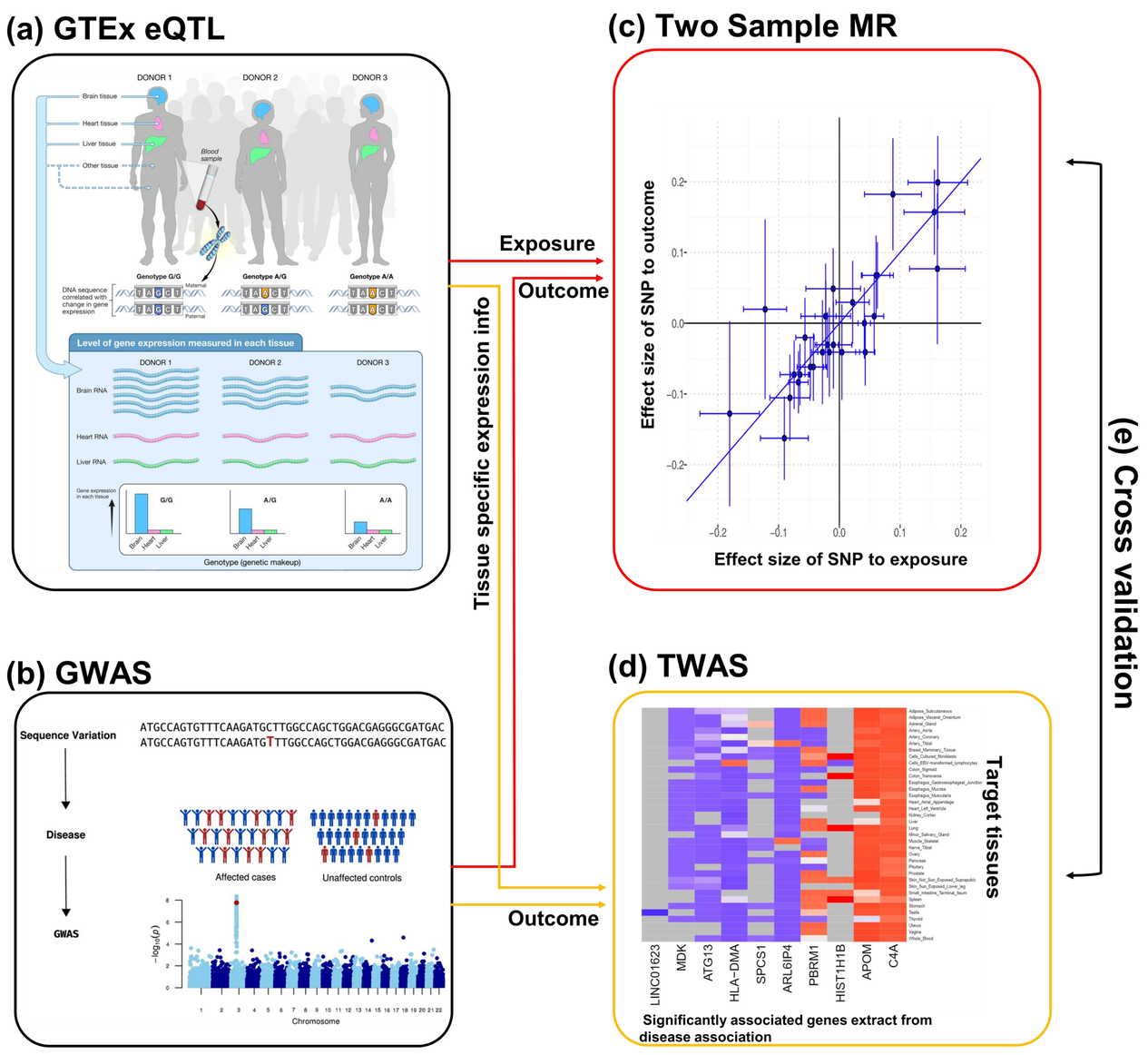

Figure 1. The workflow of new drug target discovery for brain disease.
First, we collected gene expression data from 49 tissues using the GTEx eQTL database (a). Next, we obtained brain disease-related GWAS summary statistics from the MRCIEU database (b). By using GTEx eQTL data as the exposure and brain disease GWAS data as the outcome, we performed two-sample MR analysis to identify gene expression changes with potential causal effects on brain diseases (c). Additionally, to identify tissues and genes with differential expression between disease cases and controls, we conducted TWAS analysis using MetaXcan with the GTEx 49 tissues eQTL data and case-control study results (d). Finally, we cross-validated the results to identify genes with high potential as new drug targets (e).

Reference

[1] Sanderson E. et al. *Nat Rev Methods Primers,* 2022;2:6.
[2] George Davey Smith et al. *Hum Mol Genet*, 2014;23(1):89-98.
[3] https://gwas.mrcieu.ac.uk/
[4] https://gtexportal.org/home/downloads/adult-gtex/qtl
[5] Hemani G et al. *eLife,* 2018;7:e34408.
[6] Alvaro N. Barbeira et al. *Nat Comm,* 2018;9:1825.

Result

We obtained GWAS summary statistics datasets for each disease (schizophrenia, amyotrophic lateral sclerosis, and Alzheimer's disease) from the MRCIEU database, and tissue-specific eQTL data from GTEx for conducting MR and TWAS analyses (Figure 1, Table 1).

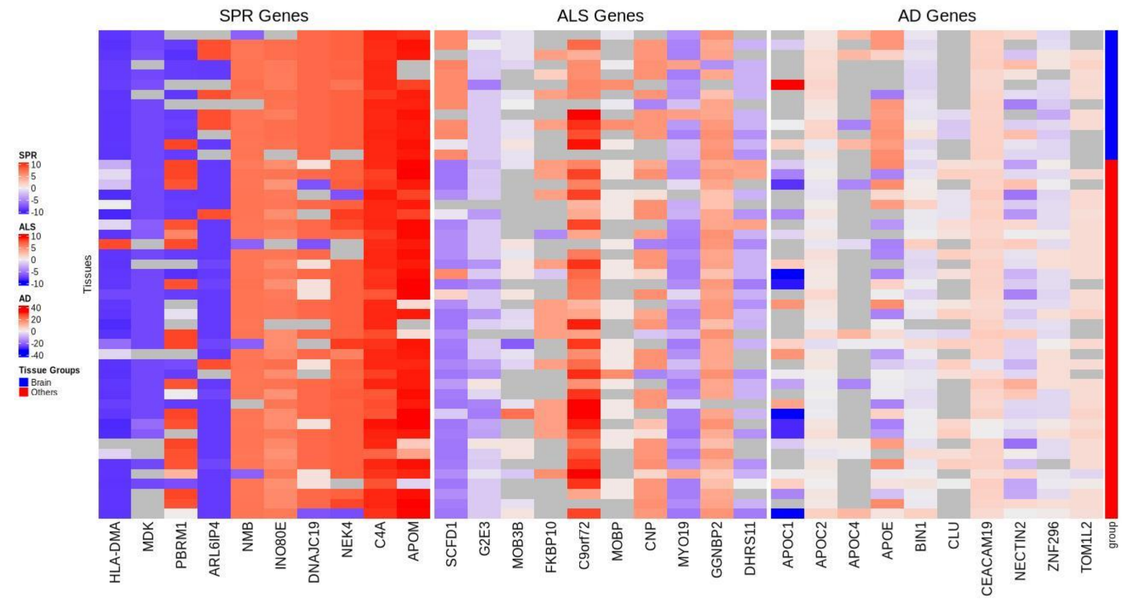

Figure 2. Heatmaps of gene expression z-score from MetaXcan results for SPR, ALS, and AD.
Each heatmap presents the z-scores of genes associated with SRP (left), ALS (middle), and ALS (right), as obtained from MetaXcan analysis. The z-scores indicate the strength and direction of the association between gene expression levels based on GWAS data and disease onset. Positive z-scores suggest that increased expression of the gene is associated with a higher risk of disease, while negative z-score indicate that increased expression is associated with a lower risk.

Table 2. Putative drug targets identified by Two-sample MR and MetaXcan analysis.

Disease	Genes	MR		MetaXcan Brain tissue	Drug Target Potential
		beta	pval		
SPR	INO80E	1.34E-01	2.49E-13	7.500	New target
	C4A	1.79E-01	4.54E-26	10.206	New target, but C4 family is currently considered as potential target for SPR because of its elevated expression in SPR (Woo, 2020, Yilmaz, 2021)
ALS	SCFD1	5.39E-02	9.69E-07	5.517	New target
	FKBP10	-5.36E-02	2.35E-05	4.135	Inconsistent
	C9orf72	2.53E-02	1.90E-03	10.097	Ustekinumab (Antibody, for the treatment Crohn's disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis)
	MYO19	-3.91E-02	5.89E-05	4.203	Inconsistent
AD	APOC1	-8.91E-03	4.81E-04	35.650	Inconsistent
	APOC2	1.49E-03	4.83E-02	5.022	Infigratinib (FGFR inhibitor, potent and selective Pan-FGFR Inhibitor, Kinase Inhibitors, for the treatment of locally advanced or metastatic cholangiocarcinoma)
	APOC4	1.61E-03	5.02E-02	9.983	Dinoprostone (activates the PGE2 receptor, Abortifacient Agents, Small Molecule, for the treatment of nonmetastatic gestational trophoblastic disease)
	APOE	-2.93E-02	8.55E-59	17.320	Inconsistent
	CEACAM19	6.14E-03	2.78E-03	5.890	New target
	TOM1L2	1.20E-02	1.06E-03	4.947	New target

Through integrated MR and TWAS analyses using GWAS and eQTL data, we identified novel drug target genes for schizophrenia, amyotrophic lateral sclerosis, and Alzheimer's disease. Our findings revealed both new therapeutic targets (SPR: INO80E and C4A; ALS: SCFD1; AD: CEACAM19 and TOM1L2) and existing drug candidates for repurposing (C9orf72, APOC2, APOC4; Figure 2, Table 2). While some of the identified genes are already linked to approved drugs, others represent promising new targets for future drug development.

Discussion

Our study using GWAS and eQTL data, identified novel drug target genes for brain diseases through integrated MR and TWAS analyses, providing promising candidates for therapeutic development and potential repurposing strategies in conditions like schizophrenia, amyotrophic lateral sclerosis, and Alzheimer's disease.

Among the genes significantly associated with the brain diseases, some already have approved drugs available, while others are known targets in treatments for other conditions, suggesting their potential for drug repurposing in brain disorders. additionally, the remaining genes represent promising new targets for therapeutic development.