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ORIGINAL RESEARCH

TEX10: A Novel Drug Target and Potential Therapeutic Direction for Sleep Apnea Syndrome

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Background: Sleep apnea syndrome (SAS) is a prevalent sleep disorder strongly associated with obesity, metabolic dysregulation, and cardiovascular diseases. While its underlying pathophysiological mechanisms remain incompletely understood, genetic factors likely play a pivotal role in SAS pathogenesis. This study investigates the causal relationships between potential drug target genes and SAS using multiple statistical approaches, aiming to provide novel insights for targeted therapeutic development.

Methods: We conducted a comprehensive genetic analysis integrating multiple methodologies to investigate gene-SAS relationships. Using publicly available GWAS and eQTL databases, we performed Mendelian Randomization (MR) analysis with the inverse variance weighted (IVW) method, validated by weighted median and MR-Egger approaches. Summary-data-based MR (SMR) analysis, coupled with HEIDI testing, assessed direct gene expression-SAS associations while controlling for linkage disequilibrium (LD). Colocalization analysis evaluated the probability of shared causal variants between SNPs, gene expression, and SAS. Statistical significance was determined using Benjamini-Hochberg multiple testing correction (FDR < 0.05). Additionally, mediation analysis explored TEX10's influence on SAS through metabolic intermediates including BMI, waist circumference, and HDL cholesterol.

Results: We identified 18 candidate drug target genes significantly associated with SAS, with MAPKAPK3, TNXB, MPHOSPH8, and TEX10 showing consistent associations across multiple analyses. TEX10, in particular, exhibited significant associations with SAS risk in blood, cerebral cortex, hippocampus, and basal ganglia (PP.H4 > 0.9). Mediation analysis suggested that TEX10 might influence SAS risk indirectly through BMI, waist circumference, and HDL cholesterol levels.

Conclusion: Our study identified multiple potential therapeutic targets causally linked to SAS, with TEX10 emerging as a key candidate gene. These findings advance our understanding of SAS pathogenesis and offer promising directions for personalized diagnostics and targeted therapies.

Keywords: druggable genes, sleep apnea syndrome, drug target, expression quantitative trait loci, Mendelian randomization, summary-data-based Mendelian randomization

Introduction

Sleep apnea syndrome (SAS) is characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep, with each episode lasting ≥10 seconds and occurring ≥5 times per hour of sleep.[1,2] Based on epidemiological evidence, SAS has an incidence rate of more than 20% in men, which is higher than the average incidence rate of 9% in women.[3,4] With the global increase in obesity rates and an aging population, the prevalence of SAS is expected to continue escalating, becoming an increasingly serious public health issue.[5,6] SAS has profound impacts on individual health and socioeconomic aspects. Health-wise, it is closely associated with various cardiovascular diseases such as hypertension,[7] coronary heart disease,[8] and heart failure,[9] metabolic disorders like type 2 diabetes,[10,11] and neurocognitive dysfunctions.[12,13] Additionally, excessive daytime sleepiness makes patients more prone to traffic accidents and workplace incidents. Socioeconomically, the medical expenses, productivity losses, and accident-related costs due to SAS amount to tens of billions of dollars annually. Despite the widespread harm of SAS, current treatment methods have significant limitations. Continuous Positive Airway Pressure (CPAP) therapy is the current gold standard but suffers from poor compliance, with long-term usage rates below 50%.[14,15] Oral appliances and surgical interventions are effective in some patients but have limited applicability.[16–18] Pharmacotherapy, as a potential

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alternative, has gained widespread attention in recent years;[19] however, no medications specifically targeting SAS have been approved to date, highlighting the urgent need to develop new effective drugs.

Genetic studies have demonstrated that SAS has a significant hereditary component, with heritability estimated between 30–40%.[20,21] Genome-wide association studies (GWAS) have identified multiple genetic variants associated with SAS risk, involving biological pathways such as respiratory control, upper airway anatomy, fat distribution, and inflammatory responses.[22–24] These findings provide important clues for understanding the molecular mechanisms of SAS and identifying potential drug targets. The application of pharmacogenomics has opened new avenues for personalized treatment and novel drug development.[25] By integrating genomic data with drug response information, researchers can predict individual responses to specific therapies and identify new drug targets.[26] In this process, expression quantitative trait loci (eQTL) analysis plays a crucial role by revealing how genetic variants influence gene expression, thereby helping to understand the functional significance of disease-associated variants.[27] Summary data-based Mendelian randomization (SMR) analysis is a powerful causal inference tool that utilizes GWAS and eQTL data to identify genes across the genome that may have causal relationships with disease risk.[28] This method has shown great potential in elucidating the mechanisms of complex diseases and identifying drug targets.[29,30]

In this study, we first conducted cis-eQTL analysis on known druggable genes to identify those regulated by SAS-associated genetic variants, serving as promising drug targets. Secondly, we employed SMR analysis to explore the causal relationships between SAS risk and gene expression, aiming to identify genes directly related to the pathogenesis of SAS. Thirdly, considering the close association between SAS and neural regulation, we performed brain tissue-specific cis-eQTL analysis to identify genes that may play key roles in the central nervous system. Finally, we conducted colocalization analysis and HEIDI tests on the selected candidate targets to enhance the reliability of our findings. Our study leveraged the harmonized GWAS meta-analysis data from UK Biobank and FinnGen, where sleep apnea cases were consistently identified through standardized disease classifications: phecode (a hierarchical system for EHR-based phenome-wide association studies) and ICD-10 (WHO's International Classification of Diseases, 10th revision). This standardized approach ensures phenotype consistency across biobanks while enabling robust genetic association analyses. From a clinical application perspective, the results of this study deepen our understanding of the pathogenesis of SAS and provide a theoretical basis for drug development and future mechanistic research. This will aid in the development of more precise diagnostic tools and personalized treatment strategies.

Materials and Methods

Research Design

This study comprises several key steps: identifying a set of druggable genes, performing cis-eQTL analysis on these genes, conducting SMR analysis between the cis-eQTLs and SAS, determining candidate drug target genes, analyzing the cis-eQTLs of these genes in brain tissue, and finally performing colocalization analysis and HEIDI tests, along with mediation analysis related to risk factors based on prior evidence. Detailed procedural information is illustrated in Figure 1. The study adheres to the guidelines outlined in the STROBE-MR statement.[31] The instrumental variables (IVs) in this study must satisfy three core assumptions:[32] (1) IVs must be strongly associated with the genetic instruments of the druggable genes; (2) IVs must be independent of other confounding factors; (3) IVs must influence SAS exclusively through the druggable genes. Although this study utilized only publicly available datasets that have been previously published and are freely accessible to researchers, with no direct involvement of human subjects in our data collection process, we obtained institutional ethics approval from The Medical Ethics Committee of Hebei Eye Hospital (approval number: 2024LW27) in accordance with standard research protocols.

Identification of Druggable Target Genes

To identify druggable target genes, we utilized two primary sources: the Drug–Gene Interaction Database (DGIdb, version 4.2.0) and the recent review on gene "druggability" by Finan et al. DGIdb is a comprehensive resource that consolidates drug–gene interaction information and annotations of druggable genes from various publications, databases, and online resources.[33–35] We specifically focused on the "category data" released by DGIdb in February 2022, which

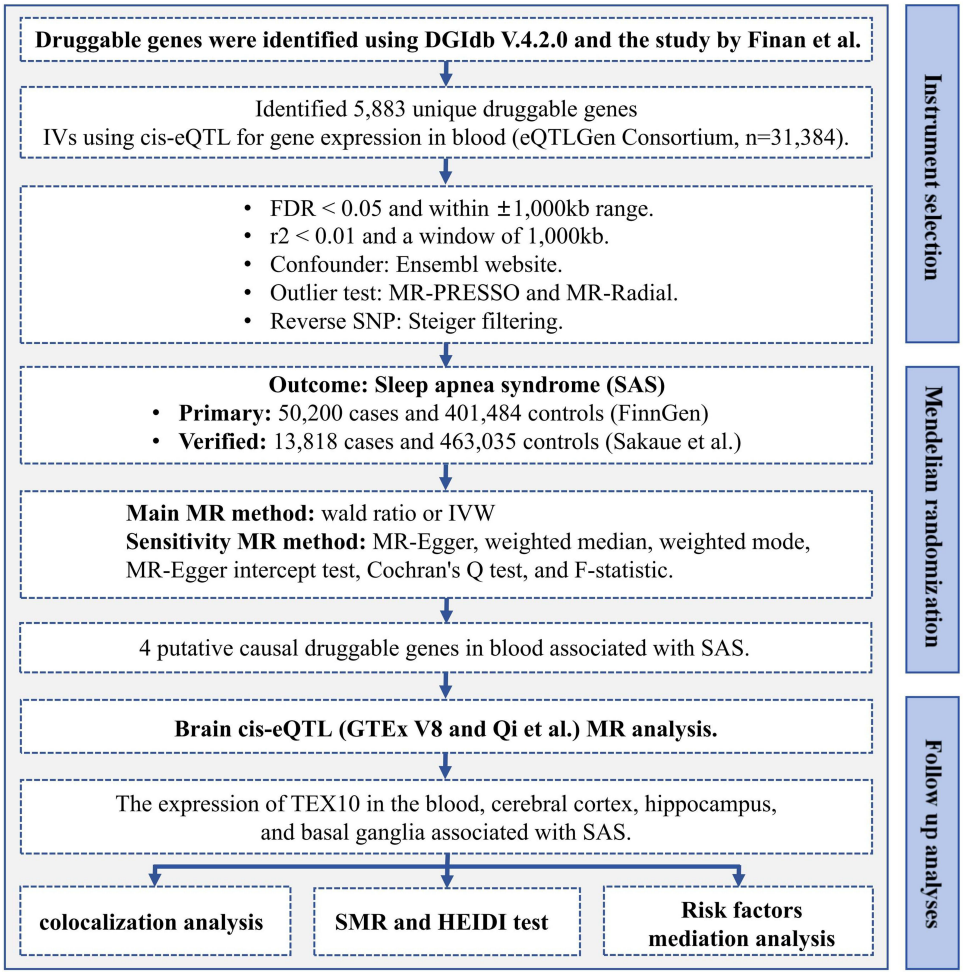

Figure 1 Flow chart for the study.
Abbreviations: eQTL, expression quantitative trait locus; GETx, The Genotype-Tissue Expression Portal; FDR, false discovery rate; MR, Mendelian randomization; IVW, inverse-variance weighted; SMR, Summary-data-based Mendelian randomization; HEIDI, heterogeneity in dependent instruments.

encompasses genes across all drug categories in DGIdb, sourced from the Ensembl database.[36] This approach ensures that our research is based on the most up-to-date and comprehensive information on druggable genes.

eQTL Datasets

Our gene expression data were primarily obtained from the eQTLGen Consortium's blood eQTL database, which includes cis-eQTL data from blood samples of 31,684 healthy individuals of European descent, covering 16,987 genes.[37] We focused on statistically significant cis-eQTL results with a false discovery rate (FDR) less than 0.05.[38] Corresponding allele frequency information was also collected for a more comprehensive analysis. To further validate our findings and enhance the reliability of the study, we incorporated additional data from two sources: brain eQTL data provided by Qi et al and eQTL data from the Genotype-Tissue Expression (GTEx) Project (version 8.0).[39,40] These supplementary datasets allowed us to verify the results observed in blood samples and explore potential differences in gene expression across different tissues, particularly the brain. Detailed information about the datasets is shown in Table S1.

GWAS Datasets

The primary GWAS data for this study were sourced from the FinnGen consortium's (release version 11),[41] which includes summary statistics for SAS. This dataset comprises 50,200 SAS patients and 401,484 control subjects, all of European ancestry. To validate the robustness of our findings, we also referenced a large-scale study by Sakaue et al,

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involving 13,818 SAS patients and 463,035 controls, also of European descent.[42] Considering potential sample overlap, we used the FinnGen SAS data as the outcome variable in our mediation analyses, while the summary statistics for risk factors were obtained from other independent cohorts. This design helps minimize potential biases and enhances the reliability of our results. Previous studies have shown that patients with SAS often develop complications associated with lifestyle-related diseases, for example, hypertension, hyperlipidemia, diabetes, and metabolic syndrome.[43] Furthermore, patients with SAS similarly need smoking cessation and restricted alcohol use to prevent deterioration. Based on the previous studies, we focused on 13 modifiable risk factors related to physiological and lifestyle indicators potentially associated with SAS: body mass index (BMI) (ukb-b-19953), fasting insulin (ebi-a-GCST90002238),[44] fasting glucose (ebi-a-GCST90002232),[44] glycine levels (ebi-a-GCST90092820),[45] waist-to-hip ratio adjusted for BMI (ebi-a--GCST90025996),[46] creatinine levels (ebi-a-GCST90025946),[46] serum uric acid levels (ebi-a-GCST90018977),[42] waist circumference (ukb-b-9405), high-density lipoprotein cholesterol (HDL cholesterol) (ieu-b-109),[47] low-density lipoprotein cholesterol (LDL cholesterol) (ieu-b-110),[47] total cholesterol (ieu-a-301),[48] triglycerides (ieu-b-111),[47] and glycated hemoglobin (HbA1C) (ieu-b-103).[49] The GWAS data for these risk factors were obtained from the IEU Open GWAS database.[50] By comprehensively considering these diverse risk factors, we aimed to assess their potential associations with SAS and explore possible mediation effects. Detailed information about the datasets is shown in Table S1.

eQTL MR Analysis

We employed rigorous eQTL selection and MR analysis methods. Initially, we identified SNPs located within ±1000 kb of each gene's transcription start site (TSS) in the druggable genome and with an FDR less than 0.05 as potential eQTLs.[38] Using European sample data from the 1000 Genomes Project, we clumped SNPs within each eQTL based on linkage disequilibrium (LD) thresholds of r^2 less than 0.01 and within a 1000 kb sliding window.[27] Phenotypes associated with IVs were identified using the Ensembl database.[36] To reduce potential confounding, we excluded SNPs directly associated with the outcomes, outcome-related traits, or known risk factors (eg, obesity, smoking, alcohol consumption). We harmonized the alleles of exposure and outcome data to ensure consistency. To improve the reliability of our results, we applied "MR-PRESSO" and "MR-Radial" outlier tests to identify and exclude outliers and used the "Steiger test" to determine the causal direction of the IVs, excluding SNPs with reverse associations.[51–54] The strength of the IVs was assessed using the F-statistic ($F=beta^2/se^2$),[55] considering ($F>10$) as indicative of sufficient instrument strength.[56,57]

In the MR analyses, we used the wald ratio method for single IVs and the inverse-variance weighted (IVW) method for multiple SNPs to calculate weighted average estimates.[58,59] Sensitivity analyses using MR-Egger,[60] weighted median,[61] and weighted mode methods were conducted to verify the robustness of our main findings.[62] Horizontal pleiotropy and heterogeneity among SNPs were assessed using the MR-Egger intercept test and Cochran's Q test.[63] Statistical significance was set at ($P<0.05$) after FDR correction.[64] Supplementary analyses using brain eQTL data were performed to validate the robustness of our findings in whole blood tissue, ensuring consistency in the IV selection process.

Colocalization Analysis

To determine whether the associated eQTLs and SAS share causal variants within gene coding regions, we performed Bayesian colocalization analysis.[65,66] We selected all SNPs within ±100kb of the TSS of each gene for colocalization analysis. This method evaluates five hypotheses: H0, no association with either eQTL or SAS; H1, association only with eQTL; H2, association only with SAS; H3, association with both eQTL and SAS through two independent SNPs; H4, association with both eQTL and SAS through a single shared SNP.[67] We used the "coloc" package in R for this analysis.[68] Results were interpreted based on the posterior probability (PP) of each hypothesis. A(PP.H4>0.7) was considered strong evidence for colocalization, indicating that eQTL and SAS share a causal variant, while PP.H4 values between 0.5 and 0.7 suggested moderate evidence.[69,70] This analysis enabled us to understand potential shared genetic mechanisms between eQTLs and SAS, providing insights for further exploration of the disease's molecular mechanisms.

Summary-Data-Based MR (SMR) Analysis

To verify the robustness of our MR results, we employed the SMR analysis along with the Heterogeneity in Dependent Instruments (HEIDI) test.[71,72] These analyses aimed to confirm the causal relationships between druggable genes and SAS further. We utilized eQTL data from three main sources: eQTLGen, Qi et al, and GTEx version 8. In the SMR analysis, only the most significant SNP for each gene was considered, specifically selecting the SNP with the smallest p-value less than 5×10^{-8} within a 1 Mb region upstream and downstream of the gene.[73] This approach ensured a focus on genetic variants most likely associated with gene expression.[27] The HEIDI test, using multiple SNPs within the locus, helped distinguish druggable genes associated with SAS risk due to shared genetic variants rather than mere LD, which is crucial for excluding false-positive results. Strict criteria were adopted for interpreting the results: when (P-SMR < 0.05) and (P-HEIDI > 0.05), the SMR results were considered statistically significant, and the association was unlikely driven by LD.[74] This stringent standard helped ensure the reliability of the identified causal relationships. All SMR and HEIDI tests were conducted using the SMR software (version 1.3.1). This comprehensive approach allowed a thorough assessment of potential causal relationships between druggable genes and SAS, providing a robust scientific basis for developing future therapeutic strategies.

Mediation Analysis

To explore the complex relationships among druggable genes, SAS, and its risk factors, we hypothesized that druggable genes might indirectly influence the occurrence and progression of SAS by affecting intermediate risk factors. To test this hypothesis, we conducted mediation MR analysis, aiming to assess whether the effect of druggable genes on SAS is mediated through known risk factors. Strict criteria were applied when selecting IVs for the risk factors: SNPs with p-values less than 5×10^{-8}, LD (r^2<0.001), and located within a ±10 Mb window around the target gene. These standards ensured that the selected IVs had sufficient statistical significance, independence, and relevance. Our analysis employed a two-step mediation MR method. First, we evaluated the effect of druggable genes on risk factors; second, we assessed the effect of risk factors on SAS. To quantify the indirect effect, we used the product of coefficients method by multiplying the effect sizes from these two steps.[75,76] The delta method was applied to calculate the standard error, accurately assessing the uncertainty of the indirect effect. This comprehensive approach allowed a precise evaluation of the complex relationships among druggable genes, risk factors, and SAS, providing important insights into the pathological mechanisms of SAS and informing the development of potential therapeutic strategies.

Results

Selection of IVs

In this study, we identified 3952 genes from the DGIdb v4.2.0 database (Table S2) and extracted 4479 genes from the review by Finan et al (Table S3). In total, 5883 genes with potential pharmacological relevance were identified for further analysis (Table S4). Using eQTL data from blood tissue, we narrowed this down to 3694 genes that were potentially relevant for drug applications. After clumping, these genes were selected for subsequent MR analysis (Table S5). The F-statistics for all SNPs were greater than 10, indicating that the selected instruments were robust and not susceptible to weak instrument bias (Table S5). Furthermore, outliers and reverse SNPs were identified and removed using RadialMR and Steiger tests. After excluding SNPs associated with SAS-related confounding, the remaining SNPs were subjected to analysis. Detailed information on the confounding SNPs is provided in Table S6.

Druggable Genes Associated with SAS

In the primary analysis, we applied FDR correction (FDR < 0.05) to the Wald ratio and IVW methods, identifying 18 candidate drug target genes for SAS (Table 1, Table S7). Notably, four potential drug target genes (MAPKAPK3, TNXB, MPHOSPH8, and TEX10) reached statistically significant levels in the validated outcomes (Table 1, Table S8a). While TNXB (FinnGen: odds ratio (OR) = 0.95; IEU: OR = 0.92) exhibited a protective effect, MAPKAPK3 (FinnGen: OR = 1.07; IEU: OR = 1.08), MPHOSPH8 (FinnGen: OR = 1.25; IEU: OR = 1.29), and TEX10 (FinnGen: OR = 1.26; IEU: OR = 1.43) were associated with increased risk of SAS (Table 1). In addition, TEX10 showed stability when considering

Table 1 The Results of Mendelian Randomization Analysis Between Druggable Genes and Sleep Apnea Syndrome (SAS)

Exposure	Methods	N_{SNP}	OR (95% CI)	*P*	FDR	P_{plei}	$P_{Q\ test}$
Druggable genes to SAS (FinnGen database)							
ANKK1	IVW	12	0.88 (0.85–0.92)	1.30E-08	4.73E-05	0.72	0.59
CXCR4	Wald ratio	1	0.48 (0.37–0.62)	5.55E-08	1.01E-04	-	-
NPM1	Wald ratio	1	1.56 (1.26–1.94)	5.29E-05	2.10E-02	-	-
MST1R	Wald ratio	1	1.84 (1.33–2.53)	1.92E-04	4.60E-02	-	-
CYP17A1	IVW	2	1.38 (1.18–1.62)	6.36E-05	2.10E-02	-	0.82
EP300	IVW	7	1.14 (1.07–1.21)	2.26E-05	1.00E-02	0.88	0.24
MAPKAP1	Wald ratio	1	0.76 (0.66–0.86)	1.64E-05	1.00E-02	-	-
ITGA2	IVW	8	1.11 (1.06–1.15)	4.11E-06	4.00E-03	0.41	0.80
ITGB3	IVW	4	0.85 (0.78–0.92)	2.17E-05	1.10E-02	0.66	0.60
KLHL18	IVW	3	1.28 (1.12–1.45)	1.63E-04	4.20E-02	0.84	0.96
MAPKAPK3	IVW	10	1.06 (1.04–1.09)	4.39E-06	3.00E-03	0.27	0.31
MGAT2	IVW	2	0.84 (0.77–0.92)	1.34E-04	3.80E-02	-	0.87
MICA	IVW	9	1.04 (1.02–1.06)	6.33E-05	2.30E-02	0.92	0.49
MPHOSPH8	IVW	5	1.25 (1.14–1.37)	1.16E-06	1.00E-03	0.21	0.44
TEX10	IVW	2	1.26 (1.11–1.42)	1.93E-04	4.40E-02	-	0.16
TIGIT	IVW	7	1.09 (1.04–1.14)	3.40E-04	4.90E-02	0.93	0.36
TNXB	IVW	6	0.95 (0.92–0.98)	3.94E-04	4.90E-02	0.48	0.26
ZNF568	IVW	2	1.38 (1.18–1.62)	7.67E-05	2.30E-02	-	0.83
Druggable genes to SAS (openGWAS database)							
MAPKAPK3	IVW	10	1.08 (1.02–1.14)	4.00E-03	2.40E-02	0.53	0.80
MPHOSPH8	IVW	4	1.29 (1.09–1.52)	2.00E-03	2.10E-02	0.47	0.55
TEX10	IVW	2	1.43 (1.22–1.68)	1.49E-05	2.68E-04	-	0.51
TNXB	IVW	6	0.92 (0.87–0.97)	4.00E-03	1.90E-02	0.94	0.42

Note: The bold italicized genes in the table represent significant genes in both the FinnGen and openGWAS database.

Abbreviations: N_{SNP}, the number of single nucleotide polymorphisms (SNPs) in the current analysis direction; OR, odd ratio; CI, confidence interval; FDR, false discovery rate; P_{plei}, *P*-value of pleiotropy test; $P_{Q\ test}$, *P*-value of heterogeneity test; WR, wald ratio method; IVW, inverse-variance weighted method.

significant results adjusted for FDR for the preliminary and validation analyses to obtain the crossover genes (Table S8b). The P-values from Cochran's Q test and the MR-Egger intercept test were all greater than 0.05, indicating no evidence of heterogeneity or directional pleiotropy among the IVs (Table 1). Additionally, our supplementary analysis revealed that the expression of TEX10 in the cerebral cortex, hippocampus, and basal ganglia, and MPHOSPH8 expression in the cerebellum, were statistically significant (P_{FDR}<0.05), potentially linking these genes to an increased risk of SAS (Figure 2, Tables S9-S10).

Subsequently, we performed colocalization analysis to assess the likelihood of shared causal genetic variants among SNPs associated with SAS and the four potential drug target genes. For TEX10, significant colocalization was observed in the blood (Figure 3A), cerebral cortex (Figure 3B), and basal ganglia across both datasets (PP.H4 > 0.9) (Figure 3A and B, Table S11). Additionally, the expression of MAPKAPK3 in the blood and MPHOSPH8 in the cerebral cortex and cerebellum showed a colocalization probability exceeding 70% in the primary results dataset. Further details are provided in Table S11.

SMR Analysis Results

To further validate the accuracy of our previous MR analyses, we conducted SMR analyses on both the primary and validation outcomes. The results demonstrated that increased genetic susceptibility of TEX10 in the eQTL data from

Outcome	Exposure	Tissue	Method	No.SNP	OR (95% CI)	*Pvalue*
SAS (FinnGen)						
	MPHOSPH8	Brain_Nucleus_accumbens_basal_ganglia	Wald ratio	1	1.03 (0.97 − 1.09)	0.378
	MPHOSPH8	Brain_Amygdala	Wald ratio	1	1.00 (0.96 − 1.04)	0.917
	MPHOSPH8	Brain_Hippocampus	Wald ratio	1	1.01 (0.99 − 1.03)	0.430
	MPHOSPH8	Brain_Cerebellum	Wald ratio	1	1.26 (1.14 − 1.39)	5.28e−06
	MPHOSPH8	Brain_Cortex(Qi et al.)	IVW	2	1.06 (1.01 − 1.10)	0.012
	TEX10	Brain_Cortex	Wald ratio	1	1.13 (1.07 − 1.19)	1.79e−06
	TEX10	Brain_Hippocampus	Wald ratio	1	1.06 (1.01 − 1.12)	0.025
	TEX10	Brain_Caudate_basal_ganglia	Wald ratio	1	1.11 (1.06 − 1.16)	1.79e−06
	TEX10	Brain_Cortex(Qi et al.)	Wald ratio	1	1.07 (1.04 − 1.11)	1.90e−06
SAS (IEU)						
	MPHOSPH8	Brain_Nucleus_accumbens_basal_ganglia	Wald ratio	1	0.94 (0.83 − 1.07)	0.357
	MPHOSPH8	Brain_Amygdala	Wald ratio	1	1.01 (0.95 − 1.08)	0.740
	MPHOSPH8	Brain_Hippocampus	Wald ratio	1	1.00 (0.96 − 1.05)	0.926
	MPHOSPH8	Brain_Cerebellum	Wald ratio	1	1.26 (1.06 − 1.49)	8.00e−03
	MPHOSPH8	Brain_Cortex(Qi et al.)	IVW	2	1.04 (0.93 − 1.16)	0.540
	TEX10	Brain_Cortex	Wald ratio	1	1.24 (1.12 − 1.37)	1.65e−05
	TEX10	Brain_Hippocampus	Wald ratio	1	1.02 (0.93 − 1.12)	0.707
	TEX10	Brain_Caudate_basal_ganglia	Wald ratio	1	1.20 (1.10 − 1.30)	1.65e−05
	TEX10	Brain_Cortex(Qi et al.)	Wald ratio	1	1.14 (1.08 − 1.21)	8.90e−06
	TNXB	Brain_Cortex(Qi et al.)	Wald ratio	1	0.86 (0.71 − 1.03)	0.101

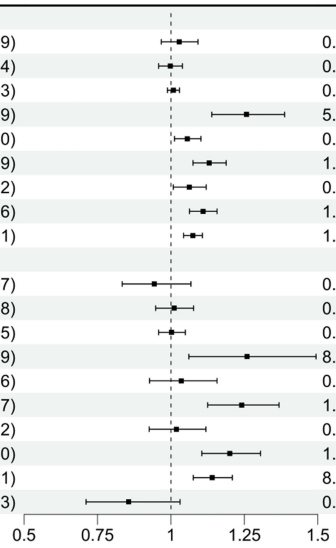

Figure 2 Forest plot shows the results of Mendelian randomization between MPHOSPH8, TEX10 genes and different region of brain. The small box represents the odd ratio (OR) value, and the short horizontal line represents the upper value (right end) and lower value (left end) of the 95% confidence interval (CI) in the current analysis direction. FinnGen represents the SAS data derived from FinnGen database; IEU represent the SAS data derived from openGWAS database.
Abbreviations: IV, inverse-variance weighted; SAS, sleep apnea syndrome.

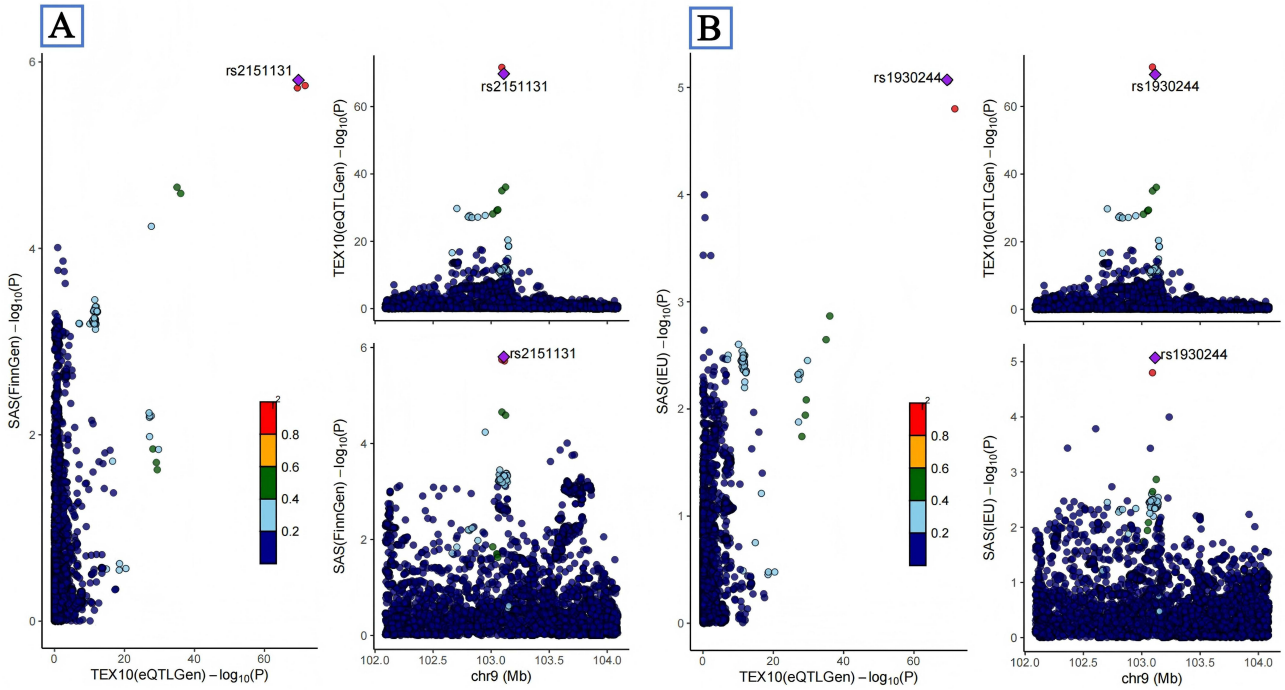

Figure 3 Colocalization analysis of SNPs associated with TEX10 expression and sleep apnea syndrome (SAS) risk in blood (**A**) and brain tissues (**B**).

whole blood, cerebral cortex, and basal ganglia was significantly associated with a higher risk of SAS (Table S12, P<0.05). Additionally, the HEIDI test p-values were all greater than 0.05, indicating that the findings are not biased by LD, thus minimizing the risk of false positives (Table S12).

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Mediation	Tissue	Exposure	Outcome	OR (95% CI)	Pvalue	adjust_Pvalue
BMI						
	eQTLGen	TEX10	SAS(FinnGen)	1.04 (1.03 − 1.06)	1.98e−08	9.89e−08
	Brain_Cortex(Qi et al.)	TEX10	SAS(FinnGen)	1.02 (1.01 − 1.02)	7.60e−08	1.90e−07
	Brain_Caudate_basal_ganglia	TEX10	SAS(FinnGen)	1.02 (1.01 − 1.03)	1.57e−07	2.62e−07
	Brain_Cortex	TEX10	SAS(FinnGen)	1.03 (1.02 − 1.03)	1.57e−07	1.96e−07
	Brain_Hippocampus	TEX10	SAS(FinnGen)	1.01 (1.00 − 1.02)	7.00e−03	7.00e−03
HDL cholesterol						
	eQTLGen	TEX10	SAS(FinnGen)	1.01 (1.00 − 1.01)	1.00e−03	6.00e−03
	Brain_Cortex(Qi et al.)	TEX10	SAS(FinnGen)	1.00 (1.00 − 1.00)	2.00e−03	4.00e−03
	Brain_Caudate_basal_ganglia	TEX10	SAS(FinnGen)	1.00 (1.00 − 1.00)	2.00e−03	3.00e−03
	Brain_Cortex	TEX10	SAS(FinnGen)	1.00 (1.00 − 1.01)	2.00e−03	2.00e−03
	Brain_Hippocampus	TEX10	SAS(FinnGen)	1.00 (1.00 − 1.00)	4.70e−02	4.70e−02
Waist circumference						
	eQTLGen	TEX10	SAS(FinnGen)	1.04 (1.03 − 1.06)	5.61e−08	2.81e−07
	Brain_Cortex(Qi et al.)	TEX10	SAS(FinnGen)	1.02 (1.01 − 1.02)	5.37e−07	1.34e−06
	Brain_Caudate_basal_ganglia	TEX10	SAS(FinnGen)	1.02 (1.01 − 1.03)	9.17e−07	1.53e−06
	Brain_Cortex	TEX10	SAS(FinnGen)	1.03 (1.02 − 1.04)	9.17e−07	1.15e−06
	Brain_Hippocampus	TEX10	SAS(FinnGen)	1.01 (1.00 − 1.02)	4.00e−03	4.00e−03
Triglycerides						
	Brain_Hippocampus	TEX10	SAS(FinnGen)	1.00 (1.00 − 1.00)	1.80e−02	4.50e−02
	eQTLGen	TEX10	SAS(FinnGen)	1.00 (1.00 − 1.00)	4.40e−02	1.11e−01

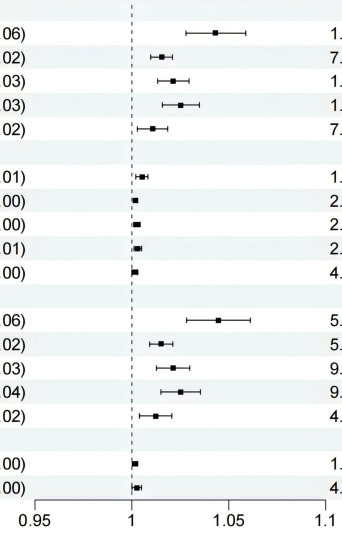

Figure 4 Mediation analysis of TEX10 expression in blood and brain regions on sleep apnea syndrome (SAS) risk through body mass index (BMI), waist circumference, high density lipoprotein (HDL) cholesterol, and triglycerides. The black small box represents the odd ratio (OR) value of the current analysis direction, and the short horizontal line represents the upper (right end) and lower (left end) value of the 95% confidence interval (CI) in the current analysis direction.
Abbreviation: FDR, false discovery rate.

Mediation Analysis

To explore potential risk factors for SAS, this study employed MR analysis to evaluate the relationships between 15 modifiable risk factors and SAS. The findings revealed that a 1 standard deviation (SD) increase in BMI (OR=1.80), waist circumference (OR=1.99), triglycerides (OR=1.10), and waist-to-hip ratio (OR=1.13) were significantly associated with an increased risk of developing SAS. In contrast, a 1 SD increase in HDL cholesterol (OR=0.89) and fasting glucose (OR=0.76) was significantly associated with a reduced risk of SAS (Table S13). Additionally, both Cochran's Q test and MR-Egger intercept test confirmed the absence of heterogeneity and directional pleiotropy among the IVs (Table S13). Notably, TEX10 levels in the blood, cerebral cortex, hippocampus, and basal ganglia were associated with four risk factors (BMI, waist circumference, HDL cholesterol, and triglycerides) for SAS. Our results showed that an increase in TEX10 gene expression leads to higher BMI, triglyceride levels, and waist circumference, and to decreased HDL cholesterol levels (see Table S14).

Further analysis investigated whether TEX10 could influence SAS development by modulating these risk factors. Mediation analysis indicated that TEX10 expression in blood, cerebral cortex, hippocampus, and basal ganglia could impact SAS through the mediating effects of BMI, waist circumference, and HDL cholesterol. Additionally, TEX10 expression in the hippocampus was found to influence SAS via triglyceride levels. Detailed results are presented in Figure 4. Mediator analysis revealed that increased TEX10 expression may influence SAS by elevating BMI (blood, OR=1.04; cerebral cortex (Qi et al), OR=1.02; basal ganglia, OR=1.02; cerebral cortex, OR=1.03; hippocampus, OR=1.01), waist circumference (blood, OR=1.04; cerebral cortex (Qi et al), OR=1.02; basal ganglia, OR=1.02; cerebral cortex, OR=1.03; hippocampus, OR=1.01), and triglyceride levels (hippocampus, OR=1.00). HDL is a beneficial type of cholesterol that helps transport excess cholesterol from the vessel walls to the liver for metabolism and excretion, thereby reducing the risk of cardiovascular disease.[77] In further analysis, the increased expression of TEX 10 may also affect SAS by reducing HDL cholesterol levels (blood, OR=1.01; cerebral cortex (Qi et al), OR=1.00; basal ganglia, OR=1.00; cerebral cortex, OR=1.00; hippocampus, OR=1.00), although the mediation effect was very small. Detailed results are presented in Figures 4 and 5.

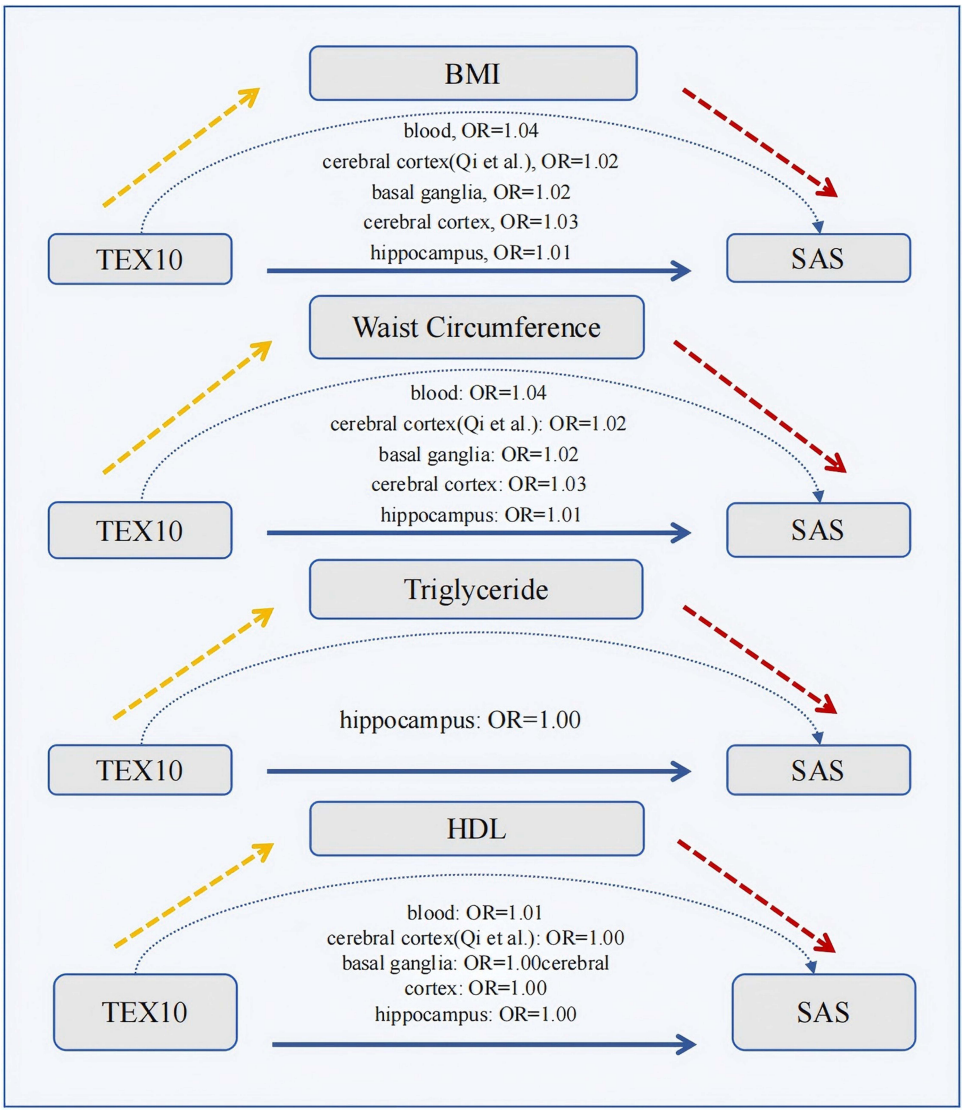

Figure 5 Results of the mediation analysis. The dashed yellow red line indicates the direct effect of TEX 10 on risk factors; the red dashed line indicates the direct effect of risk factors on SAS; the solid blue red line indicates the direct effect of TEX 10 on SAS; and the blue dashed line indicates the mediation effect of TEX 10 on SAS mediated by risk factors.

Abbreviations: BMI, body mass index; HDL, high density lipoprotein; SAS, sleep apnea syndrome; OR, the odd ratio.

Discussion

In this study, we employed MR, eQTL, SMR, and colocalization analysis to explore the relationship between potential drug target genes and SAS. Our results indicate that multiple genes may play significant roles in the pathogenesis of SAS, providing valuable insights for the development of targeted therapeutic strategies. From the initial screening of 5883 potential druggable genes, we identified 18 genes that showed significant associations with SAS. Notably, four of these genes—MAPKAPK3, TNXB, MPHOSPH8, and TEX10—demonstrated consistent associations in both the primary and validation datasets. Among these, TEX10 exhibited particularly significant impact, suggesting it may serve as an important target for SAS drug development. To further elucidate the association between these genes and SAS, we performed brain tissue-specific eQTL analyses.

Our findings indicated that TEX10 expression in the cerebral cortex, hippocampus, and basal ganglia is associated with increased SAS risk, while MPHOSPH8 expression in the cerebellum showed similar associations. Notably, TEX10 expression in multiple brain regions correlated with SAS risk. Subsequent colocalization analyses confirmed a high probability ($PP.H_4$>0.9) of shared genetic variants between TEX10 expression in blood, cerebral cortex, and basal ganglia

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and SAS, suggesting that TEX10 may play a pivotal role in SAS pathogenesis. Moreover, SMR analysis results confirmed the influence of TEX10 expression on SAS risk, further reinforcing its importance as a potential drug target. It is also noteworthy that our study identified several risk factors for SAS, including BMI, waist circumference, triglyceride levels, waist-to-hip ratio, and smoking status. These findings deepen our understanding of SAS risk factors and provide new directions for disease prevention strategies. Importantly, our mediation analysis suggests that TEX10 may impact the development of SAS by influencing risk factors such as BMI, waist circumference, and HDL cholesterol levels. This evidence unveils potential mechanisms by which TEX10 affects SAS, opening new avenues for therapies targeting this gene.

By integrating bioinformatics and statistical methods, we aim to achieve a thorough understanding of the genetic basis and pathogenesis of SAS. This will aid in developing more precise and effective individualized treatment strategies, significantly improving the quality of life and long-term health outcomes for patients with SAS. Multifactorial risk model could significantly enhance the accuracy of early identification of high-risk individuals, enabling more targeted preventive interventions.[78,79] Specifically, for individuals carrying specific TEX10 gene variants, more proactive weight management and lifestyle intervention plans can be developed. Such genotype-based individualized prevention strategies may substantially reduce the risk of SAS onset. Firstly, the expression levels of TEX10 and other candidate genes are promising as novel biomarkers for SAS. This opens up the possibility of developing rapid, accurate, and convenient diagnostic methods based on blood tests. Such noninvasive diagnostic approaches could not only improve diagnostic efficiency but also offer alternative options for patients who have difficulty undergoing traditional sleep monitoring.[80,81] However, large-scale prospective validation studies are needed before these biomarkers can be translated into clinical diagnostic tools. Secondly, the gene-phenotype associations identified in our study lay the foundation for individualized treatment of SAS.[82,83] For instance, patients with abnormal TEX10 expression may require specific therapeutic plans. This could involve developing drugs that target TEX10 or optimizing existing treatments (such as adjusting parameters of continuous positive airway pressure therapy) based on the patient's gene expression profile. Such molecular mechanism–based individualized treatment strategies are expected to significantly enhance treatment efficacy and patient adherence. Thirdly, given the close association between SAS and various metabolic and cardiovascular diseases, the gene targets identified in this study—such as TEX10—may become new avenues for managing SAS-related complications. By modulating the expression of TEX10, it might be possible to simultaneously ameliorate SAS symptoms and associated metabolic disorders, offering patients a more comprehensive health management plan. This multitarget therapeutic strategy could be particularly beneficial for patients with complex SAS. Fourth, the candidate genes identified in our study, especially TEX10, offer new research and development directions for the pharmaceutical industry. This could lead to the development of SAS therapeutics with entirely novel mechanisms of action, particularly benefiting patients who respond poorly to existing treatments. However, substantial translational research is required to move from basic findings to clinical applications.

TEX10 encodes a protein widely expressed in multiple tissues, including the central nervous system.[84] Although initially discovered in testicular tissue, subsequent studies have revealed its important roles in various key biological processes.[85–87] Combining our research results with existing literature, we can more precisely stratify SAS patients. This molecular feature–based patient stratification not only deepens our understanding of SAS-related pathophysiological processes but also aids in formulating individualized treatment strategies, optimizing clinical trial design, predicting disease prognosis, and ultimately improving patient outcomes and quality of life.

The molecular mechanisms by which TEX10 serves as a potential therapeutic target for SAS may involve several aspects: Firstly, TEX10 is involved in cell cycle control, particularly playing a critical role in the G1/S phase transition.[88] In SAS patients, repeated hypoxia–reoxygenation events lead to chronic damage of upper airway muscles and neural tissues. TEX10 may influence the development of SAS through the following mechanisms: promoting the proliferation and regeneration of upper airway muscle cells, thereby improving muscle tone and function; regulating the proliferation and differentiation of neural stem cells,[89] facilitating the repair of damaged neural tissues;[90] maintaining normal tissue renewal,[91,92] reducing chronic tissue damage caused by SAS. Secondly, our study found that TEX10 is significantly associated with metabolic parameters such as BMI, waist circumference, and HDL cholesterol levels. This suggests that TEX10 may be involved in the regulation of lipid metabolism. Given the close association between SAS and obesity and

metabolic syndrome, we propose that TEX10 may also participate in the metabolic regulation of SAS through: influencing the differentiation and function of adipose tissue, thereby regulating body weight and fat distribution; participating in the regulation of hepatic lipid metabolism, affecting blood lipid levels; regulating insulin sensitivity, impacting glucose metabolism.[93,94] These hypotheses provide new perspectives for explaining the interaction between SAS and metabolic disorders and guide the development of therapeutic strategies targeting both respiratory function and metabolic status. Thirdly, SAS patients commonly exhibit chronic systemic inflammation and increased oxidative stress.[95,96] Although the direct role of TEX10 in inflammation regulation has not been extensively studied, its involvement in cellular stress responses suggests it may participate in this process. We propose that TEX10 may influence SAS-related inflammation and oxidative stress through: regulating the expression of inflammatory factors such as signal transducer and activator of transcription (STAT3); [97] and affecting cellular adaptive responses to hypoxia–reoxygenation injury.[88,98] Verifying these hypotheses may provide a theoretical basis for developing new therapeutic strategies targeting SAS-related inflammation and oxidative stress. In summary, we propose that TEX10, as a potential therapeutic target for SAS, has a multifaceted molecular mechanism. It may influence the occurrence and development of SAS through multiple pathways, such as regulating the cell cycle and tissue regeneration, influencing metabolism and lipid metabolism, participating in inflammation and oxidative stress responses, and possibly circadian rhythm regulation. These diverse roles make TEX10 a particularly attractive therapeutic target because modulating it may simultaneously improve multiple pathophysiological aspects of SAS. However, we must acknowledge that most of the above mechanisms are still based on indirect evidence and speculation. Future research should focus on the verifying the specific mechanisms of TEX10 in SAS animal models, particularly using conditional gene knockout techniques to study its roles in different tissues.

Despite making significant progress in identifying potential drug targets for SAS, we recognize several limitations in our study that may affect the interpretation and generalization of the results. Firstly, our study is mainly based on genetic data from European populations. Considering the differences in genetic variations among different ethnic groups, our findings may not be fully generalizable to other populations.[99] Future studies should include more diverse samples to validate and extend our findings. Secondly, although we used advanced statistical methods like MR to infer the causal relationship between gene expression and SAS risk, these methods are still based on certain assumptions, such as the validity of instrumental variables and the absence of pleiotropy. While sensitivity analyses were conducted, we cannot completely rule out potential biases. Thirdly, our research is primarily based on statistical associations and bioinformatics analyses. Although we identified potential drug targets like TEX10, we lack in vivo and in vitro functional validation experiments. This limits our understanding of the specific roles these genes play in SAS pathogenesis. Besides, we acknowledge that potential unmeasured confounders, such as genetic pleiotropy, population stratification, and environmental factors, may have influenced the observed associations. Fourth, our analyses are based on static gene expression data and cannot capture temporal dynamics and tissue-specific variations in gene expression.[100–102] Considering the circadian rhythm characteristics of SAS and its complexity involving multiple organ systems, this is a significant limitation.[103,104] Fifth, our study utilized comprehensive GWAS data from multiple sources, making it challenging to precisely quantify sample overlap between datasets. While we conducted cross-analyses using different GWAS datasets to mitigate this issue, potential sample overlap may still introduce bias into our results.

Conclusion

In conclusion, using MR analysis combined with eQTL analysis, colocalization analysis, and SMR, this study systematically explored the relationship between potential drug target genes and SAS. We successfully identified 18 candidate genes significantly associated with SAS, with TEX10 showing particularly prominent importance across multiple analyses. These findings offer new perspectives for an in-depth understanding of the molecular mechanisms of SAS and lay the foundation for developing targeted prevention, diagnosis, and treatment strategies.

Data Sharing Statement

The datasets generated and/or analyzed in this study are available from public databases, with specific access links provided in Table S1.

Ethics Approval and Consent to Participate

This research was reviewed and approved by The Medical Ethics Committee of Hebei Eye Hospital (approval number: 2024LW27). Although this study utilized only publicly available datasets that have been previously published and are freely accessible to researchers, and no human subjects were directly involved in our data collection process, we obtained institutional ethics approval in accordance with standard research protocols. All data usage complied with the terms and conditions specified by the original data providers and relevant data protection regulations. The datasets used in this study had previously undergone their respective ethical review processes during their original collection and publication.

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Author Contributions

Zhitao Fan: Conceptualization, Data curation, Methodology, Project administration, Software, Writing - original draft.

Hui Su: Data curation, Software, Visualization, Writing-review & editing.

Tong Qiao: Validation, Data curation, Writing-review & editing.

Sunan Shi: Formal analysis, Writing-review & editing.

Pengfei Shi: Validation, Visualization, Writing-review & editing.

Anqi Zhang: Project administration, Writing-review & editing.

All authors have agreed on the journal of submission, reviewed and approved all versions of the article before submission and during revision, accepted the final published version, and take responsibility and accountability for the article's contents.

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Disclosure

The authors declare that no commercial or financial relationships were present that could be interpreted as potential conflicts of interest in the conduct of this research.

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