

Single-cell brain expression-guided causal analysis identifies GFM1 as a protective factor in insomnia risk

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Abstract

Background: Insomnia is a common and heritable neurological condition that lacks clearly defined causal molecular drivers. Identifying brain cell-specific genes with protective effects may uncover new therapeutic targets for sleep-related disorders.

Methods: We integrated brain single-cell gene expression profiles with insomnia genome-wide association data from the UK Biobank (109,548 cases, 277,440 controls). Using Wald ratio-based Mendelian randomization (MR), we estimated the causal effects of cell type-specific gene expression on insomnia. Significant genes were evaluated via Bayesian colocalization and Steiger filtering to confirm shared causal variants and correct expression-to-trait directionality. Independent replication used the FinnGen cohort (6,776 cases, 490,763 controls). Phenotype specificity and anatomical expression were assessed using phenome-wide association studies (PheWAS) and The Human Protein Atlas.

Results: Among multiple cell type-specific associations, GFM1 emerged as a protective gene for insomnia in excitatory neurons (OR=0.90, FDR=0.0109), and was independently replicated in FinnGen (OR=0.77, P=0.0019). Colocalization analysis supported a shared causal variant at the GFM1 locus (PP.H4=0.717), and Steiger directionality filtering confirmed the causal path from gene expression to phenotype. PheWAS showed phenotype specificity without evidence of horizontal pleiotropy. GFM1 was predominantly expressed in sleep-regulating brain regions such as the cerebral cortex, midbrain, and hypothalamus, supporting its functional relevance in sleep biology.

Conclusion: This integrative analysis identifies GFM1 as a robust, brain cell-specific protective gene for insomnia, with cross-dataset replication and functional support from colocalization, PheWAS, and expression atlases. Given its role in mitochondrial translation, GFM1 may represent a novel target for interventions aimed at sleep-related neurological conditions.

Introduction

Insomnia is a pervasive and debilitating neurological disorder characterized by persistent difficulty in sleep initiation or maintenance, affecting approximately 10% to 30% of the global population (Benjafield et al. 2025; Morin et al. 2020). Beyond its impact on quality of life, chronic insomnia is a potent risk factor for cardiovascular diseases, metabolic dysfunction, and psychiatric disorders such as major depression and anxiety (Javaheri and Redline 2017; Johnson et al. 2021; Sateia et al. 2017). Large-scale genome-wide association studies (GWAS) have recently transformed our understanding of insomnia's etiology, revealing its complex polygenic architecture and estimating its heritability at 38–59% from twin studies (Jansen et al. 2019). However, the majority of identified risk

variants reside in non-coding regions, complicating the translation of genomic signals into actionable biological insights.

A major hurdle in post-GWAS analysis is the cellular heterogeneity of the human brain. Sleep-wake regulation is not a global cerebral phenomenon but is governed by precise neurobiological signaling within specific neuronal and glial populations (Dopp et al. 2024; Tran et al. 2021). Traditional "bulk" brain tissue analyses, which average gene expression across all cell types, often mask critical cell-specific regulatory signals. The recent advent of single-cell RNA sequencing (scRNA-seq) has revolutionized this field, enabling the identification of cell type-specific expression quantitative trait loci (eQTLs) (Yazar et al. 2022; Fujita et al. 2024). By integrating these high-resolution profiles with Mendelian randomization (MR) frameworks, researchers can now prioritize causal genes within distinct cellular contexts, effectively bypassing confounding factors and reverse causation inherent in observational studies (Nguyen and Mitchell 2024; Davies, Holmes, and Davey Smith 2018; Yazar et al. 2022).

In this study, we employed an integrative pipeline to systematically evaluate the causal influence of brain cell-specific gene expression on insomnia risk. By leveraging summary statistics from the UK Biobank and validating findings in the independent FinnGen cohort, we identified GFM1 (Guanine Nucleotide Exchange Factor Mitochondrial 1) as a robust protective factor specifically within excitatory neurons. While GFM1 is known for its role in mitochondrial protein synthesis (You et al. 2020), its link to sleep-wake homeostasis remained unexplored. Through Bayesian colocalization, PheWAS, and anatomical expression mapping, we provide evidence that GFM1 represents a novel, cell-specific therapeutic target, highlighting the critical intersection between mitochondrial function and sleep biology.

Methods

Exposure data: Single-cell brain gene expression

We obtained expression quantitative trait loci (eQTL) summary statistics derived from 183 human single-nucleus RNA sequencing of brain tissue across multiple cell types, including excitatory neurons, inhibitory neurons, microglia, oligodendrocytes, astrocytes, endothelial cells and pericytes (Haglund et al. 2025). For each gene-cell type combination, top cis-eQTL variants (± 1 Mb from the transcription start site) with genome-wide significance ($P < 5 \times 10^{-8}$) and F-statistics > 10 were selected as instruments. Redundant SNPs were clumped based on linkage disequilibrium ($r^2 < 0.001$).

Outcome data: Insomnia GWAS

We used publicly available summary statistics from a large-scale genome-wide association study of insomnia in the UK Biobank, comprising 109,548 cases and 277,440 controls of European ancestry(Watanabe et al. 2022). Logistic regression was performed using PLINK 2.0 with standard quality control measures. For replication, we used insomnia GWAS data from the FinnGen consortium (Release 12), including 6,776 cases and 490,763 controls(Kurki et al. 2023).

Mendelian randomization analysis

We applied the Wald ratio method for single-instrument MR, estimating the causal effect of gene expression on insomnia risk per cell type. Effect estimates were expressed as odds ratios (OR) with 95% confidence intervals(Wang et al. 2025). Multiple testing correction was performed using the Benjamini-Hochberg false discovery rate (FDR) method.

Colocalization and directionality analysis

To assess whether the insomnia and eQTL association signals shared the same causal variant, we conducted colocalization analysis using the COLOC package. Posterior probabilities were calculated for five hypotheses (H0–H4), with PP.H4 > 0.7 indicating strong colocalization(Ye et al. 2025). Steiger directionality testing was used to confirm the direction of causality, ensuring that gene expression explained more variance in the exposure than in the outcome.

Replication analysis in independent cohort

Top MR findings were replicated in the FinnGen dataset using the same Wald ratio MR approach. Replication was defined as having consistent effect direction and a P-value < 0.05 in the FinnGen cohort.

Phenome-wide association analysis (PheWAS)

To assess pleiotropy, we performed a PheWAS using the top instrument SNPs for candidate genes across 1,500 + disease traits from the UK Biobank(Sun et al. 2023). Associations were plotted, and significance was evaluated. Traits related to neurological, metabolic, and cardiovascular systems were specifically examined.

Brain region-specific gene expression

Tissue-specific expression levels of candidate genes were obtained from the Human Protein Atlas (HPA)(Uhlen et al. 2010), which provides normalized transcript per million

(nTPM) values across human brain regions. Brain areas with high expression were identified and annotated in relation to known sleep regulatory centers (e.g., cortex, hypothalamus, brainstem).

Results

Causal inference of cell-type-specific gene expression on insomnia risk

To systematically evaluate the causal role of gene expression across distinct brain cell types in insomnia risk, we applied MR analysis using cell type-specific eQTLs as instrumental variables. The full list of instrument SNPs selected for each gene within each cell type is provided in Table S1.

Using the Wald ratio method, we estimated the causal effect of each gene-cell type pair on insomnia risk based on summary-level genome-wide association data from the UK Biobank. The results are summarized in Fig. 1 and Table S2 (full MR statistics). Several genes demonstrated statistically significant associations with insomnia after false discovery rate (FDR) correction. Notably, the strongest signals were observed in neuronal cell types—particularly excitatory and inhibitory neurons—while non-neuronal cell types (e.g., microglia, endothelial cells) showed no significant associations.

To confirm the causal directionality of these associations, we conducted Steiger filtering on each MR-significant gene to ensure that the instrumental variable explained more variance in gene expression than in the outcome. The directionality filtering results are presented in Table S3. All hits passed the Steiger test, supporting a causal path from gene expression to insomnia risk, rather than reverse causation.

Replication of positive MR findings and colocalization analysis in the discovery cohort

We sought to validate positive MR findings from the discovery dataset in an independent cohort. As shown in Fig. 2, the protective association of GFM1 expression in excitatory neurons was successfully replicated in FinnGen (OR = 0.7741, 95% CI: 0.6584–0.9102; $P = 0.0019$). In contrast, CAMLG and MTCH2 did not replicate, showing non-significant effects.

To further support the biological plausibility of GFM1, we performed Bayesian colocalization analysis in the discovery dataset to test whether the expression QTL and insomnia association shared a common causal variant. As shown in Figure S1 and detailed in Table S4, GFM1 exhibited strong colocalization at the genomic locus on chromosome 3

(posterior probability of shared signal, $PP.H4 = 0.717$), suggesting that insomnia and GFM1 expression are driven by the same genetic variant.

Figure 2. Validation of candidate genes in an independent cohort. Forest plot showing MR estimates for CAMLG, GFM1, and MTCH2 using FinnGen insomnia GWAS data.

Phenome-wide association analysis supports phenotype specificity of GFM1

To evaluate potential pleiotropy of the GFM1 instrument SNPs, we performed a PheWAS across a broad range of disease traits. As shown in Figure S2, no associations passed the significance threshold. These results indicate that the effect of GFM1 on insomnia is likely trait-specific, with no strong evidence of horizontal pleiotropy across other phenotypes.

GFM1 is highly expressed in sleep-regulating brain regions

To assess the spatial expression of GFM1 in the human brain, we analyzed RNA expression data from the Human Protein Atlas. As shown in Figure S3, GFM1 was broadly expressed across multiple brain regions, with relatively high expression in the cerebral cortex, midbrain, hypothalamus, and choroid plexus—regions previously implicated in sleep regulation. These findings support the functional relevance of GFM1 in the neurobiology of sleep and insomnia.

Conclusion

In this study, we integrated single-cell gene expression with large-scale genomic data to identify causal genes influencing insomnia risk. Through cell type-specific Mendelian randomization and independent replication, we highlighted GFM1 as a robust protective factor in excitatory neurons. Colocalization analysis supported a shared causal variant between GFM1 expression and insomnia risk, while PheWAS and brain regional expression data provided further evidence for phenotype specificity and functional relevance. Our findings underscore the importance of brain cell-specific mitochondrial regulation in sleep physiology and offer a novel molecular target for insomnia and related neuropsychiatric conditions.

As a core mitochondrial translation elongation factor, GFM1 is essential for the synthesis of oxidative phosphorylation (OXPHOS) system subunits (Gao et al. 2001; Coenen et al. 2004). Experimental models demonstrate that GFM1 deficiency triggers a robust compensatory cascade, characterized by the upregulation of electron transport chain components and the activation of PINK1/Parkin-mediated mitophagy to clear dysfunctional organelles (Ahmad et al. 2025). Within the specific context of insomnia, we propose that

optimal GFM1 expression is vital for maintaining mitochondrial proteome integrity, thereby ensuring that excitatory neurons can meet the heightened bioenergetic demands necessary to recover from prolonged wakefulness.

The cell-type-specific causal effect of GFM1 within excitatory neurons is particularly illuminating, as these cells are the primary drivers of cortical arousal and the main executors of homeostatic sleep pressure (Tononi and Cirelli 2014; Sulaman et al. 2023). Unlike inhibitory interneurons, excitatory pyramidal neurons undergo significant synaptic potentiation during wakefulness—a process that is metabolically expensive and highly dependent on efficient mitochondrial ATP production (Dworak et al. 2010; Dworak, Kim, et al. 2011; Dworak, McCarley, et al. 2011). By maintaining bioenergetic efficiency specifically in these high-demand populations, GFM1 ensures that excitatory circuits possess the metabolic resilience to "downscale" their activity during sleep. When GFM1 activity is compromised, the resulting bioenergetic deficit may impair a neuron's ability to reset its excitability threshold, fostering a state of persistent hyperarousal and subsequent sleep fragmentation. While severe GFM1 mutations manifest as dramatic clinical phenotypes—ranging from microcephaly to early-onset neurodegeneration (Ravn et al. 2015; You et al. 2020; Valente et al. 2007; Khan et al. 2022)—the subtle variations in expression observed in the general population likely act as a rheostat for cognitive and metabolic resilience. Consequently, GFM1 positions itself as a critical "bioenergetic buffer" within sleep-regulating circuits, where its sustained function shields the brain against sleep-related stressors.

In conclusion, our study identifies GFM1 as a genetically supported protective factor for insomnia. These results not only broaden our understanding of the metabolic underpinnings of sleep disorders but also point toward mitochondrial translation pathways as a promising avenue for pharmacological intervention. Enhancing mitochondrial protein synthesis or oxidative phosphorylation efficiency could represent a transformative approach to treating insomnia, shifting the focus from symptomatic sedation to the restoration of fundamental neuronal health.

Declarations

Informed consent statement

No applicable.

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Declaration of competing interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Manli Chen: Formal analysis, Investigation, Data curation, Visualization, Writing - original draft. **Xiaodong Tang:** Methodology, Software, Validation, Investigation. **Chenchen Xia:** Formal analysis, Data curation, Investigation. **Xuwu Xiang:** Conceptualization, Validation, Supervision, Writing - Reviewing and Editing. **Shengmei Zhu:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - Reviewing and Editing.

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Figures

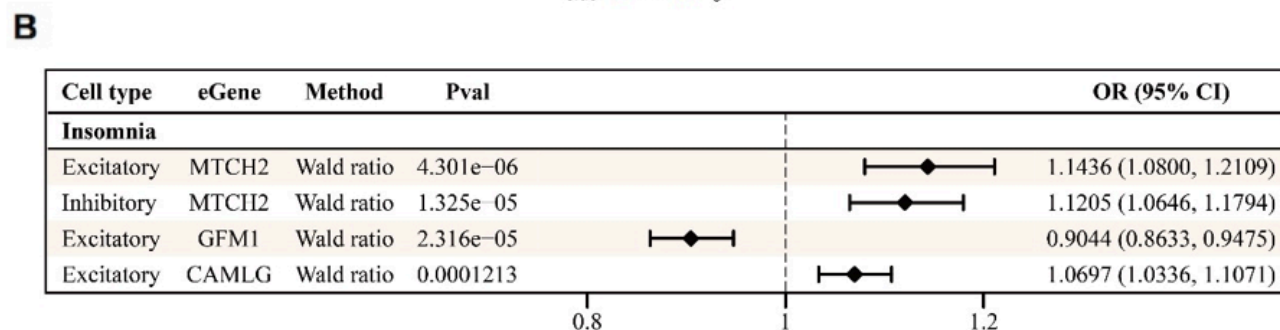
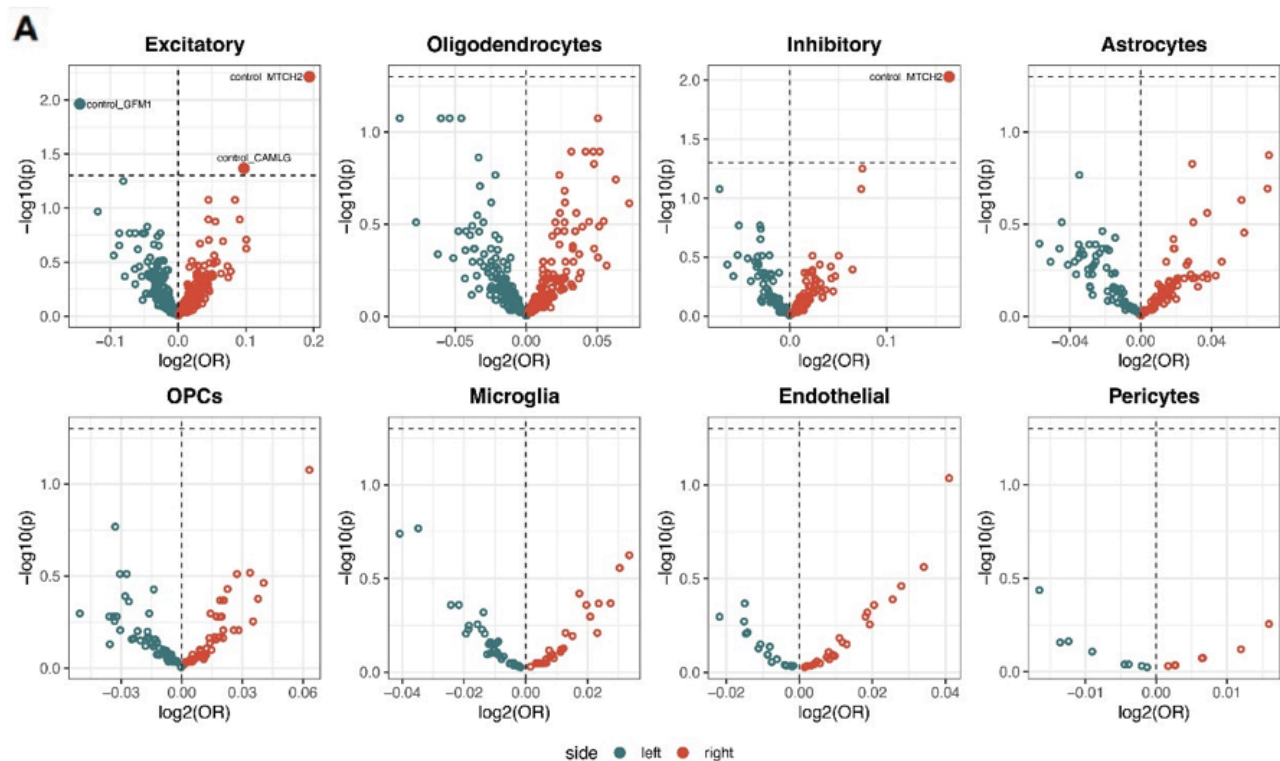


Figure 1

Single-cell Mendelian randomization identifies insomnia-associated genes across brain cell types. (A) Volcano plots showing MR estimates ($\log_2 \text{OR}$, $-\log_{10} \text{FDR}$) of gene expression on insomnia across eight brain cell types. Significant associations are labeled. (B) Forest plot of top gene-cell type pairs with $\text{FDR} < 0.05$. Odds ratios and 95% confidence intervals are shown.

Cell type	eGene	Method	Pval	OR (95% CI)
Insomnia				
Excitatory	CAMLG	Wald ratio	0.229435433	0.9450 (0.8618, 1.0363)
Excitatory	GFM1	Wald ratio	0.001937008	0.7741 (0.6584, 0.9102)
Inhibitory	MTCH2	Wald ratio	0.137748712	1.1409 (0.9586, 1.3578)

Figure 2

Validation of candidate genes in an independent cohort. Forest plot showing MR estimates for CAMLG, GFM1, and MTCH2 using FinnGen insomnia GWAS data.

Supplementary Files

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