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Causal cross-trait mapping at single-cell resolution identifies shared immunogenetic drivers of migraine and Meniere's disease

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Abstract

Background Migraine and Meniere's disease (MD) show high clinical comorbidity, shared symptoms such as vertigo and overlapping mechanisms like neurogenic inflammation suggest common pathophysiology. However, the core immunogenetic drivers underlying this comorbidity, particularly at cellular resolution, remain uncharacterized.

Methods We integrated cross-trait genetic analyses using summary statistics from large genome-wide association study (GWAS) and single-cell expression quantitative trait locus (sc-eQTL), followed by Bayesian colocalization. Candidate genes were validated with independent single-cell RNA sequencing (scRNA-seq) and their therapeutic potential was assessed via drug repurposing and Phenome-wide association studies (PheWAS).

Results We identified a significant genetic correlation (rg = 0.226) and 4 high-confidence shared prioritized genes (cell division cycle 42 [CDC42], dicarbonyl and L-xylulose reductase [DCXR], GTP binding protein 4 [GTPBP4], sterol-c5-desaturase [SC5D]). Single-cell analyses confirmed their cell-type-specific dysregulation. Drug target interrogation identified existing pharmacological agents interacting with these genes, including Lorlatinib for CDC42. PheWAS highlighted distinct safety profiles for each target, informing future therapeutic development priorities.

Conclusions This study reveals a shared immunogenetic basis between migraine and MD at single-cell resolution, providing novel targets and a translational roadmap for therapeutic development.

Clinical trial Not applicable.

Keywords Migraine, Meniere's disease, Vestibular dysfunction, Immunity, Multi-omics

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Introduction

Vestibular dysfunction, characterized by symptoms such as vertigo, dizziness, and imbalance, represents a significant clinical challenge due to its heterogeneous origins [1]. Meniere's disease (MD), a classic and debilitating peripheral vestibular disorder, exhibits a frequent comorbidity with migraine [2–4]. Epidemiological evidence indicates that these conditions co-occur more often than would be expected by chance, with individuals affected by migraine facing a two- to three-fold increased risk of developing MD [4–6]. Vertigo, a hallmark of MD, is also a prominent symptom in migraine subtypes, including vestibular migraine (VM) [7, 8]. Together, this clinical comorbidity supports the existence of shared underlying pathophysiological mechanisms.

Proposed links between migraine and vestibular disorders include several intersecting pathways, such as dysregulated neurovascular inflammation, ion channel dysfunction, and central sensitization [9, 10]. Notably, neuro-immune interactions, particularly those involving calcitonin gene-related peptide (CGRP) and mast cell-mediated pathways, are implicated in both disorders, suggesting a potential unifying immunogenetic basis [11]. Despite these insights, a critical gap remains: the precise molecular and cellular mechanisms that mechanistically connect the brain trigeminovascular system to endolymphatic homeostasis in the inner ear are poorly defined [12]. Moreover, existing evidence relies largely on clinical correlations or isolated pathway studies, lacking a systematic, genetics-driven strategy to identify putative causal immune-related genetic factors underlying their co-occurrence [13–15].

Conventional bulk eQTL MR, while powerful, averages gene expression signals across heterogeneous cell populations, potentially obscuring cell-type-specific effects and reducing mechanistic resolution [16]. In contrast, single-cell expression quantitative trait loci (sc-eQTL) MR leverages single-cell transcriptomic data to assign genetic regulatory effects to specific cell subtypes, thereby reducing cellular heterogeneity and enabling more precise mapping of disease-relevant cell populations [16]. Critically, several studies have demonstrated that sc-eQTL MR findings can be successfully translated into functional validation and drug target prioritization, supporting the tier-based prioritization strategy we adopt in the present study [17–19]. To address this gap, we implemented an integrative, multi-stage analytical framework. First, we quantified the genetic correlation between migraine and vestibular dysfunction using linkage disequilibrium score regression. We then performed cross-trait Mendelian randomization (MR) and Bayesian colocalization analyses, incorporating sc-eQTL data from 14 immune cell types to pinpoint shared genetically instrumented genes. These genetic findings were further validated and characterized using independent single-cell RNA sequencing (scRNA-seq) data from disease-specific cohorts. Finally, we assessed the translational potential of high-confidence targets through drug-repurposing analyses and phenome-wide safety profiling. This study provides the first single-cell-resolution atlas of the shared immunogenetic architecture between migraine and vestibular dysfunction, offering novel mechanistic insights into their comorbidity and highlighting promising avenues for therapeutic intervention.

Materials and methods

Study design

This study employed a multi-stage, cross-trait integrative framework to systematically identify and validate shared immunogenetic drivers between migraine and vestibular dysfunction, represented by MD. The overall analytical workflow is summarized in Fig. 1. All analyses were conducted using publicly available genetic summary statistics and single-cell transcriptomic datasets. As no individual-level data were generated or accessed, this study did not require additional ethical approval.

Exposure data and instrument selection

The cis-expression quantitative trait loci (cis-eQTL) data were obtained from the OneK1K cohort, a large-scale single-cell RNA sequencing dataset of peripheral blood mononuclear cells (PBMCs) from 982 healthy donors of European ancestry [20]. In the original study, eQTL mapping was performed separately for each of 14 major immune cell types using a linear mixed model that accounted for covariates including age, sex, batch, and the first 5 genotyping principal components, as well as a random effect to capture donor relatedness. cis-eQTLs were defined as genetic variants located within ± 1 Mb of the transcription start site of each gene. Summary statistics for all significant cis-eQTL associations ($P < 5 \times 10^{-08}$) were downloaded from the public repository (https://onek1k.org). A total of 26,597 independent cis-eQTLs (after LD clumping) were used as instrumental variables (IVs) in this study, which selections adhered to the three core assumptions of MR [21]: (1) relevance (strong association with the exposure, i.e., gene expression), (2) independence (no association with confounders), and (3) exclusion restriction (influence on the outcome solely via the exposure). To satisfy these assumptions, a stepwise filtering protocol was implemented. First, single nucleotide polymorphisms (SNPs) strongly associated with gene expression ($P < 5 \times 10^{-08}$) were selected. Second, to ensure independence among IVs, linkage disequilibrium (LD) clumping was performed using a strict threshold ($r^2 < 0.001$ within a 10,000 kb window) based on the 1000 Genomes European reference panel, retaining the most significant SNP per locus. To assess instrument strength,

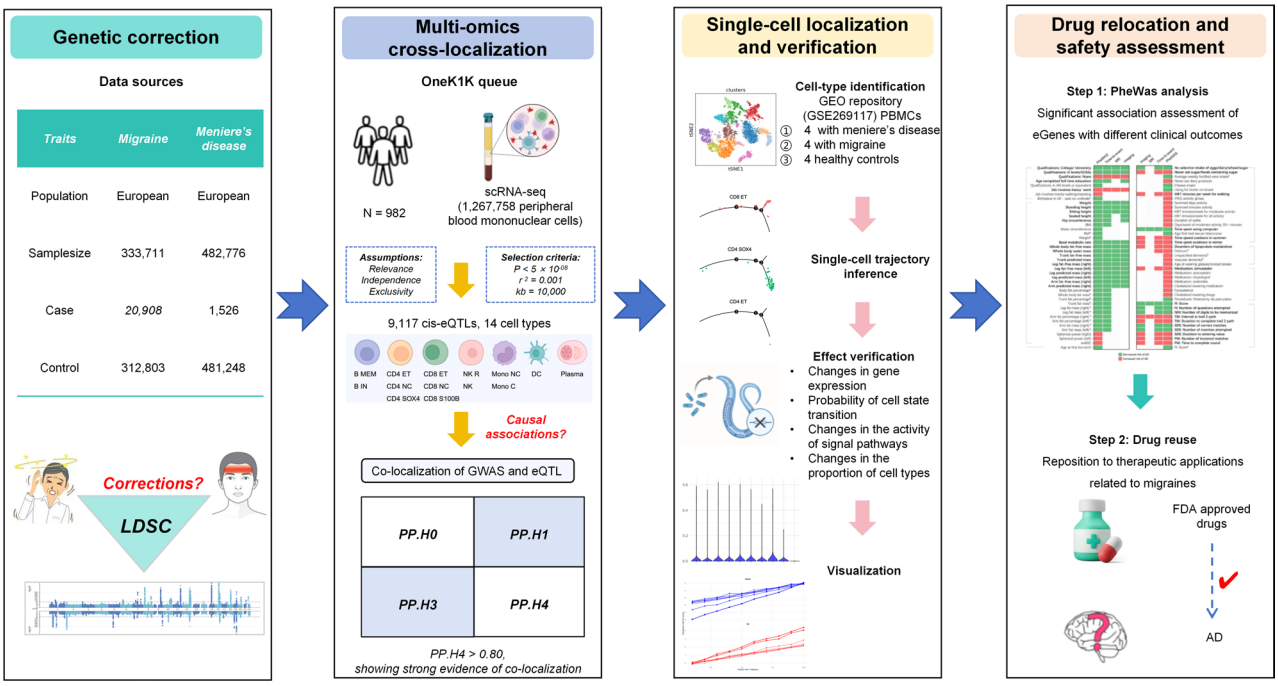

Fig. 1 Overview of research data sources and design process. As illustrated by the directional arrows, the multi-stage integrative framework operates sequentially from left to right. Stage 1 (Genetic Correlation Estimation): LDSC is applied to GWAS summary statistics for migraine and Meniere's disease to estimate their genetic correlation (rg). Stage 2 (Multi-omics Cross-tissue Localization): cis-eQTLs from 14 immune cell types—derived from the OneK1K cohort—are rigorously filtered using the following criteria: genome-wide significance ($P < 5 \times 10^{-08}$), low linkage disequilibrium (LD $r^2 < 0.001$), strong instrument strength (F-statistic > 10), and exclusion of pleiotropic variants via PhenoScanner annotation. Abbreviations: cis-eQTLs: cis-expression quantitative trait loci; sc-eQTL: single-cell expression quantitative trait loci; LDSC: linkage disequilibrium score regression; CD4 NC: CD4 naïve and central memory T cells; CD8 NC: CD8 naïve and central memory T cells; CD4 ET: CD4 + T cells with an effector memory or central memory phenotype; CD8 ET: CD8 + T cells with an effector memory or central memory phenotype; CD4 SOX4: SOX4-expressing CD4 + T cells; CD8 S100B: S100B-expressing CD8 + T cells; NK: natural killer cells; NK R: natural killer recruiting cells; B IN: immature B cells; B MEM: memory B cells; Mono C: classical monocytes; Mono NC: non-classical monocytes; DC: dendritic cells; Plasma: plasma cells; PBMC: peripheral blood mononuclear cell; GWAS: genome-wide association studies; PheWAS: phenome-wide association studies

we calculated the *F*-statistic for each SNP using the formula:

$$F = \beta^2 / SE^2$$

where β represents the effect size on gene expression and SE its standard error. An *F*-statistic > 10 was considered indicative of sufficient instrument strength to avoid weak instrument bias. The proportion of variance in gene expression explained by each IV (R^2) was estimated using the formula:

$$R^2 = 2 \times MAF \times (1 - MAF) \times \beta^2$$

where MAF is the minor allele frequency. Third, to mitigate potential horizontal pleiotropy, all candidate IVs were queried against the PhenoScanner V2 database to exclude those associated with known major risk factors or comorbidities of migraine and MD ($P < 1 \times 10^{-05}$). Finally, palindromic SNPs were removed during the harmonization of exposure and outcome datasets.

Outcome data

Summary-level genome-wide association studies (GWAS) data for migraine and MD were obtained from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/). All cases were defined based on ICD-10 codes. Detailed sample sizes, ancestry information, and study identifiers for each GWAS are provided in TableS1.

Genetic correlation analysis

The genetic correlation between migraine and MD was estimated using Linkage Disequilibrium Score Regression (LDSC). Precomputed LD scores from HapMap3 SNPs, matched to the 1000 Genomes European population, were used. The GWAS summary statistics for both traits were regressed against these LD scores to estimate the genetic correlation coefficient (rg) and its standard error. A positive rg indicates shared genetic risk variants, while a negative rg suggests opposing genetic effects. Statistical significance was assessed via a two-sided Z-test ($P < 0.05$).

Cross-trait Mendelian randomization and colocalization analysis

To identify genes whose immune cell-specific expression exerted a shared putative genetically predicted effects on both migraine and MD risk, cross-trait MR analysis was performed. The same set of rigorously filtered, cell-type-specific sc-eQTLs served as exposure IVs, and their effects on each disease outcome were estimated independently. Multiple MR methods were employed for robustness: the inverse-variance weighted (IVW) method was used as the primary analysis when ≥ 2 independent IVs were available; the weighted median method served as a sensitivity analysis; the Wald ratio was applied for single-IV analyses [22, 23]. For genes with multiple independent IVs (≥ 2 SNPs), we performed several sensitivity analyses to assess the robustness of MR findings: (1) Cochran's Q test to evaluate heterogeneity among IV-specific estimates, with $P < 0.05$ indicating significant heterogeneity; (2) MR-Egger regression to test for directional pleiotropy, with the intercept term indicating whether pleiotropy is biasing the estimates (an intercept $P < 0.05$ suggests presence of directional pleiotropy); (3) leave-one-out analysis to assess whether any single SNP was driving the overall effect estimate; and (4) Steiger filtering to confirm the direction of causality.

To evaluate whether the genetic associations identified by MR were driven by shared causal variants, Bayesian colocalization analysis was performed for all shared candidate genes from the cross-trait MR [24]. This analysis computes posterior probabilities (PP) for five competing hypotheses (H0-H4). Standard Bayesian colocalization (COLOC) assumes a single causal variant per locus. In regions with allelic heterogeneity, this assumption may be violated, potentially inflating or deflating posterior probabilities for shared signals (PP.H4). We focused on PP.H4, which represents the probability that the gene expression and the disease trait share a single causal variant within the genomic locus. A PP.H4 > 0.80 was considered strong evidence for colocalization, consistent with the original COLOC framework and widely adopted in recent sc-eQTL MR studies [25–27]. Because Bayesian colocalization provides posterior probabilities that inherently account for the likelihood of competing hypotheses, we did not apply additional multiple testing correction across cell types. Genes meeting this threshold in colocalization analyses with either migraine or MD were defined as high-confidence shared genes and prioritized for downstream validation.

After identifying a set of genes whose immune cell-specific expression showed a significant putative causal effect on both migraine and MD after false discovery rate correction (FDR < 0.05). These shared candidate genes were subsequently classified into 3 priority tiers based on the strength of genetic evidence and functional annotation: Priority 1 (P1): Genes that satisfied all of the following criteria: (1) the most significant p-values in both MR analyses, (2) strong evidence of colocalization (PP.H4 > 0.8) with both disease, and (3) functional enrichment in neuroinflammatory or immune-related pathways. Priority 2 (P2): Genes with significant MR associations for both traits but weaker colocalization evidence or less clear functional relevance. These genes were carried forward for exploratory analysis of their expression patterns in single-cell data. Priority 3 (P3): Genes with the weakest combined evidence, serving as a background list [28]. Furthermore, among the shared genes, we examined the concordance of their putative causal effect directions (β values) on the diseases. A majority exhibited concordant effects, while a subset showed discordant effects suggesting potential disease-specific regulatory mechanisms.

Single-cell RNA-seq validation and mechanistic exploration

High-confidence shared genes were validated and functionally explored using independent scRNA-seq datasets (GSE269117) encompassing PBMCs from 4 migraine patients, 4 MD patients, and 4 healthy controls (HCs) [29, 30]. All analyses were performed using R (V4.2.1) with the Seurat package (V4.3.0). First, the scRNA-seq data underwent standard preprocessing, including quality control, which filtered to retain cells meeting the following criteria: (1) number of detected genes (nFeature_RNA) between 200 and 2500; (2) mitochondrial gene percentage (percent.mt) < 10%; and (3) total UMI count (nCount_RNA) > 500; normalization, which expression data were normalized using the SCTransform method (V2) with regression of mitochondrial percentage and cell cycle scores; and dimensionality reduction, which the first 30 principal components were used for UMAP dimensionality reduction and graph-based clustering (FindNeighbors and FindClusters functions with resolution was 0.5). Cell clusters were annotated using canonical marker genes.

Then, we performed differential expression testing between disease groups (migraine *vs.* controls, MD *vs.* controls) using the Wilcoxon rank-sum test for each cell type. Genes with absolute $\log_2$(fold-change) > 0.25 and FDR-adjusted $P < 0.05$ were considered statistically significant. Results for high-confidence genes were visualized and compared across disease states using dot plots and feature plots. To investigate the dynamic expression patterns of candidate genes during immune cell differentiation and activation, we performed pseudotime analysis using Monocle 3. For each major cell lineage, we extracted the relevant cell subsets and constructed a new CellDataSet object using normalized expression values. Dimension reduction was performed using UMAP via the reduce dimension, and cells were ordered along a trajectory. Candidate gene expression was projected

onto the pseudotime axis and visualized, and branch-dependent expression was assessed using Moran's I test for spatial autocorrelation ($P < 0.05$ indicating significant branch-dependent expression).

Third, to predict the functional impact of key candidate genes, a computational knockout simulation was conducted using scTenifoldKnk (v1.0.2). This tool constructs gene regulatory networks via robust tensor decomposition, then simulates the network-wide transcriptional consequences of knocking down a target gene by comparing the perturbed network to the original [31]. For prioritized gene, we performed separate analyses within the most relevant immune cell subpopulation (as determined by cell-type-specific expression patterns). The analysis pipeline consisted of: (1) constructing a GRN for the selected cell type using scTenifoldNet; (2) performing virtual knockdown of the target gene by setting its regulatory interactions to 0; (3) comparing the perturbed and original networks to identify genes with significant expression changes ($|\log_2 FC| > 0.5$ and adjusted $P < 0.05$); and (4) ranking genes by their predicted differential expression.

Phenome-wide association study for target safety profiling

A PheWAS was conducted to assess the potential pleiotropy and off-target effects of the prioritized candidate genes, informing their viability as therapeutic targets. Analysis utilized exome-based PheWAS summary statistics from the AstraZeneca PheWAS portal (https://azphewas.com/). For each candidate gene, we retrieved all genome-wide significant associations. To control for multiple testing, a Bonferroni-corrected significance threshold was applied for each gene separately. The AstraZeneca PheWAS portal reports associations across approximately 13,000 binary traits and 5,000 continuous traits, but we restricted our analysis to the primary phenotype categories (disease endpoints, biomarkers, and medication use) to reduce redundancy. For each candidate gene, we considered associations to be significant if their P-value fell below a gene-specific Bonferroni-corrected threshold ($\alpha = 0.05 / N$), where N represents the total number of independent tests performed for that gene.

Results

Significant genetic correlation between migraine and Meniere's disease

First, we confirmed a significant positive genetic correlation between migraine and MD at the genomic level (Fig. 2A-B). LD score regression analysis revealed a genetic correlation coefficient of $rg = 0.23$ (95% confidence interval [CI]: 0.203 to 0.249; $se = 1.15 \times 10^{-02}$), which was highly significant ($P = 2.65 \times 10^{-85}$). This indicates a low-to-moderate, positive shared genetic basis between the two disorders. The cross-trait intercept from bivariate LDSC was 5.60×10^{-02} ($se = 4.80 \times 10^{-02}$), confirming that sample overlap does not bias the genetic correlation estimate.

Selection of immune cell-specific instrumental variables

Gene expression data were obtained from 14 distinct immune cell types, with sample sizes ranging from 643 to 982 donors. The cellular composition of the sc-eQTL reference dataset is summarized in Figure S1. CD4 naïve/central memory T cells (CD4 NC), CD8 + effector/central memory T cells (CD8 ET), and classical monocytes (Mono C) constituted the largest proportions. Other characterized cell types included CD8 naïve/central memory T cells (CD8 NC), CD4 + effector/central memory T cells (CD4 ET), SOX4-expressing CD4 + T cells (CD4 SOX4), S100B-expressing CD8 + T cells (CD8 S100B), natural killer cells (NK), NK recruiting cells (NK R), immature B cells (B IN), memory B cells (B MEM), non-classical monocytes (Mono NC), dendritic cells (DC), and plasma cells.

Applying a stringent significance threshold ($P < 5 \times 10^{-08}$) to cis-eQTL associations across all cell types yielded 26,597 gene-level associations. Subsequent LD clumping ($r^2 < 0.001$, window size = 10,000 kb) identified 9,117 independent, cell-type-specific SNPs as IVs for downstream MR analysis (Table S2). All retained instruments demonstrated adequate strength, with F-statistics ranging from 29.66 to 1371.07 (median = 59.38) and R^2 values from 0.03 to 0.60 (Table S2). Most target genes were instrumented by a single IV, while a smaller subset was associated with multiple independent IVs, potentially enabling more robust causal inference.

Cross-trait Mendelian randomization and colocalization identify shared causal genes

Using sc-eQTLs from 14 immune cell types as IVs, we performed cross-trait MR analysis. Among 9,117 genes tested, 18 genes derived from 7 immune cell subsets showed a significant putative causal effect on the risk of both migraine and MD ($P < 0.05$; Tables S3-S7). Analysis of the effect directions revealed that 8 genes had concordant effects on risk for both diseases, suggesting a shared disease-promoting mechanism. In contrast, 10 genes exhibited discordant effect directions, implying more complex, disease-specific regulatory roles (Fig. 3A & Table S7). Sensitivity analyses supported the robustness of these findings. Cochran's Q test showed no significant heterogeneity for any of these genes ($P > 0.05$ for all), and MR-Egger intercepts were not significantly different from zero ($P > 0.05$ for all), suggesting no evidence of directional pleiotropy (Tables S4 & S6). Leave-one-out analyses confirmed that no single SNP disproportionately influenced the effect estimates. Steiger filtering

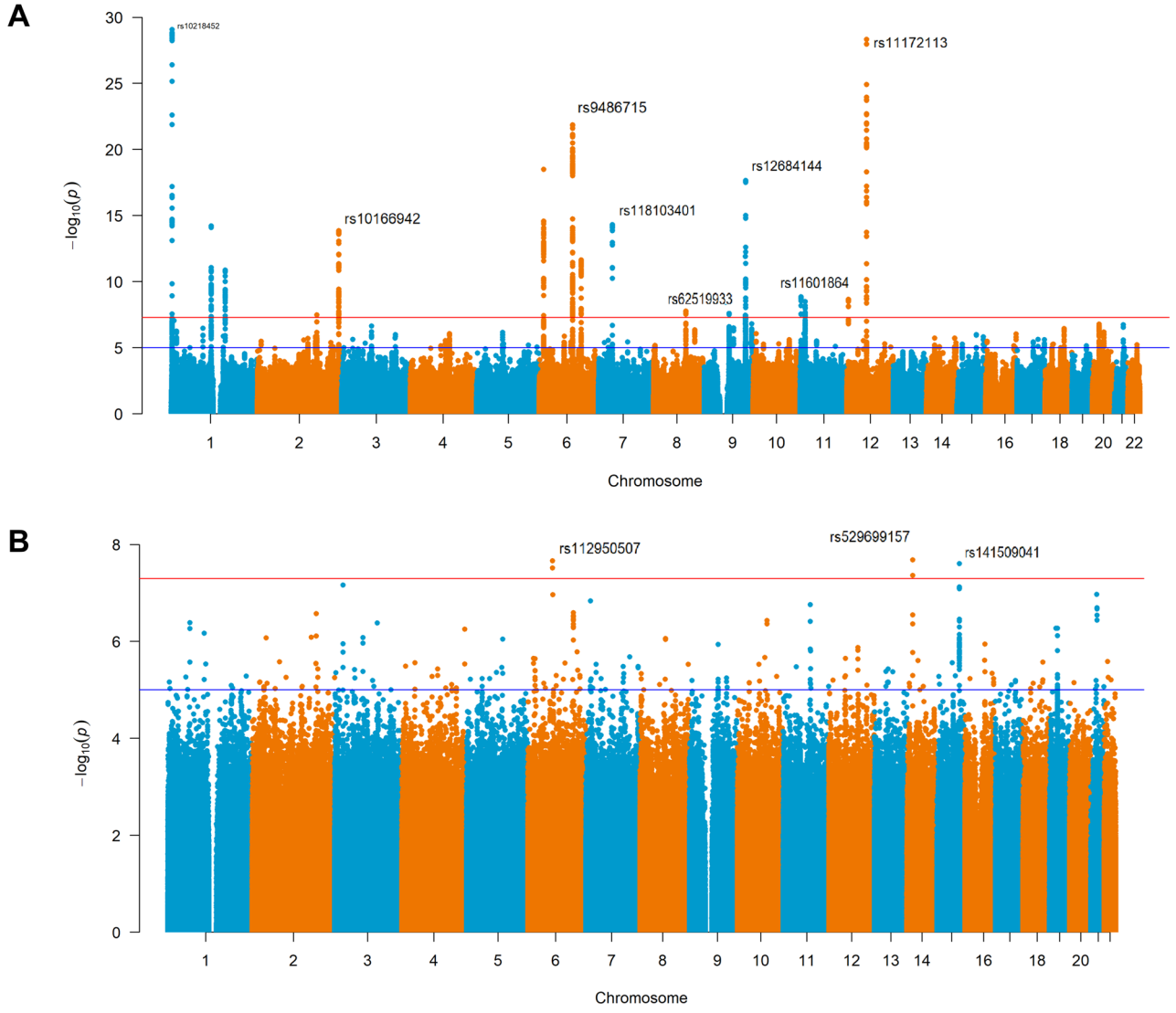

Fig. 2 Genetic correlations between migraine and Meniere's disease. (**A**) Manhattan plots showing the strength of the association of migraine. (**B**) Manhattan plots showing the strength of the association of Meniere's disease. Abbreviations: CIs: Confidence intervals

confirmed the expected direction of causa lity for all 18 genes ($P < 0.05$).

To evaluate whether these associations were driven by shared causal variants, we performed Bayesian colocalization analysis on all 18 shared candidate genes. 4 genes demonstrated strong colocalization (PP.H4 > 0.80) with both diseases. CDC42 (MD: PP.H4 = 0.868, migraine: PP.H4 = 1.000), DCXR (MD: PP.H4 = 1.000, migraine: PP.H4 = 1.000), GTPBP4 (MD: PP.H4 = 0.948, migraine: PP.H4 = 0.999), and SC5D (MD: PP.H4 = 1.000, migraine: PP.H4 = 1.000) (Fig. 3B & Table S8). Notably, DCXR and SC5D achieved PP.H4 = 1.000 for both traits, indicating exceptionally strong evidence for shared causal variants. The remaining 14 genes showed substantially weaker colocalization evidence (PP.H4 ranging from 0.12 to 0.67), suggesting that for these genes, the MR associations may be driven by distinct causal variants for each trait or by linkage disequilibrium rather than true shared signals. Even among the 4 prioritized genes, we observed variation in the posterior probability distribution. For example, CDC42 in the MD analysis exhibited a non-negligible posterior probability for distinct causal variants (PP.H3 = 0.233), indicating that while a shared variant is strongly supported (PP.H4 = 0.868), some uncertainty remains. In contrast, all 4 genes in the migraine analysis and DCXR/SC5D in the MD analysis showed PP.H4 ≥ 0.999 with negligible probabilities for competing hypotheses. We therefore defined these 4 genes as high-confidence candidates for downstream analysis, while acknowledging that genes with intermediate PP.H4 values (0.500 to 0.800) in the full set of 18 may still represent true positives that require larger sample

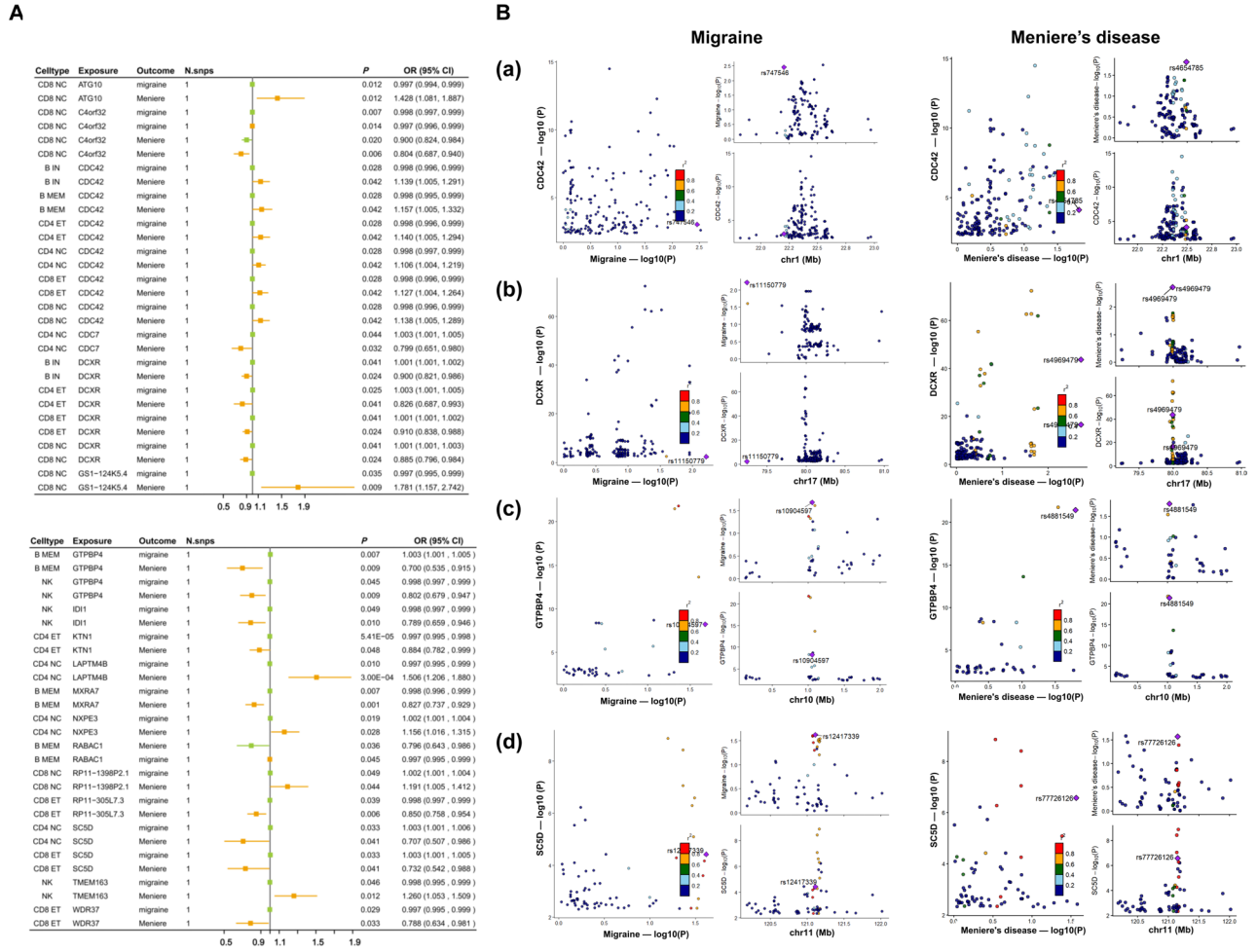

Fig. 3 Causal relationships of shared genes with migraine and Meniere's disease, and their colocalization results. (**A**) Cross-trait MR results showing shared causal genes, colored by concordant or discordant effect directions on migraine and Meniere's disease risk. (**B**) Bayesian colocalization analysis for high-confidence shared genes. (a) CDC42. (b) DCXR. (c) GTPBP4. (d) SC5D. PP.H4 indicates the posterior probability for a shared causal variant. Abbreviations: CIs: Confidence interval; OR: Odd ratio; cis-eQTLs: cis-expression quantitative trait loci; CD4 NC: CD4 naïve and central memory T cells; CD8 NC: CD8 naïve and central memory T cells; CD4 ET: CD4 + T cells with an effector memory or central memory phenotype; CD8 ET: CD8 + T cells with an effector memory or central memory phenotype; CD4 SOX4: CD4 + T cells expressing SOX4; CD8 S100B: CD8 + T cells with expression of S100B; NK: Natural killer cells; NK R: Natural killer recruiting cells; B IN: Immature B cells; B MEM: Memory B cells; Mono C: Classical monocytes; Mono NC: Nonclassical monocytes; DC: Dendritic cells; Plasma: Plasma cells; LDSC: Linkage Disequilibrium Score Regression; CDC42: Cell Division Cycle 42; DCXR: Dicarbonyl And L-Xylulose Reductase; GTPBP4: GTP Binding Protein 4; SC5D: Sterol-C5-Desaturase

sizes for definitive colocalization. Among these high-confidence shared genes, 3 (CDC42, DCXR, SC5D) exhibited discordant effect directions (e.g., increased migraine risk but decreased MD risk). We interpret this as reflecting context-dependent regulation, where the same gene may have opposing effects in different tissues or at different disease stages, rather than true protective effects. Such discordance does not invalidate the shared biology; rather, it highlights the complexity of gene regulation across tissue contexts.

Single-cell transcriptomic validation highlights cell-type-specific dysregulation

To characterize the immune cell landscape and expression patterns of high-confidence shared genes, we analyzed scRNA-seq data from PBMCs of migraine patients, MD patients, and healthy controls. UMAP dimensionality reduction visualized the composition and distribution of major immune cell types in both cohorts (Fig. 4A). Consistent with the cellular origins of our IVs, CD4 + T cell subsets, CD8 + T cell subsets, and classical monocytes dominated the cellular composition, suggesting these cell types are potential mediators of shared pathophysiology (Fig. 4B). Visualization of expression patterns suggested cell-type-specific dysregulation of CDC42, DCXR, GTPBP4, and SC5D in both disease groups, with effect sizes varying across cell types (Fig. 4C). We emphasize that these expression patterns are observational and do not prove causality; rather, they provide supportive evidence that the genetically

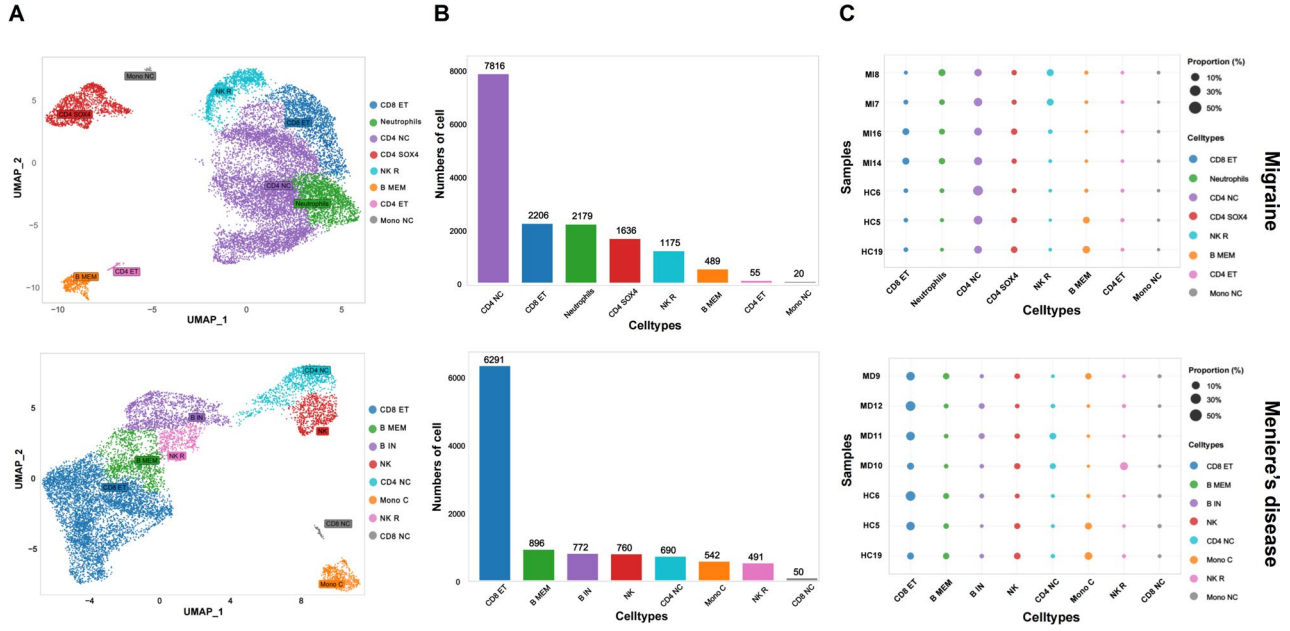

Fig. 4 Single-cell profiling of immune cell composition in patient PBMCs. (**A**) UMAP visualization of major immune cell types in migraine and Meniere's disease cohorts. (**B**) Scatter plot displaying differences in cell numbers across immune subsets between patient groups. (**C**) Dot plot illustrating the expression intensity and cellular proportion of high-confidence shared genes across annotated cell types and individual samples. Abbreviations: PBMCs: Peripheral blood mononuclear cells; CD4 NC: CD4 naïve and central memory T cells; CD8 NC: CD8 naïve and central memory T cells; CD4 ET: CD4 + T cells with an effector memory or central memory phenotype; CD8 ET: CD8 + T cells with an effector memory or central memory phenotype; CD4 SOX4: CD4 + T cells expressing SOX4; CD8 S100B: CD8 + T cells with expression of S100B; NK: Natural killer cells; NK R: Natural killer recruiting cells; B IN: Immature B cells; B MEM: Memory B cells; Mono C: Classical monocytes; Mono NC: Nonclassical monocytes; DC: Dendritic cells; Plasma: Plasma cells

prioritized genes are dysregulated in the predicted cell types and disease contexts.

Pseudotime trajectory analysis revealed bifurcating differentiation paths from naïve to activated states across multiple immune lineages (Fig. 5A-G). Projection of candidate gene expression onto pseudotime axes demonstrated temporal heterogeneity in their upregulation: some genes peaked early during activation, while others showed progressive upregulation throughout the trajectory. This pattern suggests different genes may be involved in the initiation versus maintenance stages of inflammatory activation.

To generate testable hypotheses about the functional role of these genes, we performed in silico knockdown simulations using scTenifoldKnk within disease-relevant immune cell contexts. Baseline expression patterns of each gene across immune cell subtypes confirmed cell-type-specific dysregulation in both diseases (Figures S2-S9). Simulated knockdown of each gene predicted widespread transcriptional reprogramming, with distinct sets of downstream genes affected in migraine versus MD contexts (Figures S10-S17). For example, CDC42 knockdown in classical monocytes predicted upregulation of pro-inflammatory cytokines (IL1B, TNF) and chemokines (CCL3, CCL4) in the migraine context but not in MD, suggesting context-dependent regulatory effects. Pseudotime trajectory analysis of these responsive genes illustrated their dynamic changes along cellular state transitions upon genetic perturbation (Figures S18-S25). We emphasize that these predictions require experimental validation and should be interpreted as hypothesis-generating rather than confirmatory.

Drug repurposing potential and systemic safety profiles of shared targets

Interrogation of drug–gene interaction databases revealed a network of pharmacological agents associated with the prioritized genes, though these associations range from direct inhibition to indirect pathway-level interactions and should be interpreted as hypothesis-generating rather than definitive therapeutic claims. We systematically evaluated the druggability and repurposing potential of the prioritized high-confidence shared genes. By interrogating the DrugBank and DGIdb databases, we identified existing pharmacological agents targeting these genes. Among the 4 top-priority genes, CDC42 was associated with the approved inhibitor Lorlatinib (used in non-small cell lung cancer) and the investigational agent Mahatinib. This association indicates pharmacological interaction, not clinical suitability for repurposing. For DCXR, only experimental compounds were recorded. Notably, SC5D was linked to an approved therapy for vitamin B2 deficiency. No known drugs

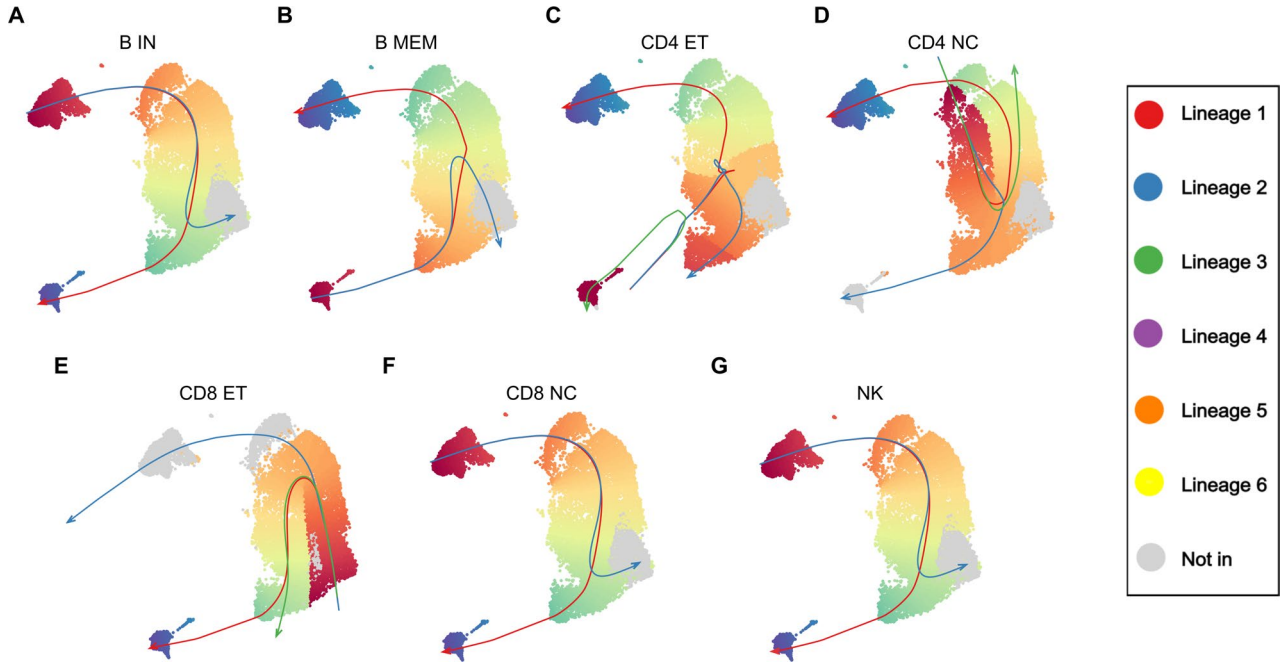

Fig. 5 Pseudotime analysis reveals dynamic expression of shared genes during immune cell activation. (**A**) B IN. (**B**) B MEM. (**C**) CD4 ET. (**D**) CD4 NC. (**E**) CD8 ET. (**F**) CD8 NC. (**G**) NK. The branching trajectories of the significant cell subpopulations inferred by the Monocle 3 algorithm illustrate the process by which they evolve from their initial state to the activated state. Abbreviations: CD4 NC: CD4 naïve and central memory T cells; CD8 NC: CD8 naïve and central memory T cells; CD4 ET: CD4 + T cells with an effector memory or central memory phenotype; CD8 ET: CD8 + T cells with an effector memory or central memory phenotype; NK: Natural killer cells; B IN: Immature B cells; B MEM: Memory B cells

targeting GTPBP4 were identified in the queried databases (Table S9).

To assess the potential pleiotropic effects and systemic safety risks, we performed PheWAS using exome-based summary statistics from the UK Biobank. The analysis revealed distinct systemic association profiles for each gene (Fig. 6). CDC42 showed significant genetic associations with several immune-related and metabolic traits (Table S10). DCXR exhibited limited widespread phenotypic associations, suggesting a potentially favorable safety profile for therapeutic modulation (Table S9). SC5D was significantly associated with lipid metabolism traits, indicating a need to evaluate potential off-target metabolic effects (Table S2). Similarly, GTPBP4 demonstrated associations with a range of hematological and biochemical parameters (Table S13). These PheWAS findings highlight both the repurposing opportunities and the specific safety considerations that should inform future development of therapies targeting these shared immunogenetic drivers.

Discussion

This integrative study delineates, for the first time, a shared immunogenetic architecture between migraine and MD at single-cell resolution. By employing a cross-trait analytical framework, we identified 4 high-confidence causal genes (CDC42, DCXR, GTPBP4, and SC5D) whose immune cell-specific expression influences the risk of both disorders. Notably, three of these genes (CDC42, DCXR, SC5D) exhibited discordant effect directions, suggesting a complex interplay of shared and disease-specific mechanisms. These findings position dysregulated immune responses, mediated by specific cell subpopulations, as a central pathophysiological link between migraine and vestibular dysfunction.

The observation that three of 4 high-confidence genes exhibit discordant effect directions warrants careful interpretation. This finding might appear to conflict with the expectation that comorbid diseases would share risk alleles with concordant effects. However, we propose that this discordance actually illuminates the complexity of shared pathophysiology rather than undermining it. Shared biological pathways can produce opposite phenotypic outcomes depending on tissue context, developmental timing, or disease stage—a phenomenon well-recognized in immunology and neurobiology. For instance, NF-κB signaling promotes neuronal survival in some contexts but drives neuroinflammation in others [32]; TGF-β family members can be either pro- or anti-inflammatory depending on cellular microenvironment [33]. Within this framework, the 4 genes we identified may represent shared molecular hubs within a common neuro-immune pathway, where their perturbation leads to different downstream consequences in the trigeminovascular system versus the inner ear. This interpretation is consistent with the established biology of these genes.

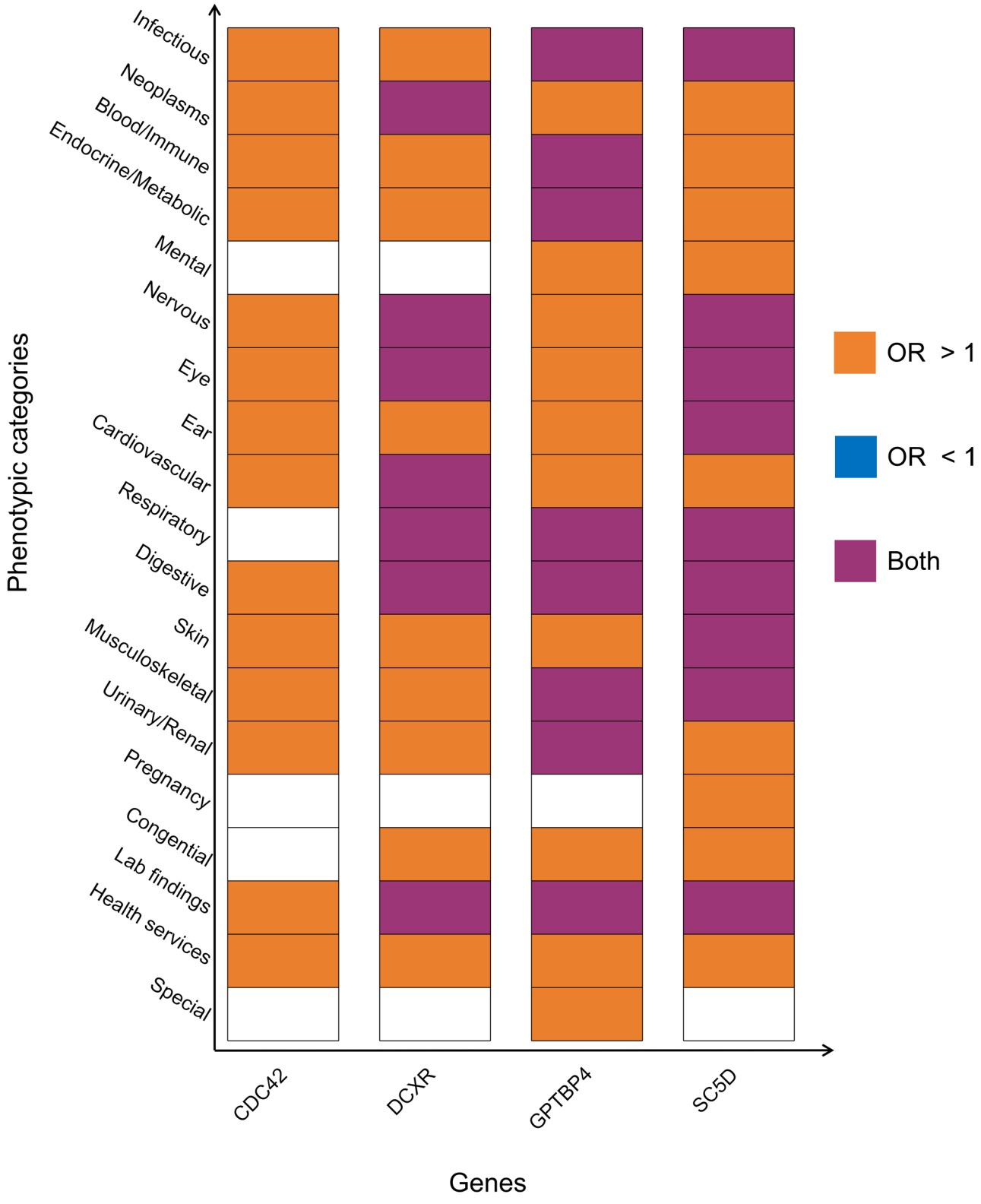

Fig. 6 Phenome-wide safety profiles of shared target genes. The plot displaying the significance PheWAS results for each high-confidence shared gene, including CDC42, DCXR, SC5D, and GTPBP4 (Bonferroni-corrected $P < 1.25 \times 10-02$ [4 / 0.05]). Each point represents a phenotype trait. Traits are categorized and colored by OR value. Abbreviations: OR: Odds ratio; CDC42: Cell Division Cycle 42; DCXR: Dicarbonyl And L-Xylulose Reductase; GTPBP4: GTP Binding Protein 4; SC5D: Sterol-C5-Desaturase; PheWAS: Phenome-wide association study

For example, CDC42 regulates cytoskeletal dynamics in diverse cell types, promoting immune cell migration and vascular permeability in meningeal tissues while maintaining tight junction integrity in the blood-labyrinth barrier [34]. Thus, the same gene can influence disease risk in opposite directions through tissue-specific mechanisms, yet both effects originate from disruption of a shared fundamental process (cytoskeletal regulation). Importantly, epidemiological comorbidity does not require identical genetic effect directions. Comorbidity could arise through multiple mechanisms: (1) cumulative burden across multiple discordant genes that collectively predispose to both conditions; (2) shared pathway perturbation with tissue-specific thresholds for phenotypic expression; or (3) sequential effects where one condition creates permissive conditions for the other. Our findings support a model wherein migraine and MD share a core immunogenetic pathway, but the net phenotypic outcome in each tissue reflects the integrated effect of multiple genes acting in context-dependent manners.

CDC42, a master regulator of cytoskeletal dynamics and cell migration, showed opposing effect directions—increased migraine risk but decreased MD risk. Rather than viewing this discordance as contradictory to shared pathophysiology, we interpret it as revealing tissue-specific consequences of disrupting a common molecular hub. Within the trigeminovascular system, CDC42 activity in immune cells may facilitate perivascular infiltration and neurogenic inflammation [35]; conversely, within the inner ear, CDC42 may be essential for maintaining blood-labyrinth barrier integrity, where its relative underexpression could compromise barrier function [36, 37]. Both effects stem from CDC42's core function in cytoskeletal regulation, but the phenotypic outcome differs based on the tissue-specific requirements for this process.

Critically, our gene knockdown simulations provided functional context for these genetic associations. By modelling the transcriptional consequences of reducing gene expression within key immune cell subsets, we predicted that perturbing these high-confidence genes—particularly the discordant ones—would lead to widespread and specific alterations in downstream pathways [38]. The predicted upregulation of pro-inflammatory cytokines (e.g., IL1B) and chemokines following CDC42 knockdown aligns with its postulated role in facilitating neurogenic inflammation in migraine [35]. Conversely, the simulated knockdown of SC5D in similar cells predicted dysregulation of genes involved in endothelial integrity and lipid metabolism, a finding consistent with its potential role in inner ear barrier function and its observed PheWAS association with metabolic traits [39]. This computational validation bridges the gap between genetic association and putative mechanism, suggesting that these genes are not merely risk markers but active, cell-type-specific regulators of disease-relevant transcriptional programs. The temporal specificity of their expression during immune cell activation, revealed by pseudotime analysis, further underscores their likely involvement in stage-specific pathological processes.

These results bridge major pathophysiological theories. The shared immunogenetic framework offers a plausible mechanism linking trigeminovascular activation in migraine to endolymphatic homeostasis dysregulation in MD [40, 41]. Immune cells, particularly Mono C and effector memory T cells, could serve as mobile mediators, simultaneously affecting meningeal and inner ear environments via cellular infiltration or cytokine signaling [42, 43]. This aligns with a recent sc-eQTL MR framework that identified immune cell drivers in migraine [28]; by extending this approach to MD, our findings suggest that similar immune-mediated mechanisms may underlie both disorders. This provides a biological basis for symptom overlap and co-occurrence. Furthermore, our findings intersect with the established role of CGRP: immune cells modulated by genes like CDC42 could influence CGRP release from sensory nerves, while CGRP itself may feedback on immune cells to alter expression of genes like DCXR, creating a feed-forward loop of neuroimmune dysregulation [44].

Beyond elucidating shared mechanisms, our findings challenge the traditional nosological boundaries between neurological and otological disorders. The identification of a core set of immunogenetic drivers common to migraine and MD suggests that these conditions may represent different clinical manifestations of a shared systemic predisposition, centered on dysregulated immune-neural crosstalk [29]. This paradigm shift from viewing them as entirely separate entities to recognizing them as part of a spectrum of neuroimmunological sensory disorders has profound implications [45]. It encourages a move beyond symptom-based classification towards a mechanism-based taxonomy, which could improve diagnostic accuracy, especially in cases with overlapping or atypical presentations [46]. Future diagnostic criteria might incorporate genetic or cellular biomarkers derived from such shared pathways to identify patient subsets most likely to exhibit comorbidity or respond to immunomodulatory therapies [47].

From a translational perspective, our drug repurposing and safety assessment yields actionable insights with direct clinical implications. The identification of Lorlatinib, which is a third-generation ALK inhibitor approved for non-small cell lung cancer that also exhibits CDC42 inhibitory activity, raises the question of whether this agent might be repurposed for migraine or MD [48]. However, we emphasize that direct clinical repurposing would be clinically unrealistic and potentially dangerous given its safety profile. Lorlatinib is associated with

significant adverse effects including hyperlipidemia, cognitive impairment, mood changes, and fatigue—effects that are unacceptable for chronic use in non-malignant conditions [49]. Rather than advocating for immediate clinical repurposing, we propose a more measured translational framework that separates target identification from drug repurposing. First, the compound could serve as a valuable tool in preclinical disease models to functionally validate CDC42's role in neuro-immune crosstalk. Second, the genetic identification of CDC42 as a shared driver should incentivize medicinal chemistry efforts to develop more selective CDC42 inhibitors with improved safety profiles. Conversely, the lack of known drugs for GTPBP4 and the experimental status of DCXR binders highlight a niche for novel therapeutic development targeting these pathways. Critically, the PheWAS safety profiles dictate a stratified development strategy. The association of SC5D with lipid metabolism traits, while not precluding it as a target, strongly suggests that any therapeutic agent would require careful monitoring of metabolic parameters in clinical trials [50]. The relatively PheWAS profile of DCXR enhances its attractiveness as a target, suggesting a potentially wider therapeutic window [51]. The pleiotropy observed for CDC42 and GTPBP4 further suggests that cell-type-specific delivery systems may be necessary to harness therapeutic benefits while mitigating systemic risks. Thus, our study moves beyond mere gene discovery to outline a translational roadmap.

These insights directly inform a more personalized and proactive clinical management strategy. For the clinician, the evidence of a strong shared immunogenetic basis supports systematically screening migraine patients for vestibular symptoms, and vice versa, enabling earlier diagnosis and comprehensive care [52]. Our prioritized gene list and their associated cell types provide candidate peripheral biomarkers that could be measured in patient blood to stratify disease risk, predict comorbidity, or monitor treatment response. From a therapeutic development perspective, the discordant effects of genes like CDC42 underscore that therapeutic efficacy and safety may be highly context-dependent [53]. This necessitates the development of sophisticated delivery systems to precisely direct therapeutic action. Consequently, future research must pivot towards functional validation in disease-specific microenvironments and the design of targeted clinical trials that select patients based on their immunogenetic profile, ultimately paving the way for precision medicine in sensory disorders.

Several limitations should be acknowledged. First, the research data is derived from individuals of European ancestry. The applicability of the conclusions to other populations remains to be verified. Second, a fundamental limitation is our reliance on PBMCs as the source of both eQTL data and single-cell validation. While peripheral immune cells are increasingly recognized as active participants in neurological and otological disorders—capable of trafficking to the meninges, inner ear, and associated ganglia—they likely represent only a subset of the immune cells relevant to disease pathogenesis. Consequently, our findings should be interpreted as identifying peripheral immunogenetic signatures that associate with disease risk and may serve as accessible biomarkers, rather than as definitive evidence of inner ear-specific mechanisms. Future studies integrating spatial transcriptomics of human post-mortem tissues, along with experimental models that permit tissue-specific genetic manipulation will be essential to validate whether the regulatory mechanisms inferred from peripheral data operate locally within affected tissues. It is worth noting that sc-eQTL data used in this study were derived from healthy donors, which may not reflect gene regulation under inflammatory conditions characteristic of active migraine or MD. While this conservative approach avoids confounding by disease state and provides a baseline reference for genetic effects on gene expression, it may underestimate or miss regulatory effects that are only manifest during inflammation. Future studies incorporating sc-eQTL data from patient cohorts during active disease states would complement our findings. Third, our findings are contingent upon the diagnostic accuracy of the GWAS input data. The GWAS of MD used in this study includes only 1,526 cases, resulting in an imbalanced case–control ratio that may limit statistical power and precision of effect estimates. While we mitigated this by using strong instruments (F-statistics > 10) and requiring colocalization support (PP.H4 > 0.8), the modest case number remains a limitation. In addition, MD is notoriously difficult to phenotype accurately in large biobank studies, as it shares overlapping clinical features with VM and ICD-10 coding may be applied loosely by non-specialists to any recurrent vertigo of unclear etiology [2]. This diagnostic uncertainty is well-recognized in the field, poor clinical phenotyping and misdiagnosis of family members with vestibular disorders represent major obstacles to genetic discovery [54]. (1) Future studies need GWAS of rigorously phenotyped MD and VM cohorts using standardized diagnostic criteria; (2) direct comparison of genetic architecture between clinically confirmed MD and VM patients; and (3) integration with tissue-specific regulatory data from inner ear and trigeminal ganglion. Before obtaining these data, our findings should be interpreted as identifying genetic drivers. Sixth, our colocalization analysis employed the standard COLOC framework, which assumes that each locus has a single causal variant. Although this assumption is reasonable for many genomic regions, allelic heterogeneity (multiple independent variations affecting the same trait)

may violate this model and affect the estimation of PP.H4. For the 4 prioritized genes, PP.H4 values were exceptionally high, suggesting that even if multiple signals exist, a shared variant is very likely. Nevertheless, future studies employing multi-signal colocalization methods (e.g., SuSiE-based coloc or fine-mapping approaches) could provide a more detailed dissection of loci with complex architecture. Finally, all genetic data used in this study are derived from individuals of European ancestry. While this homogeneity reduces confounding due to population stratification, it limits the generalizability of our findings to other ancestral groups. Future efforts to generate diverse ancestry GWAS for both traits are urgently needed to determine whether the shared immunogenetic architecture we identified is conserved across populations or represents population-specific effects.

Conclusions

In summary, this study provides the first single-cell-resolution atlas of putative shared immunogenetic drivers between migraine and MD as currently ascertained in large-scale genetic studies. We identify key genes with both concordant and discordant effects and reveal its biological complexity. The 4 genes (GTPBP4, CDC42, DCXR, SC5D) represent shared molecular hubs within a common neuro-immune pathway, with GTPBP4 potentially reflecting core pathway components that operate similarly across tissues, while CDC42, DCXR, and SC5D identify points of tissue-specific regulation. These findings elevate systemic and local immune dysregulation as a central component in the comorbidity of sensory system disorders and propose novel, genetically-informed targets for therapeutic development. The path from genetic target identification to clinical application will require selective inhibitor development, rigorous preclinical validation, and careful safety assessment.

Abbreviations

B IN	Immature B Cells
B MEM	Memory B Cells
CD4 ET	CD4 + Effector/Central Memory T cells
CD4 NC	CD4 Naïve/Central Memory T cells
CD4 SOX4	SOX4-expressing CD4 + T cells
CD8 ET	CD8 + Effector/Central Memory T cells
CD8 NC	CD8 Naïve/Central Memory T cells
CD8 S100B	S100B-expressing CD8 + T cells
CDC42	Cell Division Cycle 42
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
cis-eQTL	cis-expression Quantitative Trait Loci
DC	Dendritic Cells
DCXR	Dicarbonyl and L-Xylulose Reductase
FDR	False Discovery Rate
GTPBP4	GTP Binding Protein 4
GWAS	Genome Wide Association Studies
IVs	Instrumental Variables
IVW	Inverse-Variance Weighted
LD	Linkage Disequilibrium
LDSC	Linkage Disequilibrium Score Regression
MD	Meniere's disease
Mono C	Classical Monocytes
Mono NC	Non-Classical Monocytes
MR	Mendelian Randomization
NK	Natural Killer Cells
NK R	NK Recruiting Cells
PBMCs	Peripheral Blood Mononuclear Cells
PP	Posterior Probabilities
SC5D	Sterol-C5-Desaturase
sc-eQTL	Single Cell-expression Quantitative Trait Loci
scRNA-seq	Single Cell RNA-sequencing
SNPs	Single Nucleotide Polymorphisms
VM	Vestibular Migraine

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

X.H., Y.W. and S.Y. supported the conception and design of this project, X.H. and C.P. acquired and analyzed the data, B.L., S.J. and S.C. contributed to data quality control, X.H. and Y.H. produced the first draft. All authors contributed intellectual content to the revised manuscript and have read and approved the final manuscript.

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Data availability

Data are available in a public, open access repository. We downloaded data from the IEU OPEN GWAS (https://gwas.mrcieu.ac.uk/), DrugBank (https://go.drugbank.com/), Drug-Gene Interaction Database (https://dgidb.org/) and the AstraZeneca PheWAS Portal (https://azphewas.com/).

Code availability

The R code used for the analyses in this study is available from the corresponding author upon reasonable request.

Declarations

Ethical approval

No need for ethical approval as used of anonymous open data.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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