Vestibular migraine as a vestibulo-trigeminal interface phenotype: a triangulation study across genetics, peripheral multiomics and human cell atlases

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Abstract

Background

Vestibular migraine (VM) is clinically established, but the biological problem is narrower and harder: whether VM has its own causal architecture or instead reflects migraine liability that is preferentially expressed through vestibular systems. We tested the latter possibility by asking whether migraine-vertigo overlap converges on vestibular and trigeminal programs.

Methods

We used four evidence layers: population-scale migraine-related and vertigo-related GWAS summary statistics, with FinnGen as the primary backbone; an independent external vertigo GWAS meta-analysis for supportive anchoring; disease-labeled peripheral blood transcriptomic and multiomic datasets spanning VM, migraine, Meniere disease, and healthy controls; and human trigeminal ganglion and vestibular or inner-ear single-cell atlases for biological localization. We quantified genome-wide and local migraine-vertigo overlap, prioritized shared-liability loci and genes, and then asked whether downstream layers supported the same signal.

Results

Migraine-related and vertigo-related phenotypes showed strong genome-wide genetic correlation, including overall migraine versus vertigo ($rg = 0.5277$, $SE = 0.0525$, $p = 9.18 \times 10^{-24}$), migraine with aura versus vertigo ($rg = 0.5698$, $SE = 0.0734$, $p = 8.61 \times 10^{-15}$), and migraine without aura versus vertigo ($rg = 0.4710$, $SE = 0.0615$, $p = 1.90 \times 10^{-14}$). Local analyses identified 8 shared blocks, and shared-liability prioritization yielded 204 candidate loci. Of these, 133 were matched in an independent external vertigo GWAS, 19 showed nominal support, and 71.3% were directionally concordant. Cross-layer integration converged on six prioritized genes, including five higher-confidence candidates. Representative locus-level reinforcement highlighted ARMC9 and TECTA, with ARMC9 showing the more stable cross-layer profile through nominal external support and vestibulo-trigeminal localization. Cell-atlas summaries supported a vestibulo-trigeminal landing pattern, whereas peripheral blood datasets were only partially informative and did not provide exclusive support.

Conclusions

The data do not justify claiming a VM-specific causal architecture. However, they do support a narrower interpretation: VM is more plausibly read as a vestibulo-trigeminal interface phenotype arising from shared migraine liability than as a wholly separate disease entity. That framework is useful precisely because clinically adjudicated population-scale VM data remain limited.

Background

Vestibular migraine (VM) is one of the most common causes of recurrent episodic vertigo in neurological and vestibular practice [1–2]. Updated diagnostic criteria have made the syndrome more reproducible across studies and clinics [1, 3]. Recent clinical work has described meaningful heterogeneity within that framework [4]. The central question is therefore no longer whether VM can be recognized clinically, but what kind of biological entity it represents: a distinct disorder, or a vestibularly weighted expression of migraine susceptibility [5–6].

That distinction matters because it determines what should count as informative evidence. If VM mainly reflects migraine biology expressed through vestibular systems, then shared liability and biologic localization should carry more weight than any single peripheral signature [7–8]. If VM is biologically separable from migraine, one would expect clearer divergence. The current evidence base is uneven: migraine is now increasingly tractable as a disorder of sensory-network susceptibility [9–10], with population-scale genetics and downstream interpretation advancing rapidly [11–14], whereas rigorously adjudicated vestibular phenotypes remain relatively scarce and are often absorbed into broader vertigo or comorbidity categories [5, 13].

That imbalance makes a direct disease-specific inference difficult, but not impossible. Rather than asking for a population GWAS of strictly adjudicated VM that does not yet exist, one can ask whether the component shared by migraine-related and vertigo-related phenotypes carries a biologic signature relevant to VM. That is a narrower claim, but it is also the claim the currently available data can actually test.

Open-data resources now make that narrower question tractable. Population-scale migraine and vertigo GWAS allow formal cross-trait analysis [15–17], and established methods can quantify overlap both genome-wide and regionally [18–19]. Disease-labeled peripheral datasets address a different issue: whether programs derived from shared liability show a directionally compatible pattern in clinically annotated VM, migraine, and Meniere disease samples [20–22]. Trigeminal ganglion and vestibular or inner-ear cell atlases answer yet another question:where such signals land biologically, and are therefore more informative for localization than blood alone [23–24].

We therefore did not use this study to mimic a de novo GWAS of clinically adjudicated VM [25–26]. Instead, we asked whether the overlap between migraine-related and vertigo-related population phenotypes defines a signal that remains coherent across downstream layers and localizes to biologically plausible vestibular and trigeminal programs.

That is a deliberately constrained question. Under this framework, support for a VM-relevant model depends on convergence across evidence layers: population-scale overlap, regional concordance, locus prioritization, atlas localization, and only limited but directionally compatible support in peripheral disease-labeled data, rather than on any single dataset.

Methods

Study design and inferential framework

The study combined four evidence layers that answer different parts of the same question: population-scale genetics, external vertigo data, disease-labeled peripheral blood datasets, and atlas-based localization. The point was not redundancy. Each layer is informative for a different reason and vulnerable to a different bias. Following triangulation principles, we treated agreement across these layers as more persuasive than a signal seen in only one of them [25-26]. The study was therefore designed for biological interpretation of VM, not for direct genome-wide discovery of clinically adjudicated VM.

Data sources and prespecified analytic roles

FinnGen provided the main discovery layer for migraine-related and vertigo-related phenotypes [15]. Independent vertigo GWAS datasets were used only as an external anchoring layer [16-17]. Disease-labeled support came from publicly available PBMC multiomic datasets spanning VM, migraine, Meniere disease, and healthy controls, supplemented by bulk PBMC transcriptomic context from Meniere disease [20,22]. Biological localization relied on trigeminal ganglion and vestibular or inner-ear single-cell atlases [23-24], with GTEx used only for tissue-expression context [27]. These roles were fixed in advance as discovery, anchoring, disease-relevance support, tissue-context support, or localization (Supplementary Tables S1-S3).

Phenotype definition and VM-like shared liability

Because no widely available population-scale GWAS yet captures rigorously adjudicated VM, we did not treat VM as a directly measured discovery phenotype. Instead, we defined VM-like shared liability as the latent component jointly indexed by migraine-related and vertigo-related population phenotypes. That definition is intentionally narrower than disease identity, but it matches what the available data can support.

GWAS harmonization and quality control

Before analysis, all summary statistics were brought into a common format. This involved harmonizing column structure, aligning genome builds where needed, applying quality-control filters, excluding problematic strand-ambiguous variants, and deriving a shared high-quality SNP set for cross-trait analyses.

Genome-wide and local cross-trait analyses

The genetic layer included SNP-based heritability, genome-wide cross-trait genetic correlation, local overlap analysis, and shared-liability modeling [18-19]. We treated both genome-wide and regional overlap as evidence of shared liability, not as proof that migraine and vertigo define the same disease. The inferential boundaries for those claims are listed in Supplementary Table S2, and the compact discovery-layer summary is given in Supplementary Table S4.

Cross-layer gene prioritization and evidence integration

We prioritized loci by asking which signals survived contact with more than one layer: discovery strength, external lookup support, localization, and peripheral disease relevance. A prespecified evidence matrix then separated higher-confidence from lower-confidence candidates, and manuscript-level claims were restricted to genes supported across discovery, anchoring, and localization layers (Supplementary Tables S2 and S5).

Representative locus-level reinforcement analyses

To see how the shared-liability framework reads at the locus level, we examined two representative higher-confidence loci: TECTA (SHARED_L1/rs11172113) and ARMC9 (SHARED_L2/rs56304645). They were chosen as exemplars, not as the only loci of interest. For each locus, we considered the shared-liability statistics, external lookup results, approximate Wakefield ABF credible sets [28],

integrated evidence matrices, and atlas-based localization summaries. When a locus was absent from the precomputed local-overlap block table, local cross-trait coherence was recalculated directly within the prespecified locus window.

Peripheral disease-labeled validation

Peripheral blood bulk summaries and donor-level single-cell summaries were used to ask a limited question: whether liability-derived candidate programs showed the same directional pattern in disease-labeled samples [20,22]. We did not treat blood as a localization layer, because neither blood expression nor blood-based regulatory signal can establish vestibular tissue origin.

Cell-atlas localization analyses

Trigeminal ganglion and vestibular or inner-ear single-cell atlases were used to place candidate programs in plausible cell compartments [23-24,29]. We treated these atlas signals as localization, not as proof that any single cell type is uniquely causal.

Interpretive boundaries

Three boundaries were set in advance. First, the study addresses biological interpretation of VM rather than disease-specific discovery. Second, the external vertigo dataset functions as anchoring support, not formal replication. Third, peripheral blood data are supportive and non-exclusive, whereas the main inferential weight rests on population-genetic overlap and atlas-based localization. The overall design and evidentiary hierarchy are summarized in Fig. 1 and Table 1.

Figure 1. Study design and inferential framework. The analysis integrated four evidence layers: population-scale genetics, external vertigo anchoring, disease-labeled peripheral blood data, and atlas-based localization. These layers were interpreted jointly rather than treated as interchangeable evidence for vestibular migraine.

Table 1. Overview of datasets and analytical layers used in the study..

Data layer	Dataset / source	Disease or trait domain	Sample type	Ancestry / population	Sample size	Case definition / phenotype granularity	Primary in this s
Population genetics	FinnGen migraine / vertigo GWAS outputs	Migraine + vertigo-related traits	GWAS summary statistics	European ancestry	3 trait pairs; 8 shared blocks; 204 loci; 3 formal rg estimates	Population-scale registry endpoints	Primary shared-liability discove backbo
External anchoring	Independent vertigo GWAS meta-analysis	Vertigo	GWAS summary statistics	European ancestry	204 queried loci	Meta-analytic broad vertigo phenotype	Externa replicat anchori
Candidate prioritization	candidate_genes_final.csv	Final candidate genes	Gene list	Not applicable	6	Final downstream candidate set	Downst prioriti summa
Expression support	summary_gtex_expression.csv	Candidate gene expression	GTEx summary table	Public reference	6	Per-gene max/mean median TPM summary	Auxiliar tissue-express support
Disease-labeled validation	summary_bulk_module_scores.csv	VM / MD / HC	PBMC bulk module summary	Clinically labeled samples	41 labeled samples	Group-labeled summary file	Bulk validati layer
Disease-labeled validation	summary_scrna_module_scores.csv	VM / MI / MD / HC	PBMC donor-level scRNA module summary	Clinically labeled samples	23	Donor-level mean module score + cell counts	Single-c disease relevan validati
Cell atlas localization	summary_trigeminal_localization.csv	Trigeminal compartment	Module-level atlas summary	Human atlas summary	38028	Neuron vs non-neuron compartments	Trigemi landing localiza
Cell atlas localization	summary_vestibular_localization.csv	Vestibular compartment	Module-level atlas summary	Human atlas summary	23792	Adult vs fetal compartments	Vestibu landing localiza

Abbreviations: VM, vestibular migraine; MI, migraine; MD, Meniere disease; HC, healthy controls; PBMC, peripheral blood mononuclear cell; GWAS, genome-wide association study.

Footnote: Each dataset was used for a distinct analytic purpose and was not interpreted as interchangeable evidence.

Large language model assistance was used only during manuscript preparation for language editing, structural revision, and formatting support under author supervision. It was not used for data analysis, result generation, or scientific decision-making. The authors reviewed all outputs and take full responsibility for the manuscript.

Results

Migraine and vertigo share robust but incomplete genetic architecture

Formal LDSC analyses [18-19] showed strong genome-wide genetic correlation between migraine-related and vertigo-related phenotypes. The signal was present for overall migraine versus vertigo (rg = 0.5277, SE = 0.0525, z = 10.0501, p = 9.18 × 10^-24), migraine with aura versus vertigo (rg = 0.5698, SE = 0.0734, z = 7.7582, p = 8.61 × 10^-15), and migraine without aura versus vertigo (rg = 0.4710, SE = 0.0615, z = 7.6574, p = 1.90 × 10^-14). The overlap is therefore substantial but not complete, and it is not confined to the aura subtype. Local analyses identified 8 shared migraine-vertigo blocks, and shared-liability prioritization advanced 204 candidate loci for downstream review (Supplementary Table S4).

Shared-liability prioritization defines a compact candidate space

Cross-layer prioritization contracted the signal to six genes - OTOG, OTOGL, TECTA, OTOP1, ARMC9, and ZNF91. That small final set matters: the signal did not dissolve into a long tail of weak candidates, but remained compact enough to read against external and localization evidence. Final confidence classes are listed in Supplementary Table S5.

External anchoring supports generalizability without implying strict replication

External lookup recovered a meaningful subset of the discovery signal. Of the 204 shared candidate loci, 133 were matched in the independent external vertigo GWAS, 19 showed nominal support, and 92 of 129 evaluable loci were directionally concordant. This is not one-to-one replication, nor is it meant to be. However, it argue against the shared signal being unique to the FinnGen discovery layer (Supplementary Table S4). Genome-wide and local shared architecture are shown in Fig. 2, and the top shared-liability loci are listed in Table 2.

Figure 2. Shared genetic architecture of migraine and vertigo. (A) Forest plot of genome-wide rg estimates. (B) Local shared blocks; bubble size reflects the number of overlapping variants and color indicates sign concordance. (C) Top shared-liability loci with external lookup support.

Table 2. Top shared-liability loci with external vertigo support.

Locus ID	Lead variant	Chr:Pos	Shared P	Support n	Sign conc.	Ext. P	External support
SHARED_L1	rs11172113	12:57133500	6.31e-11	32	1.00	3.95e-01	Matched, concordant
SHARED_L2	rs56304645	1:3168622	1.86e-10	48	1.00	3.75e-05	Nominal, concordant
SHARED_L3	rs6601512	8:10728086	9.20e-10	358	1.00	2.66e-01	Matched, concordant
SHARED_L4	rs146245458	1:184357670	3.36e-09	7	1.00	3.69e-01	Matched, concordant
SHARED_L5	rs12642146	4:130747169	2.09e-08	4	1.00	NA	Not found
SHARED_L6	rs11190975	10:101376997	2.58e-08	42	1.00	2.92e-03	Nominal, concordant
SHARED_L7	rs73576816	13:113022566	3.14e-08	3	1.00	9.67e-01	Matched, concordant
SHARED_L8	rs9653353	2:220237061	3.25e-08	160	1.00	7.24e-02	Matched, concordant
SHARED_L9	rs10929971	2:160121855	4.16e-08	2	1.00	5.75e-01	Matched, discordant
SHARED_L10	rs72829857	6:16965821	4.32e-08	25	1.00	7.02e-01	Matched, concordant

Footnote: Shared P values are Stouffer-combined statistics from the shared-liability table. External support refers to lookup in the independent external vertigo GWAS and is used here as anchoring rather than formal replication.

Representative loci show differential cross-layer stability

Both TECTA and ARMC9 remained credible once local coherence, external lookup, approximate fine-mapping, and atlas-based localization were considered together. For TECTA, shared-liability support was strong (Stouffer p = 6.31 × 10^-11; 32 supporting variants), with 15,093 overlapping variants, a positive block z-correlation of 14.102, and sign concordance of 0.554 after recomputation within the locus window. External support was directionally concordant but not nominally significant (p = 0.395). ARMC9 showed similarly strong shared-liability support (Stouffer p = 1.86 × 10^-10; 48 supporting variants), with 18,561 overlapping variants, a block z-correlation of 5.825, and sign concordance of 0.537. Unlike TECTA, ARMC9 also showed nominal external support (p = 3.75 × 10^-5) together with adult-weighted vestibular localization and stronger trigeminal neuronal localization within the atlas framework [24,29]. The credible sets remained broad at both loci, so the signal is regional rather than fine-mapped to a single causal variant [28]. Representative locus-level follow-up is shown in Fig. 3.

Figure 3. Representative loci in cross-layer follow-up. (A) Shared-liability signal versus external anchoring. (B) Local coherence within each locus window. (C) Credible-set sizes on a log scale. (D) Localization across trigeminal and vestibular contexts.

Cell-atlas localization supports a distributed vestibulo-trigeminal landing pattern

At module level, the trigeminal atlas shifted toward the neuronal compartment (module z = 0.471) relative to the non-neuronal compartment (module z = -0.471), based on 3,873 neuronal and 34,155 non-neuronal cells [24,29]. The vestibular atlas likewise favored the adult compartment (module z = 0.236; 3,348 cells) over the fetal compartment (module z = -0.236; 20,444 cells) [23]. These

summaries do not resolve fine subclusters. They place the shared signal on a distributed vestibulo-trigeminal axis rather than in a single exclusive cell state. Localization summaries are presented in Table 3, and cross-layer gene-level integration is illustrated in Fig. 4.

Table 3. Localization summary of the prioritized candidate module in trigeminal and vestibular atlases.

Compartment	Atlas / dataset	Cell type / cell state	Enrichment statistic	Adjusted P / FDR	Leading genes	Linked biological interpretation	Cross-atlas consistency
Trigeminal	summary_trigeminal_localization.csv	Neuron	0.471	Not provided	OTOG, OTOGL, TECTA, OTOP1	Positive neuronal shift of candidate module	High
Trigeminal	summary_trigeminal_localization.csv	Non-neuron	-0.471	Not provided	ARMC9, ZNF91	Reference negative compartment shift	Supportive
Vestibular	summary_vestibular_localization.csv	Adult	0.236	Not provided	OTOG, OTOGL, TECTA, OTOP1	Adult-weighted vestibular localization signal	High
Vestibular	summary_vestibular_localization.csv	Fetal	-0.236	Not provided	ARMC9, ZNF91	Relative negative developmental compartment shift	Supportive

Footnote: These enrichment summaries indicate where the candidate program tends to localize; they do not identify an exclusive disease cell type.

Figure 4. Cross-layer evidence for the six prioritized genes. (A) Integrated evidence matrix with raw values overlaid. (B) Trigeminal-versus-vestibular weighting. (C) GTEx expression support plotted against the stronger localization value.

Peripheral blood datasets provide limited but directionally compatible disease-relevance support

The bulk PBMC summary, derived from a disease-labeled PBMC expression dataset, was uninformative in the current version because all candidate module-score values were missing [22]. In donor-level PBMC single-cell summaries, VM donors (n = 5) showed the least negative mean module score (-0.0195, SD 0.0374), followed by healthy controls (n = 5, mean -0.0336, SD 0.0384), Meniere disease (n = 8, mean -0.0501, SD 0.0205), and migraine (n = 5, mean -0.0597, SD 0.0060) [20]. The largest numerical contrast was VM versus migraine. Smaller differences separated VM from Meniere disease and healthy controls. None of the exploratory Welch tests reached conventional significance, and cell-count-weighted means preserved the same rank order. This layer therefore provides directional context, not decisive evidence, which is why blood signals are interpreted here as disease relevance rather than tissue localization [20,30]. Peripheral-layer summaries are shown in Fig. 5.

Figure 5. Peripheral disease-labeled validation. (A) Unweighted donor means with SD bars. (B) Cell-count weighting preserves the same rank order. The peripheral layer was directionally consistent but limited.

Integrated evidence supports a biologically interpretable VM framework

Cross-layer integration left six prioritized genes. Five met higher-confidence criteria (ARMC9, OTOG, OTOGL, TECTA, and ZNF91), and one met moderate-confidence criteria (OTOP1). Several of these genes, especially OTOG, OTOGL, and OTOP1, already have links to inner-ear support or interface biology [31-33]. TECTA remains more closely anchored to cochlear extracellular-matrix biology than to VM-specific biology [34]. Read together, the set fits preferential vestibular landing of shared migraine liability better than a purely peripheral vestibular disorder [8,35]. Across layers, the discovery-to-integration chain comprised three formal migraine-vertigo genetic correlation estimates, eight local overlap blocks, 204 shared candidate loci, external lookup support for 133 loci, and a final six-gene prioritized set. The final integrated evidence matrix is presented in Table 4.

Table 4. Integrated evidence matrix for the six prioritized vestibular migraine genes.

Gene	GTEx max TPM	Trigeminal localization	Vestibular localization	scRNA donor means	Support score	Level	Interpretation
ZNF91	12.879	neuron (1.152)	Adult (1.404)	VM -0.020; HC -0.034; MI -0.060; MD -0.050	4	High	Prioritized VM interface candidate
ARMC9	7.927	neuron (0.436)	Adult (0.852)	VM -0.020; HC -0.034; MI -0.060; MD -0.050	4	High	Prioritized VM interface candidate
TECTA	3.401	neuron (0.072)	Fetal (0.400)	VM -0.020; HC -0.034; MI -0.060; MD -0.050	4	High	Prioritized VM interface candidate
OTOGL	1.236	neuron (0.018)	Adult (4.414)	VM -0.020; HC -0.034; MI -0.060; MD -0.050	4	High	Prioritized VM interface candidate
OTOG	0.056	non.neuron (0.005)	Adult (4.982)	VM -0.020; HC -0.034; MI -0.060; MD -0.050	4	High	Prioritized VM interface candidate
OTOP1	0.000	neuron (0.002)	Fetal (0.028)	VM -0.020; HC -0.034; MI -0.060; MD -0.050	2	Moderate	Needs added functional support

Footnote: Blood-based findings were used as disease-relevance context, not as evidence of tissue origin or a vestibular migraine-specific biomarker. Confidence levels summarize cross-layer integration and are reported in the main text as higher or moderate confidence.

Discussion

The main result is not that vestibular migraine (VM) has now been genetically isolated as a separate disorder. It is that VM becomes biologically more intelligible when read as migraine liability expressed through vestibular and trigeminal systems. That interpretation fits the present data better than either a loose coexistence of migraine and dizziness or a sharply separate disease category [5,8,38]. Clinically, VM is now defined more consistently [1], increasingly characterized [5-6,36], and still marked by care gaps [37]. However, it remains under-resolved biologically.

That distinction matters because it changes the evidentiary hierarchy. Once VM is framed as a vestibularly weighted form of migraine biology, shared liability and localization become more informative than any single peripheral signature. This is compatible with current headache research, which places migraine within distributed sensory processing and network-level susceptibility rather than within an isolated vascular or otologic mechanism [9-10,39]. Experimental and human VM data likewise point to trigemino-vestibular interactions [40-41], an interpretation also reflected in recent pathophysiologic reviews [8,35].

The genetic results fit that model, but they should be read with discipline. The rg estimates are too strong to dismiss as incidental comorbidity, and the shared local blocks argue against pure background polygenicity [15,18-19]. At the same time, the discovery layer was built from broad vertigo phenotypes rather than rigorously adjudicated VM [5-6,8]. What this supports is VM-relevant shared architecture; what it does not support is disease-specific genetic identification of VM. These analyses also sit within a broader shift in migraine genetics from locus cataloguing toward biologic interpretation [11-12,14].

The representative loci make that boundary tangible. OTOG, OTOGL, and OTOP1 already point toward inner-ear or vestibular-facing biology [31-33], which makes them plausible candidates within a preferential vestibular-landing model. TECTA remains biologically credible, but its strongest prior anchor is cochlear extracellular-matrix biology rather than VM itself [34]. ARMC9, in contrast, remained the more stable locus once external support and atlas-based localization were considered together. The broad credible sets at both loci therefore matter: they strengthen regional convergence, but they still stop short of a single causal variant [28].

The atlas layer helps narrow where the shared signal is likely to act. Trigeminal ganglion atlases place migraine-relevant programs across both neuronal and non-neuronal compartments [24,29], while inner-ear single-cell resources distinguish adult vestibular localization from broader developmental signal [23]. Read together, our summaries fit a distributed vestibulo-trigeminal landing pattern rather than a single exclusive cell state. That reading also aligns with current VM syntheses [35] and with recent neuroimaging work suggesting altered multisensory network organization rather than a solitary focal lesion [41].

The blood-based results are weaker and should remain weaker in the argument. Peripheral transcriptomic and multiomic studies can register disease-relevant immune signals in VM, Meniere disease, and migraine [20-22,30], but they cannot localize biology to the tissue or circuit level [30]. In our data, VM showed numerically higher module scores than migraine and Meniere disease in donor-level single-cell summaries, yet donor numbers were small and the bulk PBMC layer was uninformative in the current version [20]. We therefore treat the peripheral layer as supportive context, not as a defining signal.

The dominant limitation is the phenotype available at discovery scale. We inferred a VM-relevant signal from migraine-related and broad vertigo-related phenotypes because no widely available population GWAS yet captures strictly adjudicated VM. That makes the external vertigo dataset an anchoring layer rather than definitive replication [16-17]. It also means that the atlas and blood-based layers, though useful, remain thinner than the genetic discovery layer [20,23-24]. Finally, several prioritized genes point toward vestibular-facing biology, but the present design cannot resolve whether those programs operate peripherally, centrally, or at the

interface between the two [8,35,40]. Colocalization, SMR, and finer causal mapping would substantially sharpen that question [11,14,28].

The conclusion should therefore stay narrow. We are not arguing that VM has already been isolated as a separate molecular entity. We are arguing that the available data fit better with a vestibulo-trigeminal interface phenotype, in which shared migraine liability is preferentially expressed through vestibularly relevant programs and only partly echoed in peripheral disease-labeled data [8,35,38]. The conceptual model is summarized in Fig. 6

Conclusion

These data do not isolate vestibular migraine as a separate molecular disorder. They instead support treating VM as a biologically coherent interface phenotype, in which shared migraine liability is preferentially expressed through vestibulo-trigeminal programs. Integrating population genetics, external vertigo data, disease-labeled peripheral datasets, and cell-atlas localization sharpens that interpretation while keeping clear limits on phenotype breadth, validation depth, and causal resolution.

Abbreviations

ABF, approximate Bayes factor; GTEx, Genotype-Tissue Expression; GWAS, genome-wide association study; HC, healthy controls; LD, linkage disequilibrium; LDSC, LD score regression; MD, Meniere disease; MI, migraine; PBMC, peripheral blood mononuclear cell; SNP, single nucleotide polymorphism; VM, vestibular migraine.

Declarations

Ethics approval and consent to participate

This study used only publicly available, de-identified summary statistics and publicly accessible transcriptomic, multiomic, and atlas-level datasets. No new human participants were recruited and no identifiable individual-level data were collected. Institutional ethics approval was therefore not required under local policy.

Consent for publication

Not applicable.

Availability of data and materials

All public datasets analysed in this study are identified with repositories, accession identifiers, releases, and access dates in Supplementary Table S1. These include FinnGen release 12 summary statistics and endpoint-definition resources, GWAS Catalog study GCST90085927, GEO series GSE109558, GSE269117, GSE269114, GSE197289, and GSE213796, and GTEx portal resources. Processed summary outputs generated during the current study are available from the corresponding author on reasonable request.

Code availability

Scripts used for summary-statistic harmonization, shared-liability prioritization, locus-level reinforcement, cross-layer integration, and figure generation are available from the corresponding author on reasonable request during peer review and after publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

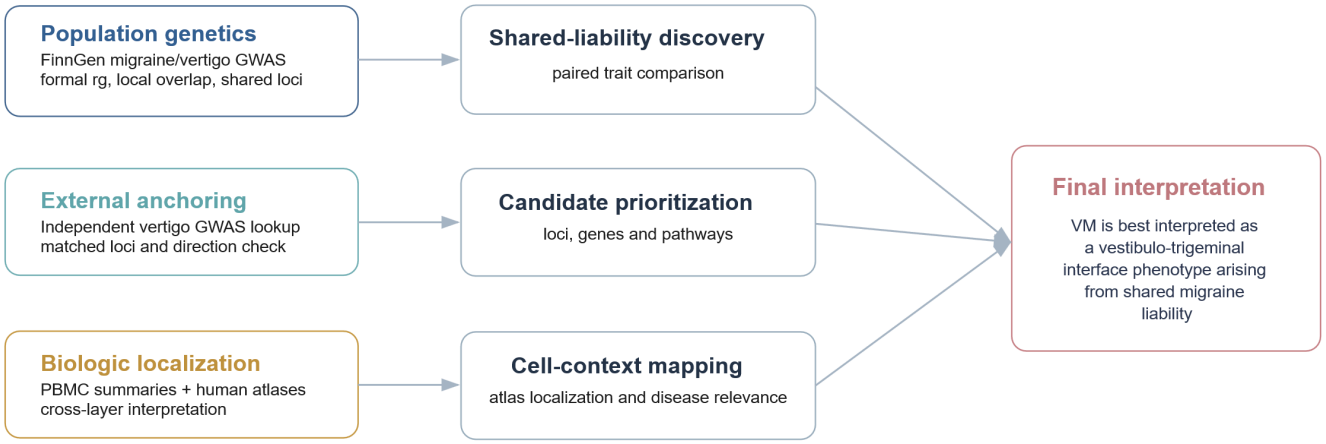

Figure 1

Study design and inferential framework. The analysis integrated four evidence layers: population-scale genetics, external vertigo anchoring, disease-labeled peripheral blood data, and atlas-based localization. These layers were interpreted jointly rather than treated

as interchangeable evidence for vestibular migraine.

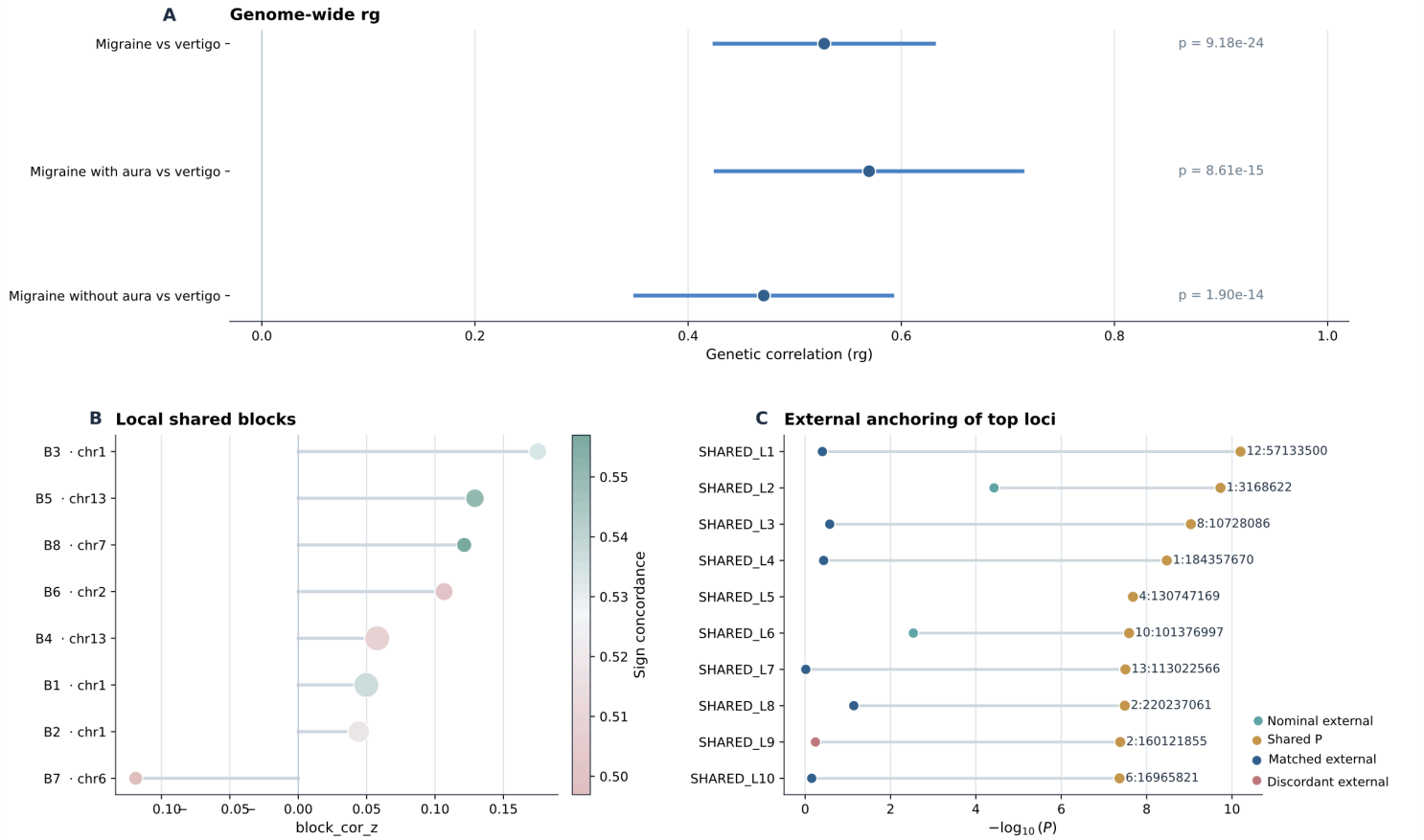

Figure 2

Shared genetic architecture of migraine and vertigo. (A) Forest plot of genome-wide rg estimates. (B) Local shared blocks; bubble size reflects the number of overlapping variants and color indicates sign concordance. (C) Top shared-liability loci with external lookup support.

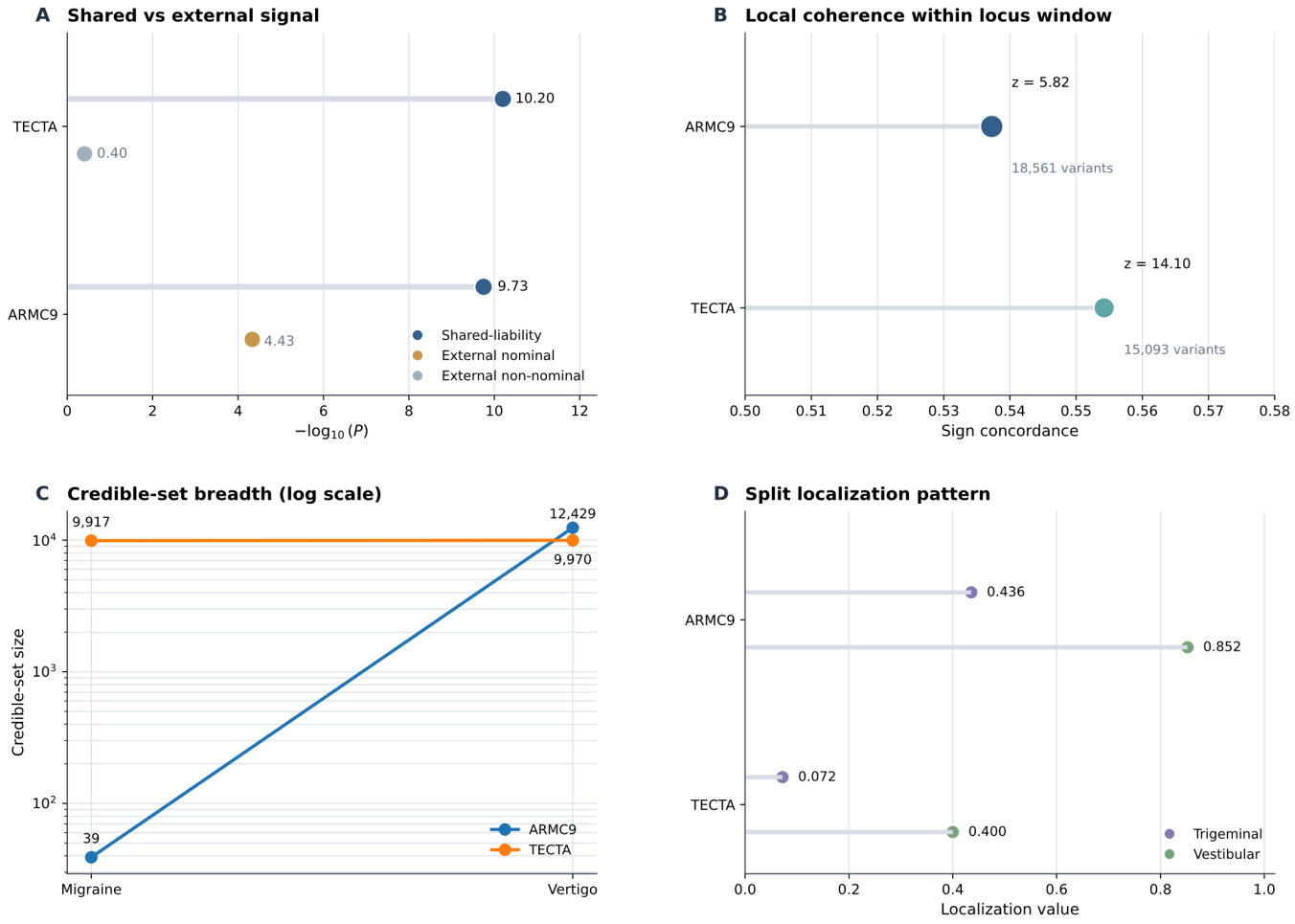

Figure 3

Representative loci in cross-layer follow-up. (A) Shared-liability signal versus external anchoring. (B) Local coherence within each locus window. (C) Credible-set sizes on a log scale. (D) Localization across trigeminal and vestibular contexts.

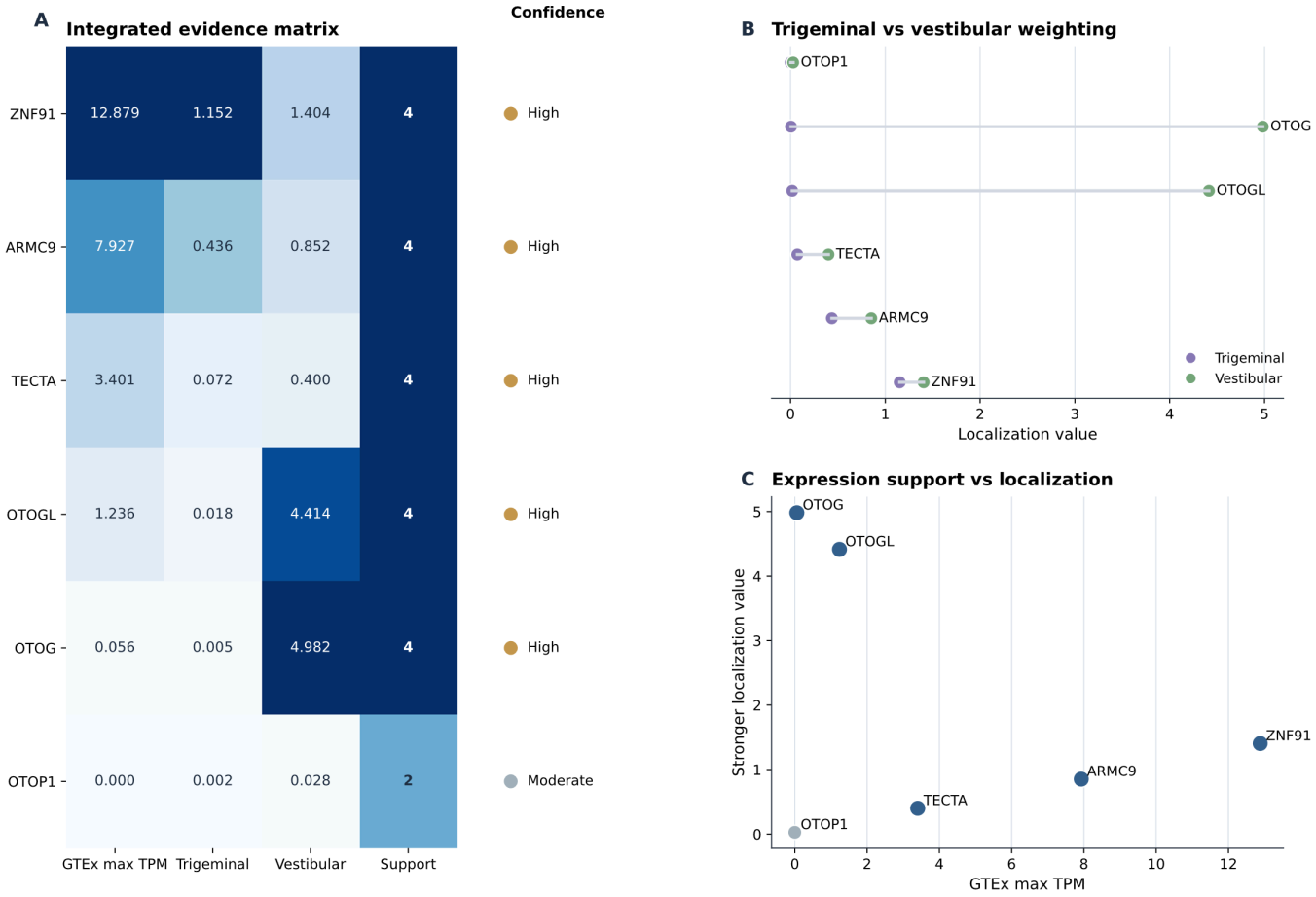

Figure 4

Cross-layer evidence for the six prioritized genes. (A) Integrated evidence matrix with raw values overlaid. (B) Trigeminal-versus-vestibular weighting. (C) GTEx expression support plotted against the stronger localization value.

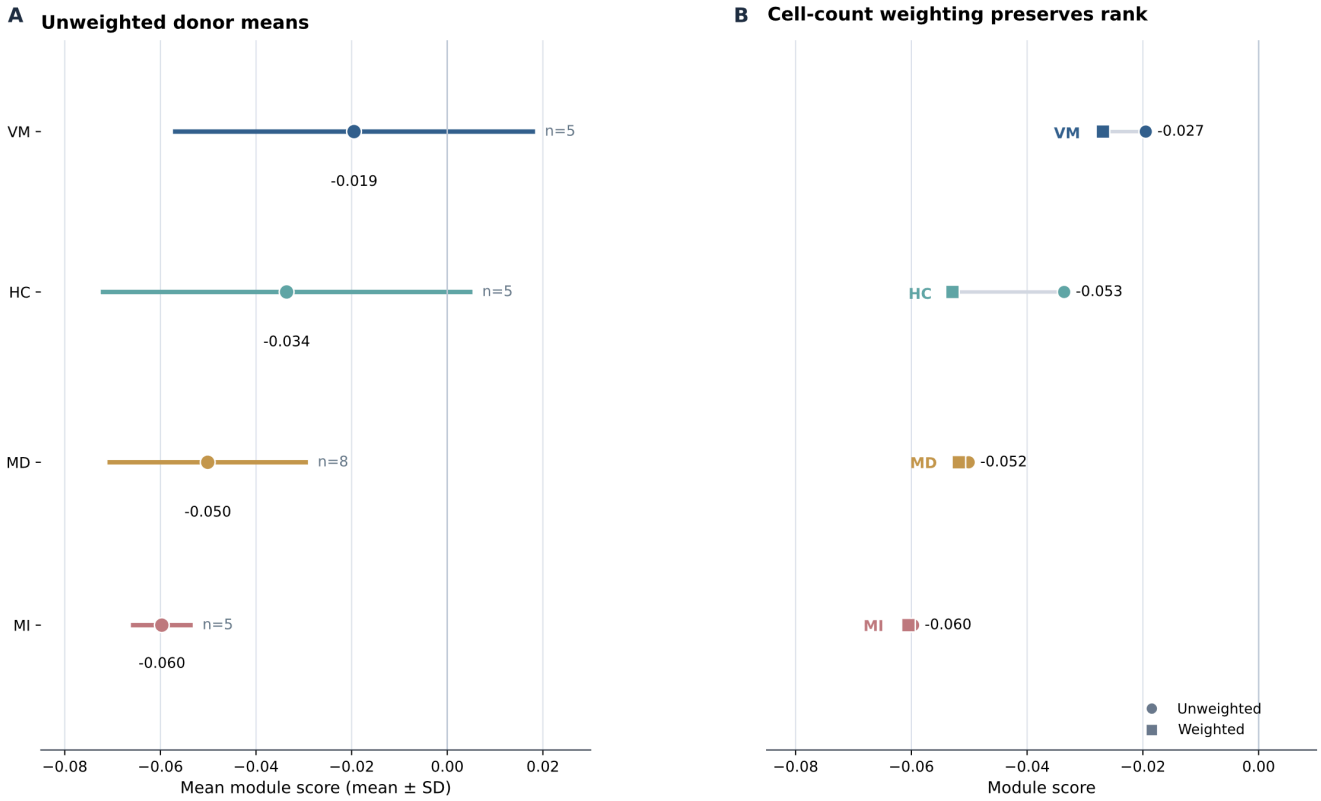

Figure 5

Peripheral disease-labeled validation. (A) Unweighted donor means with SD bars. (B) Cell-count weighting preserves the same rank order. The peripheral layer was directionally consistent but limited.

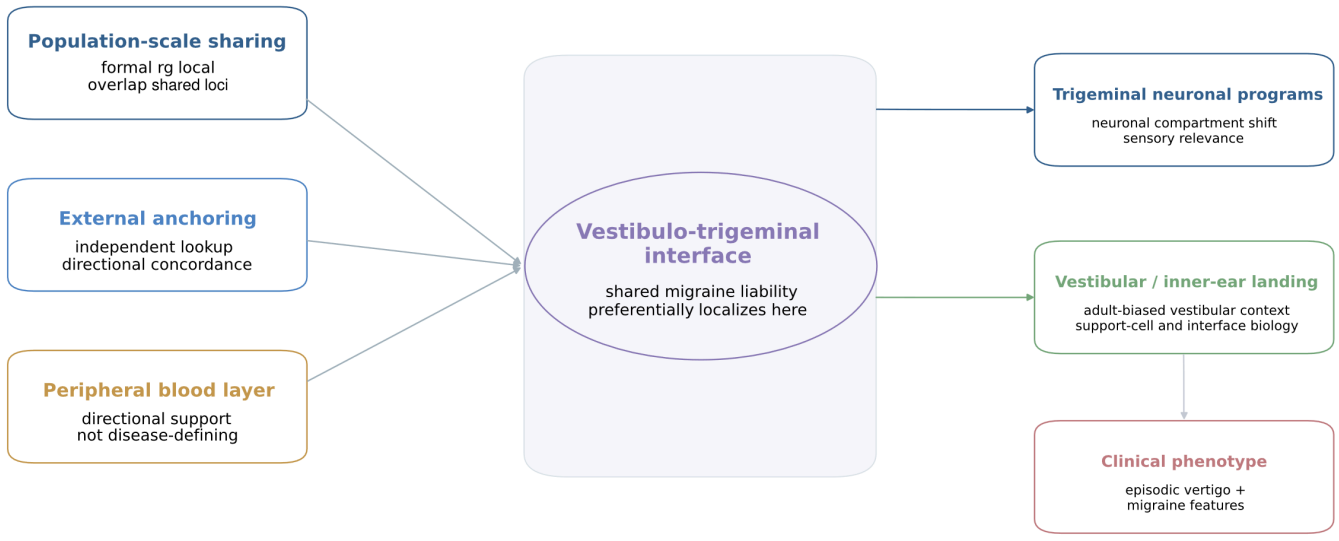

Figure 6

Conceptual synthesis. Shared migraine liability is proposed to express preferentially through vestibular and trigeminal programs, giving rise to a clinically recognizable vestibular migraine phenotype.

Supplementary Files

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