COMPUTATIONAL TARGET PROFILE

TMEM43

A Three-Disease Membrane Protein, Characterised Without An Experimental Structure

LUMA — behind a lethal cardiomyopathy, and two more Mendelian diseases. A structureless inner-nuclear-membrane protein — resolved into a topology, a **disease-variant structural map**, and a predicted pocket.

UniProt Q9BTV4 · 400 aa · Multi-pass membrane · IDG tier: T_{bio} · PDB: none · July 2026

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At A Glance

Topology	Multi-pass membrane protein (p=1.00): **four transmembrane helices** with a large (~260-residue) perinuclear-space domain; likely **homo-oligomeric** (p=0.99).
Disease Map	**Three Mendelian diseases, mapped.** **S358L** (lethal cardiomyopathy, ARVC5) sits in TM3; the Emery-Dreifuss variants in the luminal domain; the auditory-neuropathy truncation at the C-terminal helix.
Predicted Pocket	**Pocket in the luminal domain (0.74).** A residue-level cavity (~124–167) in the large perinuclear-space region — a candidate ligand / interaction site.
Function	Non-enzyme (p=1.00); a *proposed* pH-sensing cation channel (preprint only [6]) — treat as a hypothesis.
Clean Signal	Low disorder (~10%); no amyloid signal.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. Astra returns a coherent multi-pass topology and a luminal-domain pocket (amber) for a protein with no experimental structure — the platform on which the disease-variant map below is built.

1 The Gap

Few dark proteins carry a clinical burden like TMEM43. The single variant **p.Ser358Leu** causes **arrhythmogenic right-ventricular cardiomyopathy type 5 (ARVC5)** — a fully penetrant, lethal arrhythmia [3]. Other variants cause **Emery-Dreifuss muscular dystrophy** [4] and **autosomal-dominant auditory neuropathy (AUNA3)** [5]. TMEM43 (LUMA) is an inner-nuclear-membrane protein, and was recently *proposed* — in a preprint — to act as a pH-sensing cation channel [6]. Yet for all this clinical weight it has **no experimental structure in the PDB** and remains understudied at the molecular level (IDG T_{bio}) [2].

That combination — **three Mendelian diseases, near-zero structural information** — is exactly where prediction earns its keep: everything below is computed from the canonical 400-residue sequence and derived structural predictions, with no experimental TMEM43 structure used as input.

2 Topology And The Disease-Variant Map

Astra reads TMEM43 as a multi-pass membrane protein with an unusual layout: a short N-terminus, **one transmembrane helix, then a large (~260-residue) perinuclear-space domain**, and finally a cluster of **three more transmembrane helices** near the C-terminus. Placed on that map, the three disease variants fall on *different* structural elements — which is itself a mechanistic readout.

TOPOLOGY, DISEASE VARIANTS AND PREDICTED POCKET

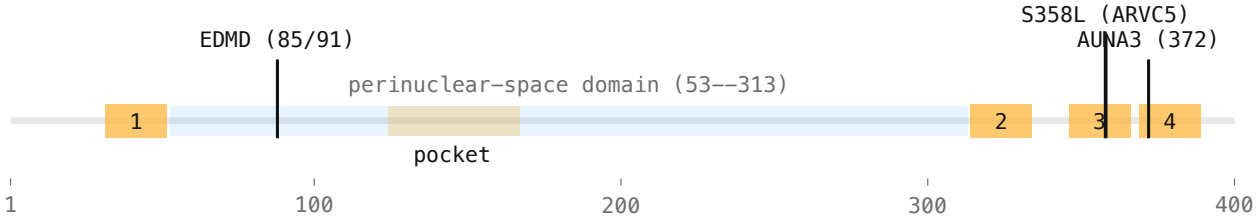

Figure 2. Topology and disease map. One N-terminal TM helix, a large perinuclear-space domain, then three C-terminal TM helices (amber). The lethal cardiomyopathy variant **S358L** lies in **TM3**; the Emery-Dreifuss variants (85/91) lie in the luminal domain; the auditory-neuropathy truncation begins at **TM4** (372). The predicted pocket (~124–167) sits within the luminal domain.

3 Reading The Variants Structurally

A structureless disease gene forces every genetics group to guess where its mutations act. Astra turns that into a ranked, testable set of hypotheses — one per variant.

DISEASE-VARIANT STRUCTURAL CONTEXT

S358L	TM3 (transmembrane)	Lethal ARVC5 [3]; a helix-packing / membrane-interface hypothesis
85 / 91	Perinuclear-space domain	EDMD [4]; perturbs partner localisation (oligomerisation largely retained)
Arg372*	TM4 / C-terminal helix	AUNA3 [5]; truncation with reduced protein stability
Pocket 124–167	Luminal domain	Predicted cavity (0.74); candidate ligand / interaction site

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of TMEM43 exists and is a useful input — but a model alone does not tell you which residues form a pocket, or place each clinical variant in its structural context. This profile is that annotation layer. As a control, the same predictors recover the known topology and pocket sites on membrane proteins whose structures *are* solved, so the TMEM43 calls are like-for-like predictions. The net effect: a lethal-disease gene with no structure becomes a **ranked, testable structural map**.

4 Post-Translational And Structural Features

Astra's supporting calls are consistent with a folded, oligomeric membrane protein:

- **Homo-oligomer (p=0.99).** TMEM43 is predicted to self-associate — consistent with reports that Emery-Dreifuss variants perturb its complexes and partner localisation [4].
- **Low disorder, no amyloid.** A well-folded protein (~10% disorder) — the luminal domain in particular is a coherent, foldable unit worth expressing on its own.
- **N-terminal acetylation.** A predicted co-translational modification consistent with a stable cytosolic/nuclear N-terminus.

5 Recommended Experimental Follow-Up

This turns a structureless disease gene into a ranked, executable plan: each prediction is paired with the experiment that would test it and the readout to watch for.

Prediction	Experiment	Readout
S358L in TM3	Membrane-insertion / oligomer assay, S358L vs WT	A structural mechanism for ARVC5
Luminal domain is foldable (53–313)	Express the luminal domain alone	A crystallisable / assayable fragment
Predicted pocket (124–167)	Fragment screen / docking at the pocket	A ligand or interaction hypothesis
Homo-oligomer	Cross-linking / native-PAGE ± disease variants	Oligomer state and its disruption
Proposed channel role [6]	Electrophysiology on purified protein	Confirm (or refute) channel activity

The lethal-cardiomyopathy variant [3] indicates where a structural mechanism would have the most clinical value.

6 Where This Fits In A Discovery Workflow

Team	What they get from this profile
Target biology / genetics	Structural context for each clinical variant
Structural biology	Predicted topology, a foldable luminal domain, and construct boundaries
Medicinal chemistry	Pocket residues for docking and ligand design
BD / platform evaluation	Evidence Orbion can prioritise dark targets quickly

7 Methods

All predictions were generated with Orbion's Astra suite from the canonical TMEM43 sequence (UniProt Q9BTV4 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [7] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [8] (modification sites) and **AstraBIND** [9] (binding pocket). Reported values are model outputs; model internals are out of scope. Confidence scores are model-estimated probabilities (0–1) that rank and gate each call — not calibrated rates of experimental success.

PREDICTION PROVENANCE

Target & input	TMEM43 · UniProt Q9BTV4, canonical isoform (400 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [7–9]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [9]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [7]–[9]

Scope And Limitations

- **Prediction, not experiment.** These are computational hypotheses to prioritise experiments — not a substitute for a structure or an assay. No result here has been validated in the wet lab.

- **The channel role is unproven.** TMEM43's proposed pH-sensing cation-channel activity rests on a single preprint [6]; the predicted pocket is in the luminal domain, not a demonstrated ion-conduction pore.
- **Variant interpretation.** The structural placements above are hypotheses for how each variant acts; the Emery-Dreifuss variants perturb localisation while oligomerisation is largely retained [4].

8 References

[1] UniProt Consortium. UniProtKB entry Q9BTV4 (TMEM43, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. TMEM43 target record — T_{bio}. pharos.nih.gov/targets/Q9BTV4.

[3] Merner N.D., Hodgkinson K.A., Haywood A.F.M., et al. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *Am. J. Hum. Genet.* **82**(4), 809–821 (2008). doi:10.1016/j.ajhg.2008.01.010.

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[5] Jang M.W., Oh D.-Y., Yi E., et al. A nonsense TMEM43 variant leads to disruption of connexin-linked function and autosomal dominant auditory neuropathy spectrum disorder. *Proc. Natl. Acad. Sci. USA* **118**(21), e2019681118 (2021). doi:10.1073/pnas.2019681118.

[6] Jang M.W., Kim H.M., Lee C.J., et al. Characterization of TMEM43 as a novel pH-sensing cation channel. *bioRxiv* 2022.11.08.515259 (2022; preprint). doi:10.1101/2022.11.08.515259.

[7] Bozkurt Ç., Vasilyeva A., Goteti A. AstraROLE2 & AstraSUIT2: Multi-Task Annotation Models for Functional Profiling of Proteins. *bioRxiv* 2025.06.21.660734 (2025). doi:10.1101/2025.06.21.660734.

[8] Bozkurt Ç., Vasilyeva A., Goteti A. AstraPTM2: A Context-Aware Transformer for Broad-Spectrum PTM Prediction. *bioRxiv* 2025.10.03.680341 (2025). doi:10.1101/2025.10.03.680341.

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