COMPUTATIONAL TARGET PROFILE

TMC7

A Dark Mechanosensory Channel, Characterised Without An Experimental Structure

The PIEZO2-tuning channel no one has solved. A structureless multi-pass TMC-family protein — Astra confirms the topology and predicts the **pore-lining cavity**, for a channel that sets the gain on touch and mechanical pain.

UniProt Q7Z402 · 723 aa · Multi-pass membrane · IDG tier: T_{dark} · PDB: none · July 2026

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At A Glance

Topology	Multi-pass membrane protein (p=1.00): ~**ten transmembrane helices** forming a large channel-like domain — the TMC-family architecture.
Pore Cavity	**High-confidence pocket (0.74).** A residue-level cavity in the TM4–TM5 region — the pore / modulator site a docking or mutagenesis campaign needs, and the one thing a fold alone will not give you.
Function	Predicted cation channel; its best-defined role is as an **inhibitory modulator of PIEZO2** in sensory neurons [3].
Modifications	Extracellular N-glycosylation (N24, N84, N96, N259, N638); an intracellular phosphosite (S89).
Clean Signal	Short disordered N-terminus only; no amyloid signal.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. The pore-lining pocket (amber) is the load-bearing prediction — the permeation / modulator site on a channel with no experimental structure.

1 The Gap

The transmembrane channel-like (TMC) family has one famous pair and six unknowns. **TMC1 and TMC2** are the mechanotransduction channels of inner-ear hair cells; **TMC3–TMC8** remain largely uncharacterised. TMC7 (subfamily C) is among the darkest: a predicted multi-pass cation channel with **no confirmed conductance of its own**, a thin literature (IDG T_{dark}) [2], and **no experimental structure in the PDB**. Its best-defined role is indirect but important — in mouse dorsal-root-ganglion neurons, TMC7 acts as an **inhibitory modulator ("suppressor") of PIEZO2**, and its loss *enhances* mechanotransduction and mechanical hypersensitivity [3]. So TMC7 sits on the touch / mechanical-pain axis, yet is structurally a blank.

That combination — **a mechanosensory channel with no structure** — is exactly where prediction earns its keep: everything below is computed from the canonical 723-residue sequence and derived structural predictions, with no experimental TMC7 structure used as input.

2 Membrane Topology

Astra reads TMC7 as a canonical multi-pass channel: **~ten transmembrane helices** (about 30% of the chain membrane-embedded) with predicted N-glycosylation on the extracellular side and a short disordered N-terminus. The load-bearing result is not that it spans the membrane — it is *where the pore-lining cavity is*, and which helices form it.

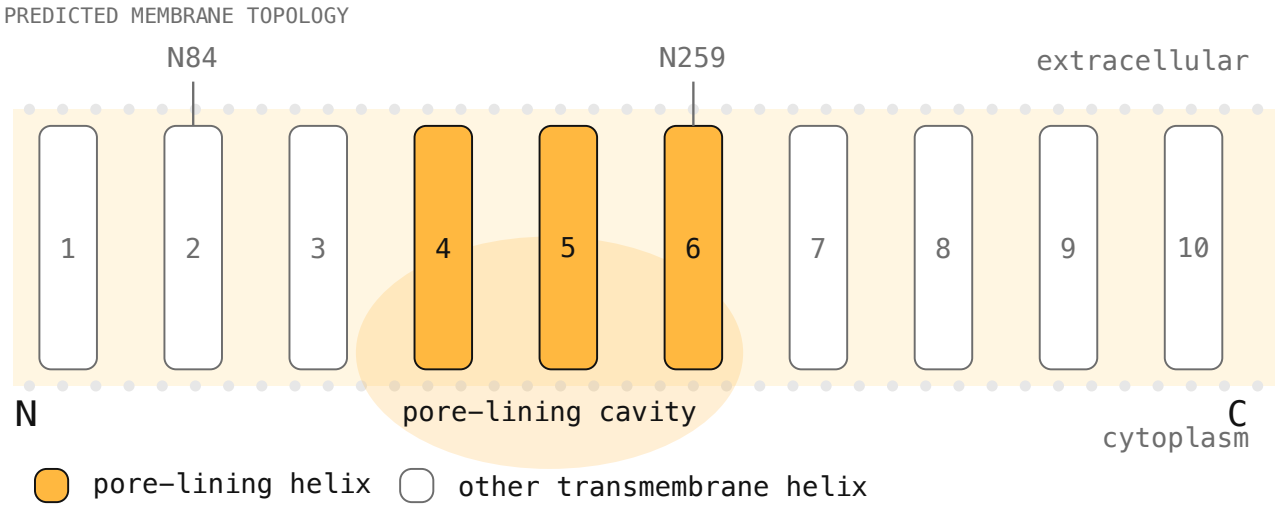

Figure 2. Predicted membrane topology. About ten transmembrane helices form the channel domain; amber marks the helices that contribute residues to the predicted pore-lining cavity, with N-glycosylation predicted on the extracellular loops. Helix numbering is schematic.

3 The Predicted Pore-Lining Cavity

Every channel has a permeation pathway; that is not the finding. The useful question is *which residues line the cavity* — the input a docking run, a modulator-design campaign, or a mutagenesis experiment needs. Astra resolves that residue set and places a **high-confidence pocket (0.74)** in the **TM4–TM5 region**. Because the contributing residues span multiple helices but converge in space, the cavity is a genuine three-dimensional prediction.

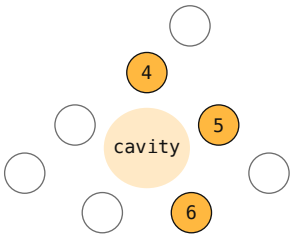

Figure 3. Schematic cross-section; amber helices (TM4–6) line the cavity.

PREDICTED PORE-LINING RESIDUES

TM4 region	359–384, 386
TM5 region	410, 414–423
Adjacent	432, 451, 454, 457–458

No known binder — a genuine orphan cavity. These residues are the first testable hypothesis for the permeation path and for any small molecule that would tune TMC7's effect on PIEZO2.

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of TMC7 exists and is a useful input — but a channel model alone does not tell you which cavity is the permeation path or which residues line it. This profile is that annotation layer. As a control, the same pocket detection recovers the known pore/ligand sites on channels whose structures *are* solved (e.g. the *C. elegans* TMC-1 complex), so the TMC7 cavity is a like-for-like prediction. The net effect: a dark channel becomes a **ranked, testable hypothesis**.

4 Post-Translational And Structural Features

The predicted features are consistent with a folded, glycosylated plasma-membrane channel:

- **Extracellular N-glycosylation (N24, N84, N96, N259, N638).** The expected surface modification

for a multi-pass plasma-membrane channel — and a set of handles for surface-expression and trafficking assays.

- **Intracellular phosphorylation (S89).** A candidate regulatory site in the disordered N-terminal region.
- **Low disorder, no amyloid.** A well-folded channel; the ordered TM core is the region for structural work.

5 Recommended Experimental Follow-Up

This turns a dark channel 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
Pore-lining cavity (TM4–TM5)	Alanine scan at the cavity + electrophysiology	Change in conductance / PIEZO2 modulation
~ten-TM topology	Surface-labelling / glycosylation mapping	Confirmed topology and orientation
PIEZO2-suppressor role [3]	Cavity-mutant rescue of the PIEZO2 phenotype	Which residues carry the modulation
Predicted cation-channel function	Reconstitution / patch on purified TMC7	Confirm (or refute) intrinsic conductance
N-glycosylation sites	N→Q mutants	Trafficking / surface-expression change

Its role on the touch / mechanical-pain axis [3] indicates where a validated TMC7 modulator would first be worth evaluating.

6 Where This Fits In A Discovery Workflow

Team	What they get from this profile
Target biology	Testable residue-level hypotheses and a validation plan
Structural biology	Predicted topology, membrane boundaries, and a cavity to focus on
Medicinal chemistry	Cavity residues for docking and channel-modulator 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 TMC7 sequence (UniProt Q7Z402 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [4] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [5] (modification sites) and **AstraBIND** [6] (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	TMC7 · UniProt Q7Z402, canonical isoform (723 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [4–6]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [6]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [4]–[6]

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.
- **Channel activity is predicted.** An intrinsic TMC7 conductance has not been demonstrated; its established role is as a modulator of PIEZO2 [3]. The pore-lining cavity is a residue-level hypothesis, not a proven permeation path.
- **Biology caveats.** The PIEZO2-modulation data are from mouse sensory neurons [3]; a human physiological role is inferred, not established.

8 References

[1] UniProt Consortium. UniProtKB entry Q7Z402 (TMC7, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. TMC7 target record — T_{dark}. pharos.nih.gov/targets/Q7Z402.

[3] Zhang X., Shao J., Wang C., et al. TMC7 functions as a suppressor of Piezo2 in primary sensory neurons blunting peripheral mechanotransduction. *Cell Rep.* **43**(4), 114014 (2024). doi:10.1016/j.celrep.2024.114014.

[4] 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.

[5] 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.

[6] Goteti A., Vasilyeva A., Bozkurt Ç. AstraBIND: Graph Attention Network for Predicting Ligand Binding Sites. *bioRxiv* 2025.11.10.687555 (2025). doi:10.1101/2025.11.10.687555.