COMPUTATIONAL TARGET PROFILE

ANO5

A dark anoctamin (TMEM16E) tied to limb-girdle muscular dystrophy, characterised without an experimental structure

ANO5 (TMEM16E) belongs to the anoctamin family, but unlike its channel relatives it is reported to act in plasma-membrane repair and lipid scrambling rather than as a chloride channel. Recessive loss-of-function mutations cause limb-girdle muscular dystrophy (LGMD2L / LGMDR12) and Miyoshi myopathy, while a dominant gain-of-function variant causes gnathodiaphyseal dysplasia — yet it has no experimental structure in the PDB and a thin functional literature. We resolve the canonical 913-residue sequence into an eight-helix topology, a residue-level pore / interface hypothesis, post-translational features and a construct / validation plan, all computed with Orbion's Astra suite from sequence alone.

UniProt Q75V66 · 913 aa · Anoctamin (TMEM16) Family · IDG tier: Tbio · PDB: none · July 2026

Have your own under-characterised target? Send a UniProt ID to contact@orbion.life for a preview like this one.

At A Glance

Fold	Eight predicted transmembrane helices; a multi-pass anoctamin / TMEM16-family membrane protein.
Pore-Lining Surface	AstraBIND pore / interface hypothesis (confidence 0.654, medium) around TM6 — a residue-level starting point for mutagenesis; no validated ligand.
Structural Anchors	N-glycosylation at six predicted sites, including N335 (UniProt).
Flexible Regions	Elevated predicted disorder at the N-terminus (1–64) and C-tail (883–910) — the cytoplasmic termini and natural truncation boundaries.
Clean Signal	Aggregation-prone segment flagged (max 0.528).

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls (amber = load-bearing / soft prediction).

1 The Gap

Most tractable membrane-protein families have been structurally explored. ANO5 has not: an IDG Tbio anoctamin with no experimental structure in the PDB and only a handful of functional studies. UniProt notes a role in annexin-dependent plasma-membrane repair and, pointedly, that it does not show the calcium-activated chloride-channel activity of some family members — so even its molecular function is unsettled. What is firm is the disease link: recessive loss-of-function ANO5 variants underlie limb-girdle muscular dystrophy (LGMD2L / LGMDR12) and Miyoshi myopathy, while a dominant gain-of-function variant causes gnathodiaphyseal dysplasia.

That combination — a solid disease association with near-zero structural information — is where prediction earns its keep: everything below is computed from the canonical 913-residue sequence, with no experimental ANO5 structure used as input.

2 Architecture And Topology

PREDICTED ARCHITECTURE

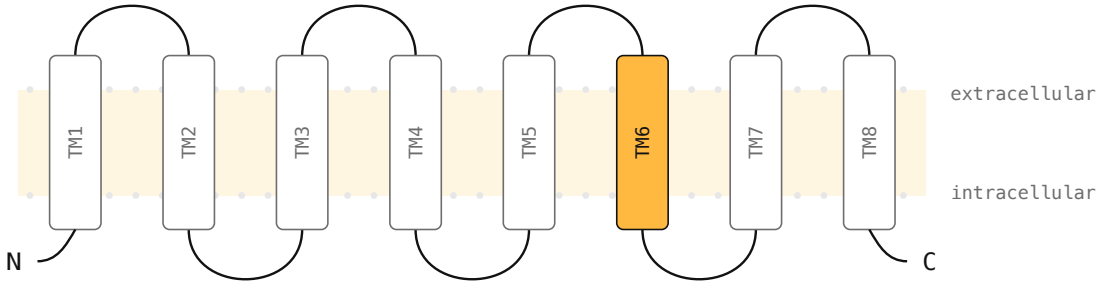

Figure 2. Predicted membrane topology from the sequence: transmembrane helices drawn in the bilayer, amber marks the pocket-lining helices, dashed loops are disordered, and the N/C termini and key modifications are placed in situ.

Element	Residues	Note
Transmembrane Helices	8 predicted	Boundaries: 300–320; 381–401; 463–483; 512–532; 558–578; 680–700; 733–753; 835–855.

PER-RESIDUE DISORDER PROFILE (ASTRAUNFOLD)

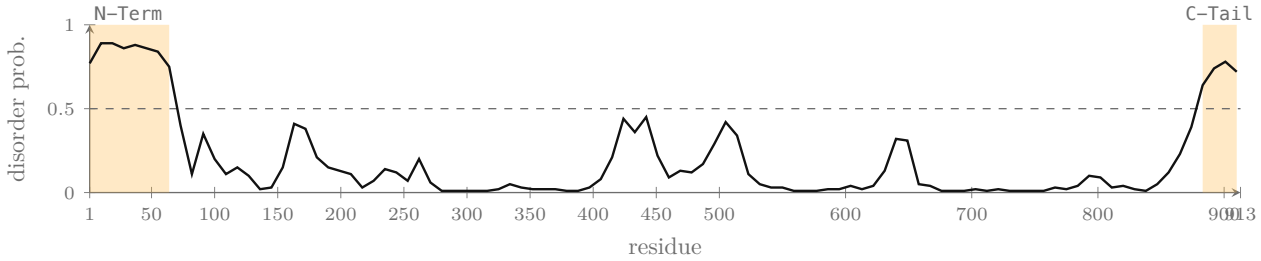

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 The Predicted Pore-Lining Surface

Astra resolves a residue-level site — the input a docking run or a mutagenesis plan actually needs. Predicted location: **Predicted pore / gating interface**.

PREDICTED POCKET / FUNCTIONAL RESIDUES

TM6	701
Loop / Surface	704, 706, 708

For this genuine orphan, AstraBIND has no ligand-bound relative to retrieve from — so these residues are a structure-based cavity prediction, not a retrieval-grounded pocket, and the score reflects cavity geometry rather than a known binding site. Treat them as an exploratory starting point for mutagenesis only; the topology, disorder and modification maps above are the higher-confidence outputs for this target. No validated ligand; not a proven druggable site.

4 Post-Translational And Structural Features

- **N-glycosylation at six predicted sites** (N335, N366, N380, N768, N778, N791) — extracellular-loop modifications (UniProt).
- **Aggregation-prone segment flagged** (AstraUNFOLD amyloid max 0.528) — worth screening in construct design.

5 Recommended Experimental Follow-Up

Prediction	Experiment	Readout
Predicted Pore / Interface Residues (TM6)	Alanine scan at the predicted TM6 residues + membrane-repair / scrambling assay	Functional change — tests the predicted site
Disordered Termini (1–64; 883–910)	N- and C-terminal truncation	Improved expression / thermostability for cryo-EM
Predicted Anoctamin / Scramblase Function	Lipid-scrambling / membrane-repair assay	Confirm the predicted functional class

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	Construct boundaries, disordered regions, fusion / deletion ideas
Medicinal Chemistry	Pocket / active-site residues for docking and SAR
BD / Platform Evaluation	Evidence Orbion can prioritise dark targets quickly

7 Methods

All predictions were generated with Orbion's Astra suite from the canonical ANO5 sequence (UniProt Q75V66): **AstraSUIT** and **AstraROLE** (membrane / functional class), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM** (modification sites) and **AstraBIND** (binding pocket). Reported values are model outputs; model internals are out of scope. No experimental ANO5 structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry Q75V66 (ANO5, human). uniprot.org.
2. Pharos (Illuminating the Druggable Genome). ANO5 target record — Tbio. pharos.nih.gov.
3. Penttilä S et al. Eight new mutations and the expanding phenotype variability in muscular dystrophy caused by ANO5. (2012). https://doi.org/10.1212/wnl.0b013e31824c4682
4. Savarese M et al. Next generation sequencing on patients with LGMD and nonspecific myopathies: Findings associated with ANO5 mutations. (2015). https://doi.org/10.1016/j.nmd.2015.03.011
5. Di Zanni E et al. Gain of function of TMEM16E/ANO5 scrambling activity caused by a mutation associated with gnathodiaphyseal dysplasia. (2018). https://doi.org/10.1007/s00018-017-2704-9