COMPUTATIONAL TARGET PROFILE

SLC38A11

An Orphan Amino-Acid Transporter, Characterised Without An Experimental Structure

The "putative" SLC38 member, deorphaned in silico. A dark, structureless multi-pass transporter — Astra confirms the **transporter** identity (p=1.00) and predicts the **substrate-binding cavity**, turning an annotation guess into a testable hypothesis.

UniProt Q08AI6 · 406 aa · Multi-pass membrane · IDG tier: T_{dark} · PDB: none · July 2026

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At A Glance

Function	**Transporter — p=1.00.** From sequence alone Astra assigns transmembrane-transporter activity (GO, p=0.94), confirming the SLC38/SNAT-family annotation for a member whose substrate is unknown.
Topology	Multi-pass plasma-membrane protein (p=1.00); **~ten transmembrane helices**, the classic amino-acid-transporter architecture.
Substrate Pocket	**High-confidence hypothesis (0.80).** A residue-level central cavity lined by **five different TM helices** — the translocation site a docking or mutagenesis campaign needs to start deorphaning.
Modifications	Predicted N-glycosylation (N44, N275) on the extracellular loops — consistent with a plasma-membrane transporter.
Clean Signal	No amyloidogenic segments predicted.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. The substrate pocket (amber) is the load-bearing prediction — the translocation site on a transporter with no experimental structure and no known substrate.

1 The Gap

The solute-carrier (SLC) superfamily is the largest group of human membrane transporters, and roughly a third of it remains **functionally orphan** — no known substrate [5]. SLC38A11 is one of these: UniProt calls it a *putative* sodium-coupled neutral amino-acid transporter, a member of the SLC38 (SNAT) family whose better-studied relatives SLC38A1/A2/A5 are validated cancer and CNS glutamine-cycle transporters [3, 4]. But SLC38A11 itself has **no confirmed substrate**, a thin literature (IDG T_{dark}) [2], and **no experimental structure in the PDB**.

That combination — a disease-relevant family with **an uncharacterised member** — is exactly where prediction earns its keep: everything below is computed from the canonical 406-residue sequence and derived structural predictions, with no experimental SLC38A11 structure used as input.

2 Membrane Topology

Astra reads SLC38A11 as a canonical multi-pass transporter: **~ten transmembrane helices** (about 47% of the chain is membrane-embedded) with short connecting loops and predicted N-glycosylation on the extracellular side. The load-bearing result is not that it spans the membrane — it is *where the substrate cavity is*, and which helices line it.

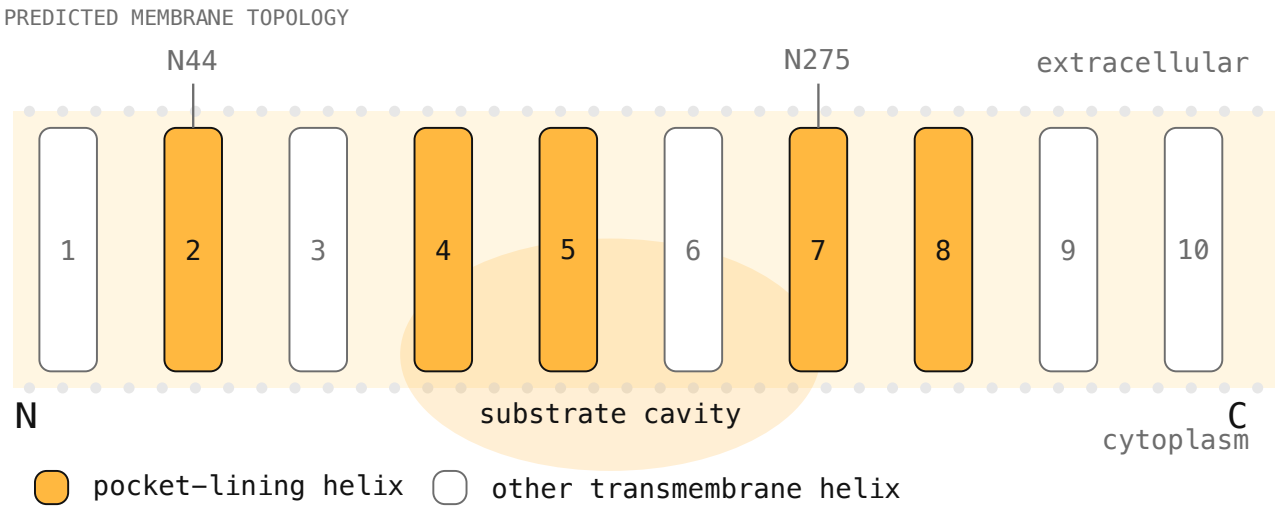

Figure 2. Predicted membrane topology. About ten transmembrane helices span the plasma membrane; amber marks the five helices that contribute residues to the predicted central substrate cavity, with N-glycosylation predicted on the extracellular loops. Helix numbering is schematic.

3 The Predicted Substrate Cavity

Every transporter has a translocation pathway; that is not the finding. The useful question is *which residues line the substrate cavity* — the input a docking run, a selectivity argument, or a mutagenesis campaign needs to start assigning a substrate. Astra resolves that residue set and places a **high-confidence pocket (0.80)** at a central cavity contributed by **five different TM helices**. Because those residues sit far apart in sequence but converge in space, the cavity is a genuine three-dimensional prediction, not a sequence motif.

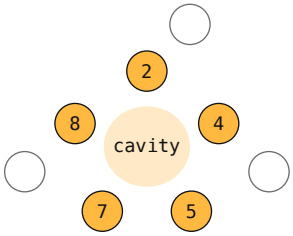

Figure 3. Schematic cross-section; amber helices (2,4,5,7,8) line the cavity.

PREDICTED SUBSTRATE-CAVITY RESIDUES

TM2	59, 62–70, 73
TM4 / TM5	125–128, 173–180
TM7	248–259
TM8	306, 309–310

No known substrate or binder — a genuine orphan cavity. The residues above are the first, testable hypothesis for what SLC38A11 might carry.

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of SLC38A11 exists and is a useful input — but a fold alone does not tell you which cavity is the substrate site or which residues line it. This profile is that annotation layer. As a control, the same pocket detection recovers the known substrate/ligand sites on transporters whose structures *are* solved, so the SLC38A11 cavity is a like-for-like prediction. The net effect: a "putative" orphan becomes a **ranked, testable deorphaning hypothesis**.

4 Post-Translational And Structural Features

The predicted features are consistent with a working plasma-membrane transporter:

- **Extracellular N-glycosylation (N44, N275).** The expected surface modification for a multi-pass plasma-membrane transporter — and a handle for trafficking / surface-expression assays.
- **Predicted disulfide/loop features.** Consistent with a folded, membrane-inserted transporter rather than a disordered protein (∼10% disorder overall).
- **No amyloid signal.** A clean, foldable transporter fold.

5 Recommended Experimental Follow-Up

This turns a "putative" annotation 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
Transporter function	Radiolabel amino-acid uptake panel (Na^+-dependent)	Confirm transport + a substrate class
Substrate cavity residues	Alanine scan at the cavity + docking	Loss/shift of transport; substrate hypothesis
∼ten-TM topology	Surface-labelling / glycosylation-mapping	Confirmed topology and orientation
N-glycosylation (N44, N275)	N→Q mutants	Trafficking / surface-expression change
Family relationship (SNAT)	Compare cavity residues to SLC38A1/A2/A5	Predicted substrate similarity / difference

The disease relevance of its SLC38 relatives [3, 4] indicates where a deorphaned SLC38A11 would first be worth pursuing.

6 Where This Fits In A Discovery Workflow

Team	What they get from this profile
Target biology	Testable residue-level hypotheses and a deorphaning plan
Structural biology	Predicted topology, membrane boundaries, and a cavity to focus on
Medicinal chemistry	Cavity residues for docking and substrate/inhibitor 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 SLC38A11 sequence (UniProt Q08AI6 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [6] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [7] (modification sites) and **AstraBIND** [8] (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	SLC38A11 · UniProt Q08AI6, canonical isoform (406 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [6–8]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [8]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [6]–[8]

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 cavity is predicted; the substrate is not named.** For a genuine orphan the honest output is a residue-level cavity hypothesis, not a substrate assignment.
- **Biology caveats.** SLC38A11's substrate and physiological role are unknown; family-level disease relevance (SLC38A1/A2/A5) does not by itself establish a role for SLC38A11. Treat function as an open question.

8 References

[1] UniProt Consortium. UniProtKB entry Q08AI6 (SLC38A11, human). uniprot.org.

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[3] Bröer S. The SLC38 family of sodium-amino acid co-transporters. *Pflügers Arch.* **466**(1), 155–172 (2014). doi:10.1007/s00424-013-1393-y.

[4] Mackenzie B., Erickson J.D. Sodium-coupled neutral amino acid (System N/A) transporters of the SLC38 gene family. *Pflügers Arch.* **447**(5), 784–795 (2004). doi:10.1007/s00424-003-1117-9.

[5] Pizzagalli M.D., Bensimon A., Superti-Furga G. A guide to plasma membrane solute carrier proteins. *FEBS J.* **288**(9), 2784–2835 (2021). doi:10.1111/febs.15531.

[6] 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.

[7] 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.

[8] 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.