COMPUTATIONAL TARGET PROFILE

MFSD8

An orphan MFS lysosomal transporter (CLN7), characterised without an experimental structure

The lysosomal transporter mutated in CLN7 Batten disease, still structurally dark. No solved structure, an MFS fold inferred from sequence, and a physiological substrate that remains debated — resolved into a twelve-helix topology, a residue-level substrate-cavity hypothesis, post-translational features and a construct plan, computed with Orbion's Astra suite from the sequence alone.

UniProt Q8NHS3 · 518 aa · MFS Lysosomal Transporter (CLN7) · 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	Twelve predicted transmembrane helices, an MFS-fold architecture; multi-pass lysosomal-membrane transporter; non-enzyme.
Substrate Cavity	A residue-level substrate-cavity hypothesis from AstraBIND (confidence 0.79, HIGH), unclassified — a starting point for docking and cavity mutagenesis, not a validated ligand.
Structural Anchors	Predicted N-glycosylation at N371 and N376 (UniProt), on the luminal face of the transporter.
Flexible Regions	Elevated predicted disorder at the cytosolic N-terminus (1–21), a cytosolic loop (246–256) and the luminal loop (371–396) — natural truncation boundaries for construct design.
Clean Signal	One aggregation-prone segment flagged (AstraUNFOLD amyloid max 0.556) — worth screening in construct design.

PREDICTION CONFIDENCE

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

1 The Gap

Most tractable membrane-transporter families have been structurally explored. MFSD8 — the gene better known as CLN7 — has not: an IDG Tbio lysosomal protein of the major facilitator superfamily, with no experimental structure in the PDB and a thin functional literature. It was first identified as a putative lysosomal transporter, and even its activity is still moving — UniProt now annotates an outward-rectifying chloride-channel function in the endolysosome — while the physiological substrate whose loss drives disease remains unidentified. Yet the interest is unambiguous: recessive loss-of-function mutations cause variant late-infantile neuronal ceroid lipofuscinosis (CLN7, a fatal childhood form of Batten disease), and a distinct set of mutations underlies a nonsyndromic macular dystrophy.

That combination — genuine clinical interest, near-zero structural information — is where prediction earns its keep: everything below is computed from the canonical 518-residue sequence with Orbion's Astra suite, with no experimental MFSD8 structure used as input. For a lysosomal orphan with no solved fold, there is nothing to look up.

2 Architecture And Topology

PREDICTED ARCHITECTURE

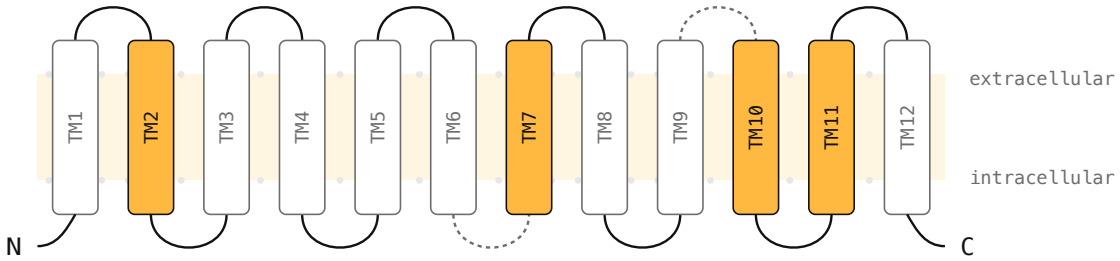

Figure 2. Predicted membrane topology from the sequence: transmembrane helices drawn in the bilayer, amber marks the pocket-lining helices, dashed loops are disordered, and the N/C termini and key modifications are placed in situ.

Element	Residues	Note
Transmembrane Helices	12 predicted	Boundaries: 41–61; 75–95; 106–126; 132–152; 174–194; 212–232; 267–287; 305–325; 338–358; 413–433; 452–472; 483–503.

PER-RESIDUE DISORDER PROFILE (ASTRAUNFOLD)

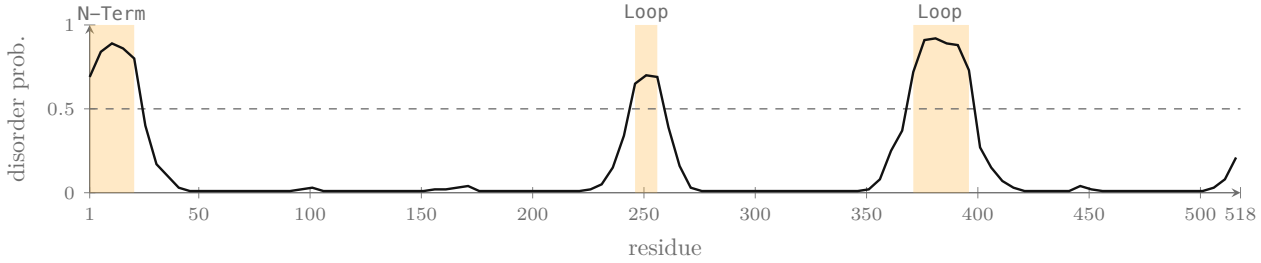

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 The Predicted Substrate Cavity

Astra resolves a residue-level site — the input a docking run or a mutagenesis plan actually needs. Predicted location: **Predicted central translocation cavity**.

PREDICTED POCKET / FUNCTIONAL RESIDUES

TM2	87
TM7	276, 278, 280–287
TM10	430, 434
TM11	461–462, 465

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 position 371, 376 (UniProt) — on the luminal loop between TM9 and TM10, the expected site for glycan attachment and a handle for trafficking studies.

- **Aggregation-prone segment flagged** (AstraUNFOLD amyloid max 0.556) — a predicted amyloidogenic stretch to screen out or engineer around when designing expression constructs.

5 Recommended Experimental Follow-Up

Prediction	Experiment	Readout
Substrate-Cavity Residues (TM7, TM10, TM11)	Cavity-lining alanine scan in a lysosomal transport / halide-flux assay	Loss of transport at the predicted site
Disordered N-Terminus and Loops (1–21, 246–256, 371–396)	Fusion-partner insertion or loop truncation	Improved expression / thermostability for cryo-EM
Predicted MFS Transporter Class	Substrate-uptake / electrophysiology in a defined lysosomal system	Confirm transport function and identify the cargo

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 MFSD8 sequence (UniProt Q8NHS3): **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 MFSD8 structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry Q8NHS3 (MFSD8, human). uniprot.org.
2. Pharos (Illuminating the Druggable Genome). MFSD8 target record — Tbio. pharos.nih.gov.
3. Siintola E et al. The novel neuronal ceroid lipofuscinosis gene MFSD8 encodes a putative lysosomal transporter. (2007). https://doi.org/10.1086/518902
4. Kousi M et al. Mutations in CLN7/MFSD8 are a common cause of variant late-infantile neuronal ceroid lipofuscinosis. (2009). https://doi.org/10.1093/brain/awn366
5. Roosing S et al. Mutations in MFSD8, encoding a lysosomal membrane protein, are associated with non-syndromic autosomal recessive macular dystrophy. (2015). https://doi.org/10.1016/j.ophtha.2014.07.040