COMPUTATIONAL TARGET PROFILE

FAM171A2

An orphan neuronal membrane protein tied by genetics to Parkinson's disease, characterised without an experimental structure

One of the darkest proteins with a credible Parkinson's link. FAM171A2 is IDG Tdark — no solved structure, no catalogued molecular function — yet it has been reported to sit on neurons and pull in α-synuclein fibrils, and to act as a genetic regulator of progranulin and neurodegeneration risk. We resolve the canonical 826-residue sequence into a signal-peptide-plus-single-pass topology, a residue-level surface-pocket hypothesis in the ectodomain, a long disordered cytoplasmic tail and a construct / validation plan, computed with Orbion's Astra suite from sequence alone.

UniProt A8MVW0 · 826 aa · Orphan; Single-Pass Membrane / Soluble · IDG tier: Tdark · 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	Predicted single-pass membrane protein: a signal peptide, a folded extracellular domain, one transmembrane helix and a long, largely disordered cytoplasmic tail.
Binding Pocket	A residue-level surface-cavity hypothesis from AstraBIND (confidence 0.819) in the extracellular domain — a starting point for docking or mutagenesis, not a validated ligand.
Structural Anchors	N-linked glycosylation at N66, N201, N221 and N265 (UniProt), all on the extracellular domain.
Flexible Regions	Elevated predicted disorder through the long cytoplasmic tail, strongest at the C-terminus (801–817) — natural construct / truncation boundaries.
Clean Signal	No amyloidogenic segments predicted — a clean aggregation profile despite the large disordered region.

PREDICTION CONFIDENCE

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

1 The Gap

Most tractable protein families have been structurally explored; FAM171A2 has not. It is IDG Tdark in the fullest sense — no experimental structure in the PDB, no UniProt function summary, and only a handful of papers to its name. What lifted it out of obscurity is disease genetics: it was reported first as a regulator of progranulin expression that modifies risk across several neurodegenerative diseases, and then as a neuronal mediator of α-synuclein fibril uptake that drives Parkinson's disease. A candidate node in α-synuclein spread, with almost nothing structural to anchor it.

That combination — a credible neurodegeneration link, near-zero structural information — is where prediction earns its keep: everything below is computed from the canonical 826-residue sequence with Orbion's Astra suite, with no experimental FAM171A2 structure used as input. For a genuine orphan, there is nothing to look up.

2 Architecture And Topology

PREDICTED ARCHITECTURE

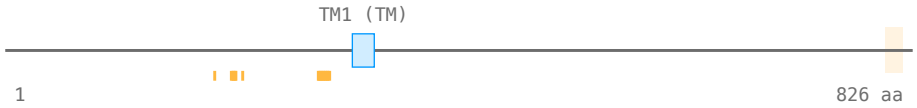

Figure 2. Predicted domain architecture along the sequence: annotated domains as boxes, disordered regions shaded, and the predicted active-site / pocket residues marked as amber ticks.

Element	Residues	Note
Transmembrane Helices	1 predicted	Boundaries: 316–336.
Signal Peptide	1–29	UniProt.

PER-RESIDUE DISORDER PROFILE (ASTRAUNFOLD)

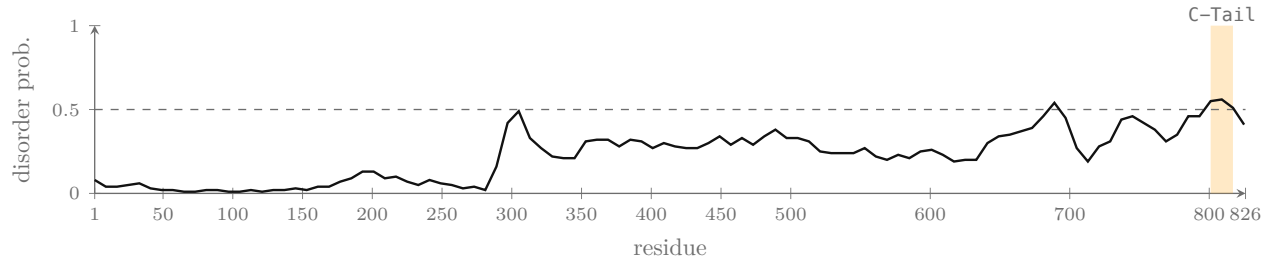

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 A Predicted Binding Pocket

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

PREDICTED POCKET / FUNCTIONAL RESIDUES

Loop / Surface	191, 206–210, 216, 285–295

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 66, 201, 221, 265 (UniProt) — four N-linked sequons clustered on the extracellular domain, consistent with a cell-surface-exposed ectodomain.
- **No amyloidogenic segments predicted.** AstraUNFOLD flags no aggregation-prone stretch — notable given the long intrinsically disordered cytoplasmic tail.

5 Recommended Experimental Follow-Up

Prediction	Experiment	Readout
Surface Pocket in the Ectodomain (AstraBIND, 0.819)	Alanine scan of the flagged ectodomain residues + α-synuclein-fibril binding assay	Reduced fibril binding / uptake — tests the predicted interaction surface
Long Disordered Cytoplasmic Tail (337–826)	Truncate to the folded ectodomain for structural work	Improved expression and crystallisability / cryo-EM behaviour
Predicted Single-Pass Topology + Surface Glycans (N66 / N201 / N221 / N265)	Surface labelling / glycosidase treatment on intact neurons	Confirms an extracellular, glycosylated ectodomain

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 FAM171A2 sequence (UniProt A8MVW0): **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 FAM171A2 structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry A8MVW0 (FAM171A2, human). uniprot.org.
2. Pharos (Illuminating the Druggable Genome). FAM171A2 target record — Tdark. pharos.nih.gov.
3. Wu KM et al. Neuronal FAM171A2 mediates α-synuclein fibril uptake and drives Parkinson's disease. (2025). https://doi.org/10.1126/science.adp3645
4. Xu W et al. The FAM171A2 gene is a key regulator of progranulin expression and modifies the risk of multiple neurodegenerative diseases. (2020). https://doi.org/10.1126/sciadv.abb3063
5. Wang Y et al. The role of FAM171A2-GRN-NF- B pathway in TBBPA induced oxidative stress and inflammatory response in mouse-derived hippocampal neuronal HT22 cells. (2025). https://doi.org/10.1016/j.ecoenv.2024.1174