COMPUTATIONAL TARGET PROFILE

FAM111B

A predicted trypsin-like serine protease behind a dominant multisystem disease, characterised without an experimental structure

The rare-disease enzyme with a predicted catalytic triad and no crystal to check it against. Dominant FAM111B mutations cause POIKTMP — a multisystem disorder of skin, tendon, muscle and lung — and the same protease has been reported as a p53-driven player in lung adenocarcinoma, yet the PDB is empty. We resolve the canonical 734-residue sequence into a topology, a residue-level active-site hypothesis, post-translational features and a construct / validation plan, computed with Orbion's Astra suite from sequence alone.

UniProt Q6SJ93 · 734 aa · Trypsin-Like Serine Protease (Predicted) · 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	Soluble, single-chain protein; predicted trypsin-like serine-protease fold; no transmembrane segments.
Active Site	The UniProt-annotated His490–Asp544–Ser650 charge-relay triad — the functional site. AstraBIND's retrieval-based detector found no ligand-bound relative and did not recover it, so we defer to the annotation (a useful negative control).
Clean Signal	No amyloidogenic segments predicted — a clean aggregation profile for construct design.

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; FAM111B has not. It is an IDG Tbio serine protease with no experimental structure in the PDB and a thin primary literature. What makes the gap matter is the biology on either side of it: dominant FAM111B mutations cause POIKTMP — hereditary fibrosing poikiloderma with tendon contractures, myopathy and progressive pulmonary fibrosis — while in oncology it has been reported as a direct p53 target that drives lung adenocarcinoma. A disease gene and a candidate oncology target, and still no fold to reason over.

That combination — genuine disease relevance, near-zero structural information — is where prediction earns its keep: everything below is computed from the canonical 734-residue sequence with Orbion's Astra suite, with no experimental FAM111B 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
Chain	1–734	Single-chain; see disorder profile and pocket below.

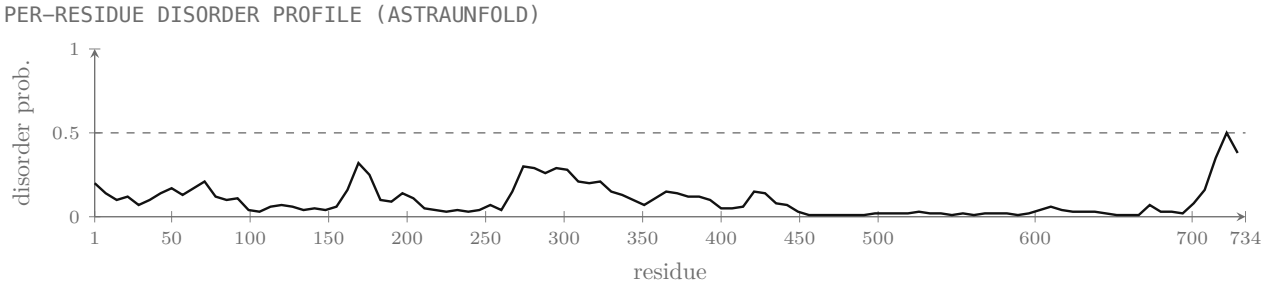

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 The Annotated Catalytic Triad

Astra resolves a residue-level site — the input a docking run or a mutagenesis plan actually needs. Predicted location: **Trypsin-like serine-protease charge-relay triad (UniProt)**.

PREDICTED POCKET / FUNCTIONAL RESIDUES

Catalytic Triad	490 (His), 544 (Asp), 650 (Ser)

For FAM111B the functional site is annotated, not predicted: UniProt places a His490–Asp544–Ser650 charge-relay triad. This target is also a useful negative control for the pocket detector — AstraBIND had no ligand-bound relative to retrieve from and returned a surface that does not overlap the triad, so we report the annotated active site rather than an invented pocket. Protease activity itself is a sequence-based inference, not experimentally confirmed here.

4 Post-Translational And Structural Features

- **Catalytic residue Charge relay system (position 490).** UniProt-annotated active site — one of three charge-relay residues that together form the His–Asp–Ser catalytic triad of a trypsin-like serine protease.
- **Catalytic residue Charge relay system (position 544).** UniProt-annotated active site — the second member of the predicted triad; the geometry of all three is what a structure would need to confirm.
- **Catalytic residue Charge relay system (position 650).** UniProt-annotated active site — the third triad residue; the trio (490 / 544 / 650) is the signature that classes FAM111B as a serine protease.
- **No amyloidogenic segments predicted.** AstraUNFOLD flags no aggregation-prone stretch — a clean profile for recombinant expression and construct design.

5 Recommended Experimental Follow-Up

Prediction	Experiment	Readout
Unknown Physiological Substrate(s)	Activity-based protein profiling / N-terminomics in FAM111B-active cells	Identify the cleaved substrates that define its pathway
Catalytic Triad (Charge Relay 490 / 544 / 650)	Serine → alanine active-site mutant + protease-activity assay	Loss of proteolysis — confirms the serine-protease call
Disordered Termini (1–32, 712–734)	N- and C-terminal truncation to the folded core	Improved expression and amenability to crystallography / cryo-EM

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 FAM111B sequence (UniProt Q6SJ93): **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 FAM111B structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry Q6SJ93 (FAM111B, human). uniprot.org.
2. Pharos (Illuminating the Druggable Genome). FAM111B target record — Tbio. pharos.nih.gov.
3. Mercier S et al. Mutations in FAM111B cause hereditary fibrosing poikiloderma with tendon contracture, myopathy, and pulmonary fibrosis. (2013). https://doi.org/10.1016/j.ajhg.2013.10.013
4. Sun H et al. FAM111B, a direct target of p53, promotes the malignant process of lung adenocarcinoma. (2019). https://doi.org/10.2147/ott.s190934
5. Kawasaki K et al. FAM111B enhances proliferation of KRAS-driven lung adenocarcinoma by degrading p16. (2020). https://doi.org/10.1111/cas.14483