COMPUTATIONAL TARGET PROFILE

MINDY4

A "Probable" Deubiquitinase, Characterised Without An Experimental Structure

A predicted function, an active-site pocket that lands on the catalytic dyad, and a modification map for a soluble enzyme with **no solved structure** and **unconfirmed activity**.

UniProt Q4G0A6 · 757 aa · Soluble (cytoplasmic) · IDG tier: T_{dark} · 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

Predicted Function	**Hydrolase enzyme — EC 3, p=1.00.** From the sequence, Astra confirms the merely-"probable" deubiquitinase annotation with near-certainty (enzyme, p=0.97).
Active Site	**Pocket lands on the catalytic dyad.** A HIGH-confidence binding pocket (0.90) whose residues include the annotated catalytic **Cys456 and His677** — the predicted active site coincides with the (unconfirmed) DUB machinery.
Fold	Soluble, cytoplasmic; a large (757 aa), predominantly ordered single chain; no membrane, disorder or amyloid signal.
Modifications	A phosphorylation-rich regulatory stretch (~210–290) and predicted ubiquitination — a regulated enzyme.
Clean Signal	No disordered or amyloidogenic segments predicted.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. Astra predicts the function (a hydrolase) *and* an active-site pocket for a protein whose enzymatic activity has never been experimentally confirmed.

1 The Gap

MINDY4 (FAM188B) is a protein caught mid-characterisation. UniProt annotates it only as a *probable* deubiquitinase — a MINDY-family enzyme predicted to cleave Lys48-linked polyubiquitin, with a catalytic dyad (Cys456/His677) *inferred* but **its enzymatic activity and substrates never experimentally confirmed**. It has **no experimental structure in the PDB** and sits at IDG T_{dark} [2]. Yet it is disease-important and searched: FAM188B is oncogenic in lung cancer, where it deubiquitinates and stabilises the FOXM1 transcription factor and correlates with poor survival [3]; its knockdown sensitises tumour cells to anoikis via EGFR down-regulation and suppresses metastasis [4].

That combination — **a disease-relevant enzyme whose activity is still unproven** — is exactly where prediction earns its keep: everything below is computed from the canonical 757-residue sequence and derived structural predictions, with no experimental MINDY4 structure used as input. For an enzyme nobody has confirmed, there is nothing to look up.

2 Sequence Architecture And Active Site

MINDY4 is a large (757 aa), **predominantly ordered** soluble chain — Astra predicts no disordered or amyloidogenic segments, so the whole protein is in principle a clean target for structural work. It localises the enzyme's machinery to a C-terminal catalytic region, and — the load-bearing result — the independently predicted binding pocket *coincides with the annotated catalytic dyad*.

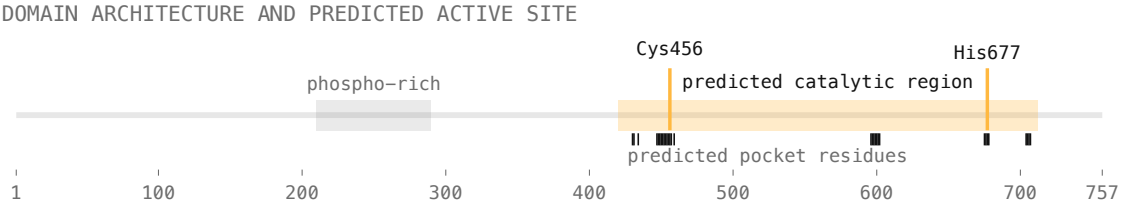

Figure 2. Sequence architecture. Astra confines the enzyme machinery to a C-terminal catalytic region (amber); the independently predicted pocket residues (ticks) cluster around the two UniProt-annotated catalytic residues, **Cys456 and His677** — i.e. the predicted active site lands on the (still-unconfirmed) deubiquitinase dyad. A phosphorylation-rich stretch (~210–290) sits N-terminal to the catalytic region.

3 The Predicted Active Site

For a protein annotated only as a "probable" enzyme, the useful questions are simple: is it really an enzyme, and where is its active site? Astra answers both from sequence. It classifies MINDY4 as a **hydrolase (EC 3, p=1.00)** — confirming the deubiquitinase call — and predicts a HIGH-confidence pocket (0.90) whose residues **include the annotated catalytic dyad Cys456 and His677**. The predicted active site is not an extrapolation into empty space: it lands on the two residues UniProt already flags as catalytic.

PREDICTED ACTIVE SITE

Catalytic dyad	Cys456 · His677 — both fall inside the predicted pocket
Pocket (N-region)	430–431, 434, 447–457, 459
Pocket (C-region)	596–602, 675–678, 704–707

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of MINDY4 exists and is a useful input — but a fold alone does not tell you whether the protein is catalytically active, which cavity is the active site, or which residues form it. This profile is that annotation layer. As a control, the same pocket detection recovers the known catalytic/ligand sites on enzymes whose structures *are* solved, so the MINDY4 active site is a like-for-like prediction rather than a guess. The net effect: a "probable" enzyme becomes a **ranked, testable hypothesis** — predicted function, predicted active site, and the mutants that would confirm both.

4 Post-Translational And Structural Features

The predicted modification map points to how this enzyme is regulated:

- **Phosphorylation-rich regulatory stretch (~210–290).** A dense cluster of predicted phosphosites N-terminal to the catalytic region — a plausible regulatory surface for switching the enzyme on or off, and a starting point for signalling studies.
- **Predicted ubiquitination.** Consistent with a deubiquitinase that is itself embedded in ubiquitin signalling (auto-regulation or turnover).
- **No membrane, disorder or amyloid signal.** A clean, soluble, ordered enzyme — the whole chain is a viable target for structural work.

5 Recommended Experimental Follow-Up

This turns an orphan sequence 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
Hydrolase / deubiquitinase class	In-vitro Ub-chain cleavage assay (K48 di-/poly-Ub)	Confirm (or refute) deubiquitinase activity
Catalytic dyad Cys456 / His677	C456A and H677A active-site mutants	Loss of activity — validates the predicted dyad
Predicted pocket residues	Activity-based / covalent-probe labelling	Probe engagement; a starting point for inhibitors
FOXM1 as a substrate hypothesis	Ub-chain assay on FOXM1 ± MINDY4	Change in FOXM1 ubiquitination / stability
Phospho-regulatory stretch (~210–290)	Phosphomimetic / phospho-null mutants	Change in DUB activity or FOXM1 / p53 output

Its oncogenic role in lung cancer [3, 4] indicates where a validated inhibitor would first be worth evaluating.

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 MINDY4 sequence (UniProt Q4G0A6 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [5] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [6] (modification sites) and **AstraBIND** [7] (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	MINDY4 · UniProt Q4G0A6, canonical isoform (757 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [5–7]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [7]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [5]–[7]

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.
- **Function and site are predictions, not assays.** Astra confidently calls MINDY4 a hydrolase and places

its pocket on the catalytic dyad — but the enzyme's activity has never been confirmed in vitro. These are hypotheses to test, not a demonstration of activity.

- **Biology caveats.** The oncogenic role rests on knockdown / over-expression studies in cancer cell lines [3, 4]; endogenous substrates beyond FOXM1 are not established. Treat the therapeutic case as a hypothesis.

8 References

[1] UniProt Consortium. UniProtKB entry Q4G0A6 (MINDY4, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. MINDY4 (FAM188B) target record — T_{dark}. pharos.nih.gov/targets/Q4G0A6.

[3] FAM188B Expression Is Critical for Cell Growth via FOXM1 Regulation in Lung Cancer. *Biomedicines* **8**(11), 465 (2020). doi:10.3390/biomedicines8110465.

[4] FAM188B Downregulation Sensitizes Lung Cancer Cells to Anoikis via EGFR Down-regulation and Inhibits Tumor Metastasis In Vivo. *Cancers* **13**(2), 247 (2021). doi:10.3390/cancers13020247.

[5] 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.

[6] 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.

[7] 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.