COMPUTATIONAL TARGET PROFILE

ADPRM

A Metalloenzyme With No Human Structure, Characterised From Its Sequence

A confirmed enzyme; an unsolved human active site. A soluble Mn-dependent hydrolase — Astra confirms the enzyme class and predicts a **di-metal active-site pocket** that lands on its catalytic residues, for a human enzyme with **no experimental structure**.

UniProt Q3LIE5 · 342 aa · Soluble · IDG tier: T_{bio} · 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=0.99.** Astra confirms the metallophosphoesterase identity (EC 3.6.1.16 / 3.6.1.53) from sequence alone.
Active Site	**Pocket lands on the di-metal centre.** A HIGH-confidence pocket (0.89), typed as a **metal (Zn/Mn) site**, whose residues include the homology-inferred catalytic set (Gln27, Asn110, His111 …).
Fold	Soluble, compact (342 aa) calcineurin-like metallophosphoesterase; predominantly ordered (∼6% disorder); no membrane or amyloid signal.
Substrates	Hydrolyses ADP-ribose, cyclic ADP-ribose and CDP-alcohols — second messengers linked to TRPM2 / immune signalling.
Open Question	The human active-site geometry has never been solved — only inferred from a distant (zebrafish) homologue.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. Astra confirms the function (a metallophosphoesterase) *and* places a metal-typed active-site pocket on the catalytic centre — for a human enzyme with no experimental structure.

1 The Gap

ADPRM is unusual among dark targets: its *chemistry* is known, but its *human structure* is not. It is a manganese-dependent hydrolase (ADPRibase-Mn family; a calcineurin-like metallophosphoesterase) that degrades **ADP-ribose, cyclic ADP-ribose (cADPR) and CDP-alcohols** [3, 4] — messengers tied to TRPM2, calcium and immune-cell signalling. Yet the **human enzyme has no experimental structure in the PDB**; its catalytic residues and di-metal centre are known only from substrate docking onto a homology model and from a distant **zebrafish** prototype (PDB 2NXF) [4, 5]. It remains understudied (IDG T_{bio}) [2], with no chemical probe.

That combination — **a real enzyme whose human active site is unsolved** — is exactly where prediction earns its keep: everything below is computed from the canonical 342-residue sequence and derived structural predictions, with no experimental human ADPRM structure used as input.

2 Sequence Architecture And Active Site

ADPRM is a compact, **predominantly ordered** soluble metallophosphoesterase. Its catalytic power comes from a **di-metal centre** coordinated by a conserved set of residues, and — the load-bearing result — the independently predicted pocket *coincides with that centre* and is typed by the model as a metal (Zn/Mn) site.

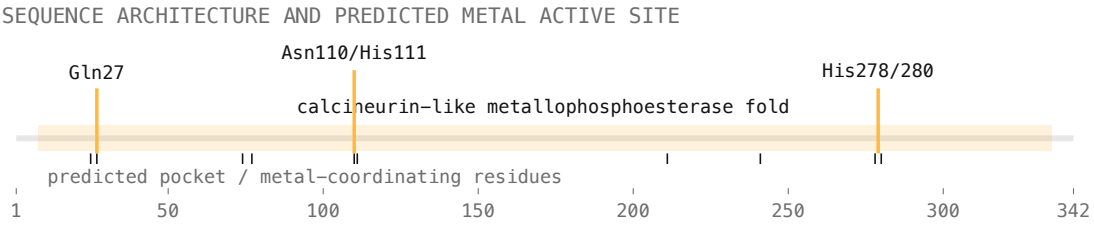

Figure 2. Sequence architecture. The predicted pocket residues (ticks) gather the conserved metal-coordinating / catalytic residues (amber) from across the sequence into one site — the di-metal active centre — rather than an incidental cavity.

3 The Predicted Active Site

For an enzyme with no human structure, the useful questions are: is the catalytic identity right, and where is the metal centre? Astra answers both from sequence. It classifies ADPRM as a **hydrolase (EC 3, p=0.99)** and predicts a HIGH-confidence pocket (0.89) **typed as a metal (Zn/Mn) site** whose residues include the homology-inferred catalytic set. The predicted active site is not an extrapolation into empty space: it lands on the residues expected to hold the di-metal centre.

PREDICTED METAL ACTIVE SITE

Pocket type	Metal (Zn/Mn) site — HIGH confidence (0.89)
Coordinating residues	25, 27, 74, 77, 110–111, 211, 241, 278, 280
Catalytic set (by homology)	Gln27 · Asn110 · His111 — inside the predicted pocket

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of human ADPRM exists and is a useful input — but a fold alone does not tell you which cavity is the catalytic metal centre or which residues coordinate it. This profile is that annotation layer. As a control, the same pocket detection recovers the known metal/ligand sites on metallophosphoesterases whose structures *are* solved (the family prototype, zebrafish 2NXF), so the ADPRM site is a like-for-like prediction. The net effect: a structureless human enzyme becomes a **ranked, testable active-site map**.

4 Post-Translational And Structural Features

Astra's supporting calls are consistent with a compact, soluble metalloenzyme:

- **Predominantly ordered (~6% disorder), no amyloid.** A clean, foldable enzyme — the whole chain is a viable target for structural work.
- **N-terminal acetylation.** A predicted co-translational modification consistent with a stable cytosolic protein.
- **Compact single domain.** No membrane signal; the catalytic metallophosphoesterase fold spans essentially the whole chain.

5 Recommended Experimental Follow-Up

This turns a structureless enzyme 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
Metallophosphoesterase / EC 3 class	ADP-ribose / cADPR hydrolysis assay (± Mn^{2+})	Confirm activity + metal dependence
Catalytic residues (Gln27, Asn110, His111)	Point mutants at the predicted set	Loss of activity — validates the site
Di-metal pocket	Metal-substitution / inhibitor soak	Metal identity; a starting point for inhibitors
cADPR-hydrolysis role [4]	Activity on cADPR ± ADPRM in cells	Effect on cADPR / TRPM2 signalling
Soluble, orderable fold	Recombinant expression + crystallisation	The first human ADPRM structure

Its links to ADP-ribose / cADPR second-messenger signalling [4] indicate 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	A foldable single domain, construct boundaries, and a defined metal site
Medicinal chemistry	Active-site / metal residues for docking and 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 ADPRM sequence (UniProt Q3LIE5 [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	ADPRM · UniProt Q3LIE5, canonical isoform (342 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.

- **Active site inferred, then predicted.** The catalytic residues are themselves homology inferences (from docking onto a non-human prototype); Astra independently converges on the same site, but neither is an experimental determination.
- **Biology caveats.** The TRPM2 / immune-signalling role of ADPR / cADPR is established background biology; ADPRM's specific regulatory role in it is proposed, not proven.

8 References

[1] UniProt Consortium. UniProtKB entry Q3LIE5 (ADPRM, human) — EC 3.6.1.16 / 3.6.1.53. uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. ADPRM target record — T_{bio}. pharos.nih.gov/targets/Q3LIE5.

[3] Canales J., Fernández A., Rodrigues J.R., et al. Mn^{2+}-dependent ADP-ribose/CDP-alcohol pyrophosphatase: a novel metallophosphoesterase family preferentially expressed in rodent immune cells. *Biochem. J.* **413**(1), 103–113 (2008). doi:10.1042/BJ20071471.

[4] Cabezas A., Ribeiro J.M., Rodrigues J.R., et al. Molecular bases of catalysis and ADP-ribose preference of human Mn^{2+}-dependent ADP-ribose/CDP-alcohol diphosphatase. *PLoS ONE* **10**(2), e0118680 (2015). doi:10.1371/journal.pone.0118680.

[5] Rodrigues J.R., Fernández A., Canales J., et al. Characterization of *Danio rerio* Mn^{2+}-dependent ADP-ribose/CDP-alcohol diphosphatase, the structural prototype of the ADPRibase-Mn-like family (PDB 2NXF). *PLoS ONE* **7**(7), e42249 (2012). doi:10.1371/journal.pone.0042249.

[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.