COMPUTATIONAL TARGET PROFILE

OVCA2

A Candidate Tumour-Suppressor Serine Hydrolase, Characterised Without An Experimental Structure

A known reaction, no structure, and no substrate. A soluble esterase from an ovarian-cancer deletion locus — Astra recovers its hydrolase identity from sequence and lands the predicted pocket on the **Ser–His–Asp catalytic triad**, for a protein with **no solved structure** and **no known physiological substrate**.

UniProt Q8WZ82 · 227 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=1.00.** From sequence alone Astra recovers the serine-hydrolase identity with near-certainty (enzyme, p=0.99).
Active Site	**Pocket lands on the catalytic triad.** A HIGH-confidence pocket (0.90) whose residues include the annotated charge-relay triad **Ser119, Asp179, His206** — the predicted active site coincides with the catalytic machinery.
Fold	Soluble; a small (227 aa) α/β-hydrolase, predominantly ordered (one short disordered insert, ~44–68); no membrane or amyloid signal.
Modifications	Predicted redox-type marks (glutathionylation, S-nitrosylation) plus phosphorylation — candidate regulation of a cysteine-adjacent active site.
Open Questions	No experimental structure; no physiological substrate; tumour-suppressor role unproven.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. Astra recovers the function (a hydrolase) *and* places an active-site pocket on the catalytic triad — for a protein with no structure and no known physiological substrate.

1 The Gap

OVCA2 was discovered by position, not by function. It sits in the **17p13.3** minimal region of allelic loss in ovarian cancer, identified alongside OVCA1 as a *candidate* tumour-suppressor gene, with its transcript reduced or undetectable in the large majority of ovarian tumours and cell lines [3]. Later work showed OVCA2 is a genuine **serine hydrolase** — it cleaves long-chain *p*-nitrophenyl alkyl esters [4] — and is degraded during retinoid-induced apoptosis [5]. But it has **no experimental structure in the PDB**, **no known physiological substrate**, and its tumour-suppressor role is unproven (later analyses favour its neighbour OVCA1/DPH1). It remains understudied (IDG T_{bio}) [2].

That combination — **a real enzyme with no structure and no substrate** — is exactly where prediction earns its keep: everything below is computed from the canonical 227-residue sequence and derived structural predictions, with no experimental OVCA2 structure used as input. There is nothing to look up.

2 Sequence Architecture And Active Site

OVCA2 is a small, **predominantly ordered** α/β-hydrolase (one short disordered insert near 44–68; no amyloid). Its catalytic apparatus is the classic serine-hydrolase **charge-relay triad**, and — the load-bearing result — the independently predicted binding pocket *coincides with that triad*.

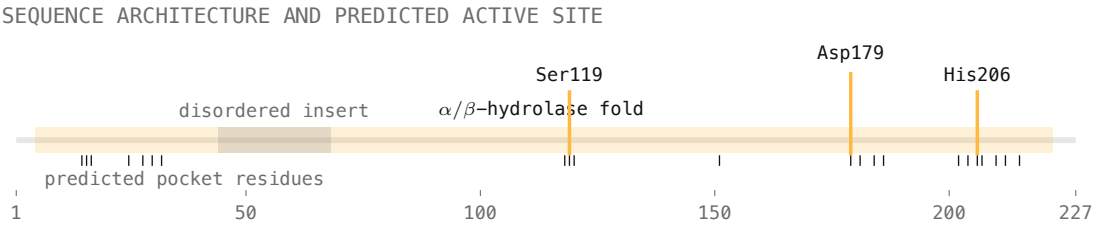

Figure 2. Sequence architecture. The predicted pocket residues (ticks) bracket all three catalytic residues — **Ser119, Asp179, His206** (amber) — so the independently predicted active site lands on the annotated charge-relay triad rather than on an incidental cavity.

3 The Predicted Active Site

For an enzyme with no structure, the useful questions are: is the catalytic identity right, and where is the active site? Astra answers both from sequence. It classifies OVCA2 as a **hydrolase (EC 3, p=1.00)** — recovering the experimentally established serine-hydrolase identity [4] — and predicts a HIGH-confidence pocket (0.90) whose residues **bracket the catalytic triad Ser119, Asp179 and His206**. The predicted active site is not an extrapolation into empty space: it lands on the residues UniProt annotates as the charge-relay system.

PREDICTED ACTIVE SITE

Catalytic triad	Ser119 · Asp179 · His206 — all fall inside the predicted pocket
Pocket (N-lobe)	15–17, 25, 28–34, 118–120
Pocket (C-lobe)	151, 179, 181–186, 202–215

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of OVCA2 exists and is a useful input — but a fold alone does not tell you 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 hydrolases whose structures *are* solved, so the OVCA2 active site is a like-for-like prediction rather than a guess. The net effect: a positionally-defined orphan becomes a **ranked, testable hypothesis** — confirmed function, located active site, and the mutants and probes that would validate both.

4 Post-Translational And Structural Features

The predicted modification map is notable for its **redox-type marks**:

- **Glutathionylation and S-nitrosylation.** Predicted cysteine-directed redox modifications — a plausible regulatory layer for a hydrolase, and consistent with OVCA2's reported turnover during retinoid-induced (oxidative-stress-associated) apoptosis [5].
- **Phosphorylation.** A small set of predicted phosphosites — candidate control points for activity or stability.
- **No membrane or amyloid signal.** A clean, soluble, compact enzyme — a viable target for structural work.

5 Recommended Experimental Follow-Up

This turns a positionally-defined orphan 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
Serine-hydrolase / esterase class	Activity-based protein profiling (fluorophosphonate probe)	Confirm an active serine hydrolase
Catalytic triad Ser119 / Asp179 / His206	S119A, D179A, H206A active-site mutants	Loss of activity — validates the predicted triad
Predicted pocket residues	Substrate-panel / fragment screen at the pocket	Substrate preference; a route to a physiological substrate
Redox modifications (Cys)	Glutathionylation / SNO detection ± oxidative stress	Redox regulation of activity
Retinoid-induced degradation [5]	Pocket-/triad-mutant stability under RA	Whether catalysis couples to turnover

Its downregulation in ovarian cancer and during retinoid apoptosis [3, 5] indicates where a validated chemical probe 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, the disordered insert, and a defined active site
Medicinal chemistry	Active-site residues for docking, ABPP and probe 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 OVCA2 sequence (UniProt Q8WZ82 [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	OVCA2 · UniProt Q8WZ82, canonical isoform (227 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.

- **Triad numbering.** We use the UniProt charge-relay annotation (Ser119/Asp179/His206); mutagenesis in [4] confirms the catalytic serine and histidine but numbers the nucleophile *Ser117* — a two-residue offset to note when designing mutants.
- **Biology caveats.** OVCA2's tumour-suppressor role is unproven (later work favours the neighbouring gene OVCA1/DPH1), and no physiological substrate is known. Treat the disease case as a hypothesis.

8 References

[1] UniProt Consortium. UniProtKB entry Q8WZ82 (OVCA2, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. OVCA2 target record — T_{bio}. pharos.nih.gov/targets/Q8WZ82.

[3] Schultz D.C., Vanderveer L., Berman D.B., Hamilton T.C., Wong A.J., Godwin A.K. Identification of two candidate tumor suppressor genes on chromosome 17p13.3. *Cancer Res.* **56**(9), 1997–2002 (1996). PMID: 8616839.

[4] Bun J.S., Slack M.D., Schemenauer D.E., Johnson R.J. Comparative analysis of the human serine hydrolase OVCA2 to the model serine hydrolase homolog FSH1 from *S. cerevisiae*. *PLoS ONE* **15**(3), e0230166 (2020). doi:10.1371/journal.pone.0230166.

[5] Prowse A.H., Vanderveer L., Milling S.W.F., et al. OVCA2 is downregulated and degraded during retinoid-induced apoptosis. *Int. J. Cancer* **99**(2), 185–192 (2002). doi:10.1002/ijc.10334.

[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.