COMPUTATIONAL TARGET PROFILE

NAT8

An orphan GNAT-family N-acetyltransferase, characterised without an experimental structure

The dark ER-membrane acetyltransferase behind one of the more reproducible kidney-function GWAS signals. NAT8 has no solved structure and a thin functional literature, yet it catalyses the final step of mercapturic-acid detoxification and N6-lysine acetylation inside the endoplasmic reticulum — and its variants track with kidney function and N-acetylated metabolite levels. We resolve the canonical 227-residue sequence into a type II membrane topology, a residue-level active-site hypothesis, and a construct / validation plan, computed with Orbion's Astra suite from sequence alone.

UniProt Q9UHE5 · 227 aa · GNAT-Family N-Acetyltransferase · 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	Predicted single-pass membrane protein — consistent with the reported type II ER-membrane topology: a cytoplasmic N-terminus, one TM anchor (43–63), and a lumenal GNAT catalytic domain.
Active-Site Region	AstraBIND unclassified hypothesis (confidence 0.738) — a residue-level, substrate/cofactor-facing starting point for docking / mutagenesis; no validated ligand.
Clean Signal	One aggregation-prone segment flagged (AstraUNFOLD amyloid max 0.531) — worth screening in construct design.

PREDICTION CONFIDENCE

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

1 The Gap

Most tractable enzyme families have been structurally explored. NAT8 (N-acetyltransferase 8) has not: an IDG Tbio target with no experimental structure in the PDB and only a handful of functional studies. It is an ER-membrane-anchored, acetyl-CoA-dependent acetyltransferase with two reported jobs — N6-acetylating lysines on lumenal proteins such as PROM1 and BACE1, and acetylating cysteine S-conjugates to form mercapturic acids, the final, excretable step in detoxifying reactive electrophiles. Interest is real: NAT8 variants are among the more reproducible GWAS hits for kidney function and circulating N-acetylated amino-acid levels — but there is almost nothing structural to look up.

That combination — genuine interest, near-zero structural information — is where prediction earns its keep: everything below is computed from the canonical 227-residue sequence with Orbion's Astra suite, with no experimental NAT8 structure used as input. For a target this dark, there is no structure to consult.

2 Architecture And Topology

PREDICTED ARCHITECTURE

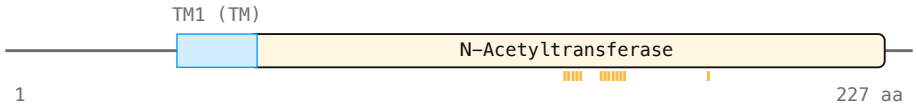

Figure 2. Predicted domain architecture along the sequence: annotated domains as boxes, disordered regions shaded, and the predicted active-site / pocket residues marked as amber ticks.

Element	Residues	Note
Transmembrane Helices	1 predicted	Boundaries: 43–63.
N-Acetyltransferase	61–220	UniProt-annotated domain.

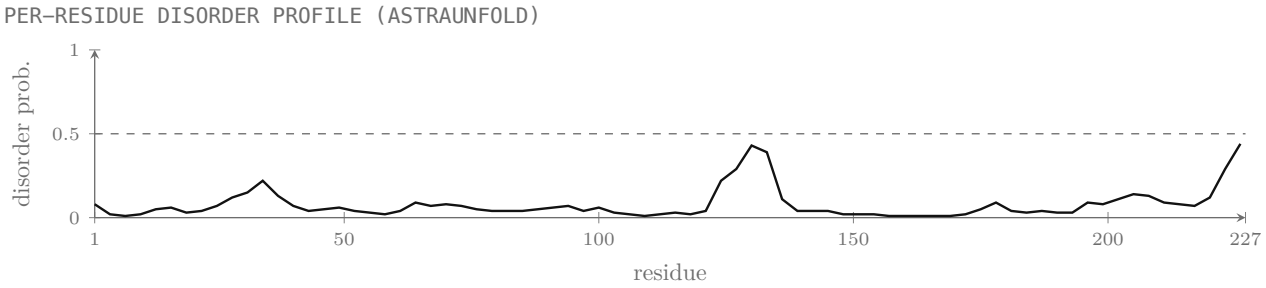

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 The Predicted Active-Site Region

Astra resolves a residue-level site — the input a docking run or a mutagenesis plan actually needs. Predicted location: **Predicted substrate / cofactor-facing residues**.

PREDICTED POCKET / FUNCTIONAL RESIDUES

N-Acetyltransferase 140–144, 149–155, 176

A residue-level hypothesis from AstraBIND. NAT8 has no ligand-bound relative for AstraBIND to retrieve from, so this is a structure-based cavity prediction rather than a retrieval-grounded one — but every predicted residue falls within the GNAT N-acetyltransferase domain (61–220), the acetyl-CoA / substrate-facing region, so it is at least domain-consistent. Treat it as a domain-level starting point for mutagenesis, not a validated pocket.

4 Post-Translational And Structural Features

- **N-acetyltransferase** (61–220) — the UniProt-annotated GNAT catalytic domain that carries the predicted acetyl-CoA / substrate-facing active site.
- **Aggregation-prone segment flagged** (AstraUNFOLD amyloid max 0.531) — a short hydrophobic stretch worth screening or engineering out when designing a soluble construct.

5 Recommended Experimental Follow-Up

Prediction	Experiment	Readout
Active-Site Region Residues	Alanine scan at the predicted site + N-acetyltransferase assay (acetyl-CoA donor; cysteine-S-conjugate or lysine acceptor)	Loss of acetyl-transfer activity at the predicted site
Disordered / Flexible Regions	Fusion-partner insertion or terminal truncation	Improved expression / thermostability for structural work
Predicted Type II Membrane Topology	Protease-protection / membrane-fractionation assay	Confirm the single-pass, lumenal-domain ER topology

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 NAT8 sequence (UniProt Q9UHE5): **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 NAT8 structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry Q9UHE5 (NAT8, human). uniprot.org.
2. Pharos (Illuminating the Druggable Genome). NAT8 target record — Tbio. pharos.nih.gov.
3. Veiga-da-Cunha M et al. Molecular identification of NAT8 as the enzyme that acetylates cysteine S-conjugates to mercapturic acids. (2010). https://doi.org/10.1074/jbc.m110.110924
4. Luo S et al. NAT8 Variants, N-Acetylated Amino Acids, and Progression of CKD. (2020). https://doi.org/10.2215/cjn.086
5. Rigby MJ et al. The endoplasmic reticulum acetyltransferases ATase1/NAT8B and ATase2/NAT8 are differentially regulated to adjust engagement of the secretory pathway. (2020). https://doi.org/10.1111/jnc.14958