MOLECULAR ATLAS · VARIANT CARD

# WFS1 I359N — Wolframin

Isoleucine → Asparagine at position 359. Transmembrane helix 2. ClinVar Uncertain significance, AlphaMissense 0.967, DynaMut2 ΔΔG -0.62 kcal/mol (destabilising).

## IDENTITY

| | |
|---|---|
| Variant | I359N (p.Isoleucine359Asparagine) |
| DNA change | c.1076T>A |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV001318136 |
| Amino acid change | Isoleucine (I) → Asparagine (N) |

## STRUCTURAL CONTEXT

| | |
|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 359 | **88.62** HIGH CONFIDENCE |
| Domain | Transmembrane helix 2 |
| Position context | Inside Transmembrane helix 2 · position 359 is bilayer-embedded |
| IDR flag | No — pLDDT well above 50 threshold |

Position 359 sits in a transmembrane helix (Transmembrane helix 2). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is medium hydrophobic (isoleucine — branched); the mutant is polar amide (asparagine — H-bond donor/acceptor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.967**

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

**-0.62** kcal/mol

Destabilising · Job 178092097384

PLDDT (ALPHAFOLD)

**88.62**

high confidence

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | UNCERTAIN SIGNIFICANCE |
| Review status | criteria provided, multiple submitters, no conflicts |
| Last evaluated | 2024/02/06 00:00 |
| Inheritance | Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6). |
| WFS1 variant landscape | I359N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- Cataract 41
- Wolfram syndrome 1
- Autosomal dominant nonsyndromic hearing loss 6
- Type 2 diabetes mellitus
- Wolfram-like syndrome

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## RESEARCH PATH DECISION TREE

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ΔΔG < 2 + binding site affected → CATEGORY 3 — docking experiments ΔΔG 2–4 → CATEGORY 2 — pharmacological chaperones ΔΔG > 4 → CATEGORY 1 — gene therapy pLDDT < 50 → CATEGORY 5 — IDR, experimental only Stable fold + functional site hit → CATEGORY 4 — site-specific docking
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**Category 3/4 — Most Druggable**

|ΔΔG|=0.62 < 2 kcal/mol (fold intact) + AlphaMissense 0.967 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.62 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.967. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.

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