MOLECULAR ATLAS · VARIANT CARD

WFS1 L734H — Wolframin

Leucine → Histidine at position 734 in lumenal domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.461 (below threshold), ΔΔG -0.47.

IDENTITY

Variant	L734H (p.Leucine734Histidine)
DNA change	c.2201T>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000593953
Amino acid change	Leucine (L) → Histidine (H) — branched aliphatic replaced by aromatic titratable basic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 734	**87.69** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 734 (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 734 in lumenal domain — same C733-C765 disulfide region (R732C, C733G, C765R). Neighbors: TYR735 (2.5 Å — Y735 partner of G736 environment), CYS733 (2.5 Å — the C733 disulfide cysteine!), MET731 (3.8 Å), TRP730 (3.8 Å). L734H sits immediately downstream of C733 — perturbing the C733-C765 disulfide region from the adjacent position. AM 0.461 below threshold but Wolfram 1 confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.461

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.47 kcal/mol

PLDDT (ALPHAFOLD)

87.69

high confidence

Destabilising · Job 177992472967

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2017/09/26 00:00
Inheritance	Wolfram syndrome 1.
WFS1 variant landscape	L734H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

RESEARCH PATH DECISION TREE

```
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
```

Category 3/4 — Most Druggable (AM under-call). |ΔΔG| 0.47. AlphaMissense 0.461 below threshold but Wolfram 1 confirms pathogenicity.

Mechanism: perturbation of C733-C765 disulfide region from adjacent position. Therapeutic: same C733-C765 microregion.

L734H is in the same C733-C765 disulfide microregion as R732C, C733G, C765R.