MOLECULAR ATLAS · VARIANT CARD

WFS1 L842F — Wolframin

Leucine → Phenylalanine at position 842 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic. AlphaMissense 0.956, DynaMut2 ΔΔG -0.61 kcal/mol (destabilising). Volume increase variant near the L829 region.

IDENTITY

Variant	L842F (p.Leucine842Phenylalanine)
DNA change	c.2524C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001518006
Amino acid change	Leucine (L) → Phenylalanine (F) — branched aliphatic hydrophobic replaced by aromatic hydrophobic. Volume increase, aromatic π-system added.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 842	**88.69** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 842 in the ER lumen (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

Position 842 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places L842 within 5 Å of GLU841 (2.5 Å), LYS843 (2.5 Å — same K843 as the K862-K843 cluster), ARG805 (3.7 Å — long-range, near A806P), SER826 (4.2 Å), and ALA844 (4.7 Å). The wild-type leucine fits cleanly into this mixed polar-basic environment. Replacing it with phenylalanine adds aromatic volume that the local pocket was not sized for. The K843 + L842 + R805 region is reorganized. The |ΔΔG| of 0.61 reflects modest fold cost. AlphaMissense's 0.956 confirms severe functional consequence. The proximity to A806P (3.7 Å through R805) and the K843 contact suggest this region is a multi-variant hub.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.956	**-0.61** kcal/mol	**88.69**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991929366	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/03/23 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	L842F is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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| = 0.61 — fold survives. AlphaMissense 0.956 confirms severe functional consequence.

Mechanism is volume mismatch in the E841-L842-K843-R805 polar-basic environment. Therapeutic strategy: site-directed at this microregion.

L842F joins A806P and the K843/K862 cluster as part of a multi-variant lumenal C-terminal target region.