MOLECULAR ATLAS · VARIANT CARD

WFS1 F783L — Wolframin

Phenylalanine → Leucine at position 783 in lumenal domain. ClinVar Conflicting including WFS1 spectrum. AlphaMissense 0.414 (below threshold), ΔΔG -0.22. pLDDT 61 borderline.

IDENTITY

Variant	F783L (p.Phenylalanine783Leucine)
DNA change	c.2347T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215370
Amino acid change	Phenylalanine (F) → Leucine (L) — aromatic replaced by branched aliphatic. Aromatic loss.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 783	**60.84** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 783 (pLDDT 61 borderline).
IDR flag	No — pLDDT well above 50 threshold

Position 783 in lumenal domain. Neighbors: PRO782 (2.5 Å — partner of G702S neighbor P782), SER784 (2.5 Å), GLN667 (4.4 Å — long-range to Y669 cluster), SER785 (4.7 Å). F783L removes aromatic. Q667 long-range contact suggests F783 mediates packing between this site and the Y669-C673 cluster. AM 0.414 under-call; WFS1 spectrum confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.414

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.22 kcal/mol

Destabilising · Job 177992473308

PLDDT (ALPHAFOLD)

60.84

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/07/31 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	F783L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Inborn genetic diseases

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 4 — Stable Fold, Function Disrupted (AM under-call, pLDDT borderline). |ΔΔG| 0.22. AlphaMissense 0.414 below threshold.

Mechanism: lost aromatic + perturbation of long-range Q667 contact. Therapeutic: 783-667 cross-domain.

F783L identifies a long-range contact to the Y669-Q667 cluster.