MOLECULAR ATLAS · VARIANT CARD

WFS1 L187F — Wolframin

Leucine → Phenylalanine at position 187 in wolframin's N-terminal cytoplasmic domain. ClinVar Pathogenic/Likely pathogenic with broad clinical spectrum — Cataract 41, Wolfram-like syndrome, DFNA6. AlphaMissense 0.954, DynaMut2 ΔΔG -1.42 kcal/mol (destabilising). A conservative-looking substitution with substantial structural cost.

IDENTITY

Variant	L187F (p.Leucine187Phenylalanine)
DNA change	c.559C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002193625
Amino acid change	Leucine (L) → Phenylalanine (F) — a medium-sized branched hydrophobic replaced by a larger aromatic hydrophobic. Volume increase plus π-electron system added.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 187	**83.50** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 187 sits in the cytosol-facing region of wolframin with good AlphaFold confidence (pLDDT 84).
IDR flag	No — pLDDT well above 50 threshold

Position 187 sits in wolframin's N-terminal cytoplasmic domain. The AlphaFold model places L187 within 5 Å of ASN188 (2.5 Å), LYS186 (2.5 Å), TYR184 (3.6 Å), MET183 (3.9 Å), and ASN203 (4.1 Å). The local environment is mixed — aromatic (Y184), polar (N188, N203), basic (K186), and hydrophobic (M183, L187 itself). Replacing leucine with phenylalanine at this position is more disruptive than the chemistry pair suggests. Phenylalanine is roughly 50% larger by side-chain volume and introduces an aromatic ring where leucine had only branched aliphatic carbons. The local pocket — packed against TYR184 (3.6 Å) and MET183 (3.9 Å) — was sized for leucine. Adding a phenyl ring forces local rearrangement. The |ΔΔG| of 1.42 kcal/mol reflects this volume mismatch. The fold absorbs the substitution but at

meaningful energetic cost. The introduced aromatic ring also creates a new potential π-π stacking opportunity with TYR184 — but at a geometry not optimized for it in the wild-type fold, so this contact may or may not form productively. The clinical breadth — Cataract 41, Wolfram-like syndrome, DFNA6 hearing loss — confirms severe functional consequence across multiple tissue contexts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.954	**-1.42** kcal/mol	**83.50**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991404378	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2024/04/16 00:00
Inheritance	Autosomal dominant pattern indicated by association with DFNA6 (WFS1-related hearing loss) and Wolfram-like syndrome.
WFS1 variant landscape	L187F is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41
- Wolfram-like syndrome
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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| = 1.42 kcal/mol — meaningful but below the Cat 2 threshold. AlphaMissense 0.954 + three documented clinical phenotypes confirm severe functional consequence.

The mechanism is volume mismatch in a cytoplasmic packing pocket (TYR184, MET183 environment). Therapeutic strategy: site-directed binders that occupy the disrupted packing region, or pharmacological chaperones biasing the fold toward the wild-type leucine geometry.

The clinical breadth (three phenotypes across both AD and tissue-specific presentations) makes this a high-value docking target.

L187F demonstrates that 'conservative' substitutions in chemistry tables can be structurally non-conservative — what looks like a small change in side-chain class (aliphatic to aromatic) becomes substantial when packed into a pocket that wasn't sized for the larger residue. The Atlas's neighbor analysis surfaces the specific contacts (TYR184, MET183) that the substitution perturbs, making the geometric target visible.
