MOLECULAR ATLAS · VARIANT CARD

WFS1 L804P — Wolframin

Leucine → Proline at position 804 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic, associated with DFNA6 (WFS1-related hearing loss). AlphaMissense 0.999 (deep pathogenic signal), DynaMut2 ΔΔG -0.44 kcal/mol (destabilising). A fold-intact variant with severe local backbone disruption.

IDENTITY

Variant	L804P (p.Leucine804Proline)
DNA change	c.2411T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000430096
Amino acid change	Leucine (L) → Proline (P) — a flexible, medium-sized hydrophobic side chain replaced by a rigid, ring-locked amino acid that kinks the polypeptide backbone wherever it appears.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 804	**91.94** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 804 sits inside the ER lumen at the heart of wolframin's largest soluble region, in a high-confidence local environment (pLDDT 92).
IDR flag	No — pLDDT well above 50 threshold

Position 804 sits deep in wolframin's C-terminal lumenal domain (residues 653–869), the protein's largest soluble region and the documented interaction interface with ATF6 and the Na+/K+ ATPase β1 subunit. The AlphaFold model places L804 against immediate sequence neighbors ARG805 (2.4 Å) and VAL803 (2.5 Å), and into a hydrophobic pocket containing PHE840 (3.3 Å) and ILE777 (3.8 Å). The leucine side chain contributes branched hydrophobic packing into that pocket, supporting the local fold geometry of two distant segments of the lumenal domain. Replacing leucine with proline at this position has a structural cost that DynaMut2's |ΔΔG| of 0.44 understates. Proline is the only amino acid whose backbone is locked into a ring — its phi angle is constrained, it cannot serve as a hydrogen-bond donor in the backbone, and it forces a kink at the

position it occupies. When proline is introduced into a region with defined secondary structure, the local geometry has to rearrange to accommodate it, and the disruption propagates a few residues in either direction along the chain. The ΔΔG value reflects the energetic cost of the global fold absorbing this disruption — modest, because the lumenal domain has flexibility to spare. But the local geometric perturbation around residues 803–805 will be substantial, and the lost packing against PHE840 and ILE777 is unrecoverable without further fold rearrangement. AlphaMissense's 0.999 score reflects this: the model recognizes the deep pathogenic signal of an introduced proline even when global stability is only modestly perturbed.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.999

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.44 kcal/mol

Destabilising · Job 177991412243

PLDDT (ALPHAFOLD)

91.94

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2016/02/18 00:00
Inheritance	Autosomal dominant pattern indicated by association with DFNA6 (WFS1-related hearing loss 6). Likely contributes to the WFS1-related dominant spectrum rather than classical AR Wolfram syndrome 1.
WFS1 variant landscape	L804P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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 —
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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| = 0.44 kcal/mol — well below the fold-integrity threshold. The wolframin fold survives the substitution, but local geometry around position 804 is severely disrupted by the introduced proline.

The therapeutic strategy here is unusual for the Atlas: the lesion is geometric, not interaction-based. A small molecule that stabilizes the local α-helical geometry around residues 803–805 could compensate for the backbone kink introduced by proline. Alternative: a chaperone that biases the fold toward the wild-type local geometry during synthesis would shift the population toward functional protein.

AlphaMissense's near-maximum score (0.999) confirms that the field's clinical observation of pathogenicity matches the structural prediction — this is a real lesion despite the small ΔΔG. The variant illustrates a category of pathogenicity the Atlas captures well: severe local geometric disruption with mild global energetic cost.

L804P is one of several proline-introduction variants in the Atlas (L543P, L402P, P504L is the inverse). When proline appears or disappears from a position with defined secondary structure, the structural cost is qualitatively different from a typical amino acid swap. The Atlas's |ΔΔG| < 2 framing applies, but the therapeutic vector shifts subtly — chaperones that stabilize local geometry become as relevant as site-directed binders.
