

WFS1 L829P — Wolframin

Leucine → Proline at position 829 in wolframin's C-terminal luminal domain. ClinVar Pathogenic/Likely pathogenic with the full clinical spectrum — DFNA6 hearing loss, type 2 diabetes, inborn genetic diseases. AlphaMissense 0.997 (near-maximum), DynaMut2 $\Delta\Delta G$ -1.02 kcal/mol (destabilising). Another proline-introduction variant with substantial structural cost.

IDENTITY

Variant	L829P (p.Leucine829Proline)
DNA change	c.2486T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004521
Amino acid change	Leucine (L) → Proline (P) — flexible branched hydrophobic replaced by rigid helix-breaking residue. Same proline-introduction mechanism as L402P, L543P, L723P, L804P.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 829	85.56 HIGH CONFIDENCE
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain · position 829 near the C-terminus of the soluble domain (pLDDT 86).
IDR flag	No — pLDDT well above 50 threshold

Position 829 sits in wolframin's C-terminal luminal domain near the C-terminus. The AlphaFold model places L829 within 5 Å of GLU830 (2.4 Å), ILE828 (2.5 Å), HIS696 (3.9 Å — long-range across the fold), LEU833 (4.2 Å), and PHE840 (4.4 Å). The HIS696 contact at 3.9 Å is particularly notable: a residue 133 sequence positions away brought into structural contact through the folded geometry of the luminal domain. The wild-type leucine at 829 contributes branched hydrophobic packing into this multi-residue contact environment. Replacing it with proline introduces backbone constraint where flexibility was needed, breaks any α -helical character of the local region, and likely perturbs the long-range L829-H696 contact. The $|\Delta\Delta G|$ of 1.02 is larger than the other proline-introduction variants in the Atlas (L723P 0.19, L402P

+0.16, L543P 0.34) — reflecting that this position is more structurally constrained, and the proline kink has farther to propagate. AlphaMissense's 0.997 (near-maximum) confirms severe functional consequence. The broad clinical spectrum (DFNA6 hearing loss, type 2 diabetes, inborn genetic diseases) reflects the multi-tissue impact of disrupting this fold-locking position.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.997

am_class: **LPath** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$

-1.02 kcal/

mol

Destabilising · Job
177990267194

PLDDT (ALPHAFOLD)

85.56

high confidence

CLINICAL EVIDENCE

ClinVar classification

PATHOGENIC/LIKELY PATHOGENIC

Review status

criteria provided, multiple submitters, no conflicts

Last evaluated

2025/07/30 00:00

Inheritance

Autosomal dominant pattern indicated by DFNA6 association.

WFS1 variant landscape

L829P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)
- Type 2 diabetes mellitus

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G$ 2–4 → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → 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. $|\Delta\Delta G| = 1.02$ kcal/mol — fold survives but with meaningful cost. AlphaMissense 0.997 + three documented phenotypes confirm severe functional consequence.

The mechanism is proline-induced backbone disruption at a position with long-range structural contact (HIS696 at 3.9 Å, 133 residues away in sequence). Therapeutic strategy: stabilize the L829-H696 long-range contact via small molecules engaging both sides of the contact.

The clinical breadth makes this a high-value docking target across multiple tissue contexts.

L829P's long-range H696 contact (133 sequence positions away) is exactly the kind of structural relationship invisible to sequence-based analysis. The Atlas surfaces it through the PDB neighbor extraction. Drug discovery aimed at the L829-H696 contact is a target that pre-atlas analysis could not have identified.