MOLECULAR ATLAS · VARIANT CARD

WFS1 P607L — Wolframin

Proline → Leucine at position 607 inside TM9. ClinVar Conflicting including monogenic diabetes, T2D, DFNA6. AlphaMissense 0.416 (below threshold), ΔΔG -0.27. Same position as P607R — proline-removal pair.

IDENTITY

Variant	P607L (p.Proline607Leucine)
DNA change	c.1820C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045441
Amino acid change	Proline (P) → Leucine (L) — rigid helix-breaking replaced by branched aliphatic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 607	**65.88** CONFIDENT
Domain	TM9 (589-609), helical transmembrane
Position context	TM9 (residues 589–609) · position 607 (pLDDT 66 borderline). Same as P607R.
IDR flag	No — pLDDT well above 50 threshold

Position 607 same neighbors as P607R: LEU608 (2.5 Å), VAL606 (2.5 Å), LEU610 (4.1 Å), SER605 (4.5 Å). P607L is the second pathogenic substitution at 607 (with P607R). Both remove the wild-type proline kink at TM9's end. P607L is the conservative hydrophobic substitution; P607R adds charge. AM 0.416 below threshold but multi-phenotype confirms pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.416

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.27 kcal/mol

Destabilising · Job 177992473138

PLDDT (ALPHAFOLD)

65.88

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/29 00:00
Inheritance	Multi-phenotype AD.
WFS1 variant landscape	P607L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- Type 2 diabetes mellitus
- 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 (AM under-call). |ΔΔG| 0.27. AlphaMissense 0.416 below threshold but multi-phenotype confirms pathogenicity.

Mechanism: same TM9 kink-removal as P607R. Therapeutic: TM9 site-directed.

P607L + P607R confirm position 607 as TM9 multi-substitution hotspot.