

WFS1 P607R — Wolframin

Proline → Arginine at position 607 inside TM9. ClinVar Conflicting.
AlphaMissense 0.922, $\Delta\Delta G$ +0.03 (neutral). pLDDT 66 borderline. Proline-removal in TM9 with charge introduction.

IDENTITY

Variant	P607R (p.Proline607Arginine)
DNA change	c.1820C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001297726
Amino acid change	Proline (P) → Arginine (R) — rigid helix-breaking replaced by large positively-charged amine. Removes constraint, introduces charge into bilayer.

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 near the end of TM9 (pLDDT 66 borderline).
IDR flag	No — pLDDT well above 50 threshold

Position 607 sits near the end of TM9. Neighbors: LEU608 (2.5 Å), VAL606 (2.5 Å), LEU610 (4.1 Å), SER605 (4.5 Å). The wild-type proline likely defines a helix-end geometry. Replacing it with arginine removes the kink and introduces charge near the membrane-water interface. The near-zero $\Delta\Delta G$ reflects fold accommodation through the arginine extending toward solvent. AlphaMissense 0.922 confirms severe consequence. P607L (Atlas card next) is the same position with leucine — both pathogenic.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 $\Delta\Delta G$	PLDDT (ALPHAFOLD)
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0.922

am_class: **LPath** —
threshold > 0.564

0.03 kcal/mol

Stabilising · Job
177992458317

65.88

confident

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2023/05/03 00:00

Inheritance

Not specified.

WFS1 variant landscape

P607R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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 4 — Stable Fold, Function Disrupted. $\Delta\Delta G \approx 0$ — fold unchanged. AlphaMissense 0.922 confirms severe consequence.

Mechanism: loss of TM9 helix-end kink plus charge introduction. Therapeutic: site-directed at the TM9 C-terminal region.

P607R + P607L (next card) are both at position 607 — multi-substitution hotspot in TM9. First Atlas TM9 variants.