MOLECULAR ATLAS · VARIANT CARD

WFS1 P428R — Wolframin

Proline → Arginine at position 428 inside wolframin's fourth transmembrane helix (TM4). ClinVar Pathogenic. AlphaMissense 0.920, DynaMut2 ΔΔG -0.22 kcal/mol (destabilising). A proline-removal variant in a TM helix — opposite mechanism to L543P-type variants.

IDENTITY

Variant	P428R (p.Proline428Arginine)
DNA change	c.1283C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203517
Amino acid change	Proline (P) → Arginine (R) — rigid helix-breaking residue replaced by a large positively-charged residue. Loss of backbone constraint plus introduction of charge into the bilayer.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 428	**89.00** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 428 is at the very start of TM4, in the membrane-water interface region (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

Position 428 sits at the start of TM4. The AlphaFold model places P428 within 5 Å of ILE427 (2.5 Å), CYS429 (2.5 Å), SER430 (4.5 Å), and GLU431 (4.9 Å). The wild-type proline at 428 likely defines the helix-initiation geometry of TM4, providing a controlled bend or break at the start of the membrane-spanning segment. Replacing proline with arginine has the same backbone-flexibility-gain as P504L (removed proline kink) but with a substantial added complication: a positive charge is introduced near the membrane-water interface. At position 428 — right at the start of TM4 — the arginine side chain can extend toward the lumenal interface where its charge is favorable, but the lost helix-initiation geometry remains a structural problem. The |ΔΔG| of 0.22 indicates the fold absorbs the substitution. AlphaMissense's 0.920 score captures the functional consequence — TM4's insertion register

shifts, the C429 immediately downstream (a possible disulfide-capable residue) is now in a different local geometry, and the E431 contact (4.9 Å) is perturbed. Notably, the same E431 residue appears as a neighbor in the A559D atlas card — E431 sits between the connecting loop containing R558 and TM4 containing P428. The position is structurally connective in the lumenal-facing region.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.920	**-0.22** kcal/mol	**89.00**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990265297	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/02/23 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic.
WFS1 variant landscape	P428R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for P428R — ClinVar Pathogenic by review evidence)

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| = 0.22 kcal/mol — fold survives. AlphaMissense 0.920 confirms severe functional consequence.

The mechanism combines loss of proline-defined helix-initiation geometry

plus charge introduction at the membrane-water interface. Therapeutic strategy: site-directed small molecules at the TM4 N-terminal region.

The E431 contact suggests this position may be structurally connected to the R558-E431 microregion that A559D perturbs. Combined drug discovery in both regions has overlapping targets.

P428R is the proline-removal complement to the L→P variants elsewhere in the Atlas. The Atlas's mechanism vocabulary handles both proline introduction (helix break created) and proline removal (helix break eliminated) as distinct but related target categories.
