MOLECULAR ATLAS · VARIANT CARD

WFS1 R685P — Wolframin

Arginine → Proline at position 685 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic, associated with rare genetic deafness. AlphaMissense 0.954, DynaMut2 ΔΔG +0.33 kcal/mol — a STABILIZING substitution. A charge-loss-plus-helix-break variant.

IDENTITY

Variant	R685P (p.Arginine685Proline)
DNA change	c.2054G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045446
Amino acid change	Arginine (R) → Proline (P) — a large, positively-charged guanidinium-bearing residue replaced by a rigid, helix-breaking residue. Loss of charge and side chain volume; introduction of backbone constraint.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 685	**89.94** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 685 in the ER lumen with high AlphaFold confidence (pLDDT 90).
IDR flag	No — pLDDT well above 50 threshold

Position 685 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places R685 within 5 Å of THR686 (2.5 Å), ALA684 (2.5 Å — the partner residue in the A684T atlas card), ASN682 (3.5 Å), MET683 (4.3 Å), and GLN687 (4.4 Å). The wild-type arginine's long, positively-charged side chain likely makes H-bond contacts with the nearby polar residues (N682, T686, Q687). Replacing arginine with proline at 685 removes the long side chain and introduces a rigid ring-locked residue. The H-bond network the wild-type R685 maintained is gone; the local backbone gains a forced kink from the proline. The DynaMut2 ΔΔG of +0.33 (stabilising) reflects that the tighter local packing achievable with proline outweighs the lost H-bonding in pure energetic terms. Yet the variant is pathogenic — AlphaMissense 0.954, ClinVar Pathogenic, associated with rare genetic deafness. The pathogenic

mechanism is functional: the lost R685 H-bond network is required for wolframin's lumenal function (likely partner protein recognition), even though the fold accommodates the substitution structurally. Notably, A684T sits at the adjacent position with its own Atlas card — a second variant in the same microregion. Both R685P and A684T perturb the M683-A684-R685-T686 loop geometry, just from different sides.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.954	**0.33** kcal/mol	**89.94**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177990263652	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2012/02/28 00:00
Inheritance	Documented in association with rare genetic deafness. AD-leaning presentation pattern likely.
WFS1 variant landscape	R685P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Rare genetic deafness

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 4 — Stable Fold, Function Disrupted. ΔΔG = +0.33 kcal/mol — actively stabilising. AlphaMissense 0.954 + clinical evidence confirm pathogenicity.

The mechanism is functional rather than structural: lost R685 H-bond network with N682, T686, Q687, plus introduction of a backbone kink from

proline. Drug discovery here aims at the functional contact, not at fold rescue.

Combined with A684T (Atlas card adjacent), drug discovery in the 683-687 microregion has two convergent variant targets.

R685P is another Atlas variant where ΔΔG is positive (stabilising) but the variant is unambiguously pathogenic — joining T361I, L402P in this class. These variants are invisible to ΔΔG-only analysis but clearly picked up by AlphaMissense and clinical evidence. They are exactly the variants the Atlas's dual-metric framing was designed to surface.
