MOLECULAR ATLAS · VARIANT CARD

WFS1 R805W — Wolframin

Arginine → Tryptophan at position 805 in lumenal domain. ClinVar Conflicting. AlphaMissense 0.487 (borderline), ΔΔG +0.26 STABILISING. R→W class — aromatic replaces charge.

IDENTITY

Variant	R805W (p.Arginine805Tryptophan)
DNA change	c.2413C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001675945
Amino acid change	Arginine (R) → Tryptophan (W) — long positively-charged guanidinium replaced by bulky aromatic indole.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 805	**91.44** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 805 (pLDDT 91).
IDR flag	No — pLDDT well above 50 threshold

> Position 805 in lumenal domain. Neighbors: ALA806 (2.4 Å — A806P), LEU804 (2.5 Å — L804P!), PHE775 (3.4 Å — F775V!), PHE840 (3.7 Å). R805 sits in the dense 804-806 cluster (with L804P, A806P) and contacts F775 (F775V). Replacing R805 with tryptophan eliminates the positive charge and creates a tryptophan-phenylalanine aromatic cluster with F775 + F840. The variant fold packs efficiently (+0.26). AM 0.487 borderline; ClinVar Conflicting. The mechanism is loss of R805 charge from the F775-R805 ionic/cation-π contact discussed in F775V Atlas card.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.487
am_class: **Amb** — threshold > 0.564

0.26 kcal/mol
Stabilising · Job 177992470439

91.44
high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/10/28 00:00
Inheritance	Not specified.
WFS1 variant landscape	R805W is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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 = +0.26 stabilising. AlphaMissense 0.487 borderline.

Mechanism: loss of R805 cation-π contribution to F775 contact. Therapeutic: same 775-806 microregion (with L804P, A806P, F775V).

R805W is the fifth variant in the dense 775-806 microregion.
