MOLECULAR ATLAS · VARIANT CARD

WFS1 R522M — Wolframin

Arginine → Methionine at position 522. Cytoplasmic loop 4. ClinVar Uncertain significance, AlphaMissense 0.800, DynaMut2 ΔΔG -0.26 kcal/mol (destabilising).

IDENTITY

Variant	R522M (p.Arginine522Methionine)
DNA change	c.1565G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002628550
Amino acid change	Arginine (R) → Methionine (M)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 522	**76.88** HIGH CONFIDENCE
Domain	Cytoplasmic loop 4
Position context	Loop region · position 522 sits between transmembrane segments, solvent-accessible
IDR flag	No — pLDDT well above 50 threshold

> Position 522 sits in a connecting loop between transmembrane helices. Loop residues are typically solvent-exposed and often contribute to interhelical contacts or serve as recognition sites for binding partners. The wild-type residue is positively charged (arginine — guanidinium, strong H-bond donor); the mutant is hydrophobic sulfur (methionine). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.800

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.26 kcal/mol

Destabilising · Job 178092148135

PLDDT (ALPHAFOLD)

76.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/09/26 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	R522M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder
- Inborn genetic diseases

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|=0.26 < 2 kcal/mol (fold intact) + AlphaMissense 0.800 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.26 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.800. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
