MOLECULAR ATLAS · VARIANT CARD

WFS1 H407R — Wolframin

Histidine → Arginine at position 407. Transmembrane helix 4. ClinVar Uncertain significance, AlphaMissense 0.651, DynaMut2 ΔΔG -0.67 kcal/mol (destabilising).

IDENTITY

Variant	H407R (p.Histidine407Arginine)
DNA change	c.1220A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001519577
Amino acid change	Histidine (H) → Arginine (R)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 407	**90.31** HIGH CONFIDENCE
Domain	Transmembrane helix 4
Position context	Inside Transmembrane helix 4 · position 407 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 407 sits in a transmembrane helix (Transmembrane helix 4). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is titratable basic (histidine — imidazole); the mutant is positively charged (arginine — guanidinium, strong H-bond donor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.651

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

DYNAMUT2 ΔΔG

-0.67 kcal/mol

Destabilising · Job 178092155109

PLDDT (ALPHAFOLD)

90.31

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/06/12 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	H407R is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Autosomal dominant nonsyndromic hearing loss 6
- Type 2 diabetes mellitus
- Wolfram-like syndrome
- Cataract 41

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|=0.67 < 2 kcal/mol (fold intact) + AlphaMissense 0.651 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.67 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.651. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
