MOLECULAR ATLAS · VARIANT CARD

WFS1 H766Q — Wolframin

Histidine → Glutamine at position 766. C-terminal ER-lumenal (calcium binding. ClinVar Uncertain significance/Uncertain risk allele, AlphaMissense 0.934, DynaMut2 ΔΔG -0.19 kcal/mol (destabilising).

IDENTITY

Variant	H766Q (p.Histidine766Glutamine)
DNA change	c.2298C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000349324
Amino acid change	Histidine (H) → Glutamine (Q)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 766	**89.25** HIGH CONFIDENCE
Domain	C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)
Position context	C-terminal lumenal domain · position 766 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

> Position 766 sits in the C-terminal lumenal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na+/K+ ATPase β1. The wild-type residue is titratable basic (histidine — imidazole); the mutant is polar amide (glutamine — H-bond donor/acceptor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.934

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

DYNAMUT2 ΔΔG

-0.19 kcal/mol

Destabilising · Job 178092103446

PLDDT (ALPHAFOLD)

89.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE/UNCERTAIN RISK ALLELE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2018/01/12 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	H766Q is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6
- WFS1-Related Spectrum Disorders
- Wolfram syndrome 1

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|=0.19 < 2 kcal/mol (fold intact) + AlphaMissense 0.934 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=0.19 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.934. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
