MOLECULAR ATLAS · VARIANT CARD

WFS1 Y669H — Wolframin

Tyrosine → Histidine at position 669 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic (stronger tier than the Y669C variant at the same position). AlphaMissense 0.997, DynaMut2 ΔΔG -1.20 kcal/mol (destabilising). A direct structural comparator to Y669C.

IDENTITY

Variant	Y669H (p.Tyrosine669Histidine)
DNA change	c.2005T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001458745
Amino acid change	Tyrosine (Y) → Histidine (H) — a large aromatic phenol replaced by a smaller titratable imidazole ring. Aromatic character partially preserved; pKa near physiological pH means the residue can be neutral or positively charged depending on local environment.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 669	**87.75** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 669 in the ER lumen, well-folded region (pLDDT 88). Same structural environment as Y669C.
IDR flag	No — pLDDT well above 50 threshold

> Position 669 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places Y669 within 5 Å of GLN668 (2.5 Å), GLY670 (2.5 Å), TRP666 (3.8 Å), THR665 (4.0 Å), ALA671 (4.4 Å), and GLN667 (4.5 Å). The wild-type tyrosine ring makes edge-face π–π stacking with TRP666 and hydrogen-bonding contacts to nearby polar residues through its hydroxyl. Replacing tyrosine with histidine here preserves more structural character than the cysteine substitution at the same position (Y669C, Atlas card adjacent). The imidazole ring of histidine is aromatic, so some π-stacking interaction with TRP666 is preserved — although the histidine imidazole is smaller, lacks the phenol's hydroxyl arm, and presents a different electrostatic surface. Critically, histidine's pKa is close to physiological pH; the residue can be

> neutral or positively charged depending on its local environment. The ER lumen is mildly acidic, which favors the protonated, charged form. This substitution carries a larger DynaMut2 |ΔΔG| (1.20 kcal/mol) than Y669C (0.41 kcal/mol). Two factors explain the difference. First, histidine's larger volume creates steric mismatch where the tyrosine's hydroxyl arm previously projected into the local environment without conflict. Second, the introduced positive charge — when histidine is protonated in the mildly acidic ER lumen — destabilizes the local electrostatic context that the neutral tyrosine occupied. The net effect is a moderate but real destabilization of the local fold, while still leaving the protein fold globally intact. The pathogenic classification ("Pathogenic" rather than the "Likely Pathogenic" of Y669C) reflects accumulated clinical evidence — multiple submitters, multiple cases — that this specific substitution has reliable functional consequences.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.997	**-1.2** kcal/mol	**87.75**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990252046	high confidence

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CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2021/02/11 00:00
Inheritance	Inheritance pattern not specified in this ClinVar entry. The stronger ClinVar tier reflects more accumulated evidence of pathogenicity than Y669C, but the mechanism and inheritance pattern likely overlap with Y669's role in the lumenal fold.
WFS1 variant landscape	Y669H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for Y669H — ClinVar Pathogenic classification established by review evidence)

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| = 1.20 kcal/mol — modest destabilization, fold intact. AlphaMissense 0.997 confirms severe functional consequence.

The mechanism is partly preserved aromatic stacking with TRP666 (the histidine imidazole is still aromatic) plus a new pH-dependent positive charge in a polar lumenal context. The therapeutic strategy is site-directed: a small molecule that occupies the steric niche the wild-type tyrosine ring occupied, ideally with the same H-bond donor capacity that the lost hydroxyl provided.

The two-variant comparison at position 669 (Y669H vs Y669C) is a clean teaching example of how substitution chemistry — not just position — drives severity and mechanism. The Atlas captures this resolution; pre-atlas drug discovery would not have.

Y669 sits at a position where wolframin's lumenal fold packs aromatically against TRP666. Multiple ClinVar substitutions at this position (Y669C, Y669H) are pathogenic with different mechanisms and different severity. This is precisely the variant geometry that responds best to structure-based drug design: same local pocket, same therapeutic target, multiple variant chemistries requiring slight design variations.

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