

WFS1 Y650H — Wolframin

Tyrosine → Histidine at position 650 inside wolframin's tenth transmembrane helix (TM10). ClinVar Pathogenic. AlphaMissense 0.518 (AMBIGUOUS — at the likely-pathogenic threshold), DynaMut2 $\Delta\Delta G$ +0.05 kcal/mol (essentially neutral). pLDDT 69 — borderline confidence. A variant in a confidence-edge region with ambiguous AM signal but confirmed clinical pathogenicity.

IDENTITY

Variant	Y650H (p.Tyrosine650Histidine)
DNA change	c.1948T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203525
Amino acid change	Tyrosine (Y) → Histidine (H) — aromatic phenol replaced by aromatic imidazole. Both are aromatic and titratable; histidine is smaller and its imidazole has different pKa than tyrosine's phenol.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 650	68.69 CONFIDENT
Domain	TM10 (632-652), helical transmembrane
Position context	TM10 (residues 632-652) · position 650 is near the C-terminus of TM10, approaching the membrane-lumen interface. pLDDT 69 indicates borderline AlphaFold confidence.
IDR flag	No — pLDDT well above 50 threshold

Position 650 sits near the end of TM10. The AlphaFold model places Y650 within 5 Å of PHE649 (2.5 Å), VAL651 (2.5 Å), CYS647 (3.7 Å), PHE646 (3.7 Å), and TRP648 (4.4 Å). The local environment is dominated by aromatic residues (F649, F646, W648) plus a cysteine (C647) — a tightly-packed aromatic cluster at the end of TM10. The wild-type tyrosine ring participates in π -stacking with the surrounding aromatic residues (F649, F646, W648). The hydroxyl can H-bond to C647's backbone or to a nearby polar residue. The local environment is densely aromatic — a structural feature that requires precise geometric matching. Replacing tyrosine with histidine preserves some aromatic character (histidine's imidazole is aromatic) but

the geometry shifts substantially. Histidine's imidazole is smaller and oriented differently than tyrosine's phenol. The π -stacking pattern with F649/F646/W648 reorganizes. The DynaMut2 $\Delta\Delta G$ of essentially zero (+0.05) indicates fold accommodates the swap easily — both residues fit in the local pocket. But AlphaMissense's 0.518 is borderline (just below the 0.564 likely-pathogenic threshold), and ClinVar Pathogenic + the borderline pLDDT (69) together create an ambiguous interpretation. The variant is likely pathogenic by a specific mechanism (disrupted aromatic stacking geometry in the TM10 C-terminal aromatic cluster) but the AM signal is weak. This is a variant where wet-lab characterization would be especially valuable.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.518

am_class: **Amb** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$

0.05 kcal/mol

Stabilising · Job
177990266996

PLDDT (ALPHAFOLD)

68.69

confident

CLINICAL EVIDENCE

ClinVar classification

PATHOGENIC

Review status

criteria provided, single submitter

Last evaluated

2023/03/09 00:00

Inheritance

Inheritance not specified.

WFS1 variant landscape

Y650H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for Y650H — ClinVar Pathogenic by review evidence)

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G$ 2–4 → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

Category 4 — Stable Fold, Function Disrupted (borderline confidence). $\Delta\Delta G = +0.05$ kcal/mol — fold essentially unchanged.

AlphaMissense 0.518 is at the boundary of likely-pathogenic. pLDDT 69 borderline. ClinVar Pathogenic confirms clinical relevance.

The mechanism is reorganization of an aromatic stacking cluster (F646, F649, W648) at the C-terminal end of TM10. Therapeutic strategy: site-directed at the TM10 aromatic cluster. Wet-lab characterization is strongly recommended before therapeutic strategy is finalized given the AM and pLDDT borderline signals.

Y650H is a 'gray zone' variant — pathogenic by ClinVar but with borderline AlphaMissense score and borderline AlphaFold confidence. The Atlas surfaces this complexity rather than papering over it. Drug discovery here should pause for wet-lab validation rather than committing to a computational-only design strategy.