MOLECULAR ATLAS · VARIANT CARD

WFS1 Y650D — Wolframin

Tyrosine → Aspartate at position 650 inside TM10. ClinVar Likely pathogenic. AlphaMissense 0.829, DynaMut2 ΔΔG +0.38 STABILISING. pLDDT 69 borderline. Same position as Y650H (Atlas card adjacent) but with charge introduction.

IDENTITY

Variant	Y650D (p.Tyrosine650Aspartate)
DNA change	c.1948T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002783903
Amino acid change	Tyrosine (Y) → Aspartate (D) — large aromatic phenol replaced by small negatively-charged carboxylate. Volume decrease plus charge introduction.

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 near the C-terminus of TM10 (pLDDT 69 borderline).
IDR flag	No — pLDDT well above 50 threshold

> Position 650 sits at the end of TM10, in the same aromatic-rich pocket discussed in the Y650H Atlas card: PHE649 (2.5 Å), VAL651 (2.5 Å), CYS647 (3.7 Å), PHE646 (3.7 Å), TRP648 (4.4 Å). Replacing tyrosine with aspartate is more disruptive than Y650H. Y650H preserved aromatic character (histidine imidazole). Y650D eliminates the aromatic ring entirely and introduces a small carboxylate where the wild-type phenol provided bulky aromatic packing. The aromatic cluster (F646, F649, W648) loses its tyrosine partner; the new carboxylate is also unfavorable in the bilayer-embedded environment. The DynaMut2 ΔΔG of +0.38 (stabilising) is surprising — possibly because the aspartate can extend toward the lumenal face of TM10 where its charge is more compatible. AlphaMissense's 0.829 + ClinVar Pathogenic confirm severe functional consequence despite the stabilization.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.829

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

0.38 kcal/mol

Stabilising · Job 177992006596

PLDDT (ALPHAFOLD)

68.69

confident

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/01/04 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	Y650D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

```
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
```

Category 4 — Stable Fold, Function Disrupted. ΔΔG = +0.38 stabilising. AlphaMissense 0.829 confirms severe functional consequence.

Mechanism is loss of Y650 aromatic packing with the TM10 C-terminal aromatic cluster (F646, F649, W648). Therapeutic strategy: same microregion as Y650H.

Y650D + Y650H together establish position 650 as a critical aromatic-anchor position. Two variants at the same position with different chemistries — both pathogenic, same therapeutic target.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*