MOLECULAR ATLAS · VARIANT CARD

WFS1 F350I — Wolframin

Phenylalanine → Isoleucine at position 350 inside TM2. ClinVar Likely pathogenic. AlphaMissense 0.934, DynaMut2 ΔΔG +0.52 kcal/mol — STABILISING. Aromatic-to-branched-aliphatic substitution in a TM helix.

IDENTITY

Variant	F350I (p.Phenylalanine350Isoleucine)
DNA change	c.1048T>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003718608
Amino acid change	Phenylalanine (F) → Isoleucine (I) — aromatic hydrophobic replaced by branched aliphatic hydrophobic. Aromatic π-system lost; volume comparable.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 350	**93.38** HIGH CONFIDENCE
Domain	TM2 (340-360), helical transmembrane
Position context	TM2 (residues 340–360) · position 350 mid-helix, bilayer-embedded (pLDDT 93 — high confidence).
IDR flag	No — pLDDT well above 50 threshold

Position 350 sits in TM2. The AlphaFold model places F350 within 5 Å of ILE349 (2.5 Å), TYR351 (2.5 Å), SER418 (3.3 Å — TM2-TM3 cross-helix contact), SER353 (3.5 Å), and LEU347 (3.7 Å). The F350-S418 contact across helices is the structurally significant observation. The wild-type phenylalanine's aromatic ring likely makes π-stacking or edge-face contact with Y351 and aromatic packing with the surrounding helices. Replacing it with isoleucine eliminates the aromatic character and replaces it with branched aliphatic packing. The DynaMut2 ΔΔG of +0.52 (stabilising) reflects that isoleucine packs efficiently into the local hydrophobic environment. But AlphaMissense's 0.934 confirms severe functional consequence. The

mechanism is loss of aromatic π-stacking with Y351 plus perturbation of the F350-S418 TM2-TM3 cross-helix contact.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.934	**0.52** kcal/mol	**93.38**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177992005217	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/07/28 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	F350I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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 4 — Stable Fold, Function Disrupted. ΔΔG = +0.52 stabilising. AlphaMissense 0.934 confirms severe functional consequence.

Mechanism is loss of aromatic packing with Y351 plus TM2-TM3 interface disruption at S418. Therapeutic strategy: site-directed at the F350-Y351-S418 contact cluster.

> F350I joins the stabilising-but-pathogenic class. The TM2-TM3 cross-helix S418 contact identifies a previously-unseen TM-TM target.
