MOLECULAR ATLAS · VARIANT CARD

WFS1 F439C — Wolframin

Phenylalanine → Cysteine at position 439 inside TM4. ClinVar Conflicting including DFNA6 and Wolfram. AlphaMissense 0.886, ΔΔG +0.51 STABILISING.

IDENTITY

Variant	F439C (p.Phenylalanine439Cysteine)
DNA change	c.1316T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215388
Amino acid change	Phenylalanine (F) → Cysteine (C) — aromatic hydrophobic replaced by thiol-bearing residue.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 439	**92.75** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 439 mid-helix (pLDDT 93).
IDR flag	No — pLDDT well above 50 threshold

Position 439 sits in TM4. Neighbors: PHE438 (2.5 Å — second aromatic), THR440 (2.5 Å), THR442 (3.4 Å), THR436 (3.6 Å). Multiple threonines suggest polar packing in the local TM environment. Replacing F439 with cysteine eliminates aromatic packing. The fold actually stabilises (+0.51) — the local pocket likely accommodates the smaller cysteine more efficiently than the aromatic ring. But AlphaMissense 0.886 + DFNA6 + Wolfram-related clinical evidence confirm severe consequence. Mechanism is loss of aromatic packing with adjacent F438 plus free-thiol introduction in TM4.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.886	**0.51** kcal/mol	**92.75** high confidence

am_class: **LPath** — threshold > 0.564	Stabilising · Job 177992458972	

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/08/18 00:00
Inheritance	DFNA6 hearing loss + WFS1-related disorder documented.
WFS1 variant landscape	F439C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)
- Wolfram-like syndrome

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 = +0.51 stabilising. AlphaMissense 0.886 + DFNA6 confirm severe consequence.

Mechanism: lost aromatic packing in TM4 + thiol introduction. Therapeutic: TM4 site-directed.

F439C joins the F-to-C class (with F882C) — both stabilising or near-neutral ΔΔG but pathogenic by AlphaMissense + clinical.