MOLECULAR ATLAS · VARIANT CARD

WFS1 F882C — Wolframin

Phenylalanine → Cysteine at position 882 inside TM11. ClinVar Likely pathogenic, auditory neuropathy. AlphaMissense 0.496 (below threshold) — AM under-call. DynaMut2 ΔΔG -1.59 kcal/mol (destabilising). Volume loss in the TM11 aromatic cluster.

IDENTITY

Variant	F882C (p.Phenylalanine882Cysteine)
DNA change	c.2645T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002683881
Amino acid change	Phenylalanine (F) → Cysteine (C) — aromatic hydrophobic replaced by thiol-bearing residue. Massive volume loss; aromatic character lost.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 882	**82.31** HIGH CONFIDENCE
Domain	TM11 (870-890), helical transmembrane
Position context	TM11 (residues 870–890) · position 882 mid-helix, bilayer-embedded (pLDDT 82).
IDR flag	No — pLDDT well above 50 threshold

Position 882 sits inside TM11. The AlphaFold model places F882 within 5 Å of PHE881 (2.5 Å), PHE883 (2.5 Å), PHE879 (3.9 Å), ASP880 (4.2 Å), and ALA878 (4.4 Å). The local environment is a dense aromatic cluster — four phenylalanines (F879, F881, F882, F883) plus the nearby P885 (P885L Atlas card) and F884/F886 (in the broader cluster). Replacing F882 with cysteine eliminates one of the four aromatics in this cluster. The π-stacking network reorganizes; the introduced thiol can engage in oxidative disulfide chemistry if a partner cysteine is nearby (none within 5 Å here). The |ΔΔG| of 1.59 reflects substantial structural cost from the lost aromatic. AlphaMissense's 0.496 is below the 0.564 likely-pathogenic threshold — another AM under-call case. ClinVar Likely Pathogenic + auditory neuropathy + the substantial ΔΔG argue for genuine pathogenicity despite the AM signal.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.496	**-1.59** kcal/mol	**82.31**
am_class: **Amb** — threshold > 0.564	Destabilising · Job 177992009439	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/12/22 00:00
Inheritance	Auditory neuropathy documented.
WFS1 variant landscape	F882C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Auditory neuropathy

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 (AM under-call). |ΔΔG| = 1.59 — close to Cat 2. AlphaMissense 0.496 below threshold but ClinVar pathogenic + auditory neuropathy + substantial ΔΔG confirm pathogenicity.

Mechanism is loss of one aromatic from the dense TM11 phenylalanine cluster (F879-F881-F882-F883). Therapeutic strategy: site-directed at the TM11 aromatic cluster — same broader region as P885L.

F882C joins the AM-under-call class (with W639G, R629W, E202G). Drug discovery should integrate ΔΔG with AM rather than treating either as the sole pathogenicity signal.