

WFS1 F331I — Wolframín

Phenylalanine → Isoleucine at position 331 inside TM1. ClinVar Conflicting including DFNA6. AlphaMissense 0.458 (below threshold), $\Delta\Delta G$ +0.56 STABILISING.

IDENTITY

Variant	F331I (p.Phenylalanine331Isoleucine)
DNA change	c.991T>A
Gene · Protein	WFS1 · Wolframín (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000229648
Amino acid change	Phenylalanine (F) → Isoleucine (I) — aromatic replaced by branched aliphatic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 331	74.75 HIGH CONFIDENCE
Domain	TM1 (314-334), helical transmembrane
Position context	TM1 (residues 314-334) · position 331 near TM1 end (pLDDT 75).
IDR flag	No — pLDDT well above 50 threshold

Position 331 near end of TM1. Neighbors: ILE332 (2.5 Å), PHE330 (2.5 Å — adjacent existing phenylalanine), SER334 (3.5 Å), LEU327 (3.6 Å). Aromatic cluster F330-F331. Replacing F331 with isoleucine eliminates aromatic packing with F330 + lost adjacency. $\Delta\Delta G$ +0.56 stabilising; AM 0.458 under-call; DFNA6 + WFS1 spectrum confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.458am_class: **Amb** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **0.56** kcal/molStabilising · Job
177992471066

PLDDT (ALPHAFOLD)

74.75

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/04/08 00:00

Inheritance

DFNA6.

WFS1 variant landscape

F331I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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 (AM under-call, stabilising). $\Delta\Delta G$ +0.56. AlphaMissense 0.458 below threshold but DFNA6 confirm pathogenicity.

Mechanism: lost F330-F331 aromatic packing in TM1. Therapeutic: TM1 microregion.

F331I extends the TM1 cluster (now 7+ variants in or near TM1).