MOLECULAR ATLAS · VARIANT CARD

WFS1 F329I — Wolframin

Phenylalanine → Isoleucine at position 329 inside TM1. ClinVar Conflicting including WFS1 spectrum + Wolfram. AlphaMissense 0.15 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.22.

IDENTITY

Variant	F329I (p.Phenylalanine329Isoleucine)
DNA change	c.985T>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000504708
Amino acid change	Phenylalanine (F) → Isoleucine (I) — aromatic replaced by branched aliphatic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 329	**77.00** HIGH CONFIDENCE
Domain	TM1 (314-334), helical transmembrane
Position context	TM1 (residues 314–334) · position 329 near TM1 end (pLDDT 77).
IDR flag	No — pLDDT well above 50 threshold

Position 329 in TM1. Neighbors: ILE328 (2.5 Å), PHE330 (2.5 Å — F330-F331 cluster region; F331I!), ASN325 (3.6 Å — A325 in A326 region). F329I loses aromatic. Adjacent to F331I (Atlas card). Both perturb the F329-F330-F331 aromatic cluster. AM 0.15 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.154

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.22 kcal/mol

Destabilising · Job 177992502616

PLDDT (ALPHAFOLD)

77.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/02/03 00:00
Inheritance	WFS1 spectrum + Wolfram.
WFS1 variant landscape	F329I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Wolfram syndrome 1

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| 0.22. AlphaMissense 0.15 below threshold but multi-phenotype confirms.

Mechanism: aromatic loss in F329-F330-F331 TM1 cluster. Therapeutic: TM1 multi-variant target.

F329I + F331I — adjacent TM1 aromatic-loss variants in same F329-F330-F331 cluster.