MOLECULAR ATLAS · VARIANT CARD

WFS1 F515S — Wolframin

Phenylalanine → Serine at position 515. Transmembrane helix 7. ClinVar Uncertain significance, AlphaMissense 0.801, DynaMut2 ΔΔG -3.33 kcal/mol (destabilising).

IDENTITY

Variant	F515S (p.Phenylalanine515Serine)
DNA change	c.1544T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002000596
Amino acid change	Phenylalanine (F) → Serine (S)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 515	**86.50** HIGH CONFIDENCE
Domain	Transmembrane helix 7
Position context	Inside Transmembrane helix 7 · position 515 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 515 sits in a transmembrane helix (Transmembrane helix 7). Wolframin has eleven such helices anchoring it in the ER membrane; substitutions inside the bilayer-embedded segments can disrupt helix packing, lipid contacts, and the overall ER topology of the protein. The wild-type residue is large aromatic hydrophobic (phenylalanine); the mutant is small polar (serine — hydroxyl). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.801

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

-3.33 kcal/mol

Destabilising · Job 178092116465

PLDDT (ALPHAFOLD)

86.50

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, single submitter
Last evaluated	2022/06/28 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	F515S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no 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 2 — Moderately Destabilizing**
>
> |ΔΔG|=3.33 in the 2–4 range. Pharmacological chaperone candidate.
