MOLECULAR ATLAS · VARIANT CARD

WFS1 P320S — Wolframin

Proline → Serine at position 320. Transmembrane helix 1. ClinVar Uncertain significance/Uncertain risk allele, AlphaMissense 0.932, DynaMut2 ΔΔG -0.24 kcal/mol (destabilising).

IDENTITY

Variant	P320S (p.Proline320Serine)
DNA change	c.958C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000444629
Amino acid change	Proline (P) → Serine (S)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 320	**67.62** CONFIDENT
Domain	Transmembrane helix 1
Position context	Inside Transmembrane helix 1 · position 320 is bilayer-embedded
IDR flag	No — pLDDT well above 50 threshold

> Position 320 sits in a transmembrane helix (Transmembrane helix 1). 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 rigid/helix-breaking (proline — kinks backbone); 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	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.932	**-0.24** kcal/mol	**67.62**
am_class: **likely pathogenic** — threshold > 0.564	Destabilising · Job 178092103622	confident

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CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE/UNCERTAIN RISK ALLELE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2017/02/01 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented.
WFS1 variant landscape	P320S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- 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

$|\Delta\Delta G|=0.24 < 2$ kcal/mol (fold intact) + AlphaMissense 0.932 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution ($|\Delta\Delta G|=0.24$ kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.932. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.

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Every assumption documented.