MOLECULAR ATLAS · VARIANT CARD

WFS1 S855P — Wolframin

Ser→Pro p855 lumenal AM=0.09 ddg=-0.08 pLDDT=45. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	S855P (p.Serine855Proline)
DNA change	c.2563_2565delinsCCG
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000591341
Amino acid change	proline introduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 855	**45.12** BELOW IDR THRESHOLD
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain
IDR flag	YES — pLDDT 45.12 is below 50 threshold (route to Cat 5)

> Position analysis: LEU854 (2.5 Å), PRO856 (2.5 Å — adjacent existing P! Pro-Pro motif!), THR857 (4.1 Å). Pro-Pro motif created at 855-856. pLDDT 45 IDR boundary. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.091

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.08 kcal/mol

Destabilising · Job 177992516214

PLDDT (ALPHAFOLD)

45.12

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2020/07/18 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	S855P is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific 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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> **Cat 5 IDR boundary — see structural prose.** AlphaMissense below threshold (AM under-call class) but mechanism is structurally clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

> Pro-Pro motif at IDR boundary.

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