

WFS1 S790L — Wolframin

Ser→Leu p790 lumenal AM=0.09 ddg=-0.6 pLDDT=42. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	S790L (p.Serine790Leucine)
DNA change	c.2369C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000229641
Amino acid change	polar→hydrophobic

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 790	41.91 BELOW IDR THRESHOLD
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal IDR
IDR flag	YES — pLDDT 41.91 is below 50 threshold (route to Cat 5)

Position analysis: GLY789 (2.4 Å), ARG791 (2.4 Å), ASP788 (3.9 Å). pLDDT 42 deep IDR. Same position as S790W. DynaMut2 untrustworthy. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.095am_class: **LBen** —
threshold > 0.564

DYNAMUT2 ΔΔG

-0.6 kcal/molDestabilising · Job
177992519178

PLDDT (ALPHAFOLD)

41.91

BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/11/26 00:00

Inheritance

Conflicting ClinVar classifications.

WFS1 variant landscape

S790L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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

Cat 5 IDR — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

Same position as S790W — deep IDR.