

# WFS1 S790W — Wolframin

Serine → Tryptophan at position 790. ClinVar Conflicting including Wolfram. AlphaMissense 0.15 (below threshold) — AM under-call. DynaMut2  $\Delta\Delta G$  -0.81. pLDDT 42 — Category 5 IDR!

## IDENTITY

Variant	S790W (p.Serine790Tryptophan)
DNA change	c.2369C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166608
Amino acid change	Serine (S) → Tryptophan (W) — small polar hydroxyl replaced by bulky aromatic indole. Massive volume increase.

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 790	<b>41.91</b> <span>BELOW IDR THRESHOLD</span>
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain · position 790 (pLDDT 42 — deep IDR).
IDR flag	YES — pLDDT 41.91 is below 50 threshold (route to Cat 5)

Position 790 at pLDDT 42 — DEEP IDR. Sparse neighbors (GLY789, ARG791, ASP788). DynaMut2 untrustworthy. S790W introduces massive aromatic volume into a disordered region. AM 0.15 under-call. Wolfram documented.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE <b>0.145</b> am_class: <b>LBen</b> — threshold > 0.564	DYNAMUT2 $\Delta\Delta G$ <b>-0.81</b> kcal/ mol Destabilising · Job 177992504586	PLDDT (ALPHAFOLD) <b>41.91</b> BELOW IDR THRESHOLD
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## CLINICAL EVIDENCE

ClinVar classification

### CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/10/01 00:00

Inheritance

Wolfram syndrome 1.

WFS1 variant landscape

S790W is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

## 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

**Category 5 — IDR Exclusion.** pLDDT 42 deep IDR. AlphaMissense 0.15 below threshold. DynaMut2 prediction not trustworthy.

The Atlas routes Category 5 variants to wet-lab characterization.

S790W is deep-IDR — Atlas flags for wet-lab work.