MOLECULAR ATLAS · VARIANT CARD

WFS1 E593D — Wolframin

Glu→Asp p593 TM9 AM=0.11 ddg=+0.03 pLDDT=70. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	E593D (p.Glutamate593Aspartate)
DNA change	c.1779G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215362
Amino acid change	conservative carboxylate swap

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 593	**69.81** CONFIDENT
Domain	TM9 (589-609), helical transmembrane
Position context	TM9 (589-609)
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: LEU592 (2.5 Å — L592V!), LEU594 (2.5 Å), THR595 (4.5 Å — A598T region). Adjacent to L592V in TM9 cluster. The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE
0.110
am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG
0.03 kcal/mol
Stabilising · Job 177992512187

PLDDT (ALPHAFOLD)
69.81
confident

CLINICAL EVIDENCE

ClinVar classification	CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status	criteria provided, conflicting classifications
Last evaluated	2025/12/29 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	E593D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

```
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
```

Cat 4 — 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.

TM9 cluster adjacent to L592V/P607L/R/A598T.
