MOLECULAR ATLAS · VARIANT CARD

WFS1 D797V — Wolframin

Aspartate → Valine at position 797 in lumenal domain. ClinVar Conflicting. AlphaMissense 0.876, ΔΔG +0.04 (neutral). pLDDT 65 borderline.

IDENTITY

Variant	D797V (p.Aspartate797Valine)
DNA change	c.2390A>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002203531
Amino acid change	Aspartate (D) → Valine (V) — negatively-charged carboxylate replaced by branched aliphatic hydrophobic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 797	**64.88** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 797 (pLDDT 65 borderline).
IDR flag	No — pLDDT well above 50 threshold

Position 797 sits in the lumenal C-terminal region. Neighbors: VAL798 (2.4 Å), ASP796 (2.4 Å — adjacent aspartate), GLU794 (4.2 Å), THR799 (4.3 Å). Replacing D797 with valine eliminates the negative charge in a local charged cluster (D796, E794 nearby). Fold accommodates (ΔΔG essentially zero). AlphaMissense 0.876 confirms severe consequence. Same position as D797N — both pathogenic.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.876

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

0.04 kcal/mol

Stabilising · Job 177992461163

PLDDT (ALPHAFOLD)

64.88

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/03/31 00:00
Inheritance	Not specified.
WFS1 variant landscape	D797V 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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Category 4 — Stable Fold, Function Disrupted (pLDDT caveat). ΔΔG ≈ 0. AlphaMissense 0.876 confirms severe consequence. pLDDT 65 borderline.

Mechanism: charge loss from local D796-D797-E794 cluster. Therapeutic: site-directed at this charge cluster.

D797V + D797N at same position. Charge cluster D796-D797-E794 is a recognition surface; multiple variants disrupt it.