MOLECULAR ATLAS · VARIANT CARD

WFS1 D801G — Wolframin

Aspartate → Glycine at position 801 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.985, DynaMut2 ΔΔG -0.26 kcal/mol (destabilising). The inverse mechanism of glycine-removal variants: here glycine is INTRODUCED into a position that previously carried a charge.

IDENTITY

Variant	D801G (p.Aspartate801Glycine)
DNA change	c.2402A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003637018
Amino acid change	Aspartate (D) → Glycine (G) — a small negatively-charged carboxylate-bearing residue replaced by the smallest amino acid (backbone-only). Loss of charge and side chain entirely.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 801	**83.50** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 801 in the ER lumen (pLDDT 84).
IDR flag	No — pLDDT well above 50 threshold

Position 801 sits in wolframin's C-terminal lumenal domain near the C-terminus. The AlphaFold model places D801 within 5 Å of ILE802 (2.4 Å), LYS800 (2.5 Å), VAL779 (3.5 Å, longer-range), VAL798 (3.9 Å), and GLY780 (4.8 Å). Critically, LYS800 sits 2.5 Å from D801 — a salt-bridge distance. The wild-type D801 carboxylate and K800 amine form a likely intramolecular salt bridge stabilizing the local fold. Replacing aspartate with glycine eliminates the negative charge and removes the side chain entirely. The K800-D801 salt bridge breaks. The local geometry that depends on that ionic contact rearranges, and the introduced glycine permits backbone conformations that the wild-type aspartate constrained. The |ΔΔG| of 0.26 is modest — the fold absorbs the loss of a single salt bridge. But the functional consequence is severe: AlphaMissense 0.985 captures it. The lost salt bridge likely contributed to a specific lumenal geometry required for partner interactions

or for the wolframin C-terminus to engage its target proteins. Notably, VAL779 (3.5 Å) is the partner residue in the V779G atlas card (a Category 2 outlier). D801 and V779 are spatially close. Drug discovery aimed at the V779 region may also engage the D801 microenvironment.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.985	**-0.26** kcal/mol	**83.50**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990263828	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/03/18 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic classification.
WFS1 variant landscape	D801G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for D801G — ClinVar Pathogenic by review evidence)

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 3/4 — Most Druggable. |ΔΔG| = 0.26 kcal/mol — fold survives. AlphaMissense 0.985 confirms severe functional consequence.

The mechanism is loss of the K800-D801 intramolecular salt bridge plus introduction of glycine backbone flexibility into a previously constrained

position. Therapeutic strategy: site-directed small molecules that restore the K800-region electrostatic geometry the wild-type D801 carboxylate provided.

Spatial proximity to V779 (3.5 Å, see V779G atlas card) suggests this region of the C-terminus harbors multiple pathogenic variants. A drug aimed at the V779-D801 region could rescue multiple Atlas variants simultaneously.

D801G is one of the Atlas's clearest salt-bridge-loss variants. The K800-D801 ionic contact is visible in the AlphaFold model at exact salt-bridge geometry, and the substitution to glycine removes the contact completely. The Atlas's neighbor analysis surfaces the contact partner (K800 at 2.5 Å) and the spatially-adjacent Cat 2 outlier (V779). Drug discovery in this region has multiple convergent targets.
