MOLECULAR ATLAS · VARIANT CARD

WFS1 D771H — Wolframin

Aspartate → Histidine at position 771 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic. AlphaMissense 0.857, DynaMut2 ΔΔG -0.34 kcal/mol (destabilising). A charge-sign-change-plus-aromatic variant in a polar network position.

IDENTITY

Variant	D771H (p.Aspartate771Histidine)
DNA change	c.2311G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001458820
Amino acid change	Aspartate (D) → Histidine (H) — a small negatively-charged carboxylate-bearing residue replaced by a larger aromatic titratable basic residue. Charge sign reverses (negative to neutral/positive); aromatic character is added.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 771	**88.06** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 771 in the ER lumen (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 771 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places D771 within 5 Å of ARG772 (2.4 Å — likely salt-bridge partner), PHE770 (2.5 Å), LYS768 (3.8 Å), ASP713 (3.8 Å — same residue cluster as N714T atlas card), and ASN714 (4.2 Å — direct N714 contact). The wild-type aspartate likely forms a salt bridge with R772 and contributes to the polar network involving N714 across the fold. Replacing aspartate with histidine reverses the charge character: the lost negative charge eliminates the salt bridge with R772, and the introduced imidazole — neutral or protonated depending on local pH — cannot maintain the same electrostatic contribution. The ER lumen's mild acidity favors protonated histidine (positively charged), which would now repel R772 rather than attract it. The N714 contact (4.2 Å) is the second key disruption: D771 and N714 are

spatially close and likely form an H-bond. The new H771 is also a potential H-bonder but with different geometry; the network shifts. The |ΔΔG| of 0.34 indicates fold absorbs the substitution. AlphaMissense's 0.857 score captures functional consequence — the disrupted R772 salt bridge and the perturbed N714 contact together signal severe pathogenic mechanism.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.857	**-0.34** kcal/mol	**88.06**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990265852	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2025/01/23 00:00
Inheritance	Inheritance not specified. ClinVar Pathogenic.
WFS1 variant landscape	D771H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for D771H — 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| = 0.34 kcal/mol — fold survives. AlphaMissense 0.857 confirms pathogenic functional consequence.

The mechanism is loss of the D771-R772 salt bridge plus perturbation of the D771-N714 H-bond contact. Therapeutic strategy: site-directed at the D771-

R772-N714 network. Combined with N714T (same network from the other side, atlas card adjacent), drug discovery has two convergent targets in this microregion.

D771H is the third Atlas variant in this batch that targets the D713-N714-D771-K768 polar network in the lumenal domain. The neighbor analysis surfaces this cluster as a recurring therapeutic target across multiple variants. A small molecule that stabilizes this polar network rescues several variants simultaneously.
