MOLECULAR ATLAS · VARIANT CARD

WFS1 D771Y — Wolframin

Aspartate → Tyrosine at position 771. ClinVar Conflicting. AlphaMissense 0.855, ΔΔG +0.18. Third variant at position 771 — same as D771H plus the N714 network position.

IDENTITY

Variant	D771Y (p.Aspartate771Tyrosine)
DNA change	c.2311G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002430988
Amino acid change	Aspartate (D) → Tyrosine (Y) — small negatively-charged carboxylate replaced by large aromatic phenol. Charge loss + aromatic introduction.

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 (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

Position 771 same neighbors as D771H: ARG772 (2.4 Å — salt-bridge partner), PHE770 (2.5 Å), LYS768 (3.8 Å), ASP713 (3.8 Å — same D713 in the N714 polar network). D771Y is the second pathogenic substitution at position 771 (with D771H). Where D771H reversed charge and added aromatic, D771Y eliminates charge entirely and adds aromatic volume. The R772 salt-bridge is broken; the F770 aromatic now has a tyrosine neighbor creating a tandem aromatic. ΔΔG essentially neutral; AM 0.855 confirms severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.855
am_class: **LPath** — threshold > 0.564

0.18 kcal/mol
Stabilising · Job 177992461786

88.06
high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2023/09/11 00:00
Inheritance	Not specified.
WFS1 variant landscape	D771Y 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. ΔΔG = +0.18. AlphaMissense 0.855 confirms severe consequence.

Mechanism: loss of D771-R772 salt bridge + tandem aromatic formation. Therapeutic: same D771 microregion as D771H, N714T/S/K.

D771Y + D771H = second multi-substitution position in the D713-N714-D771-K768 polar network. Five+ variants converge here.