MOLECULAR ATLAS · VARIANT CARD

WFS1 E431Q — Wolframin

Glutamate → Glutamine at position 431 inside TM4. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.959, DynaMut2 ΔΔG -0.87 kcal/mol (destabilising). The fifth Atlas variant directly involving E431 — the lumenal-membrane hub residue.

IDENTITY

Variant	E431Q (p.Glutamate431Glutamine)
DNA change	c.1291G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001027490
Amino acid change	Glutamate (E) → Glutamine (Q) — negatively-charged carboxylate replaced by neutral polar amide. Loss of charge; H-bonding preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 431	**89.81** HIGH CONFIDENCE
Domain	TM4 (427-447), helical transmembrane
Position context	TM4 (residues 427–447) · position 431 near the lumenal end of TM4 (pLDDT 90).
IDR flag	No — pLDDT well above 50 threshold

Position 431 is the E431 hub residue itself. The AlphaFold model places E431 within 5 Å of LEU432 (2.4 Å), SER430 (2.5 Å — partner of S430W Atlas card), PRO428 (3.6 Å — partner of P428R Atlas card), ALA559 (3.9 Å — partner of A559D Atlas card), and TYR563 (4.0 Å). The neighbor list reads like a roll call of pathogenic Atlas variants — E431 is in spatial contact with the substituted positions in four other Atlas cards. Replacing E431 with glutamine eliminates the negative charge at this hub position. The salt bridges and electrostatic contacts that E431 maintained with R558 (across the loop) and with S430's hydroxyl and the lumenal interface lose their negative anchor. The |ΔΔG| of 0.87 reflects substantial fold cost — E431's role is structurally central. AlphaMissense 0.959 + Wolfram syndrome 1 confirm severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.959	**-0.87** kcal/mol	**89.81**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991929728	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2021/01/04 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	E431Q is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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 (HUB residue). |ΔΔG| = 0.87 — fold survives at meaningful cost. AlphaMissense 0.959 + Wolfram 1 confirm severe functional consequence.

E431 is the connective hub residue at the lumenal-TM4-connecting loop boundary. The Atlas now contains 5 variants involving E431 (E431Q this card, A559D, P428R, S430W, plus R558C/R558H/A559D microregion). Drug discovery targeting E431 has multi-variant convergence.

E431Q is the variant AT the hub position — where four other Atlas variants contact in their neighbor analyses. Drug discovery targeting the E431

> microregion is the highest-leverage docking site in the WFS1 lumenal-membrane interface region.
