MOLECULAR ATLAS · VARIANT CARD

WFS1 L664R — Wolframin

Leucine → Arginine at position 664 in wolframin's C-terminal lumenal domain. ClinVar Conflicting classifications including Wolfram syndrome 1. AlphaMissense 0.980, DynaMut2 ΔΔG -0.75 kcal/mol (destabilising). Charge introduction into a hydrophobic position.

IDENTITY

Variant	L664R (p.Leucine664Arginine)
DNA change	c.1991T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001705303
Amino acid change	Leucine (L) → Arginine (R) — branched aliphatic hydrophobic replaced by large positively-charged guanidinium-bearing residue. Charge introduction into a non-polar environment.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 664	**84.81** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 664 in the ER lumen (pLDDT 85).
IDR flag	No — pLDDT well above 50 threshold

Position 664 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places L664 within 5 Å of THR665 (2.4 Å), THR663 (2.5 Å), GLN668 (3.7 Å — same Q668 as Y669 and L672P environment), SER662 (4.4 Å), and VAL698 (4.9 Å — long-range). Replacing L664 with arginine introduces a large positive charge into a polar-leaning local environment with H-bonding partners (T665, T663, Q668, S662). The new R664 guanidinium can H-bond with these partners but pulls the local geometry into a new configuration. The Y669-C673-L672-Q668 microregion (densely populated by Atlas variants) is affected. The |ΔΔG| of 0.75 reflects fold cost. AlphaMissense's 0.980 + Wolfram syndrome 1 confirm severe functional consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.980	**-0.75** kcal/mol	**84.81**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992301789	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2022/09/23 00:00
Inheritance	Wolfram syndrome 1 documented.
WFS1 variant landscape	L664R 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. |ΔΔG| = 0.75 — fold survives. AlphaMissense 0.980 + Wolfram 1 confirm severe functional consequence.

Mechanism is charge introduction into the polar 663-665 microregion that abuts the dense Y669-C673 cluster. Therapeutic strategy: site-directed at the polar microregion adjacent to the Y669 cluster.

L664R sits at the edge of the dense Y669-C673-L672 cluster — close enough that drug discovery in the cluster region likely engages L664 as well.