MOLECULAR ATLAS · VARIANT CARD

WFS1 F775V — Wolframin

Phenylalanine → Valine at position 775. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.941, ΔΔG -1.57 (substantial destabilization). Aromatic loss in a cross-domain contact position.

IDENTITY

Variant	F775V (p.Phenylalanine775Valine)
DNA change	c.2323T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000166605
Amino acid change	Phenylalanine (F) → Valine (V) — aromatic hydrophobic replaced by branched aliphatic. Aromatic π-system lost; volume reduced.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 775	**93.69** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 775 (pLDDT 94 — high confidence).
IDR flag	No — pLDDT well above 50 threshold

Position 775 sits in the lumenal domain. Neighbors: GLU776 (2.4 Å — partner of R708 salt-bridge), LYS774 (2.5 Å), ARG708 (3.3 Å — direct R708 contact!), ALA806 (3.7 Å — partner of A806P). The wild-type phenylalanine at 775 likely participates in the R708-E776 salt-bridge geometry through cation-π interaction between F775's ring and R708's guanidinium. Replacing F775 with valine eliminates this cation-π contribution and reduces the aromatic packing supporting the R708-E776 salt bridge. The |ΔΔG| of 1.57 reflects substantial fold cost. AlphaMissense 0.941 + Wolfram 1 confirm severe consequence. F775V joins R708L, R708C, A806P as multi-variant convergence on the 775-806 microregion.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.941	**-1.57** kcal/mol	**93.69**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992300526	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/03/23 00:00
Inheritance	Wolfram syndrome 1 documented.
WFS1 variant landscape	F775V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Inborn genetic diseases

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| = 1.57 — fold survives at meaningful cost. AlphaMissense 0.941 + Wolfram 1 confirm severe consequence.

Mechanism: loss of F775 cation-π contribution to R708-E776 salt-bridge geometry. Therapeutic: same R708-E776-F775 microregion (multi-variant target).

F775V is the fourth variant in the 707-708-775-806 microregion (with V707F, R708L, R708C, A806P). Drug discovery here has multi-variant convergence.