MOLECULAR ATLAS · VARIANT CARD

WFS1 A684V — Wolframin

Alanine → Valine at position 684 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic/Likely pathogenic for WFS1-related disorder. AlphaMissense 0.886, DynaMut2 ΔΔG -0.81 kcal/mol (destabilising). A conservative hydrophobic substitution at the same position as A684T (Atlas card adjacent).

IDENTITY

Variant	A684V (p.Alanine684Valine)
DNA change	c.2051C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000030556
Amino acid change	Alanine (A) → Valine (V) — small methyl-bearing hydrophobic replaced by branched isopropyl-bearing hydrophobic. Volume increase; chemistry conservative.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 684	**87.94** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 684 in the ER lumen (pLDDT 88). Same position as A684T.
IDR flag	No — pLDDT well above 50 threshold

Position 684 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places A684 within 5 Å of MET683 (2.5 Å), ARG685 (2.5 Å), GLN687 (4.0 Å), ASN682 (4.0 Å), and THR686 (4.4 Å). The local environment is the same one described in the A684T Atlas card: adjacent to R685 (the partner residue in R685P), surrounded by polar residues. Replacing alanine with valine here introduces volume (isopropyl side chain) where the wild-type had only a methyl. The local packing — sized for alanine's small footprint — must rearrange to accommodate valine's branched side chain. The pocket adjacent to R685, M683, and the polar Q687/N682 environment is constrained; the introduced valine likely pushes R685 into a slightly different orientation. The |ΔΔG| of 0.81 is larger than A684T's 0.11 — valine's volume is harder for the local environment to accommodate than threonine's hydroxyl. AlphaMissense's 0.886 plus WFS1-related disorder clinical

association confirm pathogenic functional consequence. This is the second variant at position 684 in the Atlas (A684T atlas card adjacent), both perturbing the R685 partner-recognition geometry. Two convergent variant targets at the same position.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.886	**-0.81** kcal/mol	**87.94**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991405428	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/01/25 00:00
Inheritance	WFS1-related disorder documented; AD-leaning pattern consistent with WFS1 spectrum.
WFS1 variant landscape	A684V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-related disorder
- WFS1 Spectrum Disorder
- Rare genetic deafness

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| = 0.81 kcal/mol — fold survives. AlphaMissense 0.886 + WFS1-related disorder confirm severe functional consequence.

The mechanism is volume mismatch in the R685 microregion, perturbing R685's partner-recognition orientation. Therapeutic strategy: site-directed at the M683-A684-R685 microregion — same target as A684T and R685P.

A684V is the third variant in the Atlas converging on the 683-687 microregion (with A684T and R685P). The convergence of multiple pathogenic variants on a single therapeutic target geometry is exactly what the Atlas's neighbor analysis surfaces — drug discovery here has three convergent rescue opportunities.
