MOLECULAR ATLAS · VARIANT CARD

WFS1 V707F — Wolframin

Valine → Phenylalanine at position 707 in wolframin's C-terminal lumenal domain. ClinVar Pathogenic for classical autosomal recessive Wolfram syndrome 1. AlphaMissense 0.935, DynaMut2 ΔΔG -0.31 kcal/mol (destabilising). A conservative-to-aromatic substitution in a critical lumenal position.

IDENTITY

Variant	V707F (p.Valine707Phenylalanine)
DNA change	c.2119G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000030552
Amino acid change	Valine (V) → Phenylalanine (F) — a small branched hydrophobic replaced by a large aromatic. Volume increases substantially; π-electron system added where wild-type had only aliphatic carbons.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 707	**92.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 707 in the ER lumen with high AlphaFold confidence (pLDDT 92).
IDR flag	No — pLDDT well above 50 threshold

Position 707 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places V707 within 5 Å of ARG708 (2.4 Å), TYR706 (2.5 Å), GLU776 (3.5 Å — long-range contact), PHE704 (4.2 Å — another long-range), and ILE777 (4.5 Å). The local environment combines basic (R708), aromatic (Y706, F704), and acidic (E776) residues. The wild-type valine at 707 provides moderate hydrophobic packing into this mixed-character pocket. The branched aliphatic side chain fits cleanly between the surrounding residues without crowding. Replacing valine with phenylalanine introduces a substantial volume increase plus an aromatic ring system. The local pocket — sized for valine — must rearrange to accommodate the larger phenyl ring. The two nearby aromatics (Y706 at 2.5 Å, F704 at 4.2 Å) could engage in π-

stacking with the new F707, creating a three-aromatic cluster that the wild-type fold did not have. Whether this rearrangement is productive (stable three-aromatic stack) or destructive (disrupting Y706/F704 contacts with their own partners) depends on the specific geometry the variant fold adopts. The |ΔΔG| of 0.31 indicates the fold absorbs the substitution. AlphaMissense's 0.935 score reflects the functional consequence — the rearranged aromatic cluster disrupts whatever interaction the wild-type valine geometry enabled.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.935	**-0.31** kcal/mol	**92.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177990263996	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC**
Review status	no assertion criteria provided
Last evaluated	2008/12/15 00:00
Inheritance	Autosomal recessive Wolfram syndrome 1 phenotype documented in ClinVar.
WFS1 variant landscape	V707F 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| = 0.31 kcal/mol — fold survives. AlphaMissense 0.935 confirms severe functional consequence.

The mechanism is local volume mismatch creating an aromatic cluster (F707 + Y706 + F704) where the wild-type valine maintained a smaller hydrophobic pocket. Therapeutic strategy: site-directed small molecules that compensate for the disrupted Y706/F704 geometry by occupying the wild-type V707 niche.

V707F demonstrates that classical Wolfram syndrome 1 (AR inheritance) is well-represented in the Atlas's most-druggable category. The mechanism — local volume disruption in a lumenal pocket — is straightforward and amenable to structure-based design.
