MOLECULAR ATLAS · VARIANT CARD

WFS1 I688F — Wolframin

Isoleucine → Phenylalanine at position 688 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.406 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.64 kcal/mol (destabilising).

IDENTITY

Variant	I688F (p.Isoleucine688Phenylalanine)
DNA change	c.2062A>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003393279
Amino acid change	Isoleucine (I) → Phenylalanine (F) — branched aliphatic hydrophobic replaced by aromatic hydrophobic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 688	**89.31** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 688 in the ER lumen (pLDDT 89).
IDR flag	No — pLDDT well above 50 threshold

> Position 688 sits adjacent to several R558 microregion-related residues. The AlphaFold model places I688 within 5 Å of LEU689 (2.5 Å), GLN687 (2.5 Å — partner of Q687H Atlas card), ARG685 (3.8 Å — partner of R685P), SER691 (3.9 Å), and ALA684 (4.0 Å — partner of A684T and A684V). Replacing I688 with phenylalanine adds aromatic volume to a tightly-packed region containing R685, A684, Q687 — all known pathogenic variant positions. The F688 introduction reorganizes the local packing. The |ΔΔG| of 0.64 reflects fold accommodation. AlphaMissense's 0.406 is below threshold — AM under-call. ClinVar Pathogenic + Wolfram 1 establishes clinical relevance.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.406

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.64 kcal/mol

Destabilising · Job 177992010112

PLDDT (ALPHAFOLD)

89.31

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/12/19 00:00
Inheritance	Wolfram syndrome 1 (AR) documented.
WFS1 variant landscape	I688F 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 (AM under-call). |ΔΔG| = 0.64 — fold survives. AlphaMissense 0.406 below threshold but ClinVar Pathogenic + Wolfram 1.

Mechanism is volume mismatch in the R685-A684-Q687 multi-variant microregion. Therapeutic strategy: same target cluster as A684T, A684V, R685P, Q687H.

I688F joins the dense 684-688 multi-variant cluster — six Atlas variants (A684T, A684V, R685P, Q687H, I688F, plus broader region) converge here.