MOLECULAR ATLAS · VARIANT CARD

# **WFS1 V288G** — Wolframin

Valine → Glycine at position 288 in wolframin's N-terminal cytoplasmic domain. ClinVar Likely pathogenic for Wolfram syndrome 1. AlphaMissense 0.480 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.23 kcal/mol. pLDDT 58 borderline.

## IDENTITY

| | |
|---|---|
| Variant | V288G (p.Valine288Glycine) |
| DNA change | c.863T>G |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV003767181 |
| Amino acid change | Valine (V) → Glycine (G) — branched aliphatic hydrophobic replaced by smallest amino acid. Loss of side chain entirely. |

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## STRUCTURAL CONTEXT

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|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 288 | **58.47** CONFIDENT |
| Domain | N-terminal cytoplasmic domain (87-313) |
| Position context | N-terminal cytoplasmic domain · position 288 in a borderline-confidence region (pLDDT 58). |
| IDR flag | No — pLDDT well above 50 threshold |

> Position 288 sits in wolframin's N-terminal cytoplasmic domain. The AlphaFold model places V288 within 5 Å of VAL289 (2.5 Å), LYS287 (2.5 Å), LEU284 (4.0 Å), ALA295 (4.5 Å), and LEU286 (4.5 Å). Mostly hydrophobic environment. Replacing V288 with glycine removes the branched aliphatic side chain entirely, creating a cavity. The fold absorbs the substitution (|ΔΔG| 0.23 small) — the glycine permits backbone conformations the wild-type valine constrained, possibly compensating somewhat for the lost packing volume. AlphaMissense's 0.480 is below the threshold — AM under-call. ClinVar Likely Pathogenic + Wolfram 1 establishes clinical pathogenicity. pLDDT 58 is borderline; structural details deserve wet-lab confirmation.

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## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.480**

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

**-0.23** kcal/mol

Destabilising · Job 177992009249

PLDDT (ALPHAFOLD)

**58.47**

confident

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## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **LIKELY PATHOGENIC** |
| Review status | criteria provided, single submitter |
| Last evaluated | 2024/02/27 00:00 |
| Inheritance | Wolfram syndrome 1 (AR) documented. |
| WFS1 variant landscape | V288G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- Wolfram syndrome 1

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## 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 + pLDDT caveats).** |ΔΔG| = 0.23 — fold survives. AlphaMissense 0.480 below threshold but ClinVar Pathogenic + Wolfram 1.
>
> Mechanism is hydrophobic cavity creation. Therapeutic strategy: wet-lab validation before committing to design.

> V288G joins the AM-under-call class. The borderline pLDDT and AM signal together make this a wet-lab-priority variant.

RareResearch.AI · WFS1 Molecular Atlas · Generated by wolfram-variant-card skill *Every assumption documented.*