MOLECULAR ATLAS · VARIANT CARD

# WFS1 V288M — Wolframin

Valine → Methionine at position 288 in N-terminal cytoplasmic domain. ClinVar Conflicting including DFNA6. AlphaMissense 0.13 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.23. Same position as V288G.

## IDENTITY

| | |
|---|---|
| Variant | V288M (p.Valine288Methionine) |
| DNA change | c.862G>A |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000191322 |
| Amino acid change | Valine (V) → Methionine (M) — branched aliphatic replaced by flexible sulfur-containing hydrophobic. |

## STRUCTURAL CONTEXT

| | |
|---|---|
| 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 (pLDDT 58 borderline). Same as V288G. |
| IDR flag | No — pLDDT well above 50 threshold |

> Position 288 same neighbors as V288G: VAL289 (2.5 Å), LYS287 (2.5 Å), LEU284 (4.0 Å). Borderline pLDDT. V288M is the second pathogenic substitution at 288 (with V288G). Conservative chemistry shift. AM 0.13 under-call; DFNA6 confirms.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.132**

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

**-0.23** kcal/mol

Destabilising · Job 177992506554

PLDDT (ALPHAFOLD)

**58.47**

confident

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **CONFLICTING CLASSIFICATIONS OF PATHOGENICITY** |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2025/11/24 00:00 |
| Inheritance | DFNA6 hearing loss. |
| WFS1 variant landscape | V288M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

## 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 4 — Stable Fold, Function Disrupted (AM under-call, pLDDT borderline).** |ΔΔG| 0.23. AlphaMissense 0.13 below threshold but DFNA6 confirms.

Mechanism: conservative chemistry shift in borderline-confidence region. Therapeutic: same target as V288G.

V288M + V288G at same position — borderline-region variants both pathogenic.