MOLECULAR ATLAS · VARIANT CARD

# WFS1 M731V — Wolframin

Met→Val p731 lumenal AM=0.11 ddg=-0.86 pLDDT=85. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

## IDENTITY

| | |
|---|---|
| Variant | M731V (p.Methionine731Valine) |
| DNA change | c.2191A>G |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000374399 |
| Amino acid change | methionine chemistry lost |

## STRUCTURAL CONTEXT

| | |
|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 731 | **84.56** HIGH CONFIDENCE |
| Domain | C-terminal lumenal domain (653-869) |
| Position context | C-terminal lumenal domain |
| IDR flag | No — pLDDT well above 50 threshold |

> Position analysis: TRP730 (2.5 Å), ARG732 (2.5 Å — R732C/H!), GLY728 (3.7 Å). Adjacent to R732 multi-variant position and C733-C765 disulfide region. The Atlas's neighbor extraction surfaces this variant's contacts.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.113**

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

**-0.86** kcal/mol

Destabilising · Job 177992511572

PLDDT (ALPHAFOLD)

**84.56**

high confidence

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **CONFLICTING CLASSIFICATIONS OF PATHOGENICITY** |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2025/05/04 00:00 |
| Inheritance | Conflicting ClinVar classifications. |
| WFS1 variant landscape | M731V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- (no specific conditions catalogued)

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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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**Cat 3/4 — see structural prose.** AlphaMissense below threshold (AM under-call class) but mechanism is structurally clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

Adjacent to C733-C765 disulfide region.

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