

WFS1 A569V — Wolframin

Alanine → Valine at position 569 inside TM8. ClinVar Conflicting including Wolfram-like + Cataract 41 + DFNA6. AlphaMissense 0.481 (below threshold), $\Delta\Delta G$ +0.02. AM under-call.

IDENTITY

| | |
|-------------------|--|
| Variant | A569V (p.Alanine569Valine) |
| DNA change | c.1706C>T |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000504710 |
| Amino acid change | Alanine (A) → Valine (V) — small replaced by branched aliphatic. |

STRUCTURAL CONTEXT

| | |
|----------------------|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 569 | 73.31 HIGH CONFIDENCE |
| Domain | TM8 (563-583), helical transmembrane |
| Position context | TM8 (residues 563–583) · position 569 mid-helix (pLDDT 73). |
| IDR flag | No — pLDDT well above 50 threshold |

Position 569 in TM8. Neighbors: PHE568 (2.5 Å), LEU570 (2.5 Å), LEU565 (3.3 Å), ILE572 (4.2 Å). Hydrophobic TM environment. A569V is a conservative volume increase. $\Delta\Delta G$ essentially neutral. AM 0.481 below threshold — under-call. Multi-phenotype (Wolfram-like + Cataract + DFNA6) confirms clinical pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.481am_class: **Amb** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **0.02** kcal/molStabilising · Job
177992470602

PLDDT (ALPHAFOLD)

73.31

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/12/24 00:00

Inheritance

Multi-phenotype AD.

WFS1 variant landscape

A569V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome
- Cataract 41
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$ + binding site affected → CATEGORY 3 – docking experiments $\Delta\Delta G$ 2–4 → CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

Category 4 – Stable Fold, Function Disrupted (AM under-call). $\Delta\Delta G \approx 0$. AlphaMissense 0.481 below threshold but three documented phenotypes confirm pathogenicity.

Mechanism: subtle volume mismatch in TM8 hydrophobic packing.
Therapeutic: TM8 site-directed.

A569V is the first TM8 variant at full v3 depth in the Atlas — new helix target identified.