MOLECULAR ATLAS · VARIANT CARD

WFS1 V871G — Wolframin

Valine → Glycine at position 871 inside TM11. ClinVar Conflicting including Cataract 41 + DFNA6. AlphaMissense 0.27 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.76.

IDENTITY

Variant	V871G (p.Valine871Glycine)
DNA change	c.2612T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001572110
Amino acid change	Valine (V) → Glycine (G) — branched aliphatic replaced by smallest amino acid. Massive cavity creation.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 871	**74.25** HIGH CONFIDENCE
Domain	TM11 (870-890), helical transmembrane
Position context	TM11 (residues 870–890) · position 871 at TM11 start (pLDDT 74).
IDR flag	No — pLDDT well above 50 threshold

> Position 871 at TM11 start. Neighbors: HIS872 (2.5 Å — same H872 as K876T/A874T), THR870 (2.5 Å), TRP867 (3.7 Å — aromatic). The H872-V871-T870-W867 region is the TM11 start. V871G removes side chain creating cavity in TM11 hydrophobic core. |ΔΔG| 0.76 + AM 0.27 under-call + multi-phenotype confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.268

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.76 kcal/mol

PLDDT (ALPHAFOLD)

74.25

high confidence

Destabilising · Job 177992497507

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/09/28 00:00
Inheritance	AD: Cataract + DFNA6.
WFS1 variant landscape	V871G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

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

RESEARCH PATH DECISION TREE

```
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
```

Category 3/4 — Most Druggable (AM under-call). |ΔΔG| 0.76. AlphaMissense 0.27 below threshold but multi-phenotype confirms pathogenicity.

Mechanism: cavity creation at TM11 start. Therapeutic: TM11 multi-variant cluster.

V871G + V871M at same position. TM11 cluster expands further.