MOLECULAR ATLAS · VARIANT CARD

WFS1 A575G — Wolframin

Alanine → Glycine at position 575 inside TM8. ClinVar Conflicting with broad spectrum — Wolfram-like, Cataract 41, Wolfram. AlphaMissense 0.14 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.41.

IDENTITY

Variant	A575G (p.Alanine575Glycine)
DNA change	c.1724C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000440419
Amino acid change	Alanine (A) → Glycine (G) — small methyl-bearing replaced by smallest amino acid. Side chain removed.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 575	**80.88** HIGH CONFIDENCE
Domain	TM8 (563-583), helical transmembrane
Position context	TM8 (residues 563–583) · position 575 (pLDDT 81).
IDR flag	No — pLDDT well above 50 threshold

> Position 575 in TM8. Neighbors: VAL574 (2.5 Å), GLY576 (2.5 Å — G576S partner!), PRO571 (3.7 Å). A575G removes side chain creating cavity. Adjacent to G576S (Atlas card). Three Atlas variants in TM8 (A569V, A575G, G576S). AM 0.14 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.140

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.41 kcal/mol

Destabilising · Job 177992505073

PLDDT (ALPHAFOLD)

80.88

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/11/05 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	A575G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome
- Cataract 41
- Wolfram syndrome 1

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 under-call). |ΔΔG| 0.41. AlphaMissense 0.14 below threshold but three phenotypes confirm.

Mechanism: cavity creation in TM8. Therapeutic: TM8 multi-variant cluster.

A575G extends TM8 cluster — A569V + A575G + G576S now converge.