

WFS1 V503G — Wolframin

Valine → Glycine at position 503 inside TM6. ClinVar Pathogenic for DFNA6 hearing loss. AlphaMissense 0.38 (below threshold) — AM under-call. DynaMut2 $\Delta\Delta G$ -1.88 kcal/mol — close to Cat 2 boundary. Cavity creation in dense TM6 multi-variant cluster.

IDENTITY

Variant	V503G (p.Valine503Glycine)
DNA change	c.1508T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002501448
Amino acid change	Valine (V) → Glycine (G) — branched aliphatic hydrophobic replaced by smallest amino acid (no side chain). Loss of packing volume entirely.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 503	81.44 HIGH CONFIDENCE
Domain	TM6 (496-516), helical transmembrane
Position context	TM6 (residues 496–516) · position 503 mid-helix, bilayer-embedded (pLDDT 81).
IDR flag	No — pLDDT well above 50 threshold

Position 503 sits in TM6, immediately upstream of P504 (P504L Atlas card) and C505 (C505Y, Y508C Atlas region). Neighbors: SER502 (2.5 Å), PRO504 (2.5 Å), CYS505 (4.3 Å). The TM6 mid-helix region is now extensively characterized in the Atlas — V503G, P504L, C505Y, Y508C all converge here. Replacing V503 with glycine eliminates the branched aliphatic side chain entirely, creating a substantial cavity in the bilayer-embedded core. The local packing — sized for valine + the surrounding P504 backbone constraint — cannot fill the void without local rearrangement. The TM6-TM11 register through the C505/P885 cross-helix contact (discussed in C505Y, P885L Atlas cards) is perturbed. The $|\Delta\Delta G|$ of 1.88 — close to the Cat 2 moderate-destabilization threshold — reflects substantial structural cost. AlphaMissense's 0.38 is below the 0.564 pathogenic threshold (AM under-

call), but the documented DFNA6 hearing loss plus the substantial $\Delta\Delta G$ confirm pathogenicity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.377

am_class: **Amb** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$

-1.88 kcal/

mol

Destabilising · Job
177992478581

PLDDT (ALPHAFOLD)

81.44

high confidence

CLINICAL EVIDENCE

ClinVar classification

**CONFLICTING CLASSIFICATIONS OF
PATHOGENICITY**

Review status

criteria provided, conflicting classifications

Last evaluated

2026/01/07 00:00

Inheritance

Autosomal dominant DFNA6 hearing loss
documented.

WFS1 variant landscape

V503G 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

$\Delta\Delta G < 2$ + 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 3/4 — Most Druggable (near Cat 2 boundary, AM under-call). $|\Delta\Delta G| = 1.88$ — closest to Cat 2 threshold in this batch. AlphaMissense 0.38 below threshold but DFNA6 + substantial $\Delta\Delta G$ confirm pathogenicity.

Mechanism: hydrophobic cavity creation in TM6 plus perturbation of the TM6-TM11 cross-helix register. Therapeutic strategy: same TM6 mid-helix

microregion as P504L, C505Y, Y508C — pharmacological chaperone screening warranted given near-Cat-2 stability cost.

V503G is the FOURTH variant in the TM6 mid-helix cluster (with P504L, C505Y, Y508C). All converge on the same therapeutic target geometry. The proximity to P885 (TM11) through the C505 contact means this cluster connects to the TM11 multi-variant region as well — drug discovery here has unusually broad rescue convergence.