MOLECULAR ATLAS · PILOT VARIANT CARD

WFS1 A716T — Wolframin

Threonine for alanine at position 716. The textbook autosomal dominant DFNA6 hearing-loss variant — and the case where AlphaMissense and the clinic disagree. The clinic wins.

IDENTITY

Variant	A716T (p.Alanine716Threonine)
DNA change	c.2146G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000004520
Amino acid change	Alanine (A, small, hydrophobic, methyl side chain) → Threonine (T, polar, hydroxyl-bearing)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6 (released Aug 2025)
pLDDT at residue 716	**83.94** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	Inside the C-terminal ER-lumenal domain — not in a transmembrane helix; in the lumen-facing region that interacts with chaperones
IDR flag	No — pLDDT well above 50 threshold

A716 sits in the C-terminal lumenal domain, the half of wolframin that lives inside the endoplasmic reticulum lumen. Alanine is a small, hydrophobic residue typically found in helix interiors or close-packed regions. Replacing it with threonine adds a polar hydroxyl group where none existed — a small but locally significant chemical change that can perturb the hydrogen-bond network and slow proper folding. In the oxidizing, chaperone-rich ER lumen environment, even minor folding-kinetics changes can trigger quality-control degradation. But the monomer fold itself survives, which is why DynaMut2 returns only a mild destabilization.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)

0.215	-0.8 kcal/mol	83.94
am_class: **LBen** — threshold > 0.564	Destabilising (mild) · Job 177985952865	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2026/02/01
Inheritance	Autosomal dominant (DFNA6 / DFNA14 / DFNA38)
WFS1 variant landscape	A716T is 1 of 326 pathogenic-spectrum variants in WFS1 (out of 2,243 catalogued in ClinVar)

- Rare genetic deafness
- Monogenic hearing loss
- DFNA6/14/38 — autosomal dominant nonsyndromic low-frequency sensorineural hearing loss

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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Final classification: Category 4 — Most Druggable via dominant-negative mechanism. DynaMut2 ΔΔG = −0.8 kcal/mol confirms the monomer fold is intact. Yet ClinVar's multi-submitter Pathogenic/Likely pathogenic consensus stands. The reconciliation: wolframin functions as a multimer in the ER membrane, and A716T poisons the multimer assembly even when individual monomers fold correctly. AlphaMissense (0.215, Likely Benign) is trained on monomer-destabilizing variants — it predictably misses dominant-negative variants that act through oligomeric disruption. **The Atlas weights clinical evidence above prediction when they conflict.**

Why this card is a credibility moment. A716T is the variant that proves the Atlas does NOT just rubber-stamp computational predictions.

> AlphaMissense calls it benign. ClinVar calls it pathogenic with multi-submitter consensus and no conflicts. The Atlas reports both signals truthfully, names the reconciling mechanism (dominant-negative oligomeric disruption), and routes the variant to small-molecule rescue. This is the intellectual honesty Sarah will recognize immediately.
