MOLECULAR ATLAS · VARIANT CARD

WFS1 V779G — Wolframin

Valine → Glycine at position 779 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic with the full clinical spectrum documented — Wolfram syndrome 1, Wolfram-like syndrome, type 2 diabetes, cataract 41, and DFNA6 hearing loss. AlphaMissense 0.908, DynaMut2 ΔΔG -2.92 kcal/mol (destabilising).

IDENTITY

Variant	V779G (p.Valine779Glycine)
DNA change	c.2336T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003590739
Amino acid change	Valine (V) → Glycine (G) — a small, branched hydrophobic residue replaced by the smallest possible residue with no side chain at all.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 779	**90.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 779 sits inside the ER lumen, within wolframin's largest soluble region. It is in a structurally well-defined neighborhood (pLDDT 90).
IDR flag	No — pLDDT well above 50 threshold

Position 779 lies in wolframin's C-terminal lumenal domain (residues 653–869), the protein's largest soluble region and the primary interface for documented partner interactions with ATF6 and the Na+/K+ ATPase β1 subunit. The AlphaFold model shows V779 packed into a tight local cluster: GLY780 (2.4 Å) and THR778 (2.5 Å) are the immediate sequence neighbors, but the structural context also includes ARG703 (3.6 Å), PHE704 (4.8 Å), and ILE802 (3.8 Å) — residues from elsewhere in the lumenal fold that form a hydrophobic pocket against V779's isopropyl side chain. Replacing valine with glycine at this position is unusually disruptive because glycine has no side chain. The wild-type contributes branched hydrophobic packing into the local pocket; the mutant removes that volume entirely. The resulting cavity is

roughly the size of a methyl group and a methine — small, but structurally significant when the position was contributing to packing density. The backbone gains rotational freedom it did not have before, and the surrounding residues are no longer held in their pre-mutation geometry. This explains the |ΔΔG| of 2.92 kcal/mol — one of only two variants in the entire 245-variant Atlas to cross the 2 kcal/mol moderate-destabilization threshold. The protein still folds (|ΔΔG| is well below the 4 kcal/mol gross-misfolding line), but the fold is energetically compromised and a fraction of the translated protein will be cleared by ER quality control before reaching its functional location.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.908	**-2.92** kcal/mol	**90.12**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992005564	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/06/21 00:00
Inheritance	Both autosomal dominant and autosomal recessive forms documented. ClinVar lists this variant in association with DFNA6/14/38 (AD hearing loss), classical Wolfram syndrome (AR), and type 2 diabetes — consistent with WFS1's known dual inheritance landscape.
WFS1 variant landscape	V779G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)
- Cataract 41
- Wolfram syndrome 1
- Wolfram-like syndrome
- Type 2 diabetes mellitus

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 2 — Moderately Destabilizing. |ΔΔG| = 2.92 kcal/mol places this variant just inside the moderately destabilizing range. The fold survives but is energetically compromised; a fraction of mutant protein will misfold and be cleared before reaching functional sites.

This is a pharmacological chaperone candidate. The therapeutic strategy is not site-directed small-molecule design (the perturbation is global to a local fold, not a specific binding pocket) but rather a chaperone that stabilizes the wolframin fold and shifts the folding equilibrium toward functional protein. Analogous to CFTR correctors in cystic fibrosis: rescue the folding yield, not the catalytic site.

The breadth of clinical conditions (five documented phenotypes including both the classical AR Wolfram syndrome and the AD hearing loss pattern) makes this a particularly high-value chaperone target: a single intervention could address multiple clinical presentations across both inheritance modes.

V779G is one of only two variants in the entire Atlas (along with W700S) where |ΔΔG| exceeds 2 kcal/mol. That's two outliers out of 245 — and even these outliers sit well below the 4 kcal/mol gross-misfolding threshold that would force a gene-therapy strategy. The Atlas's central finding holds even here: WFS1 pathogenic variants do not gross-misfold. They damage the fold in measurable but tractable ways, and small molecules are the right therapeutic vector for the entire pathogenic spectrum.