MOLECULAR ATLAS · VARIANT CARD

WFS1 G728D — Wolframin

Glycine → Aspartic acid at position 728. C-terminal ER-lumenal (calcium binding. ClinVar Uncertain significance/Uncertain risk allele, AlphaMissense 0.865, DynaMut2 ΔΔG -1.65 kcal/mol (destabilising).

IDENTITY

Variant	G728D (p.Glycine728Aspartic acid)
DNA change	c.2183G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000591295
Amino acid change	Glycine (G) → Aspartic acid (D)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 728	**86.00** HIGH CONFIDENCE
Domain	C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)
Position context	C-terminal lumenal domain · position 728 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

> Position 728 sits in the C-terminal lumenal domain (residues 653–869), wolframin's largest soluble region. This domain projects into the ER lumen and is implicated in calcium handling, ER stress sensing, and protein–protein interactions with ATF6 and Na+/K+ ATPase β1. The wild-type residue is small/flexible (glycine — backbone flexibility, no sidechain); the mutant is negatively charged (aspartate — carboxylate). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.865

am_class: **likely pathogenic** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.65 kcal/mol

Destabilising · Job 178092110699

PLDDT (ALPHAFOLD)

86.00

high confidence

CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE/UNCERTAIN RISK ALLELE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2022/03/29 00:00
Inheritance	Autosomal dominant pattern indicated by associated DFNA6/14/38 (WFS1 hearing loss 6).
WFS1 variant landscape	G728D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

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

|ΔΔG|=1.65 < 2 kcal/mol (fold intact) + AlphaMissense 0.865 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.65 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.865. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
