

WFS1 D729N — Wolframin

Aspartate → Asparagine at position 729 in luminal domain. ClinVar Conflicting including Cataract 41 + DFNA6. AlphaMissense 0.12 (below threshold) — AM under-call. DynaMut2 $\Delta\Delta G$ -0.86.

IDENTITY

Variant	D729N (p.Aspartate729Asparagine)
DNA change	c.2185G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000212613
Amino acid change	Aspartate (D) → Asparagine (N) — charge loss; H-bonding preserved.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 729	87.25 HIGH CONFIDENCE
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain · position 729 (pLDDT 87).
IDR flag	No — pLDDT well above 50 threshold

Position 729 in luminal domain. Neighbors: TRP730 (2.5 Å), GLY728 (2.5 Å), PHE725 (3.8 Å). Near the L723P/P724S/P724L cluster. D729N charge loss adjacent to L723-P724 loop variant cluster. $|\Delta\Delta G|$ 0.86; AM 0.12 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.122am_class: **LBen** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.86** kcal/

mol

Destabilising · Job
177992508774

PLDDT (ALPHAFOLD)

87.25

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2026/01/05 00:00

Inheritance

AD: Cataract + DFNA6.

WFS1 variant landscape

D729N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41
- 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 (AM under-call). $|\Delta\Delta G|$ 0.86.
AlphaMissense 0.12 below threshold but multi-phenotype confirms.

Mechanism: charge loss near L723-P724 loop region. Therapeutic: site-directed at the 725-734 luminal microregion.

D729N continues charge-loss class — adjacent to L723-P724 cluster region.