MOLECULAR ATLAS · VARIANT CARD

WFS1 D211N — Wolframin

Aspartate → Asparagine at position 211 in wolframin's N-terminal cytoplasmic domain. ClinVar Pathogenic/Likely pathogenic with broad clinical spectrum (Cataract 41, DFNA6, inborn genetic diseases). AlphaMissense 0.093 (deep BENIGN). DynaMut2 ΔΔG +0.67 STABILISING. pLDDT 45 — Category 5 IDR territory.

IDENTITY

Variant	D211N (p.Aspartate211Asparagine)
DNA change	c.631G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215378
Amino acid change	Aspartate (D) → Asparagine (N) — negatively-charged carboxylate replaced by neutral polar amide. Loss of charge but H-bonding capacity preserved (different chemistry).

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 211	**44.56** BELOW IDR THRESHOLD
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 211 in a region with pLDDT 45, AT the Category 5 IDR threshold. Structural predictions are not trustworthy here.
IDR flag	YES — pLDDT 44.56 is below 50 threshold (route to Cat 5)

Position 211 sits at the boundary between wolframin's N-terminal cytoplasmic domain proper and the disordered region at its start. The pLDDT of 45 is below the 50 threshold for trustworthy structure — the Atlas formally classifies this as Category 5 (IDR exclusion). The AlphaFold model places D211 within 5 Å of only GLY212 (2.4 Å), HIS210 (2.5 Å), ASN208 (4.6 Å), and GLU209 (4.9 Å). The sparse neighbor count is itself an IDR signature — folded domains show many more contacts at typical residue positions. Replacing aspartate with asparagine eliminates the negative charge. The DynaMut2 prediction (+0.67 stabilising) is not trustworthy in this confidence region — DynaMut2 assumes a meaningful fold. AlphaMissense's 0.093 puts

the variant in likely-benign territory. And yet ClinVar Pathogenic + broad clinical spectrum (Cataract 41, DFNA6, inborn genetic diseases) establish clinical evidence. The mechanism, if pathogenic, likely involves IDR-mediated phase separation or partner binding that AlphaMissense's training does not capture.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.093	**0.67** kcal/mol	**44.56**
am_class: **LBen** — threshold > 0.564	Stabilising · Job 177991408315	BELOW IDR THRESHOLD

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/10/29 00:00
Inheritance	Documented in association with DFNA6 (AD) and Cataract 41.
WFS1 variant landscape	D211N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Cataract 41
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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 5 — IDR Exclusion. pLDDT 45 — below the 50 threshold. Computational predictions not trustworthy. AlphaMissense 0.093 below pathogenic threshold but ClinVar Pathogenic + multi-phenotype clinical evidence.

The Atlas routes this to wet-lab characterization. Therapeutic strategy should NOT be set on computational data alone.

D211N is the second IDR Category 5 variant in this session's batch (with G78R, A31G earlier). The Atlas's IDR-exclusion logic appropriately surfaces these as variants requiring experimental work before drug discovery commits to a vector.
