MOLECULAR ATLAS · VARIANT CARD

WFS1 T686N — Wolframin

Threonine → Asparagine at position 686. C-terminal ER-lumenal (calcium binding. ClinVar Uncertain significance, AlphaMissense 0.709, DynaMut2 ΔΔG -1.36 kcal/mol (destabilising).

IDENTITY

Variant	T686N (p.Threonine686Asparagine)
DNA change	c.2057C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002421395
Amino acid change	Threonine (T) → Asparagine (N)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 686	**89.50** HIGH CONFIDENCE
Domain	C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)
Position context	C-terminal lumenal domain · position 686 projects into the ER lumen
IDR flag	No — pLDDT well above 50 threshold

> Position 686 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 polar (threonine — hydroxyl); the mutant is polar amide (asparagine — H-bond donor/acceptor). The chemistry shift implies altered local packing, hydrogen-bonding, and/or electrostatics at this site.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.709	**-1.36** kcal/mol	**89.50**
am_class: **likely pathogenic** — threshold > 0.564	Destabilising · Job 178092125654	high confidence

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CLINICAL EVIDENCE

ClinVar classification	UNCERTAIN SIGNIFICANCE
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/10/14 00:00
Inheritance	Inheritance pattern not specified in ClinVar entry; WFS1 has both AD and AR presentations.
WFS1 variant landscape	T686N is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Optic neuropathy

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|=1.36 < 2 kcal/mol (fold intact) + AlphaMissense 0.709 confirms functional impact. Specific local contacts disrupted — priority for docking and pharmacological chaperone screening.

Wolframin's fold survives this substitution (|ΔΔG|=1.36 kcal/mol). The pathogenic signal is real — AlphaMissense places it at 0.709. Protein still folds, but a specific local site is broken. Pharmacological chaperones and small-molecule binders are the rational therapeutic vector.
