MOLECULAR ATLAS · VARIANT CARD

WFS1 A422V — Wolframin

Alanine → Valine at position 422 inside TM3. ClinVar Conflicting including monogenic diabetes + WFS1 spectrum. AlphaMissense 0.23 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.31 STABILISING.

IDENTITY

Variant	A422V (p.Alanine422Valine)
DNA change	c.1265C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000393388
Amino acid change	Alanine (A) → Valine (V) — small replaced by branched aliphatic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 422	**87.12** HIGH CONFIDENCE
Domain	TM3 (402-422), helical transmembrane
Position context	TM3 (residues 402–422) · position 422 at TM3 end (pLDDT 87).
IDR flag	No — pLDDT well above 50 threshold

> Position 422 at TM3 end. Neighbors: SER423 (2.4 Å), ILE421 (2.5 Å), SER418 (3.7 Å — TM2-TM3 interface, same S418 as F350I). A422V at the TM3 lumenal end. Conservative volume increase + stabilising ΔΔG. AM 0.23 under-call; multi-phenotype confirms pathogenicity. The S418 cross-helix contact is structurally significant.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.234

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

0.31 kcal/mol

Stabilising · Job 177992497673

PLDDT (ALPHAFOLD)

87.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/23 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	A422V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders
- Monogenic diabetes

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 4 — Stable Fold, Function Disrupted (AM under-call). ΔΔG +0.31. AlphaMissense 0.23 below threshold but multi-phenotype confirms pathogenicity.

Mechanism: TM3-TM2 interface perturbation at S418. Therapeutic: same target as F350I, V412L, V412A.

A422V continues TM3-TM2 interface convergence.