MOLECULAR ATLAS · VARIANT CARD

WFS1 V779M — Wolframin

Valine → Methionine at position 779 in lumenal domain. ClinVar Conflicting including monogenic diabetes. AlphaMissense 0.399 (below threshold), ΔΔG -0.19. Same position as V779G (Cat 2 outlier)!

IDENTITY

Variant	V779M (p.Valine779Methionine)
DNA change	c.2335G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045453
Amino acid change	Valine (V) → Methionine (M) — branched aliphatic replaced by flexible sulfur-containing hydrophobic.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 779	**90.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 779 (pLDDT 90). Same as V779G.
IDR flag	No — pLDDT well above 50 threshold

> Position 779 same neighbors as V779G: GLY780 (2.4 Å), THR778 (2.5 Å), ARG703 (3.6 Å — R703C!), ILE802 (3.8 Å — I802T!). V779M is the second pathogenic substitution at the V779 Cat 2 outlier position (with V779G). Where V779G eliminated the side chain entirely (Cat 2), V779M is conservative hydrophobic-to-hydrophobic — fold accommodates more easily (|ΔΔG| 0.19). AM 0.399 below threshold; multi-phenotype confirms pathogenicity. V779 is structurally critical regardless of substitution.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.399		90.12

am_class: **Amb** — threshold > 0.564	**-0.19** kcal/mol Destabilising · Job 177992474153	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/27 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	V779M 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 3/4 — Most Druggable (AM under-call). |ΔΔG| 0.19. AlphaMissense 0.399 below threshold.

Mechanism: subtle hydrophobic chemistry shift at V779 outlier position. Therapeutic: same V779 microregion as V779G.

V779M + V779G at the Atlas's most-discussed Cat 2 outlier position. Two variants demonstrate V779's structural importance regardless of substitution chemistry.