MOLECULAR ATLAS · VARIANT CARD

WFS1 V258I — Wolframin

Val→Ile p258 N-term AM=0.06 ddg=-0.39 pLDDT=71. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	V258I (p.Valine258Isoleucine)
DNA change	c.772G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000732838
Amino acid change	conservative branched-aliphatic

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 258	**71.44** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: ILE259 (2.4 Å), GLY257 (2.5 Å), LYS253 (3.5 Å — same K253 as K252E region). The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.056

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.39 kcal/mol

Destabilising · Job 177992527933

PLDDT (ALPHAFOLD)

71.44

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/06/26 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	V258I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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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Cat 4 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

Adjacent to K252-K253 region.
