

# WFS1 M632I — Wolframin

Met→Ile p632 TM10 AM=0.10 ddg=-0.44 pLDDT=74. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

## IDENTITY

Variant	M632I (p.Methionine632Isoleucine)
DNA change	c.1896G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000393390
Amino acid change	methionine chemistry lost

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 632	<b>73.75</b> HIGH CONFIDENCE
Domain	TM10 (632-652), helical transmembrane
Position context	TM10 (632-652)
IDR flag	No — pLDDT well above 50 threshold

Position analysis: SER631 (2.5 Å), VAL633 (2.5 Å), ARG629 (3.7 Å — R629W/Q neighbors!). TM10 start, adjacent to R629 multi-variant region. The Atlas's neighbor extraction surfaces this variant's contacts.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.101**am\_class: **LBen** —  
threshold > 0.564

DYNAMUT2 ΔΔG

**-0.44** kcal/

mol

Destabilising · Job  
177992514194

PLDDT (ALPHAFOLD)

**73.75**

high confidence

## CLINICAL EVIDENCE

ClinVar classification

**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**

Review status

criteria provided, conflicting classifications

Last evaluated

2025/10/13 00:00

Inheritance

Conflicting ClinVar classifications.

WFS1 variant landscape

M632I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

## RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$  + binding site affected → CATEGORY 3 – docking experiments  $\Delta\Delta G$  2–4 → CATEGORY 2 – pharmacological chaperones  $\Delta\Delta G > 4$  → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

**Cat 3/4 — see structural prose.** AlphaMissense below threshold (AM under-call class) but mechanism is structurally clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

TM10 start adjacent to R629 cluster.