MOLECULAR ATLAS · VARIANT CARD

WFS1 M518I — Wolframin

Methionine → Isoleucine at position 518 in a connecting loop. ClinVar carries conflicting classifications across diabetes-related conditions. AlphaMissense 0.966, DynaMut2 ΔΔG -0.29 kcal/mol (destabilising). A conservative hydrophobic substitution whose pathogenicity is mechanism-dependent.

IDENTITY

Variant	M518I (p.Methionine518Isoleucine)
DNA change	c.1554G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215358
Amino acid change	Methionine (M) → Isoleucine (I) — a flexible sulfur-containing hydrophobic residue replaced by a branched aliphatic hydrophobic. Both are medium-sized hydrophobic amino acids; the substitution removes the sulfur and the residue's metabolic flexibility but preserves bulk hydrophobic character.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 518	**84.12** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 518 sits in a loop region between transmembrane segments, solvent-accessible.
IDR flag	No — pLDDT well above 50 threshold

Position 518 sits in a connecting loop. The AlphaFold model places M518 within 5 Å of ALA519 (2.5 Å), ARG517 (2.5 Å), PHE515 (3.7 Å), LEU514 (3.8 Å), LEU521 (3.9 Å), and GLN520 (4.4 Å). The wild-type methionine's flexible sulfur-containing side chain fits into the surrounding hydrophobic environment (LEU514, LEU521, PHE515) with comparable steric volume to an isoleucine. Replacing methionine with isoleucine is among the most conservative substitutions chemically — both residues are medium-sized hydrophobic, and isoleucine's branched aliphatic side chain occupies similar volume to methionine's straight-chain thioether. The DynaMut2 |ΔΔG| of 0.29 kcal/mol reflects this conservatism: the fold barely notices the swap. And yet

AlphaMissense calls this pathogenic at 0.966. The mechanism is functional, not structural. Three plausible reasons: first, methionine sulfur can participate in specific protein chemistry that isoleucine cannot — oxidative regulation (Met can be oxidized to Met-sulfoxide as a redox switch), metal coordination, or specific S-mediated interactions; second, methionine residues in certain positions serve as translation initiation alternates or have post-translational modification roles that isoleucine cannot replace; third, the loop's role as a recognition surface depends on the precise methionine geometry, and isoleucine's branched structure presents a different surface even at comparable hydrophobic volume. The conflicting ClinVar classifications make sense given this profile. Conservative substitutions whose pathogenicity depends on context-specific mechanisms get classified differently by different submitters with different evidence bases.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.966

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.29 kcal/mol

Destabilising · Job 177992300347

PLDDT (ALPHAFOLD)

84.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/05 00:00
Inheritance	Documented in association with monogenic diabetes and WFS1-related spectrum disorders. Conflicting classifications reflect context-dependent functional consequence.
WFS1 variant landscape	M518I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes
- Inborn genetic diseases
- WFS1-Related Spectrum Disorders

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. |ΔΔG| = 0.29 kcal/mol — fold essentially unperturbed. AlphaMissense 0.966 confirms pathogenic signal despite conservative chemistry.

The mechanism is functional: lost methionine-specific chemistry (oxidative regulation, S-mediated interactions, or surface recognition geometry) that the otherwise-similar isoleucine cannot replace. Therapeutic strategy: site-directed at the loop's functional surface rather than at fold rescue.

This is a variant where the Atlas's dual-metric framing (ΔΔG + AlphaMissense) is essential. Pre-atlas drug discovery focused on destabilizing variants would have missed M518I entirely.

M518I illustrates the importance of methionine's chemistry beyond hydrophobic packing volume. Conservative substitutions can be pathogenic when the lost chemistry is functional rather than structural. Drug discovery targeting M518I has to work at the functional level — restoring an oxidative regulation handle, a metal coordination site, or a recognition geometry — rather than at the fold stability level.