MOLECULAR ATLAS · VARIANT CARD

# WFS1 M518K — Wolframin

Methionine → Lysine at position 518 in a connecting loop. ClinVar Conflicting including optic neuropathy. AlphaMissense 0.925, ΔΔG -0.64 (destabilising). Same position as M518I (Atlas card).

## IDENTITY

| | |
|---|---|
| Variant | M518K (p.Methionine518Lysine) |
| DNA change | c.1553T>A |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV001320487 |
| Amino acid change | Methionine (M) → Lysine (K) — flexible sulfur-containing hydrophobic replaced by long positively-charged amine. Charge introduction into a hydrophobic loop position. |

## STRUCTURAL CONTEXT

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|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 518 | **84.12** HIGH CONFIDENCE |
| Domain | Connecting loop |
| Position context | Connecting loop · position 518 (pLDDT 84). Same position as M518I. |
| IDR flag | No — pLDDT well above 50 threshold |

Position 518 same neighbors as M518I: ALA519 (2.5 Å), ARG517 (2.5 Å — adjacent existing arginine), PHE515 (3.7 Å), LEU514 (3.8 Å), LEU521 (3.9 Å). M518K is the second substitution at position 518. Unlike M518I (conservative hydrophobic-to-hydrophobic), M518K introduces a charged residue. The new K518 amine adjacent to existing R517 creates a two-basic cluster where wild-type had M518's sulfur chemistry. The |ΔΔG| of 0.64 is larger than M518I's 0.29 — the charge introduction has greater structural cost than conservative volume change. AlphaMissense 0.925 + optic neuropathy confirm severe consequence.

## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **0.925** | **-0.64** kcal/mol | **84.12** |
| am_class: **LPath** — threshold > 0.564 | Destabilising · Job 177992301187 | high confidence |

## CLINICAL EVIDENCE

| | |
|---|---|
| ClinVar classification | **CONFLICTING CLASSIFICATIONS OF PATHOGENICITY** |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2025/08/01 00:00 |
| Inheritance | Optic neuropathy documented. |
| WFS1 variant landscape | M518K is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- Optic neuropathy

## 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.** |ΔΔG| = 0.64 — fold survives. AlphaMissense 0.925 + optic neuropathy confirm severe consequence.

Mechanism: charge introduction into the M518 hydrophobic environment, creating a two-basic cluster with R517. Therapeutic: same M518 microregion as M518I.

M518K + M518I at same position — both pathogenic but through different mechanisms (charge introduction vs lost methionine chemistry).