MOLECULAR ATLAS · VARIANT CARD

WFS1 R517C — Wolframin

Arginine → Cysteine at position 517 in connecting loop. ClinVar Conflicting including Wolfram-like + Cataract 41. AlphaMissense 0.16 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.89. Same loop region as M518I, M518K.

IDENTITY

Variant	R517C (p.Arginine517Cysteine)
DNA change	c.1549C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001396272
Amino acid change	Arginine (R) → Cysteine (C) — charge loss + thiol introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 517	**87.81** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 517 (pLDDT 88).
IDR flag	No — pLDDT well above 50 threshold

> Position 517 in connecting loop, immediately upstream of M518 (M518I, M518K). Neighbors: MET518 (2.5 Å — M518 multi-variant position!), PHE516 (2.5 Å), LEU514 (3.7 Å). R517C removes positive charge from the local environment. The M518 multi-variant position (M518I, M518K) and now R517C converge on the 514-521 loop region. AM 0.16 under-call; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.157

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.89 kcal/mol

Destabilising · Job 177992501434

PLDDT (ALPHAFOLD)

87.81

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/04/15 00:00
Inheritance	Multi-phenotype.
WFS1 variant landscape	R517C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome
- Cataract 41
- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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| 0.89. AlphaMissense 0.16 below threshold but THREE phenotypes confirm pathogenicity.

Mechanism: charge loss + thiol in M518 multi-variant cluster. Therapeutic: same 514-521 loop as M518I/K.

R517C + M518I + M518K — three variants in adjacent positions converge.