MOLECULAR ATLAS · VARIANT CARD

WFS1 R653C — Wolframin

Arginine → Cysteine at position 653 in lumenal domain. ClinVar Conflicting. AlphaMissense 0.476 (below threshold), ΔΔG +0.22. pLDDT 61 borderline.

IDENTITY

Variant	R653C (p.Arginine653Cysteine)
DNA change	c.1957C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000178597
Amino acid change	Arginine (R) → Cysteine (C) — charge loss + thiol introduction.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 653	**61.31** CONFIDENT
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 653 at the start of the lumenal domain (pLDDT 61 borderline).
IDR flag	No — pLDDT well above 50 threshold

Position 653 at the lumenal domain start. Neighbors: SER654 (2.5 Å), TYR652 (2.5 Å), TYR650 (3.6 Å — Y650H/Y650D/Y650C region!), PHE649 (3.8 Å — Y650 cluster). R653C sits adjacent to the Y650 aromatic cluster (multiple Atlas variants at Y650). The introduced thiol could engage in aberrant disulfide chemistry. AM 0.476 below threshold but multi-phenotype + ClinVar Pathogenic raise concern.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.476

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

0.22 kcal/mol

Stabilising · Job 177992471653

PLDDT (ALPHAFOLD)

61.31

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/24 00:00
Inheritance	WFS1 spectrum.
WFS1 variant landscape	R653C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- WFS1-Related Spectrum Disorders

RESEARCH PATH DECISION TREE

```
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
```

Category 4 — Stable Fold, Function Disrupted (AM below threshold, pLDDT borderline). ΔΔG +0.22. AlphaMissense 0.476 below threshold.

Mechanism: charge loss + thiol near Y650 cluster. Therapeutic: same Y650 microregion. Wet-lab validation recommended.

R653C joins the AM-under-call class. Adjacency to Y650 cluster makes it of interest despite the borderline signals.