

WFS1 R177C — Wolframin

Arginine → Cysteine at position 177 in N-terminal cytoplasmic domain. ClinVar Conflicting including Wolfram syndrome 1. AlphaMissense 0.902, $\Delta\Delta G$ -0.88. Charge loss + thiol introduction.

IDENTITY

Variant	R177C (p.Arginine177Cysteine)
DNA change	c.529C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000809614
Amino acid change	Arginine (R) → Cysteine (C) — long positively-charged guanidinium replaced by short thiol.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 177	90.81 HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 177 (pLDDT 91).
IDR flag	No — pLDDT well above 50 threshold

Position 177 sits in the N-terminal cytoplasmic domain. Neighbors: LYS178 (2.5 Å — adjacent existing lysine), VAL176 (2.5 Å), GLU173 (3.7 Å — likely wild-type salt-bridge partner with R177), ARG174 (3.8 Å — second nearby arginine). The wild-type R177 contributes to a positively-charged surface patch (with K178, R174) and likely salt-bridges with E173. Replacing R177 with cysteine eliminates the positive charge contribution and introduces a free thiol in the cytosol (less prone to aberrant disulfide than ER lumen but still a misfolding consideration). $|\Delta\Delta G|$ 0.88 + AlphaMissense 0.902 + Wolfram 1 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

DYNAMUT2 $\Delta\Delta G$

PLDDT (ALPHAFOLD)

0.902

am_class: **LPath** —
threshold > 0.564

-0.88 kcal/

mol
Destabilising · Job
177992459573

90.81

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/01/23 00:00

Inheritance

Wolfram syndrome 1 documented.

WFS1 variant landscape

R177C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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

Category 3/4 — Most Druggable. $|\Delta\Delta G| = 0.88$ — fold survives.
AlphaMissense 0.902 + Wolfram 1 confirm severe consequence.

Mechanism: loss of R177-E173 salt bridge plus charge loss from cytoplasmic surface patch. Therapeutic: site-directed at the R174-R177-E173 cluster.

R177C is part of a growing R→C class (with R703C, R708C, R732C, R685C, R653C). Drug discovery for R→C variants attends to both charge loss and aberrant thiol chemistry.