

WFS1 R558C — Wolframin

Arg → Cys at position 558 · The most common WFS1 mutation in the Ashkenazi Jewish population (≈ 1 in 3 carriers) · Largest single identifiable carrier group for any WFS1 mutation worldwide

IDENTITY

Variant	R558C (p.Arg558Cys)
DNA change	c.1672C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
dbSNP · ClinVar	rs199946797 · VCV000198835
Amino acid change	Arginine (R, positive, hydrophilic) → Cysteine (C, neutral, thiol)

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6 (released Aug 2025)
pLDDT at residue 558	84.56 HIGH CONFIDENCE
Domain	Cytoplasmic loop between transmembrane helix 7 (529–549) and TM8 (563–583)
Membrane position	5 residues before TM8 start — at the cytoplasmic edge of the ER membrane interface
IDR flag	No — pLDDT 84.56 well above 50 threshold

Wolframin has eleven transmembrane helices anchoring it in the ER membrane. R558 sits in a short cytoplasmic loop directly preceding TM8. A positively charged arginine here likely contributes to membrane-proximal helix packing and electrostatic interaction with anionic phospholipid headgroups. Substituting cysteine removes the positive charge, introduces a free thiol capable of aberrant disulfide formation, and is expected to perturb helix anchoring and ER folding fidelity.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.849DYNAMUT2 $\Delta\Delta G$ **-0.5** kcal/mol

PLDDT (ALPHAFOLD)

84.56

am_class: **LPath** —
threshold > 0.564

Destabilising (mild) · Job
177985627697

High confidence, well-
folded

CLINICAL EVIDENCE

ClinVar classification

PATHOGENIC / LIKELY PATHOGENIC

Review status

Criteria provided, multiple submitters, **no conflicts**

Last evaluated

February 1, 2026

Inheritance

Both autosomal dominant and autosomal recessive forms documented

WFS1 variant landscape

R558C is 1 of 326 pathogenic-spectrum variants in WFS1 (out of 2,243 catalogued in ClinVar)

- Wolfram syndrome 1
- Wolfram-like syndrome
- WFS1-Related Spectrum Disorders
- Autosomal dominant nonsyndromic hearing loss 6
- Optic atrophy
- Type 2 diabetes mellitus
- Cataract 41 · Retinal dystrophy · Monogenic hearing loss

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

Final classification: Category 3 / 4 — Most Druggable. With DynaMut2 $\Delta\Delta G = -0.5$ kcal/mol, R558C is only *mildly* destabilizing — the wolframin fold survives the mutation. The DynaMut2 interaction map shows R558's guanidinium group makes specific ionic and polar contacts with neighboring TM7-TM8 residues, and those contacts are lost upon R→C. The fold is intact; the function is disrupted at a localized site. **This is exactly the variant profile the Atlas was built to surface — pathogenic, but structurally tractable.** Priority for docking and pharmacological chaperone screening. Gene therapy is not required.

Why this is the highest-value pilot variant: R558C is the most common WFS1 mutation in the Ashkenazi Jewish population — approximately 1 in 3 individuals carries this variant. That is the largest single identifiable carrier group for any WFS1 mutation worldwide. A druggable variant with a defined population = a real clinical pathway.