

WFS1 R558H — Wolframin

Arginine → Histidine at position 558 in wolframin's connecting loop — the SAME position as R558C, the Atlas's flagship Ashkenazi variant. ClinVar Pathogenic/Likely pathogenic, broad clinical spectrum including optic atrophy and Wolfram syndrome 1. AlphaMissense 0.760, DynaMut2 $\Delta\Delta G$ -1.31 kcal/mol (destabilising). A direct comparator to R558C.

IDENTITY

Variant	R558H (p.Arginine558Histidine)
DNA change	c.1673G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000427051
Amino acid change	Arginine (R) → Histidine (H) — large positively-charged guanidinium-bearing residue replaced by smaller titratable imidazole-bearing residue. Loss of permanent positive charge; pH-dependent charge state introduced.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 558	84.56 HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 558 — same loop as R558C, the most common Ashkenazi WFS1 variant (pLDDT 85).
IDR flag	No — pLDDT well above 50 threshold

Position 558 sits in the connecting loop between TM7 (residues 529–549) and TM8. The AlphaFold model places R558 within 5 Å of ALA559 (2.5 Å — same neighbor as A559D Atlas card), LEU557 (2.5 Å), GLY555 (3.6 Å), LEU554 (3.8 Å), and LEU556 (4.5 Å). The wild-type arginine's positive charge makes the salt bridge with E431 that the R558C Atlas card discusses, contributing to the loop's electrostatic anchoring. Replacing arginine with histidine at 558 reduces but does not eliminate the positive charge — histidine's imidazole pKa near 6 means it's neutral or protonated depending on local environment. In the slightly-acidic ER environment near the membrane interface, histidine is often partially protonated. The salt bridge with E431 may form weakly or transiently. The $|\Delta\Delta G|$ of 1.31 is meaningful — larger than R558C's -0.5. The

pH-dependent charge state of the variant introduces a new kind of regulatory possibility that the wild-type permanent arginine charge did not have. AlphaMissense 0.760 plus broad clinical spectrum (optic atrophy, Wolfram syndrome 1) confirm pathogenic mechanism. R558H is the second pathogenic substitution catalogued at position 558 — R558C is the Ashkenazi flagship; R558H represents a different chemistry at the same position with different mechanism profile.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.760

am_class: **LPath** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$

-1.31 kcal/

mol

Destabilising · Job
177991407167

PLDDT (ALPHAFOLD)

84.56

high confidence

CLINICAL EVIDENCE

ClinVar classification

PATHOGENIC/LIKELY PATHOGENIC

Review status

criteria provided, multiple submitters, no conflicts

Last evaluated

2025/11/23 00:00

Inheritance

Both AD and AR forms documented at this position more broadly; R558H clinical evidence supports the WFS1 spectrum.

WFS1 variant landscape

R558H is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Inborn genetic diseases
- Optic atrophy
- 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. $|\Delta\Delta G| = 1.31$ kcal/mol — fold survives at meaningful cost. AlphaMissense 0.760 + multiple clinical phenotypes confirm severe functional consequence.

The mechanism is partial loss of the R558-E431 salt bridge through pH-dependent histidine charge state. Therapeutic strategy: same R558-E431 microregion as R558C and A559D. A drug rescuing R558C likely partially rescues R558H — but the pH-dependent residue character makes the variant uniquely interesting for context-specific therapeutic design.

R558H is the direct chemistry-variant comparator to R558C at the most clinically important position in the Atlas. Three Atlas variants now converge on the R558 microregion: R558C (Ashkenazi flagship), R558H (this card), and A559D (adjacent position). Drug discovery here has multi-variant rescue potential.