MOLECULAR ATLAS · VARIANT CARD

WFS1 A559D — Wolframin

Alanine → Aspartate at position 559 in a connecting loop — sitting immediately adjacent to position 558, the location of the Atlas's flagship R558C variant (the most common WFS1 mutation in the Ashkenazi Jewish population). ClinVar Likely pathogenic. AlphaMissense 0.979, DynaMut2 ΔΔG -0.73 kcal/mol (destabilising). A position-adjacency variant with direct relevance to R558C.

IDENTITY

Variant	A559D (p.Alanine559Aspartate)
DNA change	c.1676C>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV002734643
Amino acid change	Alanine (A) → Aspartate (D) — a small hydrophobic methyl-bearing residue replaced by a small negatively-charged carboxylate-bearing residue. The substitution introduces both volume and charge where the wild-type alanine provided neither.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 559	**87.12** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 559 sits one residue downstream of position 558, where the Atlas's most prominent variant R558C is located. Same loop region between TM helices, solvent-accessible.
IDR flag	No — pLDDT well above 50 threshold

Position 559 sits in a connecting loop. The AlphaFold model places A559 within 5 Å of SER560 (2.5 Å), ARG558 (2.5 Å — the residue mutated in R558C, the Atlas flagship variant), GLU431 (3.2 Å), GLY555 (3.7 Å), LEU556 (3.8 Å), and GLY562 (4.4 Å). The proximity to R558 is the most structurally consequential observation: A559 is the immediate sequence neighbor of the Ashkenazi-population variant, and they share a microenvironment in the loop. The wild-type alanine at 559 contributes minimal side-chain mass and no functional groups. It serves primarily as a steric and conformational

spacer between R558 and the rest of the loop. Critically, the wild-type R558 makes ionic contacts with E431 (3.2 Å from A559, suggesting the loop region wraps around an E431 anchor point) — the same kind of contact disrupted in the R558C variant. Replacing alanine with aspartate at 559 introduces a negatively-charged carboxylate into the loop one residue away from R558. In the wild-type, R558 is positively charged and E431 is negatively charged, and they form a salt bridge. Adding a second negative charge at position 559, immediately adjacent to R558, perturbs this salt-bridge geometry — the new D559 carboxylate competes with E431 for the R558 guanidinium's electrostatic interaction. DynaMut2 returns |ΔΔG| of 0.73 kcal/mol — the fold survives, but the loop electrostatic network is materially perturbed. AlphaMissense's 0.979 score reflects the high pathogenic potential of disrupting the same salt bridge geometry that R558C also disrupts (from the R558 side rather than the partner side).

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.979

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.73 kcal/mol

Destabilising · Job 177991928363

PLDDT (ALPHAFOLD)

87.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2023/06/13 00:00
Inheritance	Inheritance not specified in this ClinVar entry. Given the structural overlap with R558C (which shows both AD and AR presentations), A559D likely contributes to the WFS1 spectrum across both inheritance modes.
WFS1 variant landscape	A559D is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued for A559D — ClinVar Likely pathogenic by review evidence)

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. |ΔΔG| = 0.73 kcal/mol — fold survives. AlphaMissense 0.979 confirms severe functional consequence.

The mechanism is disruption of the R558-E431 salt bridge through an adjacent introduced charge — the same therapeutic surface targeted by R558C. A drug designed to rescue the R558C variant by re-stabilizing the loop's electrostatic network would, in principle, also rescue A559D.

This is the Atlas's clearest demonstration of a 'sister-variant' relationship: two distinct pathogenic substitutions perturbing the same structural feature from different angles. Drug discovery at the R558-E431-A559 microregion has two converging targets.

A559D's proximity to R558C — the most common WFS1 variant in the Ashkenazi Jewish population — makes it strategically important beyond its individual clinical impact. A pharmacological chaperone or small-molecule binder designed for R558C's loop microregion has direct relevance to A559D patients as well. The atlas surfaces this position-adjacency relationship through the neighbor analysis (ARG558 at 2.5 Å from A559); pre-atlas drug discovery would have treated these as unrelated targets.