

WFS1 R629Q — Wolframin

Arg→Gln p629 loop AM=0.09 ddg=-0.63 pLDDT=60. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	R629Q (p.Arginine629Glutamine)
DNA change	c.1886G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000045443
Amino acid change	charge loss, amide preserved

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 629	59.97 CONFIDENT
Domain	Connecting loop
Position context	Connecting loop
IDR flag	No — pLDDT well above 50 threshold

Position analysis: THR628 (2.5 Å — same R629 microregion as R629W), SER630 (2.5 Å), SER626 (3.8 Å). Same position as R629W (AM under-call sister). The Atlas's neighbor extraction surfaces this variant's contacts.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.092am_class: **LBen** —
threshold > 0.564DYNAMUT2 $\Delta\Delta G$ **-0.63** kcal/

mol

Destabilising · Job
177992515559

PLDDT (ALPHAFOLD)

59.97

confident

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/06/12 00:00

Inheritance

Conflicting ClinVar classifications.

WFS1 variant landscape

R629Q is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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

Cat 3/4 AM under-call — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally clear from neighbor analysis. Therapeutic strategy: site-directed at the contacts identified above.

R629W + R629Q sister variants.