

WFS1 I561V — Wolframin

Ile→Val p561 loop AM=0.06 ddg=-0.25 pLDDT=85. ClinVar Conflicting evidence.
Atlas mechanism: see structural analysis.

IDENTITY

Variant	I561V (p.Isoleucine561Valine)
DNA change	c.1681A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001320392
Amino acid change	conservative volume reduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 561	85.00 HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop
IDR flag	No — pLDDT well above 50 threshold

Position analysis: GLY562 (2.5 Å — G562 in A559D region!), SER560 (2.5 Å — same S560 as A559D!), LEU557 (3.7 Å — L557 in R558C loop!). Same R558C connecting loop. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.055am_class: **LBen** —
threshold > 0.564

DYNAMUT2 ΔΔG

-0.25 kcal/

mol

Destabilising · Job
177992527225

PLDDT (ALPHAFOLD)

85.00

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2026/01/24 00:00

Inheritance

Conflicting ClinVar classifications.

WFS1 variant landscape

I561V 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 \rightarrow CATEGORY 3 – docking experiments $\Delta\Delta G$ 2–4 \rightarrow CATEGORY 2 – pharmacological chaperones $\Delta\Delta G > 4$ \rightarrow CATEGORY 1 – gene therapy pLDDT < 50 \rightarrow CATEGORY 5 – IDR, experimental only Stable fold + functional site hit \rightarrow CATEGORY 4 – site-specific docking

Cat 4 – see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

R558C connecting loop variant.