MOLECULAR ATLAS · VARIANT CARD

WFS1 E462G — Wolframin

Glutamate → Glycine at position 462 in a connecting loop. ClinVar Likely pathogenic. AlphaMissense 0.805, DynaMut2 ΔΔG -1.10 kcal/mol (destabilising). Loss of charge plus loss of side chain entirely.

IDENTITY

Variant	E462G (p.Glutamate462Glycine)
DNA change	c.1385A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000092252
Amino acid change	Glutamate (E) → Glycine (G) — negatively-charged carboxylate replaced by smallest amino acid. Loss of charge and side-chain mass.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 462	**84.75** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 462 in a loop region (pLDDT 85).
IDR flag	No — pLDDT well above 50 threshold

Position 462 sits in a connecting loop. The AlphaFold model places E462 within 5 Å of VAL463 (2.5 Å), THR461 (2.5 Å), LEU459 (3.7 Å), ALA458 (3.8 Å), and THR464 (4.3 Å). The local environment is hydrophobic-leaning with two threonines providing H-bond options. The wild-type glutamate's carboxylate likely engages T461 or T464 through H-bonding while extending the negative charge toward solvent. Replacing E462 with glycine eliminates both the charge and the side chain — substantial loss for a single substitution. The |ΔΔG| of 1.10 reflects this. AlphaMissense's 0.805 confirms pathogenic functional consequence. Mechanism is loss of E462's H-bonding role in the loop's polar network plus introduction of backbone flexibility where the wild-type constrained.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.805	**-1.1** kcal/mol	**84.75**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992007254	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/07/01 00:00
Inheritance	Inheritance not specified.
WFS1 variant landscape	E462G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

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| = 1.10 — fold survives. AlphaMissense 0.805 confirms severe functional consequence.

Mechanism is loss of E462 H-bonding plus backbone flexibility gain. Therapeutic strategy: site-directed at the loop polar network.

E462G is one of several charge-loss-to-glycine variants in the Atlas — substantial structural and functional cost from a single substitution removing both charge and side chain.