MOLECULAR ATLAS · VARIANT CARD

WFS1 V536E — Wolframin

Valine → Glutamate at position 536 inside wolframin's seventh transmembrane helix (TM7). ClinVar carries conflicting classifications. AlphaMissense 0.980, DynaMut2 ΔΔG -1.62 kcal/mol (destabilising). A charge-into-membrane variant with a stronger structural cost than the typical TM-helix substitution.

IDENTITY

Variant	V536E (p.Valine536Glutamate)
DNA change	c.1607T>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000432354
Amino acid change	Valine (V) → Glutamate (E) — a small, branched hydrophobic residue replaced by a negatively-charged carboxylate-bearing residue. The chemistry shift in a bilayer-embedded position is severe.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 536	**90.62** HIGH CONFIDENCE
Domain	TM7 (529-549), helical transmembrane
Position context	TM7 (residues 529–549) · position 536 is bilayer-embedded near the middle of the helix. The lipid environment penalizes carboxylate charge heavily.
IDR flag	No — pLDDT well above 50 threshold

Position 536 sits in the middle of TM7. The AlphaFold model places V536 within 5 Å of CYS537 (2.5 Å), LEU535 (2.5 Å), PHE408 (3.7 Å, from TM3 — TM3-TM7 cross-helix contact), PRO533 (3.8 Å), TYR534 (4.2 Å), and VAL532 (4.3 Å). The wild-type valine's small branched hydrophobic side chain packs into a hydrophobic environment dominated by aromatic and aliphatic residues, including the cross-helix contact to PHE408 in TM3. Replacing valine with glutamate at this position is energetically costly. Glutamate's carboxylate group is negatively charged at physiological pH; carrying that charge into the bilayer hydrophobic core requires significant local rearrangement to position the charge near water or polar headgroups. The side chain volume is also larger than valine's, so even before considering

electrostatics the local packing has to accommodate more mass. DynaMut2 returns |ΔΔG| = 1.62 kcal/mol — the highest in this batch and approaching the Category 2 threshold (|ΔΔG| ≥ 2). The fold survives, but the energetic cost is substantial. The TM3-TM7 cross-helix interface at the PHE408 contact is particularly affected: the carboxylate's polarity is incompatible with the aromatic-hydrophobic packing the wild-type maintained. The conflicting ClinVar classifications likely reflect the variant's mechanism-dependent functional consequence. In one cellular context (e.g., heterozygous expression where the partner allele compensates) the variant may produce mild phenotype; in homozygous or compound-heterozygous context it likely produces full Wolfram syndrome 1. AlphaMissense's score of 0.980 reflects the variant's high pathogenic potential when context allows.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.980	**-1.62** kcal/mol	**90.62**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177992298974	high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2024/05/31 00:00
Inheritance	Documented in association with Wolfram syndrome 1 (AR). Conflicting ClinVar classifications suggest context-dependent functional consequence.
WFS1 variant landscape	V536E is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

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 —
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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| = 1.62 kcal/mol — closest to the Category 2 threshold in this batch but still in the fold-intact range. AlphaMissense 0.980 confirms severe functional consequence.

The mechanism is charge-into-membrane disruption at the TM3-TM7 cross-helix interface (PHE408 at 3.7 Å). The introduced carboxylate is incompatible with the hydrophobic packing the wild-type valine maintained, and the helix-helix register is perturbed.

Therapeutic strategy: a small molecule that stabilizes the TM3-TM7 interface at the PHE408/V536 contact. Alternative: a pharmacological chaperone that biases the fold against the variant's locally rearranged geometry. The closer-to-Cat-2 |ΔΔG| suggests chaperone screening may be a more accessible approach than purely site-directed binders.

V536E exemplifies the boundary between Category 3/4 (site-directed binders) and Category 2 (chaperones) in the Atlas schema. With |ΔΔG| of 1.62, the variant sits in the most-druggable tier but close enough to the moderate-destabilization threshold that chaperone screening is justified alongside site-directed design. The Atlas's continuous classification (rather than binary) captures variants at this boundary cleanly.
