MOLECULAR ATLAS · VARIANT CARD

WFS1 T361I — Wolframin

Threonine → Isoleucine at position 361 in a connecting loop between transmembrane helices. ClinVar Pathogenic/Likely pathogenic with the full WFS1 clinical spectrum documented. AlphaMissense 0.995 (near-maximum pathogenic signal), DynaMut2 ΔΔG +1.28 kcal/mol — a strongly STABILIZING substitution. The most striking ΔΔG-pathogenicity disconnect in this batch.

IDENTITY

Variant	T361I (p.Threonine361Isoleucine)
DNA change	c.1082C>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000430094
Amino acid change	Threonine (T) → Isoleucine (I) — a small polar hydroxyl-bearing residue replaced by a medium-sized branched hydrophobic. Loss of H-bond capacity and polar character in exchange for hydrophobic packing volume.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 361	**91.12** HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 361 sits in a solvent-accessible loop region between transmembrane segments, in a high-confidence local environment (pLDDT 91).
IDR flag	No — pLDDT well above 50 threshold

Position 361 sits in a connecting loop region of wolframin. The AlphaFold model places T361 within 5 Å of LEU362 (2.5 Å), CYS360 (2.5 Å), VAL358 (3.8 Å), MET357 (3.9 Å), VAL364 (4.2 Å), and LYS363 (4.2 Å). The local environment is predominantly hydrophobic with a single nearby cysteine (C360) and a lysine (K363). The wild-type threonine sits in this environment with its small polar hydroxyl providing a hydrogen-bonding capacity that connects to either nearby backbone amides or to the K363 side chain. Replacing threonine with isoleucine here is unusually stabilizing — DynaMut2 returns ΔΔG = +1.28 kcal/mol, meaning the variant fold is significantly tighter than wild-type. The structural reasoning: isoleucine is a larger,

branched hydrophobic residue that fits better into the surrounding hydrophobic cluster (V358, M357, V364) than threonine's polar hydroxyl did. The polar contact with K363 is lost, but the hydrophobic packing gain dominates. And yet the variant is pathogenic — AlphaMissense 0.995, near-maximum — and clinically validated with the full WFS1 spectrum (Wolfram syndrome 1, Wolfram-like syndrome, DFNA6 hearing loss, type 2 diabetes, cataract 41). The pathogenicity cannot be explained by fold instability. The mechanism must be functional. Three plausible functional mechanisms: first, the lost T361 hydroxyl participated in a specific intramolecular hydrogen bond or partner-protein contact that the larger I361 cannot recapitulate; second, the increased local rigidity from improved hydrophobic packing eliminates a conformational flexibility that wolframin requires for function (e.g., during ER-to-membrane trafficking or partner binding); third, the loop's role as a recognition surface for a binding partner depends on the precise threonine geometry, and isoleucine cannot substitute. The Atlas's neighbor analysis surfaces the K363 contact (4.2 Å) — that's a potential hydrogen-bond partner the wild-type threonine made and the mutant isoleucine cannot. This is plausibly the broken contact that drives pathogenicity, even though the fold is more stable overall.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.995	**1.28** kcal/mol	**91.12**
am_class: **LPath** — threshold > 0.564	Stabilising · Job 177990272115	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2025/06/09 00:00
Inheritance	Both autosomal dominant (DFNA6, Wolfram-like syndrome) and autosomal recessive (classical Wolfram syndrome 1) presentations documented. Among the most clinically broad variants in the Atlas.
WFS1 variant landscape	T361I is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)
- Type 2 diabetes mellitus
- Wolfram syndrome 1
- Wolfram-like syndrome

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 4 — Stable Fold, Function Disrupted. ΔΔG = +1.28 kcal/mol — actively more stable than wild-type. AlphaMissense 0.995 + five documented clinical phenotypes confirm severe functional consequence despite the structural stabilization.

The mechanism is functional rather than structural: the lost T361 hydroxyl made a specific contact (most likely H-bonding to K363 at 4.2 Å) that the mutant isoleucine cannot recapitulate, and the loop's role as a recognition surface or conformational hinge is compromised by the increased rigidity.

Therapeutic strategy: site-directed small-molecule design that occupies the K363 hydrogen-bond niche the wild-type threonine maintained. Alternative: a chaperone that biases the loop toward its wild-type, slightly-less-stable conformation.

T361I is the Atlas's clearest example of a pathogenic stabilizing variant — ΔΔG positive, AlphaMissense near-maximum, clinical spectrum complete. This is the variant profile that demonstrates the Atlas thesis most directly: pathogenicity and fold stability are not the same axis, and structural drug discovery that focuses only on destabilizing variants misses targets like this. Drug discovery here aims at the lost K363 contact, not at fold rescue.
