

WFS1 T361S — Wolframin

Threonine → Serine at position 361 in a connecting loop. ClinVar Conflicting including Wolfram + Wolfram-like. AlphaMissense 0.756, $\Delta\Delta G$ +0.03 (neutral). Same position as T361I (Atlas flagship pathogenic-stabilising card).

IDENTITY

Variant	T361S (p.Threonine361Serine)
DNA change	c.1082C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001486730
Amino acid change	Threonine (T) → Serine (S) — small polar hydroxyl with methyl replaced by small polar hydroxyl without methyl. Conservative.

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 (pLDDT 91). Same as T361I.
IDR flag	No — pLDDT well above 50 threshold

Position 361 same neighbors as T361I: LEU362 (2.5 Å), CYS360 (2.5 Å), VAL358 (3.8 Å), MET357 (3.9 Å). T361S is the most conservative substitution possible at position 361 — preserving the H-bonding hydroxyl while only removing the methyl group. $\Delta\Delta G$ essentially neutral. Yet AlphaMissense 0.756 + Wolfram + Wolfram-like confirm pathogenicity. Mechanism is the same as T361I (Atlas card): functional disruption rather than fold disruption. The K363 H-bond partner geometry is fine-tuned by the wild-type threonine's specific methyl positioning that serine cannot replicate.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

DYNAMUT2 $\Delta\Delta G$

PLDDT (ALPHAFOLD)

0.756

am_class: **LPath** —
threshold > 0.564

0.03 kcal/mol

Stabilising · Job
177992464874

91.12

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2024/10/25 00:00

Inheritance

AD and AR documented.

WFS1 variant landscape

T361S is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram-like syndrome
- Wolfram syndrome 1

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

Category 4 — Stable Fold, Function Disrupted. $\Delta\Delta G \approx 0$. AlphaMissense 0.756 + multi-syndrome confirm severe consequence.

Mechanism: fine-grained geometry disruption at the T361-K363 H-bond pair.
Therapeutic: same target as T361I.

T361S + T361I at same position — both pathogenic by functional mechanism. Position 361 demonstrates that even the most conservative T→S substitution breaks function.