

WFS1 I802T — Wolframin

Isoleucine → Threonine at position 802 in luminal domain. ClinVar Conflicting including Wolfram + Wolfram-like. AlphaMissense 0.851, $\Delta\Delta G$ -1.99 — RIGHT AT Cat 2 boundary.

IDENTITY

Variant	I802T (p.Isoleucine802Threonine)
DNA change	c.2405T>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000976364
Amino acid change	Isoleucine (I) → Threonine (T) — branched aliphatic hydrophobic replaced by small polar hydroxyl. Major chemistry shift.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 802	87.19 HIGH CONFIDENCE
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain · position 802 (pLDDT 87).
IDR flag	No — pLDDT well above 50 threshold

Position 802 sits in the luminal domain. Neighbors: VAL803 (2.4 Å), ASP801 (2.5 Å — partner of D801G), VAL779 (3.9 Å — V779G outlier region!), PRO838 (4.1 Å). Replacing I802 with threonine introduces polarity into a hydrophobic environment near both D801G's salt-bridge region and V779G's Cat 2 outlier site. The $|\Delta\Delta G|$ of 1.99 is the largest in this batch — RIGHT AT the Category 2 threshold. The variant nearly bridges the fold-intact / moderately-destabilizing boundary. AlphaMissense 0.851 + Wolfram + Wolfram-like confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

DYNAMUT2 $\Delta\Delta G$

PLDDT (ALPHAFOLD)

0.851

am_class: **LPath** —
threshold > 0.564

-1.99 kcal/

mol
Destabilising · Job
177992461623

87.19

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2018/07/02 00:00

Inheritance

AD and AR documented.

WFS1 variant landscape

I802T is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1
- Wolfram-like syndrome

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 3/4 — Most Druggable (AT Cat 2 boundary). $|\Delta\Delta G| = 1.99$ — at the Category 2 boundary. AlphaMissense 0.851 + dual-syndrome confirm severe consequence.

Mechanism: polarity in hydrophobic environment + perturbation of V779 outlier region. Therapeutic: site-directed at the V779-D801-I802 microregion — chaperone screening may also be warranted given near-Cat-2 stability.

I802T sits at the Cat 2 threshold — Atlas's edge case for category assignment. The proximity to V779G (Cat 2 outlier) suggests this region is structurally fragile.

