

WFS1 I802M — Wolframin

Isoleucine → Methionine at position 802 in luminal domain. ClinVar Conflicting for DFNA6. AlphaMissense 0.35 (below threshold) — AM under-call. DynaMut2 $\Delta\Delta G$ -0.44 kcal/mol (destabilising). Same position as I802T (Cat 2 boundary).

IDENTITY

Variant	I802M (p.Isoleucine802Methionine)
DNA change	c.2406C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000229642
Amino acid change	Isoleucine (I) → Methionine (M) — branched aliphatic replaced by flexible sulfur-containing hydrophobic. Conservative 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). Same position as I802T.
IDR flag	No — pLDDT well above 50 threshold

Position 802 same neighbors as I802T: VAL803 (2.4 Å), ASP801 (2.5 Å — partner of D801G), VAL779 (3.9 Å — V779G Cat 2 outlier region!). I802M is the second pathogenic substitution at position 802. Where I802T introduced polarity (Cat 2 boundary $\Delta\Delta G$ of -1.99), I802M is conservative — flexible sulfur-containing hydrophobic replaces branched aliphatic hydrophobic. The fold absorbs the substitution more easily ($|\Delta\Delta G|$ 0.44). AlphaMissense's 0.35 is below threshold (AM under-call). DFNA6 clinical evidence confirms pathogenicity. Both I802T and I802M perturb the V779-D801-I802 microregion that connects the V779G Cat 2 outlier to the D801G salt-bridge position.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE 0.346 am_class: Amb — threshold > 0.564	DYNAMUT2 $\Delta\Delta G$ -0.44 kcal/ mol Destabilising · Job 177992493707	PLDDT (ALPHAFOLD) 87.19 high confidence
--	---	--

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2025/12/18 00:00

Inheritance

DFNA6 hearing loss.

WFS1 variant landscape

I802M is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)

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 (AM under-call). $|\Delta\Delta G| = 0.44$.
AlphaMissense 0.35 below threshold but DFNA6 confirms pathogenicity.

Mechanism: conservative chemistry shift in the V779-D801-I802 microregion.
Therapeutic strategy: same target as I802T, V779G, V779M, D801G, K800E.

I802M is the 5th variant in the V779-D801-I802 microregion. The cluster's structural importance is now extensively documented across multiple variants.

