

WFS1 W399G — Wolframin

Tryptophan → Glycine at position 399 in a connecting loop. ClinVar Conflicting including Cataract 41 + DFNA6. AlphaMissense 0.713, $\Delta\Delta G$ -1.06. Bulky aromatic → smallest amino acid.

IDENTITY

Variant	W399G (p.Tryptophan399Glycine)
DNA change	c.1195T>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000215386
Amino acid change	Tryptophan (W) → Glycine (G) — bulky aromatic indole replaced by smallest amino acid. Massive volume loss.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 399	76.44 HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 399 (pLDDT 76).
IDR flag	No — pLDDT well above 50 threshold

Position 399 in connecting loop. Neighbors: ASN400 (2.5 Å), GLY398 (2.5 Å — adjacent existing glycine!), ASN396 (3.9 Å), VAL395 (4.0 Å — near E394V). Replacing W399 with glycine creates G398-G399 double-glycine motif (extra backbone flexibility) and removes the aromatic side chain entirely. Two adjacent glycines in a loop produce unusual conformational freedom. $\Delta\Delta G$ 1.06 reflects this. AM 0.713 + Cataract 41 + DFNA6 confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.713DYNAMUT2 $\Delta\Delta G$

PLDDT (ALPHAFOLD)

76.44

high confidence

am_class: **LPath** —
threshold > 0.564

-1.06 kcal/

mol
Destabilising · Job
177992465049

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2026/01/04 00:00

Inheritance

AD: DFNA6 + Cataract 41.

WFS1 variant landscape

W399G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41
- 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. $|\Delta\Delta G| = 1.06$. AlphaMissense 0.713 + dual phenotypes confirm severe consequence.

Mechanism: massive volume loss + creation of G398-G399 double-glycine motif. Therapeutic: loop region site-directed.

W399G is in the same 392-399 loop region as E394V — multi-variant target cluster.