

WFS1 E394V — Wolframin

Glutamate → Valine at position 394 in a connecting loop. ClinVar Conflicting including spastic ataxia and DFNA6. AlphaMissense 0.917, $\Delta\Delta G$ +1.18 STABILISING.

IDENTITY

Variant	E394V (p.Glutamate394Valine)
DNA change	c.1181A>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000546078
Amino acid change	Glutamate (E) → Valine (V) — negatively-charged carboxylate replaced by branched aliphatic hydrophobic. Complete charge loss in a polar environment.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 394	82.06 HIGH CONFIDENCE
Domain	Connecting loop
Position context	Connecting loop · position 394 (pLDDT 82).
IDR flag	No — pLDDT well above 50 threshold

Position 394 sits in a connecting loop. Neighbors: VAL395 (2.5 Å), ALA393 (2.5 Å), VAL390 (3.8 Å), GLU391 (3.8 Å — second nearby glutamate). The wild-type E394 with nearby E391 forms a charge cluster in this loop. Replacing E394 with valine eliminates one of two negative charges; the variant fold packs more efficiently with valine in the surrounding hydrophobic environment (V395, V390, A393), producing stabilising $\Delta\Delta G$ of +1.18. Yet AlphaMissense 0.917 + spastic ataxia + DFNA6 clinical evidence confirm severe consequence. The mechanism is loss of the negatively-charged surface that the wild-type E394 contributed to — partner-recognition disruption despite structural gain.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.917

am_class: **LPath** —
threshold > 0.564

DYNAMUT2 $\Delta\Delta G$

1.18 kcal/mol

Stabilising · Job
177992457291

PLDDT (ALPHAFOLD)

82.06

high confidence

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2026/01/26 00:00

Inheritance

Spastic ataxia and DFNA6 documented.

WFS1 variant landscape

E394V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Spastic ataxia
- 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 4 — Stable Fold, Function Disrupted. $\Delta\Delta G = +1.18$ stabilising. AlphaMissense 0.917 + multi-phenotype confirm severe consequence.

Mechanism: loss of E394 charge from the local surface patch. Therapeutic: recognition-surface site-directed.

E394V joins the growing stabilising-but-pathogenic class. Pattern is consistent: charge-loss variants where fold tightens but partner recognition fails.