

WFS1 Y650C — Wolframin

Tyrosine → Cysteine at position 650 inside TM10. ClinVar Conflicting including Cataract 41 + DFNA6. AlphaMissense 0.399 (below threshold), $\Delta\Delta G$ +0.31. Third Atlas variant at position 650 (with Y650H, Y650D).

IDENTITY

| | |
|-------------------|--|
| Variant | Y650C (p.Tyrosine650Cysteine) |
| DNA change | c.1949A>G |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV001218633 |
| Amino acid change | Tyrosine (Y) → Cysteine (C) — aromatic phenol replaced by thiol. Loss of aromatic + introduction of disulfide-capable thiol. |

STRUCTURAL CONTEXT

| | |
|----------------------|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 650 | 68.69 CONFIDENT |
| Domain | TM10 (632-652), helical transmembrane |
| Position context | TM10 (residues 632–652) · position 650 (pLDDT 69 borderline). |
| IDR flag | No — pLDDT well above 50 threshold |

Position 650 same neighbors as Y650H/Y650D: PHE649 (2.5 Å), VAL651 (2.5 Å), CYS647 (3.7 Å — C647 already in close contact!), PHE646 (3.7 Å). The C647 contact suggests a potential Y650C-C647 disulfide formation. Y650C is the THIRD substitution at position 650. The new C650 could potentially form a disulfide with C647 (3.7 Å away) — possibly a beneficial or aberrant chemistry depending on the wild-type C647 state. Compare with Y650H (preserved aromatic) and Y650D (charge introduction). AM 0.399 below threshold; multi-phenotype confirms.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

DYNAMUT2 $\Delta\Delta G$

PLDDT (ALPHAFOLD)

0.399

am_class: **Amb** —
threshold > 0.564

0.31 kcal/mol

Stabilising · Job
177992473973

68.69

confident

CLINICAL EVIDENCE

ClinVar classification

CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2024/10/24 00:00

Inheritance

AD: Cataract + DFNA6.

WFS1 variant landscape

Y650C 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 4 — Stable Fold, Function Disrupted (AM under-call). $\Delta\Delta G$
+0.31. AlphaMissense 0.399 below threshold but multi-phenotype confirms
pathogenicity.

Mechanism: aromatic loss + potential aberrant disulfide with C647.

Therapeutic: same Y650 microregion as Y650H/Y650D.

Y650C completes the Y650 three-substitution series (Y650H, Y650D, Y650C)
— position 650 is a multi-substitution hotspot in TM10.