MOLECULAR ATLAS · VARIANT CARD

WFS1 C690Y — Wolframin

Cysteine → Tyrosine at position 690 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic with the full clinical spectrum documented — Wolfram syndrome 1, Wolfram-like syndrome, DFNA6 hearing loss, type 2 diabetes, and cataract 41. AlphaMissense 0.999, DynaMut2 ΔΔG -1.16 kcal/mol (destabilising). A high-pathogenicity, high-clinical-impact variant.

IDENTITY

Variant	C690Y (p.Cysteine690Tyrosine)
DNA change	c.2069G>A
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003590730
Amino acid change	Cysteine (C) → Tyrosine (Y) — a small thiol-bearing residue replaced by a large aromatic ring with a hydroxyl group. Loss of disulfide-bond potential, introduction of bulky aromatic packing, and a new H-bonding hydroxyl.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 690	**90.69** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 690 faces the ER lumen, in a well-folded region (pLDDT 91). The ER lumen's oxidizing environment supports disulfide formation in cysteines like C690.
IDR flag	No — pLDDT well above 50 threshold

Position 690 sits in wolframin's C-terminal lumenal domain (residues 653–869), the protein's largest soluble region and the primary site of documented protein-protein interactions with ATF6 and Na+/K+ ATPase β1. The AlphaFold model places C690 within 5 Å of: LEU689 (2.5 Å), SER691 (2.5 Å), THR686 (3.7 Å), GLN687 (3.8 Å), CYS673 (3.8 Å), HIS692 (4.2 Å), ILE688 (4.6 Å), and LEU833 (4.7 Å). The most structurally consequential of these is CYS673 at 3.8 Å. This spacing is consistent with a structural disulfide bond between C690 and C673 in the lumenal fold — an oxidative-environment crosslink that locks two distant segments of the domain together. The C690Y

substitution eliminates the cysteine thiol, breaking any such disulfide, and replaces it with a bulky aromatic ring carrying a hydroxyl group. Replacing cysteine with tyrosine here has three layered effects: (1) the disulfide crosslink is lost; (2) a substantial volume increase from the aromatic ring would either displace surrounding residues or be sterically disallowed in the wild-type geometry, forcing local rearrangement; (3) the tyrosine hydroxyl introduces new hydrogen-bonding potential that could either compensate (by H-bonding to GLN687, THR686, or SER691) or further perturb the local network. The DynaMut2 |ΔΔG| of 1.16 kcal/mol indicates the net effect is moderate — the fold can absorb the substitution, but at energetic cost — while the AlphaMissense score of 0.999 indicates the functional consequence is severe. Comparison with C690R (the same position with arginine substitution, also in the Atlas) is instructive: both substitutions break the inferred C690-C673 disulfide, but the tyrosine variant introduces aromatic packing where the arginine introduces charge. The two yield similar |ΔΔG| (1.16 vs 1.29) but differ in their downstream therapeutic implications.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.999

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.16 kcal/mol

Destabilising · Job 177991409971

PLDDT (ALPHAFOLD)

90.69

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	criteria provided, single submitter
Last evaluated	2024/04/30 00:00
Inheritance	Both autosomal dominant and autosomal recessive forms documented. C690Y is associated with DFNA6/14/38 (AD hearing loss), classical Wolfram syndrome (AR), Wolfram-like syndrome (AD), cataract 41, and type 2 diabetes — the full WFS1 clinical spectrum across both inheritance modes.
WFS1 variant landscape	C690Y is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Autosomal dominant nonsyndromic hearing loss 6 (DFNA6)
- Cataract 41

- Wolfram syndrome 1
- Wolfram-like syndrome
- Type 2 diabetes mellitus

RESEARCH PATH DECISION TREE

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ΔΔG < 2 + binding site affected → CATEGORY 3 — docking experiments ΔΔG 2–4 → CATEGORY 2 — pharmacological chaperones ΔΔG > 4 → CATEGORY 1 — gene therapy pLDDT < 50 → CATEGORY 5 — IDR, experimental only Stable fold + functional site hit → CATEGORY 4 — site-specific docking
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Category 3/4 — Most Druggable. |ΔΔG| = 1.16 kcal/mol — below the 2 kcal/mol fold-integrity line. The wolframin fold survives. AlphaMissense 0.999 indicates severe functional consequence despite the modest structural cost.

The mechanism combines disulfide loss (the C690-C673 inferred crosslink) with steric and electronic perturbation from the introduced aromatic ring. This is a defined, local lesion in a folded protein — exactly the profile that responds to site-directed small-molecule therapy. The drug-discovery question becomes: can we identify a compound that occupies the C690 site, restores the geometry of the surrounding pocket, and partially compensates for the lost C673 contact?

The clinical breadth of this variant (five documented phenotypes across both AD and AR inheritance) makes it one of the highest-value docking targets in the Atlas. A small molecule that rescues C690Y has potential clinical reach across the entire WFS1 patient population — not just Wolfram syndrome 1 carriers.

C690Y is one of the Atlas's most clinically broad variants — five documented phenotypes across both AD and AR inheritance modes. Paired with a near-maximum AlphaMissense score (0.999) and a fold-intact |ΔΔG| under 2, it's exactly the variant profile where the Atlas's small-molecule thesis is loudest. The protein folds, the damage is local, and the lesion sits at a defined position. Drug designers can aim at it.
