MOLECULAR ATLAS · VARIANT CARD

# WFS1 Q687H — Wolframin

Glutamine → Histidine at position 687 in wolframin's C-terminal lumenal domain. ClinVar Conflicting classifications. AlphaMissense 0.996 (near-maximum), DynaMut2 ΔΔG -0.19 kcal/mol (mild destabilising). Strong AM signal in the dense 684-688 cluster.

## IDENTITY

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|---|---|
| Variant | Q687H (p.Glutamine687Histidine) |
| DNA change | c.2061G>C |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000427196 |
| Amino acid change | Glutamine (Q) → Histidine (H) — polar amide replaced by aromatic titratable basic residue. Aromatic character introduced; pH-dependent charge added. |

## STRUCTURAL CONTEXT

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|---|---|
| AlphaFold model | AF-O76024-F1, v6 |
| pLDDT at residue 687 | **89.44** HIGH CONFIDENCE |
| Domain | C-terminal lumenal domain (653-869) |
| Position context | C-terminal lumenal domain · position 687 in the ER lumen (pLDDT 89). |
| IDR flag | No — pLDDT well above 50 threshold |

Position 687 sits in the dense 684-688 cluster discussed in the A684T, A684V, R685P, I688F Atlas cards. The AlphaFold model places Q687 within 5 Å of THR686 (2.5 Å), ILE688 (2.5 Å — partner of I688F), LEU833 (3.6 Å — long-range), ALA684 (3.8 Å — partner of A684T, A684V), and MET683 (3.9 Å). The wild-type glutamine's amide likely H-bonds with the surrounding polar residues in this cluster. Replacing Q687 with histidine introduces an aromatic imidazole with pH-dependent charge. The H-bond geometry changes substantially. The |ΔΔG| of 0.19 reflects fold accommodation. AlphaMissense's 0.996 (near-maximum) is strong pathogenic signal. ClinVar conflicting classifications suggest context-dependent functional consequence.

## COMPUTATIONAL PREDICTIONS

| ALPHAMISSENSE | DYNAMUT2 ΔΔG | PLDDT (ALPHAFOLD) |
|---|---|---|
| **0.996** | **-0.19** kcal/mol | **89.44** |
| am_class: **LPath** — threshold > 0.564 | Destabilising · Job 177992012581 | high confidence |

## CLINICAL EVIDENCE

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|---|---|
| ClinVar classification | **CONFLICTING CLASSIFICATIONS OF PATHOGENICITY** |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2025/08/17 00:00 |
| Inheritance | Conflicting classifications. AD-leaning given DFNA6 association. |
| WFS1 variant landscape | Q687H 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

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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| = 0.19 — fold survives. AlphaMissense 0.996 (near-maximum) confirms severe pathogenic mechanism.

Mechanism is amide-to-aromatic substitution disrupting the 684-688 cluster H-bond network. Therapeutic strategy: same cluster target as A684T, A684V, R685P, I688F.

> Q687H is the FIFTH Atlas variant in the 684-688 microregion. This is one of the densest multi-variant target clusters in the entire Atlas. Drug discovery here rescues five known pathogenic variants simultaneously.

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