RARERESEARCH.AI · WFS1 MOLECULAR ATLAS · NONSENSE

Y669* — WFS1 Molecular Atlas Card

Variant type: Nonsense (premature stop codon)

Position: 669

Wild-type residue: Tyrosine (Y)

Domain context (where the stop falls): C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)

SCHEMA CATEGORY: N3 — NMD-ESCAPE, MODERATE TRUNCATION — CHAPERONE EXPLORATION

Truncated protein retains substantial structure but loses C-terminal domains. Worth screening generic ER chaperones (4-PBA, TUDCA) and sigma-1 receptor agonists. Lower confidence than for missense variants, but a candidate for the high-content drug screen (Initiative 8).

NMD PREDICTION

- **Status:** NMD-escape
- **Confidence:** high
- **Reasoning:** Stop codon at position 669 is in the last exon (exon 8, starts ~aa 413). NMD does not target stop codons in the last exon — a truncated protein is produced.

TRUNCATION ANALYSIS

- **Residues retained:** 1 – 668 (75.1% of full-length protein)
- **Residues lost:** 669 – 890 (24.9% of full-length protein)

Retained domains

- N-terminal cytoplasmic (intrinsically disordered) (aa 1–310)

- Transmembrane helix 1 (aa 311–331)
- Cytoplasmic loop 1 (aa 332–340)
- Transmembrane helix 2 (aa 341–361)
- Lumenal loop 1 (aa 362–370)
- Transmembrane helix 3 (aa 371–391)
- Cytoplasmic loop 2 (aa 392–400)
- Transmembrane helix 4 (aa 401–421)
- Lumenal loop 2 (aa 422–431)
- Transmembrane helix 5 (aa 432–452)
- Cytoplasmic loop 3 (aa 453–461)
- Transmembrane helix 6 (aa 462–482)
- Lumenal loop 3 (aa 483–496)
- Transmembrane helix 7 (aa 497–517)
- Cytoplasmic loop 4 (aa 518–532)
- Transmembrane helix 8 (aa 533–553)
- Lumenal loop 4 (aa 554–573)
- Transmembrane helix 9 (aa 574–594)
- Cytoplasmic loop 5 / pre-lumenal (aa 595–599)

Partially retained at truncation point

- **C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)** — partial: aa 600–668 retained, aa 669–890 lost

Lost domains

(no full domains lost — only distal C-terminus)

CLINICAL EVIDENCE

- **Classification:** Pathogenic/Likely pathogenic
- **Review status:** criteria provided, multiple submitters, no conflicts
- **Associated conditions:** Autosomal dominant nonsyndromic hearing loss 6; Type 2 diabetes mellitus; Cataract 41; Wolfram-like syndrome; Wolfram syndrome 1; WFS1-Related Spectrum Disorders
- **cDNA change:** c.2007T>G
- **ClinVar accession:** VCV000802052
- **Last evaluated:** 2025/07/27 00:00
- **Submissions:** 1

WHY THIS VARIANT MATTERS

Moderate truncation leaves some of the protein intact, including portions of the transmembrane bundle. Whether the partial protein can be coaxed into function with chaperones is an open question — the atlas surfaces it as a candidate for the Initiative 8 drug screen, with the explicit structural data needed to design that screen.

Card generated by `wolfram-atlas-batch` skill (v1) on 2026-06-08T02:18:43.561736Z.

NMD rule and schema definitions: `reference/nmd rules.md`, `reference/cardschemaextension.md`._

WFS1 reference: UniProt O76024, AlphaFold model v6.