RARERESEARCH.AI · WFS1 MOLECULAR ATLAS · NONSENSE

Q486* — WFS1 Molecular Atlas Card

Variant type: Nonsense (premature stop codon)

Position: 486

Wild-type residue: Glutamine (Q)

Domain context (where the stop falls): Lumenal loop 3

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 486 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 – 485 (54.5% of full-length protein)
- **Residues lost:** 486 – 890 (45.5% 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)

Partially retained at truncation point

- **Lumenal loop 3** — partial: aa 483–485 retained, aa 486–496 lost

Lost domains

- 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)
- C-terminal ER-lumenal (calcium binding, calmodulin, chaperone) (aa 600–890)

CLINICAL EVIDENCE

- **Classification:** Pathogenic
- **Review status:** criteria provided, single submitter
- **cDNA change:** c.1456C>T
- **ClinVar accession:** VCV002203518
- **Last evaluated:** 2022/05/03 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 2026-06-08T02:18:12.337910Z.*

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

WFS1 reference: UniProt O76024, AlphaFold model v6.