RARERESEARCH.AI · WFS1 MOLECULAR ATLAS · NONSENSE

Q392* — WFS1 Molecular Atlas Card

Variant type: Nonsense (premature stop codon)

Position: 392

Wild-type residue: Glutamine (Q)

Domain context (where the stop falls): Cytoplasmic loop 2

SCHEMA CATEGORY: N1 — NMD-TARGETED — NULL ALLELE

Transcript degraded by NMD; no truncated protein produced. Therapeutic options: (a) translational readthrough drugs — Ataluren/PTC124, gentamicin-class aminoglycosides — may rescue partial readthrough; (b) gene therapy — allele replacement is the higher-yield long-term path. Pharmacological chaperones do not apply since no protein is made.

NMD PREDICTION

- **Status:** NMD-targeted
- **Confidence:** high
- **Reasoning:** Stop codon at position 392 is more than 50 nt upstream of the last exon-exon junction (~aa 413). The 50-nt rule predicts the transcript is degraded by nonsense-mediated decay. No truncated protein is produced; functionally a null allele.

TRUNCATION ANALYSIS

- **Residues retained:** 1 – 391 (43.9% of full-length protein)
- **Residues lost:** 392 – 890 (56.1% 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)

Lost domains

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

CLINICAL EVIDENCE

- **Classification:** Likely pathogenic
- **Review status:** criteria provided, multiple submitters, no conflicts
- **cDNA change:** c.1174C>T
- **ClinVar accession:** VCV000620122
- **Last evaluated:** 2026/02/01 00:00
- **Submissions:** 1

WHY THIS VARIANT MATTERS

This variant is biologically silent — the transcript is degraded before any truncated protein can be made. From a therapeutic standpoint, that simplifies the problem (one null allele) and points toward two specific paths: readthrough compounds that exploit the ribosome's natural ability to

bypass premature stops, or gene-level replacement therapy. The atlas surfaces this clarity directly.

Card generated by `wolfram-atlas-batch` skill (v1) on 2026-06-08T02:18:02.602375Z.

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

WFS1 reference: UniProt O76024, AlphaFold model v6.