

Q819* — WFS1 Molecular Atlas Card

Variant type: Nonsense (premature stop codon)

Position: 819

Wild-type residue: Glutamine (Q)

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

SCHEMA CATEGORY: N4 — NMD-ESCAPE, MINOR TRUNCATION — HIGHEST DRUGGABILITY

Most domains preserved; only the distal C-terminus is truncated. Highest druggability category among nonsense variants. Candidates: pharmacological chaperones for the partially-folded protein, small-molecule mimetics for the lost C-terminal sequence, and high-content screening (Initiative 8).

NMD PREDICTION

- **Status:** NMD-escape
- **Confidence:** high
- **Reasoning:** Stop codon at position 819 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 – 818 (91.9% of full-length protein)
- **Residues lost:** 819 – 890 (8.1% 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)
- Luminal loop 1 (aa 362–370)
- Transmembrane helix 3 (aa 371–391)
- Cytoplasmic loop 2 (aa 392–400)
- Transmembrane helix 4 (aa 401–421)
- Luminal loop 2 (aa 422–431)
- Transmembrane helix 5 (aa 432–452)
- Cytoplasmic loop 3 (aa 453–461)
- Transmembrane helix 6 (aa 462–482)
- Luminal loop 3 (aa 483–496)
- Transmembrane helix 7 (aa 497–517)
- Cytoplasmic loop 4 (aa 518–532)
- Transmembrane helix 8 (aa 533–553)
- Luminal loop 4 (aa 554–573)
- Transmembrane helix 9 (aa 574–594)
- Cytoplasmic loop 5 / pre-luminal (aa 595–599)

Partially retained at truncation point

- **C-terminal ER-luminal (calcium binding, calmodulin, chaperone)** — partial: aa 600–818 retained, aa 819–890 lost

Lost domains

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

CLINICAL EVIDENCE

- **Classification:** Pathogenic
 - **Review status:** no assertion criteria provided
 - **Associated conditions:** Wolfram syndrome 1
 - **cDNA change:** c.2455C>T
 - **ClinVar accession:** VCV000004517
 - **Last evaluated:** 1998/12/01 00:00
 - **Submissions:** 1
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WHY THIS VARIANT MATTERS

Late-truncation variants in the distal C-terminus are the most druggable nonsense category in WFS1. The atlas card surfaces both the small-molecule mimetic angle (rescuing the lost C-terminal sequence) and the chaperone angle (stabilizing the mostly-intact protein). High-content screening (Initiative 8) is a strong fit.

Card generated by `wolfram-atlas-batch` skill (v1) on 2026-06-08T02:19:01.086956Z.

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

WFS1 reference: UniProt O76024, AlphaFold model v6.