

# C647\* — WFS1 Molecular Atlas Card

**Variant type:** Nonsense (premature stop codon)

**Position:** 647

**Wild-type residue:** Cysteine (C)

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

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

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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).

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## NMD PREDICTION

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- **Status:** NMD-escape
- **Confidence:** high
- **Reasoning:** Stop codon at position 647 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.

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## TRUNCATION ANALYSIS

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- **Residues retained:** 1 – 646 (72.6% of full-length protein)
- **Residues lost:** 647 – 890 (27.4% 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 600–646 retained, aa 647–890 lost

### Lost domains

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

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## CLINICAL EVIDENCE

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- **Classification:** Pathogenic
  - **Review status:** criteria provided, multiple submitters, no conflicts
  - **Associated conditions:** Inborn genetic diseases
  - **cDNA change:** c.1941C>A
  - **ClinVar accession:** VCV002300477
  - **Last evaluated:** 2025/07/30 00:00
  - **Submissions:** 1
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## WHY THIS VARIANT MATTERS

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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.

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*Card generated by `wolfram-atlas-batch` skill (v1) on 2026-06-08T02:18:29.902992Z.*

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

*WFS1 reference: UniProt O76024, AlphaFold model v6.*