

# W730\* — WFS1 Molecular Atlas Card

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

**Position:** 730

**Wild-type residue:** Tryptophan (W)

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

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

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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).

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## NMD PREDICTION

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- **Status:** NMD-escape
- **Confidence:** high
- **Reasoning:** Stop codon at position 730 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 – 729 (81.9% of full-length protein)
- **Residues lost:** 730 – 890 (18.1% 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 600–729 retained, aa 730–890 lost

### Lost domains

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

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## CLINICAL EVIDENCE

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- **Classification:** Pathogenic/Likely pathogenic
  - **Review status:** criteria provided, multiple submitters, no conflicts
  - **Associated conditions:** Wolfram syndrome 1
  - **cDNA change:** c.2189G>A
  - **ClinVar accession:** VCV000432114
  - **Last evaluated:** 2023/09/01 00:00
  - **Submissions:** 1
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## WHY THIS VARIANT MATTERS

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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.

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*Card generated by `wolfram-atlas-batch` skill (v1) on 2026-06-08T02:18:51.338134Z.*

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

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