RARERESEARCH.AI · WFS1 MOLECULAR ATLAS · NONSENSE

S430* — WFS1 Molecular Atlas Card

Variant type: Nonsense (premature stop codon)

Position: 430

Wild-type residue: Serine (S)

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

SCHEMA CATEGORY: N2 — NMD-ESCAPE, MAJOR TRUNCATION — GENE THERAPY TRACK

Truncated protein produced but missing the transmembrane bundle and/or the entire C-terminal ER-lumenal domain. Too compromised for chaperone-based rescue. Gene therapy via allele replacement is the primary path.

NMD PREDICTION

- **Status:** NMD-escape
- **Confidence:** high
- **Reasoning:** Stop codon at position 430 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 – 429 (48.2% of full-length protein)
- **Residues lost:** 430 – 890 (51.8% 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)

Partially retained at truncation point

- **Lumenal loop 2** — partial: aa 422–429 retained, aa 430–431 lost

Lost domains

- 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:** Pathogenic/Likely pathogenic
- **Review status:** criteria provided, multiple submitters, no conflicts
- **cDNA change:** c.1289C>A
- **ClinVar accession:** VCV002043736
- **Last evaluated:** 2025/09/02 00:00
- **Submissions:** 1

WHY THIS VARIANT MATTERS

A truncated protein is made but stripped of the transmembrane bundle and/or C-terminal ER-lumenal domain — the regions wolframin needs for membrane anchoring and calcium-handling

function. Chaperone strategies that work for missense variants don't apply here. The card surfaces gene therapy as the primary path and quantifies the structural loss to support that decision.

Card generated by `wolfram-atlas-batch` skill (v1) on 2026-06-08T02:18:06.503676Z.

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

WFS1 reference: UniProt O76024, AlphaFold model v6.