

## c.439del — WFS1 Molecular Atlas Card

**Variant type:** Frameshift

**Frameshift point:** residue 147

**Predicted premature stop (PTC):** residue 163

**Domain context (where the frame breaks):** N-terminal cytoplasmic (intrinsically disordered)

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### SCHEMA CATEGORY: F1 — FRAMESHIFT, NMD-TARGETED — NULL ALLELE

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The frameshift creates a premature termination codon well upstream of the last exon-exon junction; the 50-nt rule predicts the transcript is degraded by nonsense-mediated decay. No frameshifted protein is produced — functionally a null allele. Therapeutic options: (a) translational readthrough drugs (Ataluren/PTC124, aminoglycosides) — notably LESS effective for frameshifts than for nonsense variants, because reading through the PTC still yields out-of-frame protein; (b) gene therapy via allele replacement is the higher-yield path.

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### PREMATURE-STOP PREDICTION

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- **Frameshift point:** aa 147
- **Predicted PTC:** aa 163 (16 codons downstream of the frame break)
- **Method:** deterministic translation of edited NM\_006005.3 CDS (frameshift position = first changed residue, HGVS convention)
- **Confidence:** high

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### NMD PREDICTION

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- **Status:** NMD-targeted
- **Confidence:** high
- **Reasoning:** Stop codon at position 163 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.

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## PROTEIN CONSEQUENCE

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- **Native (wild-type) sequence retained:** aa 1 – 146 (16.4% of full-length protein)
- **Non-native scrambled stretch:** aa 147 – 162 (16 residues of out-of-frame sequence)
- **Lost beyond the PTC:** aa 163 – 890 (728 residues)

### Native domains retained (upstream of the frameshift)

*(no domains fully retained)*

### Domain interrupted at the frameshift point

- **N-terminal cytoplasmic (intrinsically disordered)** — native aa 1–146 retained; aa 147–310 replaced by non-native sequence

### Native domains downstream of the frameshift (lost or non-native)

- 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)
  - C-terminal ER-luminal (calcium binding, calmodulin, chaperone) (aa 600–890)
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## CLINICAL EVIDENCE

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- **Classification:** Pathogenic
  - **Review status:** criteria provided, multiple submitters, no conflicts
  - **Associated conditions:** Optic atrophy; Wolfram syndrome 1
  - **cDNA change:** c.439del
  - **ClinVar accession:** VCV000620589
  - **Last evaluated:** 2021/01/01 00:00
  - **Submissions:** 1
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## WHY THIS VARIANT MATTERS

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The frame breaks early enough that the premature stop is caught by nonsense-mediated decay — the transcript is degraded before any out-of-frame protein accumulates. That makes this, in effect, a clean null allele: the atlas points the therapeutic conversation at gene replacement, and notes that readthrough drugs are a weaker fit here than for true nonsense variants because reading through the stop still yields scrambled protein.

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*Card generated by `wolfram-atlas-batch` skill (v2 — frameshift pipeline) on 2026-06-08T02:16:56.375843Z.*

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

*CDS reference: NM006005.3 (171..2843). WFS1 reference: UniProt O76024, AlphaFold model v6.\_\_*