c.57_64dup — WFS1 Molecular Atlas Card

Variant type: Frameshift

Frameshift point: residue 22

Predicted premature stop (PTC): residue 145

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

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

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.

PREMATURE-STOP PREDICTION

- **Frameshift point:** aa 22
- **Predicted PTC:** aa 145 (123 codons downstream of the frame break)
- **Method:** deterministic translation of edited NM_006005.3 CDS (frameshift position = first changed residue, HGVS convention)
- **Confidence:** high

NMD PREDICTION

- **Status:** NMD-targeted
- **Confidence:** high
- **Reasoning:** Stop codon at position 145 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.

PROTEIN CONSEQUENCE

- **Native (wild-type) sequence retained:** aa 1 – 21 (2.4% of full-length protein)
- **Non-native scrambled stretch:** aa 22 – 144 (123 residues of out-of-frame sequence)
- **Lost beyond the PTC:** aa 145 – 890 (746 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 1–21 retained; aa 22–310 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)
- Lumenal loop 1 (aa 362–370)
- Transmembrane helix 3 (aa 371–391)
- Cytoplasmic loop 2 (aa 392–400)
- Transmembrane helix 4 (aa 401–421)
- Lumenal loop 2 (aa 422–431)
- 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
- **Review status:** criteria provided, single submitter
- **cDNA change:** c.57_64dup
- **ClinVar accession:** VCV002806199
- **Last evaluated:** 2025/10/30 00:00
- **Submissions:** 1

WHY THIS VARIANT MATTERS

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.

Card generated by `wolfram-atlas-batch` skill (v2 — frameshift pipeline) on 2026-06-08T02:17:02.193947Z.

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

*CDS reference: NM*006005.3 (171..2843). WFS1 reference: UniProt O76024, AlphaFold model v6._