RARERESEARCH.AI · WFS1 MOLECULAR ATLAS · FRAMESHIFT

c.1313dup — WFS1 Molecular Atlas Card

Variant type: Frameshift

Frameshift point: residue 439

Predicted premature stop (PTC): residue 542

Domain context (where the frame breaks): Transmembrane helix 5

SCHEMA CATEGORY: F2 — FRAMESHIFT, NMD-ESCAPE — SCRAMBLED C-TERMINUS PRODUCED

The premature stop falls in the last exon (exon 8), so NMD does not degrade the transcript and a protein IS produced — native sequence up to the frameshift point, then a non-native (scrambled) stretch to the new stop. The garbled C-terminus may misfold or mis-insert and can interfere with folding/membrane insertion of the upstream domains. Behavior is highly variable and typically too compromised for chaperone rescue; gene therapy is the primary path. Wet-lab validation recommended.

PREMATURE-STOP PREDICTION

- **Frameshift point:** aa 439
- **Predicted PTC:** aa 542 (103 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-escape
- **Confidence:** high

- **Reasoning:** Stop codon at position 542 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.

PROTEIN CONSEQUENCE

- **Native (wild-type) sequence retained:** aa 1 – 438 (49.2% of full-length protein)
- **Non-native scrambled stretch:** aa 439 – 541 (103 residues of out-of-frame sequence)
- **Lost beyond the PTC:** aa 542 – 890 (349 residues)

Native domains retained (upstream of the frameshift)

- 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)
- Lumenal loop 2 (aa 422–431)

Domain interrupted at the frameshift point

- **Transmembrane helix 5** — native aa 432–438 retained; aa 439–452 replaced by non-native sequence

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

- 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.1313dup
- **ClinVar accession:** VCV002919262
- **Last evaluated:** 2023/04/11 00:00
- **Submissions:** 1

WHY THIS VARIANT MATTERS

Because the frame breaks late, in the last exon, the transcript escapes NMD and a protein is actually made: wild-type wolframin up to the break, then a stretch of non-native sequence to a new stop. That scrambled C-terminus is the wildcard — it can drag the upstream domains out of fold. The atlas quantifies exactly how much native protein survives and how long the non-native tail is — the data a wet-lab needs to predict behavior.

Card generated by `wolfram-atlas-batch` skill (v2 — frameshift pipeline) on 2026-06-08T02:15:19.648613Z.

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

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