

c.996_997del — WFS1 Molecular Atlas Card

Variant type: Frameshift

Frameshift point: residue 333

Predicted premature stop (PTC): residue 541

Domain context (where the frame breaks): Cytoplasmic loop 1

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 333
- **Predicted PTC:** aa 541 (208 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 541 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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PROTEIN CONSEQUENCE

- **Native (wild-type) sequence retained:** aa 1 – 332 (37.3% of full-length protein)
- **Non-native scrambled stretch:** aa 333 – 540 (208 residues of out-of-frame sequence)
- **Lost beyond the PTC:** aa 541 – 890 (350 residues)

Native domains retained (upstream of the frameshift)

- N-terminal cytoplasmic (intrinsically disordered) (aa 1–310)
- Transmembrane helix 1 (aa 311–331)

Domain interrupted at the frameshift point

- **Cytoplasmic loop 1** — native aa 332–332 retained; aa 333–340 replaced by non-native sequence

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

- 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

Not found in the cached WFS1 ClinVar set ([reference/WFS1clinvarvariants.csv](#))._

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 2026-06-08T02:17:21.627026Z.

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._