RARERESEARCH.AI · WFS1 MOLECULAR ATLAS · NONSENSE

E752* — WFS1 Molecular Atlas Card

Variant type: Nonsense (premature stop codon)

Position: 752

Wild-type residue: Glutamic acid (E)

Domain context (where the stop falls): C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)

SCHEMA CATEGORY: N4 — NMD-ESCAPE, MINOR TRUNCATION — HIGHEST DRUGGABILITY

Most domains preserved; only the distal C-terminus is truncated. Highest druggability category among nonsense variants. Candidates: pharmacological chaperones for the partially-folded protein, small-molecule mimetics for the lost C-terminal sequence, and high-content screening (Initiative 8).

NMD PREDICTION

- **Status:** NMD-escape
- **Confidence:** high
- **Reasoning:** Stop codon at position 752 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 – 751 (84.4% of full-length protein)
- **Residues lost:** 752 – 890 (15.6% 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)
- 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)

Partially retained at truncation point

- **C-terminal ER-lumenal (calcium binding, calmodulin, chaperone)** — partial: aa 600–751 retained, aa 752–890 lost

Lost domains

(no full domains lost — only distal C-terminus)

CLINICAL EVIDENCE

- **Classification:** Pathogenic/Likely pathogenic
- **Review status:** criteria provided, multiple submitters, no conflicts
- **Associated conditions:** Cataract 41; Autosomal dominant nonsyndromic hearing loss 6; Type 2 diabetes mellitus; Wolfram syndrome 1; Wolfram-like syndrome
- **cDNA change:** c.2254G>T
- **ClinVar accession:** VCV000215399
- **Last evaluated:** 2025/03/26 00:00
- **Submissions:** 1

WHY THIS VARIANT MATTERS

Late-truncation variants in the distal C-terminus are the most druggable nonsense category in WFS1. The atlas card surfaces both the small-molecule mimetic angle (rescuing the lost C-terminal sequence) and the chaperone angle (stabilizing the mostly-intact protein). High-content screening (Initiative 8) is a strong fit.

Card generated by `wolfram-atlas-batch` skill (v1) on 2026-06-08T02:18:55.227116Z.

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

WFS1 reference: UniProt O76024, AlphaFold model v6.