Phenotypic Expansion and Co-Segregation of a Novel UPF3B Frameshift Variant in a Five-Generation Lujan-Fryns Pedigree

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Background & Rationale

Most pathogenic UPF3B variants trigger NMD (loss of function via decay). This frameshift **c.1267_1270del, p.(Glu423LysfsTer8)** places the stop 8 nt from the final exon-exon junction within the **NMD-escape zone**.

We ask whether an NMD-escaping variant yielding a truncated protein rather than none shapes the phenotype in this family.

Methods

Clinical: IDEAS scale, facial photography, brain MRI, and echocardiography in 5 affected males.

WES: Proband; Illumina 80–100×; GRCh38, BWA/GATK (NM_080632.3).

Segregation: Bidirectional Sanger of exon 10 in 10 relatives; full concordance across 3 generations (see Figure 1).

Interpretation: Absent from gnomAD, TOPMed, and MedVarDb; ACMG/AMP → **Likely Pathogenic** (PVS1_Strong, PM2_Sup, PP1).

KEY FIGURES

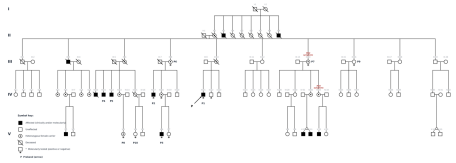


Figure 1. Five-generation pedigree. Variant present in every tested affected male and confirmed carrier, absent in every tested unaffected relative, across three generations. Filled squares = affected males; dotted circles = carriers; arrow = proband.



Figure 2. Frontal photographs, P1-P5. Marfanoid facial gestalt in P1, P2, P4, P5 (confirmed since childhood in P1; historical in others); minimal in youngest patient P3.

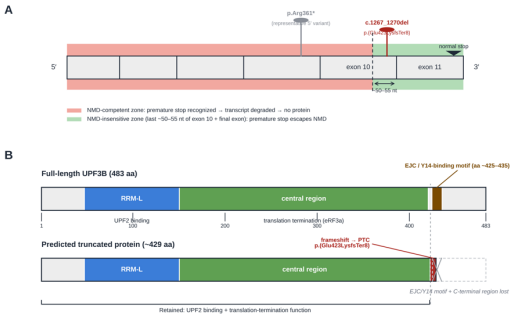


Figure 3. (A) PTC lies within the NMD-escape zone near the final exon-exon junction, predicted to escape decay. (B) Truncated protein retains RRM-L/UPF2-binding domain but loses the EJC/Y14 motif.

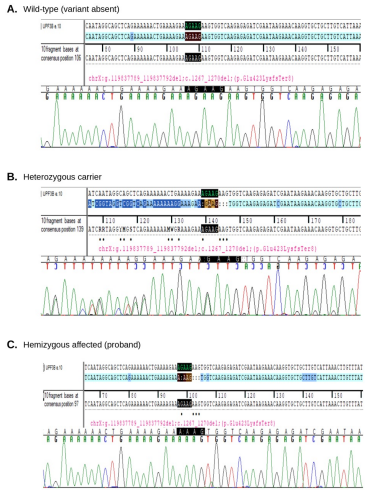


Figure 4. Sanger chromatograms, UPF3B exon 10: (A) variant-negative, (B) heterozygous carrier (overlapping peaks 3′ of the deletion), (C) hemizygous affected male.

Key Phenotypic Features

Feature	P1	P2	P3	P4	P5
Age (y)	52	50	27	62	53
IDEAS score	11	12	13	12	11
Marfanoid habitus	Y	Y	N	Y	Y
Hypernasal voice	Y	Y	Y	Y	Y
Autistic features	Y	Y	Y	Y	Y
Aortic root (mm)	24	26	28	27	25

Conclusion

- NMD-escaping variant predicted to yield a truncated protein retaining UPF2-binding but lacking the EJC/Y14 motif.
- Youngest patient (P3, 27 y) has the most severe neurobehavioral phenotype yet fewest somatic features: an intrafamilial dissociation warranting follow-up.
- Normal aortic root and brain MRI argue against overlapping structural syndromes; marfanoid habitus without true Marfan syndrome.

TAKE-HOME

Consider UPF3B sequencing in males with syndromic ID, marfanoid habitus, and normal aortic root.

Limitations: *NMD escape predicted computationally, not functionally confirmed; some affected relatives untested (declined/unavailable). Written informed consent was obtained from each patient's parent/guardian for publication of the clinical photographs shown in Figure 2.*

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