Expanding the Genotypic Spectrum for ReNU Syndrome: A Clinical Laboratory Experience

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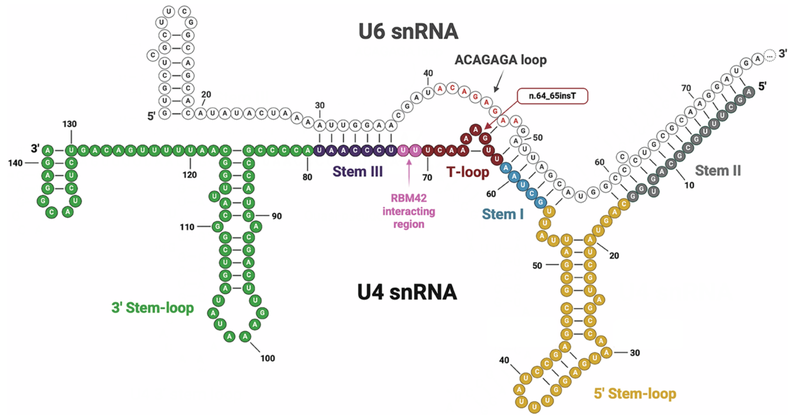
Background

- ReNU syndrome was first described in 2024.[1] It is an autosomal dominant neurodevelopmental disorder (NDD) characterized by developmental delays (DD), intellectual disability (ID), seizures, hypotonia, and microcephaly. Other features include short stature, visual impairment, and gastrointestinal issues.
- Literature suggests ReNU syndrome is emerging as one of the most prevalent causes for NDDs, estimated to account for around 0.4 - 0.5% of NDDs.[2]
- ReNU syndrome is caused by variants in the *RNU4-2* gene. This is a non-coding gene that encodes the U4 small nuclear RNA (snRNA), an essential component of the spliceosome complex responsible for pre-mRNA splicing. Pathogenic variants such as the common insertion, n.64_65insT, along with others, have been shown to disrupt the U4-U6 duplex region of the spliceosome (Figure 1).
- Detection of these variants present a diagnostic challenge due to the lack of detection on traditional exome sequencing and gene panels.
- This study sought to evaluate the clinical and genetic findings of affected individuals in our clinical laboratory cohort and assess the utility of genome sequencing (GS) in identifying and classifying *RNU4-2* variants.



Bruselles, A., Mancini, C., Chiriatti, L. et al. (2025). Expanding the mutational spectrum of ReNU syndrome: Insights into 5' stem-loop variants. *Eur J Hum Genet 33,* 432–440. https://doi.org/10.1038/s41431-025-01820-1

Figure 1. Structure of the U4/U6 snRNAs duplex with location of the c.64_65insT variant

Methods

- Retrospective case review of 12 individuals who underwent GS at our laboratory and were identified to have *RNU4-2* variants.
- Variants were classified using American College of Medical Genetics and Genomics (ACMG) guidelines and internal variant curation criteria.
- For novel variants, inheritance, presence in population databases, and in-silico prediction tools were utilized to assess pathogenicity.
- Clinical data were extracted from medical records. This included developmental history, neurological findings, and other features.

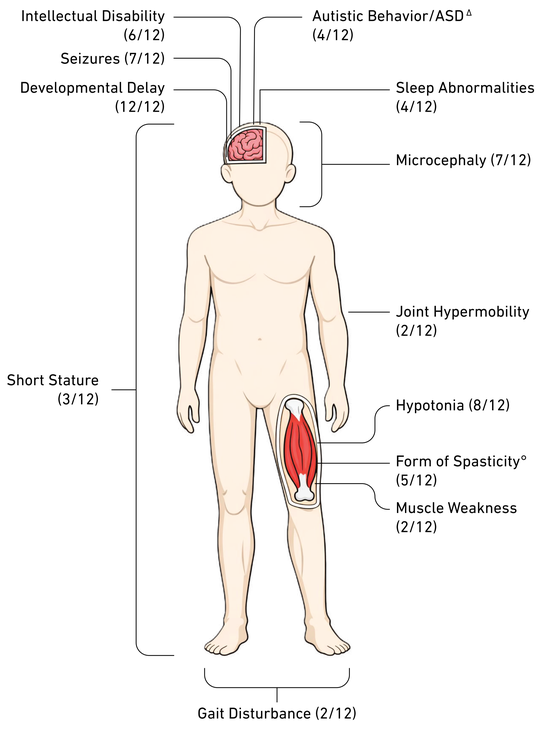
Results

Table 1. Twelve individuals found to have *RNU4-2* variants through GS.

CASE	AGE (YEARS)	*RNU4 - 2* VARIANT	CLASSIFICATION	TEST TYPE	INHERITANCE
Case 1	10	NR_003137.2: n.67A>G*	P	Trio	*De novo*
Case 2	26	NR_003137.2: n.64_65insT*	P	Trio	*De novo*
Case 3	20	NR_003137.2: n.69C>T*	P	Proband	Unknown
Case 4	14	NR_003137.2: n.76C>T*	P	Trio	*De novo*
Case 5	19	NR_003137.2: n.77_78insT*	P	Trio	*De novo*
Case 6	5	NR_003137.2: n.75C>T	LP	Trio	*De novo*
Case 7	4	NR_003137.2: n.64_65insT*	P	Trio	*De novo*
Case 8	5	NR_003137.2: n.119A>C	VUS	Trio	*De novo*
Case 9	19	NR_003137.2: n.29A>C	VUS	Trio	Paternal
Case 10	< 1	NR_003137.2: n.64_65insT*	P	Trio	*De novo*
Case 11	19	NR_003137.2: n.64_65insT*	P	Trio	*De novo*
Case 12	5	NR_003137.2: n.64_65insT*	P	Duo	Unknown

*previously reported variant, P = pathogenic, LP = likely pathogenic, VUS = variant of uncertain significance,

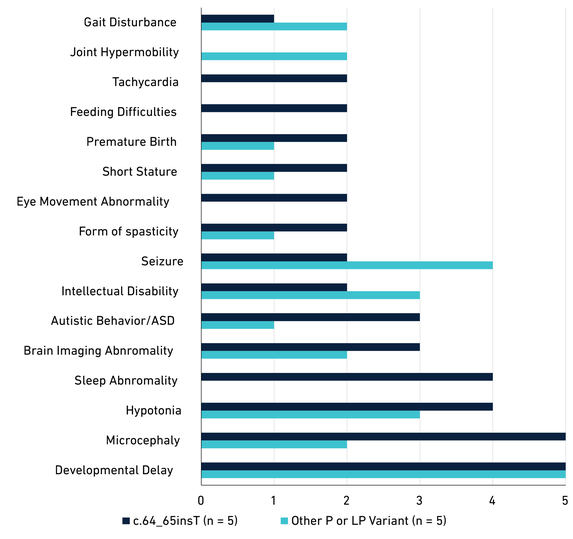
Figure 2. Clinical symptoms and features of the cohort.



△ Autism spectrum disorder, °Represents many different forms of spasticity reported including spastic diplegia, spastic paraplegia, and unspecified spasticity

Five individuals had the common n.64_65insT pathogenic (P) variant, four individuals had other previously reported P variants, and one individual had a novel likely pathogenic (LP) variant. In addition, two other individuals had VUSs.

Figure 3. Clinical Presentations of c.64_65insT versus Other P and LP Variants



Conclusions

- This study highlights the expanding genotypic spectrum of *RNU4-2*-associated ReNU syndrome.
- GS is important for identifying pathogenic variants in non-coding regions that may be missed by exome-based and targeted-variant approaches.
- Our findings support the inclusion of *RNU4-2* in diagnostic, molecular evaluation for unexplained NDDs.
- Further studies are warranted to understand the full clinical spectrum and molecular mechanisms underlying ReNU syndrome and the emerging role of other non-coding genes in rare disease diagnostics.

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References:

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