

Utility of Whole Genome Sequencing to Detect *RNU4-2* Variants Associated with ReNU syndrome

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BACKGROUND

- ReNU syndrome (RENU) is a neurodevelopmental disorder first described in 2024 characterized by global developmental delay, intellectual disability, seizures, brain anomalies, hypotonia, and other symptoms.^{1,2}
- RENU is estimated to account for 0.4% of all neurodevelopmental disorders and arises from variants in *RNU4-2*. Most RENU diagnoses have a common *de novo* n.64_65insT variant.¹
- RNU4-2* encodes spliceosome ribonucleoprotein U4 which is important for brain development.^{1,2}
- We present our clinical laboratory's experience identifying a pathogenic *RNU4-2* variant in a pediatric patient by whole genome sequencing (WGS).**

PATIENT HISTORY

- 4-year-old female with primary indications of microcephaly and global developmental delay (GDD). Medical history also notable for failure to thrive requiring a G-tube, significant motor delay, and minimal speech development.
- Prenatal course unremarkable. Born via C-section and remained in NICU for about two weeks. Noted at birth to be hypotonic and microcephalic.
- No developmental regression. Brain MRI did not show anatomic abnormalities. No seizures reported by family.
- Family history is significant for three sisters reported to be microcephalic but developmentally appropriate.

CONCLUSIONS

- RNU4-2* noncoding variants have limited, if any, coverage by most non-WGS methods. This case study reinforces the clinical utility of WGS to avoid diagnostic odysseys for RENU and supports reanalysis of pre-discovery WGS data for patients with suspected RENU.

TESTING HISTORY



- This patient's phenotype deviates from other patients in the literature with a RENU diagnosis, particularly the lack of abnormal brain imaging and seizures seen in >50% of patients in larger cohorts. These findings continue to broaden the clinical scope for patients with molecular *RNU4-2* findings.

RENU PHENOTYPE COMPARISON

Features Present	Chen et al. ¹	Greene et al. ²	Nava et al. ³	This Patient
Intellectual Disability	45/45 (100%)	42/46 (91%)	134/134 (100%)	Yes
GDD	49/49 (100%)	38/46 (83%)	133/134 (99%)	Yes
Speech Abnormality	45/48 (94%)	33/46 (72%)	108/116 (93%)	Yes
Abnormal Brain Imaging	41/45 (91%)	30/46 (65%)	107/130 (82%)	No
Ambulatory Issues	30/36 (83%)	28/46 (61%)	98/115 (85%)	Yes
Behavioral Issues / Stereotypies	30/45 (67%)	N/A	69/89 (84%)	Yes
Facial Dysmorphism	45/48 (94%)	25/46 (54%)	N/A	Yes
Microcephaly	37/48 (77%)	26/46 (57%)	97/141 (69%)	Yes
Feeding Difficulties	32/42 (76%)	N/A	80/125 (64%)	Yes
Hypotonia	39/45 (87%)	19/46 (41%)	88/138 (64%)	Yes
Vision Loss	38/48 (79%)	N/A	70/124 (56%)	N/A
Seizures	37/48 (77%)	24/46 (52%)	81/140 (58%)	No
Growth Problems / Failure to Thrive	30/43 (70%)	N/A	65/126 (51%)	Yes
Constipation	29/44 (66%)	N/A	63/123 (51%)	Yes
ASD	21/44 (48%)	N/A	52/92 (57%)	Yes
Short Stature	37/49 (76%)	16/46 (35%)	72/140 (51%)	Yes
Skeletal	27/42 (64%)	N/A	42/123 (34%)	No
Limb	23/42 (55%)	N/A	46/122 (41%)	No
Cutaneous	25/44 (57%)	N/A	28/115 (24%)	No

Table 1. Comparison of this patient's phenotype against common features in large RENU cohorts (>50% of patients in at least one cohort). Highlighted rows are those where the patient's phenotype is absent that feature.

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References:

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