Genome Sequencing Identifies Two Patients with Jeffries-Lakhani Neurodevelopmental Syndrome

Sydney A. Lau, MS, CGC[1], Bailey Hummel, MSPH, CGC[2], Alexander Y. Kim, MD, FAAP, FACMG[2], Claire McDonald, MS, MPH, CGC[3], Amitha Ananth, MD[3], Robert Rigobello, MS, CGC[1], Leah Campbell, MS, CGC[1], Eileen Barr, MS, CGC[1], Lisa Salz, MS, CGC[1], Jason Chibuk, MS, CGC[1], Xiaonan Zhao, PhD, FACMG[1,4], Wilson Wu, PhD, FACMG[1,4], Christine Eng, MD[1,4]

1. Baylor Genetics, Houston, TX, USA
2. Division of Genetics, Department of Medicine, Johns Hopkins All Children's Hospital, St. Petersburg, Florida, USA
3. Department of Genetics, UAB Medicine, Birmingham, AL, USA
4. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

GEN195

Background

- Jeffries-Lakhani neurodevelopmental syndrome (JELANS) is a recently-described autosomal recessive condition associated with *CRELD1*. Most patients with JELANS have early-onset seizures (median age 5 months), hypotonia, and global developmental delay (DD). Many have dysmorphic features, feeding difficulties, and cardiac arrhythmias.[1]
- *CRELD1* has a critical role in development of the neurological and cardiac systems.[2]
- With less than 25 individuals published in the literature, the phenotypic spectrum is still being defined.[1,2,3]
- Here, we describe two unrelated patients diagnosed with JELANS through trio genome sequencing (GS) at our clinical laboratory to improve understanding of the phenotype and clinical management for affected patients.

Patient 1

- 2-year-old male who was admitted to the PICU for status epilepticus. He also presented with DD, hypotonia, and a prolonged QTc interval. Family history was unremarkable for seizures or suspected genetic conditions.
- Previous negative genetic testing included chromosomal microarray, seizure panel, congenital hypotonia panel, and Prader-Willi syndrome testing.

DISEASE	INHERITANCE PATTERN	GENE/ VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
Jeffries-Lakhani Neurodevelopmental Syndrome	Autosomal Recessive	CRELD1: c.575G>A, p.C192Y	Sequence Variant	Heterozygous	Mother	Pathogenic
Jeffries-Lakhani Neurodevelopmental Syndrome	Autosomal Recessive	CRELD1: c.637+3A>T	Sequence Variant	Heterozygous	Father	Variant Of Uncertain Significance

Patient 1's rapid trio GS results. c.575G>A had been previously reported in patients with JELANS, while c.637+3A>T had not been described in diagnosed patients or in ClinVar.

- RNA sequencing provided functional evidence to upgrade c.637+3A>T to likely pathogenic; the variant results in abnormal splicing and introduces an out-of-frame deletion with premature stop codon.

Patient 2

- 2-year-old female referred to neurogenetics for a history of early-onset intractable epilepsy, DD, hypotonia, mild dysmorphic facial features, thin corpus callosum, nystagmus, and feeding difficulties. She reportedly had polyhydramnios and a difficult delivery. Family history was unremarkable.
- Previous genetic testing included chromosomal microarray, exome sequencing, and targeted panels; variants of uncertain significance in *MECP2* and *RAF1* were thought to be non-diagnostic due to the patient's clinical history.

DISEASE	INHERITANCE PATTERN	GENE/ VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
Jeffries-Lakhani Neurodevelopmental Syndrome	Autosomal Recessive	CRELD1: c.959del, p.Q320Rfs*25	Sequence Variant	Heterozygous	Father	Pathogenic
Jeffries-Lakhani Neurodevelopmental Syndrome	Autosomal Recessive	CRELD1: c.575G>A, p.C192Y	Sequence Variant	Heterozygous	Mother	Pathogenic

Patient 2's trio GS results were consistent with a diagnosis of JELANS. Both variants had been previously reported in affected patients.

FEATURES PRESENT	JEFFRIES *ET AL.*[1] 18 PATIENTS	ARCHER *ET AL.*[2] 3 PATIENTS	D'ALESSANDRO *ET AL.*[3] 1 PATIENT	PATIENT 1	PATIENT 2
Early-onset seizures	18/18 (100%)	3/3 (100%)	Yes (onset 5 months)	Yes	Yes
Hypotonia	18/18 (100%)	3/3 (100%)	Yes	Yes	Yes
DD	18/18 (100%)	3/3 (100%)	Yes	Yes	Yes
Intellectual Disability	18/18 (100%)	3/3 (100%)	-	-	-
Dysmorphic Features	15/18 (83%)	3/3 (100%)	Yes	-	Yes
Cardiac Issues (structural or arrhythmia)	8/18 (44%)	0/3 (0%)	-	Prolonged QTc interval	-
Brain MRI Abnormalities	10/16 (63%)	2/3 (66%)	Yes	-	Yes
Immunologic Findings	9/18 (50%)	-	-	-	-
Ocular Abnormalities	13/18 (72%)	1/3 (33%) (strabismus)	Yes	-	Yes
Feeding Difficulties	12/18 (67%)	2/3 (66%)	Yes	Yes	Yes
Abnormal Prenatal Course	5/14 (36%)	0/3 (0%)	Yes	-	Yes
Arthrogryposis	0/18 (0%)	-	Yes	-	-
Pectus Excavatum	1/18 (6%)	-	Yes	-	-

Comparison of our patients' phenotypes against common features in reported JELANS patients. All reported patients with cardiac issues, including Patient 1, harbor the c.575G>A variant.

Conclusions

- **The genetic diagnosis of JELANS for the patients described in this report provided clarity and guidance for their medical team, particularly in regard to the potential cardiac risks through avoidance of QTc prolonging agents. Patient 2 has been evaluated by cardiology; post-EKG, there are no concerns for arrhythmia, but they are continuing to be followed.**
- **Clinically validated RNA sequencing resulted in the reclassification of the VUS in Patient 1, highlighting the utility of functional evidence in identifying and clarifying the impact of novel variants.**
- **Both families can seek additional evaluation with their clinical providers as well as connect with other families living with JELANS; the diagnosis also assists with reproductive decision making, as the Patient 2's family was considering a gamete donor for future pregnancies.**
- **Genome sequencing enabled a molecular diagnosis for two patients with symptoms consistent with other patients with JELANS, contributing evidence for the true phenotypic spectrum of the disorder, which is currently limited due to the small number of reported patients.**

Presented at the National Society of Genetic Counselors (NSGC) Annual Conference, Nov 6-10, 2025, Seattle, WA.

References:

1. Jeffries, L. *et al* (2024). Biallelic CRELD1 variants cause a multisystem syndrome, including neurodevelopmental phenotypes, cardiac dysrhythmias, and frequent infections. *Genetics in medicine : official journal of the American College of Medical Genetics, 26*(2), 101023. https://doi.org/10.1016/j.gim.2023.101023
2. Archer, J. *et al* (2025). CRELD1-Associated Neurodevelopmental Disorder: Three New Individuals from Unrelated Families. *Genes, 16*(8), 972. https://doi.org/10.3390/genes16080972
3. D'Alessandro, M. *et al* (2025). Biallelic CRELD1 variants cause severe muscle weakness and infantile epilepsy. *Brain Communications, 7*(5), fcaf326, https://doi.org/10.1093/braincomms/fcaf326