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Expanding the phenotype of HNRNPU-related disorders to include brief, resolved, unexplained events (BRUE)

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INTRODUCTION:

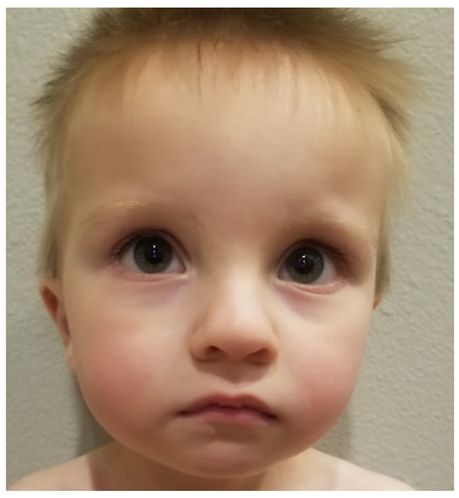
- HNRNPU is a is a highly conserved protein responsible for assisting spliceosomes in mediating transcription and alternative splicing activity.
- HNRNPU has been involved in neurodevelopmental and neurodegenerative diseases.
- Recently, Durkin et al (PMID: 32319732) reported 21 previously unreported probands with variable presentation, but usually with hypotonia, global developmental delays, and seizures [1].
- We describe a patient with a history of BRUE and mild unique facial features who was identified to have a pathogenic *de novo* nonsense mutation in *HNRNPU* (c.803+2T>C; p. ?*).* The variants are listed in Table 1.

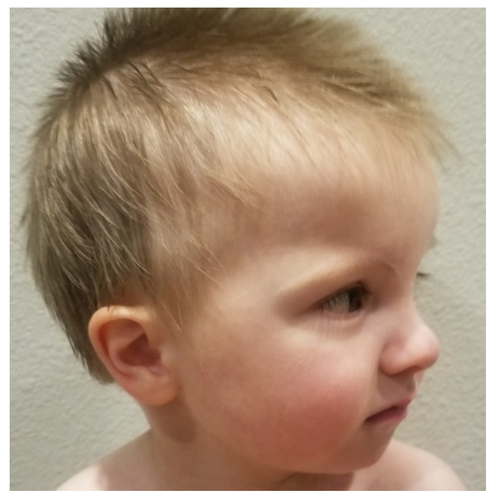
CLINICAL COURSE:

- PREGNANCY HISTORY: A choroid plexus cyst was identified on a 20-week anatomy scan but resolved by 28 weeks. NIPT was negative.
- DEVELOPMENTAL HISTORY: Gross motor skills were delayed about 6 months. He was able to sit by himself at 14 months, pull up to stand at 18 months, cruise at 20 months and walk at 20 months. At 2 years old, he was babbling and speaking 5-10 words. He communicated with hand gestures and could understand simple directions. He was responding to his name being called.
- FIRST ADMISSION (4 months old): Admitted following first apneic spell.
  - Imaging including CT, MRI, CXR, ENT, Holter monitor, and Echo. Apnea was determined to be due to gastroesophageal reflux (by exclusion).
  - He started on reflux medications at 6 months of age, which helped prevent future episodes. He had no further episodes until he was taken off medication at 18 months old, resulting in restarting the reflux medication.
  - At his 4-month inpatient stat, an episode was captured on video EEG, but without EEG correlate. Our patient was started on an AED and placed on 1.5 ml PO BID (150 mg) of Keppra (Levetiracetam), to go along with his normal bacitracin (topical – BID) and famotidine (dosing weight, oral – every 12 hrs).
- Additional apneic events occurred at 6, 18, 25, and 26 months.
- SECOND ADMISSION (28 months old): Admitted due to recurrent apneic spells and global developmental delay. Genetics was consulted. The latest episode at 26 and 28 months involved multiple apneic spells within a short period of time.

Pertinent Physical Findings

Facial/Physical Characteristics: Telecanthus, broad nasal bridge, and short palpebral fissures. Additionally, a single transverse palmar crease (right hand).





Cardiovascular: Extensive history of tachycardia with apneic and acrocyanotic spells, with first onset at 4 months. Apneic events reoccurred at 6, 18, 25, and 26 months of life. These apneic spells usually occurred within 30 minutes of feeding. During these spells, our patient becomes completely limp and appears unconscious. Atrial septal defect, sinus rhythm with intermittent 1st degree AV block, blocked premature atrial contractions, left axis deviation, right bundle branch block, and a Left Ventricular Ejection Fraction of 67%, small secundum atrial septal defect (ASD) with small left-to-right shunting.

Neurological: Global developmental delay, hypotonia, dyspraxia with cognitive disability, T2/FLAIR hyperintense signal in the white matter of the parietal lobes, left greater than right (could be due to incomplete myelination in this region), generalized slowing indicative of a mild nonspecific encephalopathy, partial onset seizures with eye opening.

Gastrointestinal: Feeding aversion history with history of significant reflux.

Clinically significant Variants

Gene Info		Variant Info		
GENE	INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
HNRNPU NM_031844.2	Autosomal Dominant	c.803+2T>C p.?	Heterozygous (*de novo*)	**Likely Pathogenic**

Additional Variants of Potential Clinical Relevance

Gene Info		Variant Info		
GENE	INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
COL4A1 NM_001845.5	Autosomal Dominant	c.3832G>A p.Gly1278Ser	Heterozygous (maternally inherited)	Unknown Significance
SCN2A NM_021007.2	Autosomal Dominant	c.82C>T p.Arg28Cys	Heterozygous (maternally inherited)	Unknown Significance
DHCR7 NM_001360.2	Autosomal Recessive	c.964-1G>C p.?	Heterozygous (maternally inherited)	**Pathogenic (carrier)**

Table 1: Chromosomal Sequencing Analysis (20,095 Gene Panel; gene sequencing with deletion and duplication analysis; genome-wide copy number analysis; TRIO).

DISCUSSION / CONCLUSIONS

Genetic testing including microarray and sequencing studies revealed the variants in Table 1. No genomic dosage anomalies were reported. The truncating *de novo* (c.803+2T>C) variant in *HNRNPU* was classified as likely pathogenic. This variant may disrupt the canonical splice donor site for exon 2 and while this mutation in novel, other canonical splice disrupting variants have been reported to be pathogenic. hnRNPs have a key role in mediating transcription, alternative splicing, and translation activity. Alternative splicing can lead to an increase in proteomic diversity. This is necessary for the flexibility of a cancerous cell to respond to various environments. There is little research surrounding hnRNP-U and its role in cancer development, but the production of alternative transcripts due to dysregulation can lead to aberrant protein isoforms with altered functions [2]. Regarding neurodegenerative diseases, hnRNPs are responsible for the regulation of translation at the presynaptic sites as well as the transportation of stabilized mRNAs along the axonal cytoskeleton to these presynaptic translation hubs. Deviation from hnRNPs' normal function can result in multiple neurological diseases, such as ALS/FTLD, SMA and AD [3]. The role of hnRNP-U in neurodegenerative diseases is not fully understood, yet it commonly presents in neurodegenerative diseases.

As more is learned, the roles of hnRNPs in other diseases will also be discovered. Understanding the roles of hnRNPs in diseases will be beneficial for developing potential therapeutic targets. For example, RNA-mediated toxicity is a hallmark of many affected neurons in neurodegenerative diseases like ALS/FTLD [4]. Hopefully future targeted antibody therapy towards these RNA foci, can attenuate this RNA toxicity. This targeted RNA-based therapy will be a critical step in reducing the expression level of the disease-propagating proteins. This suggests the addition of *HNRNPU* to all seizure-related diagnostic panels. We would also recommend including the HNRNPU-related disorders in a differential diagnosis of BRUE and recurrent apneic episodes as any underlying clonic activity may be profoundly subtle.

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