Pathogenic variants in calmodulin associated with resuscitated childhood cardiac arrest

AMY DALY, MS, LCGC
MAY 11, 2017
Calmodulin

- Calmodulin is encoded by CALM1, CALM2, and CALM3.
  - Four EF-hand calcium binding domains.
  - C-terminal domains have a higher affinity for calcium binding.

- Variants in CALM1 initially identified in two patients with CPVT-like arrhythmia (Nyegaard 2012).
  - Additional reports describe CPVT or LQTS, or both, associated with CALM1, CALM2, and CALM3 variants.
Case 1

- 5-year-old boy experienced cardiac arrest while swimming.
  - QTc prolonged of 494 msec
  - Normal echocardiogram and cardiac MRI
  - No history of symptoms before his arrest

- Asn98Ser identified in the CALM1 gene
  - Pathogenic variant previously reported in association with CPVT
  - Parental testing was negative, consistent with a de novo variant
Comparison to prior reports

- **CALM1 Asn98Ser**
  - Nyegaard (2012) identified Asn98Ser in a 23-year-old woman with a history of VF arrest at age 4 years while running.
    - No evidence of QT prolongation on ECG and normal echo

- **CALM2 Asn98Ser**
  - Makita (2014) identified in a 5-year-old boy who experienced syncope with seizures while running.
    - Subsequent episode of syncope and QTc of 478 msec
  - Anderson (2016) identified in a 2-year-old boy with sudden death while dancing.
  - Jiminez-Jaimez (2016) identified in a 7-year-old boy with SCD and a 4-year-old girl with VF.
Case 2

- 8-year-old girl experienced cardiac arrest while playing
  - Prolonged QTc of 542 msec
  - Normal echocardiogram and cardiac MRI
  - No history of symptoms before her arrest

- Asp94Ala identified in CALM3
  - Novel variant of uncertain significance located in calcium binding domain III
  - Parental testing was negative, consistent with a de novo variant
  - Reclassified as pathogenic
Variants in calmodulin

- The majority of variants have been identified in the C-terminal calcium binding domains.
Case similarities

- Phenotype
  - Cardiac arrest is a frequent presenting feature.
  - Exertion often precedes arrhythmic event.
  - Age of onset for first symptom is consistently in childhood.

- Inheritance
  - Frequently de novo

- Variant location
  - Enrichment of variants in calcium binding domains III and IV
Notable differences

- **Phenotype**
  - Variability in arrhythmia characteristics for the same CALM variant.
  - Prolonged QTc may or may not be present.

- **Inheritance**
  - Variable expressivity of inherited CALM variants.
  - Inherited CALM variants have occurred outside of the calcium binding domains (Nyegaard 2012, Marsman 2014).
Considerations for clinical practice

- Variants in CALM1, CALM2, and CALM3 are a recently recognized cause of an early-onset, highly arrhythmic phenotype in children.

- Testing of CALM1, CALM2, and CALM3 is important to consider for children presenting with VF, severe QTc prolongation, or sudden death.

- Variants in the CALM genes are considered rare. The re-testing of older children or adults with suggestive clinical histories and previously negative genetic testing may further clarify the frequency and phenotypic spectrum.
Acknowledgements

Stanford School of Medicine
Kyla Dunn, MS, LCGC
Anne M. Dubin, MD
Scott R. Ceresnak, MD
James R. Priest, MD
Kara S. Motonaga, MD

Invitae
Nicole M. Johnson, MSc, LCGC
Emily Decker, MS, LCGC
Thomas E. Callis, PhD
Jackie Tahiliani, MS, LCGC
John Garcia, PhD
Sienna Aguilar, MS, LCGC
Laura Murillo, PhD
Blanca Herrera, PhD
Daniel Beltran, PhD
Rachel Harte, PhD
Matteo Vatta, PhD, FACMG
References


