Whole Exome Sequencing Indentifies Novel SERCA-1 (ATP2A1) Variant in Patient with MHS and Normal RYR-1 Screening

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Introduction

- A recent study showed that in subjects with contracture positive malignant hyperthermia, RYR1 MH causative mutations or variants of undetermined significance were not always present (1).
- Whole exome sequencing was used to examine NAMHR subjects previously enlisted who did not have an identifiable RYR1 variant.
- Here we present one such subject and his sibling.

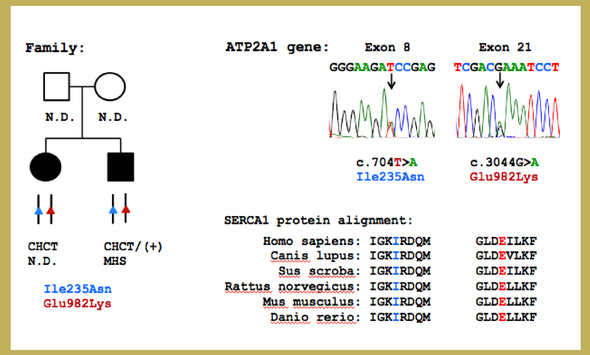
Clinical History

- Male patient presented for contracture testing following severe muscle rigidity in ICU after cardiac surgery.
- Patient with lifelong history of muscle pain, weakness, heat intolerance, inability to run, reported myalgia with statin therapy. No formal diagnosis of myopathy.
- No history of difficulty with prior general anesthetics.
- His siblings both male and female all had history of muscle weakness and inability to run, none had heat intolerance.
- His children and siblings' children do not have any muscle symptoms and are able to run normally.
- One sister enrolled in genetic study

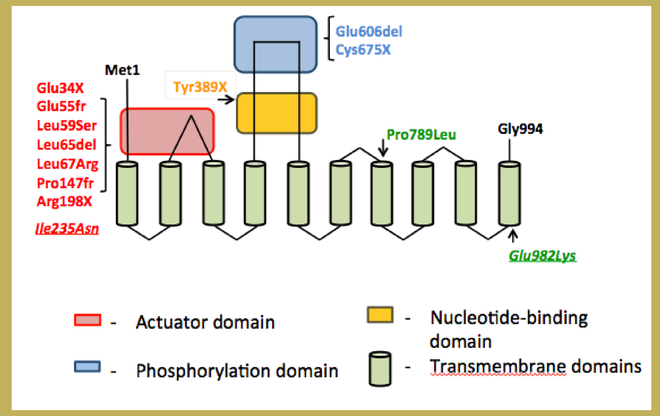
Methods for Genetic Analysis

- Whole exome sequencing (WES) was preformed using subject's genomic DNA at EdgeBio (Gaithersburg, MD).
- Analysis of WES preformed as described previously (2).
- Sanger sequencing was applied to confirm WES results and to genotype patient's sister.
- Cloning of the ATP2A1 gene transcript was done using TA-cloning kit followed by sequence analysis.

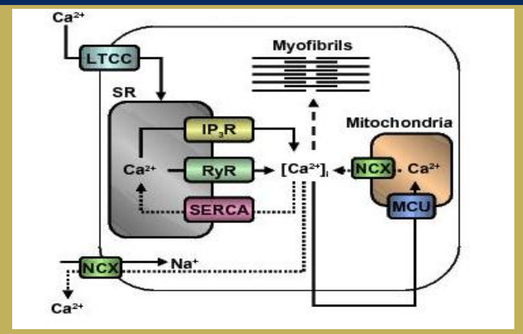
SERCA-1 Mutations in MHS Family



SERCA-1 Structure and Location of Mutations



SERCA-1 Location in Muscle Cell (3)



Contracture Test Results

- Proband had muscle histology reported as:
  - Myopathy, mild, type undetermined
  - Perivascular inflammatory response, focal mild
- Greatest contractures were 1.18 gr in 2mM caffeine and 5.74gr in 3% Halothane

Genetic Analysis Results

- Two novel variants in ATP2A1, Ile235Thr and Glu982Lsy identified in both the proband and his sister.
- These variants are predicted to alter the function of Ca (2+)ATPase in fast twitch 1 muscle.

Discussion

- The ATP2A1 mutation led to the diagnosis of Brody Myopathy in the proband and his sister.
- Brody Myopathy is an autosomal recessive disorder of muscle relaxation characterized by muscle stiffness especially following exercise.
- Highlights importance of continued research to identify genetic variants associated with malignant hyperthermia, muscular disorders prone to peri-operative complications that are not MH, and the low specificity of contracture testing.

References

1. Brandom et. al. Ryanodine receptor type 1 gene variants in the malignant hyperthermia-susceptible population in the United States. Anesth Analg.2013.May;116(5):1078-86.
2. Sambuughin N, et al. Exome sequencing reveals SCO2 mutations in a family presented with fatal infantile hyperthermia. J Hum Genet. 2013; 58: 226-228.
3. Image from Viola, HM et al. Crosstalk between L-type Ca2+ channels and mitochondria. http://aups.org.au/Proceedings/40/17-25. May 2009