Whole Exome Sequencing Identifies 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.

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 Glu982Lysy 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