Genetic signature of malignant hyperthermia risk in children: Improving assessment and prediction
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BACKGROUND:
- Malignant hyperthermia (MH) is an autosomal dominant pharmacogenetic disorder associated with uncontrolled skeletal muscle hyper-metabolism precipitated by general anesthesia.
- Pathogenic mutations in the ryanodine receptor type 1 gene (RYR1) encoding skeletal muscle-specific intracellular calcium release channel have been identified in people with MH or malignant hyperthermia syndrome (MHS).
- Up to 70% of MHS has been associated with RYR1 mutations and about 1% with mutations in calcium channel, voltage-dependent, L type, alpha 1S subunit gene (CACNA1S).
- Though MH has resulted in multiple preventable deaths and has associations with RYR1 and CACNA1S genetic variants, pre-operative utility of currently available genetic testing is limited because of poor predictive sensitivity (50%) and low reliability.

AIM:
- The overall aim of this project is to determine the genetic risk of MH in fulminant MH cases, MH susceptible children, and children without MH despite exposure to triggering agents.

STUDY DESIGN:
- This is part of a case – control genetic risk assessment study.
- Cases include (n=100) fulminant MH cases from the NAMHR of the MHAUS.
- MH susceptible children (n=34) were identified from the EMR system at CCHMC with MH 995.86 ICD-9 (with no formal diagnosis), family history of MH, Central core disease.
- Controls are (n=400) children who participated in pharmacogenetic research and had exposure to sevoflurane yet did not have signs of MH.
- All cases and controls have sequenced genetic data for RYR1 and CACNA1S.
- Anesthesia and medical records of fulminant MH cases and MHS cases were reviewed by anesthesiologists for accuracy of MH diagnosis based on high scores of clinical grading scale.
- Unsupervised hierarchical clustering is used to identify several distinct clusters of patients with high risk and low risk of MH.

RESULTS:
- Of the MH susceptible children screened (n=34), 6 damaging mutations were identified.

<table>
<thead>
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<th>Gene Name</th>
<th>Substitution</th>
<th>dbSNP ID</th>
<th>Prediction</th>
<th>SIFT Score</th>
<th>HMZ</th>
<th>HTZ</th>
<th>Global Mapper - PanMap</th>
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<tbody>
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<td>RYR1</td>
<td>F412S</td>
<td>Novel</td>
<td>DAMAGING</td>
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<td>0</td>
<td>1</td>
<td>0.06**</td>
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</table>

- *SIFT score, range 0 to 1, amino acid substitution is predicted damaging if the score is ≤ 0.05 and tolerated if > 0.05.
- ** D4500H has OR = 25.5, p=0.0001 (binomial test).
- Pathogenic rare RYR1 variant (D4500H) has been shown to be associated > 2-fold caffeine sensitivity of Ca2+ release and with fatal stress-induced MH.

CONCLUSIONS:
- Genetic risk signatures can aid in proactively and more reliably predicting MH susceptibility prior to anesthesia.
- The long-term goal of this project is to improve safety of anesthetic care and reduce morbidity and mortality due to malignant hyperthermia in children.