Sudden Unexplained Death, the Molecular Autopsy, & Genetic Purgatory

Michael J. Ackerman, MD, PhD
Windland Smith Rice Cardiovascular Genomics Research Professor
Professor of Medicine, Pediatrics, and Pharmacology
Director, Long QT Syndrome Clinic and the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory
President, Sudden Arrhythmia Death Syndromes (SADS) Foundation

USCAP 2016
Society of Cardiovascular Pathology
Seattle, WA
3/13/2016
Sudden Cardiac Death in the Young

Clinical Markers for Positive Genetic Test

<table>
<thead>
<tr>
<th>Marker</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Dx &lt; 45 yrs</td>
<td>1</td>
</tr>
<tr>
<td>MLVWT ≥ 20 mm</td>
<td>1</td>
</tr>
<tr>
<td>FH of HCM</td>
<td>1</td>
</tr>
<tr>
<td>FH SCD</td>
<td>1</td>
</tr>
<tr>
<td>Reverse-curve HCM</td>
<td>1</td>
</tr>
<tr>
<td>Hx of Hypertension</td>
<td>-1</td>
</tr>
</tbody>
</table>

Scoring range: -1 – 5 pts

Yield of Genetic Testing (%)

-5% ~ 80%

Predicting Positive Genetic Test


HCM: A Disease of the Myofilament

Modified from Spirito P et al. NEJM 336:775, 1997

Van Driest … Ackerman. AJC 90:1123-1127, 2002
Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the disease-causative mutation in an index case.

Ackerman, Priori, et al. *Heart Rhythm* 8:1308-1339, 2011 (HRS/EHRA)


**State of Postmortem Genetic Testing for Autopsy Negative SUD**

**A Mother’s Question**

Why did my 17-year-old son die?

**Evaluation of Sudden Unexplained Death**

- March 1999 – previously well 17-year-old white male found dead in bed
- Autopsy negative
- Local newspaper editorial positive – “Parents talk to your kids”
- Clue in the family history – mom “fell” from 3-meter diving board at age 9
- Negative standard evaluation – ECG, Echo
Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the disease-causative mutation in an index case.

Ackerman, Priori, et al. Heart Rhythm 8:1308-1339, 2011 (HRS/EHRA)

Autopsy Negative Sudden Unexplained Death Syndrome

In Autopsy Negative SUD, How Often Would a Molecular Autopsy Be Positive?
1. Don’t know what a molecular autopsy is.
2. 5-10%
3. 15-20%
4. 25-30%
5. > 50%
1. In the setting of autopsy negative SUDS, comprehensive or targeted (RYR2, KCNQ1, KCNH2, and SCN5A) ion channel genetic testing may be considered in an attempt to establish probable cause and manner of death and to facilitate the identification of potentially at-risk relatives and is recommended if circumstantial evidence points towards a clinical diagnosis of LQTS or CPVT specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death).
Whole exome sequencing (WES) allows for simultaneous mutational analysis of a patient's entire library of genes.

Next Generation Whole Exome Sequencing

29 consecutive sudden death cases (21 males, 26.7 ± 5.9 years) collected at the Office of the Medical Examiner, Cook County, Illinois from January 2012 to December 2013 were referred to Mayo Clinic for molecular autopsy.

Will ... Ackerman. HRS 2015

“Clinically Actionable” Variants

28 yo white male found in bed, equivocal autopsy.
14 yo white male, found unresponsive on floor after playing/exertion, negative autopsy.
27 yo black female, sudden collapse, equivocal autopsy noting cardiomyopathy.

Molecular Autopsy’s 3 Achilles’ Heels

1. Cost
   Insurance companies do NOT like to pay for things when you have died!

2. Medical Examiner’s SOP
   Paraffin-embedded tissue is NOT DNA friendly!

3. Interpreting the Molecular Autopsy
   “X” does NOT always mark the spot!

Molecular Autopsy of SCD

1. For all SUDS and SIDS cases, collection of a tissue sample is recommended for subsequent DNA analysis/genetic testing.

Genetic Testing’s Achilles’ Heel

Is the “X” that marks the spot truly THE disease-causing mutation?

What’s the “Background Noise Rate”?
What’s the Signal-to-Noise Ratio?

Sudden Cardiac Death in the Young

Autopsy Negative SUD is NOT a Good Phenotype!

LQTS – 15%
CPVT – 10%
BrS – 3%

KCNQ1, KCNH2, SCN5A, RYR2

Tester and Ackerman. Pediatric Cardiology 33:461-467, 2012

Background Noise Issue

Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: Implications for arrhythmogenic

Circulation 2003 13.5%

KCNQ1, KCNH2, SCN5A, RYR2 = ~5%

Postmortem Genetic Testing

- “Maybe” Test Result

“Possible Deleterious”
“Variant of Uncertain Significance (VUS)”

“Genetic Purgatory is a Real Place and its Scary!”
Case Presentation

$+ = \text{L537P-SCN5A} = \text{BrS1}$

Genetic Purgatory is Real

$\text{L537P VUS < 10\% POP}$

World Wide Brugada Syndrome Consortium.
SUD, Molecular Autopsy, & Genetic Purgatory

**TAKE HOME POINTS**

1. ~25% of autopsy negative SUD and 10% of SIDS - **Channelopathic!**
2. Genotype-phenotype correlations still matter after death. Autopsy negative SUD is NOT that informative.
3. Formalin-fixed paraffin embedded tissue is the enemy of a molecular autopsy.
4. “X” does NOT always mark the spot! Genetic purgatory exists! Believe in it.