State of the Molecular Autopsy

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Learning Objectives to Disclose:
• To **DETAIL** the state of postmortem genetic testing (AKA, “the molecular autopsy”) for autopsy positive and autopsy negative sudden cardiac death (SCD) in the young
• To **EXAMINE** the three Achilles’ heels that threaten to derail the molecular autopsy

Conflicts of Interest to Disclose:
• Consultant – Audentes Therapeutics, Boston Scientific, Gilead Sciences, Invitae, Medtronic, MyoKardia, and St. Jude Medical
• Royalties – AliveCor, Blue Ox Health Corp, and StemoniX
Sudden Death in the Young (SDY)
“WITHOUT THE MOLECULAR AUTOPSY, OUR FAMILY WOULD HAVE HAD TO LIVE WITH FALSE RUMORS.”
CLOSURE & CLARITY!
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%
State of Postmortem Genetic Testing

- N = 173 cases of SUD (106 males)
- Average age = 18 + 13 years (1 - 69 yrs)
- Personal or FHx of Cardiac Events = 70 (40%)

- Autopsy Negative Sudden Unexplained Death
  ~ 25 - 30%

Tester ... Ackerman. Mayo Clin Proc 79:1380 – 1384, 2004
Tester ... Ackerman. JACC 49:240-246, 2007
Age- and Sex-Specific Effect on the Yield of a Cardiac Channel Molecular Autopsy


Percent Yield (%)
LQTS Mutations - Pathogenic Basis for ~10% of SIDS or SUID

Ackerman et al. *JAMA* 286:2264-69, 2001
Tester ... Ackerman. *Cardiovasc Res* 67:388-96, 2005
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).

Ackerman, Priori, et al. *Heart Rhythm* 8:1308-1339, 2011 (HRS/EHRA)
Whole exome sequencing (WES) allows for simultaneous mutational analysis of a patient’s entire library of genes!

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
Whole exome sequencing (WES) allows for simultaneous mutational analysis of a patient’s entire library of genes!

32 (20 males) consecutive, medical examiner-referred cases of autopsy negative, exertional sudden death in the young (SDY) cases (11 ± 5 years, 2 – 19 year range).

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!
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)
Is the “X” that marks the spot truly THE disease-causative mutation?

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

Original Article

Ethnic Differences in Cardiac Potassium Channel Variants: Implications for Genetic Susceptibility to Sudden Cardiac Death and Genetic Testing for Congenital Long QT Syndrome

Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: Implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing

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Genetic Testing for LQTS Patients

LQT1

Mayo Clinic 541 Series of LQTS referrals
Tester ... Ackerman. Heart Rhythm 2:507-517, 2005
LQTS Variants in Health

LQT1

LQT2

LQT3

LQTS Variants in Health


Ackerman et al. Heart Rhythm 1:600-607, 2004
Genetic Testing for LQTS Patients

- 4% Background Rate in Healthy Caucasians
- 6-8% Background Rate in Healthy Non-Caucasians

“Exercise Extreme Caution When Calling Mutations”

Mayo Clinic 541
Series of LQTS referrals
Tester … Ackerman.
*Heart Rhythm* 2:507-517, 2005
Background Noise Issue

Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: Implications for arrhythmogenetic susceptibility and Brugada/long QT syndrome

KCNQ1, KCNH2, SCN5A, RYR2 = ~5%
Autopsy Negative SUD is NOT a Good Phenotype!

- LQTS – 15%
- CPVT – 10%
- BrS – 3%

KCNQ1, KCNH2, SCN5A, RYR2
“Postmortem Genetic Testing

- “Maybe” Test Result

“Possible Deleterious Variant of Uncertain Significance (VUS)”

“Genetic Purgatory is a Real Place and its Scary!”
The Promise and Peril of Precision Medicine: Phenotyping Still Matters Most

Jaeger P. Ackerman, BA; Daniel C. Bartos, PhD; Jamie D. Kapplinger, BS; David J. Tester, BS; Brian P. Delisle, PhD; and Michael J. Ackerman, MD, PhD

Mayo Clinic Proceedings 2016

Slide courtesy of Arthur Wilde
Sudden Death in the Young Pedigree

13-year-old Hispanic Male
Sudden death during sleep

Autopsy Findings:
- Heart weight of 430 g
- LVWT 17 mm
- Mild fiber disarray in LV

Medical examiner deemed inconclusive autopsy

Living Brother’s ECG

Clinical Genetic Testing for LQTS
Pathogenic Variant – LQT1-Causative

Negative for c.397G>A, p.V133I
V133I-KCNQ1 has a Normal Electrophysiological Phenotype
WES-Based Familial Genomic Triangulation

Sporadic p.R454W-Desmin Mutation

- Described previously as a sporadic mutation in a 15 year old with exercise intolerance and HCM and in a autosomal dominant pedigree of HCM and SCD.
- In vivo and in vitro studies show a dramatic effect on filament formation.

ACMG – “Pathogenic”

- Described previously as a sporadic mutation in a 15 year old with exercise intolerance and HCM and in a autosomal dominant pedigree of HCM and SCD.
- In vivo and in vitro studies show a dramatic effect on filament formation.
Boy’s Cardiac Death Led to Misuse of Genetic Test, Study Says

Victim’s family members were given wrong diagnoses of their own conditions

By RON WINSLOW
Oct. 31, 2016 12:01 a.m. ET

A 13-year-old boy’s sudden cardiac death led doctors to wrongly diagnose more than 20 of his relatives with a potentially lethal heart disorder in a case that illustrates the potential for genetic testing to go wrong.
The only thing worse than telling a family “I don’t know why your child died” is to tell them “we have found the answer” and be wrong!
State of the Molecular Autopsy

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!
THE GENETICS OF HEART & VASCULAR DISEASE

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