# The "Molecular Autopsy": Real Life Experience in a Medical Examiner's Office

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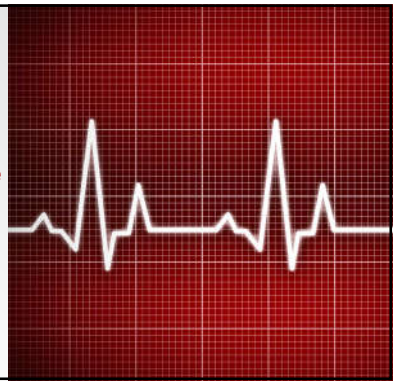

1

## Learning Objectives

- List the types of deaths that blood should be retained for postmortem genetic testing
- List the most common inherited cardiac channelopathies that cause sudden death
- List the most common inherited cardiomyopathies and the genes affected
- Define a genetic variant of uncertain significance (VUS) and its clinicopathologic implications

2

## Disclaimer

- I have NO financial interests or conflicts of interest in any genetic testing company discussed in this presentation

3

## Methods and Materials

- Decedent selection based on criteria established by NAME for postmortem genetic testing
- Expanded the selection to cases involving cardiomyopathies and aortic dissection
- Used a commercial genetic testing laboratory (Invitae)
- 2017-2019
- 37 cases tested (EDTA blood collected at autopsy)
- 5 additional cases tested from 2008-2016 (blood frozen at -85°F)

4

## Postmortem Genetic Testing (Molecular Autopsy)

| | Phone | Cost | TAT | URL |
|---|---|---|---|---|
| Invitae | 800-436-3037 | $475 | 2-3 weeks | invitae.com |
| Northwestern Sudden Death Collaboration | 312-227-2525 | free | varies | labs.Feinberg.northwestern.edu/webster |
| Ambry Genetics | 949-900-5500 | $249 | 4-6 weeks | ambrygen.com/clinician/postmortem |
| GeneDx | 301-519-2100 | $4580 | 4 weeks | genedx.com |
| Prevention Genetics | 715-387-0484 | ?? | ?? | preventiongenetics.com |
| Blueprint Genetics | 650-452-9340 | $990 | 3-4 weeks | blueprintgenetics.com |
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5

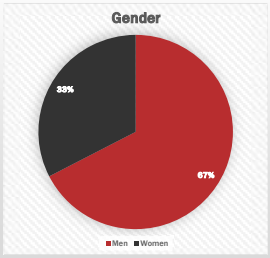
## Retaining postmortem samples for genetic testing

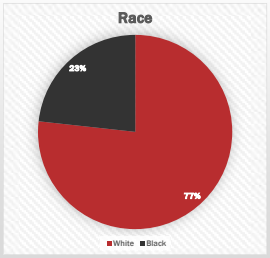
- When to retain a specimen for future testing:
  - Drowning in sober or experienced swimmer
  - Single motor vehicle accidents without mitigating factors (toxicology negative, not suicide, etc)
  - Unexplained seizure in a young person
  - Cardiomyopathy or aneurysm identified at autopsy
  - Unexplained death of a person with known family history of sudden death or inherited cardiovascular disease
  - Sudden death in a person 40 years or younger that is unexplained after a complete autopsy

Middleton O, Baxter S, Demo E, Honeywell C, Jentzen J, Miller F, Pinckard JK, et al. National Association of Medical Examiners position paper: Retaining postmortem samples for genetic testing. *Acad Forensic Pathol*, 3(2):191-194, 2013.

6

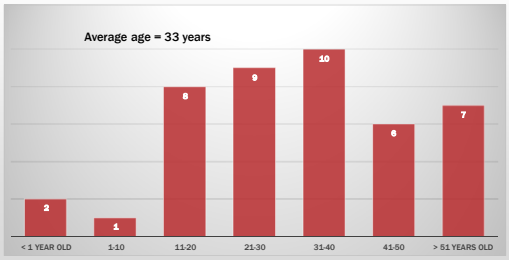
## The Decedents: Gender and Race




7

## The Decedents: Age




8

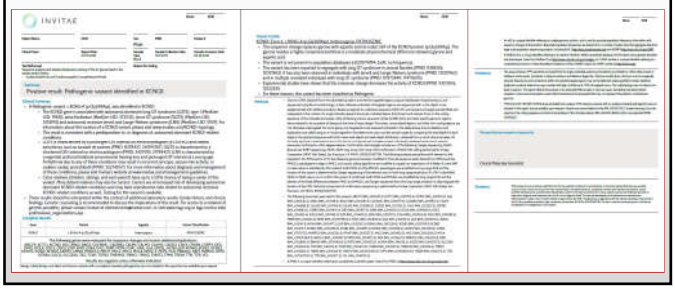
## Case #1

- 29-year-old man, former heroin addict
- Sudden witnessed collapse at his desk after eating
- Unable to be resuscitated, pronounced dead at ER
- Slight cardiomegaly, 417 g
- Blood venlafaxine = 906 ng/ml (100-500 ng/ml)
- No drugs of abuse in blood or urine
- No previous known medical conditions

**Pathogenic variant in KCNQ1 gene**

9

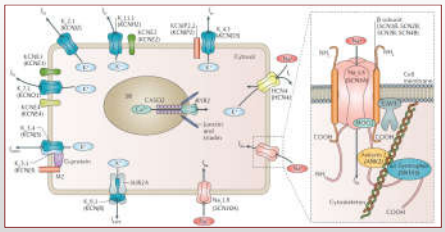
## Genetic report



10

## Cardiac Ion Channelopathies

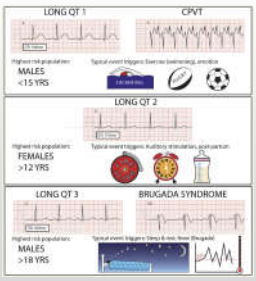
- Inherited cardiac ion channelopathies are disorders caused by mutations in ion channel genes that result in disturbances to normal heart rhythm
  - Long QT syndrome
  - Catecholamine Polymorphic Ventricular Tachycardia (CPVT)
  - Brugada syndrome
  - Short QT-syndrome



11

## Congenital Long QT Syndrome

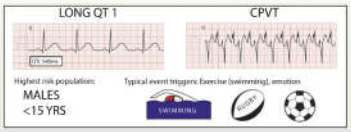
- Delayed repolarization of myocardium
- Usually autosomal dominant
- QT prolongation (QTc > 470 ms)
- Syncope, seizures, sudden death
- Triggers include exertion, swimming, emotion, sudden auditory stimuli, postpartum
- Up to 5-10% die suddenly as a sentinel event




12

## Catecholamine Polymorphic Ventricular Tachycardia (CPVT)

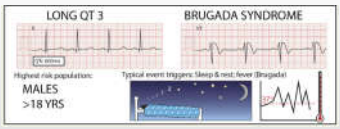
- Autosomal dominant
- Structurally normal heart
- Young men
- Normal resting ECG
- Exercise or catecholamine stress produces ventricular ectopy, syncope, SCD
- Mortality rate 30-50% by age 35
- Cardiac ryanodine receptor gene (RyR2)




13

## Brugada Syndrome

- Ventricular arrhythmia
  - Syncope, aborted cardiac arrest, SCD
- Usually men
  - Common cause of sudden death in Thailand, Philippines, Japan in men under 50 years
- Can occur at any age
  - Average age is 41 years
- Autosomal dominant in 50% of cases
- Structurally normal heart




14

## Autopsy Negative Sudden Cardiac Death (SCD)

- A negative autopsy is NOT a phenotype
- Postmortem genetic testing of individuals who die suddenly and have a phenotypically normal heart will be positive in 25-30% of cases
  - 15% Long-QT syndrome
  - 10% Catecholamine Polymorphic Ventricular Tachycardia (CPVT)
  - 3% Brugada syndrome

15

## Case #2

- 44-year-old woman
- Found dead, seated at home by her daughter
- Active lifestyle, no alcohol or drugs
- Heart = 416 grams
- Blood toxicology negative

**Pathogenic variant in DSP gene**

16

## Case #2

- DSP gene
  - Autosomal dominant arrhythmogenic right ventricular cardiomyopathy
  - Dilated cardiomyopathy with wooly hair, keratoderma, and tooth agenesis
  - Autosomal dilated cardiomyopathy with wooly hair and keratoderma (Carvajal syndrome)
- Other genes associated with Arrhythmogenic right ventricular cardiomyopathy
  - RYR2
  - DSC2
  - DSG2

17

## Case #3

- 14-year-old girl
- Witnessed collapse while walking in school hallway'
- PEA, taken to ER where she died
  - Chest radiography showed cardiomegaly
  - Chest CT showed dilated RA, slightly dilated LA,LV
- Complained of dyspnea during competitive cheerleading
- Heart = 390 grams
- Toxicology was negative
- 15-year-old brother

18

## Case #3

Pathogenic variant in TNNI3 gene

19

## Case #4

- 88-year-old woman
- Seen in the ER complaining of hip pain after she fell at home and discharged with Tramadol
- History of atrial fibrillation, mitral insufficiency, congestive heart failure with automatic cardioverter/defibrillator (AICD), previous AV node ablation
- History COPD, Type 2 diabetes mellitus, CVA, macular degeneration
- Returned to hospital with altered mental status, diagnosed with hip fracture, ?tramadol overdose
- Deteriorated clinically, transferred to hospice where she died

20

## Variant of Uncertain Significance (VUS) in GLA gene

21

## Variant of Uncertain Significance (VUS)

- A variant that cannot be classified as pathogenic nor benign
- A variant of uncertain significance should not be used in clinical decision making

22

## Results

- Of the 32 cases tested,
  - 8 (25%) had recognized pathogenic variants
  - 17 (53%) had genetic variants of uncertain significance
  - 7 (22%) showed no genetic mutations
- In 17 cases (53%), there was a correlation between the clinical and/or pathological findings found in the decedent and that expected based on the affected gene found during the molecular autopsy.

23

## Summary

- We find postmortem genetic testing is affordable and helps to corroborate the clinical and pathological findings in individuals who die from heritable cardiovascular disease.

24