Genetic Testing is a Blessing: 
Cardiac Channelopathies

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Common Inherited Diseases that Cause 
Sudden Arrhythmic Death Syndrome (SADS)

- More than 50% of SADS deaths are genetic in nature.¹

The Family of Genetic Tests for Inherited Cardiac Syndromes

Cardiac Channelopathies

<table>
<thead>
<tr>
<th>Test</th>
<th>Gene/Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS</td>
<td>KCNQ1 (0.071)</td>
</tr>
<tr>
<td></td>
<td>KCNE1 (0.075)</td>
</tr>
<tr>
<td></td>
<td>KCNE2 (0.016)</td>
</tr>
<tr>
<td></td>
<td>GKNL4 (0.071)</td>
</tr>
<tr>
<td></td>
<td>AKAP9 (0.011)</td>
</tr>
<tr>
<td></td>
<td>SNTA1 (0.011)</td>
</tr>
<tr>
<td>BRS Test</td>
<td>SCN5A</td>
</tr>
<tr>
<td>CPVT Test</td>
<td>RYR2*</td>
</tr>
</tbody>
</table>

Cardiomyopathies

<table>
<thead>
<tr>
<th>Test</th>
<th>Gene/Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVC Test</td>
<td>DSP</td>
</tr>
<tr>
<td></td>
<td>DSG2</td>
</tr>
<tr>
<td></td>
<td>DSC2</td>
</tr>
<tr>
<td></td>
<td>TMEM40</td>
</tr>
<tr>
<td>DCM Test</td>
<td>LAMA4</td>
</tr>
<tr>
<td></td>
<td>MYH7</td>
</tr>
<tr>
<td></td>
<td>MYBPC3</td>
</tr>
<tr>
<td></td>
<td>MYBPC3</td>
</tr>
<tr>
<td></td>
<td>TNN1</td>
</tr>
<tr>
<td></td>
<td>NML2</td>
</tr>
<tr>
<td></td>
<td>NTL3</td>
</tr>
<tr>
<td>HCM Test</td>
<td>MYH7</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>NTL3</td>
</tr>
</tbody>
</table>

* See the FAMILAN technical specification sheet for coverage areas.

Increased Awareness of and Improved Testing for LQTS Are Revealing a Higher Prevalence

- Inherited LQTS is now known to affect 1:2,500 people.¹
- It is estimated that 2,000-3,000 children and young adults die each year in the United States due to LQTS.²

Challenges in Diagnosing LQTS – ECG Variability

- ~33% of mutation-positive LQTS patients have a QT interval (≤ 480 msec) that overlaps normal, healthy individuals.2


Schwartz Score

- Schwartz score results are frequently inconclusive.1

<table>
<thead>
<tr>
<th>Probability</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2-3</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
</tr>
</tbody>
</table>

THE BENEFITS OF GENETIC TESTING?

Genetic Testing for Prevention

Frequency of Cardiac Events

Subjects from the International LQTS Registry & BIOMED LQTS Research Group
Gene Mutation Location Further Defines LQTS Risk

For LQT1 and LQT2 patients, there is significantly higher risk for cardiac events when mutations are located in the transmembrane/pore region.1,2

Examples of LQT1 and LQT2 Transmembrane Mutations

Genetic testing is the only method available to determine mutation location.

Risk for Asymptomatic Parents of Probands
Risk of an Initial Cardiac Event for Asymptomatic Parents of Probands Extends Into Adulthood.


Genetic Testing for Therapy
Effectiveness of β-Blocker Treatment

Rate of cardiac events over five years for subjects from the International LQTS Registry
Genetic Testing for Therapy

<table>
<thead>
<tr>
<th>TEST RESULTS</th>
<th>ISSUE</th>
<th>DIRECTED THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT 2</td>
<td>Auditory stimuli trigger events.</td>
<td>Remove alarm clocks etc. from bedroom. Beta blocker therapy advised.</td>
</tr>
<tr>
<td>LQT 3</td>
<td>Relatively low risk of exercise. High mortality rates despite beta blocker therapy.</td>
<td>Supervised recreational activity could be considered. ICD therapy advised.</td>
</tr>
</tbody>
</table>

Genetic Testing for Prognosis

- LQT1 patients are more likely than either LQT2 or LQT3 patients to experience a cardiac event.\(^1\)
- Although the incidence of cardiac events is lower for LQT3 patients, the probability of death per cardiac event is increased.\(^1\)

Symptoms in CPVT

- If left untreated, 30% of CPVT patients will develop symptoms by age 10, and ~80% by age 40.\(^1\)

Challenges in Diagnosing CPVT

- CPVT cannot be diagnosed on the basis of a resting ECG.\(^1,2\)
- Exercise stress testing is an important part of a CPVT workup.
  - However, in as many as 20% of CPVT patients, formal exercise stress testing will not produce ventricular ectopy.\(^1\)
- During exercise stress testing, bidirectional VT with a beat-to-beat 180-degree rotation of the QRS complex is often observed.\(^1\)
Differentiate CPVT from LQTS

- CPVT is a LQTS mimicker.¹
- As many as 30% of CPVT patients have been misdiagnosed as having “Long QT with normal QTc.”²³

<table>
<thead>
<tr>
<th>Factor</th>
<th>Distinguishes CPVT From LQTS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (Syncope, Seizures, Sudden Cardiac Death)</td>
<td>NO</td>
</tr>
<tr>
<td>Symptom Trigger(s) (Exercise, Emotional Stress)</td>
<td>NO</td>
</tr>
<tr>
<td>Age of Onset (Childhood and Adolescence)</td>
<td>NO</td>
</tr>
<tr>
<td>Resting ECG</td>
<td>Variable</td>
</tr>
<tr>
<td>Exercise Stress Test</td>
<td>Variable</td>
</tr>
<tr>
<td>Genetic Mutation Found</td>
<td>YES</td>
</tr>
</tbody>
</table>

Genotyping Family Members of Known Probands Is Essential to Risk Management

- All first-degree relatives, regardless of age, should be genotyped for the proband’s gene mutation(s).¹²³
- An asymptomatic parent with an LQTS mutation has a high probability of having children at risk for cardiac events.¹
- Approximately 33% of untreated siblings carry the proband’s gene mutation(s) and will have a cardiac event by 40 years of age.²

CASE

- A 12 year old boy passes out while swimming. He is appropriately resuscitated. The QTc on the ECG is 455 msec (indeterminate). Genetic testing comes back positive for long QT type 1.
  - Subsequent genetic testing in his 8 year old sibling is positive but negative in the 6 year old sibling. Parents also undergo testing and the mother is found to be a carrier. Genetic testing in this scenario was helpful for which of the following?

  - A. The 12 year old boy
  - B. The 8 year old sibling
  - C. The 6 year old sibling
  - D. Future offspring off all 3 children
  - E. The parents

Index Case (12 year old)

- Probability of LQTS:
  - intermediate (Schwartz Score: 3)
  - High with genetic testing
- Therapy:
  - Initiate beta blockers but no need for ICD
- Prevention:
  - Limit strenuous activities.
- Prognosis:
  - good
- Helpful:
  - yes
8 year old sibling

- Probability of LQTS:
  - Intermediate (Schwartz Score: 2)
  - High with genetic testing (Positive family history and genotype positive)
- Therapy:
  - Initiate beta blockers but no need for ICD
- Prevention:
  - Limit strenuous activities.
- Prognosis:
  - good
- Helpful:
  - yes

6 year old sibling

- Probability of LQTS:
  - Intermediate (Schwartz Score: 2)
  - Low with genetic testing (Positive family history and genotype negative)
- Therapy:
  - No need to initiate beta blockers or ICD
- Prevention:
  - No limitations
- Prognosis:
  - good
- Helpful:
  - yes
Future offspring off all 3 children

- Probability of LQTS:
  » Depends on genetic test of parent
- Recommendation
  » genetic testing for all offspring of genotype positive subjects but not of genotype negative subjects.
- Helpful:
  » yes

The Parents

- Probability of LQTS:
  » High in mother
  » Low in father
- Recommend
  » genetic testing for all siblings of mother but not of father.
- Therapy:
  » Initiate beta blockers but no need for ICD
- Prognosis:
  » good
- Helpful:
  » yes
On 15 February 2006, 14 year old Shauna Stuewe was lost to Sudden Cardiac Arrest (SCA). An accomplished Gymnast and talented cheerleader, Shauna was both physically fit and the picture of health at the time her death.

Shauna had been seen by a Pediatric Cardiologist who performed various tests including EKGs, Echocardiogram and Holter Monitor and concluded that Shauna was in good health, no further cardiac evaluation was needed and no restrictions were placed on her activities.

Genetic autopsy testing on Shauna later revealed a gene mutation for CPVT.

Her younger sister, who was also completely asymptomatic and an athlete, was subsequently found to be positive for CPVT by genetic testing. She now has an ICD.

The Role of Genetic Testing

| Disease diagnosis/confirmation of diagnosis | ✓ |
| Comprehensive risk assessment | ✓ |
| Advise appropriate lifestyle modifications | ✓ |
| Develop comprehensive treatment plan | ✓ |
| Aid in whether to place ICD | ✓ |
| Family testing/asymptomatic/pre-symptomatic identification | ✓ |
| Enables genetic counseling | ✓ |
Questions

Concerns with genetic testing

- **Cost:**
  - Make testing less expensive
  - bundle all channelopathy tests into one test.
- **Insurability**
  - Universal insurance for all
- **Psychological trauma to families**
  - Availability of genetic councilors
- **False positives and false negatives**
  - Improve sensitivity and specificity of test
- **Significance of rare genotypes**
  - Increase awareness of clinical significance of rare genotypes
# Test Yield

<table>
<thead>
<tr>
<th>Channelopathy</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT Syndrome (LQTS)</td>
<td>75%</td>
</tr>
<tr>
<td>Brugada Syndrome</td>
<td>15-20%</td>
</tr>
<tr>
<td>Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)</td>
<td>50-55%</td>
</tr>
</tbody>
</table>