Triggers for sudden death in LQT6 patients with MiRP1 (KCNE2) mutations: hypothermia, bradycardia, AV block, and cardiac memory

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International Dead Sea Symposium
Fellows’ Case Competition
35 year-old female admitted with unwitnessed cardiac arrest

- Successfully resuscitated and hemodynamically stable
- Previously healthy
- No family history of sudden death
- Echocardiogram unremarkable
Prior ECG
ECG upon admission
During therapeutic hypothermia
Clinical course

- IV magnesium
- Rewarming
- Resolution of AV block
- Shortening of QTc
- EP study
  - No VA conduction
  - VT not inducible with ventricular extrastimuli
  - AVN and AP block (2:1) cycle length: 450 ms
- Dual-chamber ICD
Genetic Testing

- Inherited cardiomyopathy (including PRKAG2), ARVC, CPVT and Brugada panels: negative

- LQT panel: missense mutation in *KCNE2* (170T>C (Ile57Thr))
Updated family history

- No family members with pre-excitation
- Mother, father, sister, brother: normal ECG with QTc < 450 ms
- Sister: QTc 460 ms
- Daughter (age 7): QTc 450 ms
- Son (age 2): QTc 428 ms
Discussion
MiRP1 (**KCNE2**)  

- **Mink-related Peptide 1 (MiRP1)**  
  - β-subunit that is a component of multiple ion channels  
  - co-assembles with hERG to form $I_{Kr}^1$  
    - affects $I_{Kr}$ gating, conductance  
  - **KCNE2** mutations result in LQT6  
    - 1% of all LQT patients$^2$  

MiRP1-hERG interaction

Reduced $I_{Kr}$ current

QT-prolongation

TdP
MiRP1 role in bradycardia and AV block?

- Serves as β-subunit for HCN channels in SAN and AVN
  - Regulates HCN expression\(^3,4\), gating\(^3-6\), and current\(^5-6\)
  - Case reports of LQT6 patients also describe sinus bradycardia\(^1,6\)

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MiRP1 role in bradycardia and AV block?

MiRP1-hERG interaction

Reduced $I_{Kr}$ current

MiRP1-HCN interaction

Reduced $I_f$ current

Bradycardia and AV block

QT-prolongation

TdP
Role of cardiac memory in QT prolongation

- 91 patients with AV block associated with or without QRS morphology change
  - With QRS morphology change: QT 648 ± 84 ms (QTc 505)
  - Without morphology change: QT 561 ± 84 ms (QTc 441)

ECG upon admission
Role of cardiac memory in QT prolongation

- Sudden change in QRS noted immediately prior to Torsades de Pointes
  - Change in QRS morphology: OR 5.4 (p = 0.016) for TdP

MiRP1-hERG interaction

Reduced $I_{Kr}$ current

MiRP1 role in AP?

Loss of pre-excitation

Cardiac memory

QT-prolongation

TdP

MiRP1-HCN interaction

Reduced $I_{f}$ current

Bradycardia and AV block

Loss of pre-excitation

Cardiac memory

QT-prolongation

TdP
Conclusions

• LQT6 patients are predisposed to bradycardia and AV block via MiRP1-HCN interactions

• Loss of pre-excitation during AV block prolongs QT interval due to cardiac memory

• Hypothermia, bradycardia, AV block, and T wave memory contributed to Torsades de Pointes
Acknowledgements

- Dr. Melvin Scheinman, UCSF
- Dr. Sanjay Bindra, Regional Medical Center
- Dr. Mohan Viswanathan, Stanford University
- Julianne Wojciak, MS, UCSF
References


Additional Figures
MiRP1 role in bradycardia and AV block?

- Also serves as β-subunit for HCN channels
  - Regulates HCN expression\(^3,4\), gating\(^3-6\), and current density\(^5-6\)

Role of T wave memory in QT prolongation

Table 4. Predictors of Torsade de Pointes During AVB

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>6.3 (1.3–30.6)</td>
<td>0.023</td>
</tr>
<tr>
<td>Age (for 10-yr increase)</td>
<td>1.3 (0.7–2.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>QRS width at baseline (for 10-ms increase)</td>
<td>0.94 (0.77–1.13)</td>
<td>0.99</td>
</tr>
<tr>
<td>Baseline R-R (for 100-ms increase)</td>
<td>0.77 (0.50–1.19)</td>
<td>0.25</td>
</tr>
<tr>
<td>Baseline QT (for 10-ms increase)</td>
<td>1.05 (0.89–1.24)</td>
<td>0.55</td>
</tr>
<tr>
<td>Baseline QTc (for 10-ms increase)</td>
<td>1.17 (0.99–1.38)</td>
<td>0.059</td>
</tr>
<tr>
<td>R-R during AVB (for 100-ms increase)</td>
<td>0.99 (0.86–1.13)</td>
<td>0.87</td>
</tr>
<tr>
<td>QRS width during AVB (for 10-ms increase)</td>
<td>0.96 (0.85–1.08)</td>
<td>0.99</td>
</tr>
<tr>
<td>Complete AVB*</td>
<td>2.6 (0.3–21.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>QT during AVB (for 10-ms increase)</td>
<td>1.19 (1.08–1.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc during AVB (for 10-ms increase)</td>
<td>1.20 (1.08–1.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTcF during AVB</td>
<td>1.19 (1.08–1.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in QRS morphology</td>
<td>4.7 (1.3–16.9)</td>
<td>0.017</td>
</tr>
<tr>
<td>Change in QRS morphology and axis</td>
<td>10.9 (2.0–60.2)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Multivariable analysis

Model 1 (without QTc)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>9.6 (1.5–59.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Complete AVB*</td>
<td>2.1 (0.1–23.1)</td>
<td>0.54</td>
</tr>
<tr>
<td>R-R during AVB (for 100-ms increase)</td>
<td>1.1 (0.9–1.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>QRS width during AVB (for 10-ms increase)</td>
<td>0.9 (0.7–1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Change in QRS morphology</td>
<td>5.4 (1.4–21.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>Change in QRS axis</td>
<td>3.1 (0.7–13.5)</td>
<td>0.130</td>
</tr>
<tr>
<td>Change in QRS morphology and axis</td>
<td>10.7 (2.0–57.6)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Model 2 (with QTc)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc (for 10 ms increase)</td>
<td>1.3 (1.1–1.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Female sex</td>
<td>6.8 (1.1–41.9)</td>
<td>0.022</td>
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<tr>
<td>Complete AVB*</td>
<td>3.0 (0–14.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>R-R during AVB (for 100-ms increase)</td>
<td>1.1 (1.1–1.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>QRS width during AVB (for 10-ms increase)</td>
<td>0.9 (0.7–1.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>Change in QRS morphology</td>
<td>1.7 (0.3–8.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Change in QRS axis</td>
<td>1.4 (0.3–7.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Change in QRS morphology and axis</td>
<td>1.6 (0.1–18.1)</td>
<td>0.70</td>
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