Long QT Syndrome Type 3: Lessons from mouse models

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Bristol Heart Institute
Inherited Long QT Syndrome

- Prolonged QT interval
- Syncope & Sudden Cardiac Death
- Ventricular Arrhythmias (TdP)

# Inherited Channel Mutations

<table>
<thead>
<tr>
<th>LQTS</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Protein</th>
<th>Ion Current</th>
<th>Trigger</th>
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<tbody>
<tr>
<td>1</td>
<td>11p15.5</td>
<td>KCNQ1</td>
<td>KvLQT1</td>
<td>$I_{KS}$</td>
<td>Exercise, emotion</td>
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<td>2</td>
<td>7q35-36</td>
<td>KCNH2</td>
<td>HERG</td>
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<td>3</td>
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<td>Nav1.5</td>
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<td>4</td>
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<td>Ankyrin-B</td>
<td>$I_{Na-Kr}$, $I_{Na-Ca}$, $I_{Na}$</td>
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<td>MinK</td>
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<td>8</td>
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<td>Cav1.2</td>
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<td>9</td>
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<td>SCN4B</td>
<td>Navβ4</td>
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<td>Exercise, post-partum</td>
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</table>
Long QT syndrome type 3

- 1.7-8% genotyped patients

- Gain of function mutation in the Scn5a gene

- Encodes the $\alpha$-(pore-forming) subunit of the cardiac Na$^+$ channel

- Increased late Na$^+$ current ($I_{Na}$)

‘Window’ current hypothesis

L-type Ca$^{2+}$ channel ‘window’

EAD

‘Conditioned’ AP

Normal AP

INa
Genotype-specific triggers for cardiac events

QTc = 498, 497, 506 ms p = NS

Schwartz, P. J. et al. Circulation 2001;103:89-95
Lethal cardiac events according to 3 classified triggers in 3 genotypes

Schwartz, P. J. et al. Circulation 2001;103:89-95
Cumulative Probability of a Cardiac Event In LQT1, LQT2, and LQT3 Groups

LQT1 53%, LQT2 29%, LQT3 6%

Cumulative Probability of Death in LQT1, LQT2, and LQT3 Groups

20% of events fatal in LQT3 vs 4% in LQT1 & LQT2 (P<0.001)

Event-Free Survival in β-blocker treated patients

Cardiac events: 32% in LQT3 vs 10% in LQT1 & 23% in LQT2 (P<0.001)

Indications for Device Implantation

LQT3 patients need ICDs: True or False?

Poor prognosis in patients with events in the first year of life

2 months QTc 648 ms
1 week QTc 650 ms
2 months QTc 550 & 700 ms

## Rare Genetic Variants in LQTS Genes Identified in 26 SIDS Cases

<table>
<thead>
<tr>
<th>Genetic Variants</th>
<th>Classification</th>
<th>Functional Effect</th>
<th>No. of SIDS Cases</th>
<th>No. of Controls</th>
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<td>KCNE2</td>
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</table>

Life-threatening neonatal arrhythmia

Preterm female infant 35 weeks gestational age

Mice as Models for Investigating Cardiac Arrhythmias

Advantages

• Ease of molecular manipulation
• Common physiological structures
• Action potential heterogeneity
• Similar ionic currents
• Demonstrable atrial and ventricular arrhythmias

Disadvantages

• Mouse heart rate 600–700/min
• Shorter action potential duration without plateau
• $I_{to}$ is predominant repolarizing current (cf $I_{Kr}$ & $I_{Ks}$)
• Markedly different ECG appearance
Mouse Models of LQT3

- Mechanism of arrhythmogenesis
- Effect of β-blocker therapy
- Other therapeutic options
Mechanism of Arrhythmogenesis

- ΔKPQ 1505-1507 deletion in channel inactivation domain by homologous recombination in ES cells

1. Triggered Activity

2. Re-entry facilitated by transmural dispersion of repolarization (spatial)
Optical Mapping of Mouse re-entrant VT

Paced Electrogram Fractionation Analysis of LQT3 Mouse

S1S2 reduced on each occasion by 1 millisecond
Increased Electrogram Fractionation in LQT3 Mice

Transmural dispersion of repolarization

Wild Type Mouse

Increased TDR in LQT3 Mice

Increased TDR in LQT3 Mice

Proposed Arrhythmogenesis in LQTS

- Prolonged QT Interval
  - Early After Depolarizations
  - Triggered Activity
  - Dispersion of repolarization (Spatial and temporal)
  - Functional conduction block
  - pVT (TdP)
  - Re-entrant excitation
Effect of β-blocker therapy
Protective effect of β-adrenoreceptor agonist isoproterenol

“Scn5aΔ/+ are mice are sensitive to rate accelerations or premature beats... β-blockers would suppress these triggers during sudden sympathetic surges “

“However, β-receptor activation was anti-arrhythmic, possibly shortens the action potential, reduces transmural dispersion”

Propranolol increases electrogram fractionation

Propranolol suppresses EADs in LQT3 Mice

Propranolol *increases* TDR in LQT3 Mice

Propranolol causes AV block in Ambulant LQT3 Mice

SCn5a Δ/+ KPQ Mouse

100 ms

What other potential drugs?
Therapeutic Targets

![Diagram showing Therapeutic Targets](image-url)
Mexiletine
Effect of Mexiletine on QTc in LQT3 Patients

Mexiletine shortens APD during bradycardia in LQT3 Mouse Model

Mexiletine prevents inducible pVT in LQT3 Mouse Model

Nifedipine
Results

Results

Percentage of MAPs displaying EADs

- **Scn5a+/Δ** alone
- **Scn5a+/Δ** + 1 nM Nifed
- **Scn5a+/Δ** + 10 nM Nifed
- **Scn5a+/Δ** + 100 nM Nifed
- **Scn5a+/Δ** + 300 nM Nifed
- **Scn5a+/Δ** + 1 µM Nifed
Results

- $IC_{50} = 79$ nM

- Nifedipine exerts $IC_{50}$ block of $I_{Ca-L}$ at 50nM at holding potential of -40 mV in isolated guinea pig myocytes

Results

The bar chart shows the number of hearts with and without VT under different conditions:

- Scn5a+/Δ alone
- Scn5a+/Δ + 1nM Nifed
- Scn5a+/Δ + 10 nM Nifed
- Scn5a+/Δ + 100 nM Nifed
- Scn5a+/Δ + 300 nM Nifed
- Scn5a+/Δ + 1 µM Nifed

The x-axis represents different conditions, and the y-axis represents the number of hearts. The chart indicates the number of hearts with VT (shaded) and no VT (white).
Results

P > 0.05
Results

P > 0.05

[Bar chart showing the effect of nifedipine on APD90 (Action Potential Duration at 90% repolarization) in WT alone and with various concentrations of nifedipine (1nM, 10nM, 100nM, 300nM, 1µM).]

- Endo APD90
- Epi APD90
- ΔAPD90

WT alone, WT + 1nM Nifed, WT + 10nM Nifed, WT + 100nM Nifed, WT + 300nM Nifed, WT + 1µM Nifed
Results

Scn5a+/Δ  Scn5a+/Δ  WT  WT
+ 1 µM nifedipine  + 1 µM nifedipine

VERP (ms)

P > 0.05
Results

300 nM Nifedipine inhibits L-type Ca\(^{2+}\) current in ΔKPQ Scn5a KPQ mice

![Graph showing the effect of Nifedipine on Ca\(^{2+}\) current]
300 nM Nifedipine does not inhibit Na⁺ current in ΔKPQ Scn5a KPQ mice
Nicorandil
Effect of Nicorandil on Clinical TWA

26 year old Female with nocturnal TdP
QTc 620 ms

Effect of Nicorandil on Human MAPs

MAPs recorded from inferoseptal LV

Anti-arrhythmic effects of Nicorandil in LQT3 Mouse Model

Nicorandil reduces spatial TDR

Nicorandil reduces *temporal* TDR

Untreated SCN5a +/Δ

SCN5a +/Δ & Nicorandil 20 µM

Nicorandil reduces *temporal* TDR

Summary

• LQT3 remains lethal in high risk groups
• Identifiable lower risk groups
• Triggered initiation maintained via re-entry (spatial/temporal heterogeneity of repolarization)
• Anti-adrenergic strategy reduces ‘triggers’
• Mexiletine/nifedipine/nicorandil offer anti-arrhythmic effects
Acknowledgements

- Dr Andrew Grace
- Prof Chris Huang
- Dr Matthew Killeen
- Dr Sandeep Hothi
ECG Characteristics

# LQTS Management Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence†</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No participation in competitive sports</td>
<td>I</td>
<td>Includes patients with the diagnosis established by means of genetic testing only</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>I</td>
<td>For patients who have QTc-interval prolongation (&gt;460 msec in women and &gt;440 msec in men)</td>
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<td></td>
<td>IIa</td>
<td>For patients with a normal QTc interval</td>
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<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>I</td>
<td>For survivors of cardiac arrest</td>
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<tr>
<td></td>
<td>IIa</td>
<td>For patients with syncope while receiving beta-blockers</td>
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<tr>
<td></td>
<td>IIb</td>
<td>For primary prevention in patients with characteristics that suggest high risk; these include LQT2, LQT3, and QTc interval &gt;500 msec‡</td>
</tr>
</tbody>
</table>

* Data are from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology, in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Guidelines are adapted from Zipes et al.52
† Levels of evidence are as follows: I, conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective; II, conditions for which there is conflicting evidence or divergence of opinion, or both, about the usefulness and efficacy of a procedure or treatment; IIa, conditions for which the weight of evidence or opinion is in favor of usefulness and efficacy; and IIb, conditions for which the usefulness and efficacy are less well established by evidence or opinion.
‡ Other indicators of risk may include the specific site of mutation14 and the postpartum period.18