Congenital Long QT Syndrome: Clinical Aspects and Management Advice

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• Nothing to disclose
Congenital Long QT Syndrome

The most common inherited arrhythmia
## Long QT syndrome

<table>
<thead>
<tr>
<th>LQTS Type</th>
<th>Gene</th>
<th>Protein</th>
<th>Current</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>Kv7.1</td>
<td>IKs↓</td>
<td>40%–45%</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2</td>
<td>KV11.1</td>
<td>IKr↓</td>
<td>30%–35%</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>Nav1.5</td>
<td>INa↑</td>
<td>10%</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK2</td>
<td>Ankyrin-B</td>
<td>Na+/K+↓</td>
<td>1%</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1</td>
<td>MinK</td>
<td>IKs↓</td>
<td>1%</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>MiRP1</td>
<td>IKr↓</td>
<td>Rare</td>
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<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>Kir2.1</td>
<td>IK1↓</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1C</td>
<td>CaV1.2</td>
<td>ICa-L↑</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Caveolin 3</td>
<td>INa↑</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>SCNβ4 subunit</td>
<td>INa↑</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>Yotiao</td>
<td>IKs↓</td>
<td>Rare</td>
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<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>Syntrophin-α1</td>
<td>INa↓</td>
<td>Rare</td>
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<tr>
<td>LQT13</td>
<td>KCNJ5</td>
<td>Kir3.4</td>
<td>IKACH↓</td>
<td>Rare</td>
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<tr>
<td>LQT14</td>
<td>CALM1</td>
<td>Calmodulin 1</td>
<td>Calcium signalling</td>
<td>Rare</td>
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<tr>
<td>LQT15</td>
<td>CALM2</td>
<td>Calmodulin 2</td>
<td>Calcium signalling</td>
<td>Rare</td>
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<tr>
<td>LQT16</td>
<td>TRDN</td>
<td>Triadin</td>
<td>ICa-L↑</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Jervell and Lange-Nielsen syndrome (autosomal recessive)**

| JLN1   | KCNQ1 | Kv7.1 | IKs↓ | Rare |
| JLN2   | KCNE1 | MinK  | IKs↓ | Rare |
Congenital Long QT Syndrome:

- LQTS: SNUH experience
- Clinical Aspects
- Management Advice
LQTS. SNUH experience

- 105 LQTS patients (female 48; 46%), 2000~2017
- 67% symptomatic, 33% asymptomatic
- The first symptom: 10.5 years (0.00 – 80).
LQTS. SNUH experience

- Fetal arrhythmia: 4%
- Bradycardia: 2%
- Palpitation: 3%
- Dystonia: 7%
- Emotion: 19%
- Sleep: 19%
- Exercise: 30%
- Unidentified: 14%
- Anesthesia: 14%

First presentation symptom:
- Syncope or seizure: 54%
- Syncope with stress during exercise: 68%
- Syncope without stress: 29%
Genotype in 90 patients

'Second hit'
Compound/Digenic heterozygosity
8/90 (8.9%)

Multiple LQTS(LQTMs)
KCNH2 + SCN5A
KCNQ1 + TAZ
ANK2 + RyR2(CPVT)

Jervell and Lange-Neilsen syndrome:
- All had compound heterozygotic mutations
  - of deletion and missense mutation of KCNQ1
1) KCNQ1 exon 1-16 combined heterozygous
   (i) c.828-830delCTC, p.S277del deletional mutation
   (ii) c.921G>A, p.V307V splicing mutation,
3) KCNQ1 exon 7-10 large deletion and c.1893dup frame shift mutation
4) KCNQ1 exon 8-11 large deletion and c.684-2A>G(IVS4) mutation.

Ahn KJ et al, unpublished
Case. 6 y old girl visited ER d/t seizure with long Hx of intractable epilepsy for 5 y, department of NR and Hx of rescued cardiac arrest (3y old)

ECG; long QT QTc>580ms, T alternas, TdP
Dx: LQTS propranolol

SCN5A; 3988G>C (p.Ala1330Pro)
Dx: LQTS type 3

T wave alternans,

polymorphic VT, VF
LQT3 6y/F
Epicardial ICD implantation
using tranvenous ICD lead, Dual chamber pacing
LQT3  6y/F. initially frequent ICD shock therapy
→ Now, 11 years of age, no sx on propranolol + high dose mexiletine
Case. 13y/F
frequent syncope and seizure like episode
rescued cardiac arrest, during sleeping

*KCNJ2 mutation (+); LQT7
 c.245G>A p.Arg82Gln (R82Q)*

Andersen-Tawil syndrome
Andersen-Tawil syndrome Family
with periodic paralysis, KCNJ2 Mutation family (LQTS 7)

Andersen-Tawil syndrome
• Hypokalemic periodic paralysis
• Ventricular arrhythmia
• Skeletal anomalies
• Facial characteristics

Hypertelorism
low-set ears, small mandible and clinodactyly

KCNJ2 G215D

Journal of Child Neurology
25(4) 490–493
Sudden Cardiac Arrest during Anesthesia in a 30 m old boy with Syndactyly: A Case of **Timothy Syndrome** (LQTS 8)

**CACNA1C** mutation

Missense mutation c.1216G>A in exon 9

Exon 9

intron

Timothy Syndrome (LQTS 8)

- **L-type calcium channel Cav1.2 mutation**
- Severe QTc prolongation (often with neonatal and fetal 2:1 AV block → bradycardia)
- **Multisystem involvement**
  - **Face**: distinct craniofacial features
    - Round face, baldness, abnormal dentition
  - Congenital heart defects
  - **Syndactyly**
  - **Hypoglycemia**
  - Immunologic abnormalities
  - Neurological disease:
    - Developmental delay and autism

(Cell 2004;119:19–31)
LQTS. SNUH experience

- No therapy: 10
- Implantable cardioverter defibrillators (ICD) and/or left cardiac sympathetic denervation (LCSD): 30
- Mexiletine or Flecaïnide add: 6 (4 of LQT3, 2 of LQT4-7)
- Beta-blocker: 56 (80%)

Ahn KJ et al, unpublished
LQTS. SNUH experience

- All survived except one LQT3 patient with cardiomyopathy
- Breakthrough cardiac event-free survival curve for entire genetic verified long QT syndrome.

Ahn KJ et al, unpublished
# Phenotype–genotype-related risk stratification

<table>
<thead>
<tr>
<th>Clinical risk factors(^a)</th>
<th>Combined risk factors(^a)</th>
<th>Genetic risk factors(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely high risk (≥80%)</td>
<td>Timothy syndrome (LQT-8)</td>
<td>Jervell–Lange-Nielsen syndrome</td>
</tr>
<tr>
<td>QTc ≥ 600 ms</td>
<td></td>
<td></td>
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<tr>
<td>≥10 cardiac events &lt; age 18 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk (≥50%)</td>
<td></td>
<td>Compound or digenic heterozygosity</td>
</tr>
<tr>
<td>QTc ≥ 550 ms</td>
<td>LQT-1 + male 0–14 years old</td>
<td>Certain LQT-1 mutations</td>
</tr>
<tr>
<td>≥2 but &lt; 10 cardiac events before age 18 years</td>
<td>LQT-2 + female 15–40 years old</td>
<td>C-loop mutations</td>
</tr>
<tr>
<td>Cardiac event &lt; age 7 years</td>
<td></td>
<td>A341V</td>
</tr>
<tr>
<td>Cardiac event on appropriate beta-blocker treatment</td>
<td></td>
<td>Certain LQT-2 mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pore mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CALM1 or CALM2 mutations</td>
</tr>
<tr>
<td>Intermediate risk (30–49%)</td>
<td></td>
<td>LQT-3</td>
</tr>
<tr>
<td>QTc = 500–549 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 cardiac events &lt; age 18 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (&lt;30%)</td>
<td></td>
<td>LQT-1 minor genotypes</td>
</tr>
<tr>
<td>QTc &lt; 500 ms</td>
<td>LQT-1 + female 0–14 years old</td>
<td></td>
</tr>
<tr>
<td>No cardiac event &lt; age 18 years</td>
<td>LQT-2 + male 0–40 years old</td>
<td></td>
</tr>
</tbody>
</table>

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\(^a\) See reference [1].

Current Opinion 2017
### Management of LQTS

- Beta blocker therapy
- Surgical left cardiac sympathetic denervation (LCSD)
- Device therapy: pacemaker, ICD
- Life style modification
- Genotype specific management

#### Beta blocker therapy
- **Up to 97% reduction in the risk of CA/SCD**
- **64% reduction in the risk of CA/SCD in adolescent period**
- **Ideal beta blocker**
  - nonselective β blockers with crossing blood brain barrier
  - _nadolol_ and _propranolol_ are commonly used
    - Na channel blocking effect +
  - _Nadolol_: one of the more effective drugs, hydrophilic long-acting, noncardioselective
β blockers

Close functional coupling of β-Adrenergic receptor and $I_{ks}$ signaling

LQT1; KCNQ1 mutation ($I_{ks}$)
LQT5; KCNE1 ($I_{ks}$)
LQT8; CACNA1C ($I_{CaL}$)
β blocker failure

- β blocker failure
  - 10% in LQT1
  - 23% in LQT2
  - 32% in LQT3

- β blocker failure in LQT1
  - noncompliance
  - the use of QT prolonging drugs

Percentage of patients remaining continuously on prescribed β-blockers over time after initiation of β-blocker therapy.

Circulation 2008; 116: 345–52
Circulation 2008; 116: 345–52
Circulation 2007; 115: 2481–9
Left Cardiac Sympathetic Denervation

• Since 1970 for LQTS
• left cervicothoracic sympathectomy
• high thoracic left sympathectomy

**Indication of LCSD**

experience of syncope despite beta-blocker therapy
LQT1: BB intolerance
arrhythmia storms and shocks with an ICD

• Thoracotomy
• Video assisted thoracoscopic surgery (VATS)

Genotype specific consideration

**LQT1 Patients**

- **Higher risk:**
  - Mutations in the transmembrane region (C-loop mutations)
  - Boy 0-14y old

- **Very high efficacy of beta blocker: nadolol, atenolol, propranolol>> metoprolol**
  - very low rate of life-threatening cardiac events with beta blocker
    (1.2% for 4.7 years)

- **Gene carrier of LQT1; <15y, boys**
  should be treated with beta-blockers

- Beta blocker resistant pts; **LCSD** and ICD

- Behavioral Issue;
  - LQT1 patients were not be allowed to participate in competitive sports.
  
  → Recent change in recommendation;
  
  ‘**return-to-play’ approach in USA under BB,**
  
  shared decision making, with AED

  - Swimming; hazardous, high association with swimming and syncope

  - Avoid QT prolonging drug
Genotype specific consideration

**LQT2 Patients**

- **Higher risk**
  - Missense mutations in the transmembrane pore regions and N-terminus
  - Female 15-40y old
- **Lower efficacy of beta-blocker therapy** in LQT2 patients
  - *nadolol, propranolol*
- LQT2 pts with beta blocker should be carefully followed up for residual symptoms → implantation of an **ICD**
- **Environmental Issue:**
  - *Avoidance of unexpected auditory stimuli* in the bedroom that can cause a startle reaction
  - **High risk during postpartum time:** increased risk (HR 2.7)
  - **Maintain a serum K level 4 mEq/L,** especially vulnerable when their potassium levels are low
  - Avoid QT prolonging drug
Genotype specific consideration

• **LQT3 Patients**
  
  – Events tend to occur at rest or during sleep (at slower heart rates).
  – Mixed phenotypes, ‘**sodium channel overlap syndrome**’

• **Beta-blocker therapy**: propranolol
  
  higher break through events rate (32% beta blocker failure)
  
  - 83% reduction in cardiac events in women

• Early primary **ICD** intervention in high-risk LQT3.

• **Additional sodium channel blockers**
  
  – mexiletine, flecainide ;
    
    ECG: may shorten the QT interval; limited data on prognosis
  
  – Ranolazine; ↓I(Kr), ↓ late I(Na)) → ↓QTc

• **Pacemaker** for associated bradycardia
LQT3
Mexiletine

Lidocaine test
Shorten QT interval by IV lidocaine

Pre-  After-

LQTS with bradycardia
functional 2:1 AV block

Mexiletine:
shorten the QTc interval in LQT3 patients,
reducing arrhythmic events with no pro-arrhythmic complications

Circulation 1997;96:2038–47
Proposed management strategy in LQTS

**LQTS 0-40 years**

**Low risk pts**
- No Sx and QTc <500ms
- LQT1 female 0-14 yrs
- LQT2 male and female 0-14yrs
- LQT1 male and female 15-40yrs
- LQT2 male 15-40yrs

  - Life style modification
    - Consider BB on individual basis
  - Syncope or inc QTc to >500ms during FU
  - Initiate BB

**High risk LQT1,2**
- One or more of the following:
  - Prior syncope without BB
  - QTc>500ms
  - LQT1 male 0-14yrs
  - LQT2 female 15-40yrs

  - Life style modification
    - Routine BB
  - Consider ICD ; BB noncompliance, intolerance
  - Syncope with BB
  - ICD+medication
    - LCSD in LQT1

**LQT3 and other types**
- Routine BB
  - Add Mexiletine in LQT3
  - Add Flecainide in LQT7

**Secondary prevention pts**
- Prior ACA

**ICD + BB**
- Frequent ICD Shock
- Add medication
  - LCSD
  - RFCA for triggering PVC