Dynamic and Abnormal T Wave morphologies in Long QT Syndrome: A key Word for Clinical Diagnosis
Minoru Horie
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COI:
Dynamic and Abnormal T Wave morphologies in Long QT Syndrome: A key Word for Clinical Diagnosis

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Department of Cardiovascular Medicine, Shiga University of Medical Science

None to declare in regard to this presentation
Causative genes for LQTS

<table>
<thead>
<tr>
<th>Geneotype</th>
<th>Gene</th>
<th>Function</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>(I_{Ks})↓</td>
<td>30-35%</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2</td>
<td>(I_{Kr})↓</td>
<td>25-30%</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>(I_{Na})↑</td>
<td>5-10%</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK2</td>
<td>(I_{Na,K})↓, (I_{NCX})↓</td>
<td>1-2%</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1</td>
<td>(I_{Ks})↓</td>
<td>1%</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>(I_{Kr})↓</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>(I_{K1})↓</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1c</td>
<td>(I_{Ca,L})↑</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>(I_{Na})↑</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>(I_{Na})↑</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>(I_{Ks})↓</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>(I_{Na})↑</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT13</td>
<td>KCNJ5</td>
<td>(I_{KACH})↓</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT14</td>
<td>CALM1</td>
<td>(I_{Ca,L})↑</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT15</td>
<td>CALM2</td>
<td>(I_{Ca,L})↑</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>LQT16</td>
<td>CALM3</td>
<td>(I_{Ca})↑</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

1. Mutations are identified in nearly 70% of the LQTS patients.
2. More than 90% of the identified mutations are in LQT1-3.

ECG T-Wave Pattern in Congenital LQTS

$I_{Na}$
LQT3 (SCN5A)

$I_{Kr}$
LQT2 (HERG)

$I_{Ks}$
LQT1 (KVLQQT1)

II

aVf

V5

Late-appearing T wave

Notched T wave

Low and prolonged T wave

Broad-based prolonged T wave

Exercise Stress Test in a 23 yo female pt

Pre Exercise

HR 64/min

V5

QTc 464ms

Post Exercise

HR 110/min

V5

QTc 647ms

Exercise prolonged QTc and T wave morphology!!

(Takenaka et al, Circulation 2003)

Suspected LQT1
Genetic test

KCNQ1 exon 7

Control

A344E (C1031A)
Symbols in grey: phenotype positive
+ : genotype positive, - genotype negative

2019/6/24
T-wave Morphology Combination Score (MCS)


\[ \text{MCS} = \text{Asymmetry} + \text{Notch} + 1.6 \times \text{Flatness} \]

MCS = 0.73
MCS = 0.99
MCS = 2.53
T waves are distinct among genotypes.

EDITORIAL COMMENTARY

Long QT syndrome presents not only as QT prolongation but also as abnormal T-wave morphology.

Minoru Horie, MD, PhD

From the Department of Cardiovascular and Respiratory Medicine, St. Luke’s International Hospital, Otsu, Japan.
T wave alternans is a rare but most typical ECG features showing an alternative beat-to-beat change of T wave morphology.

Its presence indicates electrophysiological instability which leads to malignant ventricular arrhythmias.

Often associated with a marked prolongation of QT interval (long QT syndromes)
LQT Type 8 (or esp. Timothy syndrome)
LQT Type 14-16, calmodulin 1-3
Fatal cardiac arrhythmias in the early stage of life.
Require often ICD implantation
T wave alternans
(bidirectional VT in CPVT-type CALM mutations)
Splawski I et al. CaV1.2 Calcium Channel Dysfunction Causes a Multisystem Disorder Including Arrhythmia and Autism. Cell 119, 19-31, 2004

Bradycardia due to functional AVB (94%) was even more frequent than VT (71%).

T wave alternans and functional 2:1 AVB: hallmarks of severe LQTS
Timothy Syndrome (LQT8: CACNA1C-I_{Ca,L})

- Splawski I et al. CaV1.2 Calcium Channel Dysfunction Causes a Multisystem Disorder Including Arrhythmia and Autism. Cell 119, 19-31, 2004
LTCC and E-C Coupling in Heart

Ca-induced Ca release (CICR)
Ca dependent inactivation of LTCC (CDI)
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LTCC and E-C Coupling in Heart

Ca-induced Ca release (CICR)
Ca dependent inactivation of LTCC (CDI)
T wave alternans: 6 mo girl baby

- Embryonic bradycardia
- At 2 mo, collapse due to TdP (VF)
- QT prolongation with T wave alternans and 2:1 AV block
- From 4 mo, episodes of seizures unrelated to TdPs
- Dysmorphic features (a high arched palate, full cheeks, and congenital clasped thumb, but no syndactyly)
- Multiple hospital admissions for respiratory infections

→ Timothy syndrome (or LQT8)
T wave alternans: 6 mo girl baby
T wave alternans: 6 mo girl baby
functional 2:1 AVB
T wave alternans: 6 mo girl baby mexiletine effect

Before med.

Mexiletine initiation

Mexiletine stable
Genetic Testing using a NGS: MiSeq

Targeted panel

SCN5A, SCN10A, SCN1B, SCN3B, GPD1L, CACNA1C, CACNB2, CACNA2D1, HCN4, KCND3, KCNE3, KCNE5, KCNJ8, MOG1 (RANGRF), TRPM4 KCNQ1, KCNH2, ANKB, KCNE1, KCNE2, KCNJ2, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5, RYR2, CASQ2, CALM1, CALM2, CALM3, TRDN, KCNE4, TCAP, SLC8A1, DSP, PKP2, DSG2, DSC2, JUP, GJA5, GJA1, CAMK2D, KCNN2, KCNA5, KCNIP2, LMNA
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SCN5A, SCN10A, SCN1B, SCN3B, GPD1L, CACNA1C, CACNB2, CACNA2D1, HCN4, KCND3, KCNE3, KCNE5, KCNJ8, MOG1 (RANGRF), TRPM4, KCNQ1, KCNH2, ANKB, KCNE1, KCNE2, KCNJ2, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5, RYR2, CASQ2, CALM1, CALM2, CALM3, TRDN, KCNE4, TCAP, SLC8A1, DSP, PKP2, DSG2, DSC2, JUP, GJA5, GJA1, CAMK2D, KCNN2, KCNA5, KCNIP2, LMNA

CACNA1C c.1235g>t, p.R412M (Arg → Met)
CACNA1C: c1235g>t, p.R412M

Heterozygous variant
Topology of L-type Calcium Channel alpha-subunit
Functional Analysis of LTCC: Patch clamp study on pathologic mutations
CACNA1C R412M mutation produced a significant late Ca current.
CACNA1C R412M mutation disrupted a voltage-dependent inactivation gate of LTCC
In summary

- LQTS = QT prolongation plus abnormal T waves.
- Especially, T wave alternans is a rare but typical ECG features in LQTS.
- TWA associated with functional 2:1 AV block and sinus brady may suggest the genotypes of LQT8 and 14-16 calmodulin).
Thank YOU for your ATTENTION!

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