Long QT Syndrome

Lia Crotti

Rome Cardiology Forum 2014

31st January

University of Pavia,
IRCCS Istituto Auxologico Italiano, Milan, Italy
Institute of Human Genetics, HelmholtzZentrum Munchen, Neuherberg, Germany
Congenital Long QT Syndrome

- Genetically transmitted
- Manifests in young age
- Prolonged QT interval
- Frequent syncope or cardiac arrest during emotional or physical stress
- High mortality among symptomatic and untreated patients
Long QT Syndrome: genetic basis

80% of the cases with a clear diagnosis
MP, 18 yrs, male SD  QTc V2  621 ms  QTc V5  595 ms
DIAGNOSIS

• Easy in typical cases presenting with QT prolongation and arrhythmic events

• In borderline cases diagnostic criteria were proposed to support the diagnostic process.

The idiopathic long QT syndrome: pathogenetic mechanisms and therapy

P. J. Schwartz and E. Locati

Eur Heart J 1985
# QTc Behavior During Exercise and Genetic Testing for the Long-QT Syndrome

Peter J. Schwartz, MD; Lia Crotti, MD, PhD

## Electrocardiographic Findings

<table>
<thead>
<tr>
<th></th>
<th>Electrocardiographic Findings</th>
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<tbody>
<tr>
<td>A</td>
<td>QTc</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 480 ms</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>460 – 479 ms</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>450 – 459 (male) ms</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>QTc 4th minute of recovery from exercise stress test ≥ 480 ms</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>TORSADE DE POINTES</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>T WAVE ALTERNANS</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>NOTCHED T WAVE IN 3 LEADS</td>
<td>1</td>
</tr>
<tr>
<td>F</td>
<td>LOW HEART RATE FOR AGE</td>
<td>0.5</td>
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## Clinical History

<table>
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<tr>
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<tr>
<td>A</td>
<td>SYNCOPE</td>
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<tr>
<td></td>
<td>WITH STRESS</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>WITHOUT STRESS</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>CONGENITAL DEAFNESS</td>
<td>0.5</td>
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## Family History

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A</td>
<td>FAMILY MEMBERS WITH DEFINITE LQTS</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>UNEXPLAINED SUDDEN CARDIAC DEATH BELOW AGE 30 AMONG IMMEDIATE FAMILY MEMBERS</td>
<td>0.5</td>
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## Schwartz Score

<table>
<thead>
<tr>
<th>Score Range</th>
<th>Probability of LQTS</th>
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<tr>
<td>≤ 1 point</td>
<td>Low probability of LQTS</td>
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<tr>
<td>1.5 to 3 points</td>
<td>Intermediate probability of LQTS</td>
</tr>
<tr>
<td>≥ 3.5 points</td>
<td>High probability of LQTS</td>
</tr>
</tbody>
</table>

_Circulation 2011_
HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

Silvia G. Priori, MD, PhD, (HRS Chairperson)¹, Arthur A. Wilde, MD, PhD, (EHRA Chairperson)², Minoru Horie, MD, PhD, (APHRS Chairperson)³, Yongkeun Cho, MD, PhD, (APHRS Chairperson)⁴, Elijah R. Behr, MA, MBBS, MD, FRCP⁵, Charles Berul, MD, FHR, CCDS⁶, Nico Blom, MD, PhD⁷,*-¹, Josep Brugada, MD, PhD⁸, Chern-En Chiang, MD, PhD⁹, Heikki Huikuri, MD¹⁰, Prince Kannankeril, MD¹¹,‡, Andrew Krahn, MD, FHR¹², Antoine Leenhardt, MD¹³, Arthur Moss, MD¹⁴, Peter J. Schwartz, MD¹⁵, Wataru Shimizu, MD, PhD¹⁶, Gordon Tomaselli, MD, FHR¹⁷,‡, Cynthia Tracy, MD¹⁸,%%

Heart Rhythm, Vol 10, No 12, December 2013
Expert Consensus Recommendations on LQTS Therapeutic Interventions

Class I

1. The following lifestyle changes are recommended in all patients with a diagnosis of LQTS:
   a) Avoidance of QT-prolonging drugs (www.qtdrugs.org)
   b) Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss.

2. Beta-blockers are recommended for patients with a diagnosis of LQTS who are:
   a) Asymptomatic with QTc ≥470 ms and/or
   b) Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF).

3. Left cardiac sympathetic denervation (LCSD) is recommended for high-risk patients with a diagnosis of LQTS in whom:
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4. ICD implantation is recommended for patients with a diagnosis of LQTS who are survivors of a cardiac arrest.

5. All LQTS patients who wish to engage in competitive sports should be referred to a clinical expert for evaluation of risk.

Class IIa

6. Beta-blockers can be useful in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.

7. ICD implantation can be useful in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.

8. LCSD can be useful in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.

9. Sodium channel blockers can be useful, as add-on therapy, for LQT3 patients with a QTc > 500 ms who shorten their QTc by >40 ms following an acute oral drug test with one of these compounds.
Survival after the first syncope in 233 LQTS patients

*Schwartz PJ, AHJ 1985*
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Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Higher Recurrence of Events Under Metoprolol

Priya Chockalingam, MBBS, PtID,† Lia Crotti, MD, PtID,‡ Giulia Girardengo, MD,‡
Jonathan N. Johnson, MD,¶ Katy M. Harris, MS, RN,¶ Jeroen F. van der Heijden, MD, PtID,#
Richard N. W. Hauer, MD, PtID,# Britt M. Beckmann, MD,** Carla Spazzolini, DVM, MS,‡
Roberto Rordorf, MD,§ Annika Rydberg, MD, PtID,†† Sally-Ann B. Chur, MBChB, MSc (MED), PtID,†
Markus Fischer, MD,‡‡ Freek van den Heuvel, MD, PtID,§§ Stefan Kääb MD, PtID,**
Nico A. Blom, MD, PtID,†¶ Michael J. Ackerman, MD, PtID,¶ Peter J. Schwartz, MD,‡¶†**
Arthur A. M. Wilde, MD, PtID*

(J Am Coll Cardiol 2012;60:2092–9)

383 LQT1/LQT2 ptz

27% symptomatic
CA/SD despite BB therapy
271 ptz. LQTS – all symptomatic

LQT1  4%
LQT2  4%
LQT3  17%

Schwartz et al., 2001
“All 3 centers recommended implantation for .... identification of an SCN5A mutation.”

“No one with a known SCN5A mutation has had an appropriate ICD discharge”
Who Are the Long-QT Syndrome Patients Who Receive an Implantable Cardioverter-Defibrillator and What Happens to Them?

Data From the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry

Peter J. Schwartz, MD; Carla Spazzolini, DVM; Silvia G. Priori, MD, PhD; Lia Crotti, MD, PhD; Alessandro Vicentini, MD; Maurizio Landolina, MD; Maurizio Gasparini, MD; Arthur A.M. Wilde, MD; Reinoud E. Knops, MD; Isabelle Denjoy, MD; Lauri Toivonen, MD; Gerold Mönnig, MD; Majid Al-Fayyadh, MD; Luc Jordaens, MD; Martin Borggrefe, MD; Christina Holmgren, MD; Pedro Brugada, MD, FAHA; Luc De Roy, MD; Stefan H. Hohnloser, MD; Paul A. Brink, MD

Population Under Study

• Patients 233
• Follow-up 5 years
• 9% asymptomatic

(Circulation. 2010;122:1272-1282.)
Genotype and cardiac events before ICD implant

- **LQT1**
  - n=37
- **LQT2**
  - n=61
- **Double mutations**
  - n=15
- **LQT3**
  - n=31

**p<0.001**
All LQT3 patients need an ICD: True or false?

Peter J. Schwartz, MD, FHRS, Carla Spazzolini, DVM, MS, Lia Crotti, MD, PhD

(Hearth Rhythm 2009;6:113–120)
Cardiac Events in LQT3 patients on BB therapy.

Mean FU 9 years

Events in the first year of life (4/22, 18%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Count (Percentage)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden Death (SD)</td>
<td>3 (14%)</td>
<td>βB; βB; βB +Mexiletine</td>
</tr>
<tr>
<td>Cardiac Arrest (CA)</td>
<td>1 (4.5%)</td>
<td>βB+PM+Mexiletine</td>
</tr>
</tbody>
</table>

No events in the first year of life (18/22, 82%)

| SD/CA                  | 0                  |
| Syncope                | 2 (11%)            | LCSD; βB           |
| No symptoms            | 16 (89%)           | βB and/or LCSD     |
In TG DeltaKPQ-SCN5A mice, drug-induced life-threatening arrhythmias were observed in 55% of the mice. By contrast, none of the mice pre-treated with propranolol developed malignant arrhythmias.
Sodium Channel Mutations and Risk of Cardiac Events in Long QT Syndrome Type 3

Wilde AM, AJ Moss, MJ Ackerman, PJ Schwartz et al – In preparation

- 407 LQT3 pts
- 107 pts on β-blocker therapy
- 7 deaths (4 with CA in the 1st year of life)

Mortality for pts on β-blocker therapy w/out events in the 1st year of life:

2.8%
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LQTS patients with a CA in the first year of life are a small (<2%) but very-high risk group for subsequent near-fatal and fatal cardiac events during the first decade of life.
An ACA in the first year of life was associated with an HR of 23.4 (p 0.01) for a subsequent ACA/LQTS-related SCD during the 1- to 10-year period.
Prevalence of Long-QT Syndrome Gene Variants in Sudden Infant Death Syndrome

Marianne Arnestad, MD*; Lia Crotti MD*; Torleiv O. Rognnum, MD; Roberto Insolia, BSc; Matteo Pedrazzini, BSc; Chiara Ferrandi, BSc; Ashild Vege, MD; Dao W. Wang, MD; Troy E. Rhodes, MD, PhD; Alfred L. George, Jr, MD; Peter J. Schwartz, MD

(Circulation. 2007;115:361-367.)

201 SIDS cases
227 controls

A functional mutation in LQTS genes was identified in:

19/201 (9.5%)

95% C.I. 5.8-14.4%
Long QT Syndrome–Associated Mutations in Intrauterine Fetal Death

91 cases with unexplained IUFD

Antepartum Intrauterine fetal Demise (IUFD) and Long QT Syndrome
Malignant LQTS causing life-threatening arrhythmias during the perinatal period

- Life-threatening arrhythmias starting in utero and/or during the first months of life
- ECG signs of severe electrical instability: 2:1 functional AV block, T-wave alternans
- SCD could be the first manifestation of the disease: diagnosis only through molecular autopsy
Life-threatening arrhythmias in the first year of life in the Pavia’s database:

TOT 12:
- 3 Jervell Lange-Nielsen (double KCNQ1 mutation)
- 9 Romano Ward

**Pie Chart**

- **3** Jervell Lange-Nielsen
- **1** Romano Ward Patients
- **1** KCNQ1
- **4** SCN5A
- **1** KCNH2
- **Unknown**
Proband 1

Presentation

- VF at 6 month (16 VF in the first 2 years of life)
- QTc 630 ms
- T wave alternans (TWA)
- Intermittent 2:1 AV block → ICD
Proband 1

Basal ECGs

TdP / VF onset
Proband 1

T Wave Alternans
Proband 2

Presentation

- Fetal bradycardia at 21 weeks gestation
- First VF at 3 weeks and then recurrent episodes
- Bradycardia, QTc 690 ms, 2:1 AV block, T-wave alternans
- Right parietal lobe cerebral infarction
- Developmental delay
Proband 2

Basal ECG at birth

T-wave alternans

2:1 AV block
Whole Exome Sequencing

- Performed on the 2 probands and their parents
- Searched for novel variants
  1. Not inherited (de novo)
  2. Predicted to have deleterious effects
Whole Exome Sequencing

Proband 1

- Total coding variants: 21,191
- De novo: 31
- Nonsynonymous: 24
- Novel: 2
- Sanger validated: 1

Proband 2

- Total coding variants: 18,735
- De novo: 36
- Nonsynonymous: 26
- Novel: 8
- Sanger validated: 2
Calmodulin Mutations Associated with Recurrent Cardiac Arrest in Infants

Circulation. published online February 6, 2013;
Calmodulin Mutations

Potential Mechanisms

- Calmodulin serves for Ca\textsuperscript{2+}-dependent inactivation of L-type Ca\textsuperscript{2+} channels.
- Calmodulin is required for Iks activation during sympathetic activation.
- Calmodulin is involved in INa inactivation.
D130 G, a *CALM 1* mutation identified in 2 of our patients, when expressed in a fetal isoform evokes a persistent $I_{Na}$ significantly larger compared to that of wild-type $Na_v 1.5$. The preferential effect of CaM-D130G on fetal $Na_v 1.5$ helps explain the early onset of arrhythmia.
VALIDATION

• Cohort of 82 LQTS patients genotype-negative / phenotype-positive

• Direct search for mutations in CALM1, CALM2, CALM3

• CALM1 mutations discovered in 2 subjects
In our LQTS cohort of genotype-negative/phenotype-positive patients only four had extremely malignant arrhythmias with onset in infancy.

In three of these four we found calmodulin mutations.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>VF</th>
<th>QTc</th>
<th>TWA</th>
<th>2:1 AVB</th>
<th>Seizures</th>
<th>Developmental delay</th>
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<tbody>
<tr>
<td>Proband 1</td>
<td>F</td>
<td>6 months</td>
<td>+</td>
<td>630 ms</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
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<tr>
<td>Proband 2</td>
<td>F</td>
<td>prenatal</td>
<td>+</td>
<td>690 ms</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Case 3</td>
<td>M</td>
<td>1 month</td>
<td>+</td>
<td>610 ms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Case 4</td>
<td>M</td>
<td>? neonatal</td>
<td>+</td>
<td>&gt;600 ms</td>
<td>+</td>
<td>-?</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Subject</td>
<td>Treatments</td>
<td>Mutation</td>
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</tr>
<tr>
<td>Proband 1</td>
<td>βB, MEX, VER, FLEC, LCSD, RCSD, ICD</td>
<td>CALM1-D130G</td>
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<td>Proband 2</td>
<td>βB, MEX, ICD</td>
<td>CALM2-D96V</td>
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<td>Case 3</td>
<td>βB, MEX, ICD</td>
<td>CALM1-D130G</td>
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<td>Case 4</td>
<td>βB, MEX, LCSD, ICD</td>
<td>CALM1-F142L</td>
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</table>
Clinical implications

• Patients with life-threatening arrhythmias in the first year of life are usually not fully responders to anti-adrenergic therapy and also to association of therapies.

• Despite the young age and the potential complications associated with device implantation in small subjects, an ICD should be carefully evaluated
Who Are the Long-QT Syndrome Patients Who Receive an Implantable Cardioverter-Defibrillator and What Happens to Them?

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Population Under Study

• Patients 233
• Follow-up 5 years
• 9% asymptomatic
Indications at ICD implants

- Previous cardiac arrest
- Syncopal events despite full antiadrenergic therapy (possibly including LCSD)
- Asymptomatic patients with QTc > 550 msec, with signs of high electrical instability (i.e. T wave alternans, 2:1 AV block) or other evidence of being at very high risk (i.e. very long sinus pauses that might favour EAD)
THANK YOU

Peter J. Schwartz
Matteo Pedrazzini
Federica Dagradi
Margherita Torchio
Alice Ghidoni
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German Research Center for Environmental Health
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CALM Mutations and Life-Threatening Arrhythmias

Mutations in Calmodulin Cause Ventricular Tachycardia and Sudden Cardiac Death

Mette Nyegaard,1,8,* Michael T. Overgaard,2,8 Mads T. Søndergaard,2 Marta Vranas,1 Elijah R. Behr,3 Lasse L. Hildebrandt,2 Jacob Lund,2 Paula L. Hedley,4,5 A. John Camm,3 Göran Wettreell,6 Inger Fosdal,7 Michael Christiansen,4 and Anders D. Børglum1,*

Gene: CALM1

Population: 1) a large Swedish family with a severe dominantly inherited form of CPVT-like arrhythmia
2) a man of Iraqi origin with a de novo mutation
A mutation in *CALM1* encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence

Roos F. Marsman, MSc¹ *, Julien Barc, PhD¹,² *, Leander Beekman, BSc¹, Marielle Alders, PhD³, Dennis Dooijes, PhD⁴, Arthur van den Wijngaard⁵, PhD, Ilham Ratbi⁶, MD, Abdelaziz Sefiani, MD, PhD⁶, Zahurul A. Bhuiyan, MD, PhD⁵,⁷, Arthur A.M. Wilde, MD, PhD¹,⁸, Connie R. Bezzina, PhD¹

**Gene:** *CALM1*

**Population:** a Moroccan family:
- 4 siblings CA/SCD
- mother and a sibling are asymptomatic mutation carriers

Gene: CALM2

Population: 12 Japanese probands (mutation identified in a 19 months girl with syncope and CA)

190 genotype-negative Japanese LQTS probands (mutation identified in a 5 yrs boy with episodes of exercise-induced syncope)

98 genotype-negative Caucasian LQTS probands (mutation identified in an adult female with history of neonatal LQTS and subsequent features consistent with CPVT)