GENETIC EVALUATION OF ARRHYTHMIAS

Ramon Brugada-Terradellas
Dean, School of Medicine
Director, Clinical Cardiovascular Genetics Center
Universitat de Girona

ramon@brugada.org
SUDDEN CARDIAC DEATH

• Natural death from cardiac cause within one hour after first symptom.

• Incidence
  – General Population 1/1000 year
  – Previous coronary disease 5% year
  – FE < 30% or HF (MADIT II) 15% year
  – Aborted SCD 20% year
SUDDEN CARDIAC DEATH

• Role of genetic factors
  – Epidemiological studies
  – Genetic predisposition to drug-induced arrhythmias
  – Monogenic diseases
DNA MOLECULE

Genes contain instructions for making proteins.

Proteins act alone or in complexes to perform many cellular functions.
Hypertrophic Cardiomyopathy

Assymetric hypertrophy of the left ventricle.

Most common cause of sudden cardiac death in the athlete

- **MYBPC3** (Myosin-Binding protein C)
- **MYH7/MYHCB** (Myosin heavy-chain β)
- **MYL2** et **MYL3** (Myosin light-chain)
- **TNNI3** (Troponin I)
- **TNNT2** (Troponin T)
- **TPM1** (Tropomyosin-1)
- **ACTC** (α -actin proprotein)
- **TTN** (titin)
Arrhythmogenic Right ventricular Dysplasia

Right ventricular dilatation

Myocardial substitution by fibro adipose tissue

Sudden death is often the first symptom

- **PKP2** (plakophilin-2)
- **DSP** (desmoplakin)
- **DSC2** (desmocollin-2)
- **JUP** (plakoglobin)
- **DSG2** (desmoglein-2)
The diagram illustrates the ion transport processes and potential changes across a cell membrane. Key components include:

- **NaK ATPase** and **NaCa exchange** mechanisms for sodium and calcium transport.
- **Sarcoplasmic reticulum** with **Ca²⁺ buffers** for calcium regulation.
- **I⁰** and **Iₖ-Chr** currents are depicted, along with **K⁺** and **Na⁺** ion channels.
- The membrane potential changes from **-90 mV** to **0 mV** with **K⁺** and **Na⁺** ions moving in and out of the cell, respectively.

The diagram also highlights the **sarcoplasmic reticulum's role in calcium regulation** and the **potential changes across the membrane**.
**QT PROLONGATION**

- **Antimalarial**
  - Chloroquine, Halofantrine
- **Antianginal**
  - Bepridil, Israpidine, Nicardipine
- **Antiarrhythmic Drugs**
  - **Class IA**
    - Quinidine, Procainamide
    - Disopyramide
  - **Class III**
    - N-acetylprocainamide, sotalol, Ibutilide, dofetilide
- **Antibiotics**
  - Erythromycin, Trimethoprim & Sulfamethaxazole, Pentamidine
  - Clarithromycin, Azithromycin
- **Antihistamines**
  - Terfenedine, Astemizole, diphenhydramine
- **Muscle Relaxant**
  - Tizanidine
LONG QT SYNDROME

- Syncopal episodes
- Ventricular arrhythmias / SCD
- Prolongation of the QT interval
  - Romano-Ward
    » Autosomal dominant
  - Jervell and Lange-Nielsen
    » Autosomal recessive
# Long QT Syndrome

<table>
<thead>
<tr>
<th>Electrocardiographic Findings*</th>
<th>Points</th>
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<tbody>
<tr>
<td>A. QTc†</td>
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<tr>
<td>{ &gt;480 ms¹/²</td>
<td>3</td>
</tr>
<tr>
<td>460-470 ms¹/²</td>
<td>2</td>
</tr>
<tr>
<td>450 (male) ms¹/²</td>
<td>1</td>
</tr>
<tr>
<td>B. Torsade de pointes‡</td>
<td>2</td>
</tr>
<tr>
<td>C. T wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>D. Notched T wave in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>E. Low heart rate for age§</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Clinical History

| A. Syncope‡                   |        |
| { With stress                 | 2      |
| Without stress                | 1      |
| B. Congenital deafness        | 0.5    |

### Family HistoryⅠ

| A. Family members with definite LQTS§. | 1      |
| B. Unexplained sudden cardiac death below age 30 among immediate family members. | 0.5    |
LQTS - Risk Stratification

- **Lower risk**
  - QTc < 500
  - Male LQT2
  - LQT1

- **Intermediate risk**
  - QTc < 500
  - Female LQT2
  - Female LQT3
  - Male LQT3

- **Higher risk**
  - QTc ≥ 500
  - LQT1
  - LQT2
  - Male LQT3

- **Risk ≥ 50%**

- **30% ≤ Risk < 50%**

- **Risk < 30%**
## Therapy for LQTS

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<td>high risk; these include LQT2, LQT3, and QTc interval &gt;500 msec‡</td>
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Potassium channel: Gain of function

- $\text{IKr}$
- $\text{IKs}$
- $\text{IK1}$

$\text{Na}^+$

$\text{K}^+$
Idiopathic Short QT Interval: A New Clinical Syndrome?

Ihor Gussak, Pedro Brugada, Josep Brugada, R. Scott Wright, Stephen L. Kopecky, Bernard R. Chaitman, Preben Bjerregaard

Short QT Syndrome: A Familial Cause of Sudden Death

Fiorenzo Gaita, MD; Carla Giustetto, MD; Francesca Bianchi, MD; Christian Wolpert, MD; Rainer Schimpf, MD; Riccardo Riccardi, MD; Stefano Grossi, MD; Elena Richiardi, MD; Martin Borggrefe, MD
Idiopathic Short QT Interval: A New Clinical Syndrome?

De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero

Mutation in the KCNQ1 Gene Leading to the Short QT-Interval Syndrome

A Novel Form of Short QT Syndrome (SQT3) Is Caused by a Mutation in the KCNJ2 Gene

Short QT syndrome: Should we push the frontier forward?

Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls

QTc < 300 ms ?

QTc < 310 ms ?

QTc < 320 ms ?

QTc < 330 ms ?

QTc < 340 ms ?
Short QT: Genetic etiology

Sudden Death Associated With Short-QT Syndrome Linked to Mutations in HERG

Short QT Syndrome and Atrial Fibrillation Caused by Mutation in KCNH2

Mutation in the KCNQ1 Gene Leading to the Short QT-Interval Syndrome

De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero

A Novel Form of Short QT Syndrome (SQT3) Is Caused by a Mutation in the KCNJ2 Gene
Short QT: Treatment

Congenital Short QT Syndrome and Implantable Cardioverter Defibrillator Treatment: Inherent Risk for Inappropriate Shock Delivery

RAINER SCHIMPF, M.D., CHRISTIAN WOLPERT, M.D., FRANCESCA BIANCHI, M.D.,* CARLA GIUSTETTO, M.D.,* FIORENZO GAITA, M.D.,* URS BAUERSFELD, M.D.,† and MARTIN BORGGREFE, M.D.

Short QT Syndrome: Pharmacological Treatment

Fiorenzo Gaita, MD,* Carla Giustetto, MD,* Francesca Bianchi, MD,† Rainer Schimpf, MD,‖ Michel Haissaguerre, MD,‡ Leonardo Calò, MD,§ Ramon Brugada, MD,‖ Charles Antzelevitch, PhD,¶ Martin Borggrefe, MD,† Christian Wolpert, MD†

Further Insights into the Effect of Quinidine in Short QT Syndrome Caused by a Mutation in HERG

CHRISTIAN WOLPERT, M.D., RAINER SCHIMPF, M.D., CARLA GIUSTETTO, M.D.,* CHARLES ANTZELEVITCH, PH.D.,† JONATHAN CORDEIRO, PH.D.,† ROBERT DUMAINE, PH.D.,† RAMON BRUGADA, M.D.,† KUI HONG, M.D.,† URS BAUERSFELD, M.D.,† FIORENZO GAITA, M.D.,* and MARTIN BORGGREFE, M.D.
Sodium channel: Loss of function

Diagram showing the normal and abnormal electrical activity in cardiac muscle cells.
- Prolonged PR
- RBBB
- ST segment ↑
- Negative T waves
Japó: Pokkuri
Tailàndia: Lai Tai
Les Filipines: Bangungut
Type 1
“Coved”

Type 2 & 3
“Saddle back”

NON DIAGNOSTIC
Brugada syndrome: Controversial Issues

- Sudden Cardiac Death
- Syncope
- Asymptomatic patients
BRUGADA SYNDROME, VALUE OF EPS

![Graph showing survival depending on inducibility.]

% free of cardiac arrest

Age (years)

Non-inducible
Inducible
Brugada syndrome: Type I ECG pattern

- Do not ignore the ecg.

- ECG pattern under an acute inducer is a medical emergency.

- Investigate the family members.

- Consider inducibility at EPS
CPVT
Research in Genetics of Cardiovascular Diseases

- **BRUGADA SYNDROME**
  - SCN5A
  - 45 years old.
  - No medical problems.
  - Cardiac arrest.
  - 32 years old.
  - Sister.
  - Sudden Cardiac Death

- **FAMILIAL CORONARY DISEASE**
  - MEF2A
  - 46 years old man.
  - Myocardial Infarction
  - Father and uncle had a heart attack before age 50

- **SHORT QT SYNDROME**
  - KCNH2
  - 36 years old.
  - No medical problems.
  - Cardiac arrest.
  - 3 months old son.
  - Sudden Cardiac Death

- **HYPERTROPHIC CARDIOMYOPATHY**
  - MYOSIN HEAVY CHAIN
  - 15 year old athlete.
  - Sudden Cardiac Death
  - 2 brothers and an uncle died suddenly while running

- **DILATED CARDIOMYOPATHY**
  - LAMIN A/C
  - 14 year old boy.
  - Enlarged heart
  - 22 year old brother with heart transplantation.

- **LONG QT SYNDROME**
  - KCNQ1
  - 6 years old girl.
  - Sudden Cardiac Death
  - Mother drowned in a swimming pool

- **MARFAN SYNDROME**
  - FIBRILLIN-1
  - 26 year old
  - Dilated aorta

- **DILATED CARDIOMYOPATHY**
  - LAMIN A/C
  - 14 year old boy.
  - Enlarged heart
  - 22 year old brother with heart transplantation.
Clinical Cardiovascular Genetics Center

- Brugada Syndrome
- Short QT Syndrome
- Long QT Syndrome
- Hypertrophic Cardiomyopathy
- Coronal Disease
- Sudden Cardiac Death
- Marfan Syndrome
- Hypertension
- Gene Diet Interaction
- Arrhythmogenic Dysplasia
- Dilated Cardiomyopathy
- Congenital Heart Disease

Response to Medications
CLINICAL CARDIOVASCULAR GENETICS CENTER
Familial Sudden Cardiac Death
Confirm a genetic diagnosis

MISSENSE MUTATION
MYOSIN HEAVY CHAIN
Reach a diagnosis

54 yrs
SYNCOPE

DELETION
DESMOPLAKINE
- 36 morts sobtades
- 24 desfibril.ladors (ICD)
- 7 ICDs en no portadors.
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Risc Stratification

- **Higher risk**: QTc ≥ 500
  - LQT1
  - LQT2
  - Male LQT3

- **Intermediate risk**: QTc = 500
  - Female LQT2
  - Female LQT3
  - Male LQT3

- **Lower risk**: QTc < 500
  - Male LQT2
  - LQT1

Risk stratification categories:
- Risk ≥ 50%
- 30% ≤ Risk < 50%
- Risk < 30%
Sudden Death and Genetics

WHAT DO WE NEED NEXT?

- Fast genetic testing
- Effective genetic testing
- Cost effective.
- Which enables testing in patients without a clear diagnosis.
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<td>Arritmias supraventriculares</td>
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<tr>
<td>Fibri-laci auricular</td>
<td>Autosómica dominant</td>
<td>1q21, 3p21, 10q22, 11q15, 11q23, 13q13, 21q22, 17q23</td>
<td>SCN5A, KCNQ1, KCNQ2, KCNE3, KCNE2, KCNE1, KNAC1</td>
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<tr>
<td>Alteraciones de conducción</td>
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<tr>
<td>Bloqueig brancia familiar</td>
<td>Autosómica dominant</td>
<td>19p13, 3q21</td>
<td>SCN5A</td>
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<td>Arritmias ventriculares</td>
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<tr>
<td>Síndrome de Brugada</td>
<td>Autosómica dominant</td>
<td>3p21, 3p24</td>
<td>SCN5A, GPD1-L</td>
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<td>Síndrome de QT curt</td>
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<td>7q35, 11p17, 17q23</td>
<td>HERG, KCNE1, KCNE2</td>
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<td>Romano-Ward</td>
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<td>3p21, 4q35, 7q35, 11q15, 11q23, 12q21, 17p22, 21q22, 15q13</td>
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<td>Jervell-Lange-Neisai</td>
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<td>17q22, 21q22, 15q13</td>
<td>KCNQ1, MKNK2, MKNK3</td>
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<td>Taquicardia ventricular catecolaminergica</td>
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<td>1q32, 2q21, 10q22, 14q11, 17q21</td>
<td>RYR2, CASQ2</td>
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<td>Miocardiopatia hipertrófica</td>
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<td>1q32, 1p32, 14q12, 14q11, 17q23</td>
<td>Tropo, Trop, Trop, Trop, Trop</td>
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<td>Dreifuss</td>
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<td>Steiner</td>
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<td>Mi-PK, Emery, Emery, Emery</td>
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Sudden Cardiac Death
Genetic diagnosis

- Mutation array
- Resequencing array
- Full genome sequencing