KVLQT1: A Gene for SUDEP and a Biomarker for Sudden Unexplained Death in Epilepsy (SUDEP)

Diagnostic and Therapeutic Opportunity

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Epilepsy Therapy Project, CURE
Dana Foundation,
SUDEP – The Ultimate Epilepsy Co-Morbidity

_Couzin, Science_ 2008 321: 31-33
Florence Joyner (Flo-Jo)
Epilepsy (1960-1998)

3 Gold medals in Seoul 1988 Olympics
Still holds World Record 100 meters in 10.49 s.
Died 10 years later suddenly, no cause, age 38

Daisy Garland
Epilepsy (1998-2004)

Seizure onset at 3 months
Dravet Syndrome diagnosed at 2 yrs
Died suddenly in bed at 6 years.
Mortality in Epilepsy

1. Mortality rate in epilepsy population is 2-3x > general population.

2. Causes:
   - Status epilepticus 12.5%
   - Accidents 1.2 – 6.5%
   - Suicide 5.1%
   - SUDEP 2 – 18%

3. Sudden Unexplained Death in Epilepsy (SUDEP)
   “unexpected non-traumatic mortality that occurs under benign circumstances in otherwise well individuals with epilepsy with or without evidence of seizure and excluding status epilepticus. Postmortem examination does not reveal a toxicological or anatomical cause of death.

4. Risk factors:
   - Frequent intractable GTC Seizures
   - Age 20-40 years
   - Frequent changes of AEDs
   - Early onset epilepsy
   - AED polytherapy

5. Definite causes of SUDEP are still unknown
A Molecular Basis for Cardiac Arrhythmia: 
HERG Mutations Cause Long QT Syndrome

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Katherine W. Timothy,‡ G. Michael Vincent,‡§ 
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therefore, provides a unique opportunity to study life-threatening cardiac arrhythmias at the molecular level. 
A molecular basis for LQT was not previously known.

\[ \text{ICa,L ((CACNA1c))} \]
\[ \text{INa ((SCN5A))} \]
\[ \text{IKs ((KvLQT1 + minK))} \]
\[ \text{IKr ((HERG + MiRP1))} \]
\[ \text{IK1 ((KCNJ2/Kir2.1))} \]
Long QT Syndrome

- Incidence ~1/2,000
- Heart rate adjusted prolongation of QT interval (QTc) on ECG

- 10% LQTS cases: negative on resting ECG

- > 2/3 of cases with positive ECG are not recognized in the community
  - 96% of QT experts
  - 62% arrhythmia experts
  - < 25% internists correctly classify all QT intervals as normal or prolonged

Rate-correction formula (Bazett’s):

\[ QTc \text{ (msec)} = \frac{QT \text{ (msec)}}{\sqrt{RR \text{ (sec)}}} \]
Selective localization of cardiac SCN5A sodium channels in limbic regions of rat brain

H.A. Hartmann, L.V. Colom, M.L. Sutherland & J.L. Noebels

Nature Neuroscience, 1999, 2:593-595

Can ion channels co-expressed in heart and brain cause SUDEP? Dual phenotype rather than a coincidence
Dual Phenotype of Epilepsy and Cardiac Arrhythmias
KCNQ1 and the MinK subunit are expressed in Mouse and Human Brain
KCNQ1 Potassium Channels in Forebrain
Mice with Human KvLQT1 Mutations

Both mutations cause loss of KvLQT1 current, prolonged cardiac membrane repolarization, and LQT

Casimiro et al, *Genomics*, 2004
KCNQ1 Mutants Display Seizures in Forebrain and spontaneous cardiac arrhythmias

A new ion channel gene for epilepsy
KCNQ1 Potassium Channels in Vagal Nerve Nuclei

Cortical Discharges Often Trigger Cardiac Asystole
Convulsive Seizures in *Kvlqt1* Knockin Mice

Not all seizures trigger arrhythmias.
Monitored SUDEP Terminal Event

EEG Seizure

EKG

End of Seizure

Sudden Bradycardia

Arrhythmias

Asystole

Final Heart Beat
“Seizure Phenotypes” in Genotyped LQT Syndromes

Johnson et al, Neurology 2009 72:224-31
Practice Guidelines For LQT Therapy

Diagnosis

- QTc > 460msec (m), 440msec (f) but risk is a continuum
- usually <40 yrs of age
- 1:2000; most mutations silent throughout life
- may require stress testing to elicit EKG
- emotional stress, sudden loud noise, sleep triggers
- variable penetrance, r/o other causes, hypocalcemia, hypothyroidism, drugs
- cardiac echo, MRI show no abnormalities

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<thead>
<tr>
<th>Variable</th>
<th>LQT1</th>
<th>Genetic Subtype</th>
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<tbody>
<tr>
<td>Disease-associated gene</td>
<td>KCNQ1</td>
<td>KCNH2</td>
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<tr>
<td>In vitro effect</td>
<td>Decreased k1</td>
<td>Decreased k0</td>
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<tr>
<td>Setting of arrhythmia[1]</td>
<td>Emotional or physical stress, swimming, diving</td>
<td>Emotional or physical stress, sudden loud noise</td>
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<td>Typical resting ECG[2]</td>
<td>Broad T wave</td>
<td>Low-amplitude T wave with notch</td>
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<tr>
<td>ECG at onset of arrhythmia[6]</td>
<td>No pause</td>
<td>Pause</td>
</tr>
<tr>
<td>QT change with exercise</td>
<td>Failure to shorten</td>
<td>Normal</td>
</tr>
<tr>
<td>QT shortening with nesiletine[7]</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Clinical response to beta-blockers[4]</td>
<td>Yes</td>
<td>Less than LQT1 response</td>
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- Beta blockade is mainstay of therapy
- Pacemaker

Roden D. NEJM 2008 358:169-76
Summary

Dual Phenotype of Cardiac Arrhythmias and Epilepsy

“Primary” Cardiac Syncopy  $ightarrow$ “Primary” Epilepsy

KvLQT1 (and other LQT genes)

Implications for Early Diagnosis and prevention of SUDEP

1. Early cardiac (EKG) evaluation of all idiopathic epilepsy patients
2. If positive, formal cardiac evaluation with genotyping
3. Specific therapy for cardiac arrhythmia and epilepsy
To tell, or not to tell?

**Girl's death mirrored mother's**

JOHN STAPLES

A TEENAGER died after suffering a severe epileptic fit while asleep in her bed in a situation that almost mirrored her mother's death eight years previously, a fatal accident inquiry heard yesterday.

Colette Findlay, 17, had been diagnosed at the age of ten as suffering from epilepsy, months after her mother Dianne had died.

But doctors did not warn the girl or her family that her condition could result in sudden death as they believed it to be benign, the inquiry was told.

The family of Colette, which includes two aunts who brought her up following her mother's death, have criticised the lack of information and treatment she received following the diagnosis.

But yesterday a doctor warned the hearing at Glasgow Sheriff Court of the dangers of telling youngsters with epilepsy of the rare possibility they could die suddenly.

Professor John Stephenson, who was involved in the original diagnosis at Glasgow's Yorkhill Hospital in 1991, said letting a child know this could lead to suicide and told the inquiry that had happened recently and resulted in legal action against a health authority. He said: "There was no policy for raising this issue with families in 1991 when Colette was diagnosed."

"I actually don't know of anyone who would discuss sudden death with a patient suffering benign epilepsy, it would do more harm than good in the majority of cases I suspect."

"At worst, by giving this information a patient could commit suicide, as has happened now with a local authority being sued over it."

Prof Stephenson said a specialist nurse had been taken on in Glasgow in the mid-1990s to help the families of people with epilepsy by giving them advice, including leaflets of possible symptoms and problems.