Genetic Variations in SUDEP

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Disclosure

None
Learning Objectives

Purpose of gene identification and genetic screening in SUDEP?

Genetic variability, analytic tools, and disease causality

Screening of candidate SUDEP genes

Clinical implication of SUDEP genetics
The purpose of gene identification and screening in SUDEP

SUDEP mechanisms

Identify patients at risk

Prevention
Primer on the most common genetic variations

The many flavors genetic variations

Analytic tools

What is a “disease causing” genetic change
Genetic variations

**Microscopic**
- Structure
- Number

**Polygenic**
- Angelman; Smith-Magenis

**Submicroscopic**
- G1
- G2
- G3

**Whole Gene(s)**
- G1
- G2
- G3

**Monogenic or Polygenic**
- G2'
- G3'

**Monogenic**
- G1
- G2
- G3

**In-Gene**
- Gene DUP
- Gene DEL

**In-Gene DUP**
- Gene2

**CNV**
- Whole Gene(s)
- In-Gene

**SNP**
- AGGCCAAATCGCATT

**NL**
- Gene DUP
- Gene DEL
Tools in genetic research

- Clinical history
- Exam
- Morphometrics

Biomarkers

Genetics
Evidence for a disease causing gene, mutation?

**DEFINITE**

**PROBABLE**

**POSSIBLE**
New SCN5A mutation in a SUDEP victim with idiopathic epilepsy

Dag Aurlien, Trond P. Leren, Erik Taubøll, Leif Gjerstad

Neurological Department, Stavanger University Hospital, P.O. Box 8100, 4068 Stavanger, Norway
Department of Medical Genetics, Rikshospitalet University Hospital, Oslo, Norway
Department of Neurology, Rikshospitalet University Hospital, Oslo, Norway

**Fig. 1.** Identification of mutation R523C in the SCN5A gene by DNA sequencing. The figure shows the DNA sequence of the anti-sense strand of nucleotides 1548–1585 of the SCN5A gene in a normal subject (upper panel) and in the SUDEP victim (lower panel). Above the electropherograms are shown the nucleotide compositions (A = adenosine; C = cytosine; G = guanosine; T = thymidine). Heterozygosity for an adenosine at nucleotide 1567 in the SUDEP victim is indicated by the arrow. This mutation changes codon 523 from CGT (arginine, R) to TGT (cysteine, C).

SCN5A VUS
SUDEP candidate LQT genes contain much variation

Post-Mortem Review and Genetic Analysis of Sudden Unexpected Death in Epilepsy (SUDEP) Cases

Emily Tu, BSC1,2; Richard D. Bagnall, PHD1; Johan Duflou, MBCHB2,3; Christopher Semsarian, MB BS PHD1,2,4

Table 2. DNA variants in LQTS genes identified in SUDEP cases.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Exon</th>
<th>Amino acid change</th>
<th>MAF (%)</th>
<th>Controls (n = 170)</th>
<th>dbSNP European controls†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SUDEP (n = 48)</td>
<td></td>
</tr>
<tr>
<td>KCNQ1</td>
<td>rs1057128</td>
<td>13</td>
<td>Ser546Ser</td>
<td>20.8</td>
<td>11.7–20.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs11601907</td>
<td>16</td>
<td>Tyr662Tyr</td>
<td>25.0</td>
<td></td>
<td>30.6</td>
</tr>
<tr>
<td>KCNH2</td>
<td>rs36210422</td>
<td>4</td>
<td>Arg176Trp</td>
<td>1.0</td>
<td>0</td>
<td>0–1.1</td>
</tr>
<tr>
<td></td>
<td>rs740952</td>
<td>6</td>
<td>Ile489Ile</td>
<td>9.4</td>
<td></td>
<td>14.3–19.1</td>
</tr>
<tr>
<td></td>
<td>rs33959111</td>
<td>7</td>
<td>Leu564Leu</td>
<td>45.8</td>
<td></td>
<td>27.7–33.3</td>
</tr>
<tr>
<td></td>
<td>rs1137617</td>
<td>8</td>
<td>Tyr652Tyr</td>
<td>37.5</td>
<td></td>
<td>44.4–44.6</td>
</tr>
<tr>
<td></td>
<td>rs36210421</td>
<td>13</td>
<td>Arg1047Leu</td>
<td>4.2</td>
<td>2.9</td>
<td>1.8</td>
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<tr>
<td>SCN5A</td>
<td>rs6599230</td>
<td>2</td>
<td>Ala29Ala</td>
<td>19.8</td>
<td>11.1–28.3</td>
<td></td>
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<tr>
<td></td>
<td>rs45533640</td>
<td>3</td>
<td>His118His</td>
<td>1.0</td>
<td>NA</td>
<td></td>
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<tr>
<td></td>
<td>rs1805124</td>
<td>12</td>
<td>His558Arg</td>
<td>19.8</td>
<td>9.5–19.1</td>
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<tr>
<td></td>
<td>rs45522138</td>
<td>12</td>
<td>Leu561Leu</td>
<td>1.0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rs36210423</td>
<td>12</td>
<td>Ala572Asp</td>
<td>1.0</td>
<td>0.6</td>
<td>0.4</td>
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<tr>
<td></td>
<td>rs7420407</td>
<td>17</td>
<td>Glu1061Glu</td>
<td>6.3</td>
<td></td>
<td>12.5–14.0</td>
</tr>
</tbody>
</table>

Epidemiologic, molecular, and functional evidence suggest A572D-SCN5A should not be considered an independent LQT3-susceptibility mutation

David J. Tester, BS,* Carmen Valdivia, MD,† Carole Harris-Kerr, PhD,‡ Marielle Alders, PhD,§ Benjamin A. Salisbury, PhD,‡ Arthur A. M. Wilde, MD, PhD,‖ Jonathan C. Makielski, MD,† Michael J. Ackerman, MD, PhD*
Genetic Analysis of Hyperpolarization-Activated Cyclic Nucleotide-Gated Cation Channels in Sudden Unexpected Death in Epilepsy Cases

Emily Tu, PhD; Louise Waterhouse, BMedSc; Johan Duflou, MMed, FRCPA; Richard D. Bagnall, PhD; Christopher Semsarian, MBBS, PhD

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<th>MAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SUDEP (n ≥ 47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls (n ≥ 160)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dbSNP*</td>
</tr>
<tr>
<td>HCN1</td>
<td>Novel</td>
<td>1</td>
<td>Gly46Val</td>
<td>2.1</td>
</tr>
<tr>
<td>HCN2</td>
<td>Novel</td>
<td>8</td>
<td>Phe738Cys</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>8</td>
<td>Pro802Ser</td>
<td>1.2</td>
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<tr>
<td>HCN3</td>
<td>rs61812063</td>
<td>1</td>
<td>Lys69Arg</td>
<td>3.1</td>
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<tr>
<td></td>
<td>rs35001694</td>
<td>8</td>
<td>Pro630Leu</td>
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</tr>
<tr>
<td>HCN4</td>
<td>Novel</td>
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<td>Gly36Glu</td>
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<tr>
<td></td>
<td>rs62641689</td>
<td>8</td>
<td>Val759Ile</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>8</td>
<td>Gly973Arg</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>8</td>
<td>Arg1044Trp</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Bold indicates novel variants which were absent in controls; MAF = minor allele frequency.

*No genotype frequencies are available in dbSNP except rs35001694 and rs62641689.
Dually expressed epilepsy genes: SUDEP candidate

**SCN1A** (I1867T)
Table 2. Heart rate and QT and QTc intervals on standard ECG

<table>
<thead>
<tr>
<th></th>
<th>DS</th>
<th>ES/AED</th>
<th>ES/no-AED</th>
<th>HC</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (ms)</td>
<td>605 ± 79</td>
<td>657 ± 91</td>
<td>659 ± 88</td>
<td>660 ± 103</td>
<td>0.17</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>325 ± 37</td>
<td>333 ± 32</td>
<td>340 ± 33</td>
<td>353 ± 35</td>
<td>0.07</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>373 ± 14</td>
<td>379 ± 17</td>
<td>385 ± 29</td>
<td>378 ± 22</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Delogu AB et al. Epilepsia 52(Suppl. 2):55-58, 2011

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BRIEF COMMUNICATION

A case of SUDEP in a patient with Dravet syndrome with SCN1A mutation

*François Le Gal, †Christian M. Korff, *Christine Monso-Hinard, †Michael T. Mund,
*Michael Morris. *Alain Malafosse, and †Thomas Schmitt-Mechelke

c.[504dupA]

Epilepsia, 51(9):1915–1918, 2010
doi: 10.1111/j.1528-1167.2010.02691.x
De Novo Pathogenic SCN8A Mutation Identified by Whole-Genome Sequencing of a Family Quartet Affected by Infantile Epileptic Encephalopathy and SUDEP

Krishna R. Veeramah,1 Janelle E. O’Brien,4 Miriam H. Meisler,4 Xiaoyang Cheng,5 Sulayman D. Dib-Hajji,6 Stephen G. Waxman,5 Dinesh Talwar,6,7,9 Santhosh Girirajan,10 Evan E. Eichler,10 Linda L. Restifo,2,7,8 Robert P. Erickson,3,6 and Michael F. Hammer1,*


11,292 variants called in 1,2,3, or 4
34 variants de novo in 1

Filter (i.e. 1000 Genomes)

SCN8A variants de novo in 1
c.5302A>G/Asn1768Asp

Is SCN8A? major effect gene? modifier gene phenotype?

SCN8A contribution: epilepsy phenotype? cardiac phenotype? SUDEP? Both?

Neuronal culture

Electrophysiology

WGS
SUDEP mechanism(s) and cause(s):

Genetic prediction is complex

Klassen et al. Cell 2011

Slide not available
Clinical implications of SUDEP genetics

• SUDEP gene discovery is important for understanding mechanism and risk prediction

• Genetic variation occurs on many levels and in many genes

• Careful multi-level analysis is essential to prove contribution/causality

• Genetic risk prediction is complex
Research support

NINDS
NS067013 (AMG), NS-049130 and NS076916 (JLN)
CURE
Epilepsy Foundation
Dana Foundation
Emma Bursick Memorial Fund
Fiorito Fund for SUDEP Research
Blue Bird Circle Foundation