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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
Ion channels phosphorylopathy:

A link between genomic variations and heart arrhythmia

3rd International Conference on Clinical & Experimental Cardiology
April 15-17, 2013

Saverio Gentile, Ph.D
Loyola University Chicago, USA
gene name
hERG-1: human ether-a-go-go-related gene 1

Protein name:
Kv11.1: Voltage-gated potassium channel 11.1

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gene name
CACNA1C: calcium channel, voltage-dependent, L type, alpha 1C subunit

Protein name:
Cav 1.2; L-type

---

Tissues

Brain
Hypophysis
Heart
Pancreas
Intestine
More than 290 mutations on Kv11.1 channel are associated with Long QT syndrome

Drug-induced torsades de pointes: The evolving role of pharmacogenetics
Patrick T. Fitzgerald, MDs, Michael J. Ackerman, MD, PhD Heart Rhythm, 2005
Ribbon representation of the Kv1.2-Kv 2.1 paddle chimera tetramer (PDB 2R9R, K+ ions shown as green spheres) viewed from the side with the extracellular solution above. http://lab.rockefeller.edu/mackinnon/
T3 stimulates hERG1 channel activity

Kv11.1 currents

- E4031
- control
- T3

Charge (pC) vs. time (min)

- hERG

Gentile et al, PNAS 2008
Gentile et al, PNAS 2006
T3 regulates hERG-K897T through PI3K but not through Rac and PP5.

Gentile et al, PNAS 2008
Gentile et al, PNAS 2006
hERG-SNP K897T is associated with cardiac ventricular arrhythmia and sudden death.
T3 inhibits hERG1-K897T activity
T3 regulates hERG-K897T through PI3K but not through Rac and PP5.
Conclusion

-Kv11.1-897T is a substrate for PKB (Phosphorylopathy by creating a phosphosite)

-Inhibition of Kv11.1 by PKB links a human SNP to a fatal cardiac phenotype
Long QT2 Mutation on the Kv11.1 Ion Channel Inhibits Current Activity by Ablating a Protein Kinase C Consensus Site.

Donovan, Lansu, Williams, Denning, and Saverio Gentile
MOLECULAR PHARMACOLOGY 2012, Vol. 82, No. 3

PKC motif
Kv11.1-WT 887-R-K-L-S- F -R
pS (PKC) -R-K-X-S-hyd-R/K

![Graph showing current activity](image1)

![Western blot analysis](image2)

![Graph showing relative density](image3)
Timothy syndrome mutation creates a CAMKII consensus site

CAMKII \(-R-x-x-S/T\)

\(\text{A) CaV1.2.....436-G-W-D-S-439}\)

\(\text{KN-62= CAMKII inhibitor}\)

\(\text{B) CaV1.2.....436-R-W-D-S-439}\)

\(\text{C) CaV1.2.....436-R-W-D-S-439 + KN-62}\)

\(\text{D) CaV1.2.....436-R-W-D-S-439A}\)
Conclusion

We propose that aberrant phosphorylation, or “phosphorylopathy,” of the CaV1.2 channel protein contributes to the excitotoxicity associated with LQT8.
Ion channel Phosphorylopathies:

Mutations that creates or disrupts phosphorylation sites on ion channels

1. Creation of kinase consensus site by adding a phosphorylatable residue
   - PKB motif
     - hERG-1 897K 892- R R R T D K -897
     - hERG-1 897T 892- R R R T D T -897

2. Disruption of kinase consensus site by removing a docking residue
   - PKC motif
     - Kv11.1 887R 887- R K L S F R -892
     - Kv11.1 887H 887- H K L S F R -892

3. Creation of kinase consensus site by adding a docking residue
   - CAMKII motif
     - Cav1.2 406G 406- G W D S -409
     - Cav1.2 409R 406- R W D T -409

Kv11.1 Ion channel malfunction and Cardiac arrhythmia

CaV1.2 Ion channel malfunction and Cardiac arrhythmia
## Ion channels phosphorylopathy: A link between genomic variations and heart arrhythmia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>SNP</th>
<th>PO4</th>
<th>Kinase</th>
<th>Disease</th>
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<tr>
<td>CACNA1C</td>
<td>Cav1.2</td>
<td>S1545P</td>
<td>-60%</td>
<td>CAMKII</td>
<td>Timothy</td>
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<tr>
<td>KCNH2</td>
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<td>K897T</td>
<td>+94%</td>
<td>PKB</td>
<td>LQT2</td>
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<td>MYOK, EPI</td>
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<td>TRPC6</td>
<td>TRPC6</td>
<td>P15S</td>
<td>+96%</td>
<td>CK1</td>
<td>GMS</td>
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<td>TRPV4</td>
<td>OTRPC4</td>
<td>P19S</td>
<td>+94%</td>
<td>CK2</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Thanks (a lot) to:

Mr. Alexander J. Donovan  
Research Assistant  
2010-2011  
Now Ph.D Student in the Chemistry Department @ UIC

Miss. Katherine Lansu  
Research assistant  
2011-2012  
Now Ph.D Student @ UNC
T3/TRH-dependent regulation of hERG1 channel activity

Gentile et al, PNAS 2008
Gentile et al, PNAS 2006
Summary of the values for the long open times, $\tau_{o2}$, as well as the frequency of mode 2 openings from the indicated number of patches expressing each construct.

**CAMKII** - R-x-x-S/T

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**CaV1.2**……436-R-W-D-S-439

**CaV1.2**……436-R-W-D-A-439
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- R P R T T S -

hERG-1 897K 892- R R R T D K -897
hERG-1 897T 892- R R R T D T -897

PKC motif
- R K X S X R -

Kv11.1 887R 887- R K L S F R -892
Kv11.1 887H 887- H K L S F R -892

CaV1.2 Ion channel malfunction and Cardiac arrhythmia

CAMKII motif
- R X D T -

Cav1.2 406G 406- G W D S -409
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Disruption of kinase consensus site by removing a docking residue

Creation of kinase consensus site by adding a phosphorylatable residue
gene name
CACNA1C: calcium channel, voltage-dependent, L type, alpha 1C subunit

Protein name:
Cav 1.2; L-Type

L-Type Ca2+ Channel Function During Timothy Syndrome
Rose E. Dixon, Edward P. Cheng, Jose L. Mercado, Luis F. Santana
Trends in Cardiovascular Medicine Volume 22, Issue 3, April 2012, Pages 72–76
Phosphorylation requires recognition of a specific kinase signature
Thanks' for your kind attention!!!!!!
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