About OMICS Group

OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

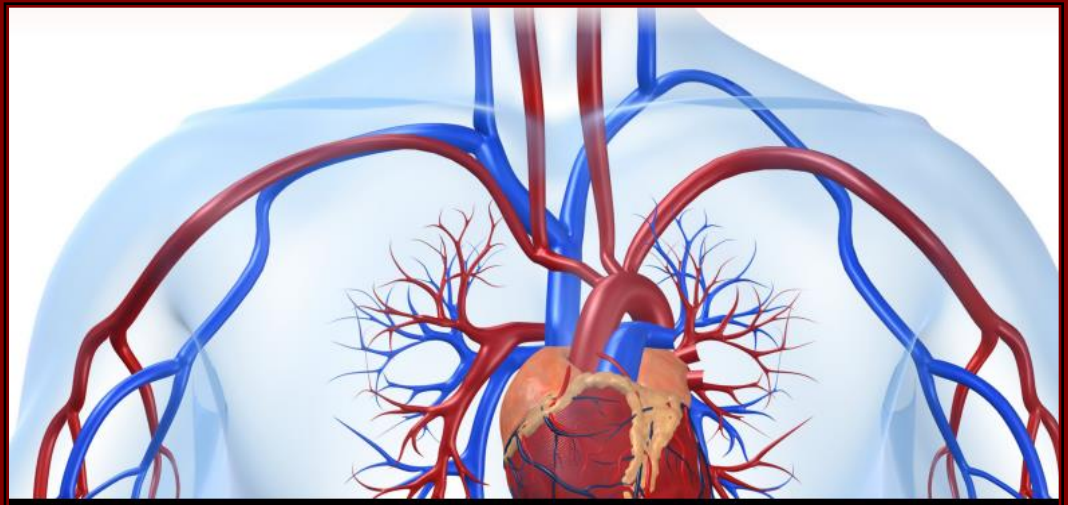
About OMICS Group Conferences

OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

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

gene name

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

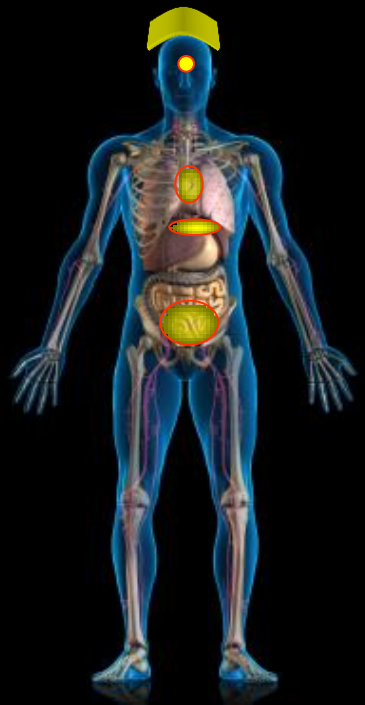
Protein name:
Cav 1.2; L-type

Brain

Hypophysis

Pancreas

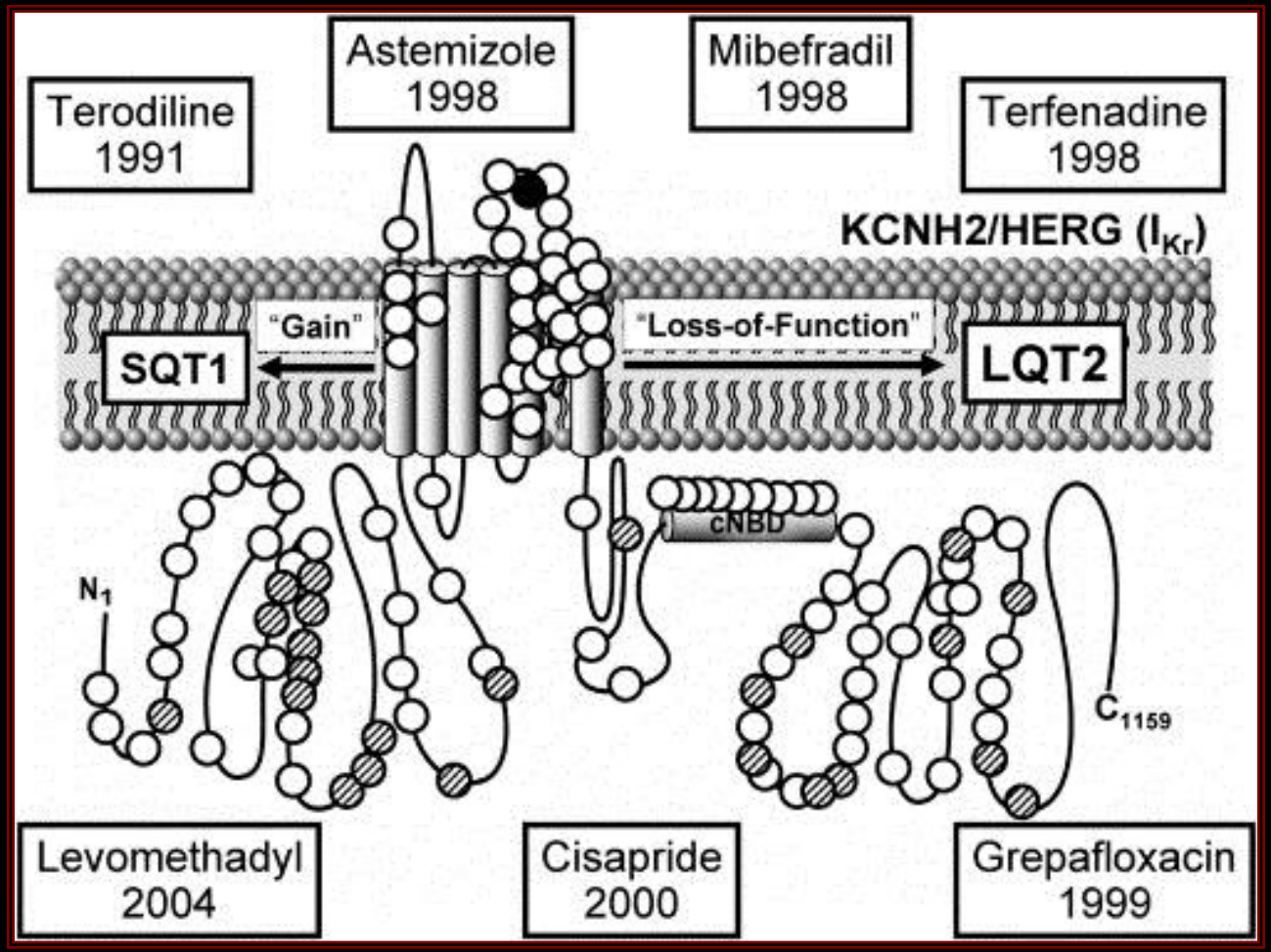
Intestine



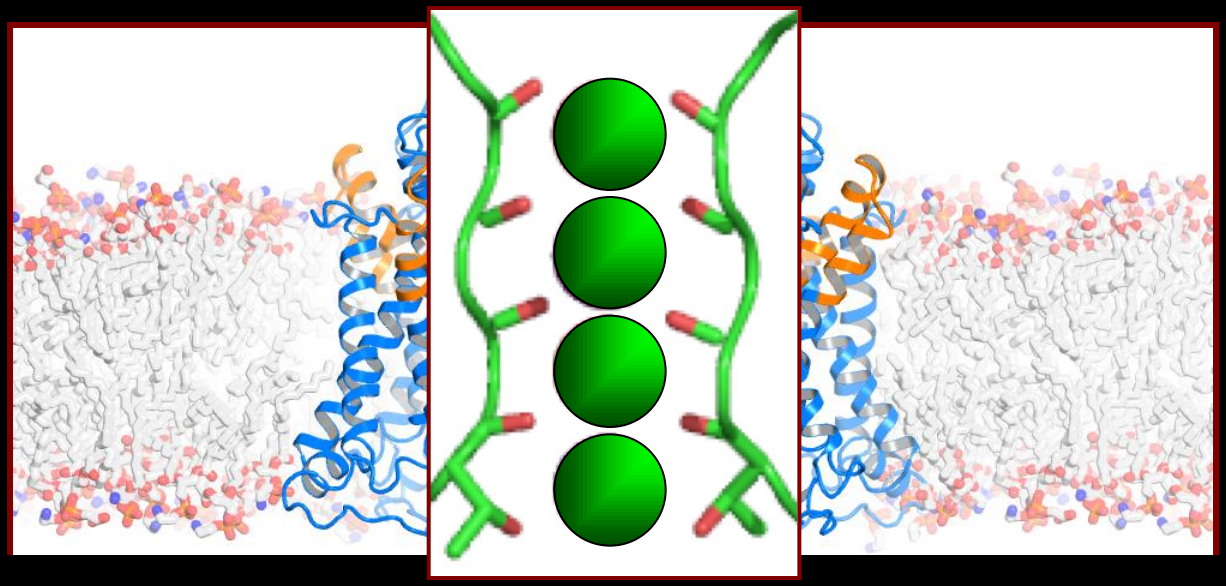
Tissues

Heart

More than 290 mutations on Kv11.1 channel are associated with Long QT syndrome

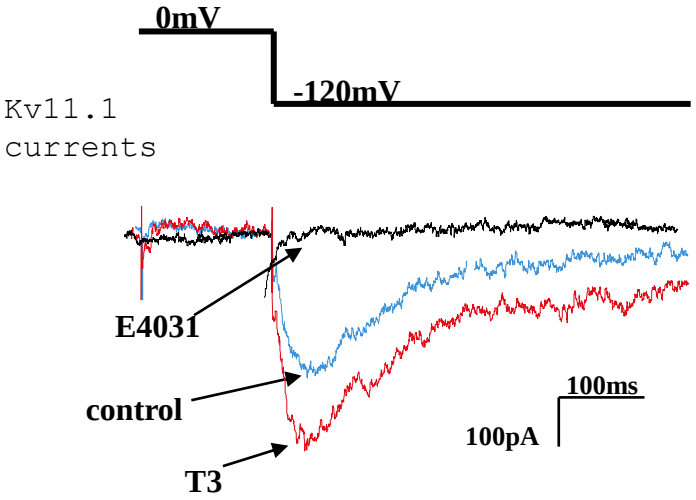


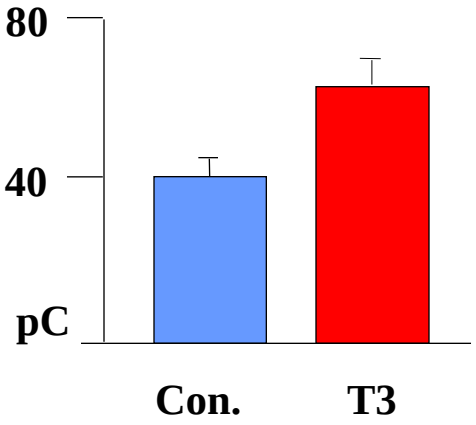
Drug-induced torsades de pointes: The evolving role of pharmacogenetics
Patrick T. Fitzgerald, MDa, Michael J. Ackerman, MD, PhD Heart Rhythm, 2005

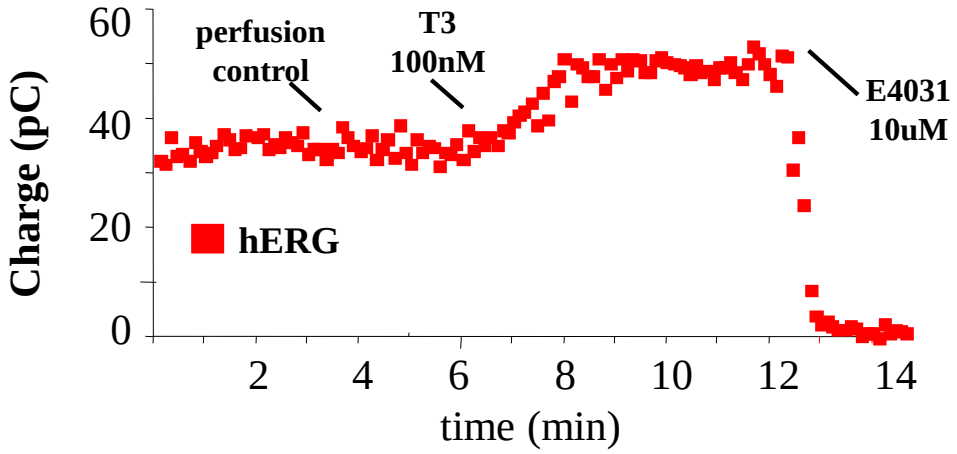


Ribbon representation of the Kv1.2-Kv 2.1 paddle chimera tetramer (PDB 2R9R, K+ ions shown as green spheres) viewed from the side with the extracellular solution above. http://lab.rockefeller.edu/mackinnon/

T3 stimulates hERG1 channel activity

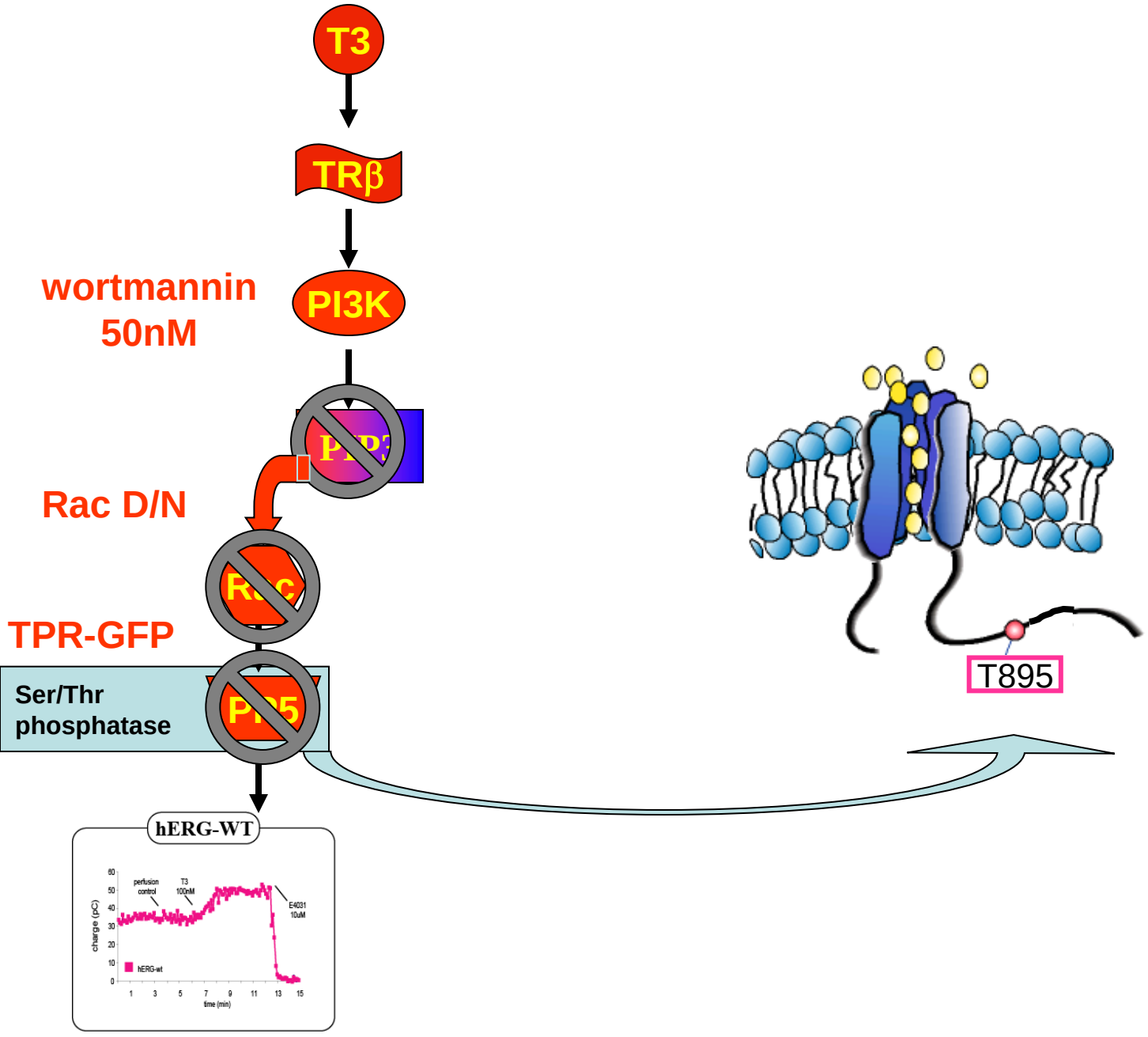






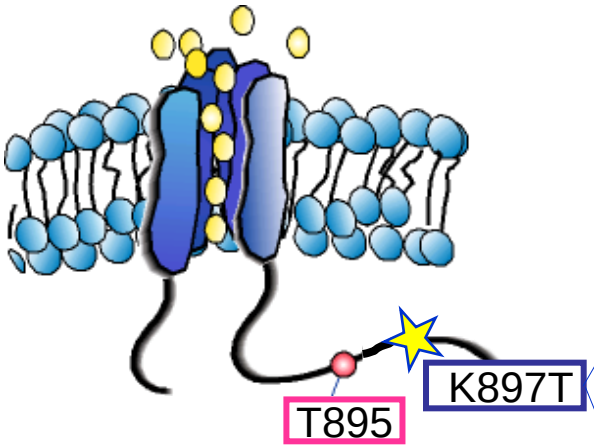
Gentile et al, PNAS 2008
Gentile et al, PNAS 2006

T3 regulates hERG-K897T through PI3K but not through Rac and PP5

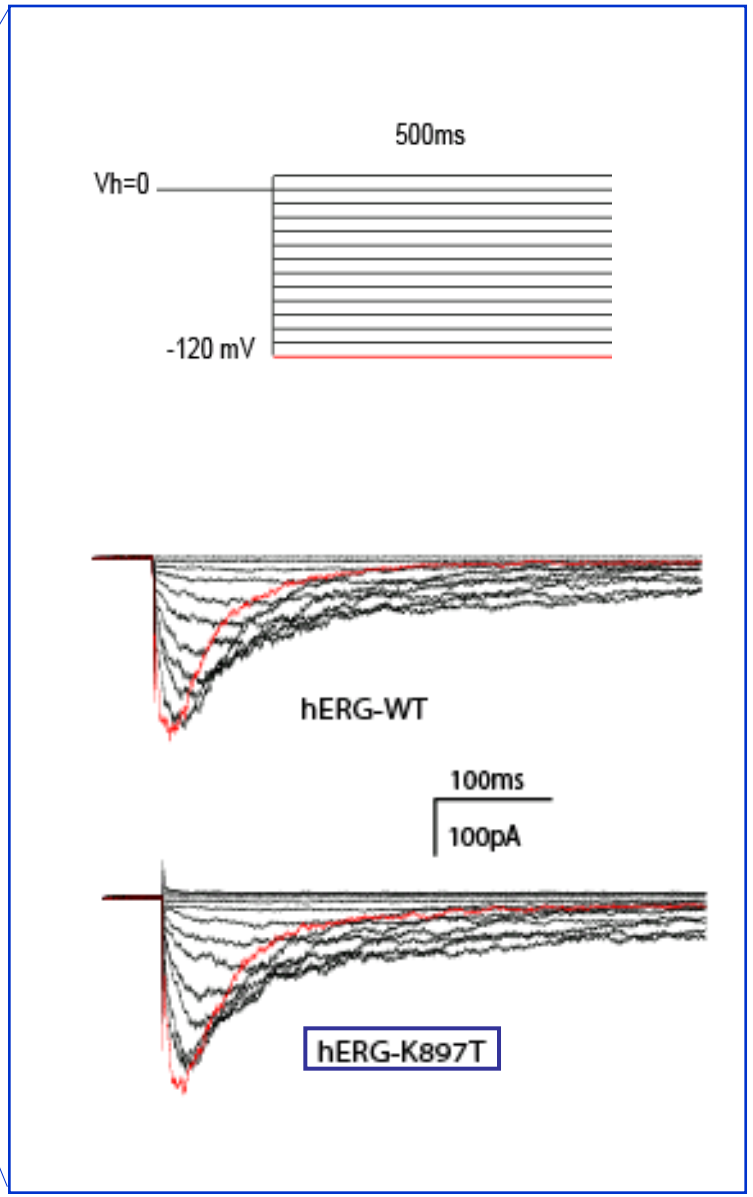


Gentile et al, PNAS 2008
Gentile et al, PNAS 2006

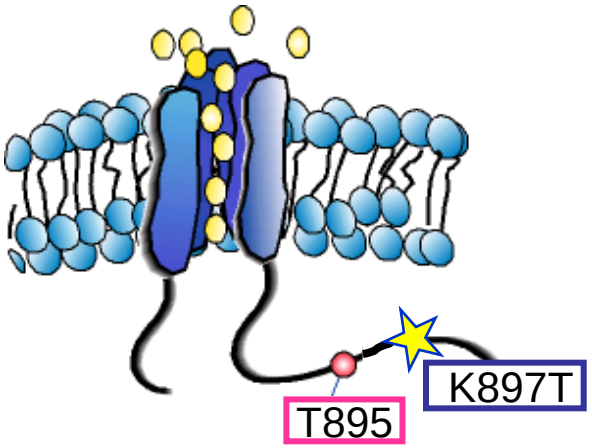
The LQT2-related K897T hERG variant is not different from WT hERG

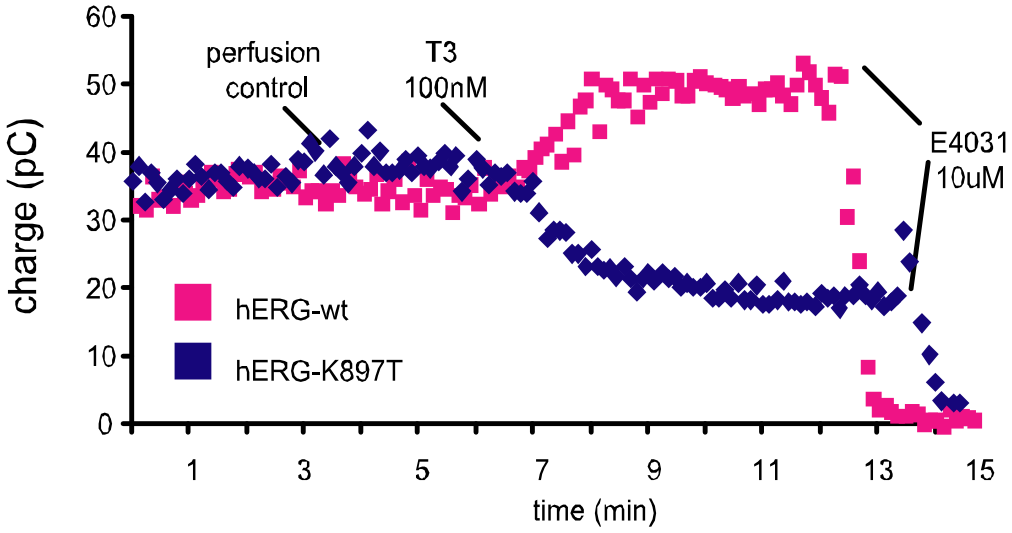


hERG-SNP K897T is associated with cardiac ventricular arrhythmia and sudden death

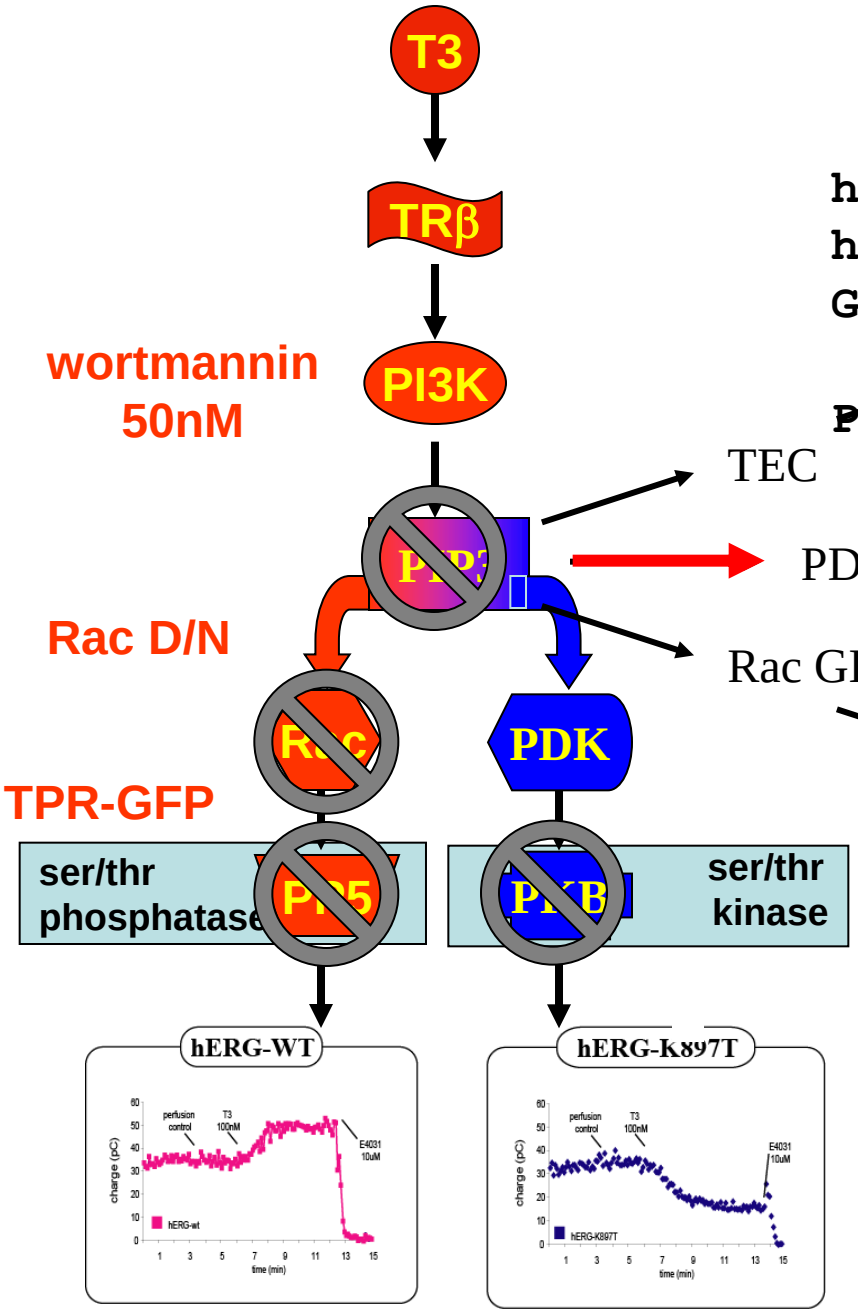


T3 inhibits hERG1-K897T activity





T3 regulates hERG-K897T through PI3K but not through Rac and PP5




```
hERG-1 897K    892- R R R T D K -897
hERG-1 897T    892- R R R T D T -897
GSK-3            4- R P R T T S -9
```

PLC

PKB active site → proliferation

TEC

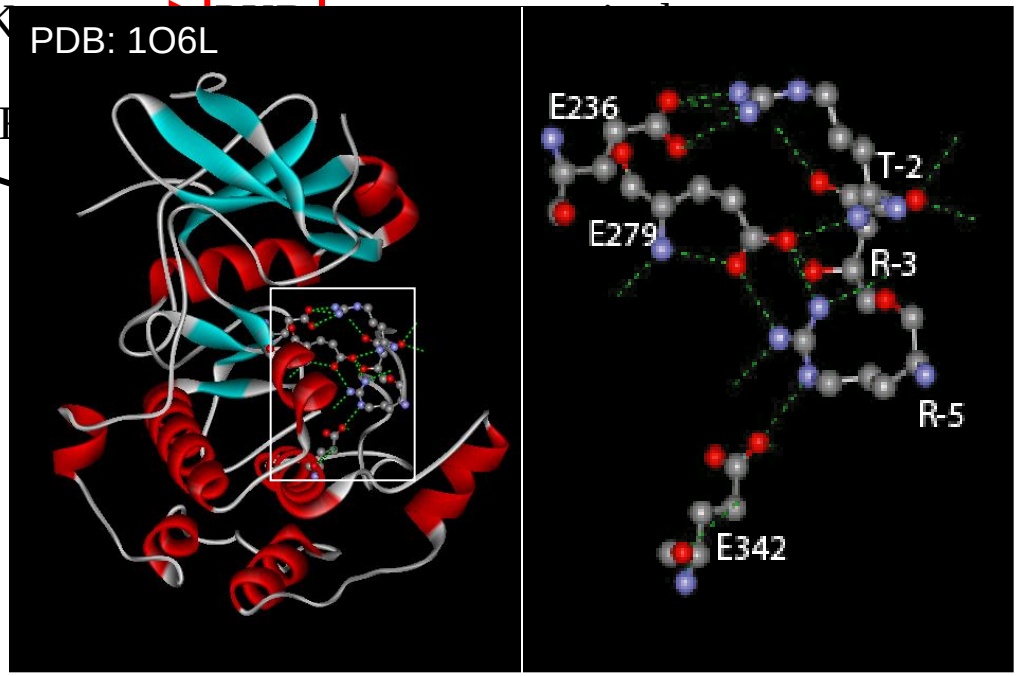
PKC

PDK

Rac GE

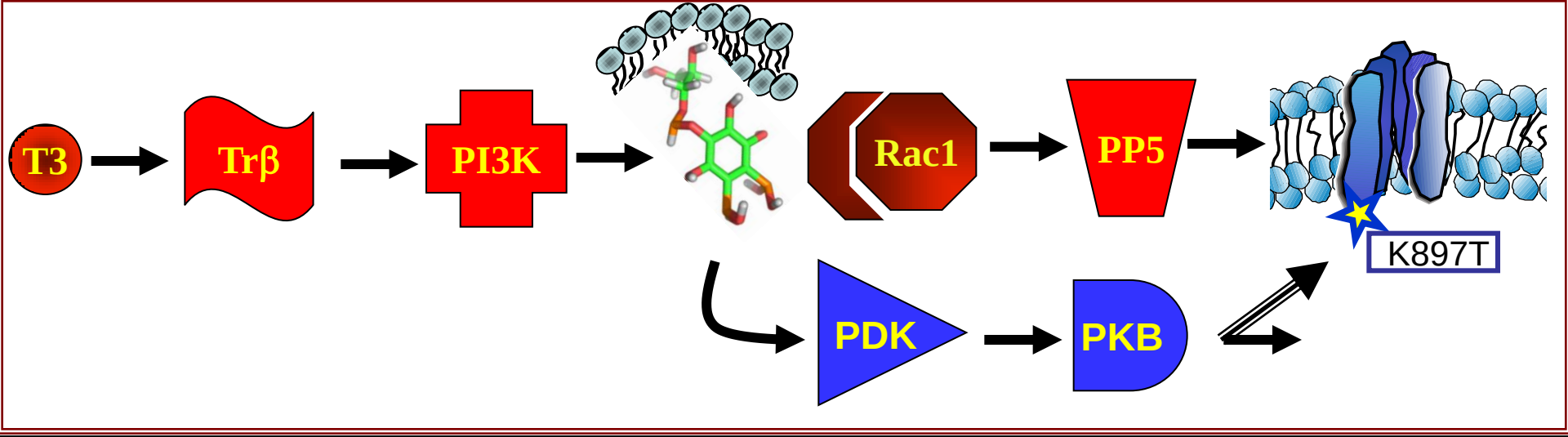
E E E

342 279 236



Crystal structure of PKB in complex with GSK-3 peptide

Model structure of PKB in complex with Kv11.1 peptide



Conclusion

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

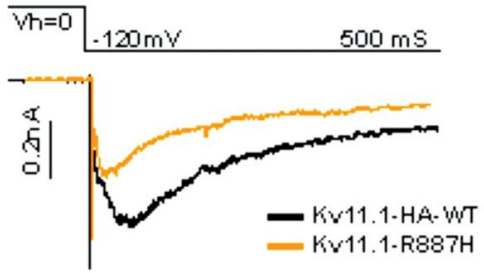
-Inhibition of Kv11.1 by PKB links a
human SNP to a fatal cardiac phenotype

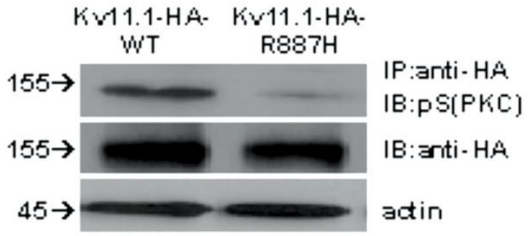
Long QT2 Mutation on the Kv11.1 Ion Channel Inhibits Current Activity by Ablating a Protein Kinase C Consensus Site.

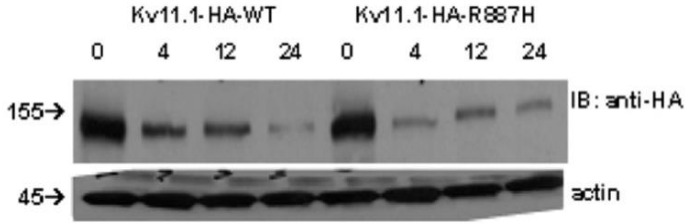
Donovan, Lansu, Williams, Denning, and Saverio Gentile

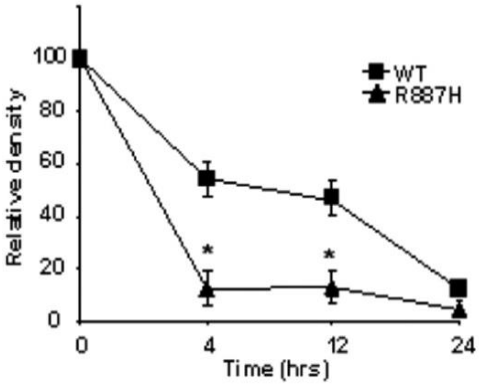
MOLECULAR PHARMACOLOGY 2012, Vol. 82, No. 3

```
PKC motif          R-R-X-S-hyd-R/K
Kv11.1-WT      887-R-K-L-S- F -R
Kv11.1-R887H   887-H-K-L-S- F -R
pS (PKC)           -R-K-X-S-hyd-R/K
```

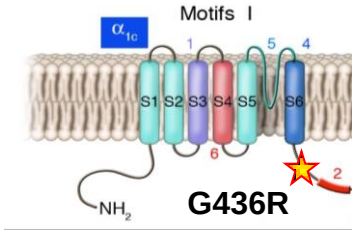


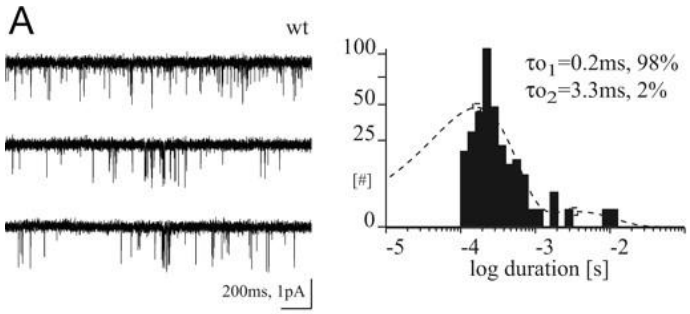


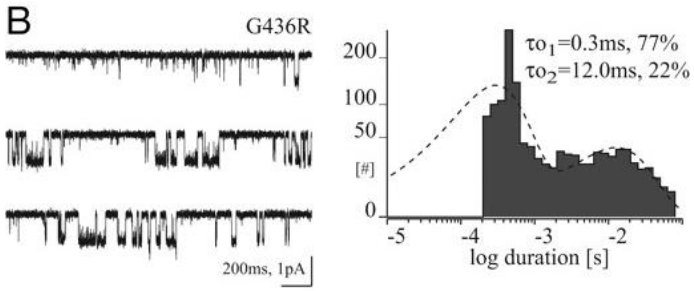




Timothy syndrome mutation creates a CAMKII consensus site



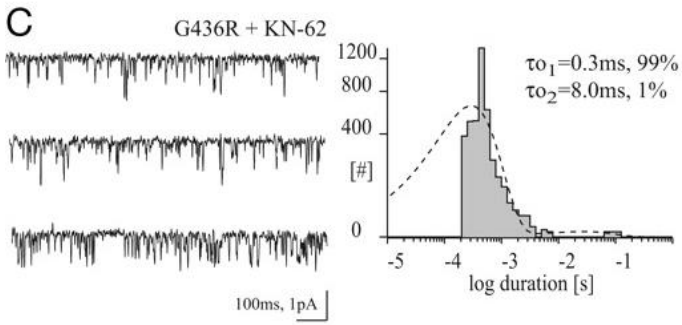


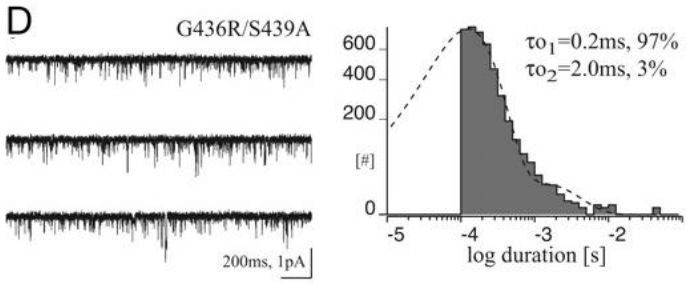


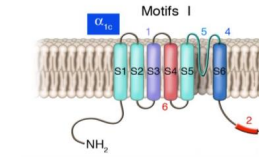
CAMKII -R-x-x-S/T

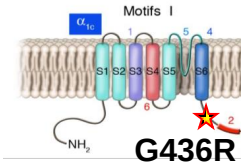
A)CaV1.2……436-G-W-D-S-439

KN-62= CAMKII inhibitor

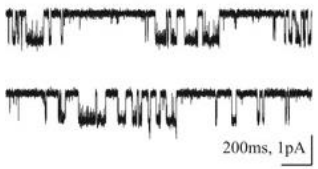


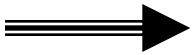






G436R





Calcium
TOXICITY

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

Kv11.1 Ion channel malfunction and Cardiac arrhythmia

CaV1.2 Ion channel malfunction and Cardiac arrhythmia

1

Creation of kinase consensus site by adding a phosphorylable residue

PKB motif			-	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	

2

Disruption of kinase consensus site by removing a docking residue

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	

3

Creation of kinase consensus site by adding a docking residue

CAMKII motif			-	R	X	D	T	-	
Cav1.2 406G	406-	G	W	D	S	-409			
Cav1.2 409R	406-	R	W	D	T	-409			

Ion channels phosphorylopathy:

A link between genomic variations and heart arrhythmia

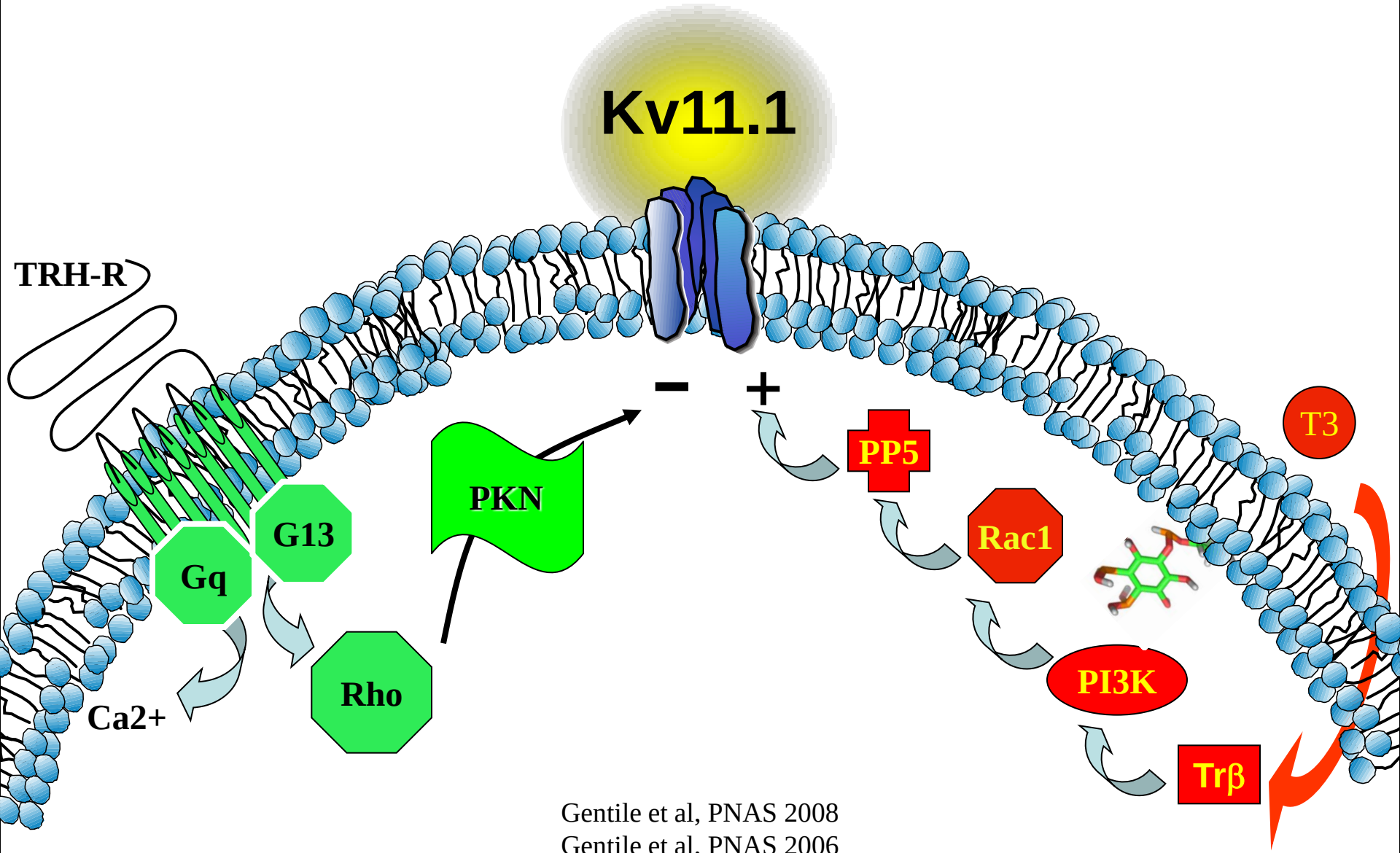
Gene	Protein	SNP	PO4	Kinase	Disease
CACNA1C	Cav1.2	S1545P	-60%	CAMKII	Timothy
KCNH2	Kv11.1	K897T	+94%	PKB	LQT2
KCNH2	Kv11.1	R176W	-94%	PKA	LQT2
KCNH2	Kv11.1	T474I	-90%	PKA	LQT2
KCNQ1	Kv7.1	G179S	+73%	GSK3	LQT1
KCNQ1	Kv7.1	Y184S	+80%	CAMKII	LQT1
KCNQ1	Kv7.1	S566F	-76%	CAMKII	LQT1
KCNQ1	Kv7.1	W392R	+75%	CAMKII	LQT1
KCNQ1	Kv7.1	A525T	+67%	PKA	LQT1
KCNQ1	Kv7.1	R583C	-91%	CAMKII	LQT1
KCNQ2	Kv7.2	N780T	+99%	CAMKII	MYOK,EPI
KCNJ1	Kir1.1	S219R	-79%	PKA	Bartter Syn.
KCNJ13	Kir1.4	T175I	-90%	CAMKII	Bartter Syn.
KCNJ12	Kir2.2	S15L	-99%	GSK3	Not reported
TRPC6	TRPC6	P15S	+96%	CK1	GMS
TRPV4	OTRPC4	P19S	+94%	CK2	Not reported

Thanks (a lot) to:

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

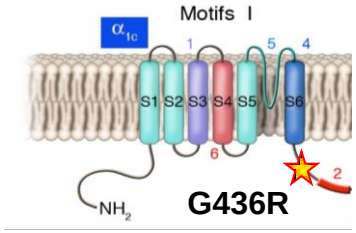
Miss. Katherine Lansu
Research assistant
2011-2012
Now Ph.D Student @ UNC

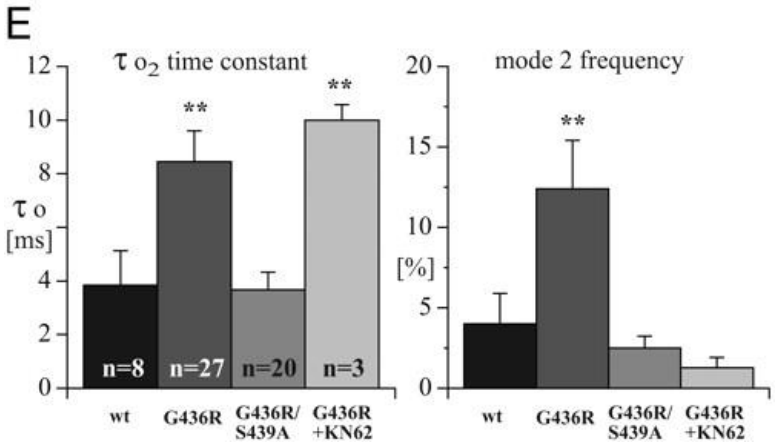
T3/TRH-dependent regulation of hERG1 channel activity



Gentile et al, PNAS 2008
Gentile et al, PNAS 2006

Timothy syndrome mutation creates a CAMKII consensus site






```
CAMKII        -R-x-x-S/T
CaV1.2.....436-G-W-D-S-439
CaV1.2.....436-R-W-D-S-439
CaV1.2.....436-R-W-D-A-439
```

Summary of the values for the long open times, τo2, as well as the frequency of mode 2 openings from the indicated number of patches expressing each construct.

Ion channel Phosphorylopathies:

Mutations that creates or disrupts phosphorylation sites on ion channels

Kv11.1 Ion channel malfunction and Cardiac arrhythmia

CaV1.2 Ion channel malfunction and Cardiac arrhythmia

1

Creation of kinase consensus site by adding a phosphorylable residue

PKB motif			-	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	

2

Disruption of kinase consensus site by removing a docking residue

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	

3

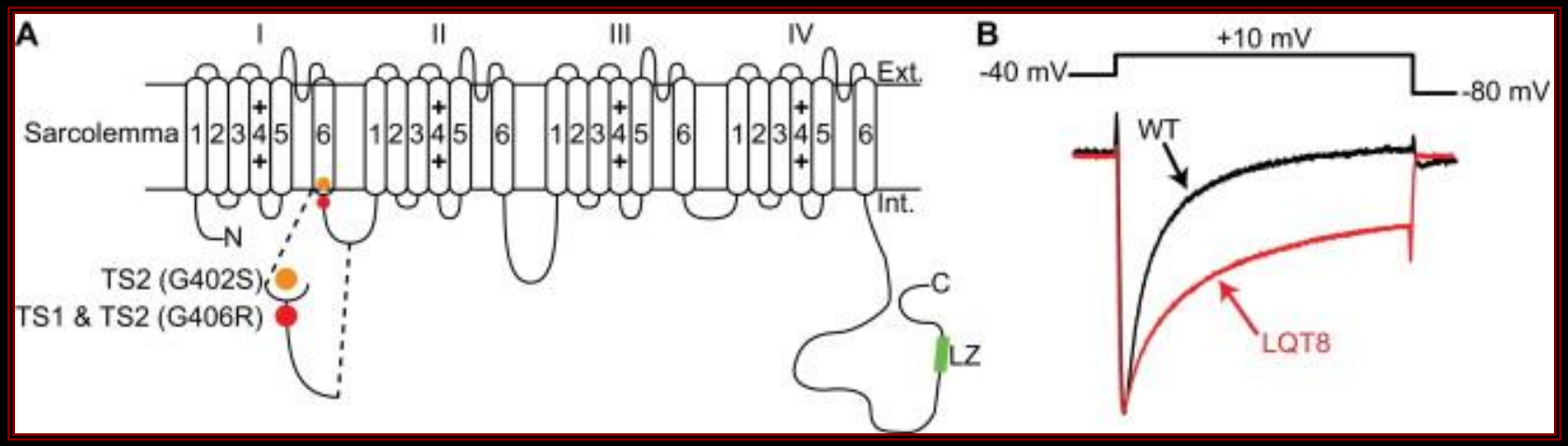
Creation of kinase consensus site by adding a docking residue

CAMKII motif			-	R	X	D	T	-	
Cav1.2 406G	406-	G	W	D	S	-409			
Cav1.2 409R	406-	R	W	D	T	-409			

gene name

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

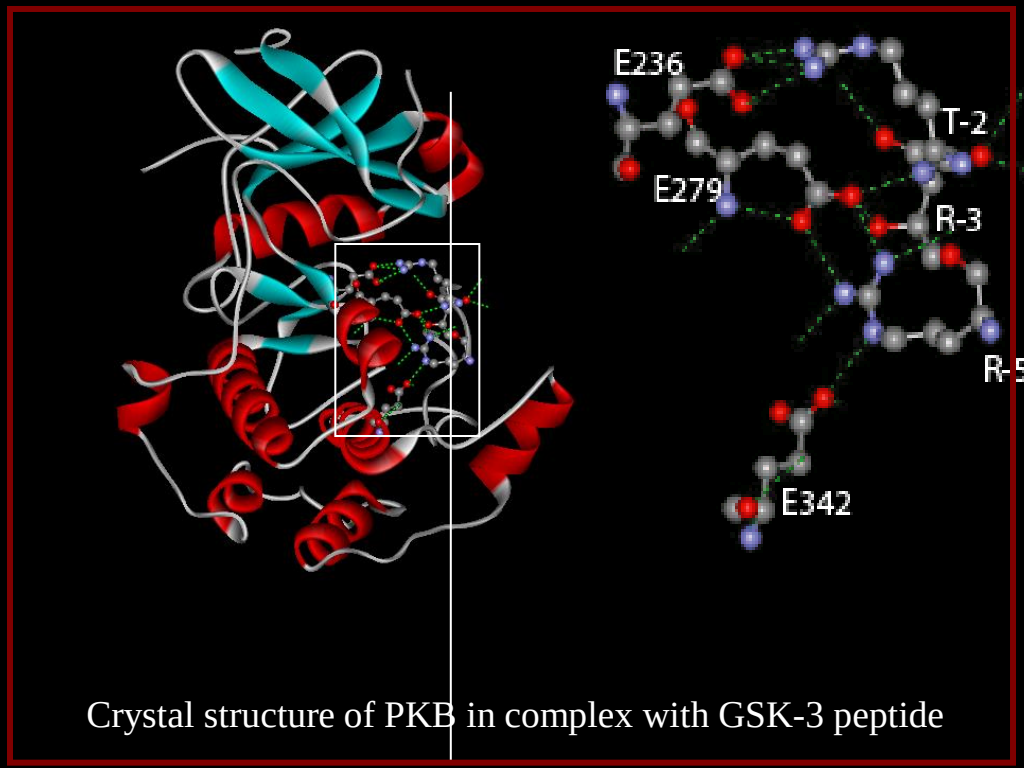
Protein name:
Cav 1.2; L-Type



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

Kinase Landscape (http://www.cbs.dtu.dk/services/NetPhosK)



Crystal structure of PKB in complex with GSK-3 peptide

Thanks' for your kind attention!!!!!

Let Us Meet Again

We welcome you all to our future conferences of OMICS Group International

Please Visit:

www.omicsgroup.com

www.conferenceseries.com

http://cardiology.conferenceseries.com/