Ion channel mutations and disease:

Insights from theoretical models

Genetic mutations in Na^+ channels underlie clinical syndromes

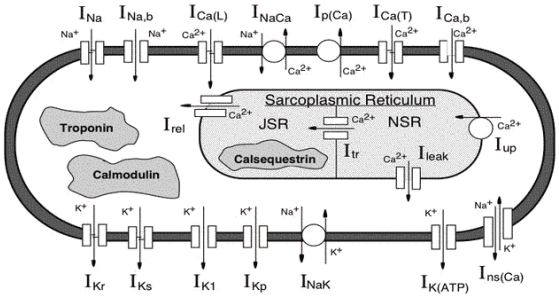
- SCN5A (Cardiac) The Long-QT syndrome, Brugada Syndrome, Isolated cardiac conduction disorder
- SCN4A (Skeletal) hyperkalemic periodic paralysis, paramyotonia congenita and potassium-aggravated myotonias
- SCN1A (CNS) epilepsy, familial autism
- SCN2A (CNS) epilepsy
- SCN3A (CNS) familial autism
- SCN8A (CNS) epilepsy

Integration:

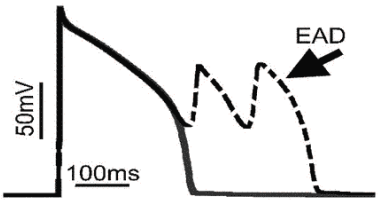
1. genetic mutation

3p 21-24

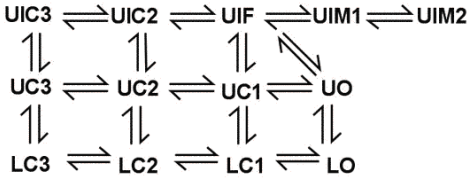
LQT3, SCN5A



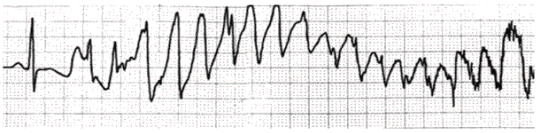
3. cardiac cell model



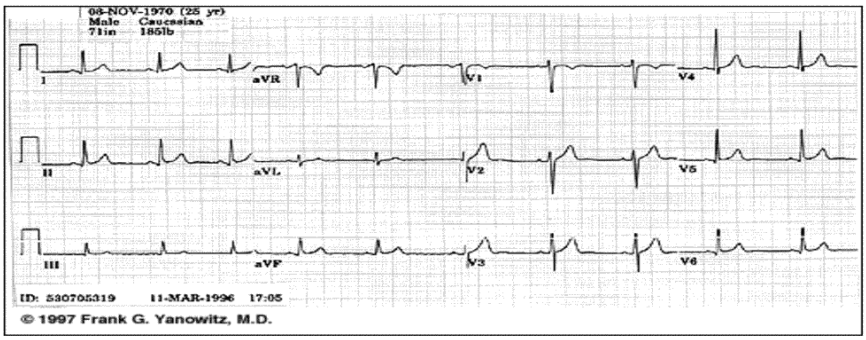
2. altered channel function



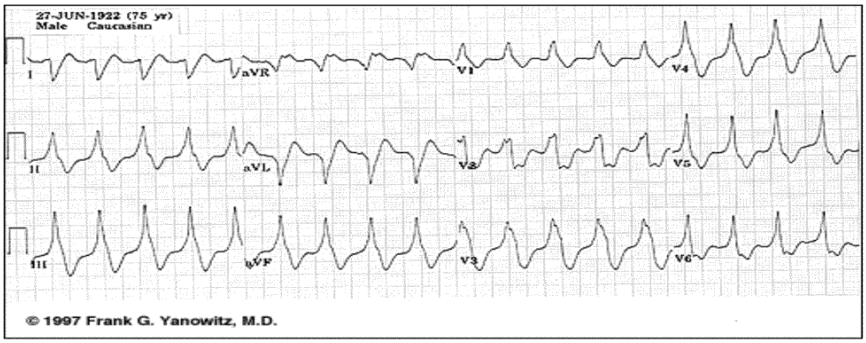
4. cardiac arrhythmia



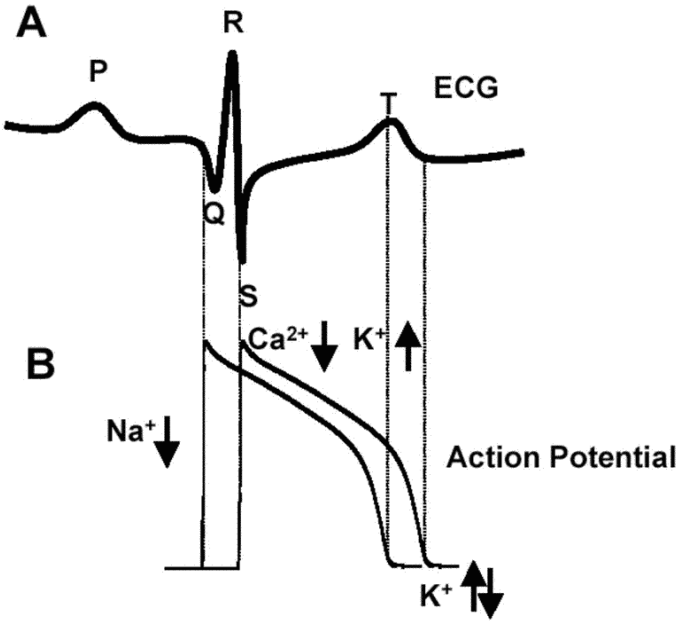
Normal ECG



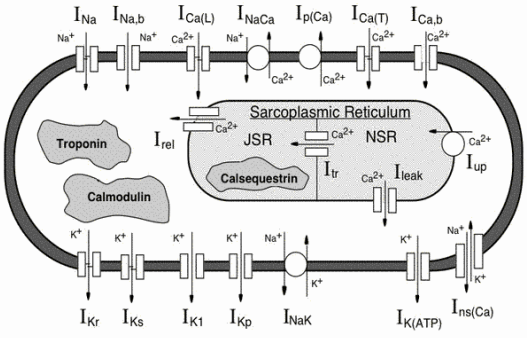
Ventricular tachycardia



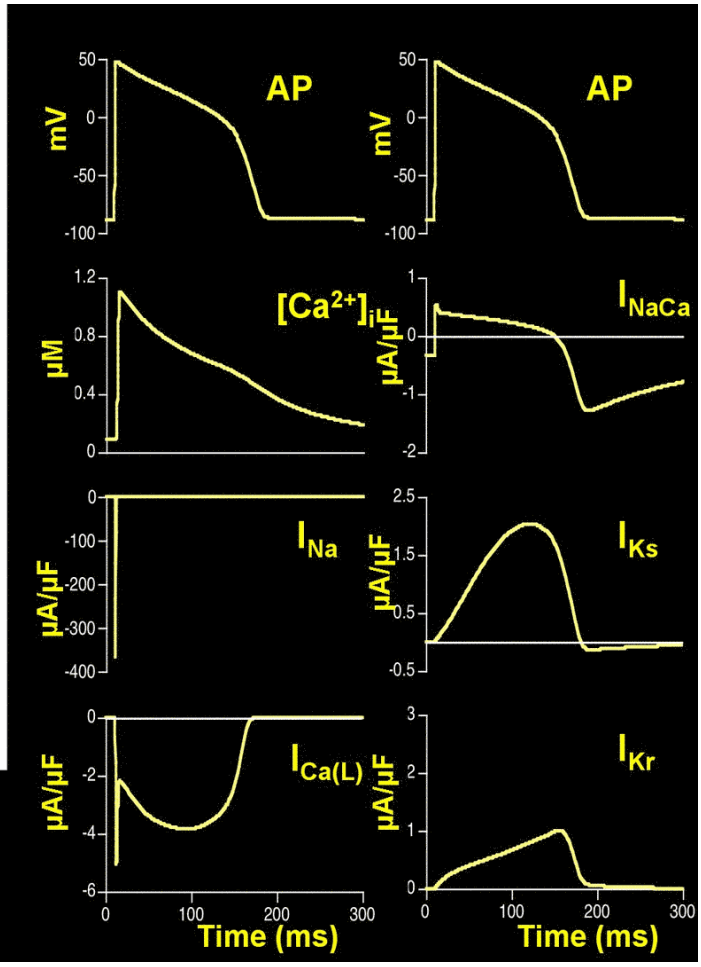
The ECG reflects cellular electrical processes



Luo-Rudy AP model



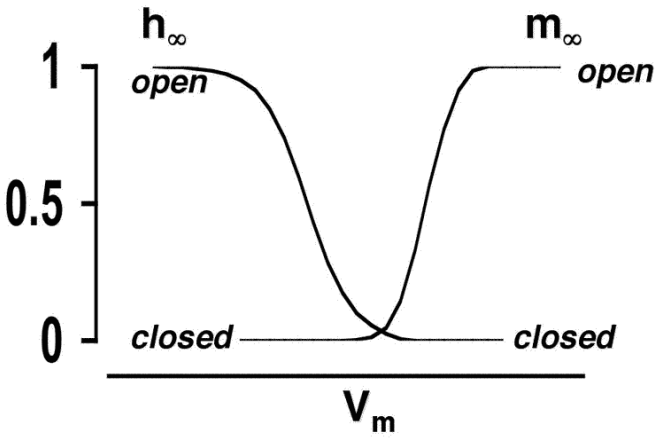
$$I_s = G_s \bullet P_{O,s} \bullet (V_m - E_s)$$



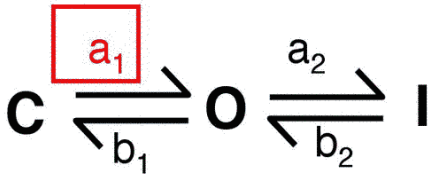
Colleen E. Clancy, PhD, Columbia University, New York, NY (KITP Ventricular Workshop 10-9-03) Cellular models

The Hodgkin-Huxley framework

$$I_{Na} = m^3 h^* g_{Na} * (E-E_{Na})$$



Markov models can incorporate mutations that affect discrete transitions



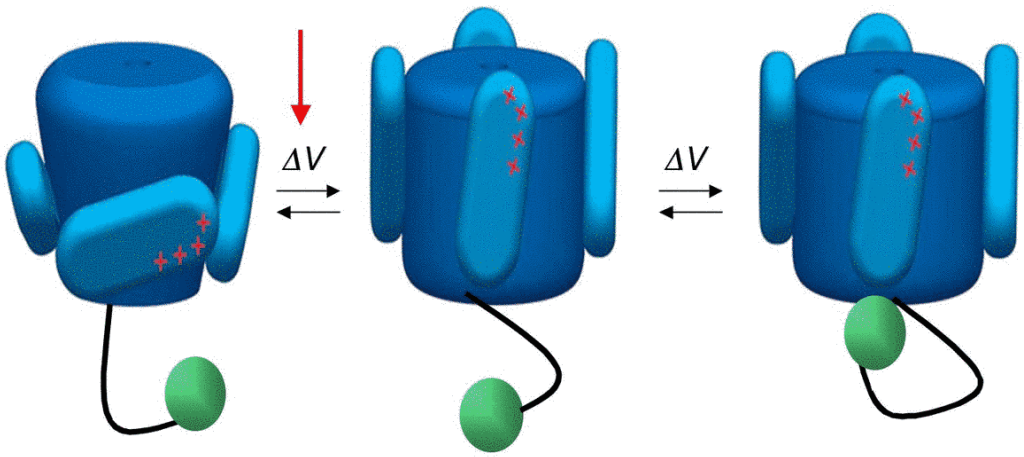


Figure adapted from Y. Jiang et al. Nature. 2003 May 1;423(6935):33-41.

Computation of state probabilities

$$C \underset{b_1}{\overset{a_1}{\rightleftharpoons}} O \underset{b_2}{\overset{a_2}{\rightleftharpoons}} I$$

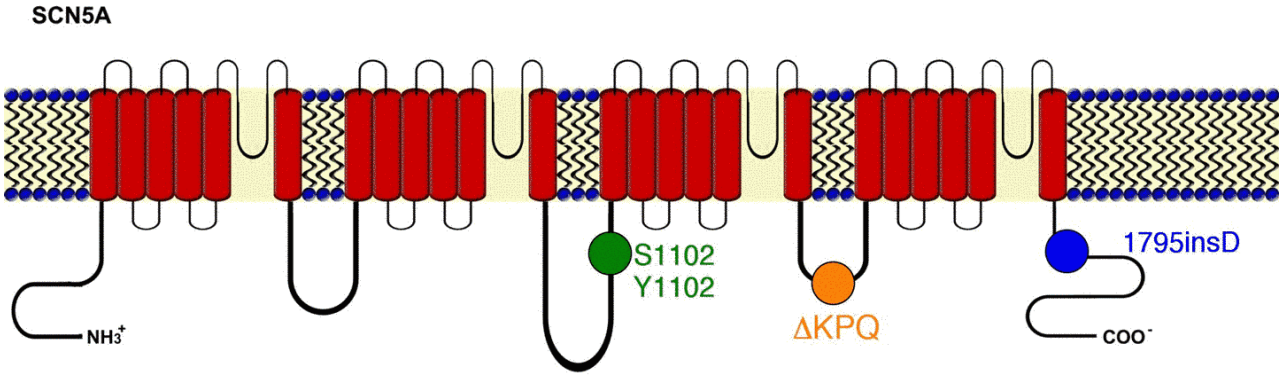
$$dP_i/dt = \sum_{j=1}^{N}[k_{ji} \bullet P_j(t,V_m)] - \sum_{j=1}^{N}[k_{ij} \bullet P_i(t,V_m)]$$

$dC/dt = P(O) \bullet b_1 - P(C) \bullet a_1$

$dO/dt = P(C) \bullet b_1 + P(I) \bullet b_2 - (P(O) \bullet (a_2 + b_1))$

$dI/dt = 1 - P(O) - P(C)$

Cardiac I_{Na}



ΔKPQ

The first mutation linked to Long-QT Syndrome

Three amino acid deletion in the channel inactivation gate.

1795insD*

Single amino acid insertion underlies

BOTH

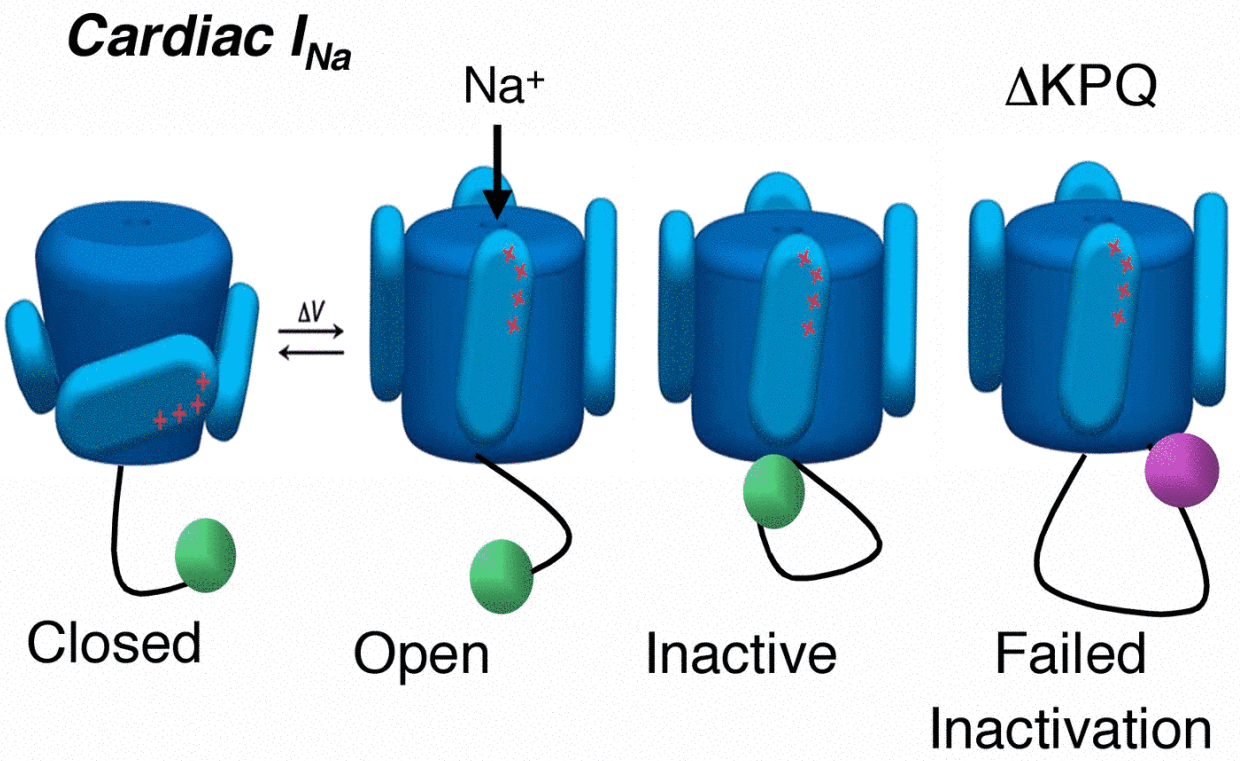
Long QT and Brugada Syndromes

S or Y 1102**

Genetic polymorphism in 13.2% of african americans

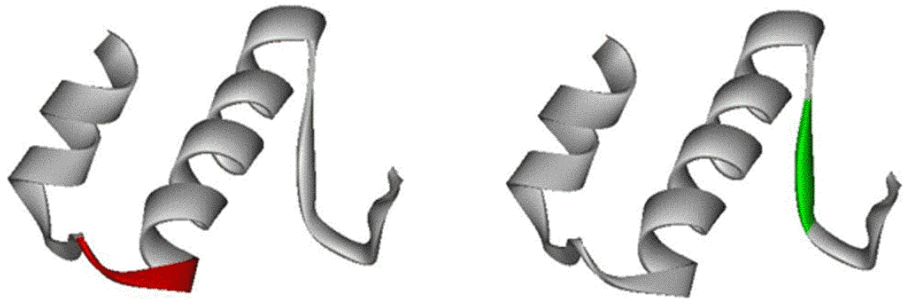
Predisposition to drug induced arrhythmia.

•Clancy and Rudy. 1999. Nature. 400. 566-569.



ΔKPQ channels may fail to inactivate

The Na+ channel III-IV linker → Fast inactivation

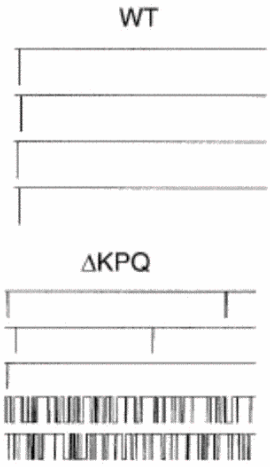


DNFNQQKKKLGGQDIFMTEEQKKYYNAMKKLGSKKPQKPIPRPLNKYGFIFD

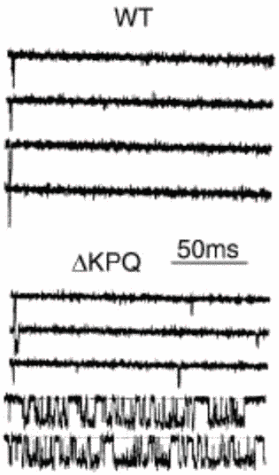
Kinetics of I_{Na}

Single channels

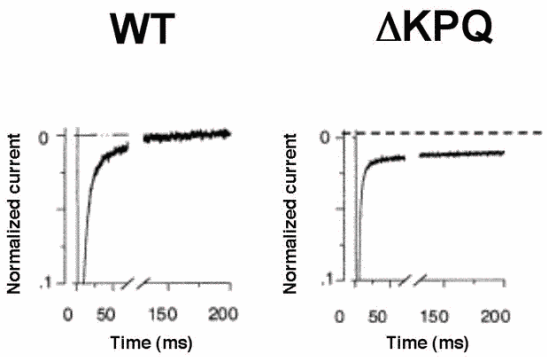
Simulation*



Experiment**



Whole cell ***

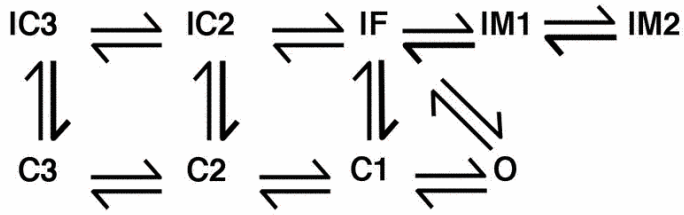


* Clancy and Rudy. 1999. Nature. 400. 566-569.
**Chandra, Starmer and Grant. 1998. AJP. H1643-H1654

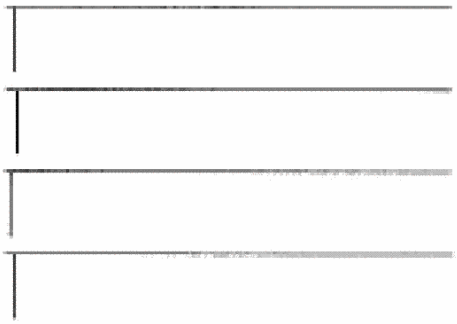
*** Bennett et al. 1995. Nature. 376. 683-685.

Modeling kinetics of I_{Na}

Markovian I_{Na}

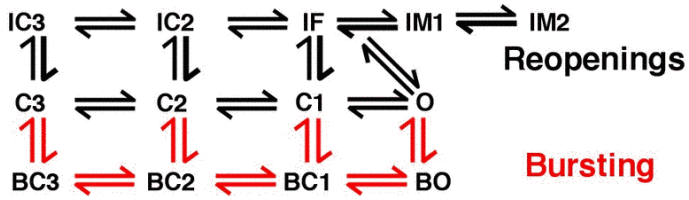


Simulated I_{Na} gating*



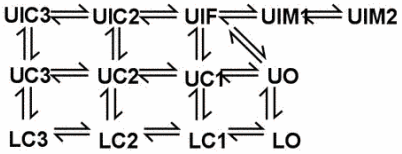
Modeling kinetics of ΔKPQ I_{Na}

Clancy-Rudy* Markovian I_{Na}

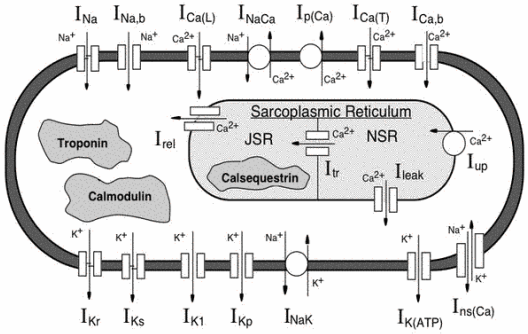


Simulated I_{Na} gating*

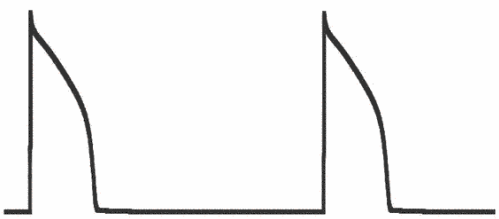
Markovian I_{Na}



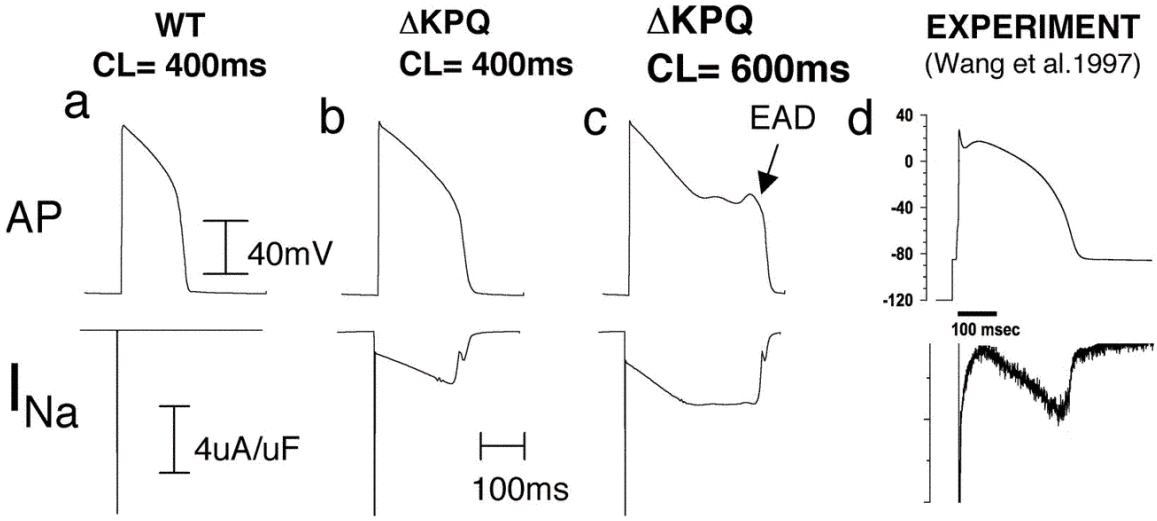
Luo-Rudy AP model



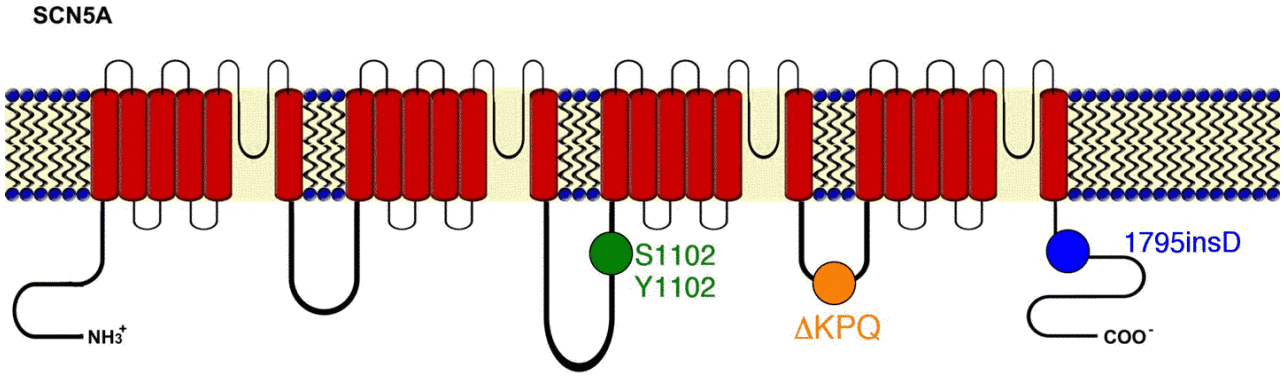
Action potential simulations



ΔKPQ Prolongs the Action Potential



Cardiac I_{Na}



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Single amino acid insertion underlies

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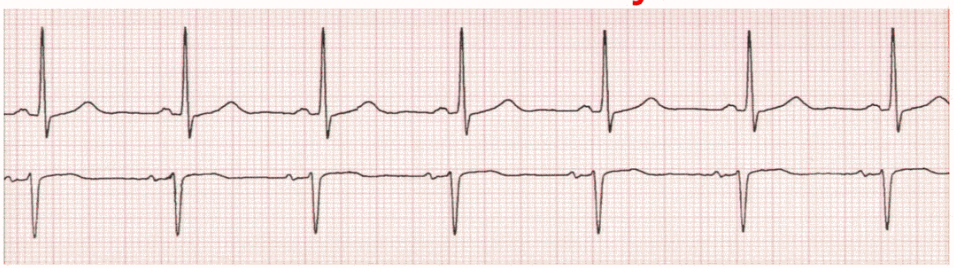
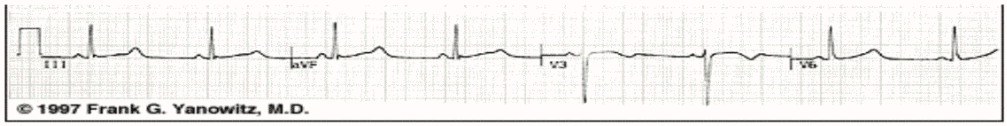
From Clancy and Rudy.
Circulation: 2002:105:1208-1213.

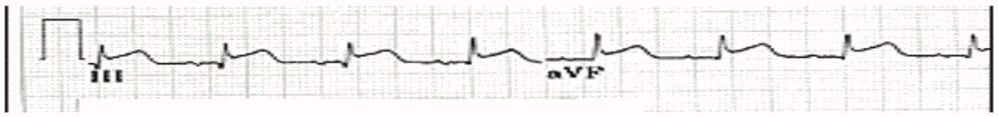
Normal Sinus Rhythm



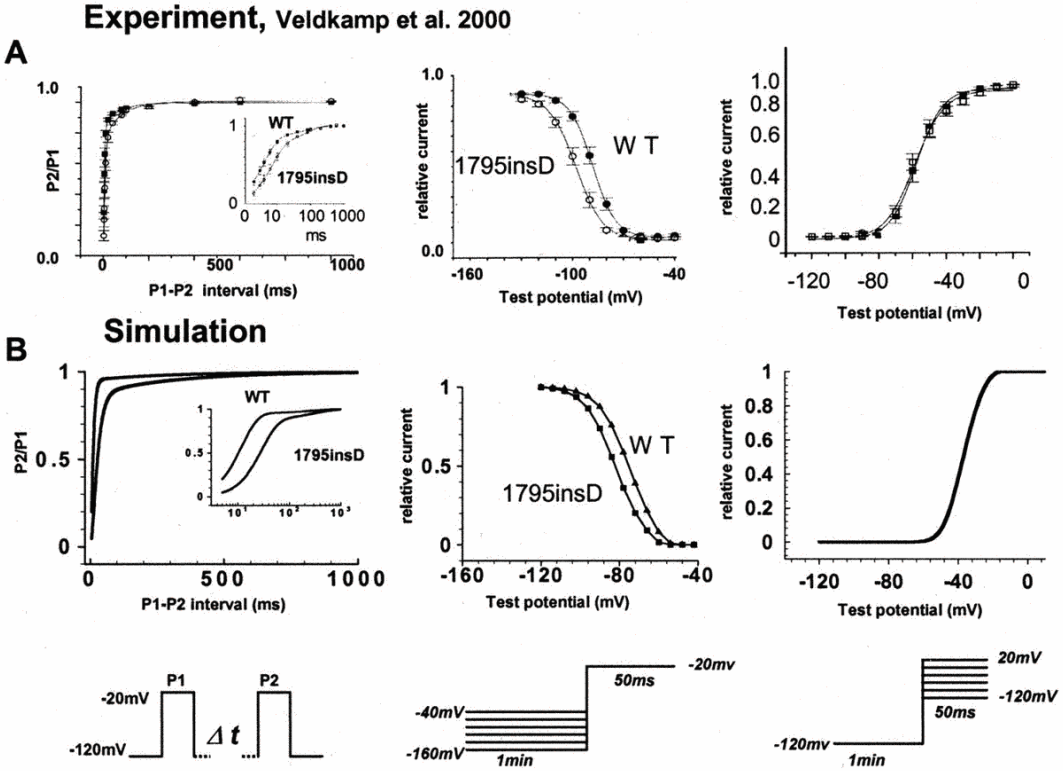
Long QT interval



ST segment elevation

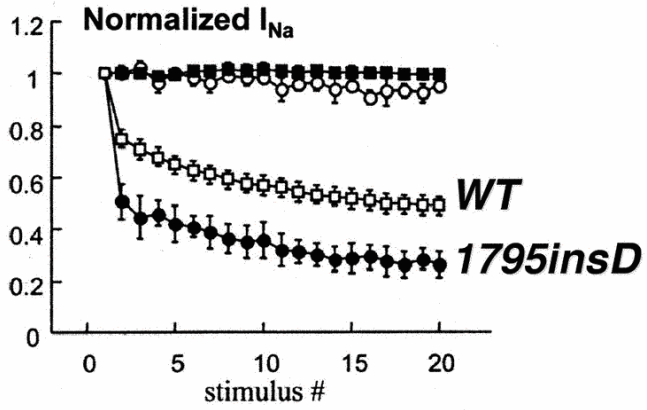


The 1795insD mutation slows recovery from inactivation and reduces channel availability

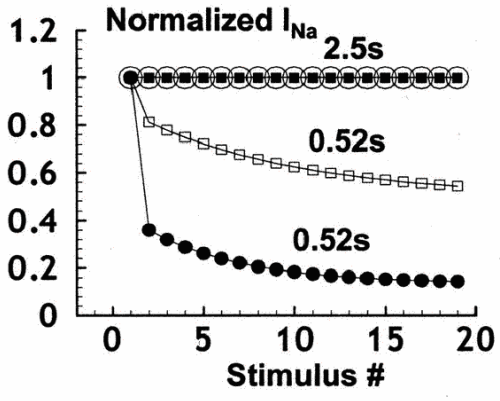


1795insD induced slower recovery from inactivation results in rate dependent current reduction

Experiment (Veldkamp et al.)

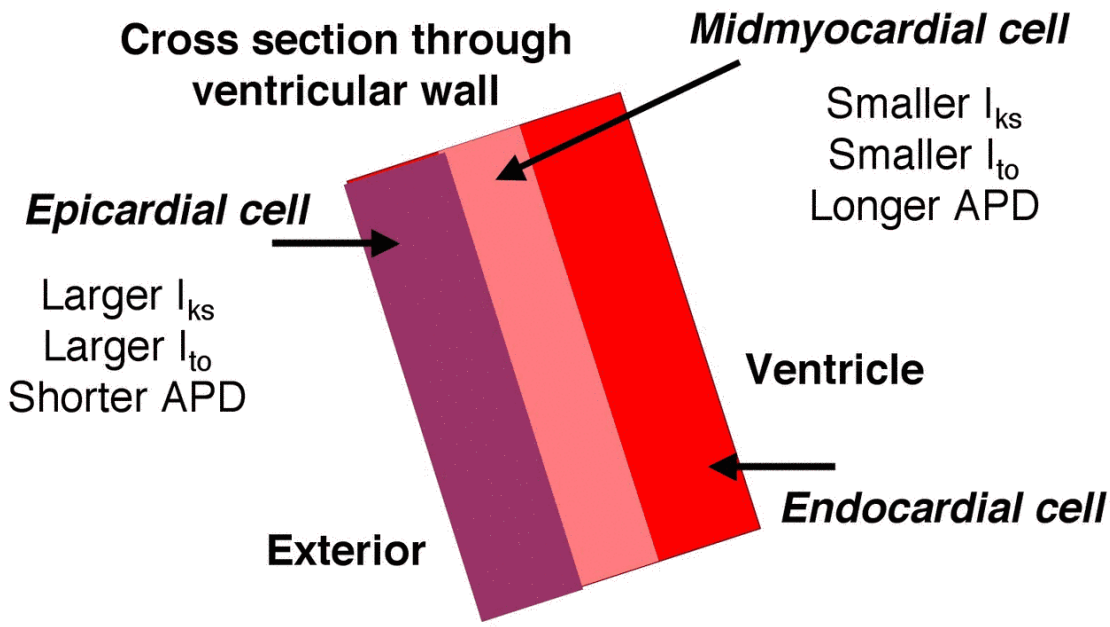


Simulation

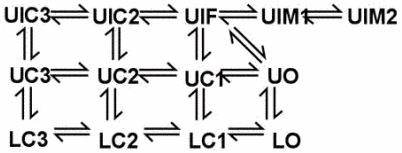


Epicardial vs. Midmyocardial cells

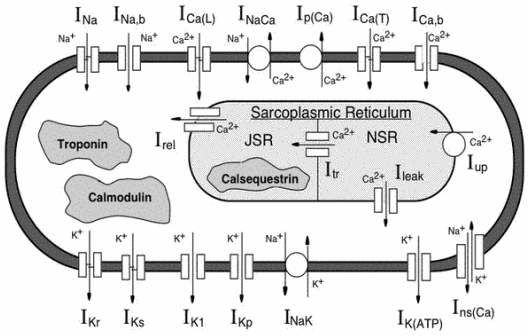
APD = Action Potential Duration



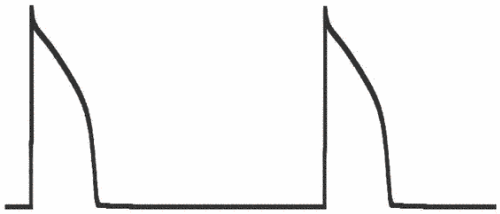
Markovian I_{Na}



Luo-Rudy AP model



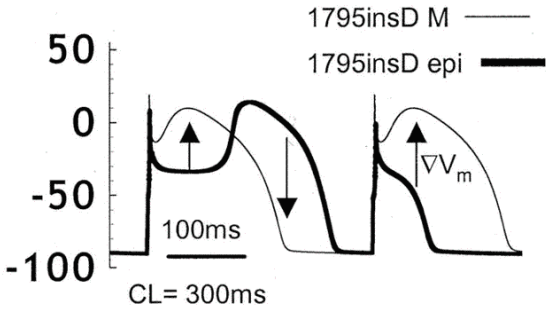
Action potential simulations



1795insD interaction with the heterogeneous myocardium

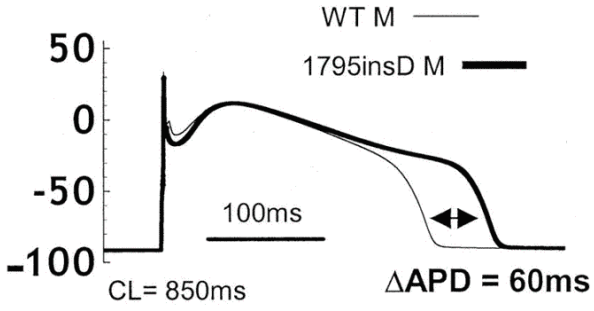
1795insD altered recovery kinetics underlies:

A ST elevation

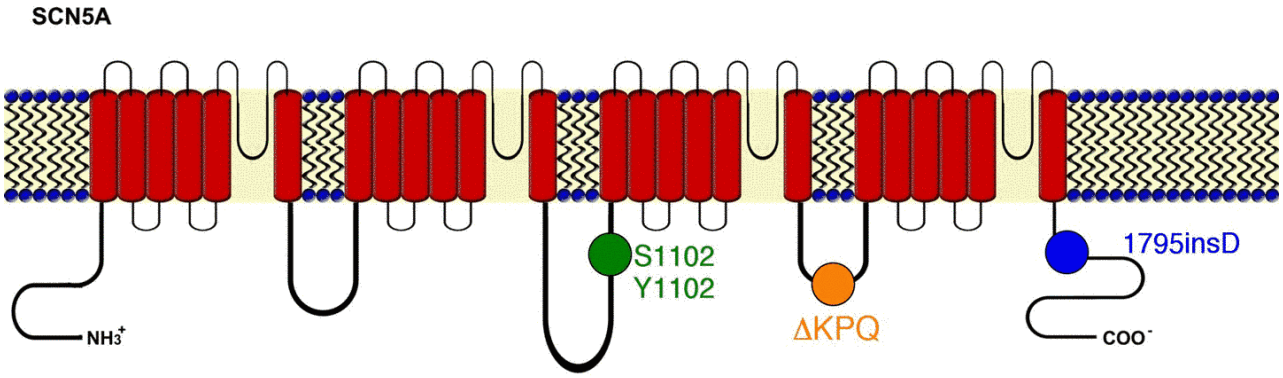


1795insD destabilizes inactivation (bursting channels) leading to:

B QT prolongation



Cardiac I_{Na}



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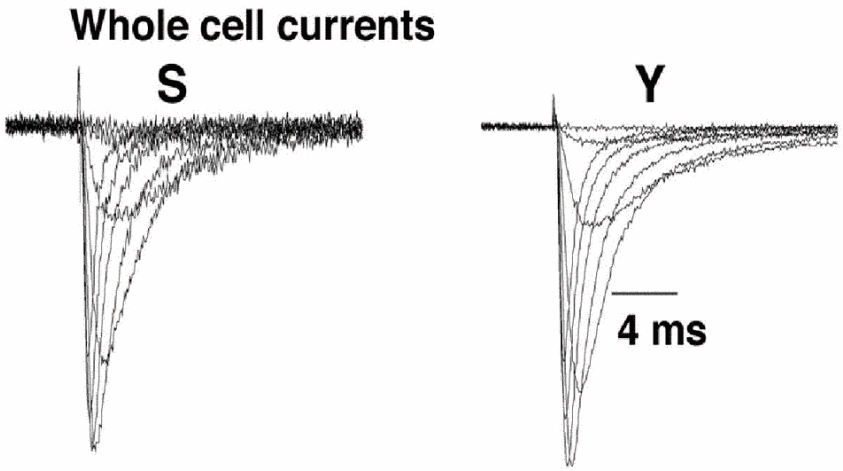
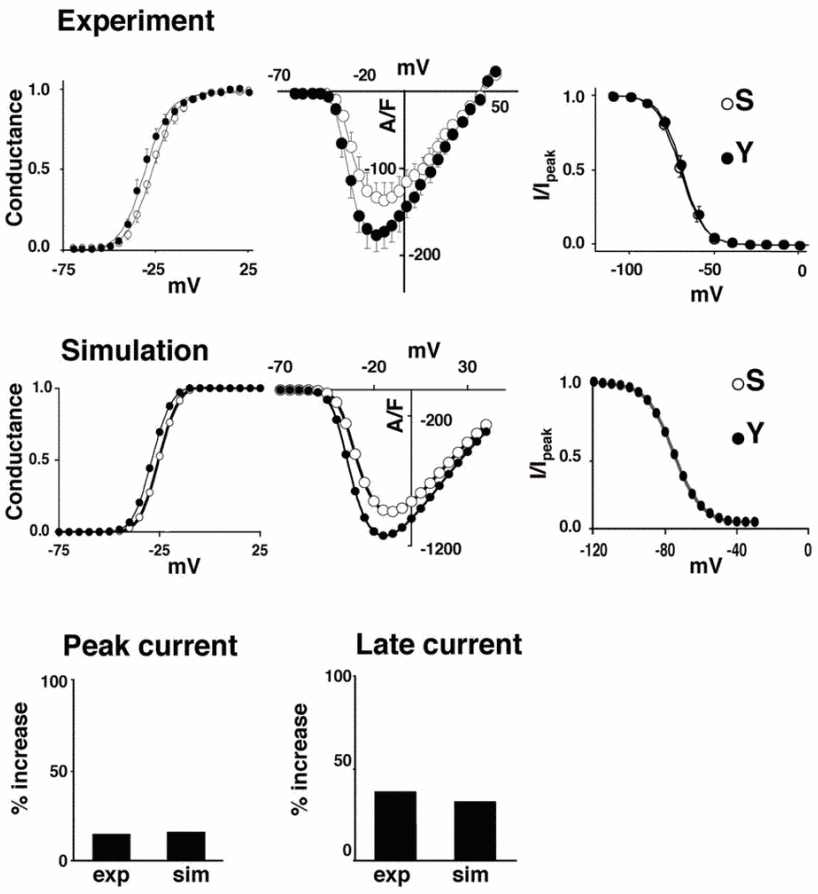
From Splawski, I. et al. 2002. Science. 297. 1333-36.

The Y1102 polymorphism has subtle effects on channel gating

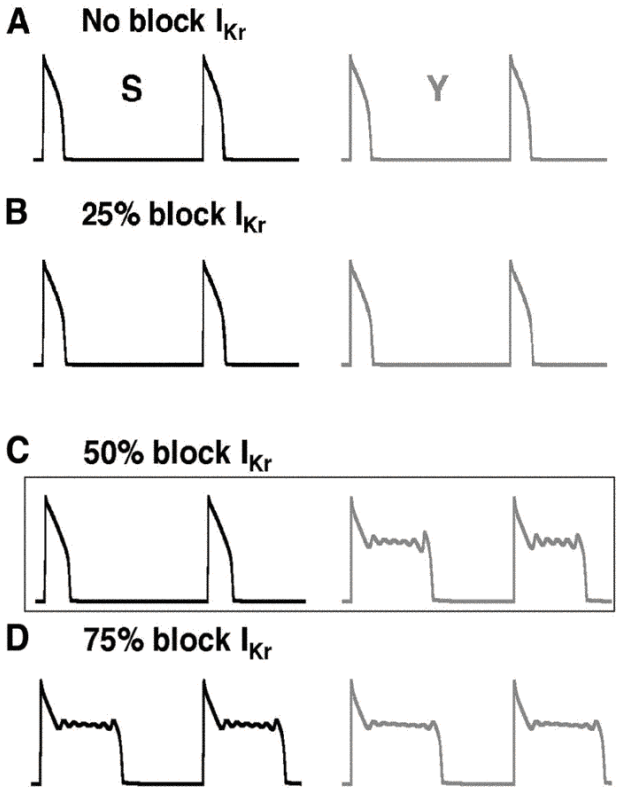


Y1102 causes a -5mV shift in activation gating.

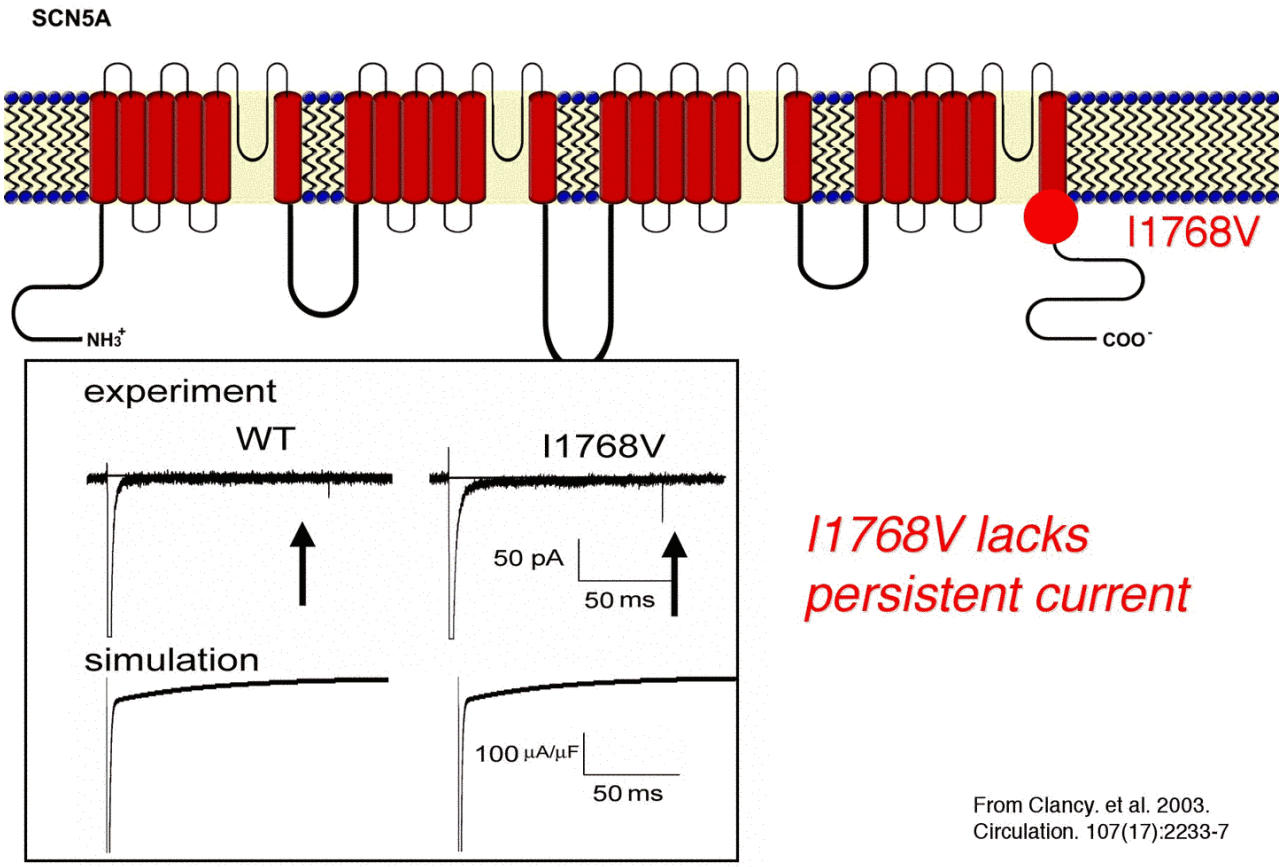
Consistent with experiments, the simulation predicts a 20% increase in peak current.



Y1102 facilitates development of triggered arrhythmias in the presence of K^+ channel block



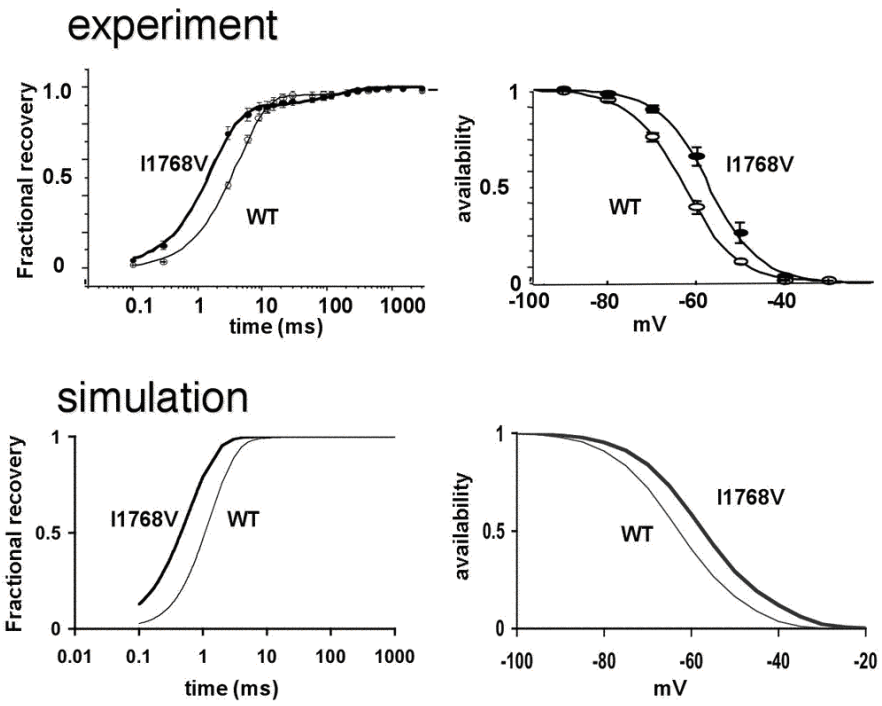
The LQT-3 mutation I1768V is unlike the others



I1768V lacks persistent current

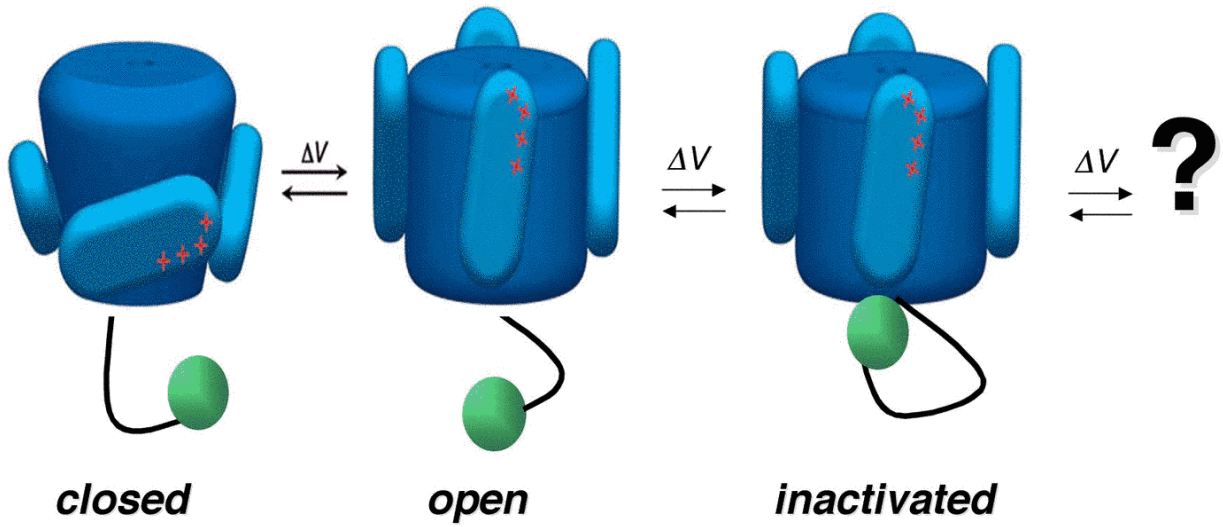
From Clancy. et al. 2003. Circulation. 107(17):2233-7

I1768V alters channel recovery from inactivation



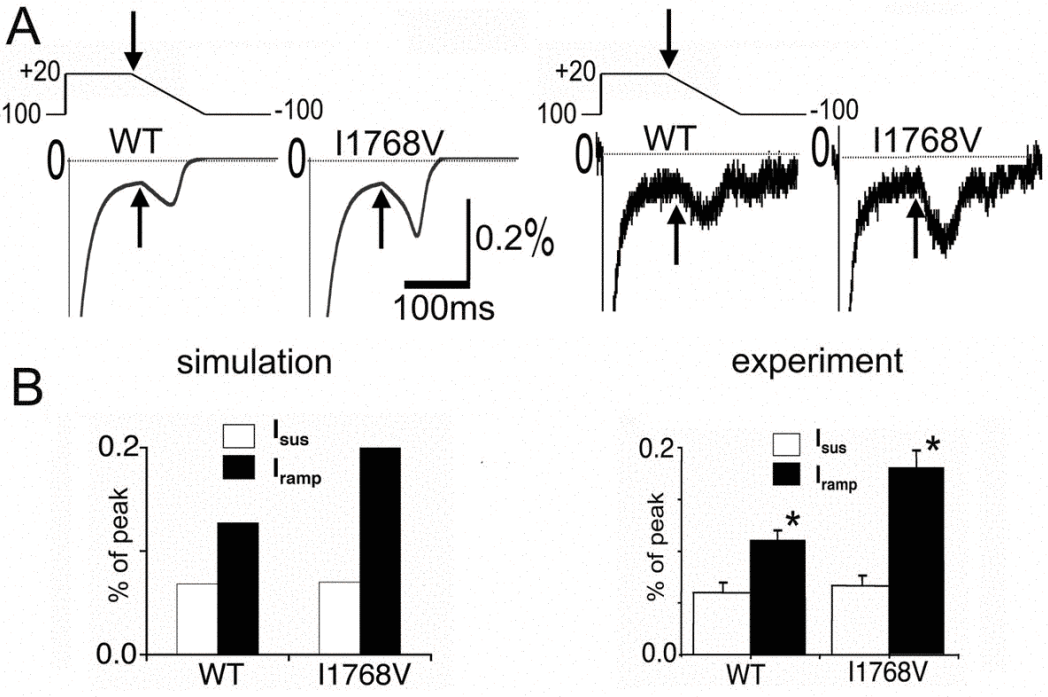
Question: *Can we use theoretical techniques to guide experiments and elucidate the mechanism of I1768V induced Long-QT?*

Exploration of non-equilibrium gating in cardiac Na^+ channels

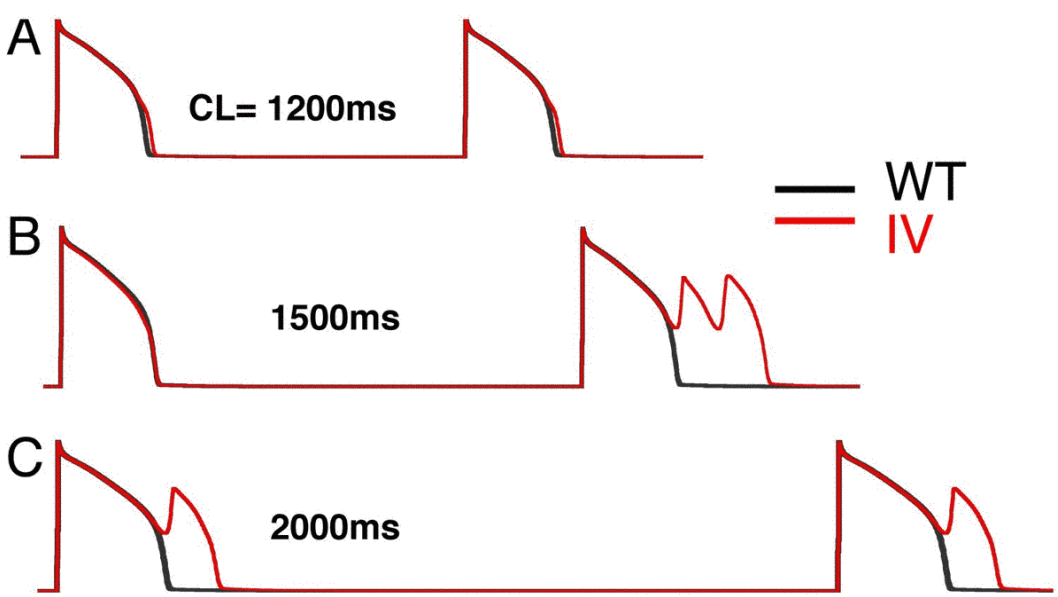


Does I1768V affect transitions out of the inactivation state?

The negative ramp protocol



I1768V prolongs the action potential



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Yoram Rudy (CWRU)

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Igor Splawski (Harvard University)

Mark Keating (Harvard University)