

HRC2010 - Birmingham, October 4th 2010
NOVEL MECHANISMS AND THERAPUETIC TARGETS

Genetic and Genomics

Andrew Grace
Papworth Hospital and Cambridge University

‘ The Human as an Experimental System in Molecular Genetics ’

- **The core of genetics is to screen for mutations that cause detectable, heritable changes in biological form or function**

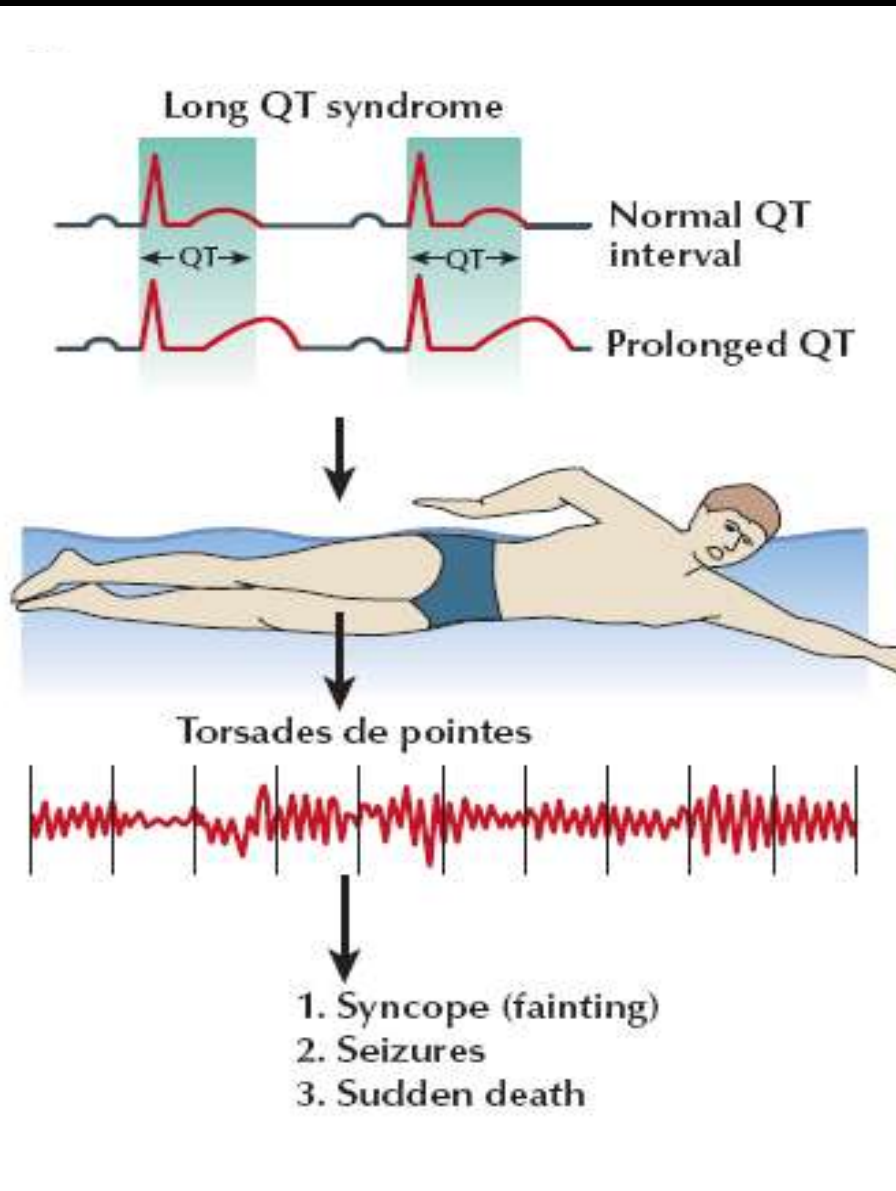
Ray White, *Science* 1988

‘ The Human as an Experimental System in Molecular Genetics ’

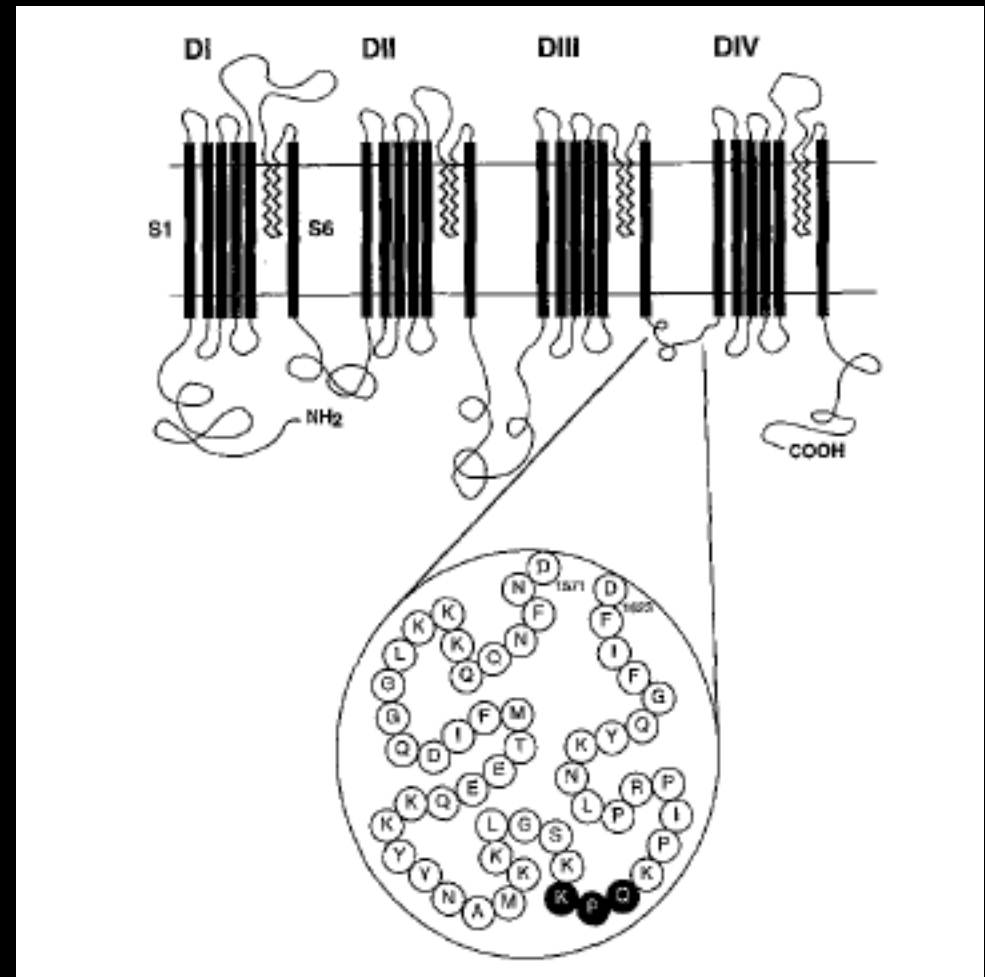
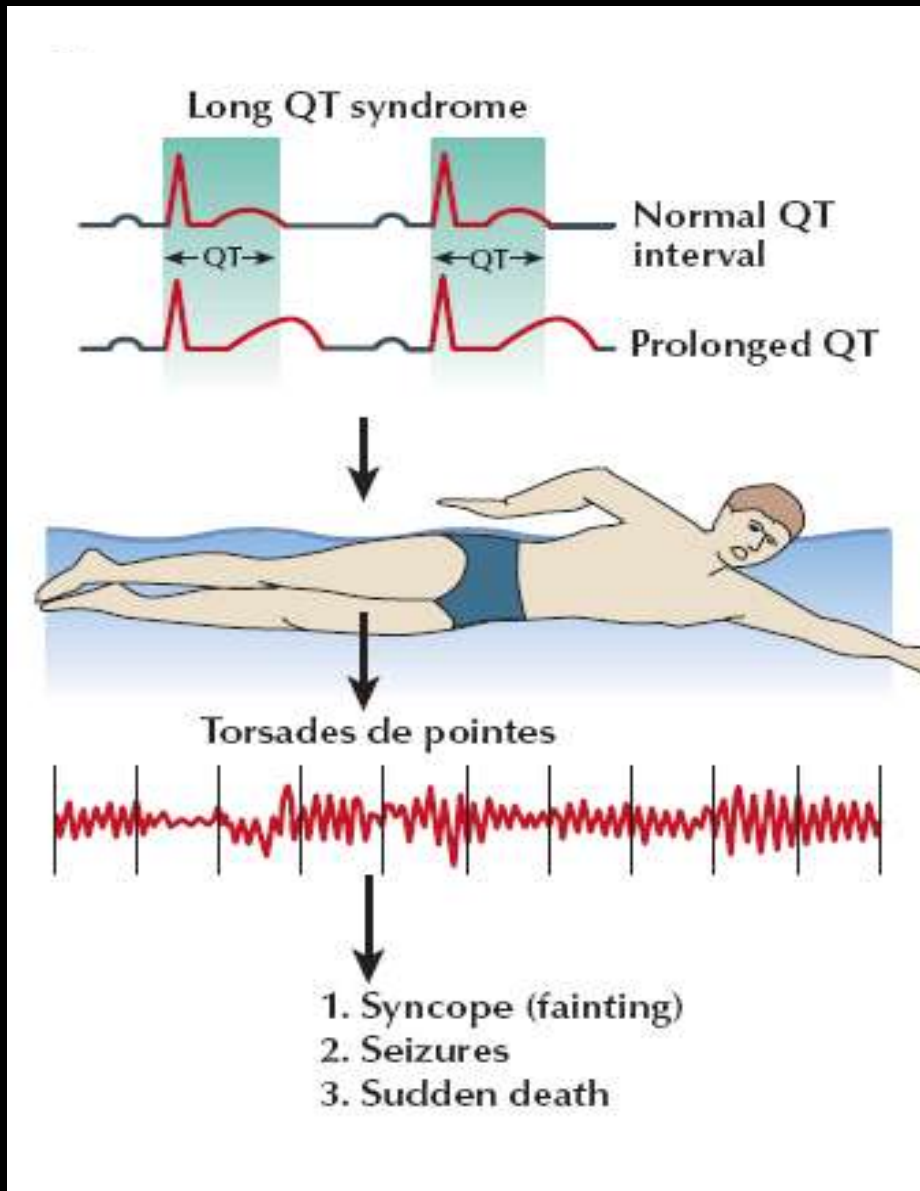
- The core of genetics is to screen for mutations that cause detectable, heritable changes in biological form or function**
- Human genes have historically been identified when affected by mutations producing genetic disease**

Ray White, *Science* 1988

Long QT Syndrome



Long QT Syndrome



Cell, Vol. 80, 805-811, March 10, 1995, Copyright © 1995 by Cell Press

SCN5A Mutations Associated with an Inherited Cardiac Arrhythmia, Long QT Syndrome

'Monogenic' Disorders

Simple Mendelian disorders caused by ~1000 Disease-causing genes

e.g. Hypertrophic cardiomyopathy, Long-QT syndrome, Brugada syndrome etc.

'Monogenic' Disorders

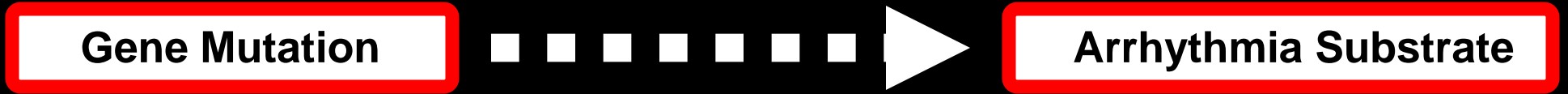
Simple Mendelian disorders caused by ~1000 Disease-causing genes

e.g. Hypertrophic cardiomyopathy, Long-QT syndrome, Brugada syndrome etc.

Characterisation 'monogenic' diseases

- 1. Careful phenotyping**
- 2. Genotyping: positional cloning, candidate gene**
- 3. Genetic modifiers**

ARRHYTHMIAS AND GENETIC HEART DISEASE



Gene Mutation

Arrhythmia Substrate

ARRHYTHMIAS AND GENETIC HEART DISEASE

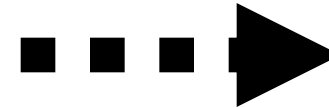
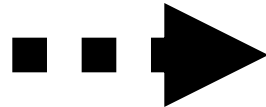
Gene Mutation



Arrhythmia Substrate

Indirect Relationship e.g. Hypertrophic Cardiomyopathy

**Sarcomere
Mutation**



**Ventricular
Fibrillation**

ARRHYTHMIAS AND GENETIC HEART DISEASE

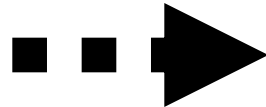
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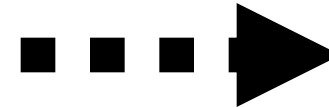
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Indirect Relationship e.g. Hypertrophic Cardiomyopathy

**Sarcomere
Mutation**



**Structural
Disorganization**



**Ventricular
Fibrillation**

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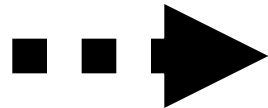
Gene Mutation



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Indirect Relationship e.g. Hypertrophic Cardiomyopathy

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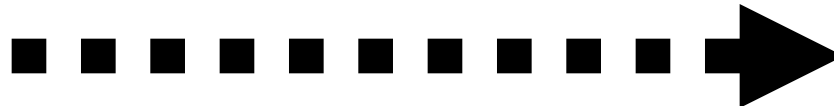
**Structural
Disorganization**



**Ventricular
Fibrillation**

Putative Direct Relationship e.g. Brugada Syndrome

**Ion channel
Mutation**



Ventricular Fibrillation

Mutations in Cardiac Ion Channel Genes responsible for Cardiac Arrhythmias

TABLE 1. Genes and proteins causing inherited arrhythmogenic diseases

Protein family	Phenotype	Locus	Gene	Protein	Protein function	Functional abnormality
Ion channels	LQT1	11p15.5	<i>KCNQ1</i>	KVLQT1	I _{Ks} alpha subunit	loss of function
	LQT5	21q22.1-22.2	<i>KCNE1</i>	MinK	I _{Ks} beta subunit	loss of function
	LQT-JLN1	11p15.5	<i>KCNQ1</i>	KVLQT1	I _{Ks} alpha subunit	loss of function
	AFIB1	11p15.5	<i>KCNQ1</i>	KVLQT1	I _{Ks} alpha subunit	gain of function
	LQT-JLN2	21q22.1-22.2	<i>KCNE1</i>	MinK	I _{Ks} beta subunit	loss of function
	LQT2	7q35-q36	<i>HERG</i>	HERG	I _{Kr} alpha subunit	loss of function
	LQT6	21q22.1-22.2	<i>KCNE2</i>	MiRP1	I _{Kr} beta subunit	loss of function
	LQT3	3p21-23	<i>SCN5A</i>	SCN5A	I _{Na} alpha subunit	gain of function
	BrS1	3p21-23	<i>SCN5A</i>	SCN5A	I _{Na} alpha subunit	loss of function
	Lenegre	3p21-23	<i>SCN5A</i>	SCN5A	I _{Na} alpha subunit	probable loss of function
	mixed phenotypes	3p21-23	<i>SCN5A</i>	SCN5A	I _{Na} alpha subunit	loss or gain are possible
Anchoring proteins	And1	17q23	<i>KCNJ2</i>	Kir2.1	I _{K1} channel	loss of function
Ca ²⁺	LQT4	4q25-27	<i>ANK2</i>	ankyrin B	ion channel targeting	loss of function
	CPVT1	1q42-43	<i>RyR2</i>	RyR2	calcium release	loss of function
	CPVT2	1p11-13.3	<i>CASQ2</i>	CASQ2	calcium storage	unknown

Considerations specific to humans

- Highest order experimental system for genetics
- Powerful documentation of phenotypes
- Expert phenotypers (doctors), records over time
- room for improvement

Considerations specific to humans

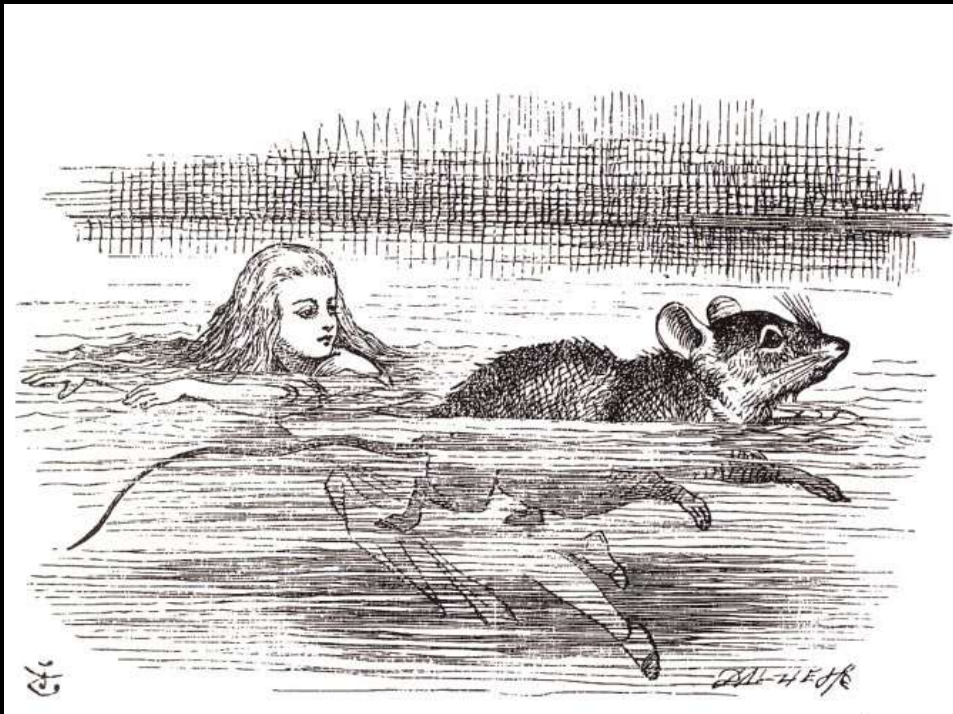
- Highest order experimental system for genetics
- Powerful documentation of phenotypes
- Expert phenotypers (doctors), records over time
 - room for improvement

- BUT not the best experimental system for intervention
- - overlong generation time, social proscriptions to controlled crosses etc.

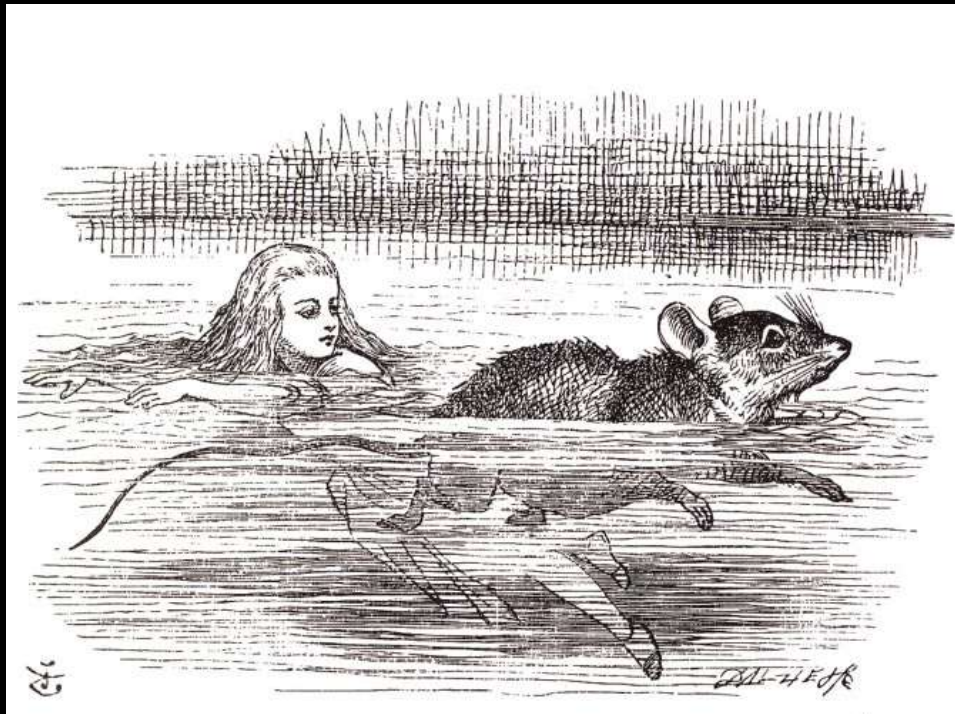
GM mice as the functional bridge - technical issues

Gene-targeting technique

- Germ-line modifications



GM mice as the functional bridge - technical issues



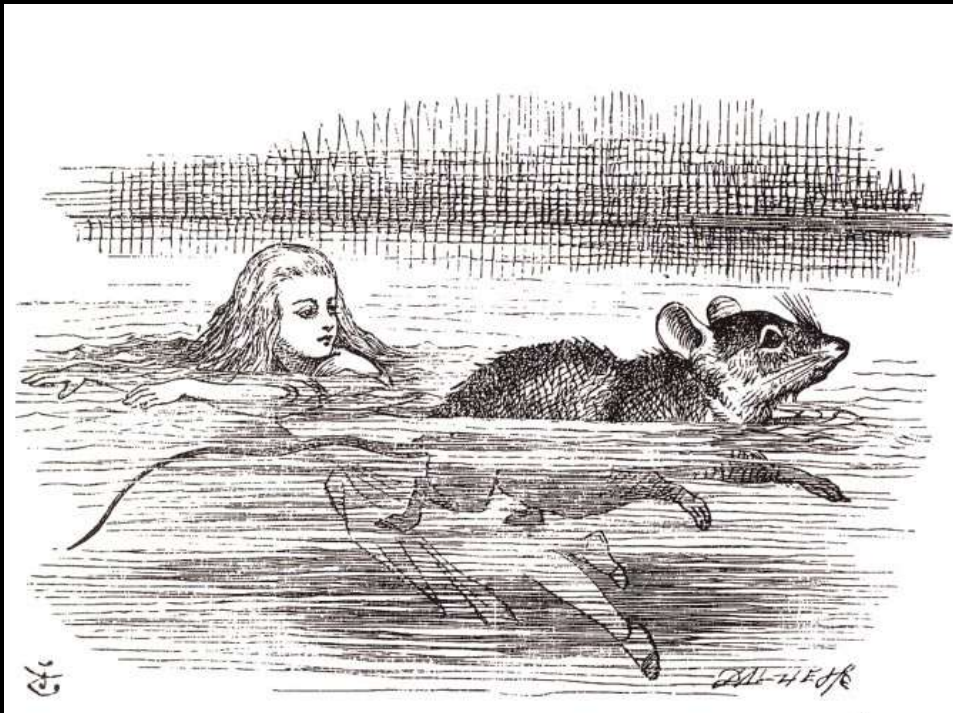
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- Germ-line modifications

Choice of gene

- Sodium > potassium channels

GM mice as the functional bridge - technical issues



Gene-targeting technique

- Germ-line modifications

Choice of gene

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Method of Interrogation

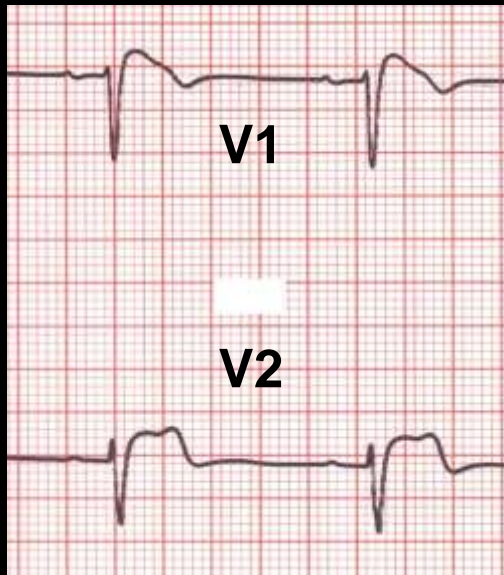
- Physiological range (HR >550)
- Translational measurements
- Comprehensive assays

GM Mouse Models of Cardiac Arrhythmias (Cambridge Group)

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<i>Scn3b</i>						

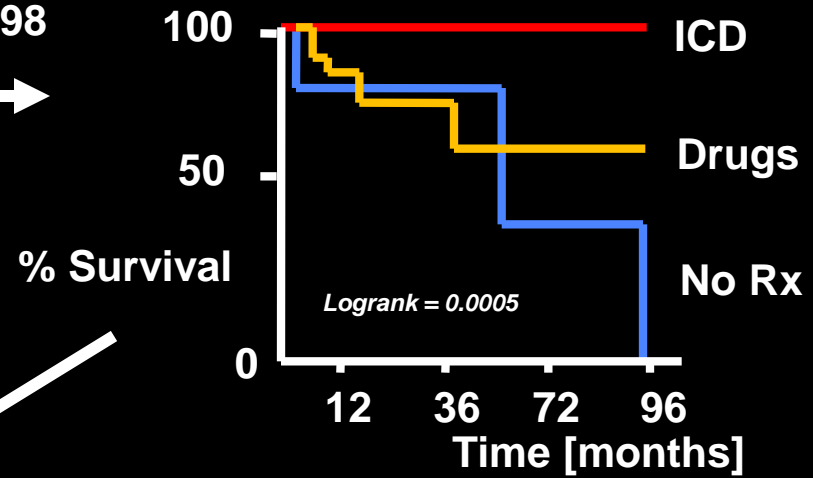
Brugada Syndrome: ECG and Ventricular Arrhythmias



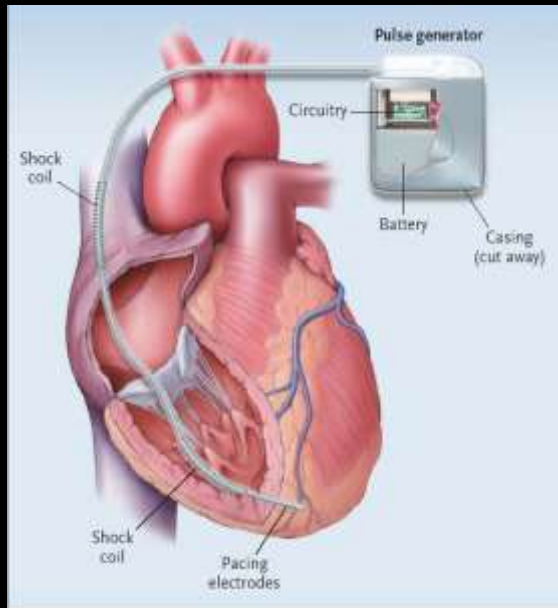
07.1998



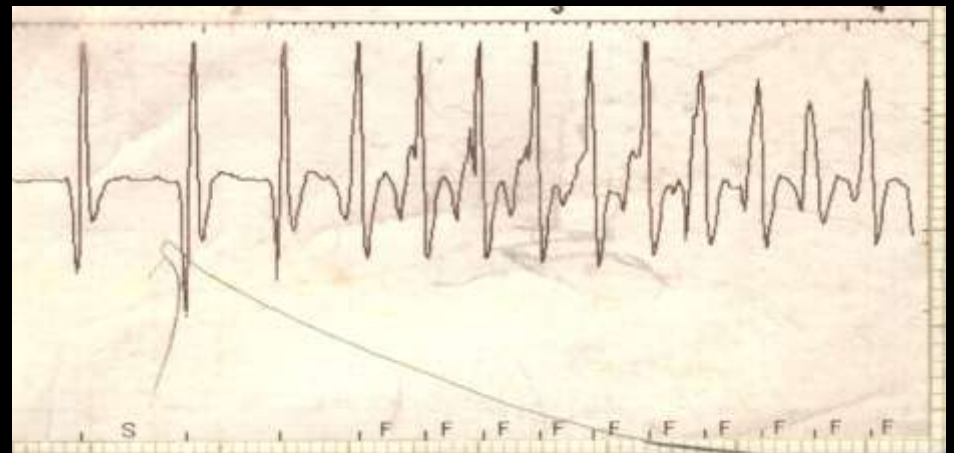
Survival according to treatment (n=63)



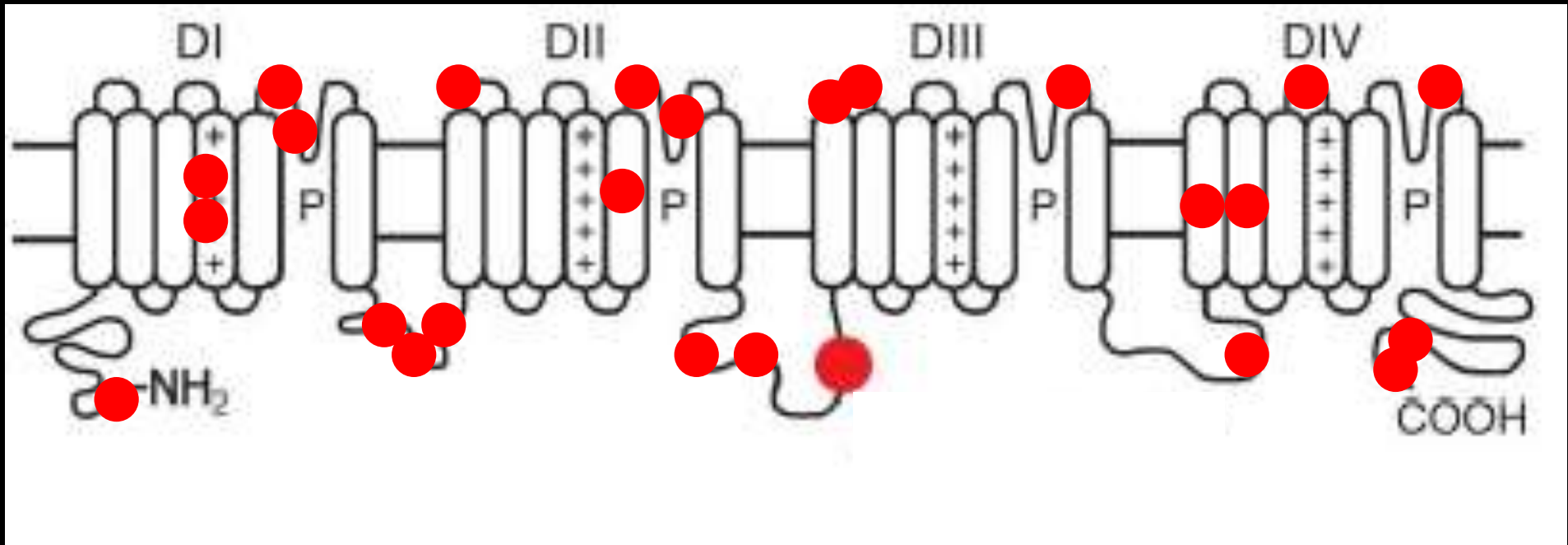
Brugada *et al.* Circulation 1998;97:457-60



01.2000

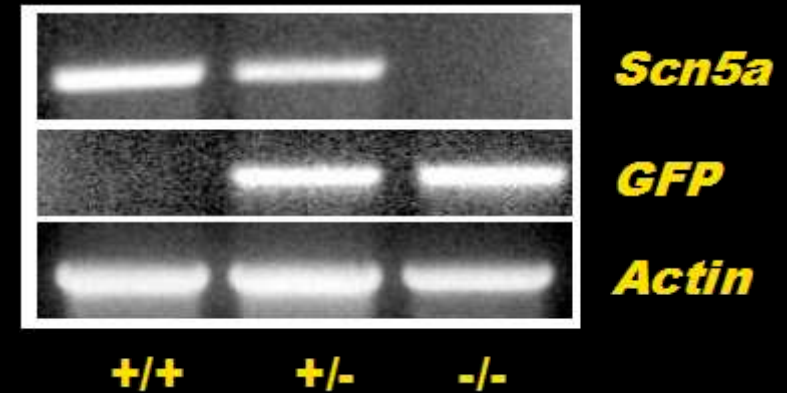
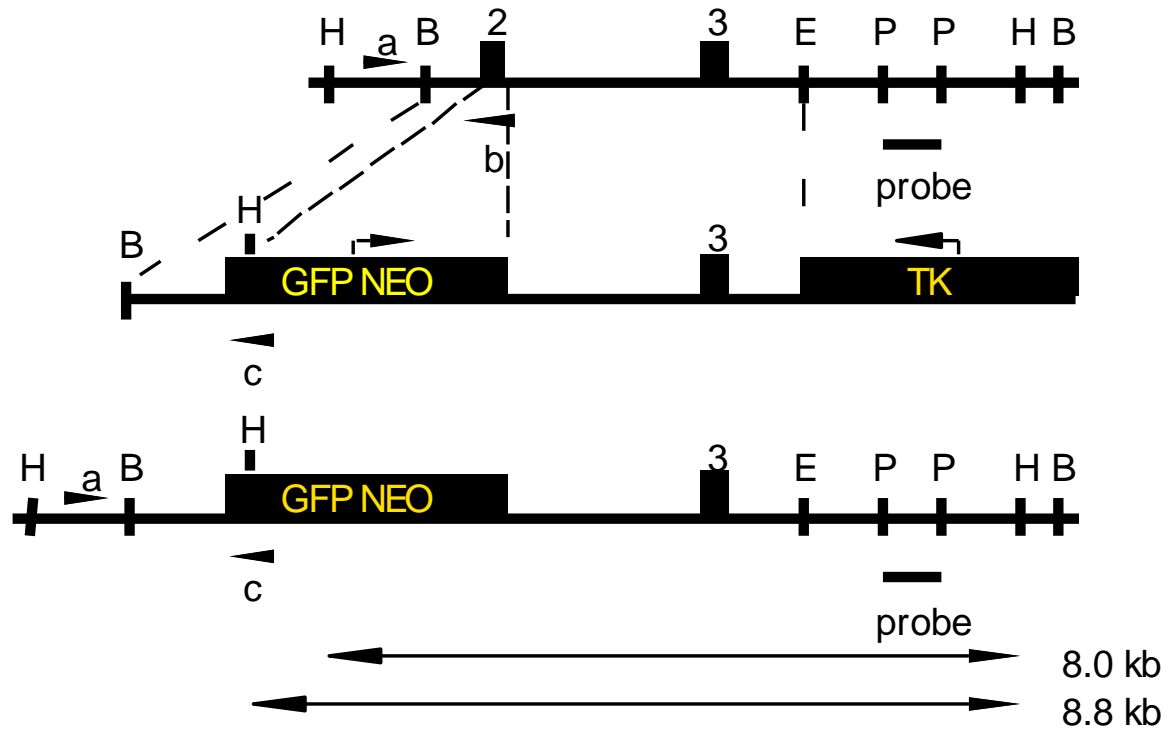


Brugada Syndrome: *SCN5A* Mutations



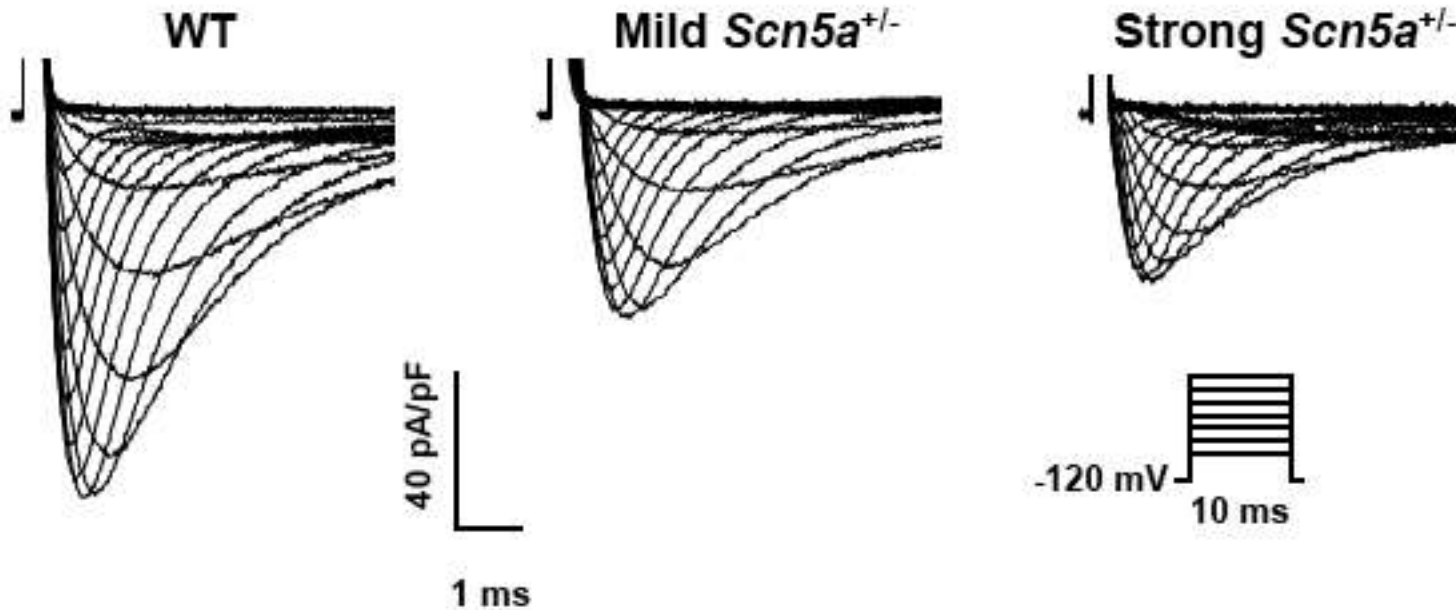
- Association first described 1998
- *SCN5A*: TTX-insensitive sodium channel, 28 exons, 80 kb
- Four homologous domains, each 6 membrane spanning segments
- Brugada mutations(> 120) are loss-of-function

GM MOUSE MODEL



HALF THE SODIUM CHANNELS

A



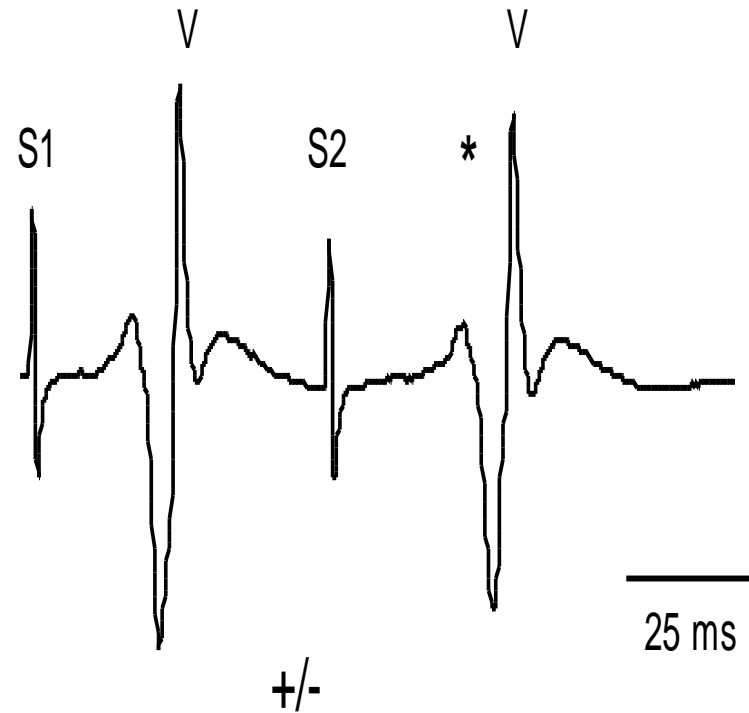
Wild-type (n=6)
37 ± 9 pA/pF

***Scn5a*^{+/-} (n=5)**
21 ± 5 pA/pF

SLOW CONDUCTION

WILD-TYPE

MUTANT (*Scn5a*^{+/-})



Slowed conduction and ventricular tachycardia after targeted disruption of the cardiac sodium channel gene *Scn5a*

G. Alex Papadatos^{1,2}, Polly M. R. Wallenstein^{1,2}, Catherine E. G. Head^{1,2}, Rosemary Ratcliff^{1,2}, Peter A. Brady², Klaus Benndorf³, Richard C. Saurares^{4,5}, Ann E. D. Trezise¹, Christopher L.-H. Huang¹, Jamie I. Vanclayberg¹, William H. Colledge¹, and Andrew A. Grace^{1,2,6*}

¹Section of Cardiovascular Biology, Department of Biochemistry, University of Cambridge, Tennis Court Road, Cambridge CB2 1QW, United Kingdom;

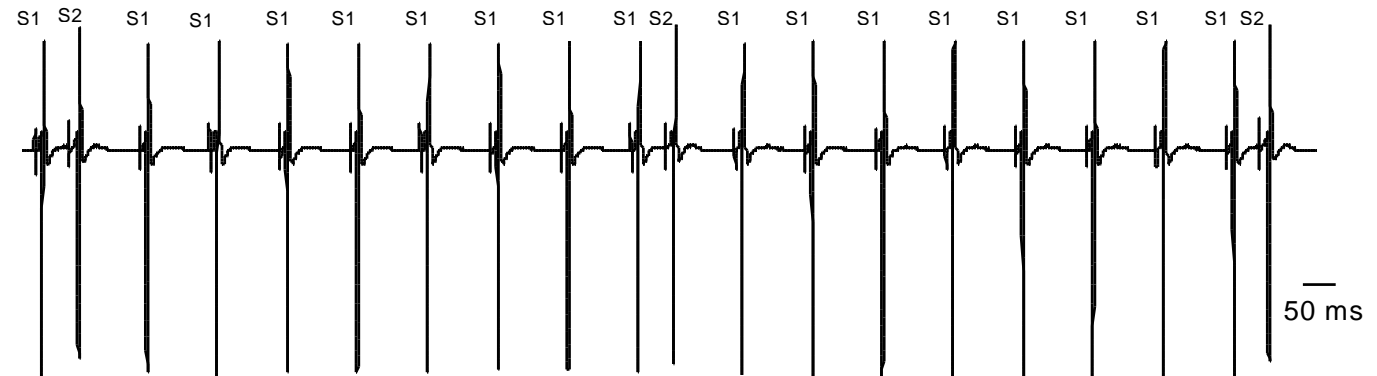
²Department of Physiology, University of Cambridge, Downing Street, Cambridge CB2 3EG, United Kingdom; ³Department of Medicine,

University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom; ⁴Friedrich-Schiller-Universität Jena,

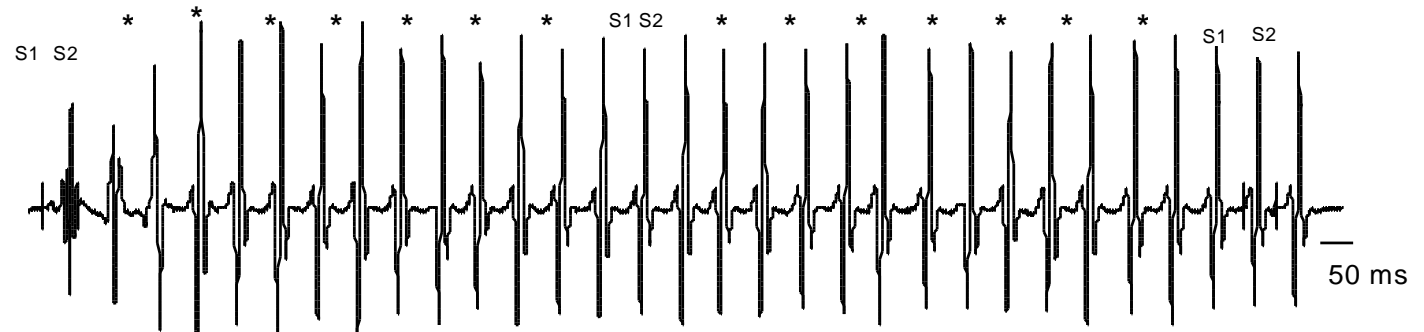
Institut für Physiologie, Arbeitsgruppe Herz-Kreislauf-Physiologie, 07408 Jena, Germany and ⁵Department of Anatomy and

Developmental Biology, University of Queensland, St. Lucia Qld 4072, Australia

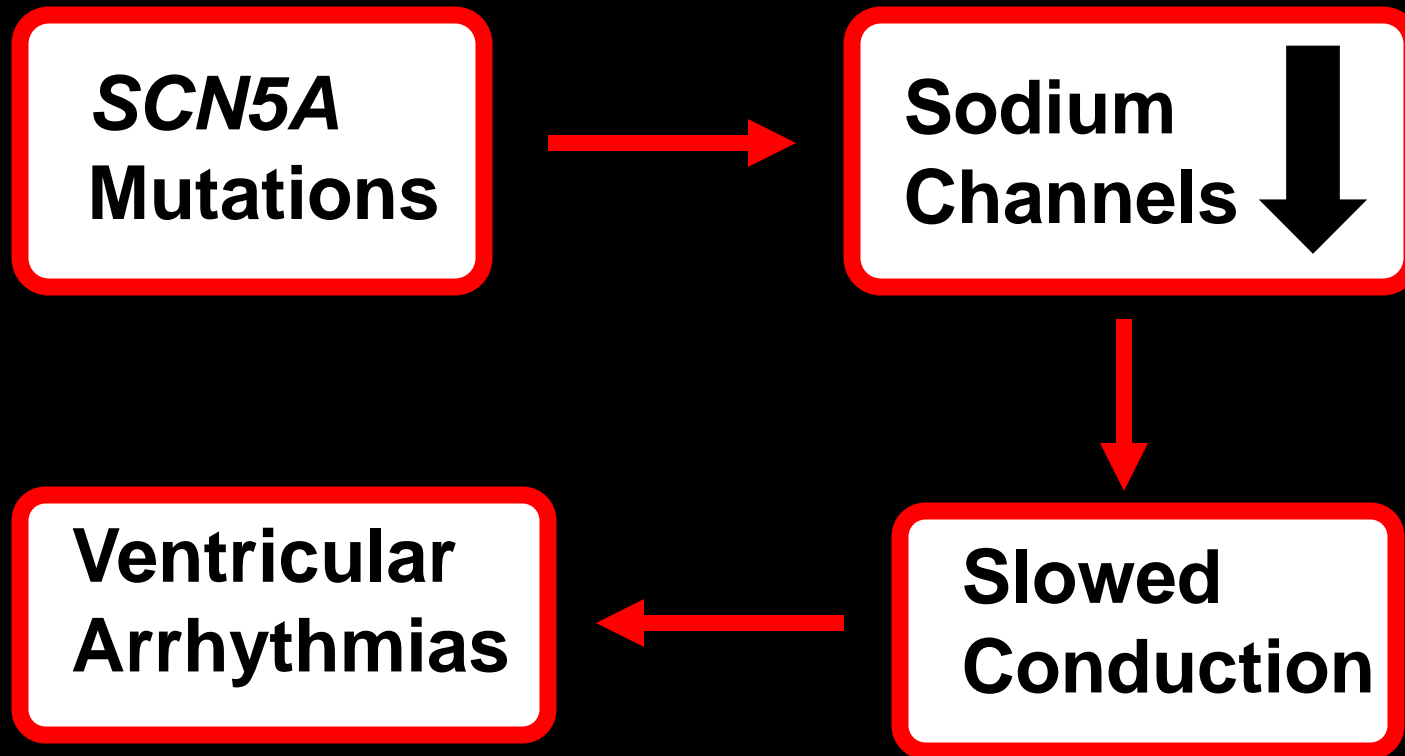
Wild-type



***Scn5a*^{+/-}**



GENES AND FUNCTION (Brugada Syndrome)



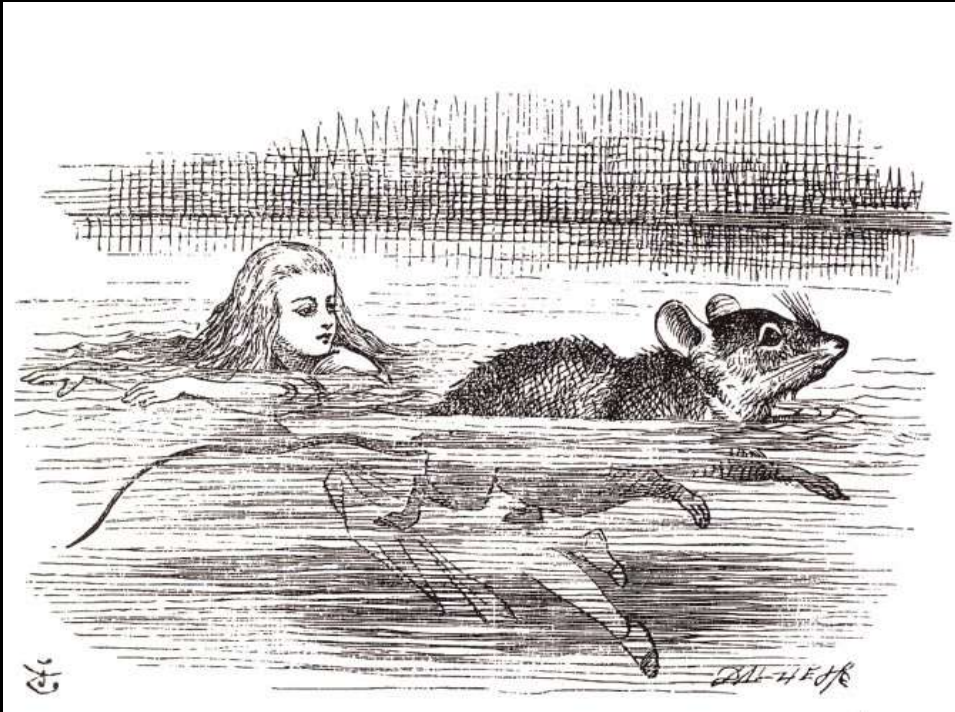
GM Mouse *Scn5a* phenotypes

1. Long QT syndrome (2005-2007) - Δ KPQ 1505-1507
2. Brugada/idiopathic VF (2002-2007)
3. Lev-Lenègre disease/atrioventricular block (2002-2007)
4. Sinus node dysfunction (2002, 2005)
5. Atrial arrhythmias (2007)
6. Dilated Cardiomyopathy - but structural change (2005-2007)
7. Population based risk: SCD, SIDS, drugs (2007)

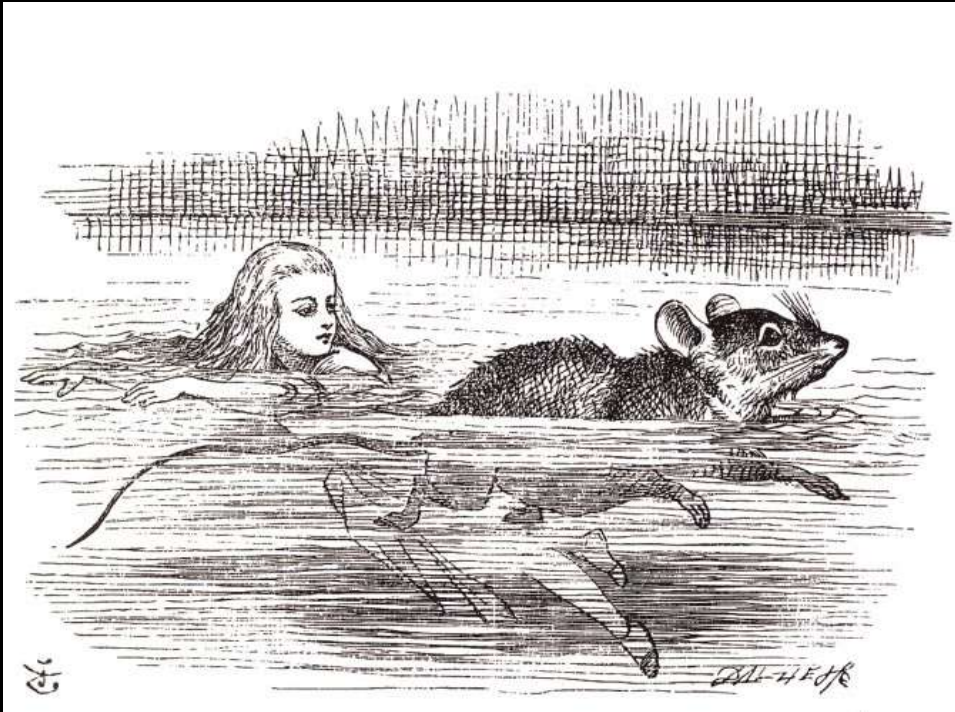
GM mice and cardiac electrophysiology

Therapeutics

- *Scn5a*/deltaKPQ/nifedipine
- *Scn5a*+/-/quinidine
- AF drug discovery



GM mice and cardiac electrophysiology



Therapeutics

- *Scn5a*/deltaKPQ/nifedipine
- *Scn5a*+/-/quinidine
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Mechanisms \blacktriangle Risk Stratification

- Structural changes
- ARVC/exercise
- Invasive phenotyping and risk

Complex Disease Syndromes

Phenotypes not exhibiting classic Mendelian recessive or dominant inheritance attributable to a single gene locus

Practical difficulties

Incomplete penetrance and phenocopy

Genetic heterogeneity

Polygenic inheritance

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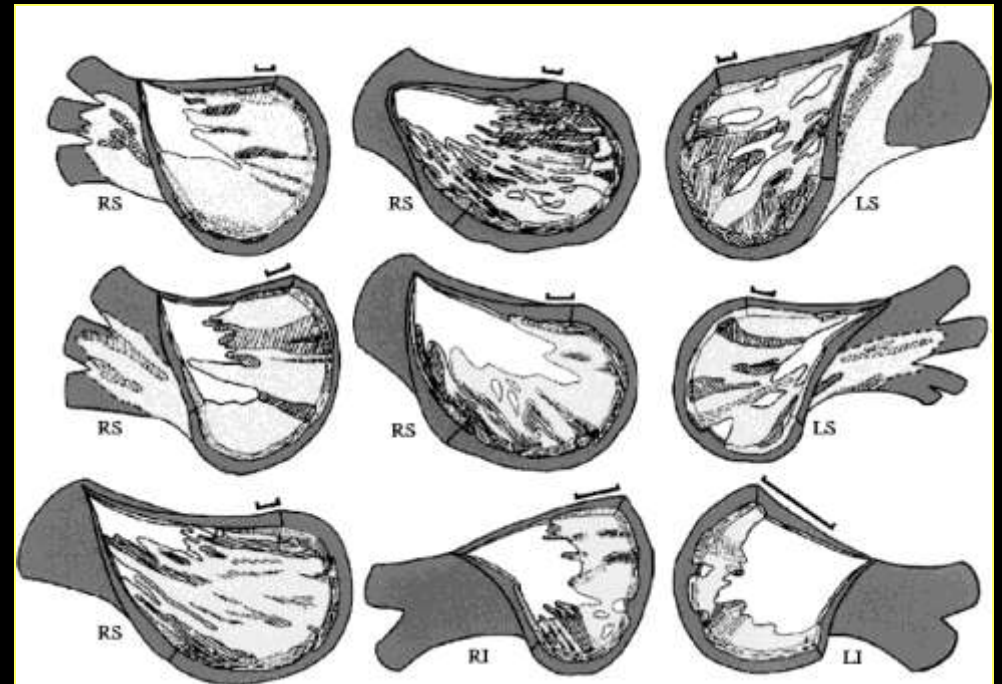
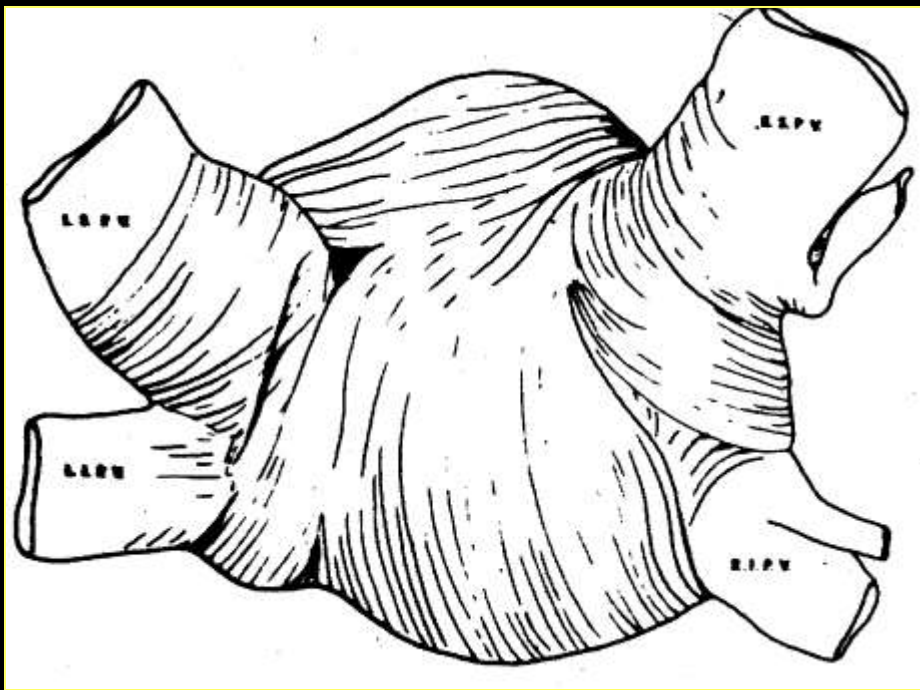
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SUBSTRATE FOR ATRIAL FIBRILLATION

MUSCULATURE OF THE PULMONARY VEINS

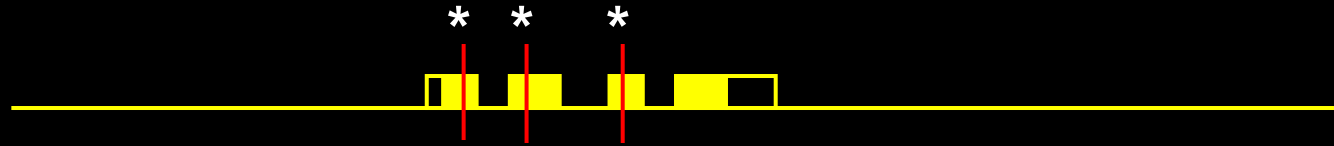


Nathan and Eliakim; Circulation 1966; 34:412

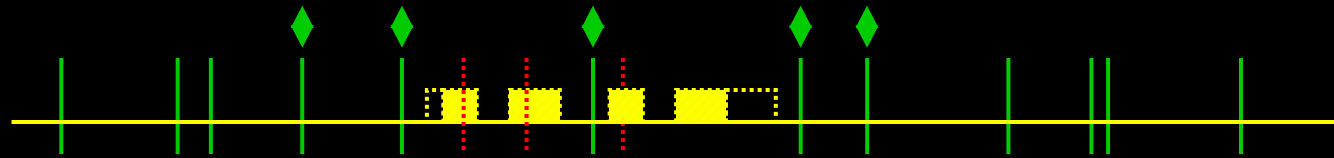
Ho et al; Heart 2001; 265-270

ASSOCIATION STUDIES

Direct

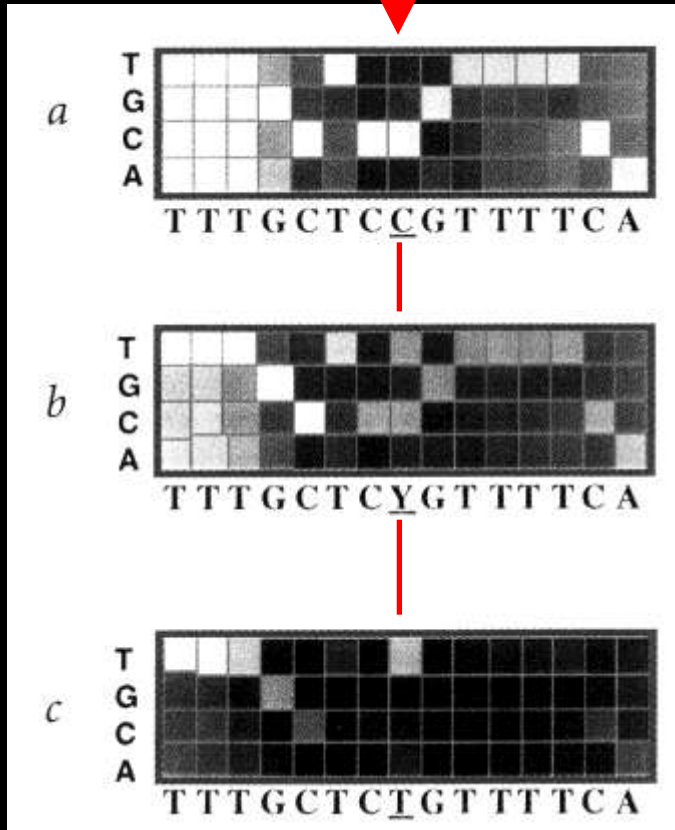


Indirect



SINGLE NUCLEOTIDE POLYMORPHISMS - SNPs

...GCTCCGTTT...
...GCTCTGTTT...



IN THE GENOME:

- ~ 90% of all variants
- ~ 1 SNP / 1.25 kb between any two genomes
- ~ 2.5 million variants between two genomes

Variants conferring risk of atrial fibrillation on chromosome 4q25

Table 1 | Analysis of the association of rs2200733 and rs10033464 on chromosome 4q25 with AF/AFI

Sample (cases/controls)	rs2200733 T* Frequency§	OR (95% CI)	P	rs10033464 T*† Frequency§	OR (95% CI)
Iceland 					
Discovery (550/4,476)	0.191 (0.114)	1.84 (1.54–2.21)	2.0×10^{-11}	0.110 (0.080)	1.42 (1.13–1.77)
Replication (2,251/13,238)	0.166 (0.108)	1.64 (1.49–1.81)	2.7×10^{-23}	0.108 (0.080)	1.40 (1.24–1.58)
Combined (2,801/17,714)	0.171 (0.110)	1.68 (1.53–1.83)	1.9×10^{-30}	0.108 (0.080)	1.40 (1.25–1.55)
Other European ancestry					
Sweden (143/738)	0.179 (0.098)	2.01 (1.38–2.93)	0.00027	0.172 (0.111)	1.65 (1.14–2.41)
United States (636/804)	0.229 (0.139)	1.84 (1.51–2.23)	9.8×10^{-10}	0.105 (0.083)	1.30 (1.00–1.69)
Combined¶	– (–)	1.88 (1.58–2.23)	1.2×10^{-12}	– (–)	1.41 (1.13–1.75)
All European ancestry					
Combined¶	– (–)	1.72 (1.59–1.86)	3.3×10^{-41}	– (–)	1.39 (1.26–1.53)
Hong Kong					
Hong Kong (333/2,836)	0.605 (0.528)	1.42 (1.16–1.73)	0.00064	0.190 (0.218)	1.08 (0.84–1.39)

- Genome-wide association scan with replication in other populations

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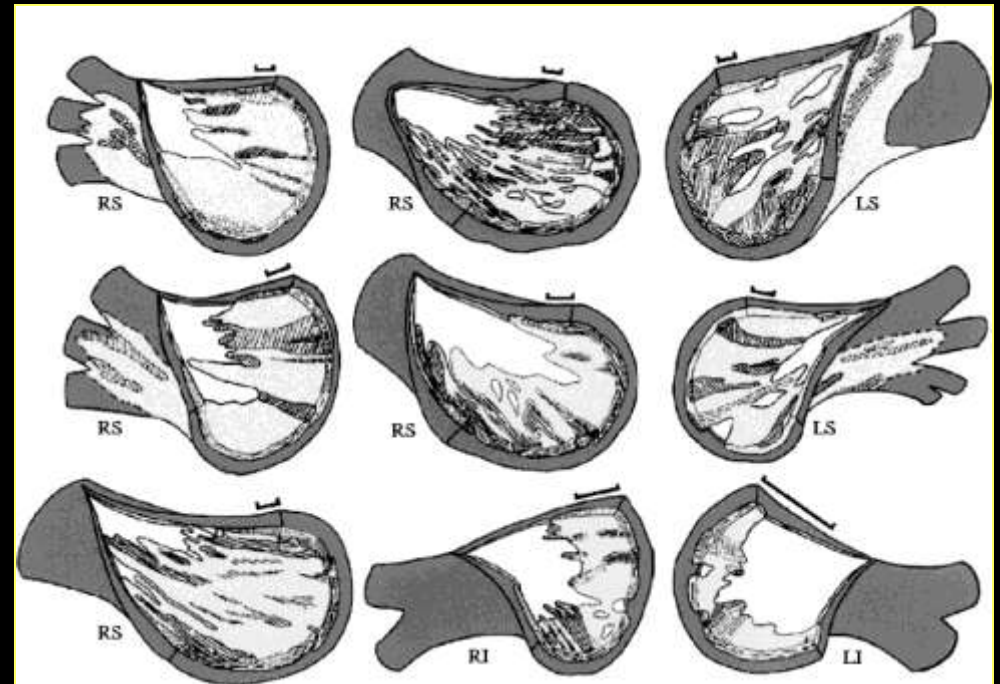
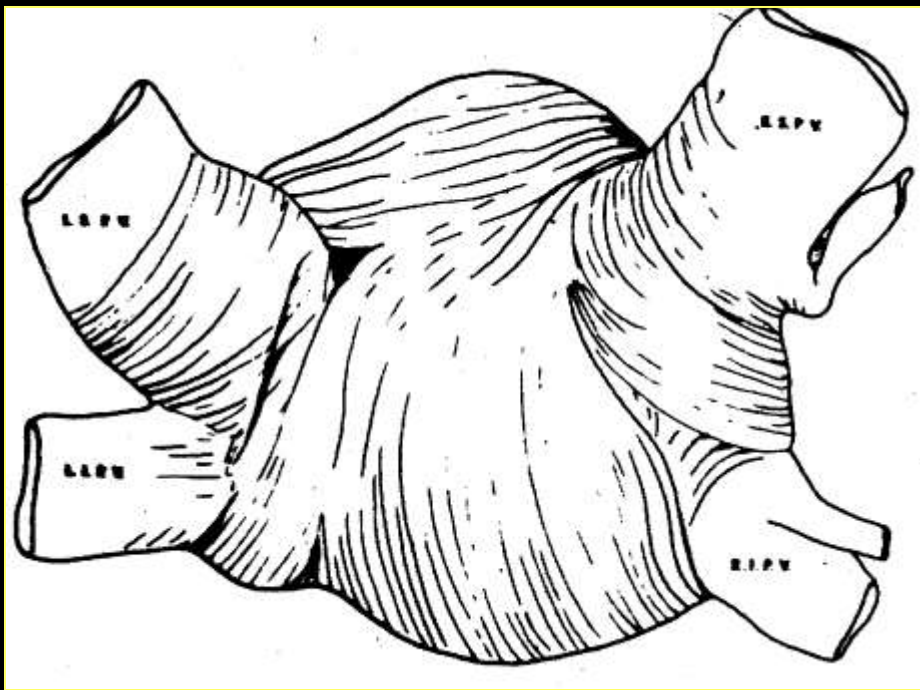
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- Genome-wide association scan with replication in other populations
- Variants adjacent to *PITX2* - critical function in left-right asymmetry in heart
- *Pitx2c* plays key role in determination ‘pulmonary myocardium’

SUBSTRATE FOR ATRIAL FIBRILLATION

MUSCULATURE OF THE PULMONARY VEINS



Nathan and Eliakim; Circulation 1966; 34:412

Ho et al; Heart 2001; 265-270

Genome-wide association study of PR interval

The electrocardiographic PR interval (or PQ interval) reflects atrial and atrioventricular nodal conduction, disturbances of which increase risk of atrial fibrillation. We report a meta-analysis of genome-wide association studies for PR interval from seven population-based European studies in the CHARGE Consortium: AGES, ARIC, CHS, FHS, KORA, Rotterdam Study, and SardiNIA ($N = 28,517$). We identified nine loci associated with PR interval at $P < 5 \times 10^{-8}$. At the 3p22.2 locus, we observed two independent associations in voltage-gated sodium channel genes, *SCN10A* and *SCN5A*. Six of the loci were near cardiac developmental genes, including *CAV1-CAV2*, *NKX2-5 (CSX1)*, *SOX5*, *WNT11*, *MEIS1*, and *TBX5-TBX3*, providing pathophysiologically interesting candidate genes. Five of the loci *SCN5A*, *SCN10A*, *NKX2-5*, *CAV1-CAV2*, and *SOX5*, were also associated with atrial fibrillation ($N = 5,741$ cases, $P < 0.0056$). This suggests a role for common variation in ion channel and developmental genes in atrial and atrioventricular conduction as well as in susceptibility to atrial fibrillation.

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ARRHYTHMIAS AND GENETIC HEART DISEASE



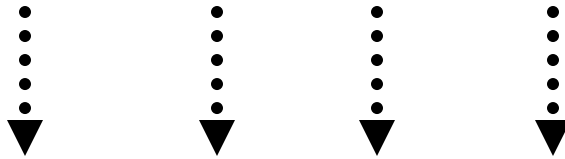
ARRHYTHMIAS AND GENETIC HEART DISEASE

Gene Mutation

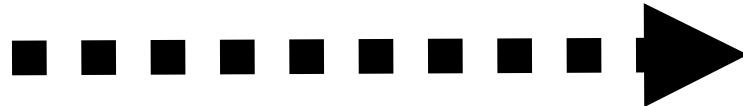


Arrhythmia Substrate

GENETIC/ENVIRONMENTAL MODIFIERS



**Putative
Mutation**

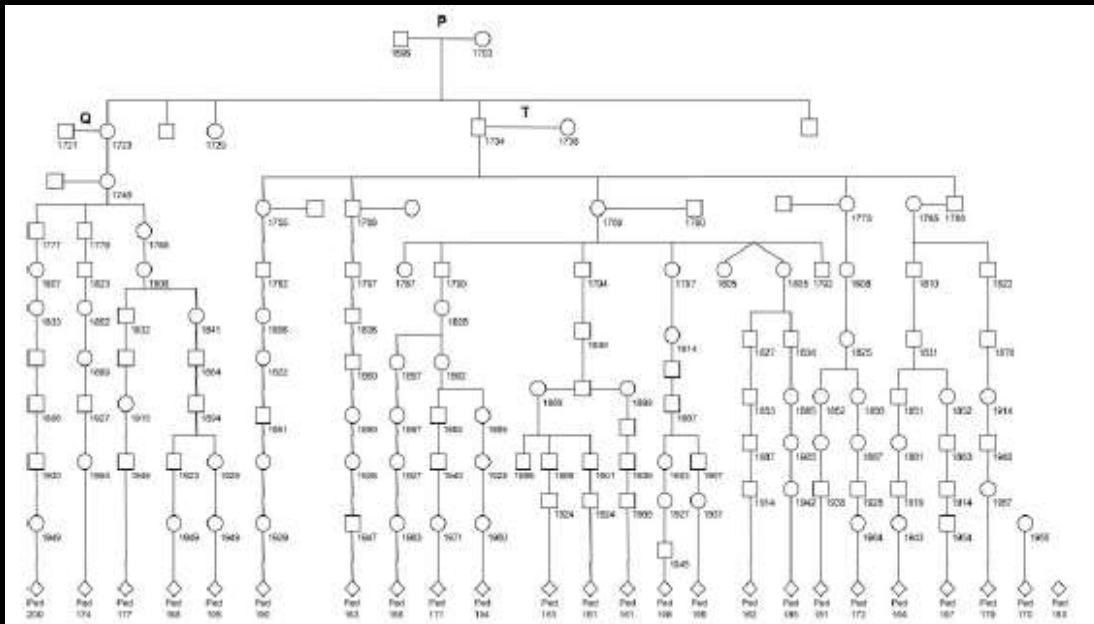


Ventricular Arrhythmia

Phenotypic Variability and Unusual Clinical Severity of Congenital Long-QT Syndrome in a Founder Population

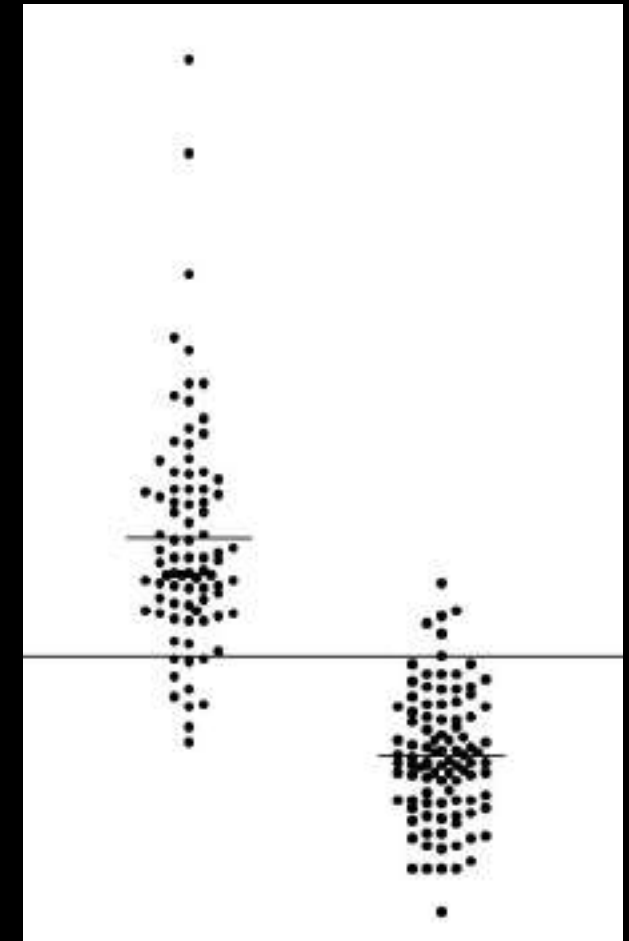
Circulation 2005;112:2602-10

... Founder Effect (1730)
... *KCNQ1* (A341V)
... Variable significant risk



680 msec →

430 msec →



A341V-Carrier
(n = 166)

Non-carrier
(n = 154)

Genetic Basis of Clinical Arrhythmias: where next?

Genotype (high-throughput)

- Complex disease
- Genetic modifiers

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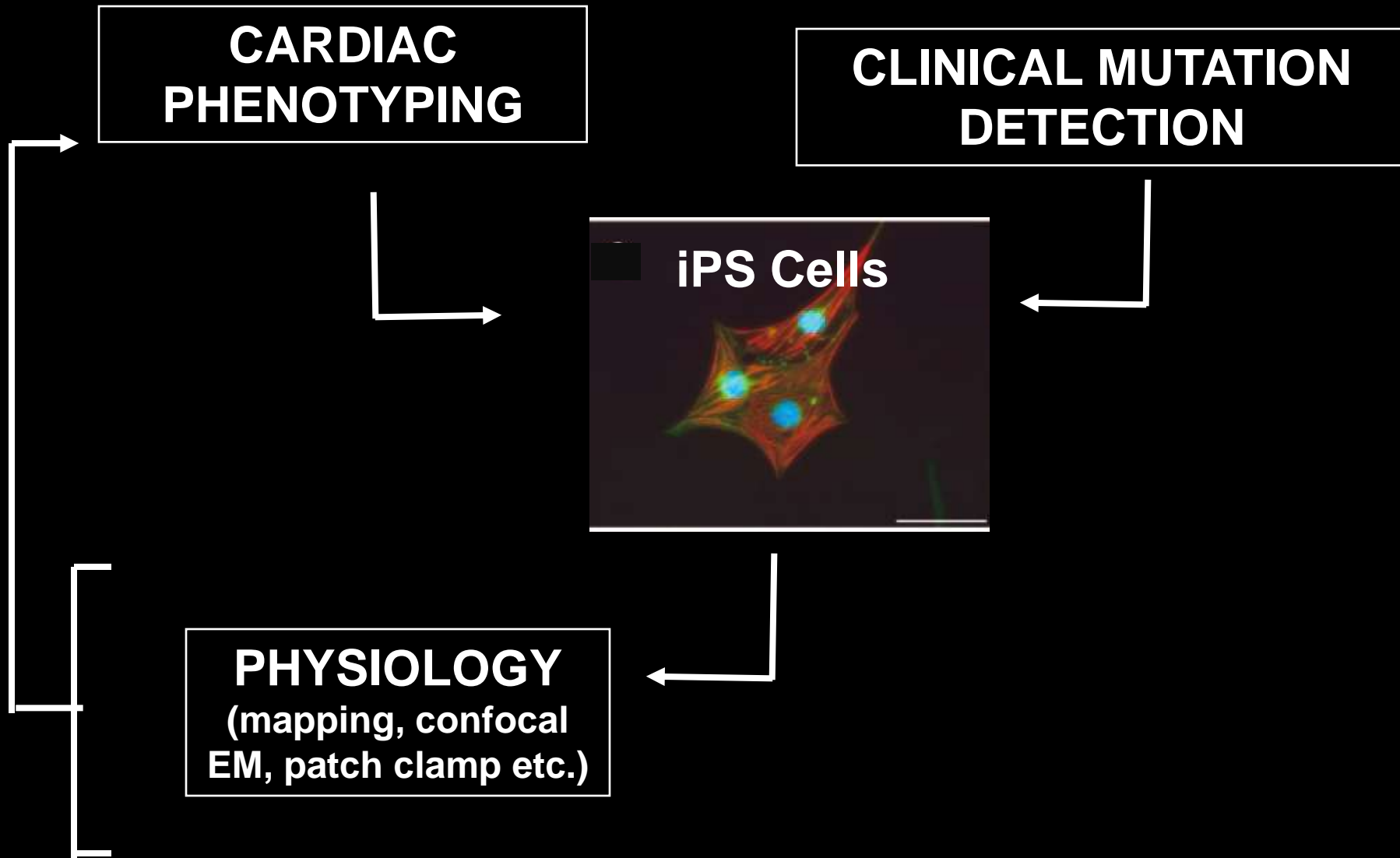
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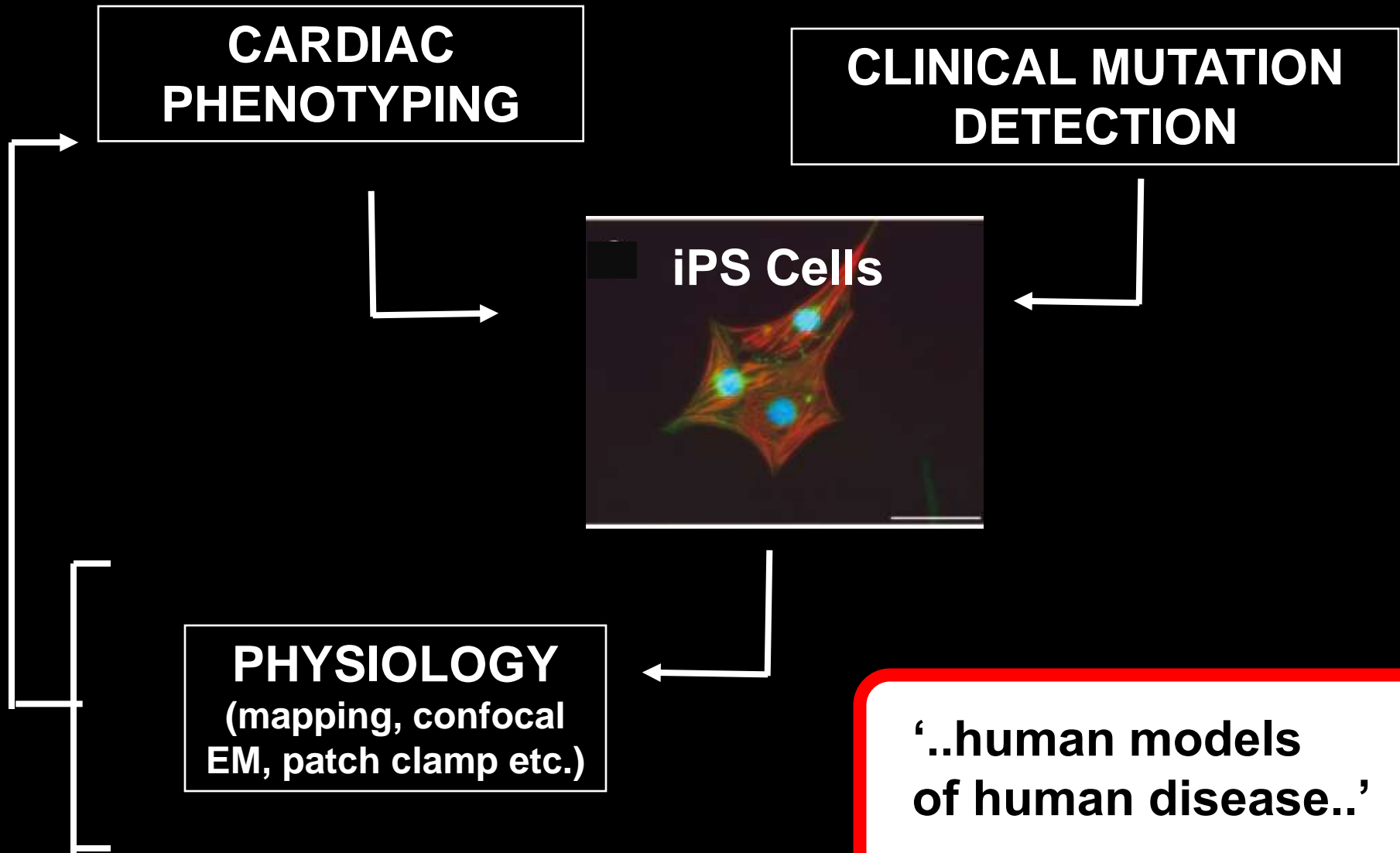
Phenotype

- Mechanisms (mice)
- Mechanisms (Stem Cell Models)

iPS Cells linking genes to function (2008-)



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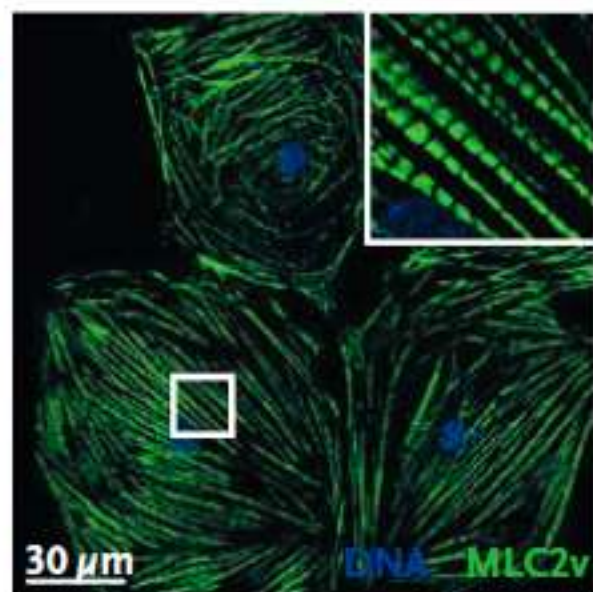
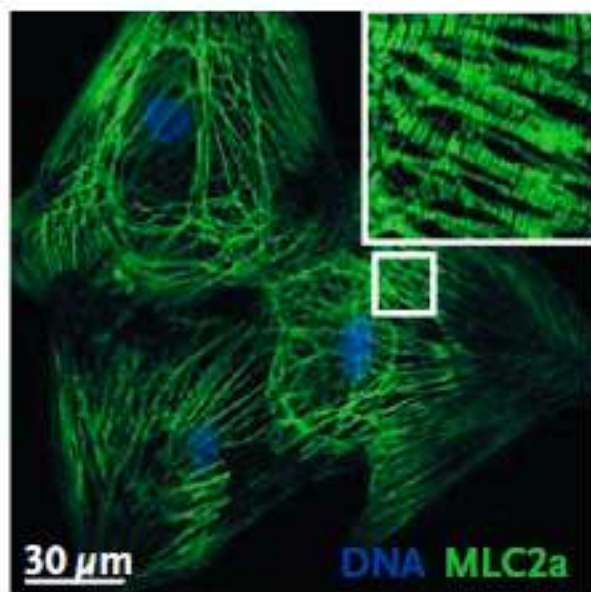
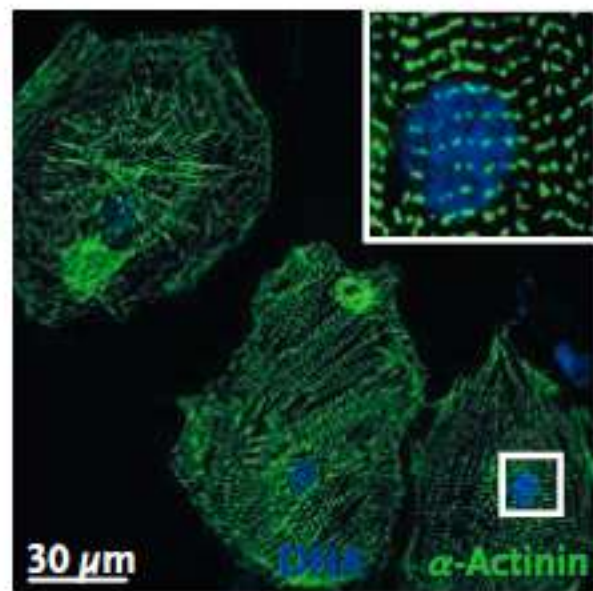
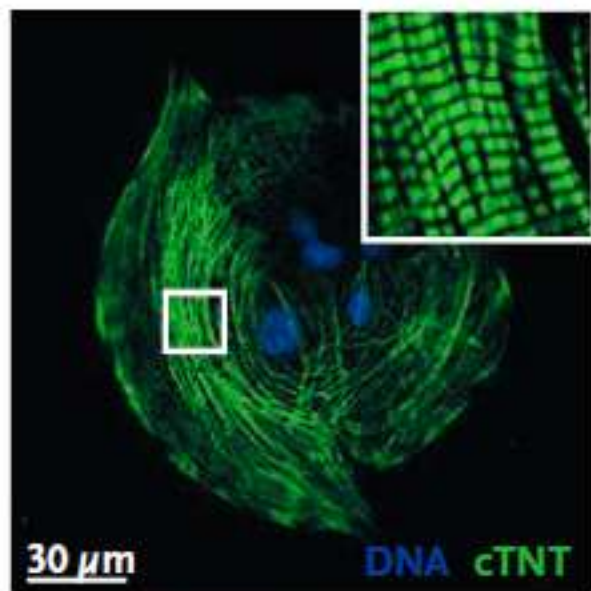
**'..human models
of human disease..'**

Chien, Nature 2008 453:302

ORIGINAL ARTICLE

Patient-Specific Induced Pluripotent Stem-Cell Models for Long-QT Syndrome

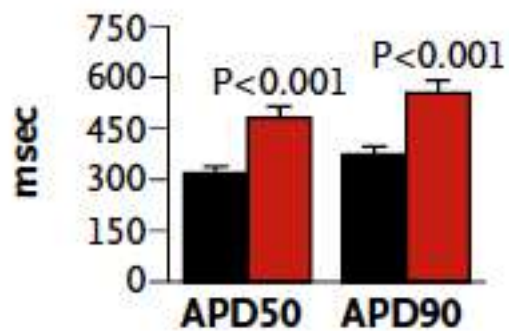
Alessandra Moretti, Ph.D., Milena Bellin, Ph.D., Andrea Welling, Ph.D., Christian Billy Jung, M.Sc., Jason T. Lam, Ph.D., Lorenz Bott-Flügel, M.D., Tatjana Dorn, Ph.D., Alexander Goedel, M.D., Christian Höhnke, M.D., Franz Hofmann, M.D., Melchior Seyfarth, M.D., Daniel Sinnecker, M.D., Albert Schömig, M.D., and Karl-Ludwig Laugwitz, M.D.



Ventricular
MLC2a HCN4 MLC2v



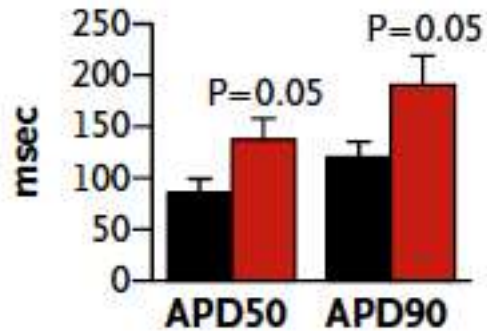
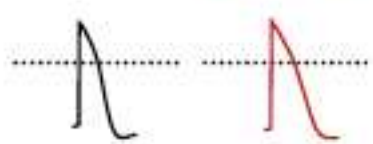
Control **LQT1**



Atrial
MLC2a HCN4 MLC2v



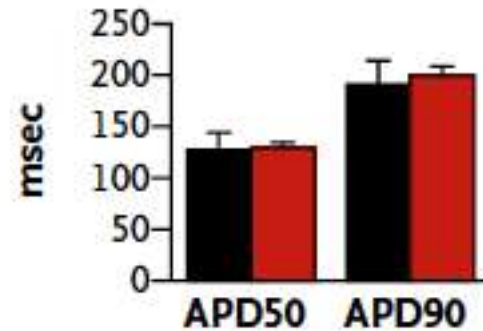
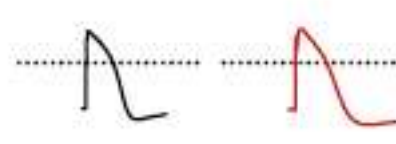
Control **LQT1**



Nodal
MLC2a HCN4 MLC2v



Control **LQT1**



250 msec
40 mV

■ Control
■ LQT1

Predicted clinical benefits of a genetic description of disease

- **New taxonomy of disease: mechanisms > phenotype**
- **Predisposition phenotypes e.g. pharmacogenomics**

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- Implementation will be problematic**