

Heart Rhythm Congress – Birmingham, October 3rd 2011

Genetics and Sudden Cardiac Death

Andrew Grace

University of Cambridge - Papworth Hospital

ARRHYTHMIAS AND GENETIC HEART DISEASE



Gene Variant

Arrhythmia Substrate

ARRHYTHMIAS AND GENETIC HEART DISEASE

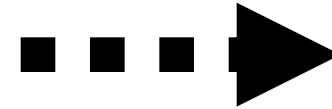
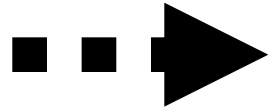
Gene Variant



Arrhythmia Substrate

Indirect Relationship e.g. Hypertrophic Cardiomyopathy

**Sarcomere
Mutation**



**Ventricular
Fibrillation**

ARRHYTHMIAS AND GENETIC HEART DISEASE

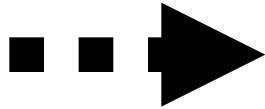
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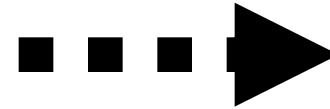
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**Structural
Disorganization**



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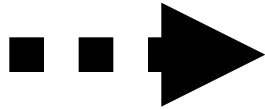
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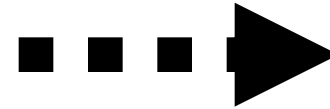
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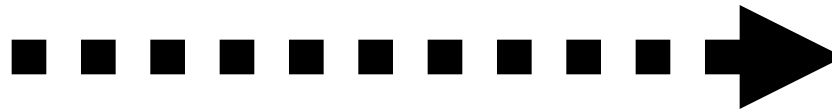
**Structural
Disorganization**



**Ventricular
Fibrillation**

Putative Direct Relationship e.g. Brugada Syndrome

**Ion channel
Mutation**



**Ventricular
Fibrillation**

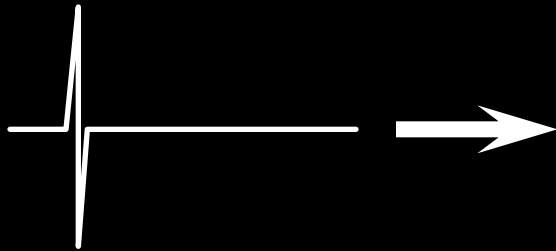
What is the 'big idea' :-

'The determinants for arrhythmogenic risk and sudden cardiac death (SCD) reside within the heart and can be read directly'

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Stimulus



Substrate

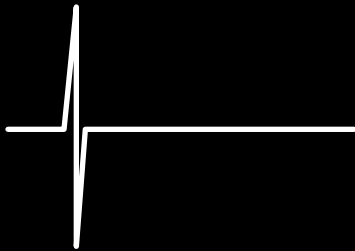
Read-out



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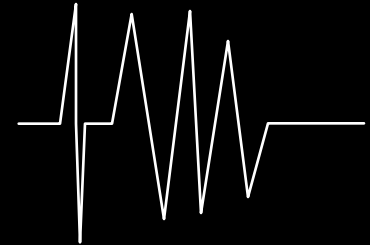
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Substrate

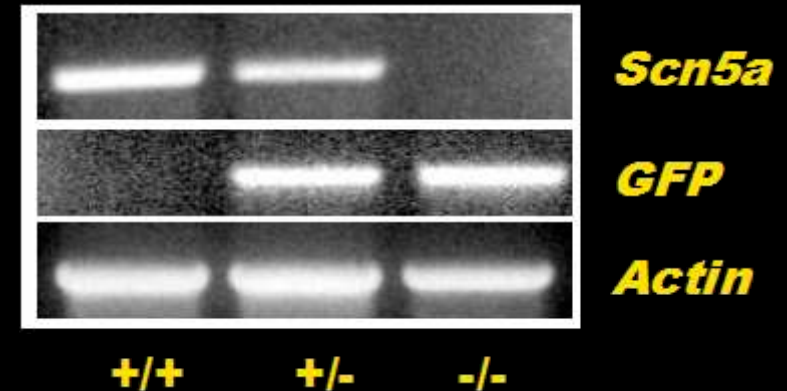
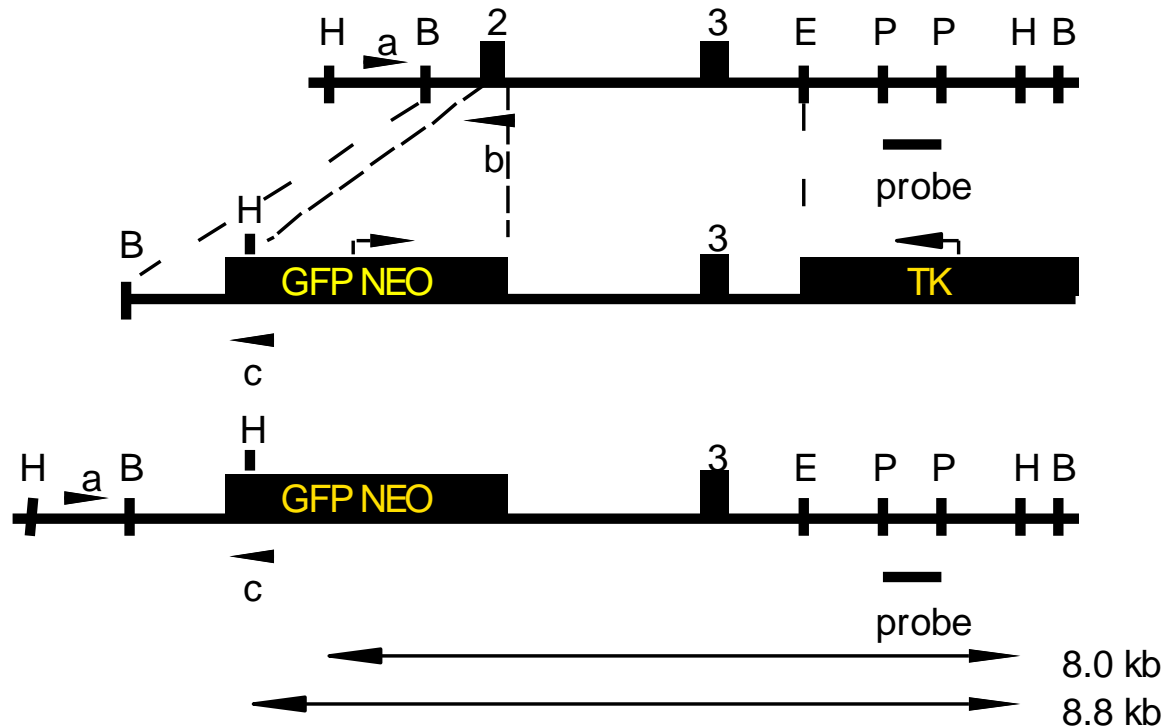


Read-out



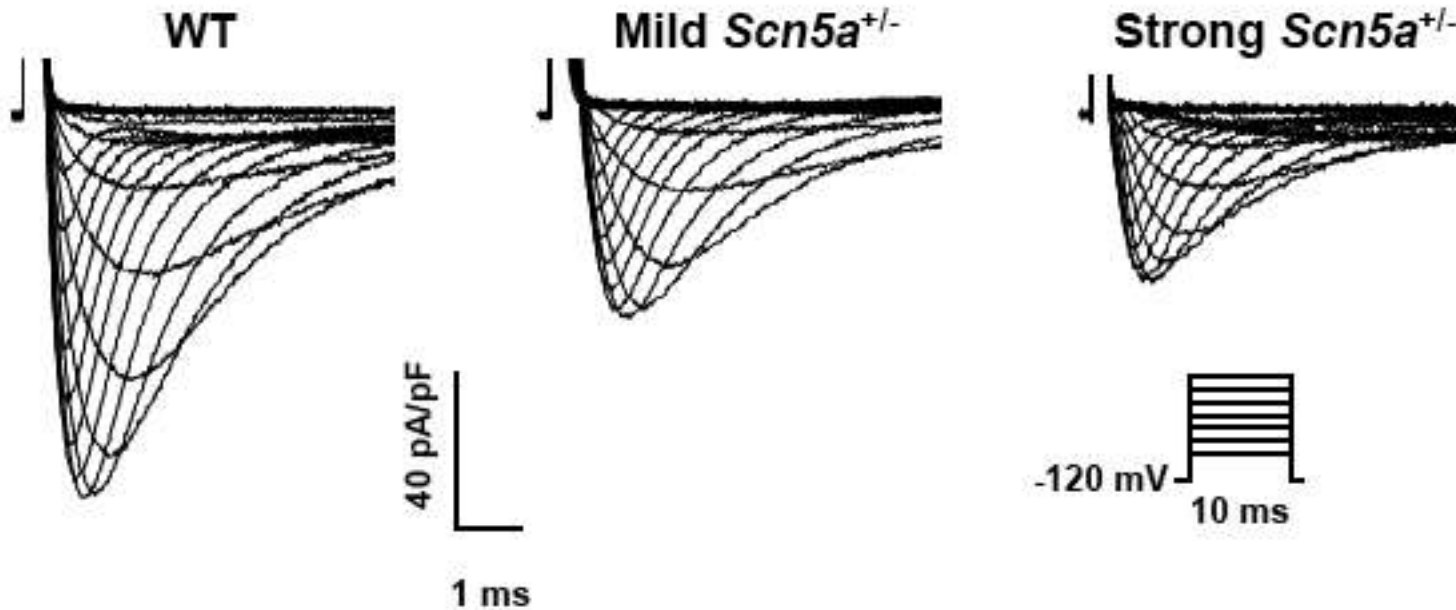
Provides potential for risk assessment and rescue

'BRUGADA' MOUSE MODEL



HALF THE SODIUM CHANNELS

A



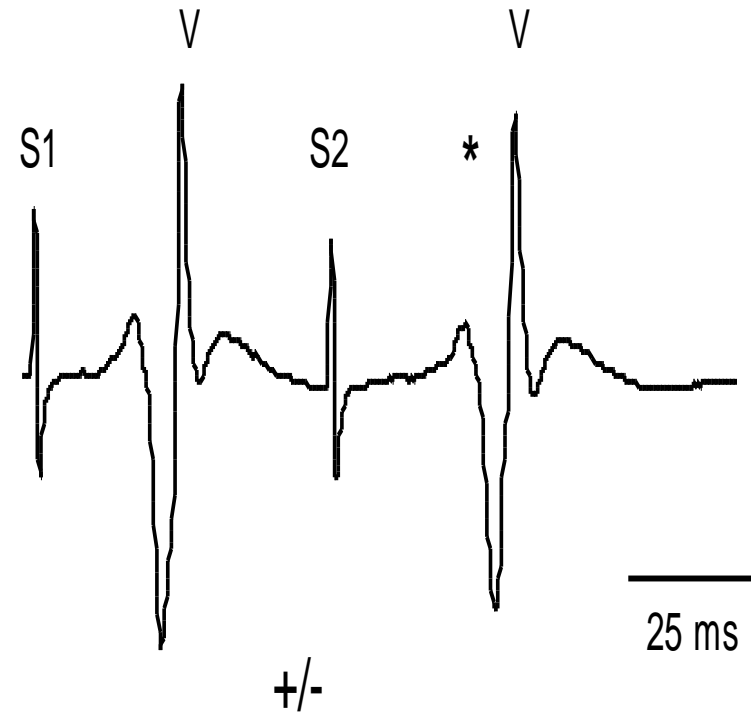
Wild-type (n=6)
37 ± 9 pA/pF

***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. Saurma^{4,5}, Ann E. D. Trezise¹, Christopher L.-H. Huang¹, Jamie I. Vandenberg⁶, William H. Colledge¹, and Andrew A. Grace^{1,2,3,4}

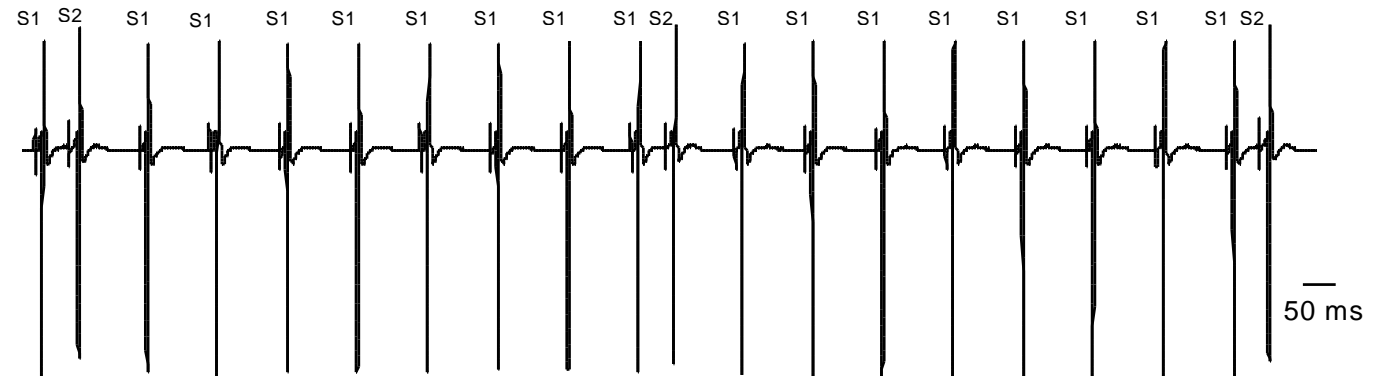
¹Section of Cardiovascular Biology, Department of Biochemistry, University of Cambridge, Tennis Court Road, Cambridge CB2 1QW, United Kingdom;

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

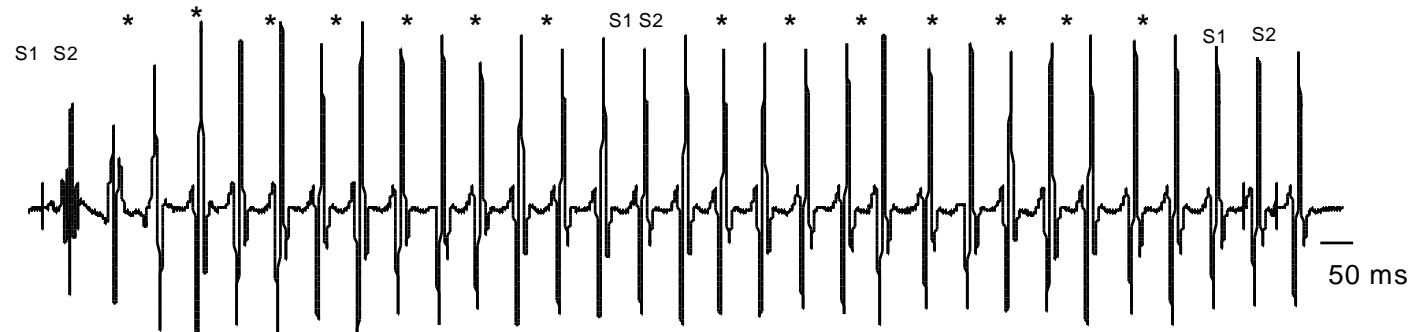
University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom; ⁴Friedrich-Schiller-Universität Jena,

Institut für Physiologie, Abteilung Herz-Kreislauf-Physiologie, 07408 Jena, Germany and Department of Anatomy and Developmental Biology, University of Queensland, St. Lucia Qld 4072, Australia

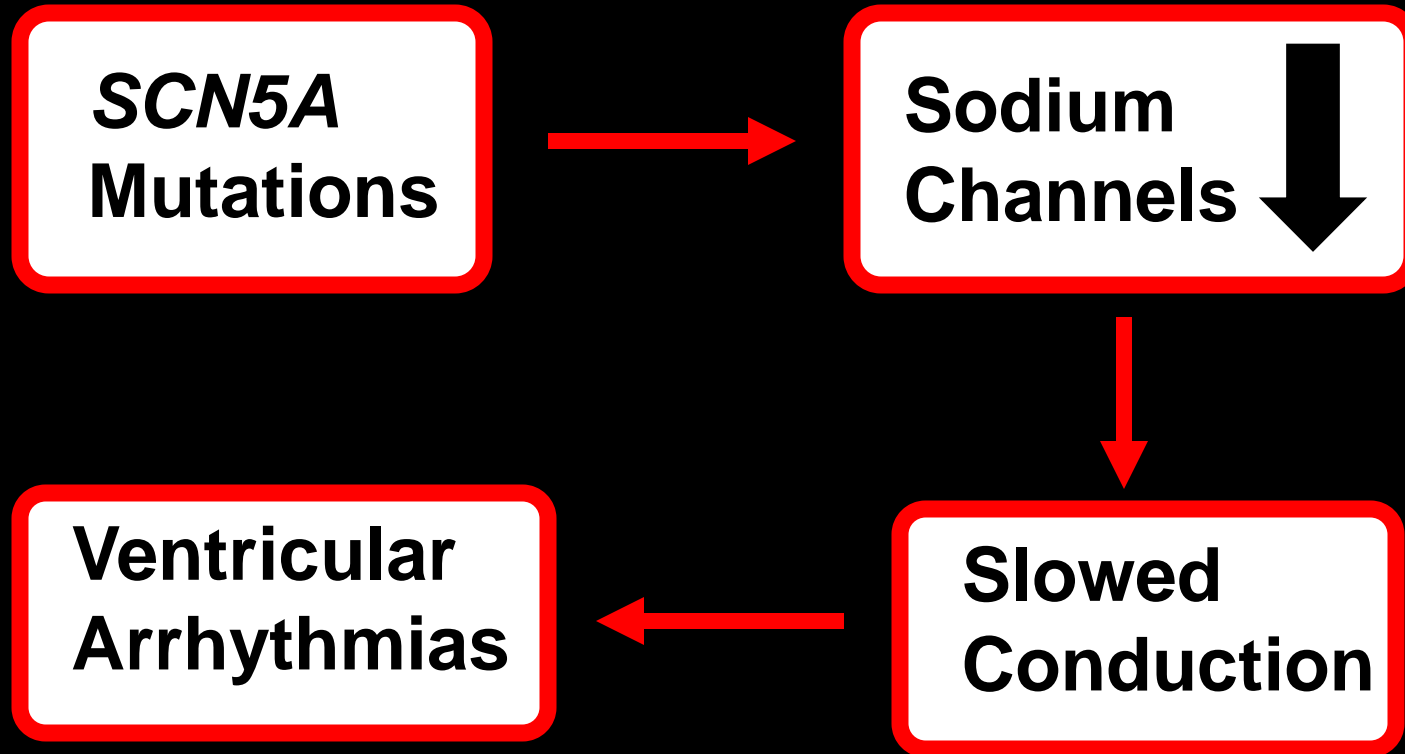
Wild-type



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



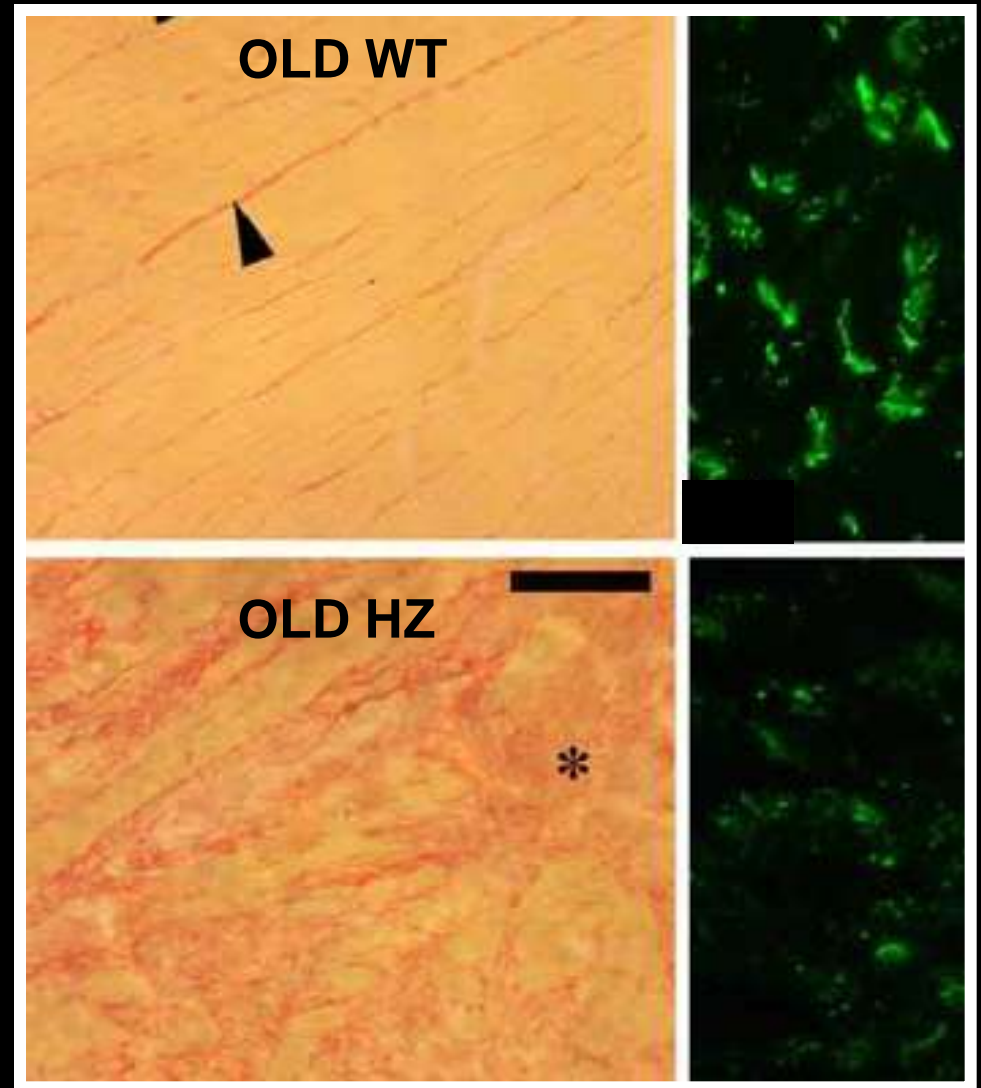
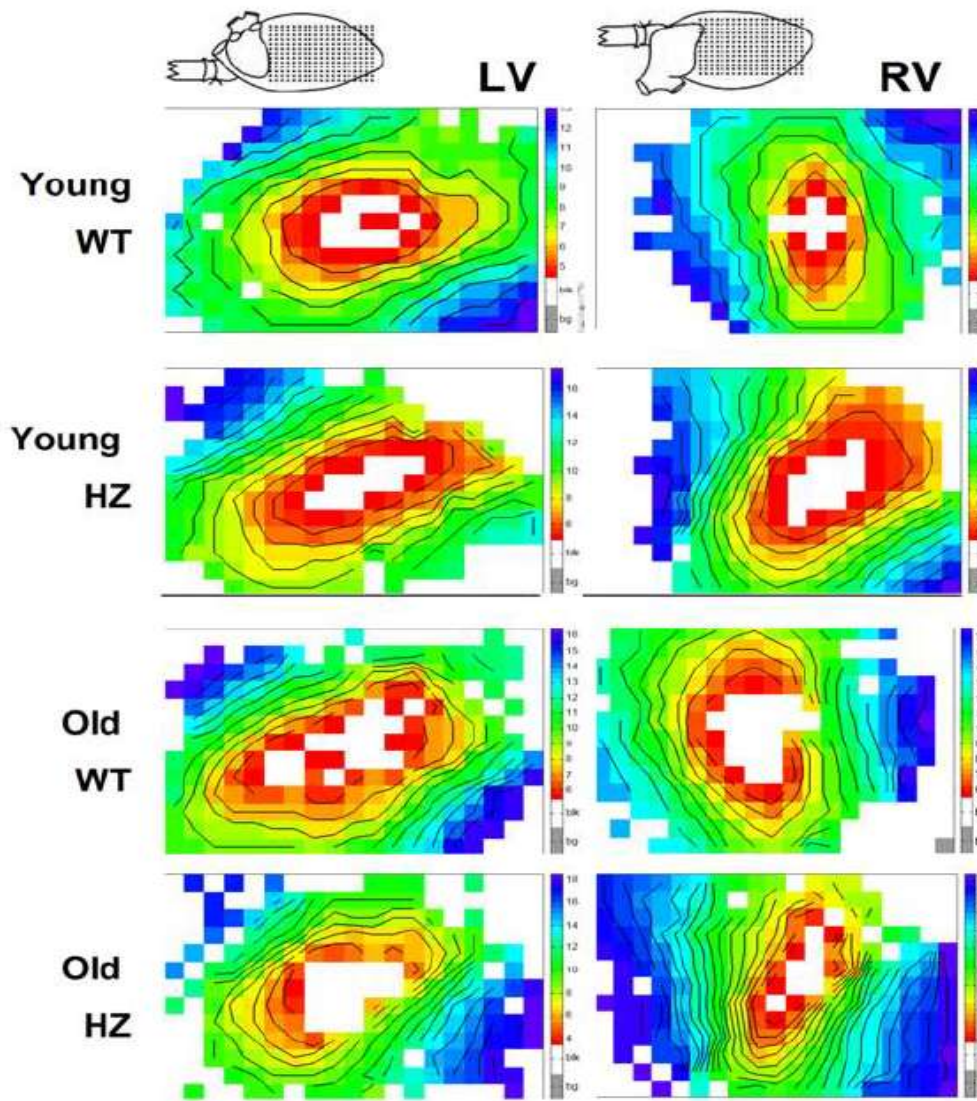
Speculative mechanism (Brugada Syndrome)



Structural observations in *SCN5A*-mutant and 'Brugada' patients

- **Lev-Lenegre disease (1998)**
- **DCM (2005)**
- **Questions re phenotypes and overlap - mainly
ARVC**
- **Conflicting observations - imaging, histology etc.**

Interstitial fibrosis in old *Scn5a*^{+/-} mutants



Intrauterine lethality in *Scn5a* $-/-$ mutants

Failure of ventricular development

Scn5a +/-



Scn5a -/-



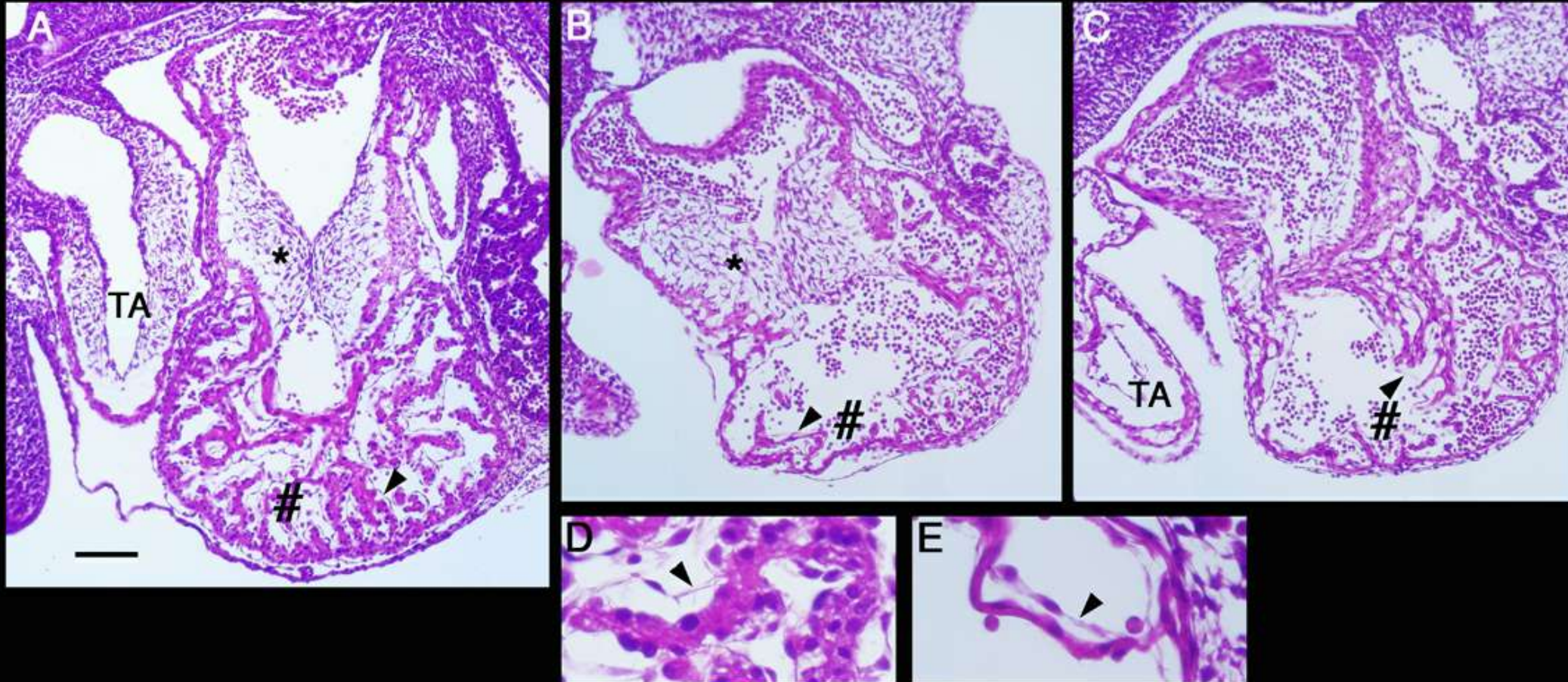
EC 10.5

Intrauterine lethality in *Scn5a* $-/-$ mutants

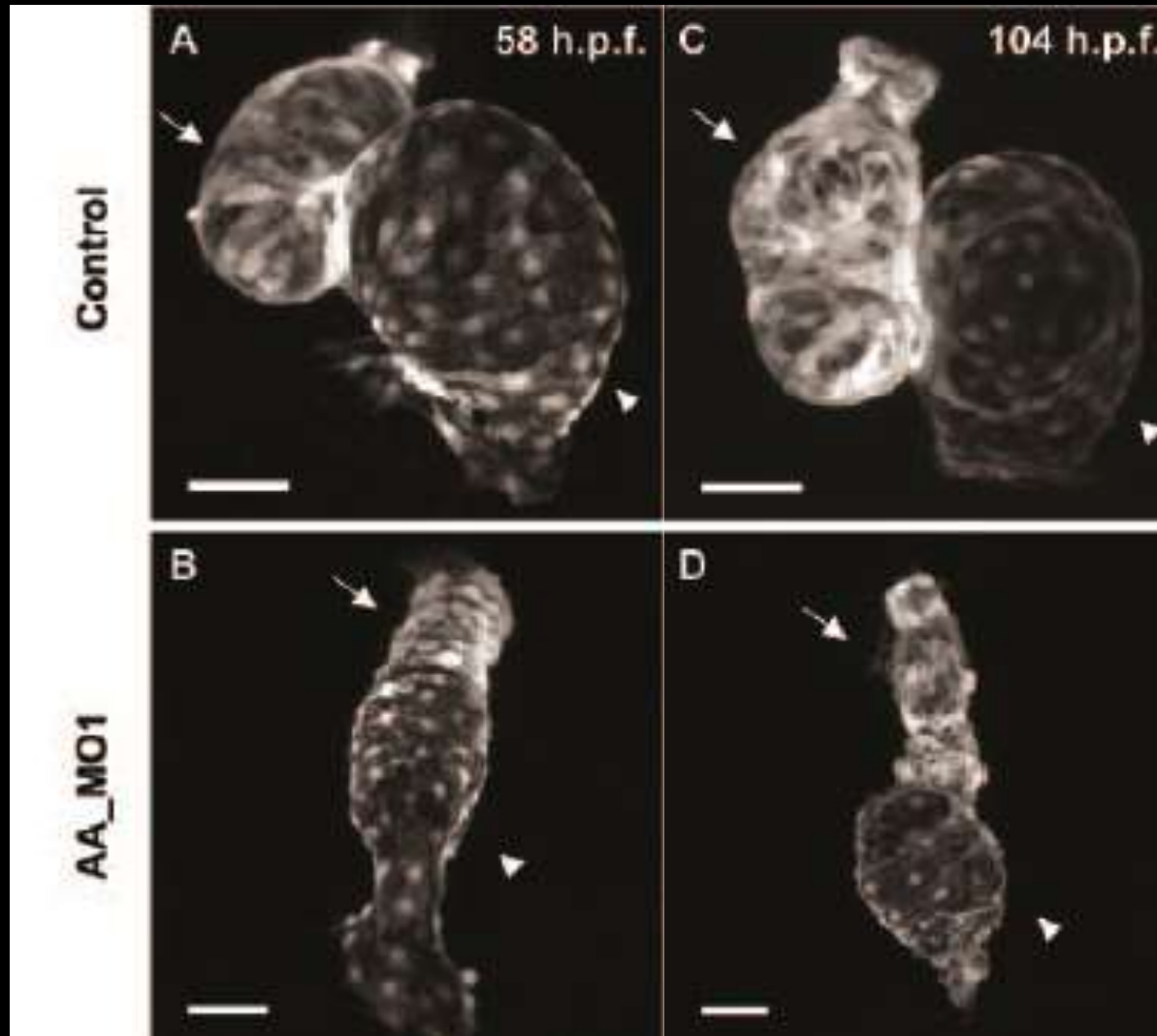
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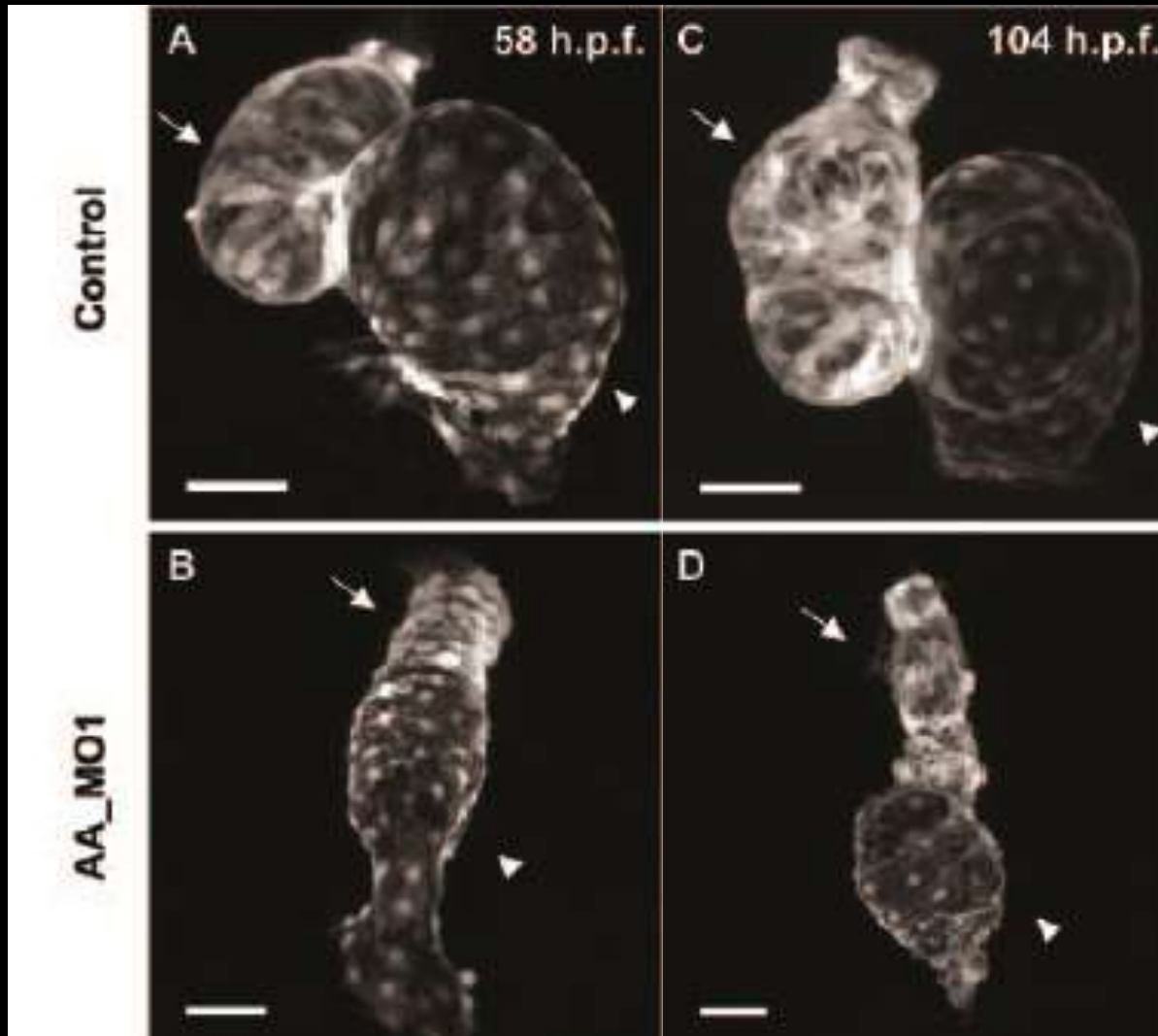


Voltage-gated Sodium Channels are required for heart development in Zebrafish



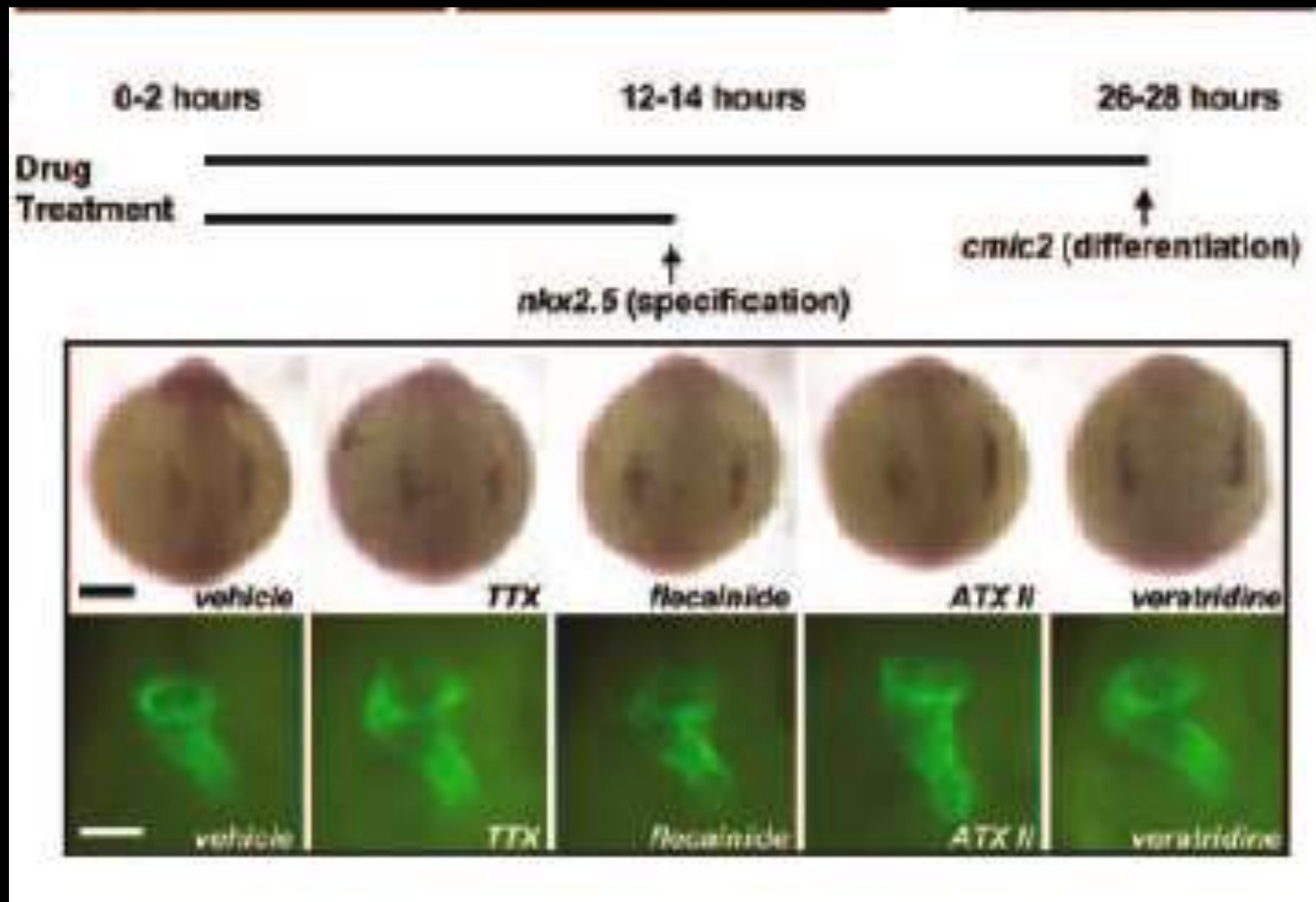
- Anti-sense knockdown *scn5Laa*, *scn5Lab* (homologues *Scn5a*)

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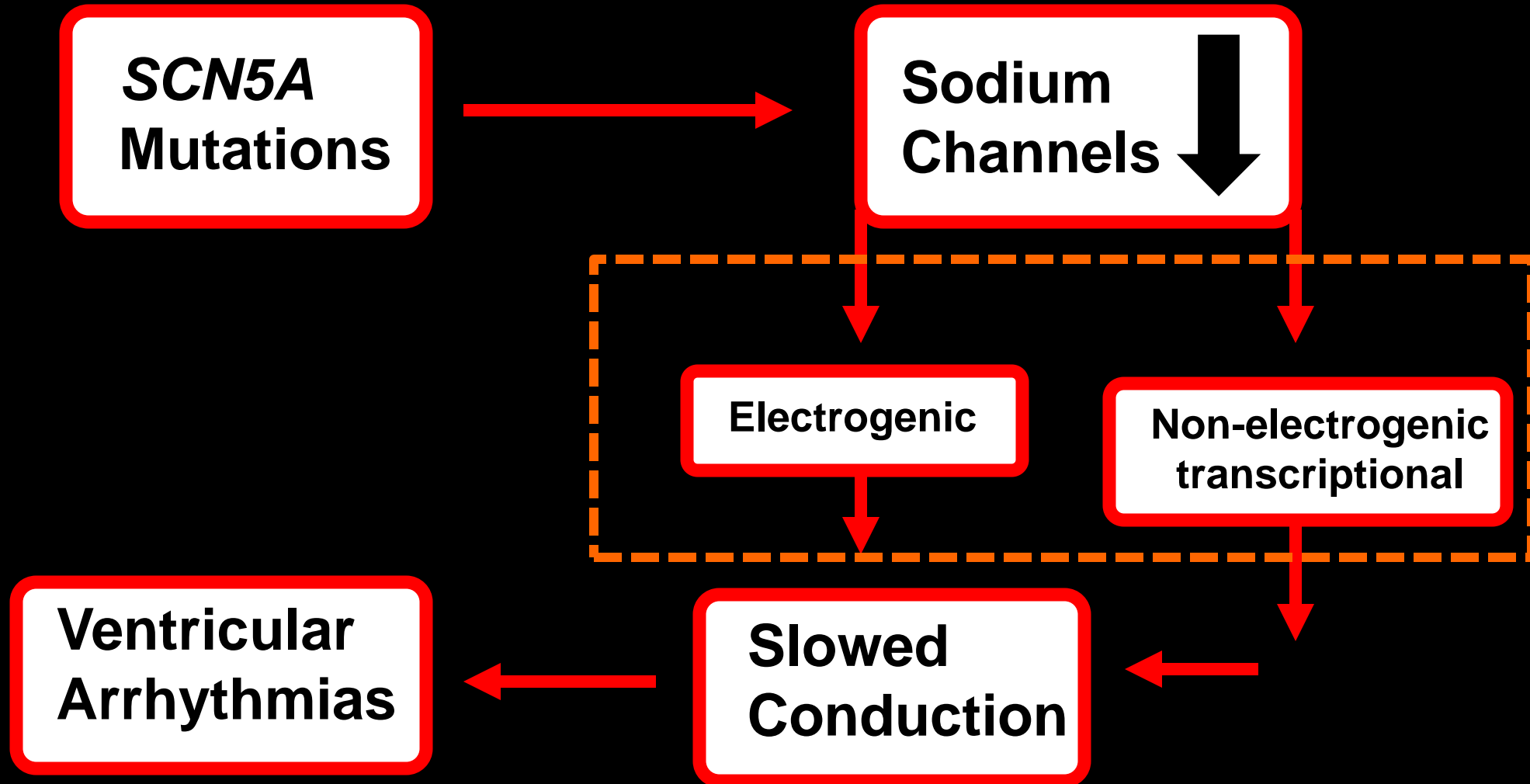


- Anti-sense knockdown *scn5Laa*, *scn5Lab* (homologues *Scn5a*)
- Marked dysmorphogenesis
- Reduced precursors
- Decreased expression *nkx2.5*, *gata4* and *hand2*.

Voltage-gated Sodium Channels may regulate early cardiac development independently of membrane electrophysiology



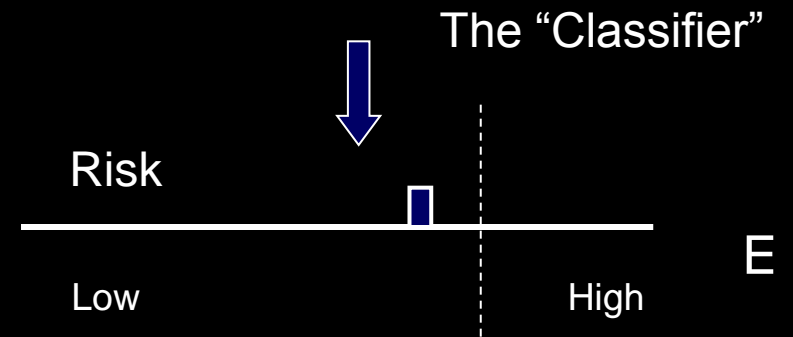
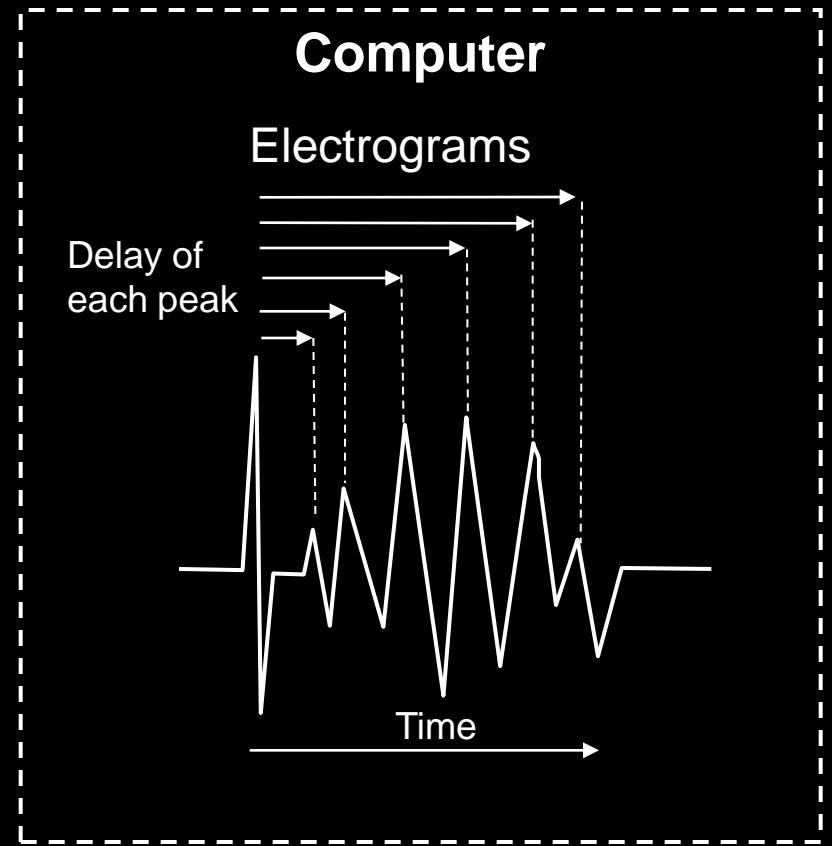
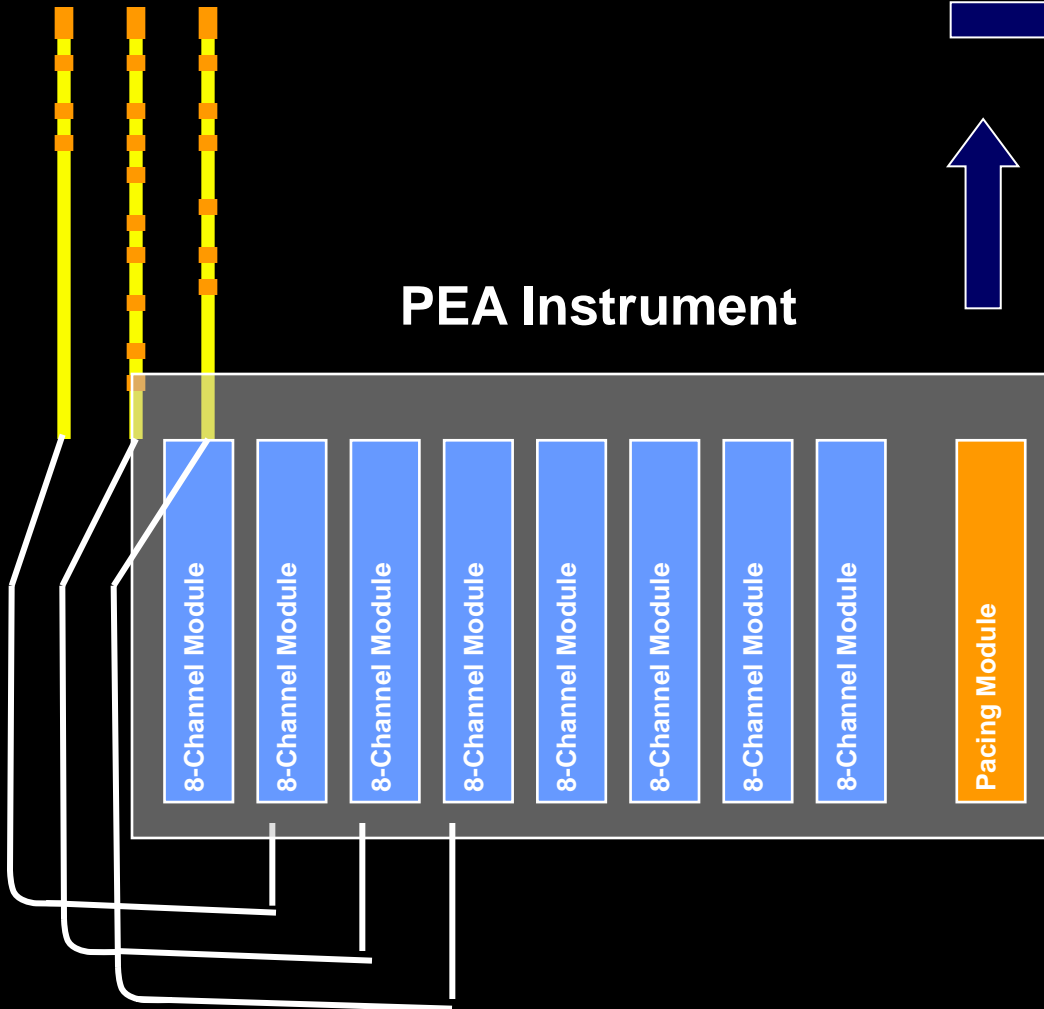
Proposed mechanism Brugada Syndrome 2005 -2011



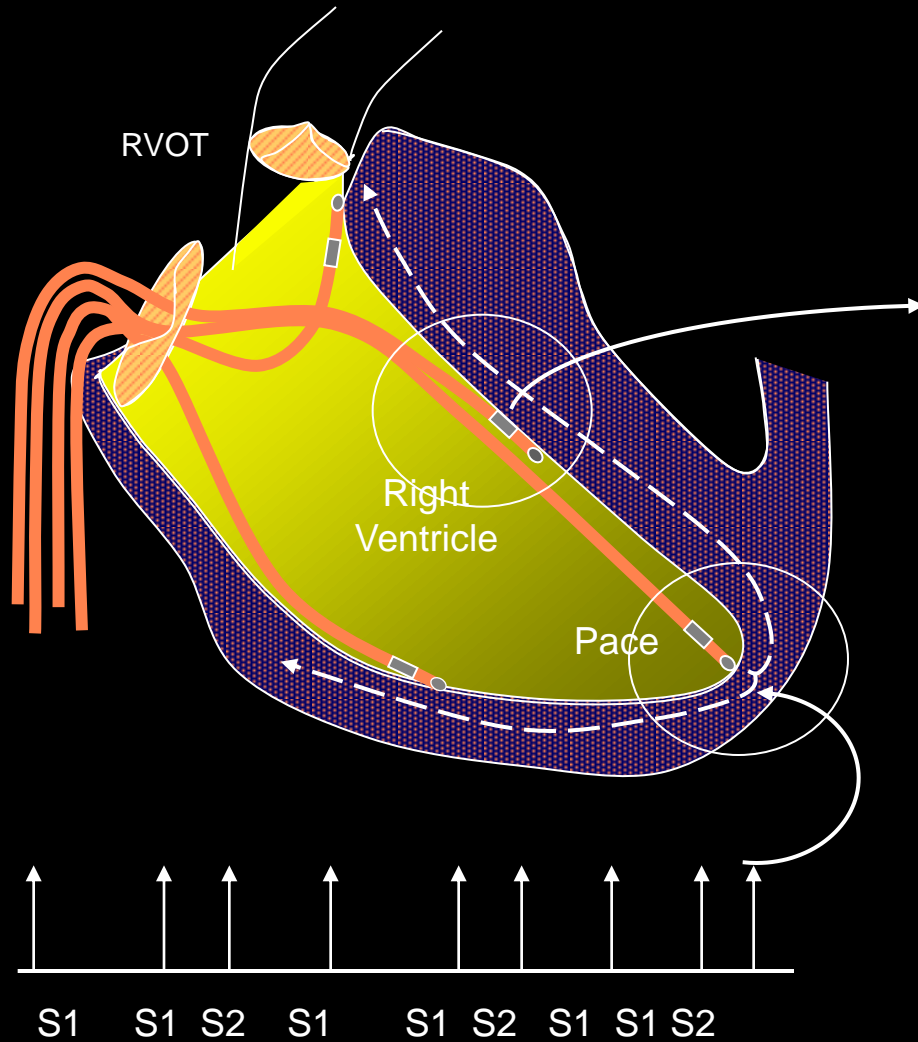
CLINICAL SET-UP

Diagnostic catheters inserted into patient

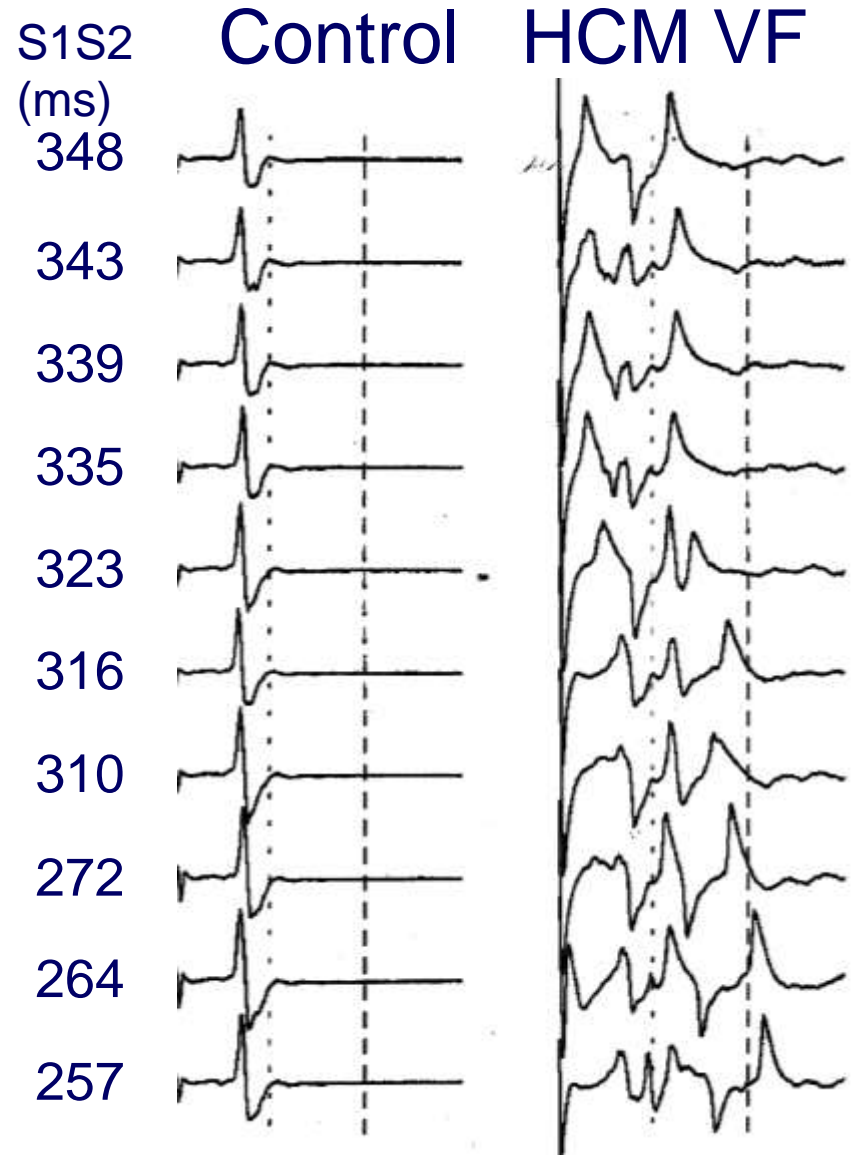
PEA Instrument



HYPERTROPHIC CARDIOMYOPATHY



S1S2 : 450 to 220 ms in 1 ms steps

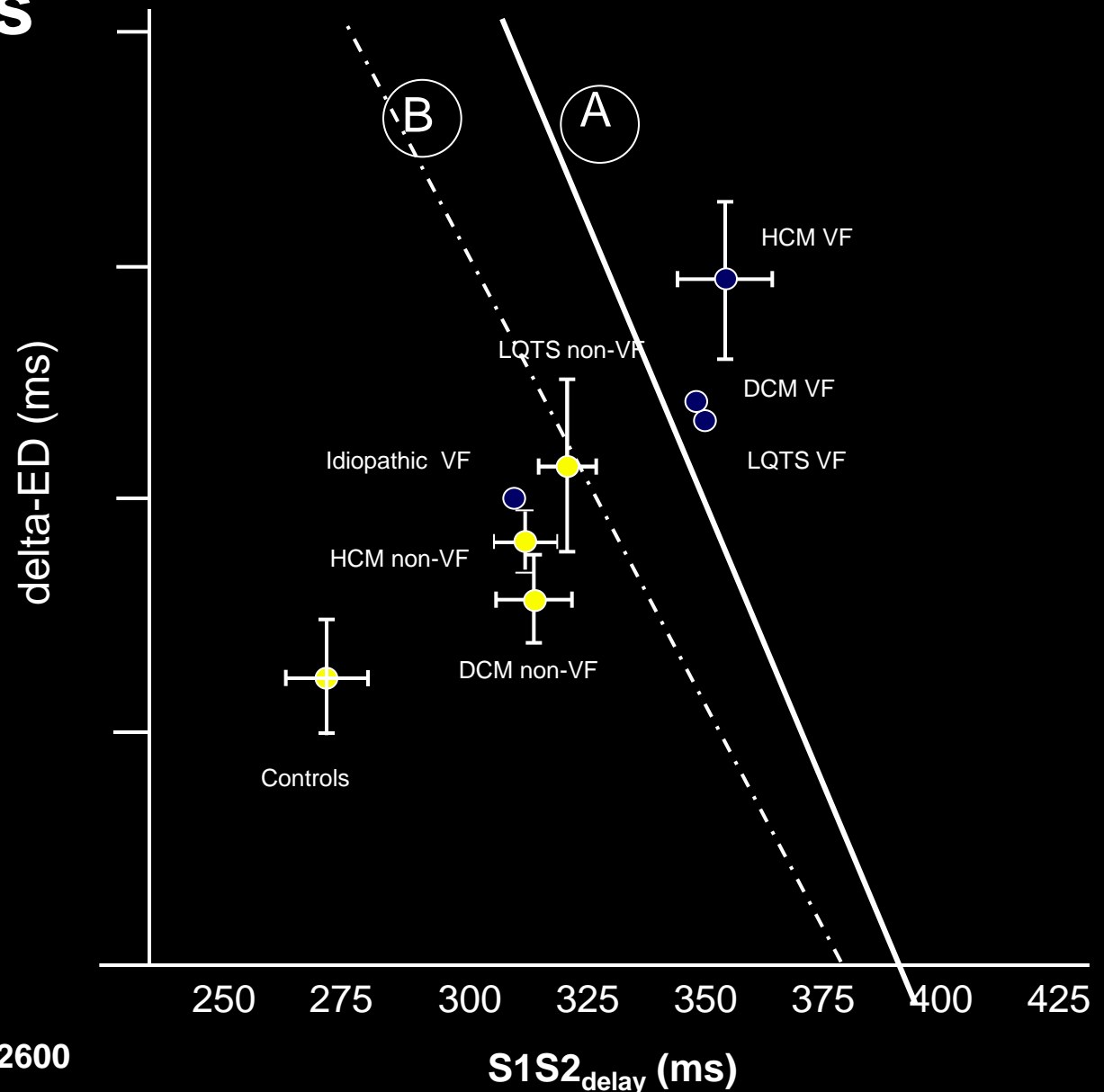


Sudden Cardiac Death predicted with Paced Electrogram Analysis

Retrospective

**266 patients
multitude of
diseases**

**61 history of
ventricular
fibrillation**

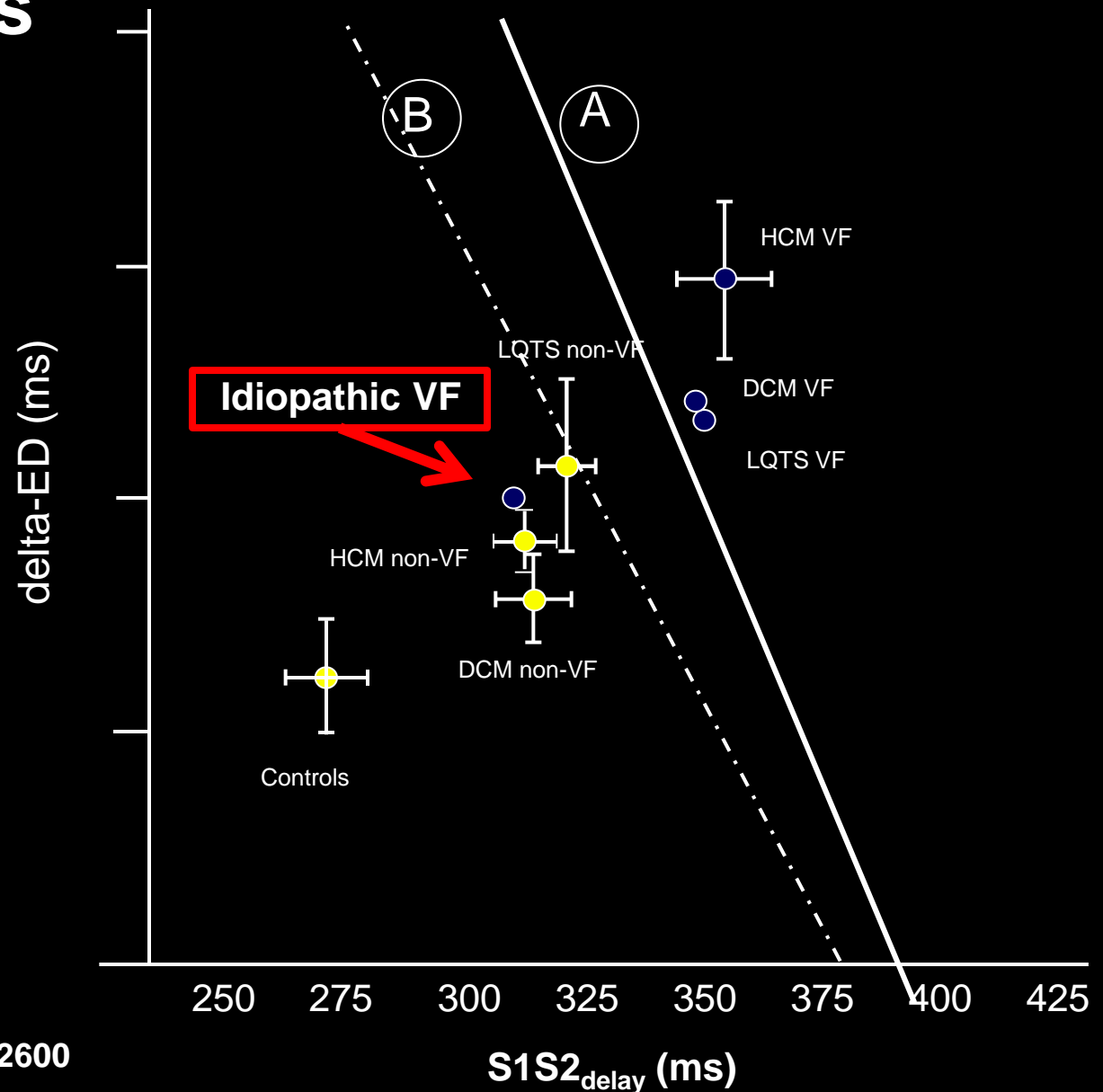


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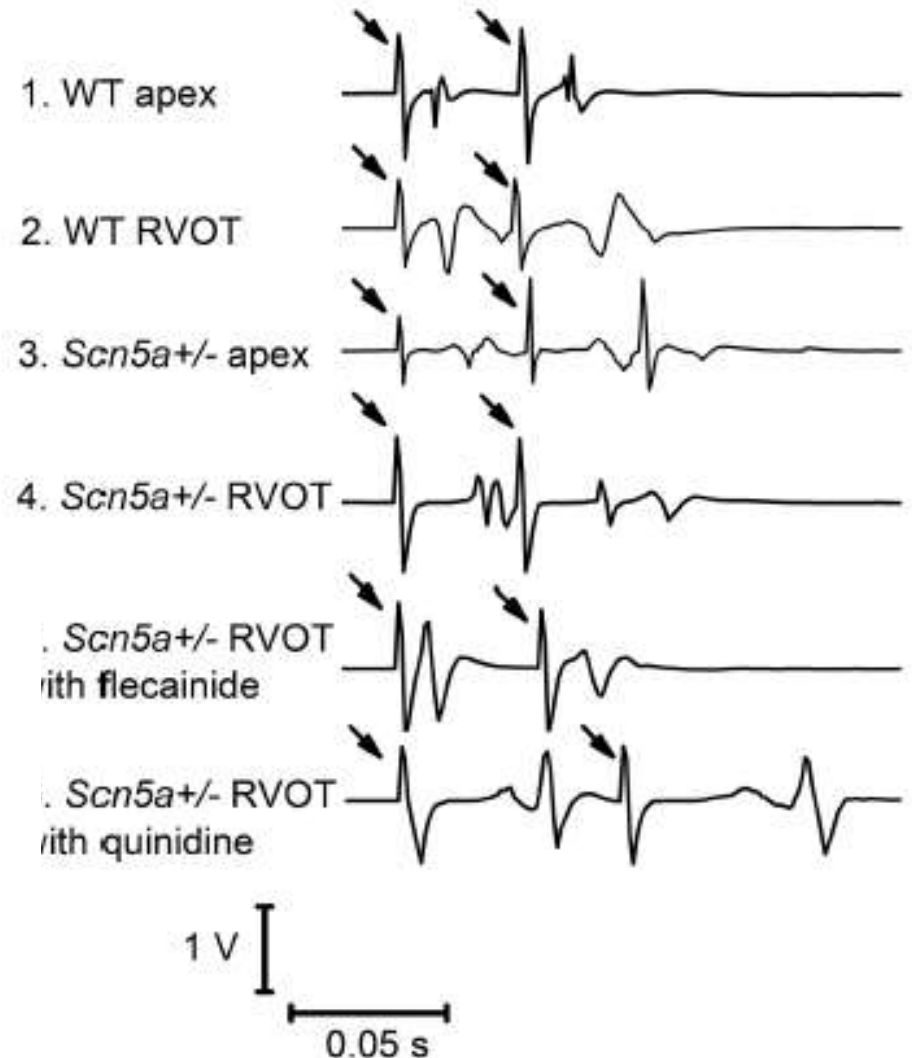
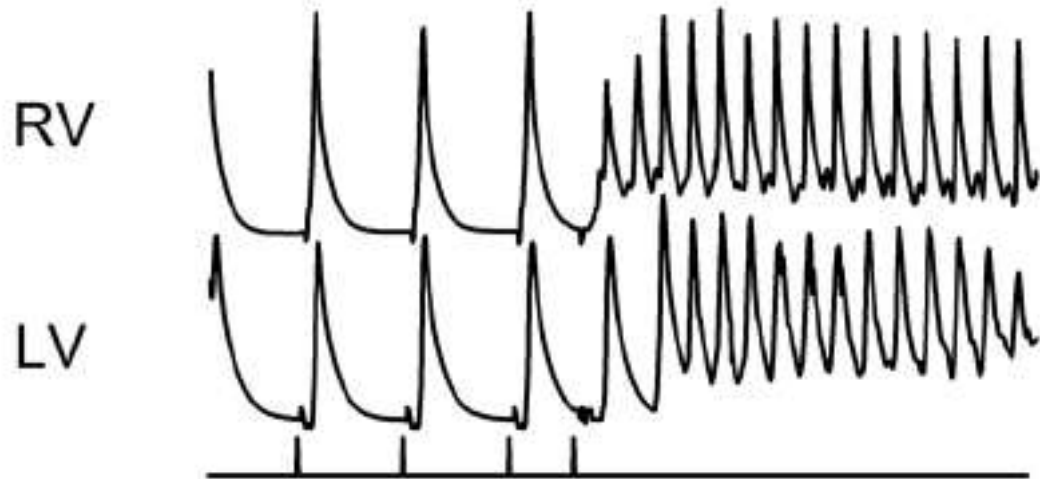
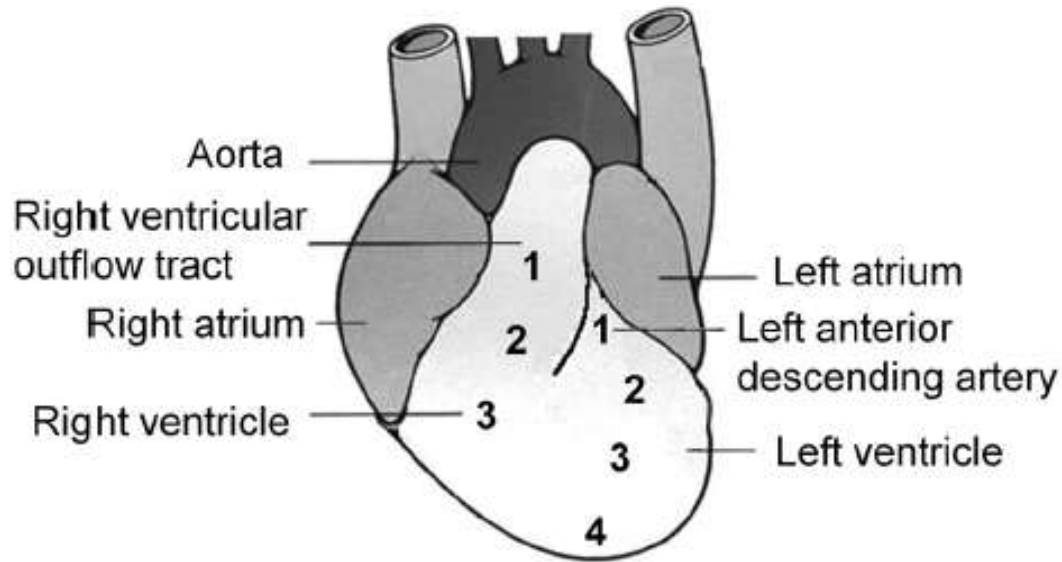
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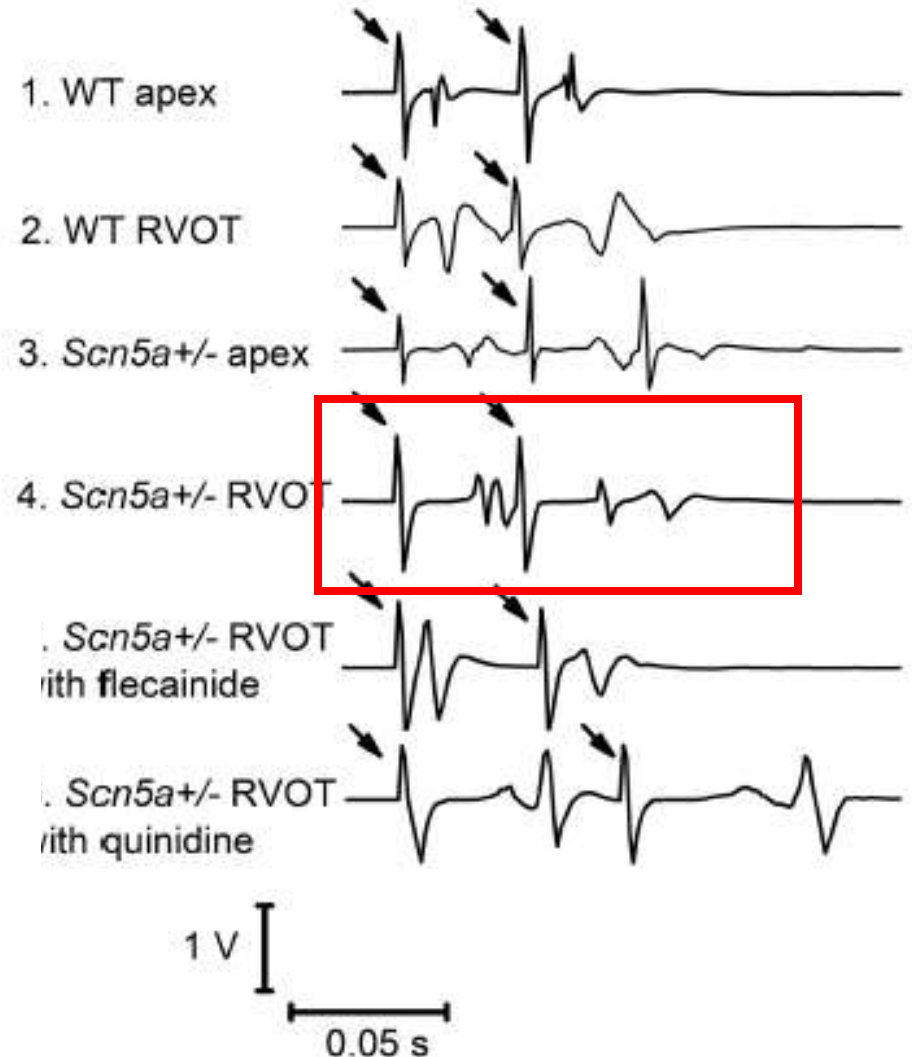
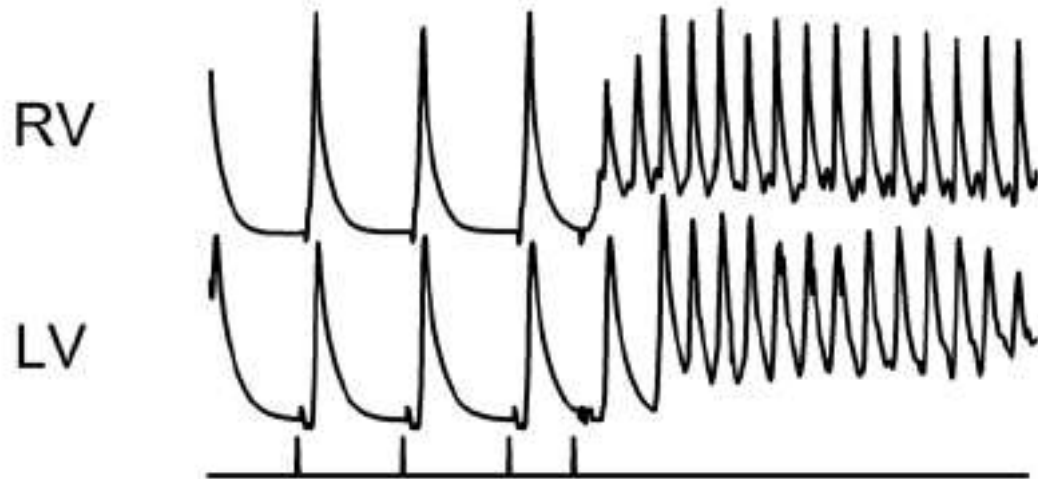
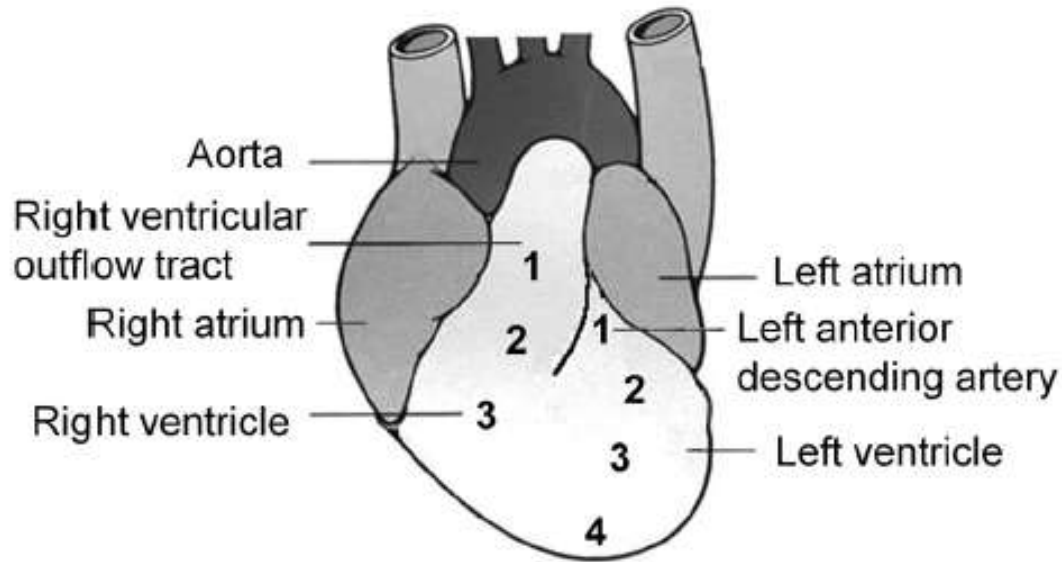
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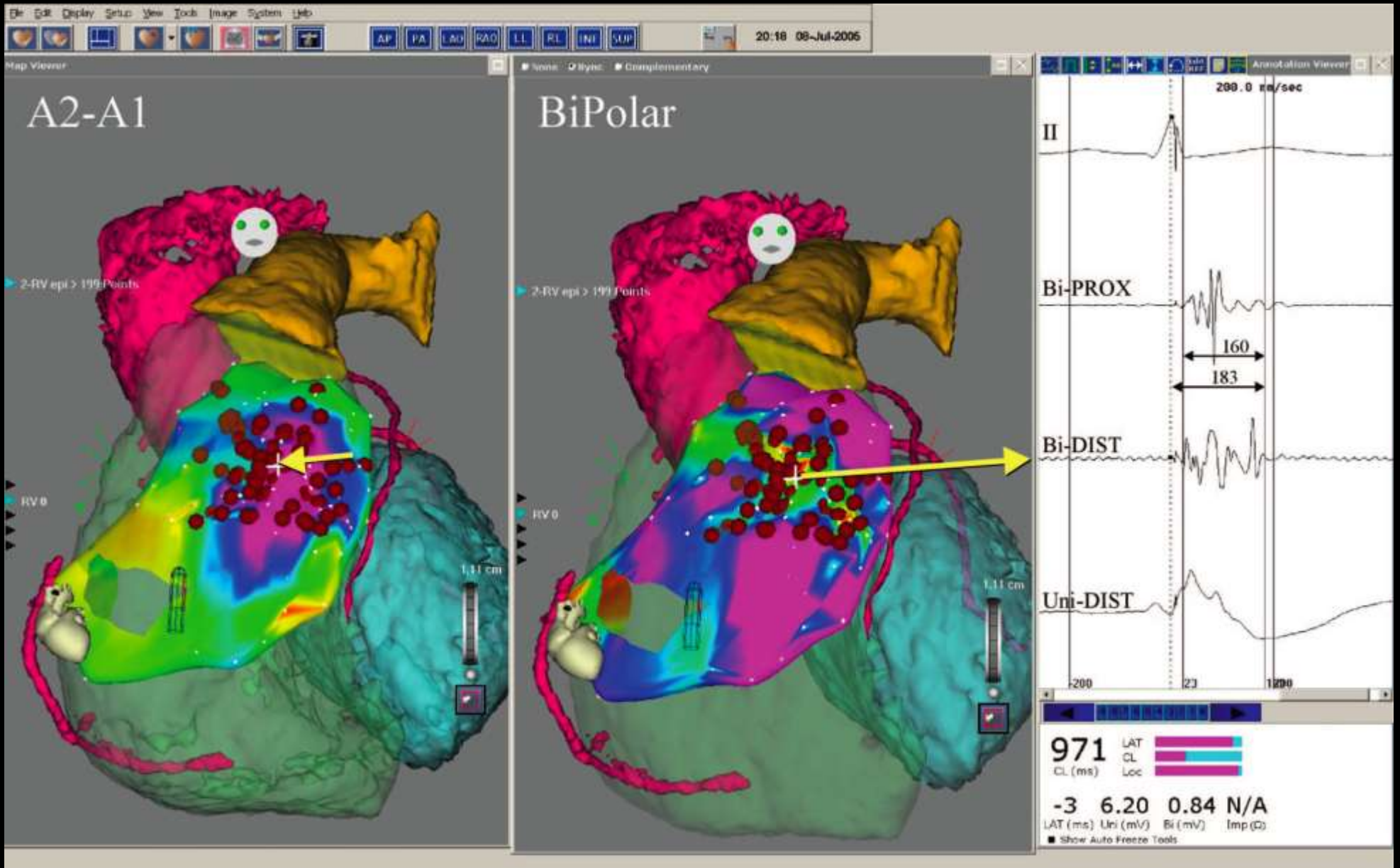


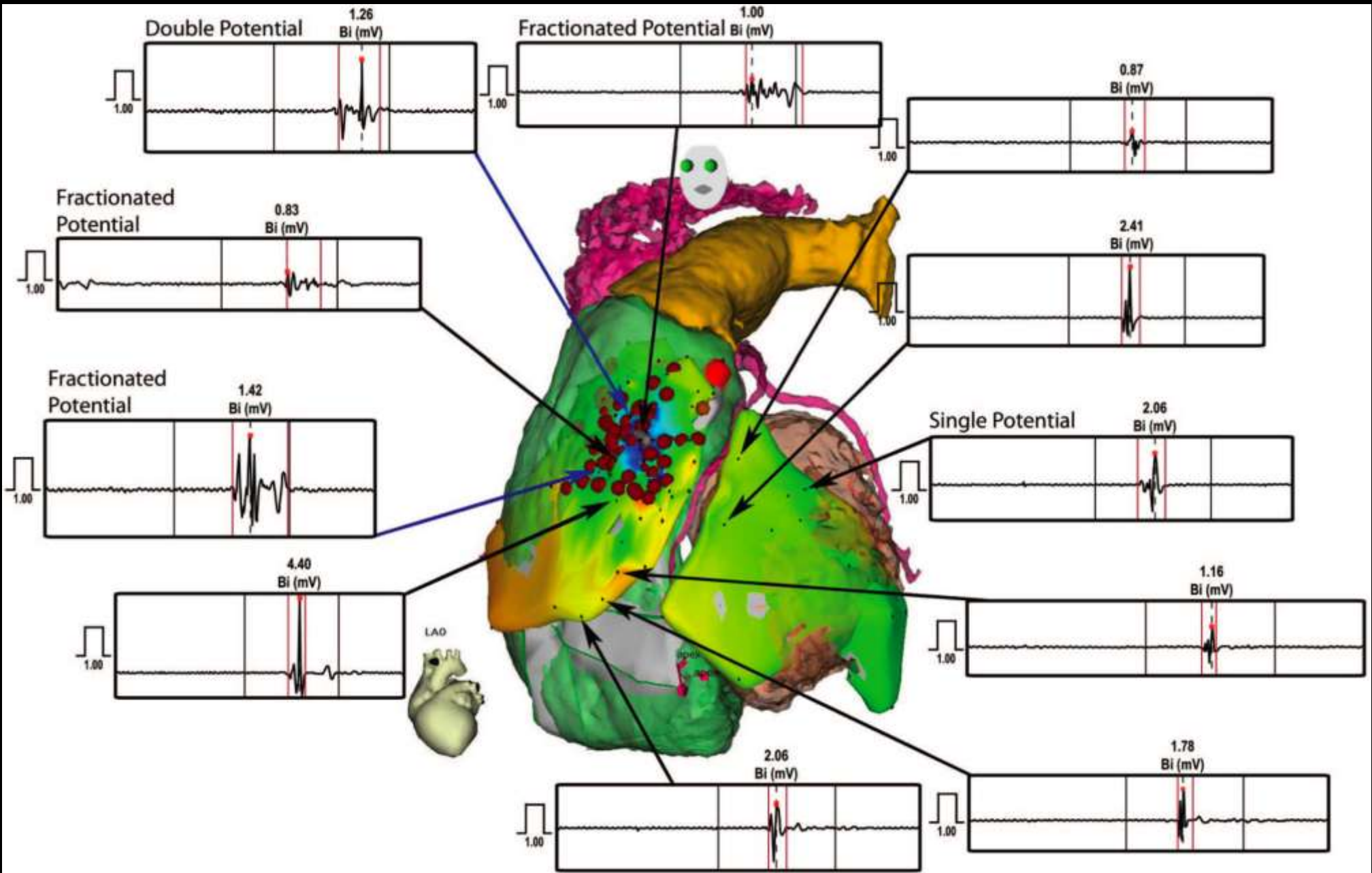
Spatial and temporal heterogeneities confined to RVOT



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Delayed ECG effects of anterior epicardial ablation

Before Ablation

1 Mo. Post Ablation

3 Mo. Post Ablation

V1

V1

V1

V2

V2

V2

V3

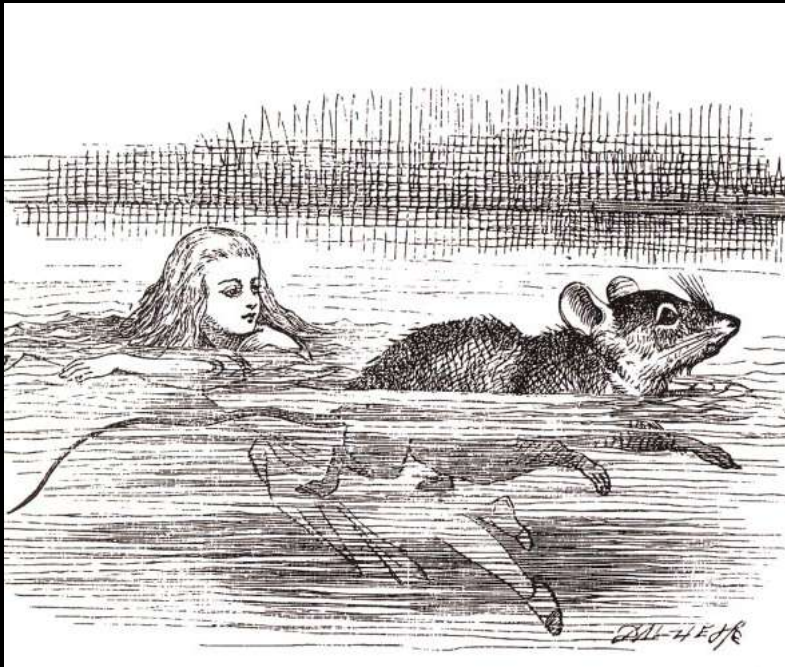
V3

V3

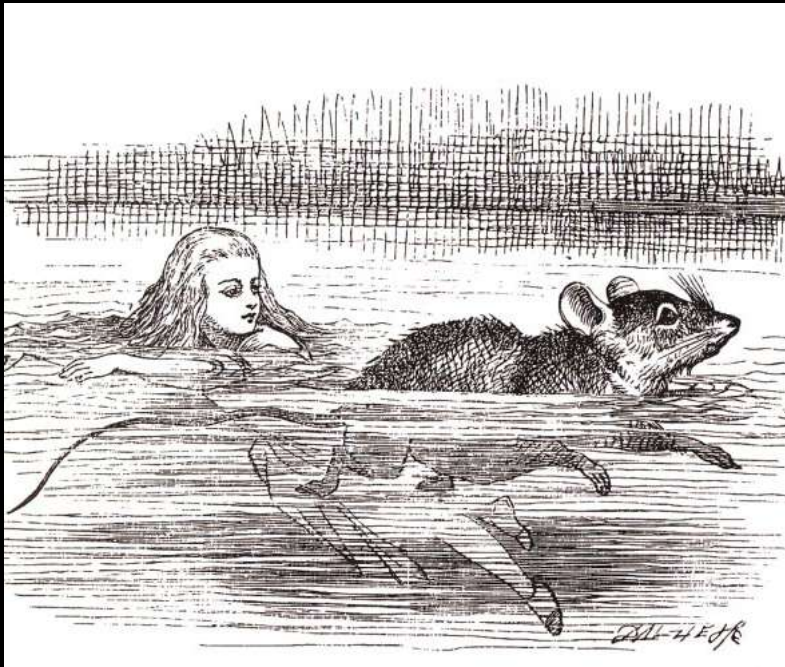
Genes to arrhythmias and sudden cardiac death

Model systems/pathogenesis

- Conventional (mouse/zebrafish etc.)
- Human models human disease (iPS)



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Clinical translation

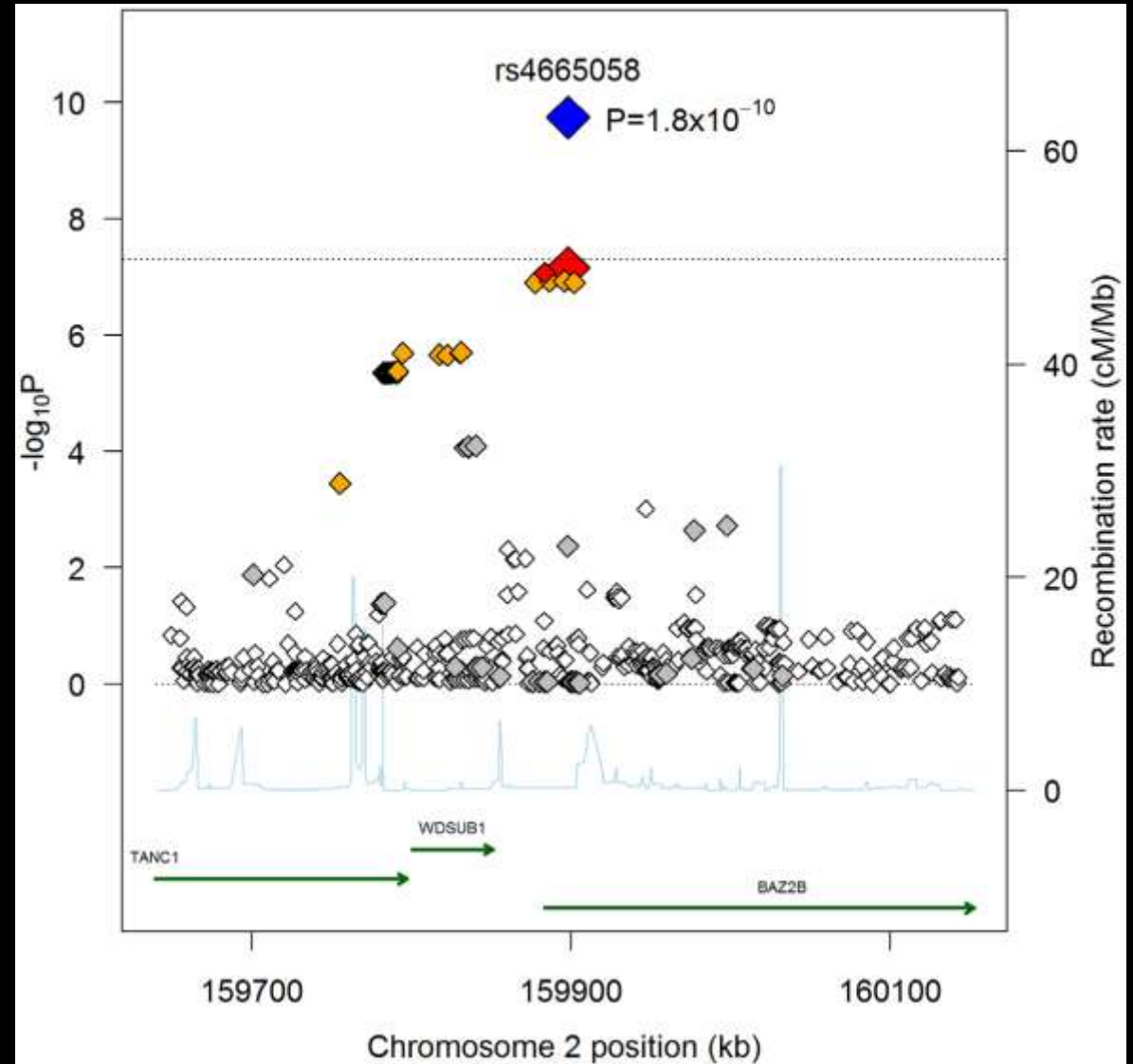
- Phenotyping by understanding mechanism
- Targeted therapeutics by understanding mechanism

SCD Susceptibility Locus at 2q24.2 in European Ancestry Individuals

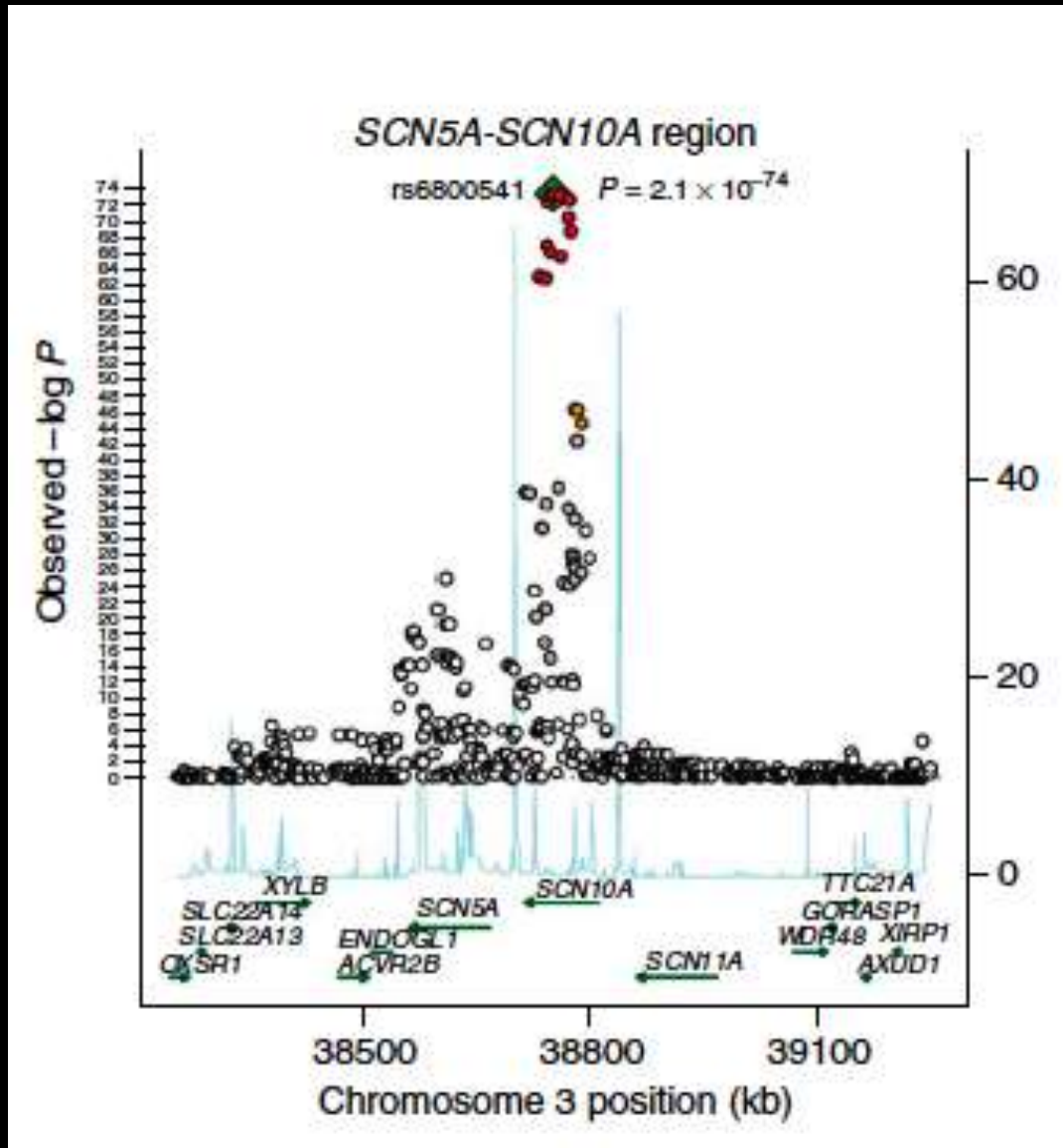
- **GWAS**
- **Meta-analysis (5 studies)**
- **n = 1,293 SCD cases and > 20,000 controls**
- **Increase risk 1.92-fold per allele**

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Voltage-gated Sodium Channels are associated with indices of cardiac conduction



- GWAS
- Meta-analysis 7 studies
- $n = 28,517$
- role of common variants in channel/developmental genes in conduction

S1103Y Cardiac Sodium Channel Variant associated With ICD Discharge in Afro-Americans

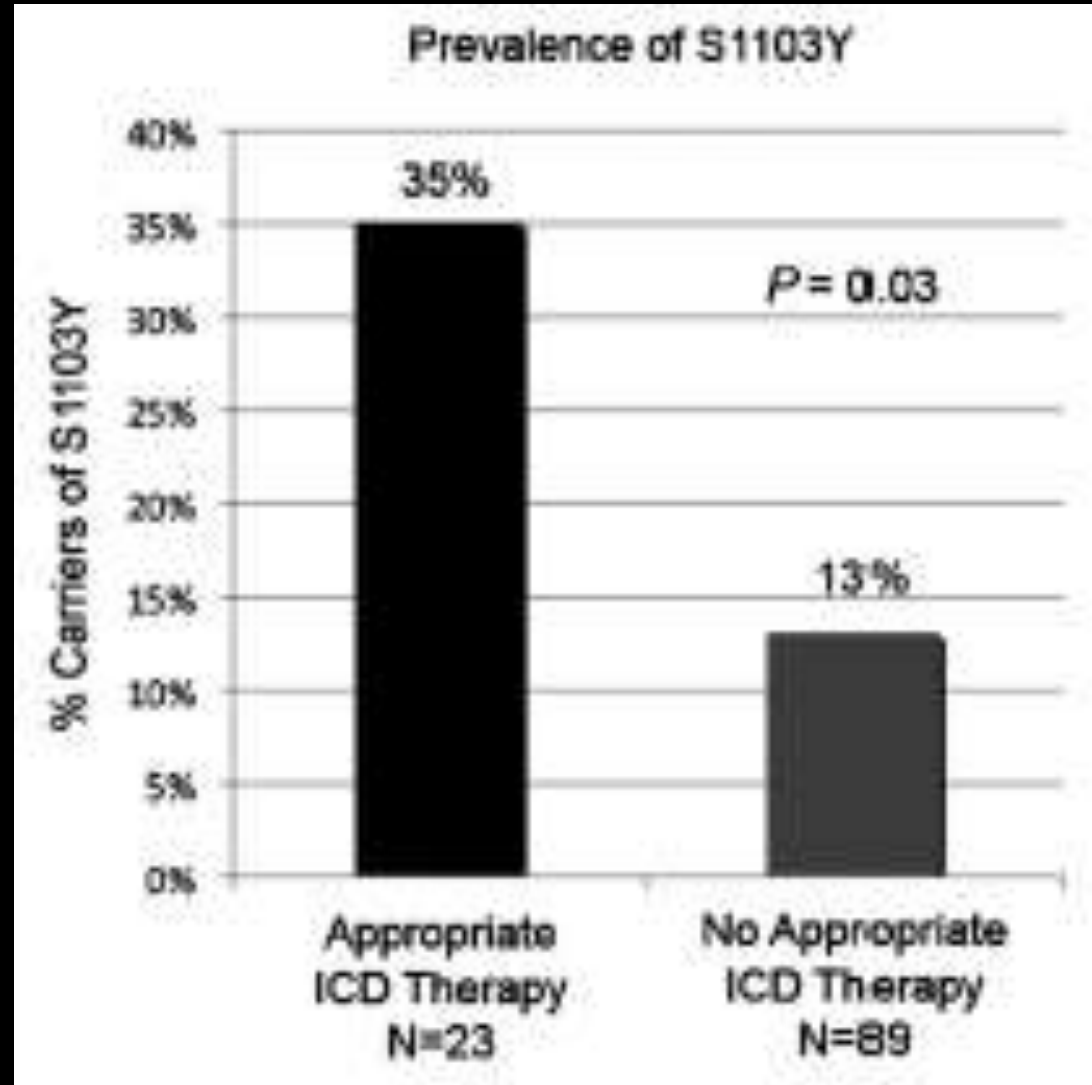
- **Long association variant with risk in Afro-Americans**
- **Duke EPGEN repository**

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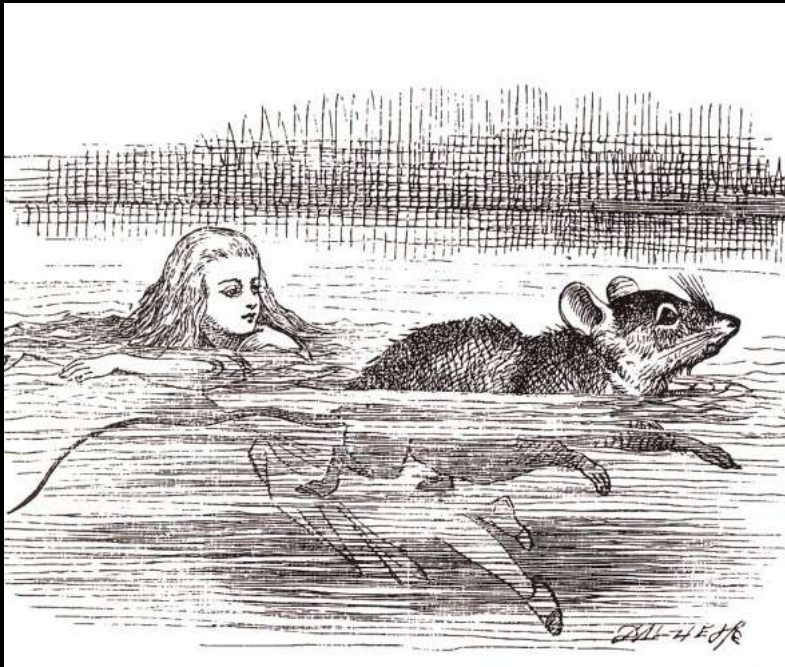
- Long association variant with risk in Afro-Americans
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- Black patients (n=112)
- EF < 35%; primary prevention
- Hazard ratio for ICD therapy in Y1103 carriers - 4.33 (1.60 – 11.73)

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- Targeted therapeutics by understanding mechanism

Routine clinical applications of genetics

- Not yet other than targeted family screening
- Further identification of causal variants: bioinformatics fine mapping, re-sequencing etc.