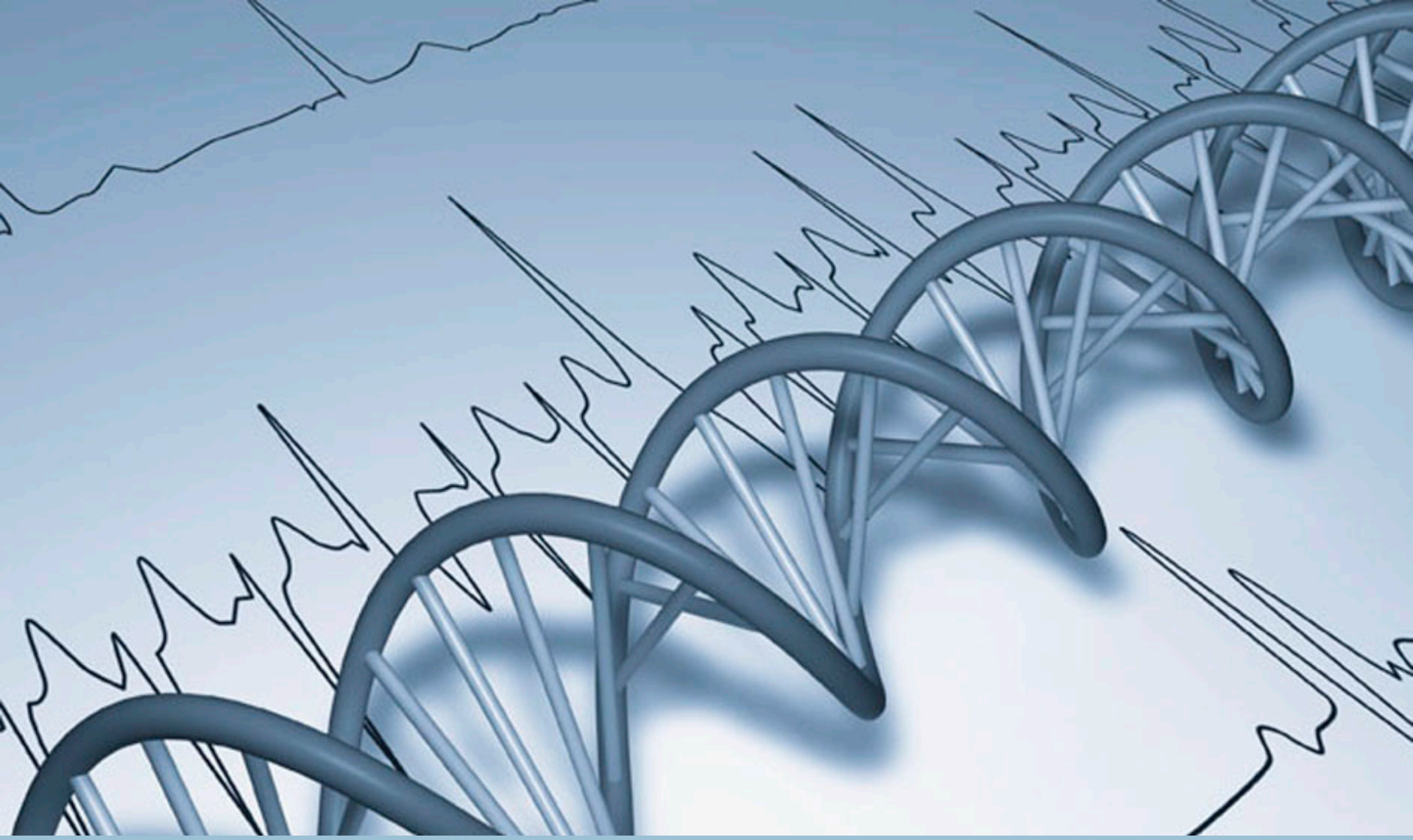
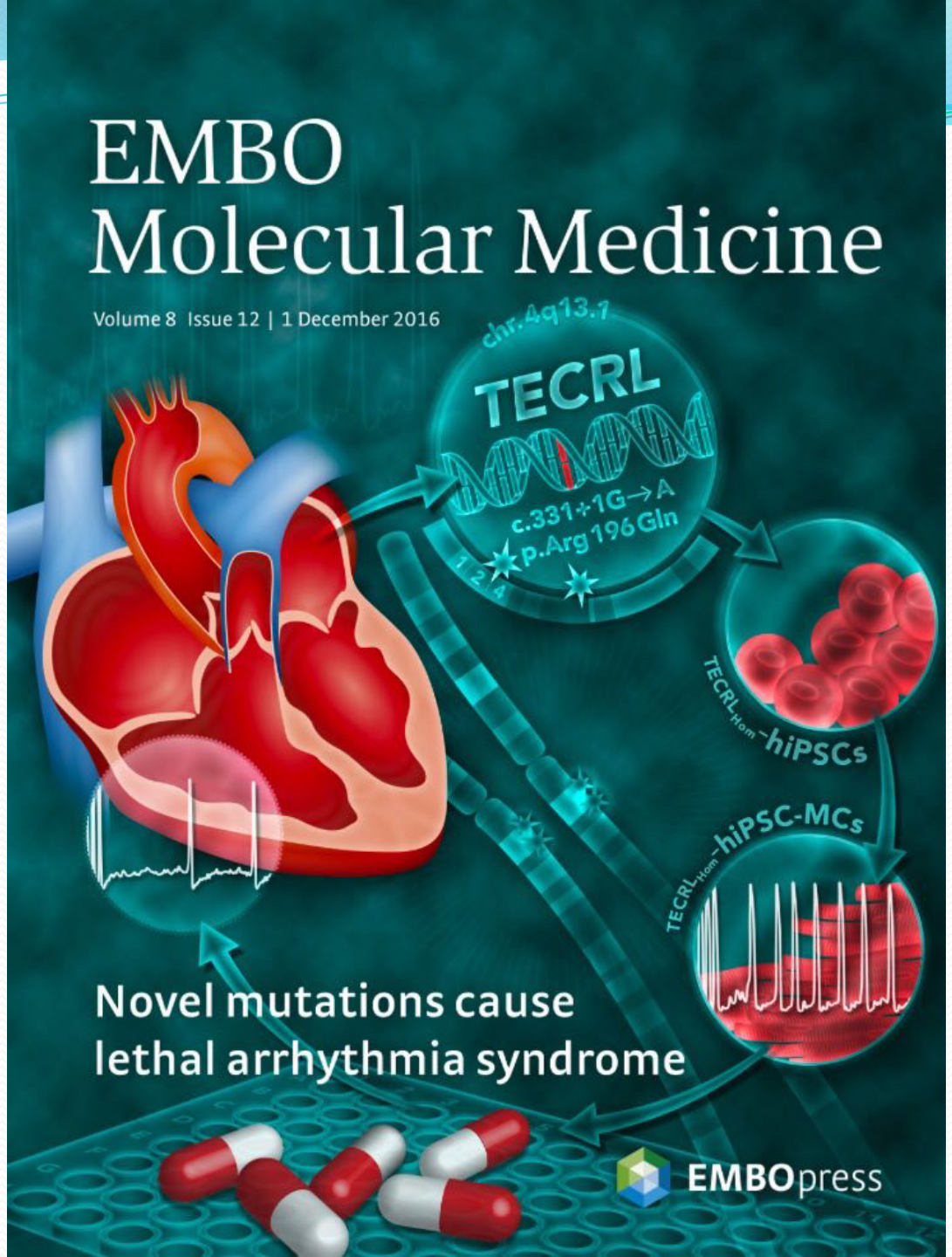


TECRL, a new life-threatening inherited arrhythmia gene

Z. Bhuiyan, MBBS, Ph.D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Molecular Medicine
Volume 8 Issue 12 | 1 December 2016
chr.4q13.1
TECRL
c.331+1G→A
p.Arg196Gln
TECRL Hom -hiPSCs
TECRL Hom -hiPSC-MCs
Novel mutations cause
lethal arrhythmia syndrome
EMBOpress

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): Genetic Features

CPVT (1): Autosomal Dominant, Chromosome 1q42-43

Cardiac Ryanodine Receptor-2 (*RYR2*) Gene

CPVT (2): Autosomal Recessive, Chromosome 1p13-21

Calsequestrin 2 (*CASQ2*) Gene

CPVT3: OMIM # 614021

A Novel Early Onset Lethal Form of Catecholaminergic Polymorphic Ventricular Tachycardia Maps to Chromosome 7p14-p22

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ARTHUR A. M. WILDE, M.D., PH.D.,† and LIHADH AL-GAZALI, M.D., F.R.C.P.§

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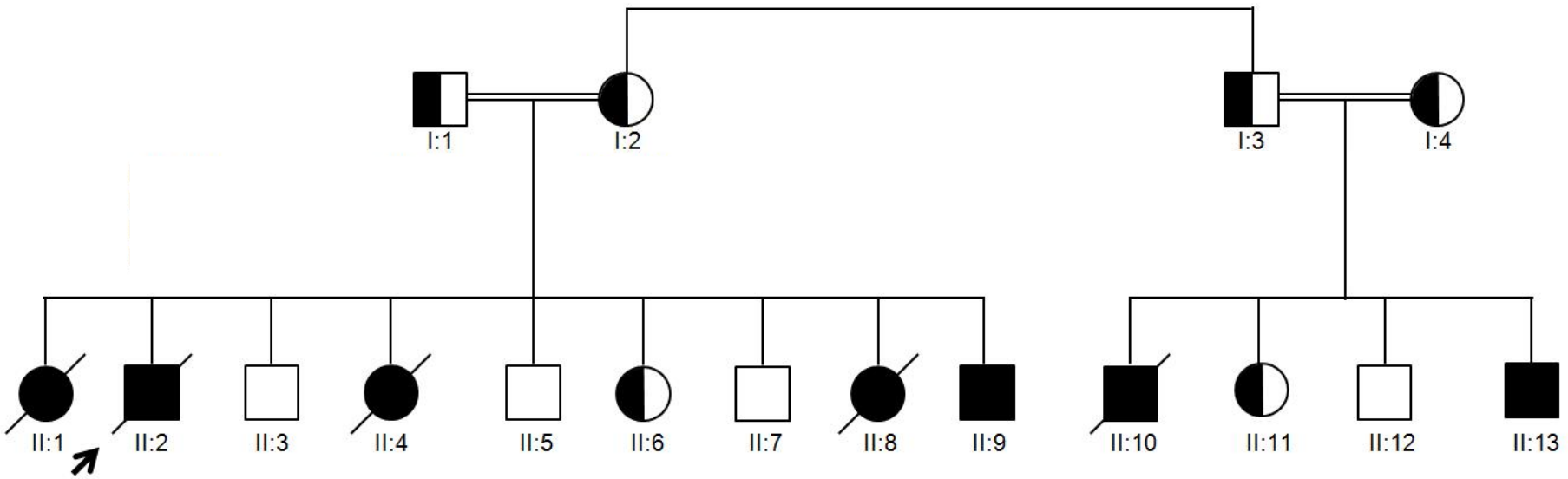
J Cardiovasc Electrophysiol. 2007 Sep;18(10):1060-6.

Origin of the Patients in this Study

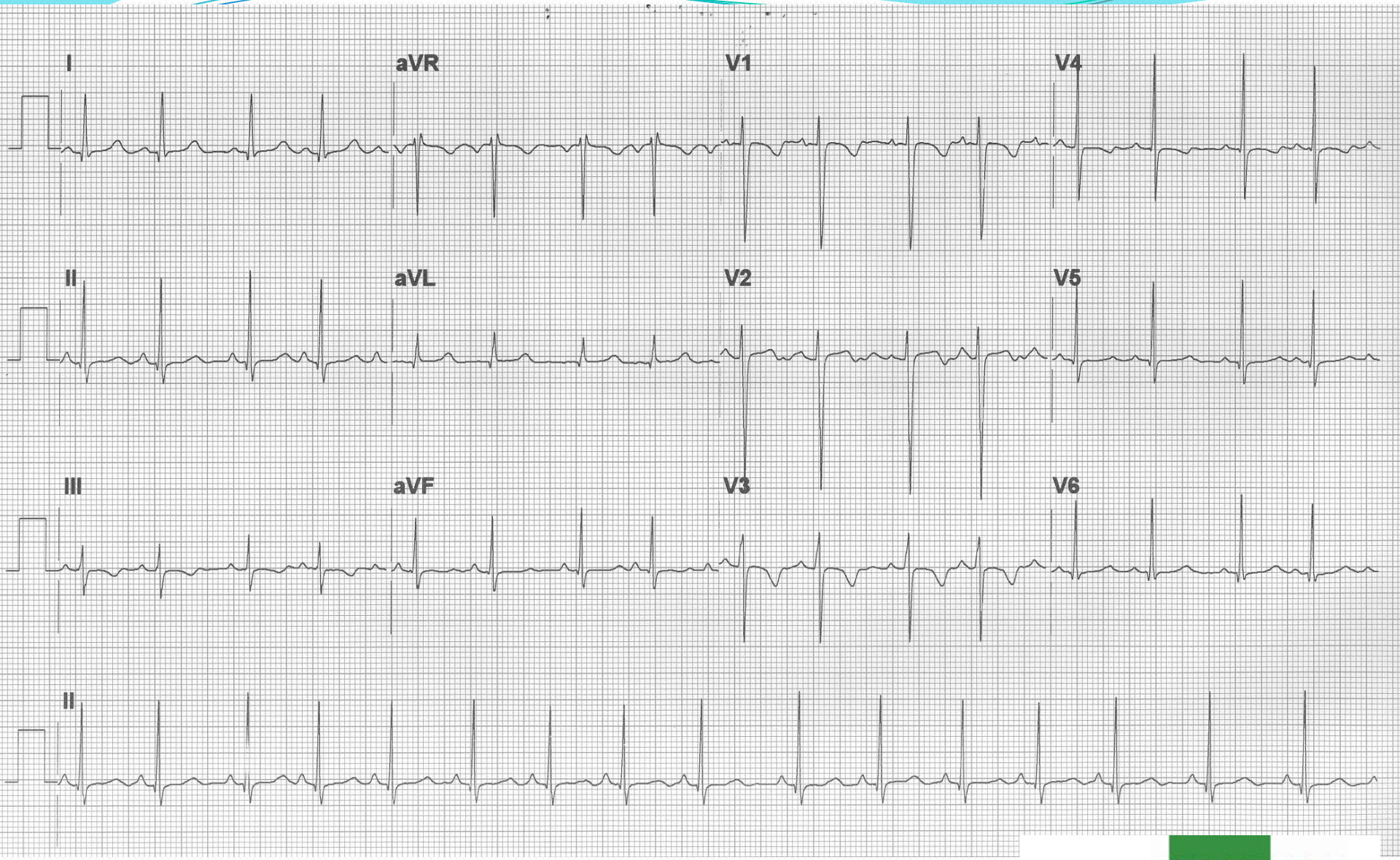
CPVT3 Family-Sudan



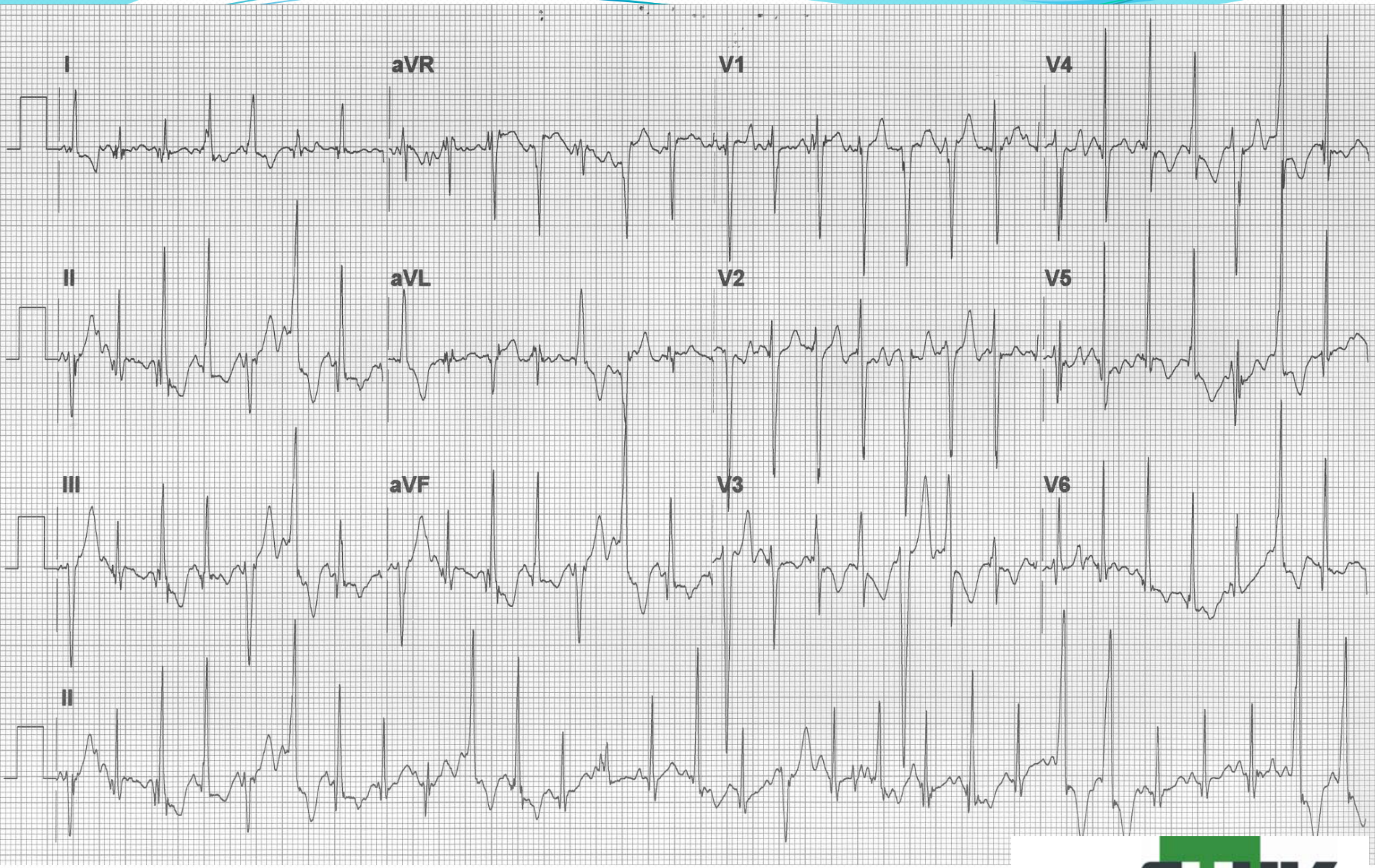
CPVT3 Family-Sudan

Subject in current pedigree	Subject in previous pedigree (Bhuiyan et al., 2007)	Gender	Triggers for cardiac arrest	Age at first syncopal episode	Current condition	ECG	QTc (ms)	Other cardiac nomalies
IV:1	IV:1	F	Playing	10	Deceased	NA	NA	No
IV:2	IV:2	M	Skating	12	Deceased	Sinus rhythm	450-490 (Bhuiyan *et al*, 2007)	No
IV:4	IV:4	F	Playing	8	Deceased	Sinus rhythm	470-480 (Bhuiyan *et al*, 2007)	VSD/Infundibular stenosis
IV:8	IV:8	F	Dancing	8	Deceased	Sinus rhythm	460-470	VSD/Pulmonary atresia
IV:9	Not yet born	M	Running	2.5	Severe brain damage since 2014	Yes	420	No
IV:10	IV:9	M	Running	7	Deceased	Yes (Bhuiyan *et al*, 2007)	480 (Bhuiyan *et al*, 2007)	No
IV:13	Not yet born	M	Running	4	ICD implanted and no syncope since	Sinus rhythm , 1 ECG showing mild QT prolongation (Fig. 1B of this manuscript)	450 (Fig. 1B of this manuscript)	No

ECG at Rest

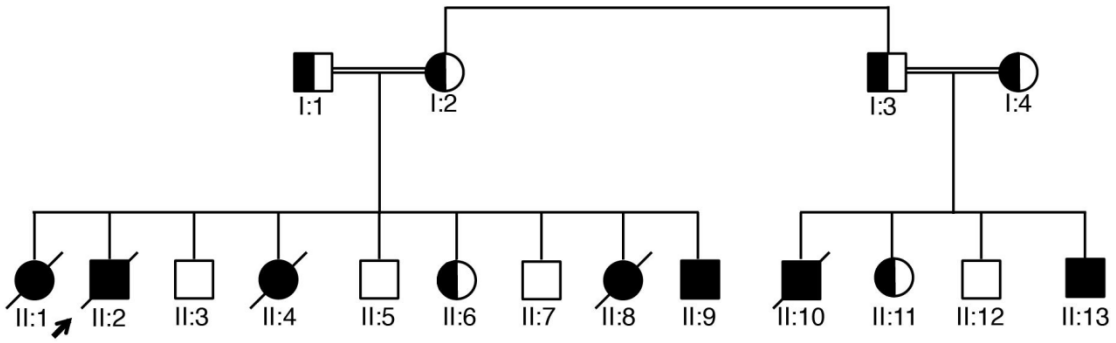


ECG at Stress

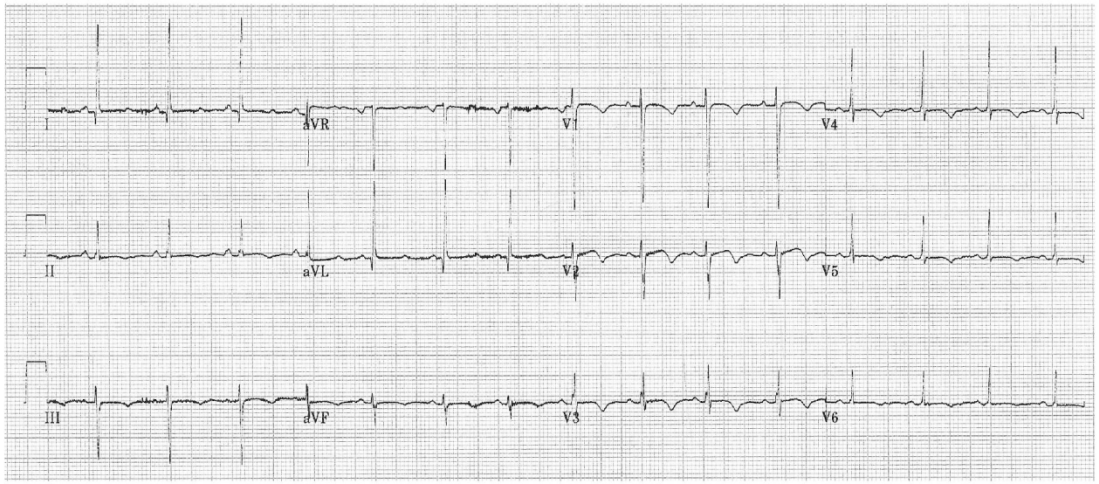


ECG from Patient II:13

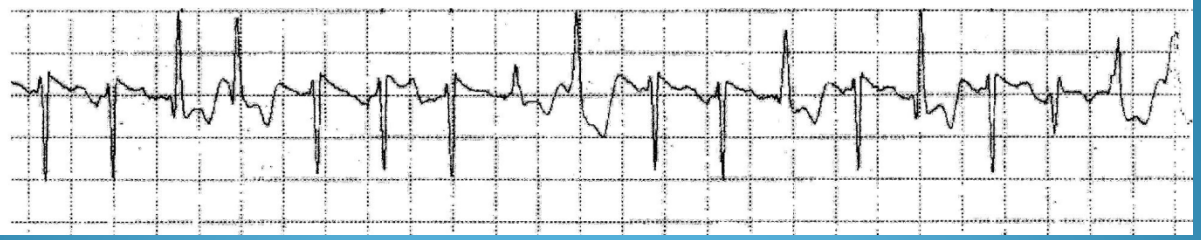
A



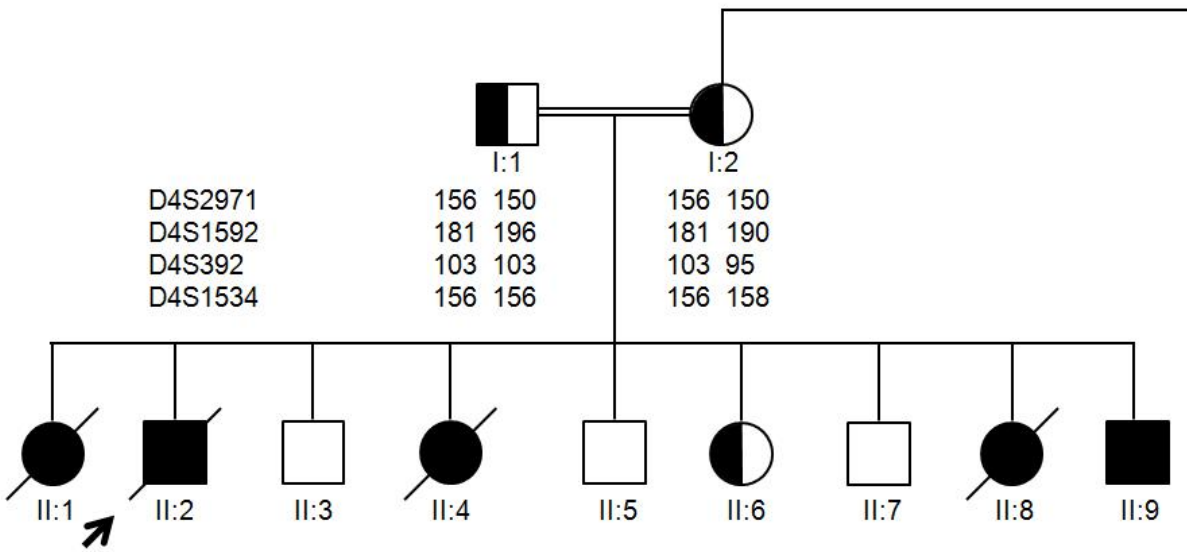
B



C

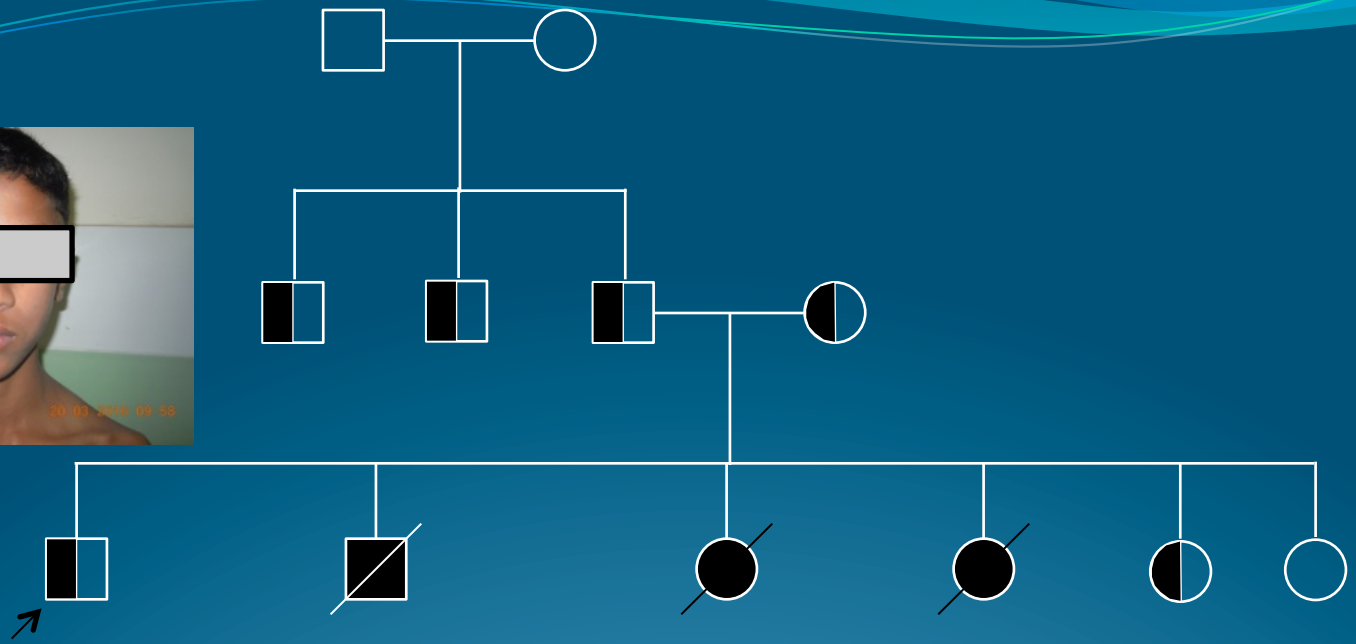


CPVT3 Family-Sudan



	II:1	II:2	II:3	II:4	II:5	II:6	II:7	II:8	II:9	II:10	II:11	II:12	II:13
D4S2971	156 156	150 150	156 156	150 150	150 156	150 150	156 156			156 152	156 152	150 152	156 156
D4S1592	181 181	181 190	181 181	196 190	181 190	196 190	181 181			181 181	181 173	190 173	181 181
D4S392	103 103	103 95	103 103	103 95	103 95	103 95	103 103			103 103	103 103	95 103	103 103
D4S1534	156 156	156 158	156 158	156 158	156 158	156 158	156 156			156 156	158 156	158 156	156 156

CPVT3 Family-Bangladesh



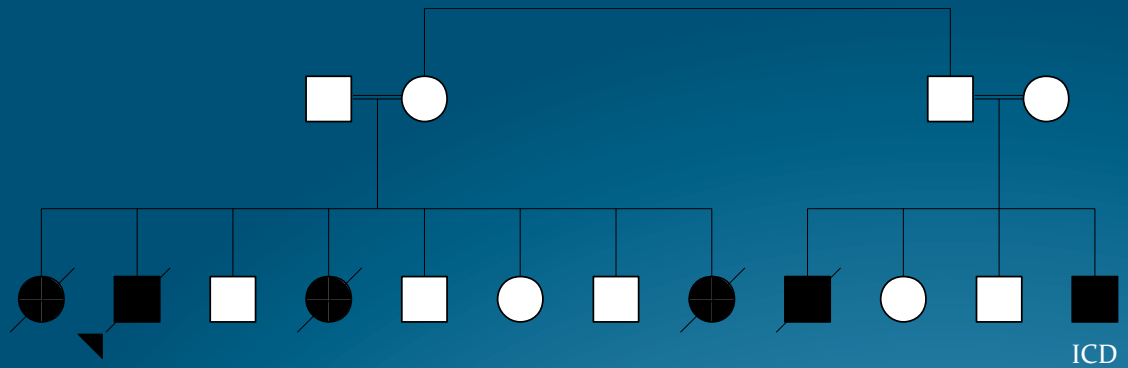
At 1 yr: Convulsion during breast feeding
Between 5 and 6 yrs: Synope 3 times, during cycling and playing.
Died at 12 yrs, syncope during playing

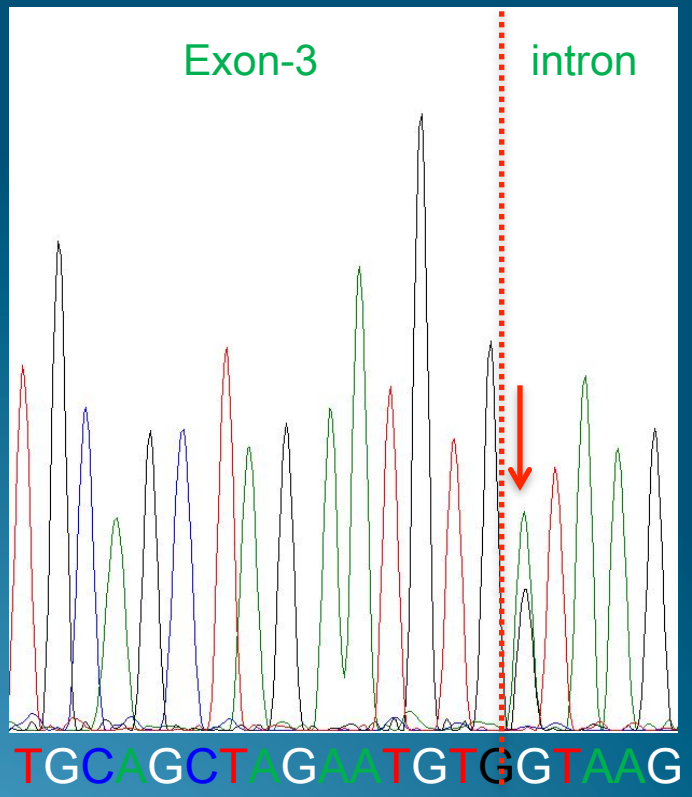
First syncope at 7 yrs, Recurrent syncope: 5 times.
Died during 6th syncope, while preparing bed at night (15 yrs of age)

First syncope at 7 yrs during playing,
Second syncope: during swimming
3rd syncope: during fruit picking.

She was emotionally depressed due to her sisters death. While standing at water in a pond, she had syncope and died at 13 yrs.

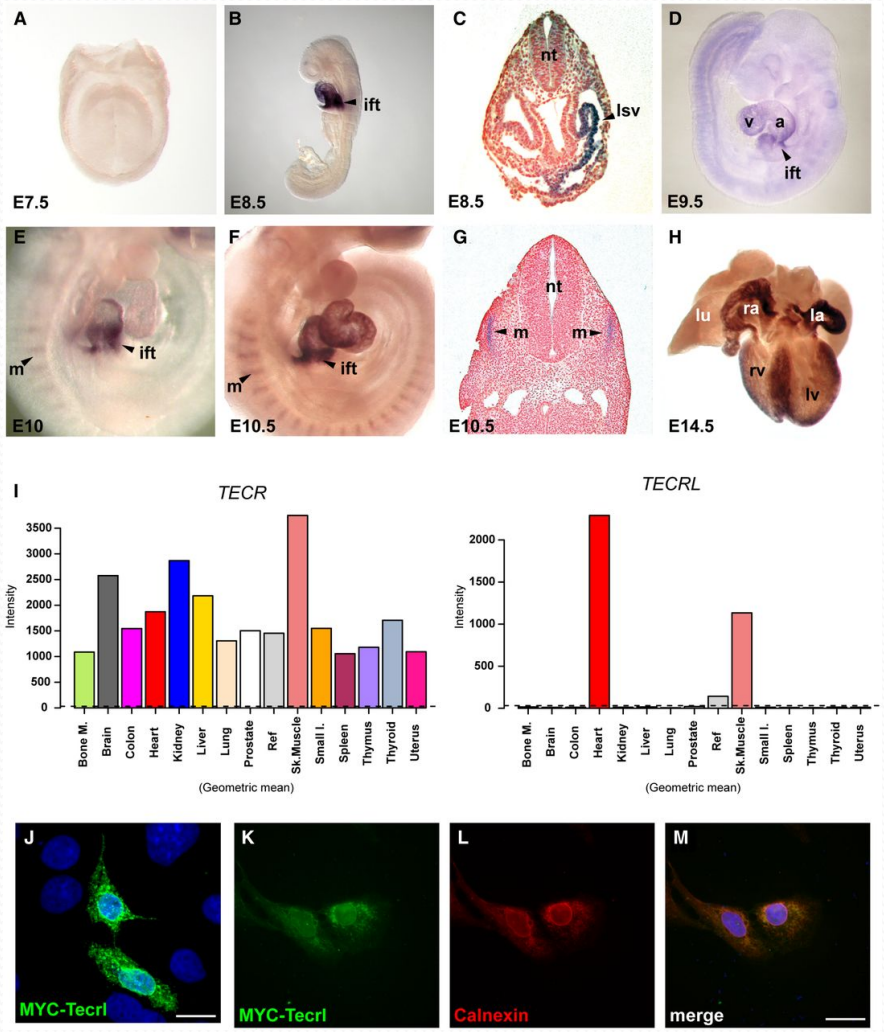
CPVT3 family-Exome Sequencing





Chromosome-4

Spatiotemporal, tissue, and sub-cellular expression analysis of TECRL



Harsha D Devalla et al. EMBO Mol Med. doi:10.15252/emmm.201505719

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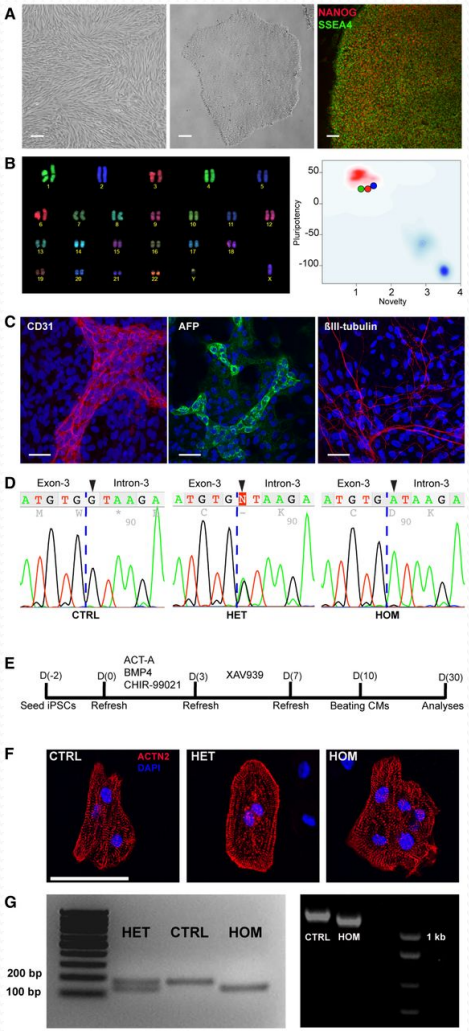
Generation of hiPSCs and differentiation to cardiomyocytes



Harsha D Devalla et al. EMBO Mol Med. doi:10.15252/emmm.201505719

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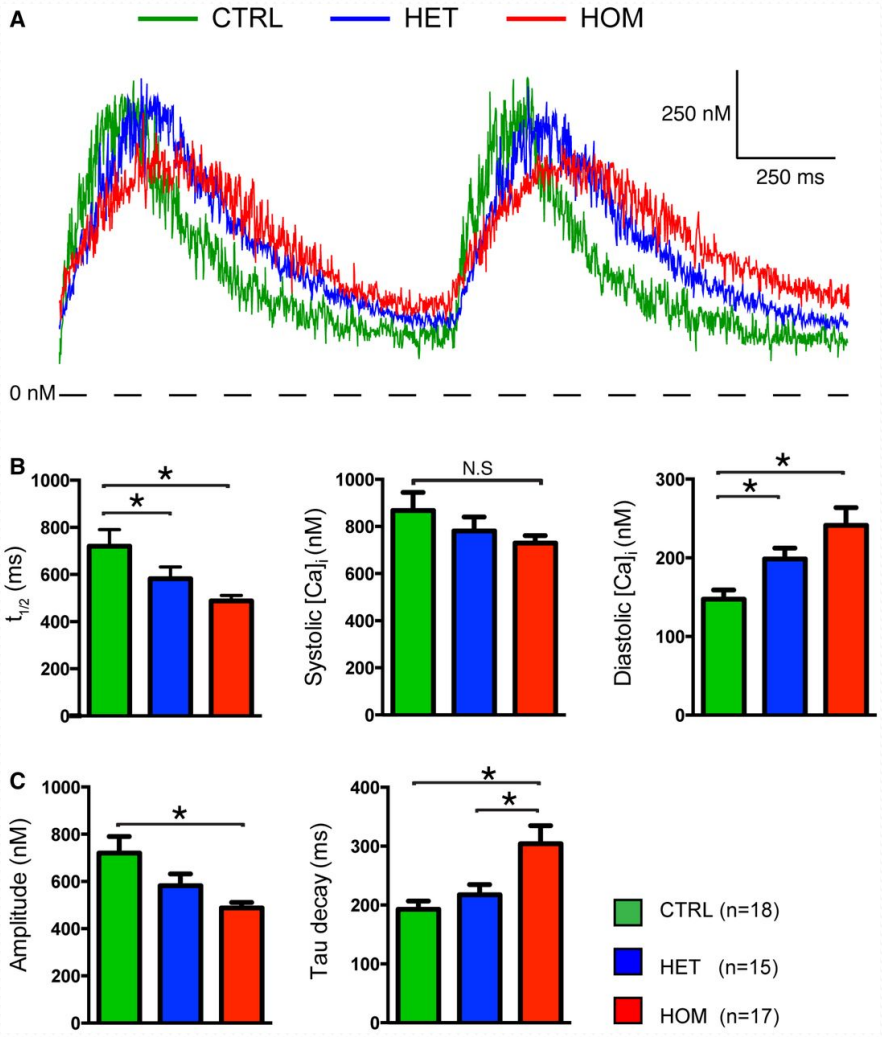
Whole–cell [Ca2+]i transients in hiPSC–CMs



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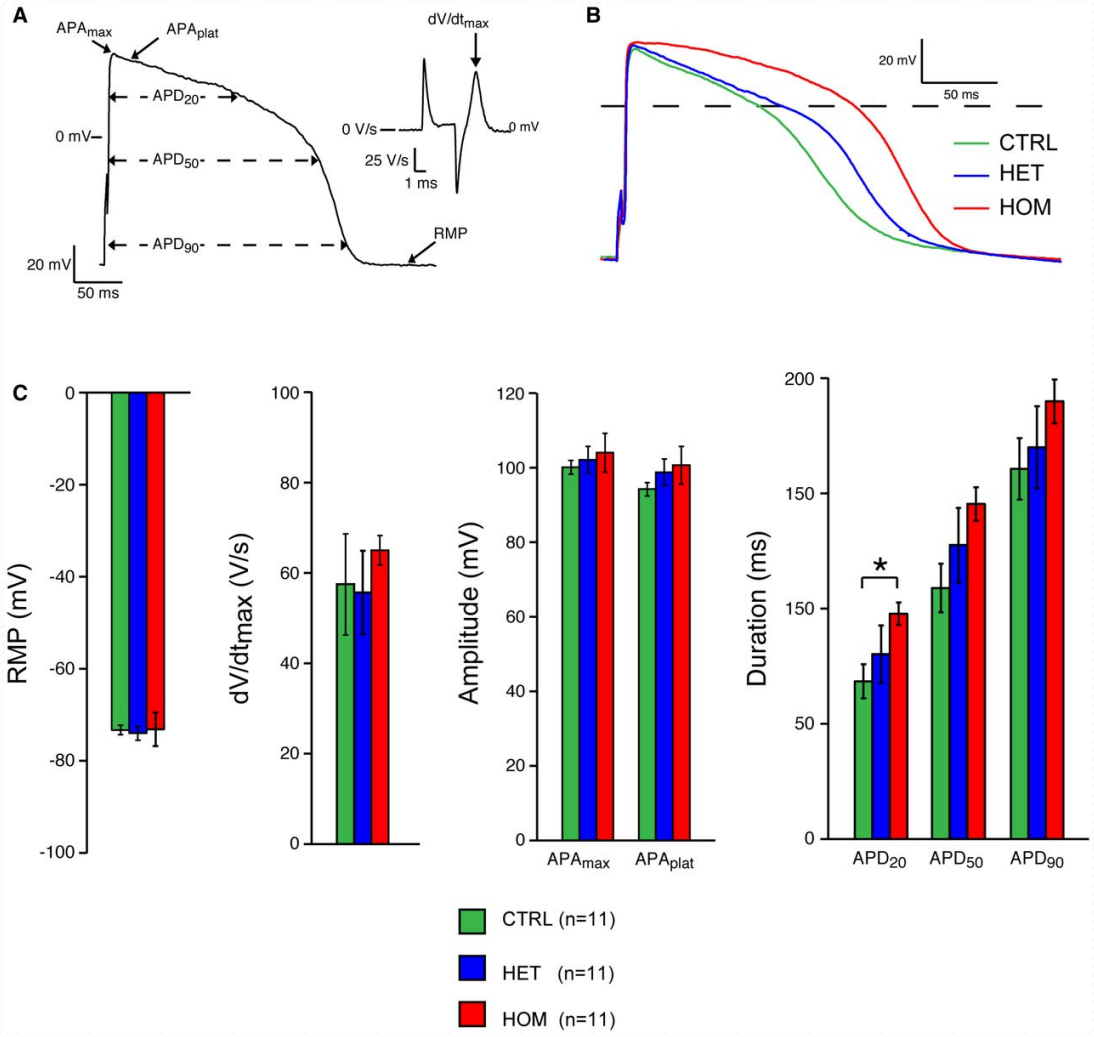
AP characteristics of TECRL–hiPSC–CMs



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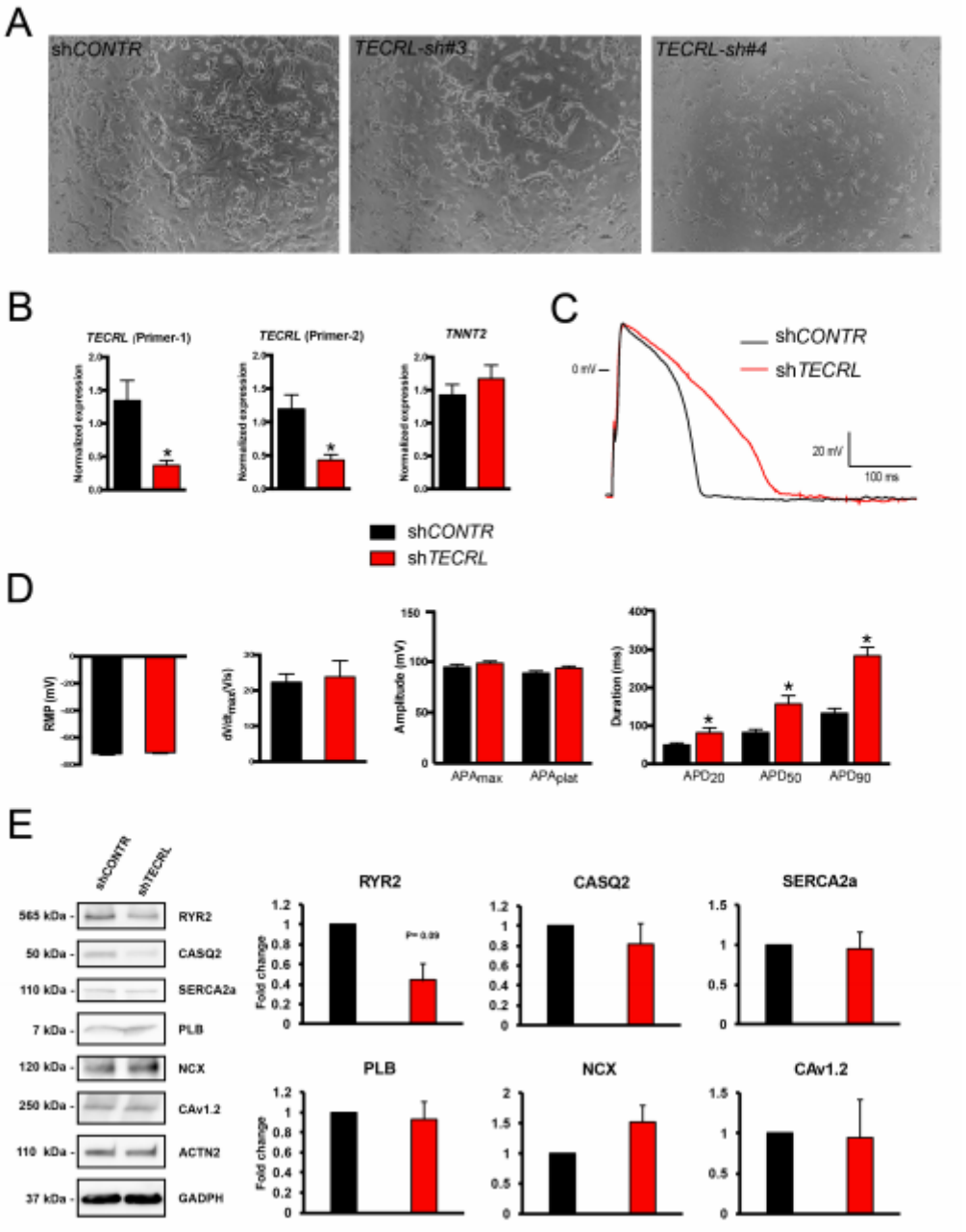
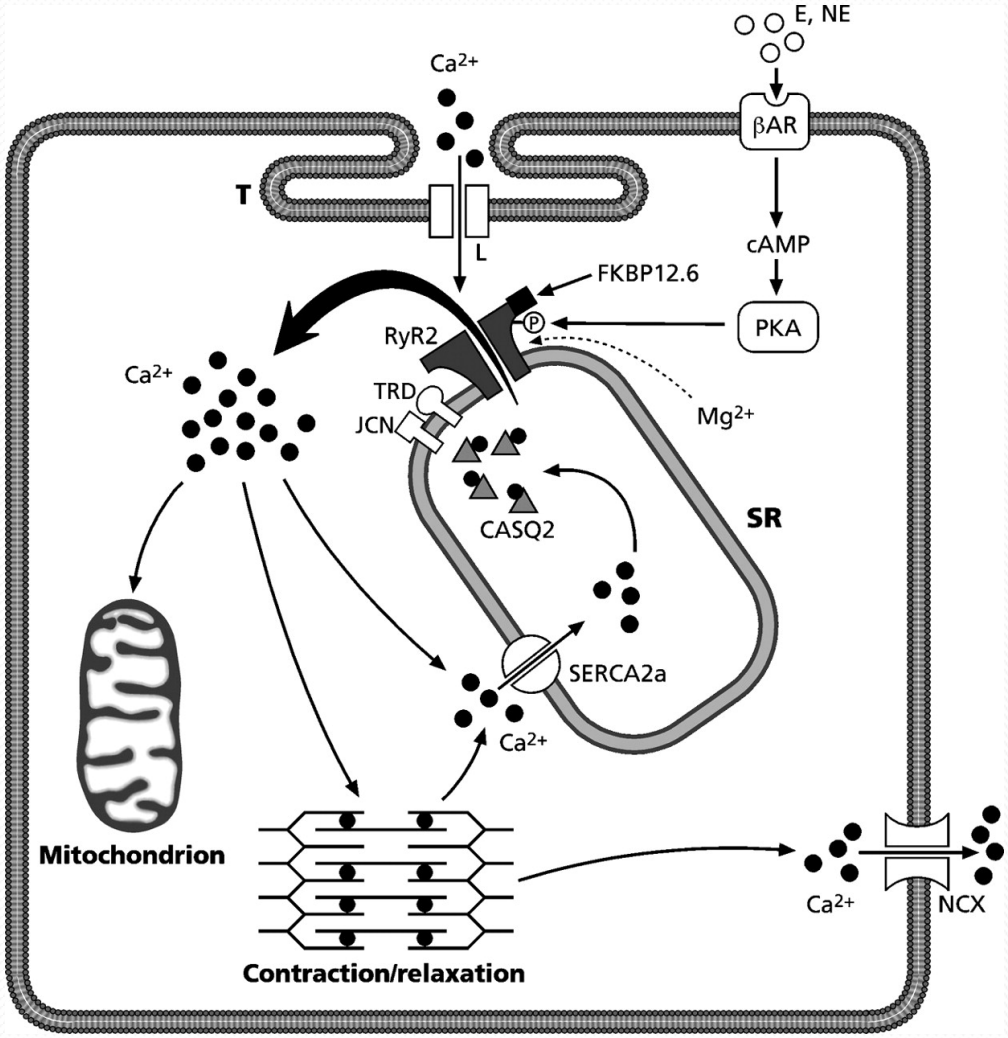
shRNA-mediated knockdown of TECRL in hESC-CMs.



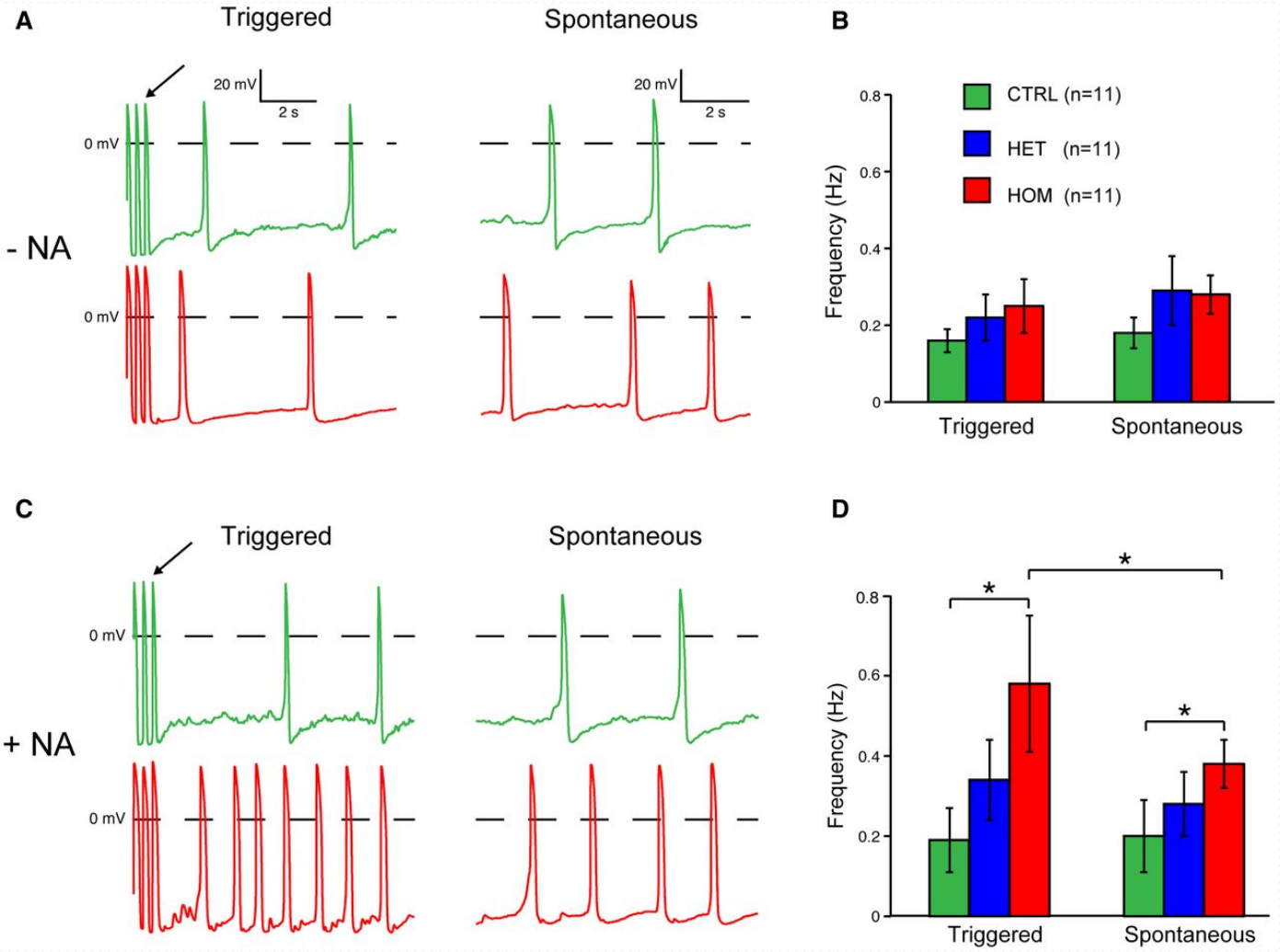
Regulation of the RyR2 channel function in cardiac myocytes.



Kimmo Kontula et al. Cardiovasc Res 2005;67:379-387

During diastole, the calcium ions are pumped back into the sarcoplasmic reticulum via the SR Ca2+-ATPase (SERCA2a) or into the extracellular fluid via the sarcolemmal NCX sodium/calcium exchanger

TECRLHom–hiPSC–CMs demonstrate increased susceptibility to triggered activity in response to NA



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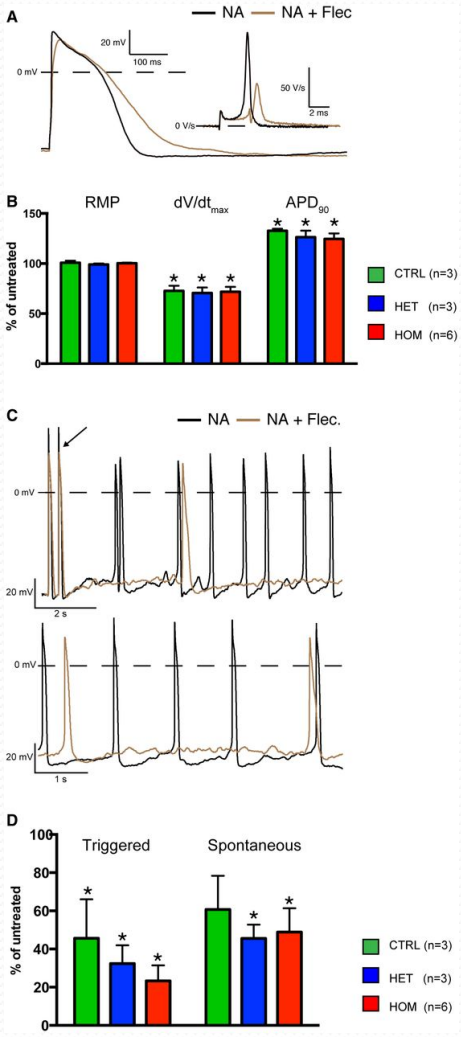
Flecainide alleviates triggered activity in TECRLHom–hiPSC–CMs



Harsha D Devalla et al. EMBO Mol Med. doi:10.15252/emmm.201505719

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Conclusion

- CPVT3 is a new type of Catecholaminergic Polymorphic Ventricular Tachycardia.
- TECRL is the Causal Gene
- Highly malignant arrhythmia, if not treated earlier, patient might die before reaching 15 yrs
- Defect in Calcium Ion Handling in Cardiomyocytes
- Flecainide could be an Effective Therapeutic Approach in CPVT3 patients.

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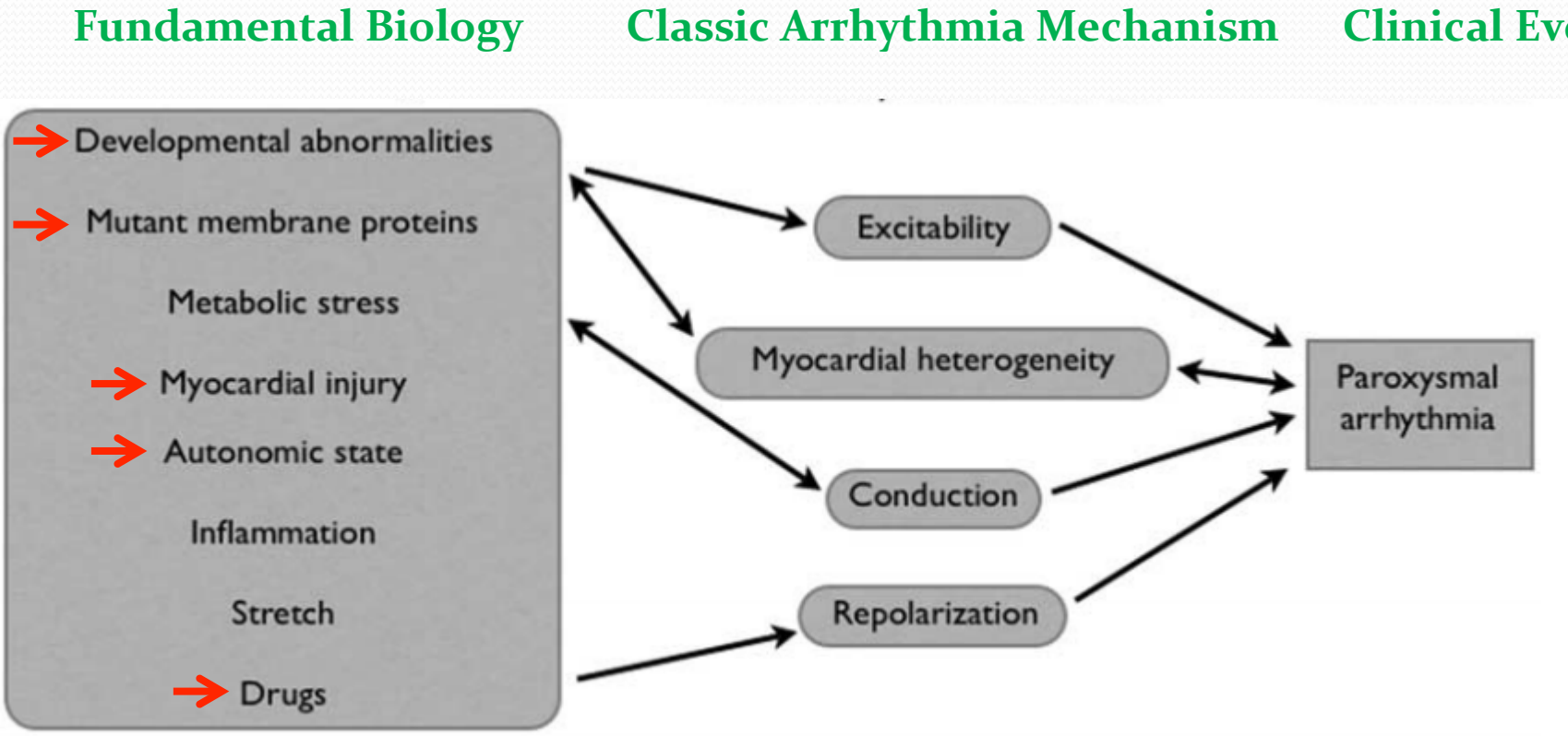
United Arab Emirates University
Dr. Elhadi Aburawi
Prof. Lihadh Al-Gazali

Rajshahi Medical College, Bangladesh
Dr. Zahidus Sayeed

Arrhythmogenesis



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Common Variation in Fatty Acid Genes and Resuscitation from Sudden Cardiac Arrest

Catherine O. Johnson, PhD, MPH[1], **Rozenn N. Lemaitre, PhD, MPH**[1], **Carol E. Fahrenbruch, MSPH**[2], **Stephanie Hesselson, PhD**[3], **Nona Sotoodehnia, MD, MPH**[1], **Barbara McKnight, PhD**[4], **Kenneth M. Rice, PhD**[4], **Pui-Yan Kwok, MD, PhD**[3], **David S. Siscovick, MD, MPH**[1,5], and **Thomas D. Rea, MD, MPH**[5]

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[5]Dept of Epidemiology, University of Washington

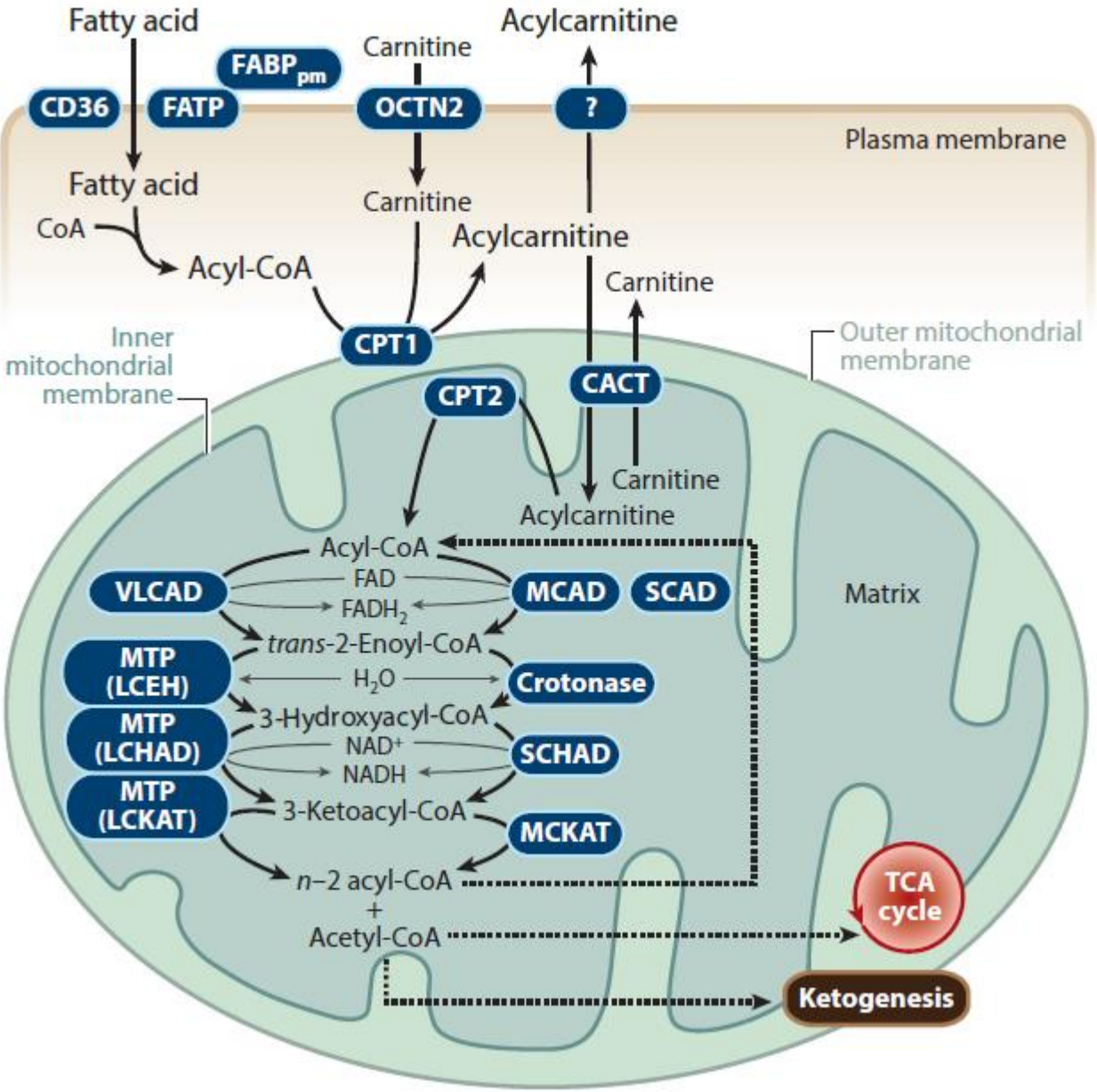
Abstract

Background—Fatty acids provide energy and structural substrates for the heart and brain and may influence resuscitation from sudden cardiac arrest (SCA). We investigated whether genetic variation in fatty acid metabolism pathways was associated with SCA survival.

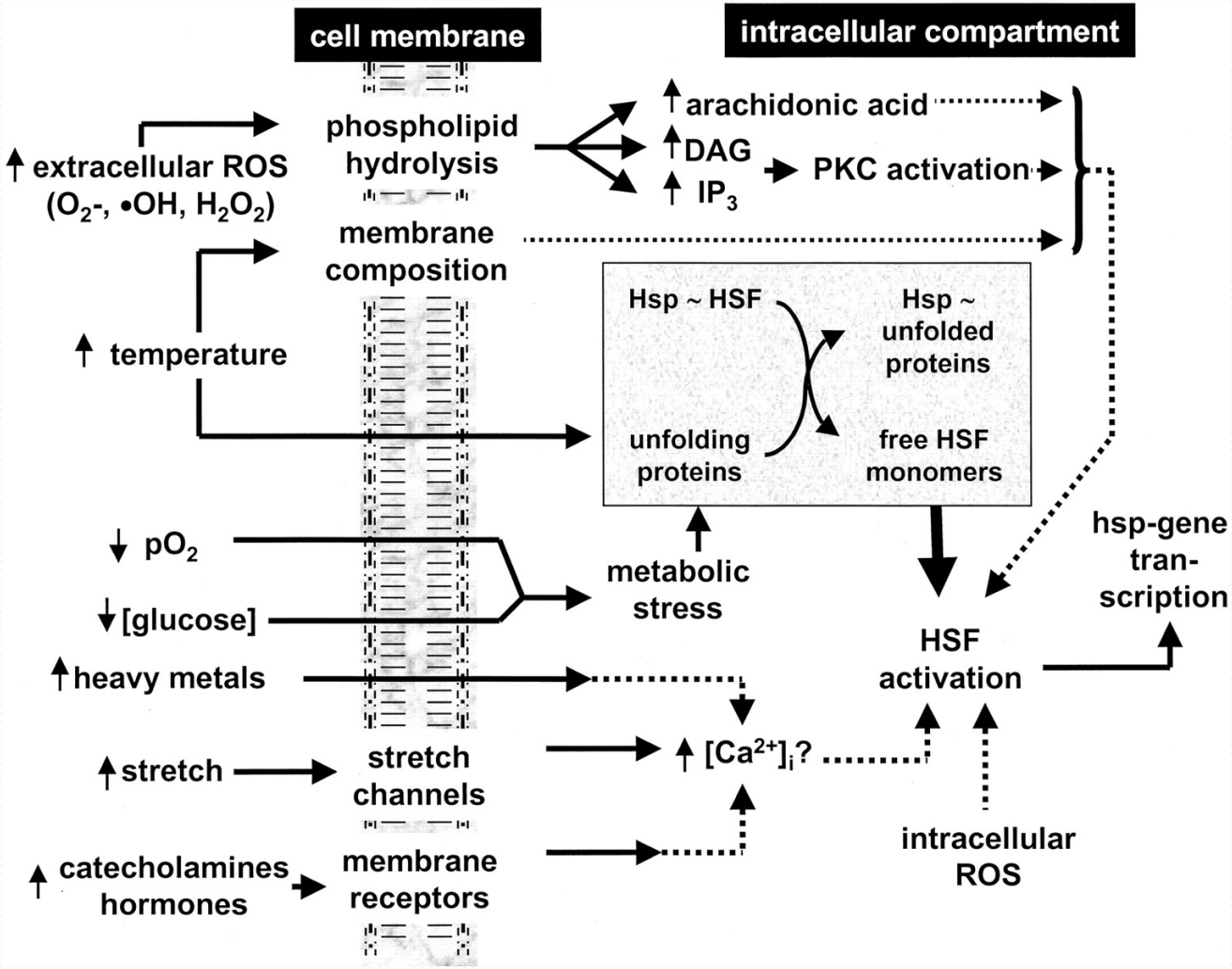
Methods and Results—Subjects (mean age 67, 80% male, Caucasian) were out-of-hospital SCA patients found in ventricular fibrillation in King County, WA. We compared subjects who survived to hospital admission (n=664) with those who did not (n=689), and subjects who survived to hospital discharge (n=334) with those who did not (n=1019). Associations between survival and genetic variants were assessed using logistic regression adjusting for age, gender, location, time to arrival of paramedics, whether the event was witnessed, and receipt of bystander CPR. Within-gene permutation tests were used to correct for multiple comparisons. Variants in five genes were significantly associated with SCA survival. After correction for multiple comparisons, SNPs in *ACSL1* and *ACSL3* were significantly associated with survival to hospital admission. SNPs in *ACSL3*, *AGPAT3*, *MLYCD*, and *SLC27A6* were significantly associated with survival to hospital discharge.

Conclusions—Our findings indicate that variants in genes important in fatty acid metabolism are associated with SCA survival in this population.

Genes in Cardiac Fatty Acid Oxidation Pathway and Electron Transfer Chain



Extracellular and intracellular stresses that can lead to the activation of the heat shock factor (HSF) and subsequent heat shock protein (hsp)-gene transcription.



Luc H. E. H. Snoeckx et al. Physiol Rev 2001;81:1461-1497

Physiological Reviews


Thank you