PEDIRHYTHM VII

Pediatric and Congenital Rhythm Congress VII

4 - 7 February 2017 / Grand Hotel Palace - Thessaloniki, GREECE

CACNA1C mutations and variable phenotypic spectrum. Case report and literature review.

Department of Paediatric Cardiology and Arrhythmology
Bambino Gesù Children Hospital & Scientific Institute
Rome - Italy

No conflict of interest to declare.

Bambino Gesù
Ospedale Pediatrico

Birth

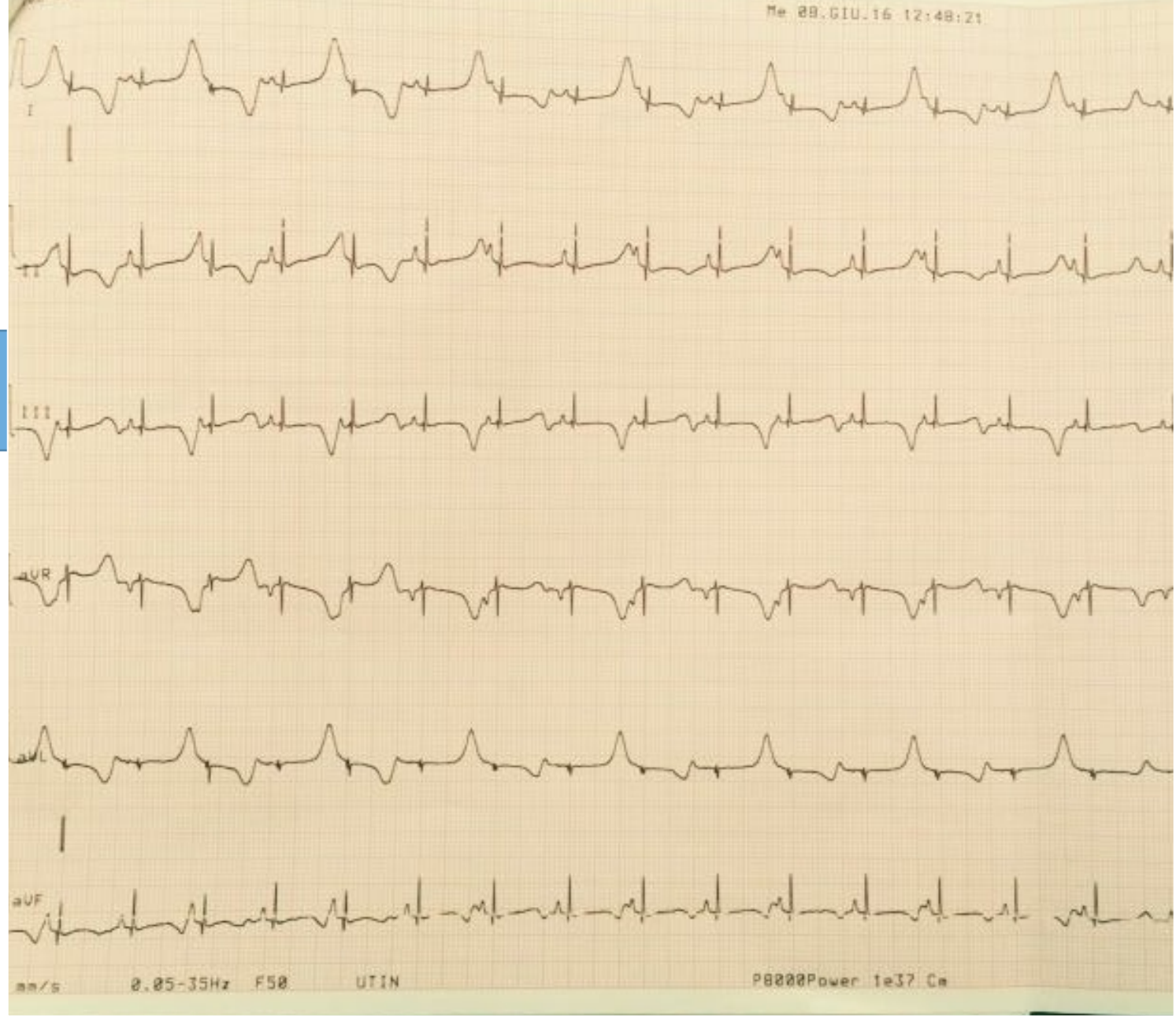
June 2016

Normal pregnancy and delivery

No **apparent** exposure to teratogenic factor

Newborn girl
BW 2.5kg, L 46cm

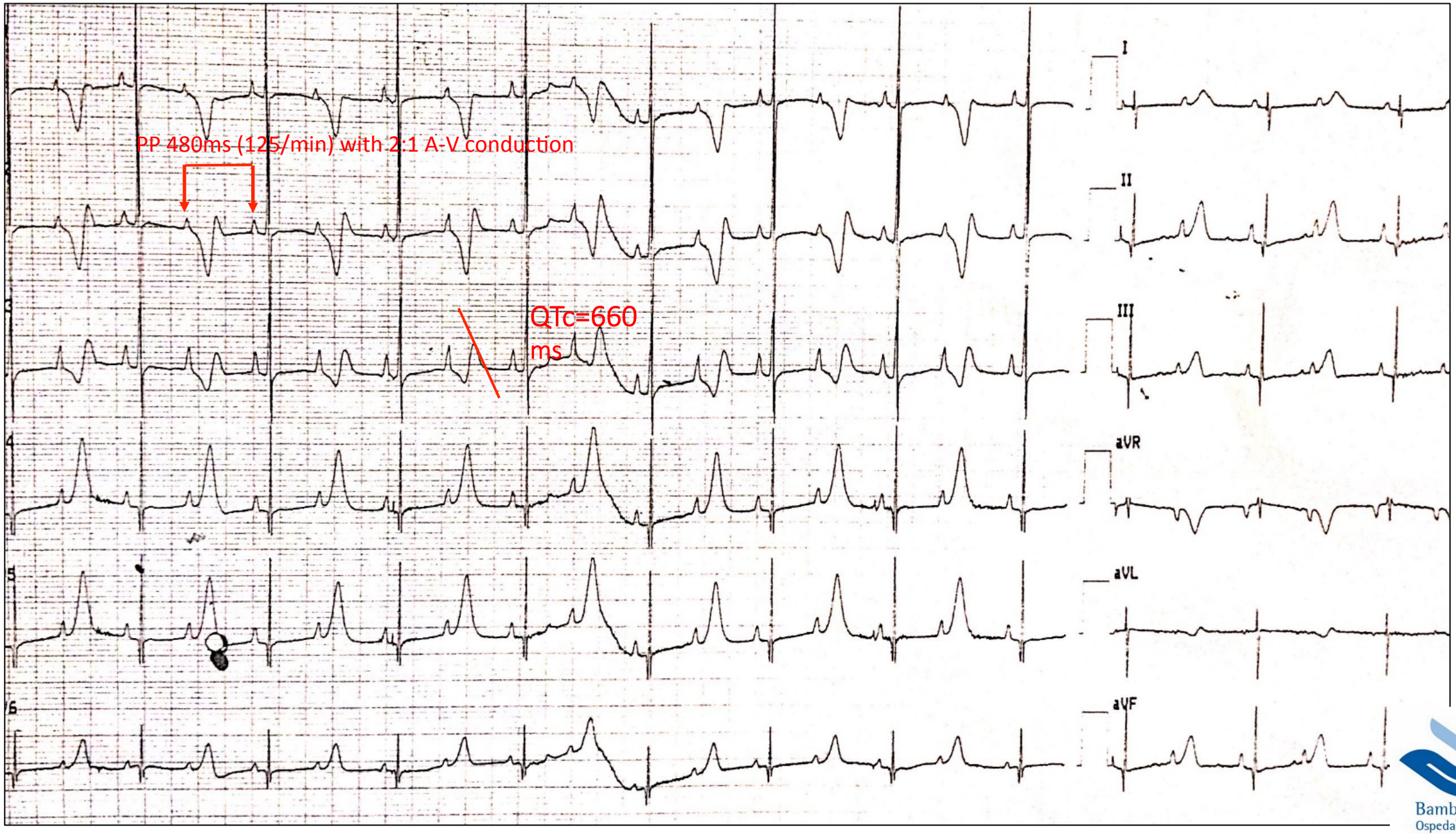
At 2 hr:



Attacks of severe bradycardia…
down to 45-50 bpm

Bambino Gesù
Ospedale Pediatrico

A few hours later…LQT with **2:1 AV functional block**



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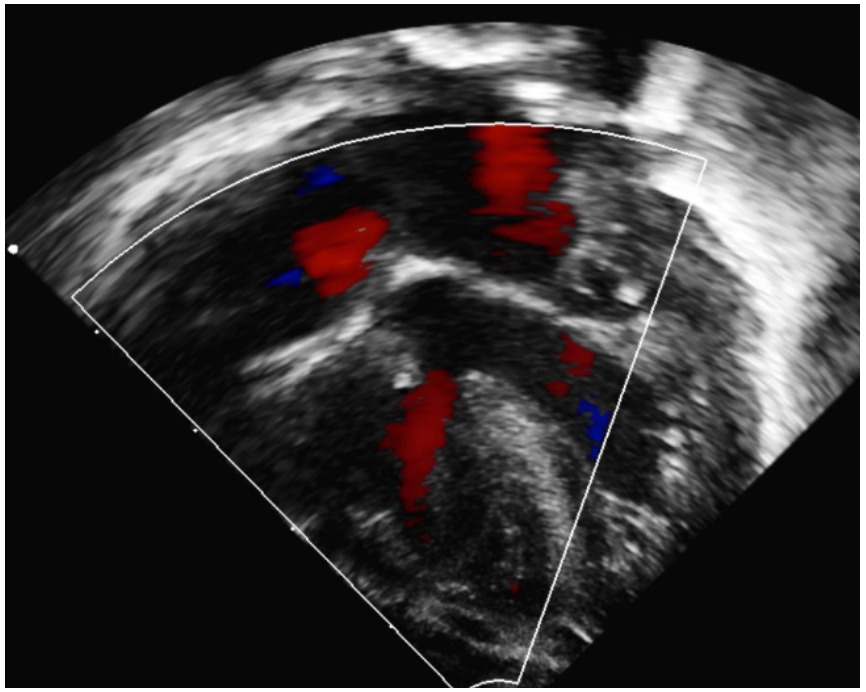
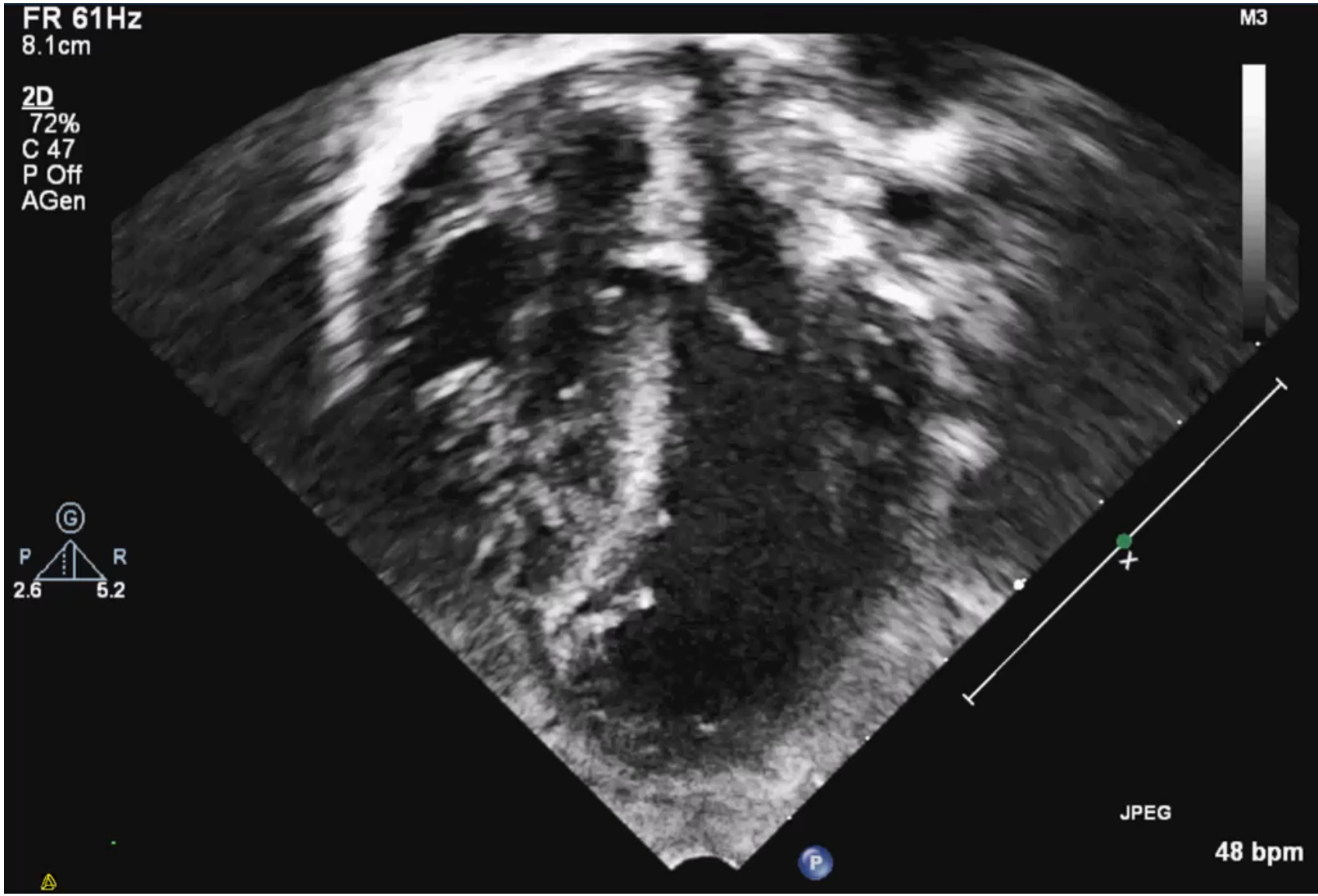
Echocardiogram





Asymmetric hypertrophy of IVS.

RV apical hypertrabeculation.

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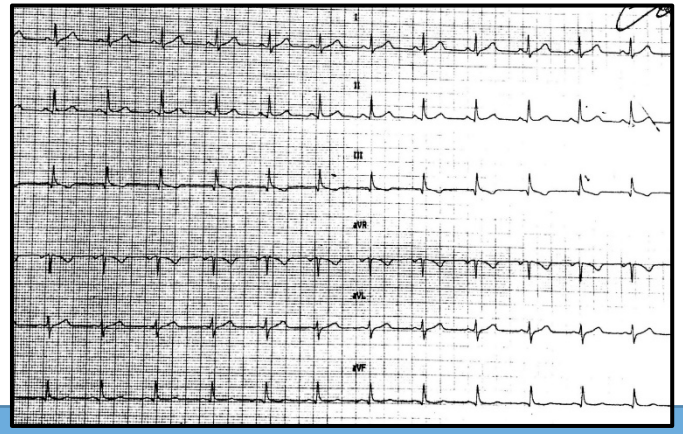
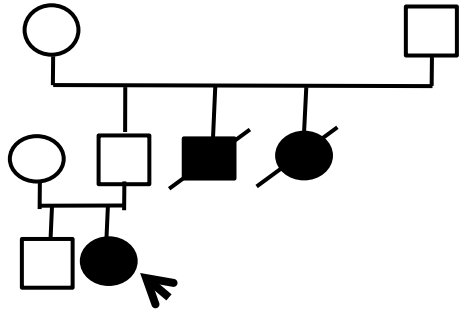
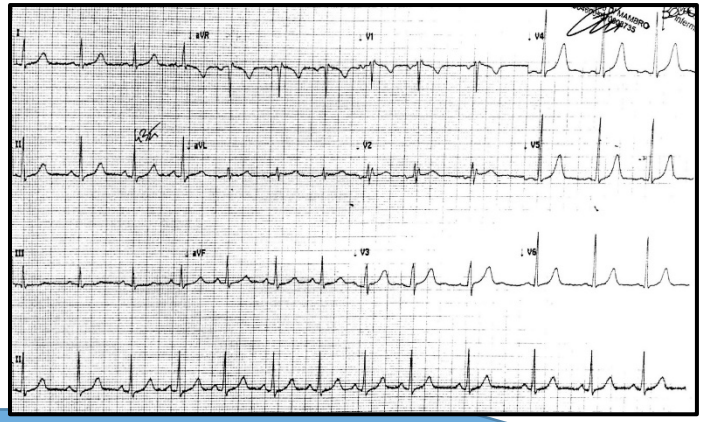
Family History.
Ethnic Background:
Asian - Bangladesh







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No exposure apparent teratogenic factor

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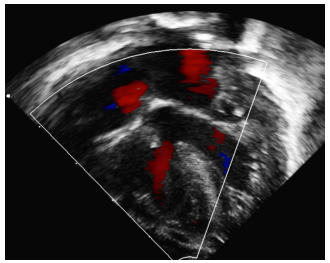

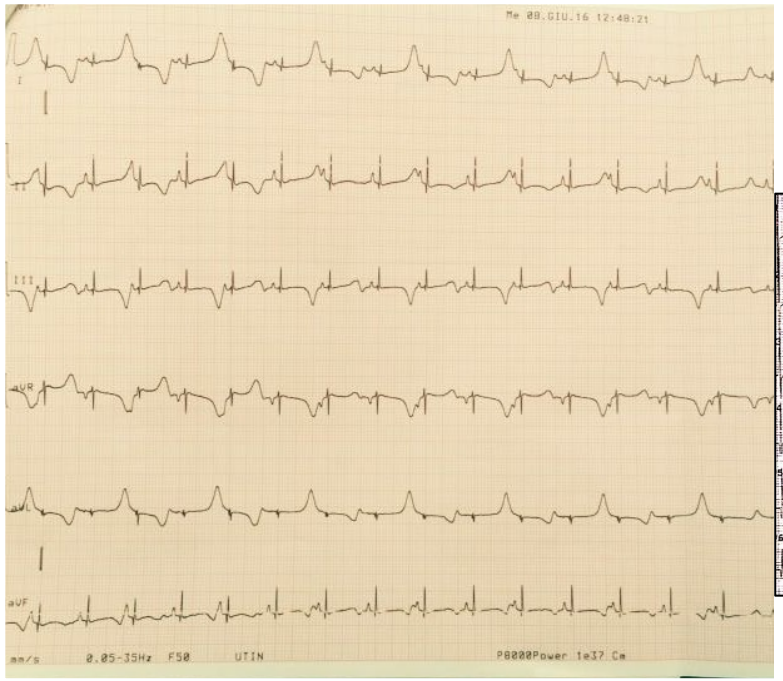

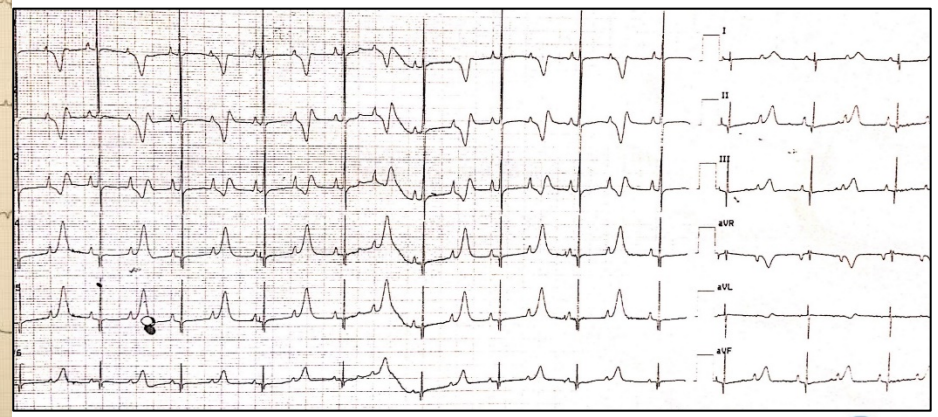

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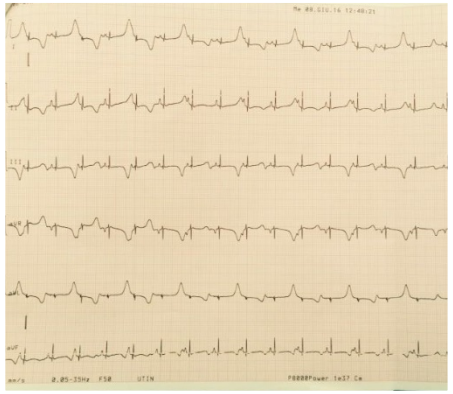
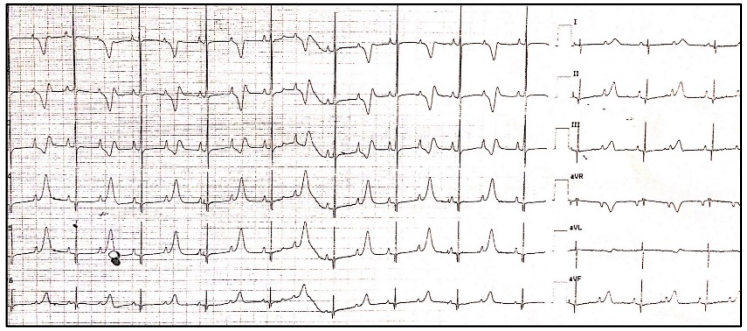
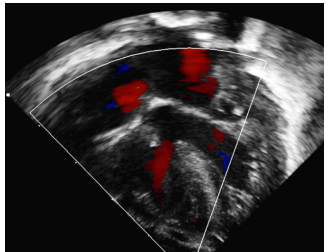
Birth

June 2016

July 2016



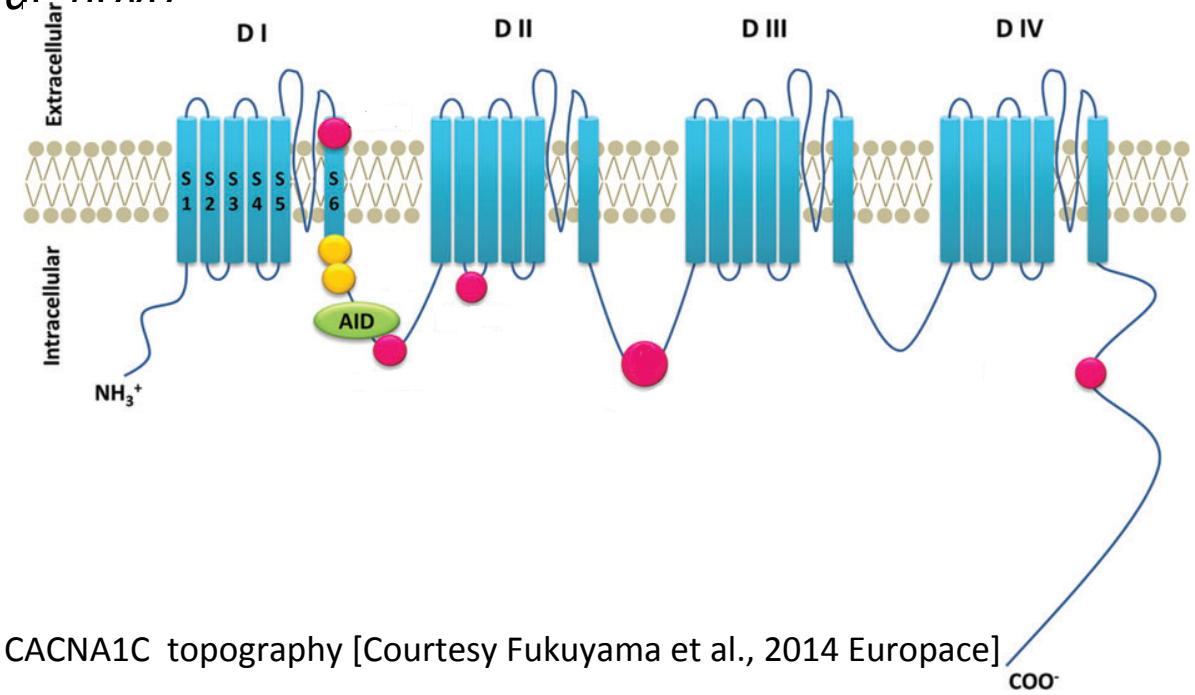




NGS Analysis: *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2 and CACNA1C* resulted in:

heterozygous mutation of *CACNA1C*

NM_000719: c.1216G>A; p.Gly406Arg (rs79891110), *de novo*



CACNA1C topography [Courtesy Fukuyama et al., 2014 Europace]

For the complex phenotype, Exome sequencing was performed that turned to be negative for CMP genes.

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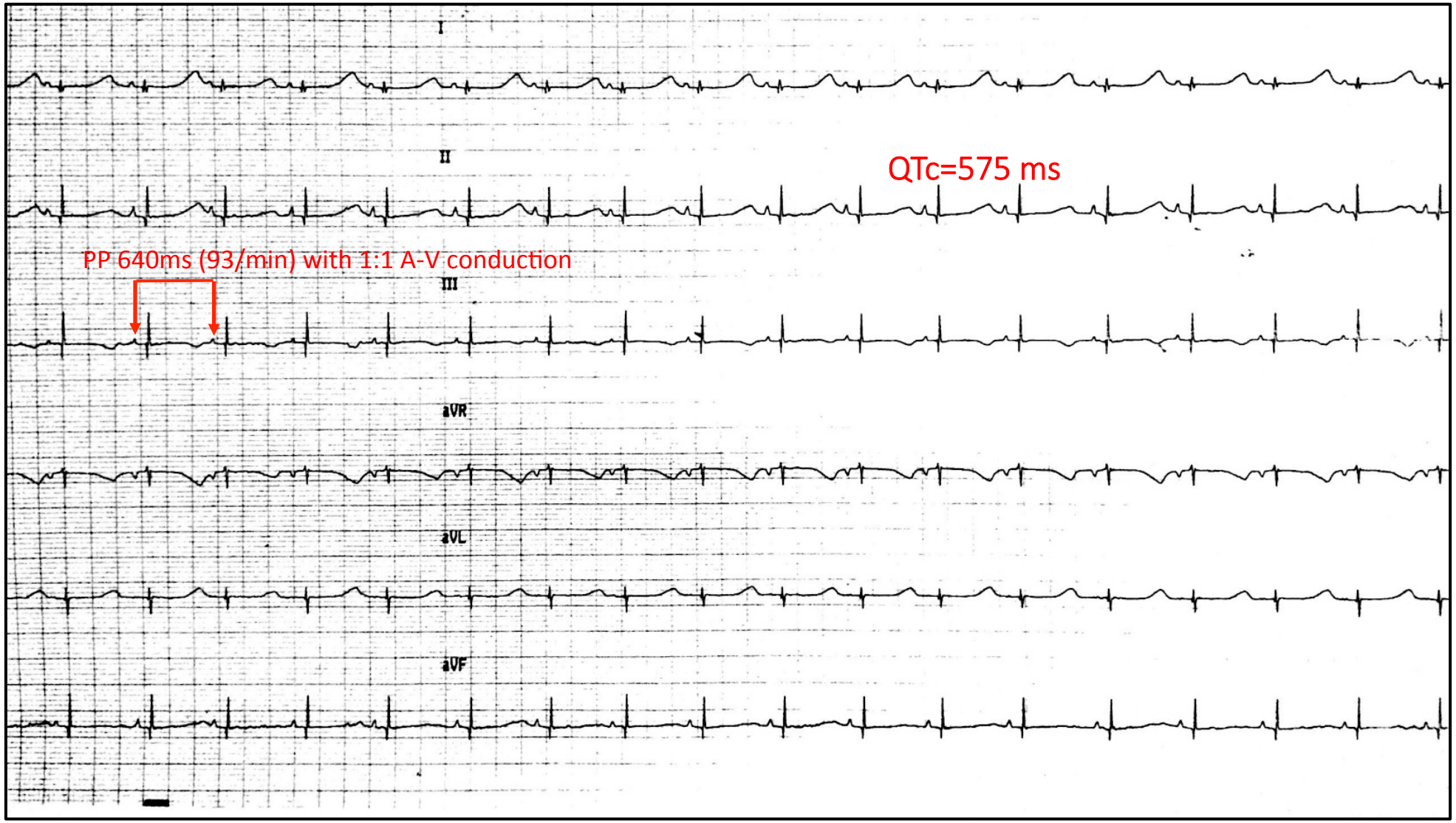
Started beta blocker therapy (propranolol titrated)



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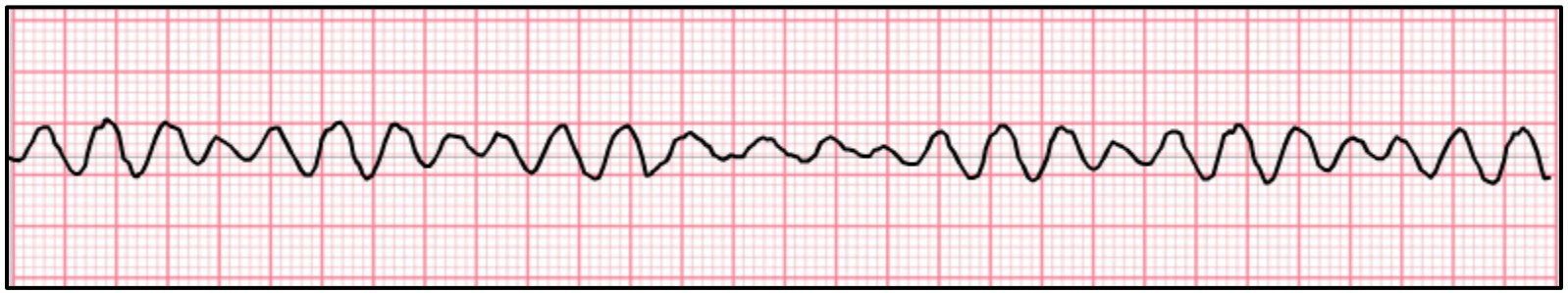
Critical events (1)

During anesthesia induction…

VENTRICULAR FIBRILLATION occurred



…resuscitated…

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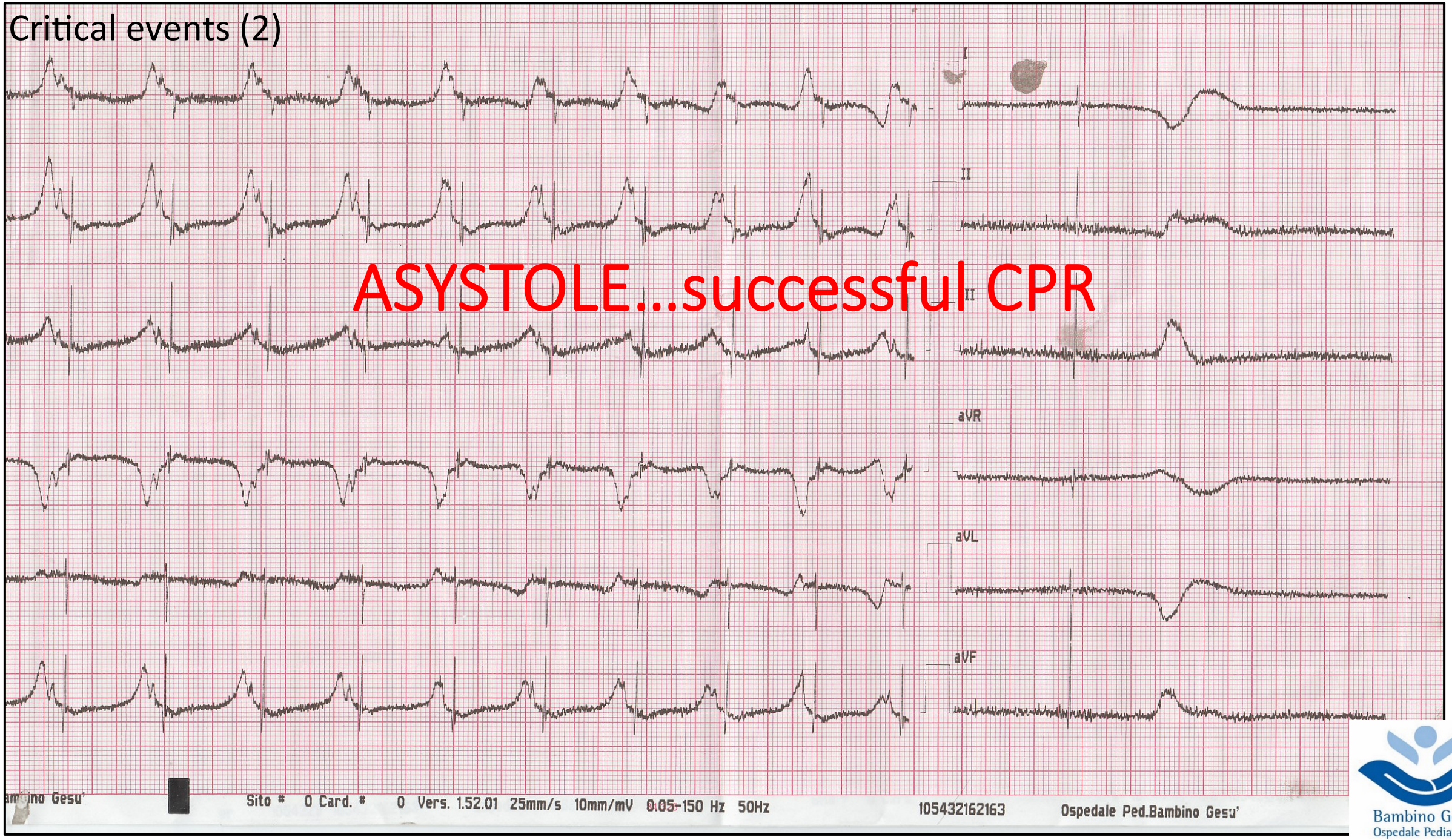
Critical events (2)



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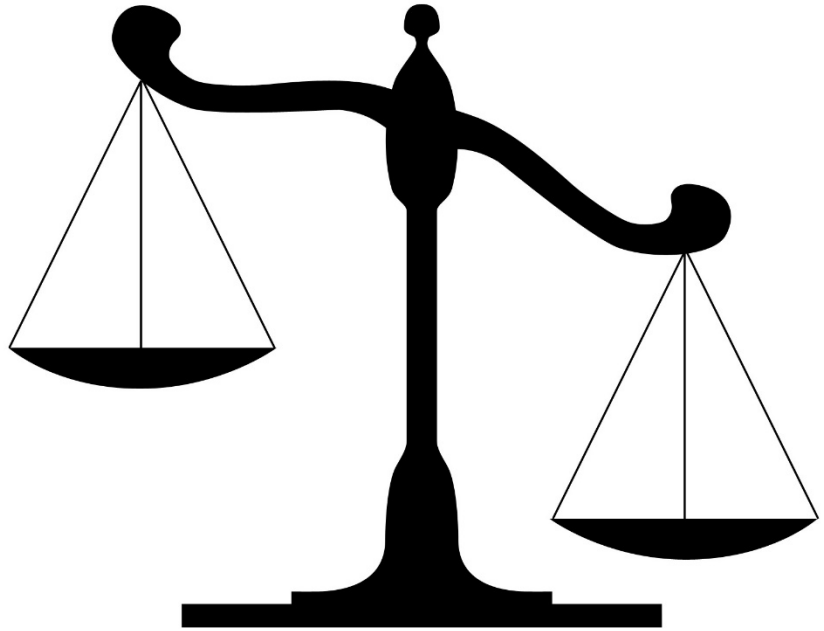
What to do next??

W=6.1 Kilograms…



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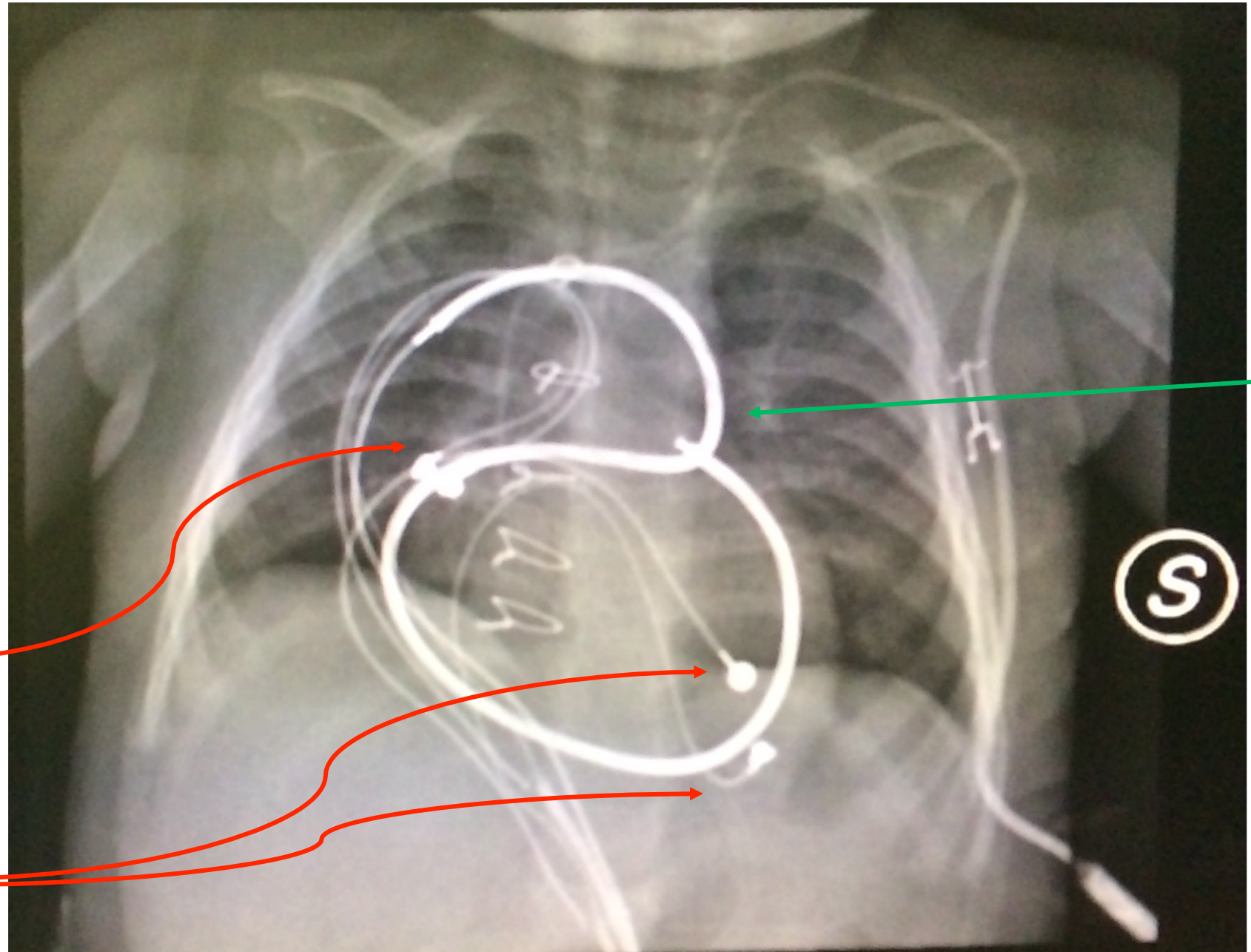
Epicardial dual-chamber PMK-ICD implant + PDA closure



Single coil
(figure-of-8
epicardial loop)

Atrial lead

Ventricular
lead

Postoperative procedure complicated by chylothorax

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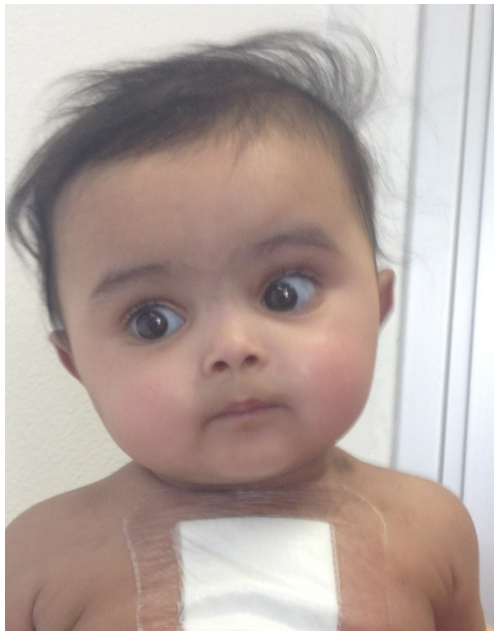
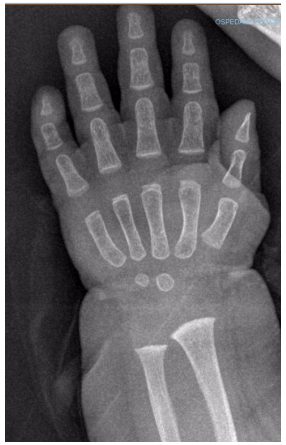
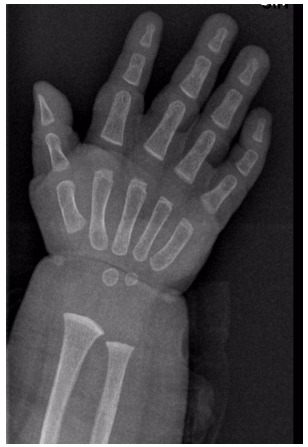
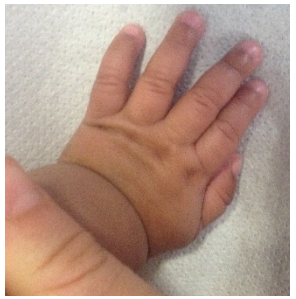
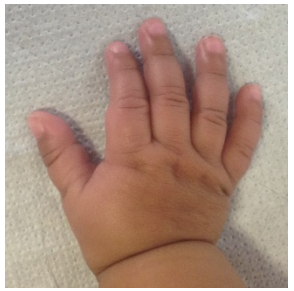
Extracardiologic Phenotype and Multiorgan Screening











Normal brain US

Normal eye visit

Normal abdominal US

Formal neurocognitive evaluation at 7 months: Regular development escept for very mild hypotonia (consider 6 months hospital stay!!!!).

2 septic attacks related to CVL (*Staphylococcus epidermidis, Enterobacter cloacae).*

Never spontaneous spesis. Immunologic work up within normal.

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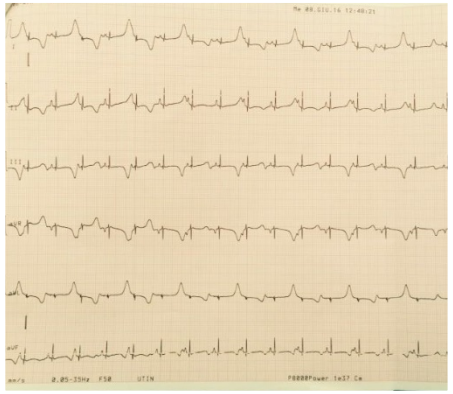
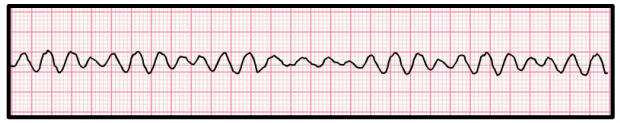
A.M.

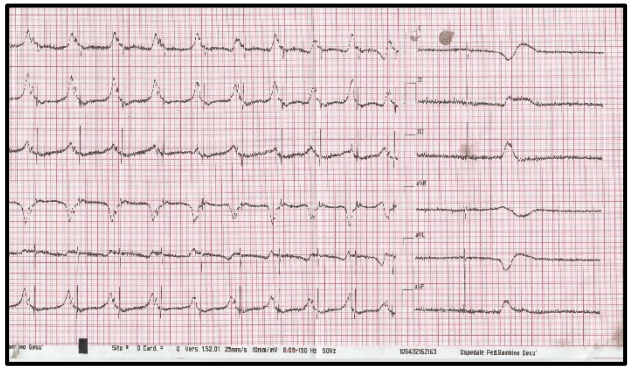
June 2016 | July 2016 | November 2016 | January 2017



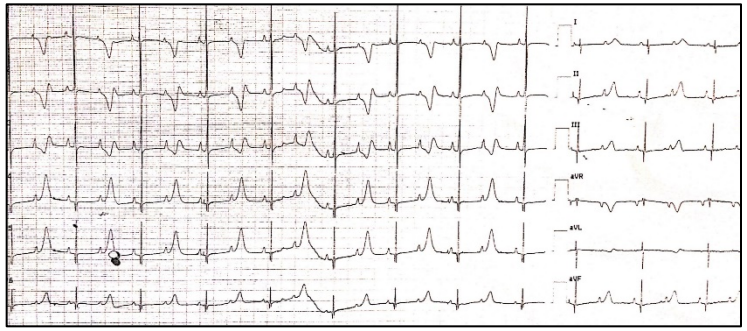
CACNA1C c.1216G>A; p.Gly406Arg *de novo*.

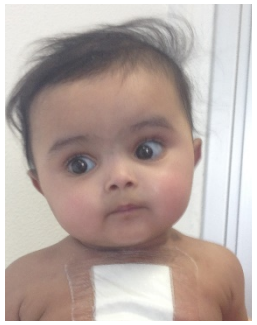
Exome: negative for CMP genes

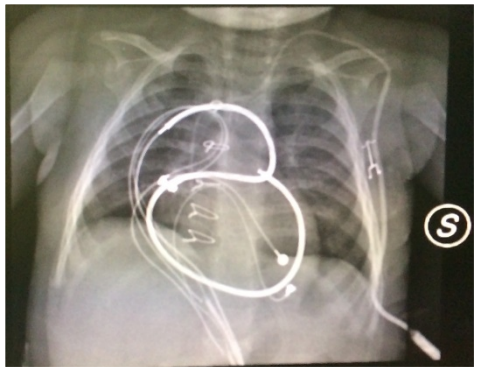




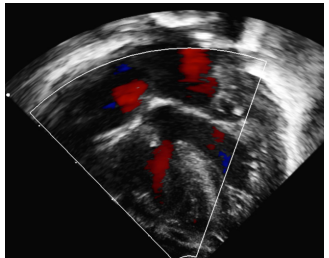
At home and doing well







Chylothorax



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Long QT Syndromes (LQTS)

Genes Mutated in >1% of LQTS

Gene	Disease Name	% of LQTS Attributed to Mutation of This Gene	Proportion of Reported Pathogenic Variants Detected by Test Method	
			Sequence analysis	Gene-targeted deletion/duplication analysis
KCNQ1	LQTS type 1	30%-35%	97%-98%	2%-3%
KCNH2	LQTS type 2	25%-30%	97%-98%	
SCN5A	LQTS type 3	5%-10%	All variants reported to date	None reported

Genes Mutated in <1% of LQTS

Gene	Disease Name	Comment
ANK2	LQTS type 4	<1%
KCNE1	LQTS type 5	<1%
KCNE2	LQTS type 6	<1%
KCNJ2	LQTS type 7	<1%
CACNA1C	LQTS type 8	<1%
CAV3	LQTS type 9	<1%
SCN4B	LQTS type 10	Rare (2 cases)
AKAP9	LQTS type 11	Rare (1 case)
SNTA1	LQTS type 12	Rare (3 cases)
KCNJ5	LQTS type 13	Rare (2 cases)
CALM1	LQTS type 14	<1%
CALM2	LQTS type 15	<1%

NCBI: Books: GeneReviews. Long QT Syndrome. National Center for Biotechnology Information; web site. www.ncbi.nlm.nih.gov/books/NBK1403. [Alders and Imke Christiaans - June 18, 2015]

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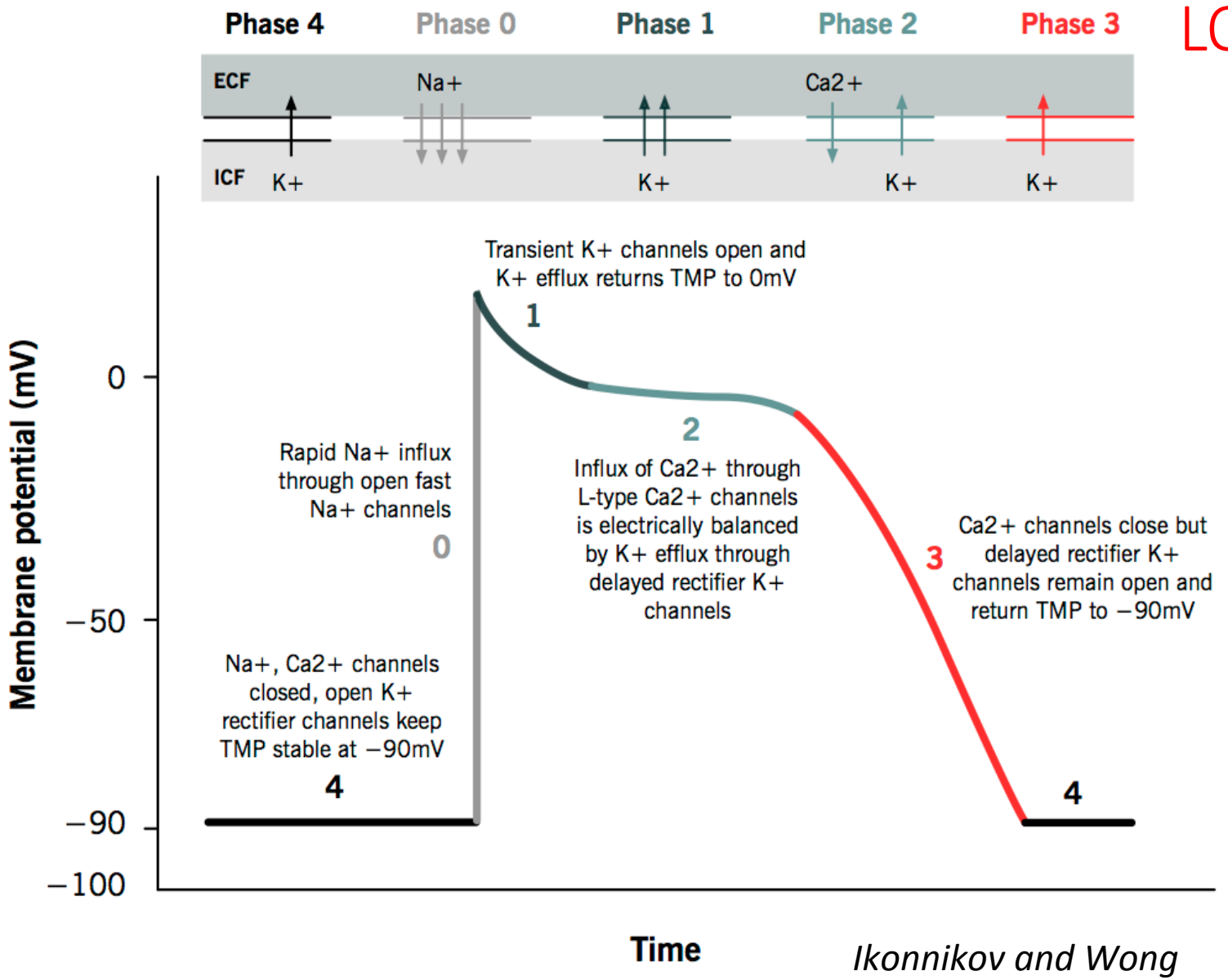
Action potential of cardiac muscle cells

LQTS 8

CACNA1C has a critical role for:

- ✓ plateau phase of cardiac action potential,
- ✓ cellular excitability,
- ✓ excitation-contraction coupling,
- ✓ regulation of gene expression



Ikonnikov and Wong

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C A C N A 1 C

eNeuro

New Research

Cognition and Behavior

Deletion of the Mouse Homolog of *CACNA1C* Disrupts Discrete Forms of Hippocampal-Dependent Memory and Neurogenesis within the Dentate Gyrus

Stephanie J. Temme,[1] Ryan Z. Bell,[2] Grace L. Fisher,[2] and Geoffrey G. Murphy[1,2,3]

DOI:http://dx.doi.org/10.1523/ENEURO.0118-16.2016

Cacna1c in the Prefrontal Cortex Regulates Depression-Related Behaviors via REDD1

Zeeba D Kabir[1,4], Anni S Lee[1,2,4], Caitlin E Burgdorf[1,2], Delaney K Fischer[1], Aditi M Rajadhyaksha[1], Ethan Mok[1], Bryant Rizzo[1], Richard C Rice[1], Kamalpreet Singh[1], Kristie T Ota[3], Danielle M Gerhard[3], Kathryn C Schierberl[1,2], Michael J Glass[2], Ronald S Duman[3] and Anjali M Rajadhyaksha[*,1,2]

BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology Doi: 10.1111/bcpt.12720

Electrocardiogram Alterations Associated With Psychotropic Drug Use and CACNA1C Gene Variants in Three Independent Samples

Chiara Fabbri[1], Giuseppe Boriani[2], Igor Diemberger[3], Maria Giulia Filippi[4], Gloria Ravegnini[4], Patrizia Hrelia[4], Alessandro Minarini[5], Diego Albani[6], Gianluigi Forloni[6], Sabrina Angelini[4,*] and Alessandro Serretti[1,*]

Differential Roles for L-Type Calcium Channel Subtypes in Alcohol Dependence

Stefanie Uhrig[1], David Vandael[2], Andrea Marcantoni[2], Nina Dedic[3], Ainhoa Bilbao[1], Miriam A Vogt[4], Natalie Hirth[1], Laura Broccoli[1], Rick E Bernardi[1], Kai Schönig[5], Peter Gass[4], Dusan Bartsch[5], Rainer Spanagel[1], Jan M Deussing[3], Wolfgang H Sommer[1,6], Emilio Carbone[2] and Anita C Hansson[*,1]

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CACNA1C

Loss-of-function → Brugada S. [Burashnikov 2010]

Gain-of-function

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C A C N A 1 C

Cardiac Only Timothy Syndrome (COTS):

<5 reports in literature

Arrhythmias:

- **severe prolongation of the QT interval (*QTc of 480 ms - 700 ms*) (100%)**
- **ventricular tachyarrhythmias (VT, TdP, VF) (84%)**
- **bradycardia, functional AV block (81%)**
- **T-wave alternans (70%)**

B. Congenital Heart Defects:

- **PDA, PFO, VSD, vascular ring, TOF**

C. Cardiomyopathy:

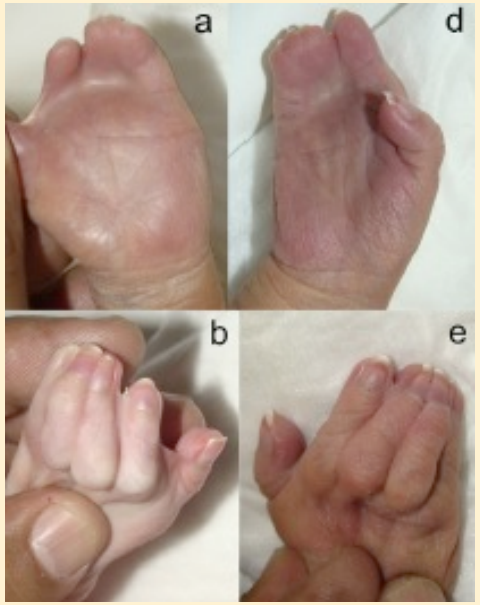
- **HCMP**

Gain-of-function

Timothy Syndrome (TS)

Exctracardiac Abnormalities:

- ✓ Cutaneous Syndactyly
- ✓ Facial dysmorphism
- ✓ Autism spectrum disorder
- ✓ Immunodeficiency
- ✓ Intermittent hypoglycemia



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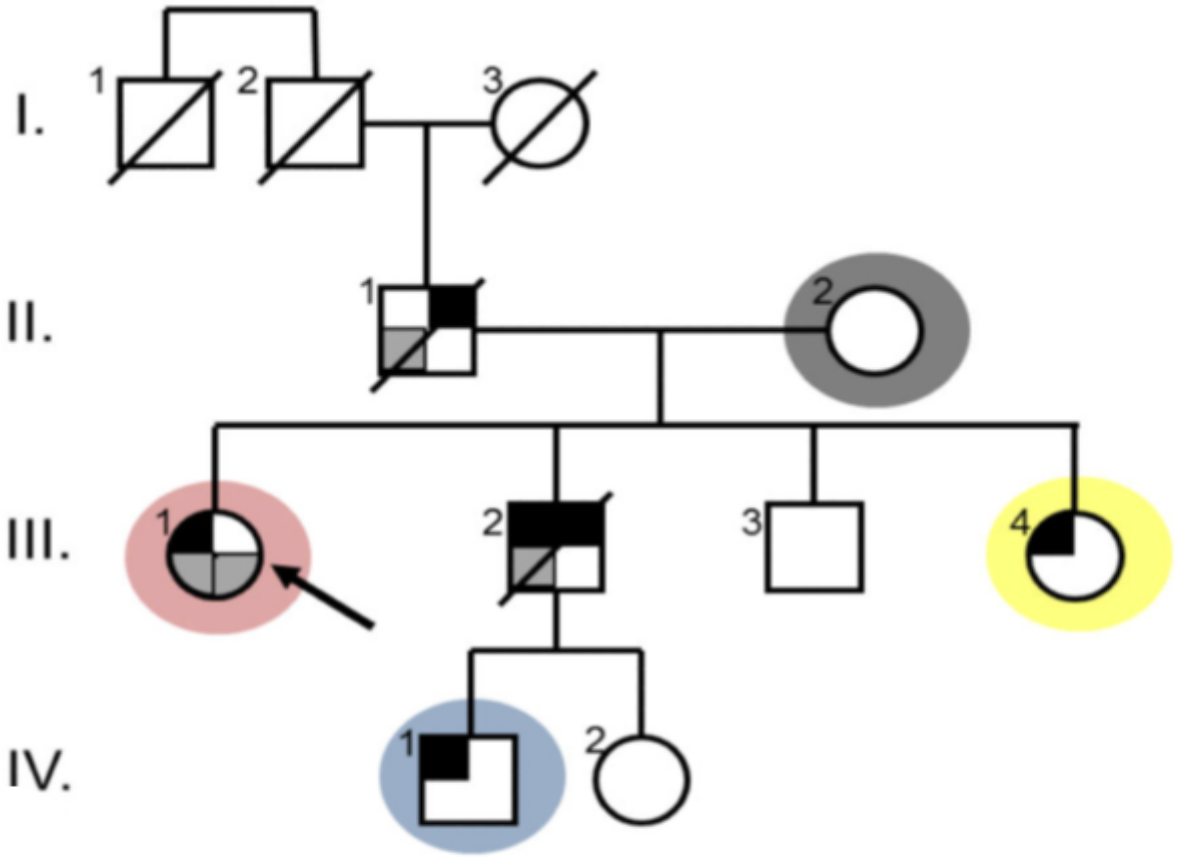
CACNA1C-Mediated Clinical Phenotypes



LQTS

Sudden Cardiac Death

Cardiomyopathy

Congenital Heart Defect

Filtering Strategy

		# of variants
		146,020
Filter 1	• Exclude all variants with a call quality of <20, read depth <10 or found in top 1% of genes with high variability.	116,332
Filter 2	• Exclude all variants with a frequency >0.01% in the NHLBI ESP, 1000 Genomes Project, and Complete Genomics Genomes.	9,545
Filter 3	• Exclude all synonymous and noncoding variants with the exception of potential splice site variants.	1,099
Filter 4	• Familial filtering based on autosomal dominant inheritance model, with index case (III.1), III.4, and IV.1 as positive cases, and II.2 as negative control.	29
Filter 5	• Utilize biological plausibility filter in Ingenuity, with disease presets of LQTS, cardiomyopathy, sudden cardiac death, and diseases consistent with these phenotypes.	1

Arg518Cys CACNA1C

Boczek et al., 2015

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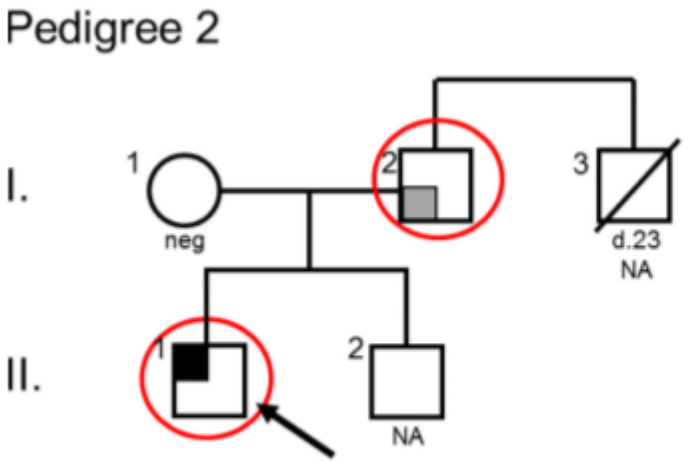
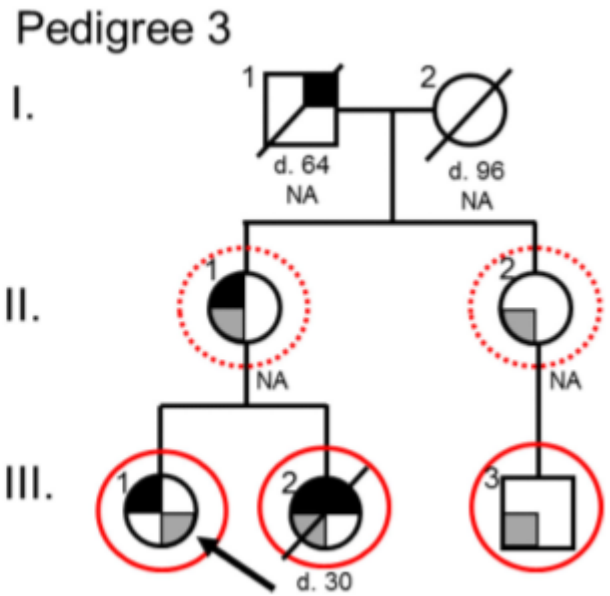
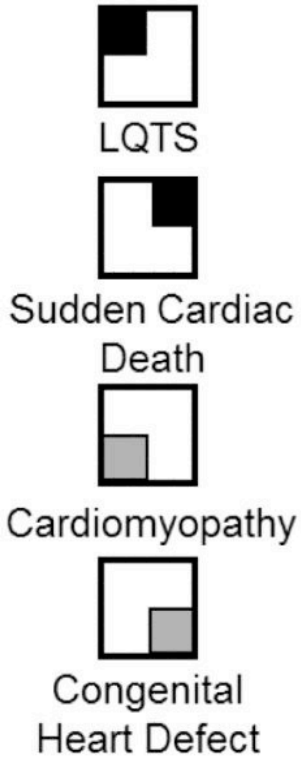
CACNA1C-Mediated Clinical Phenotypes







Families Harboring p.Arg518Cys/His.

Boczek et al., 2015

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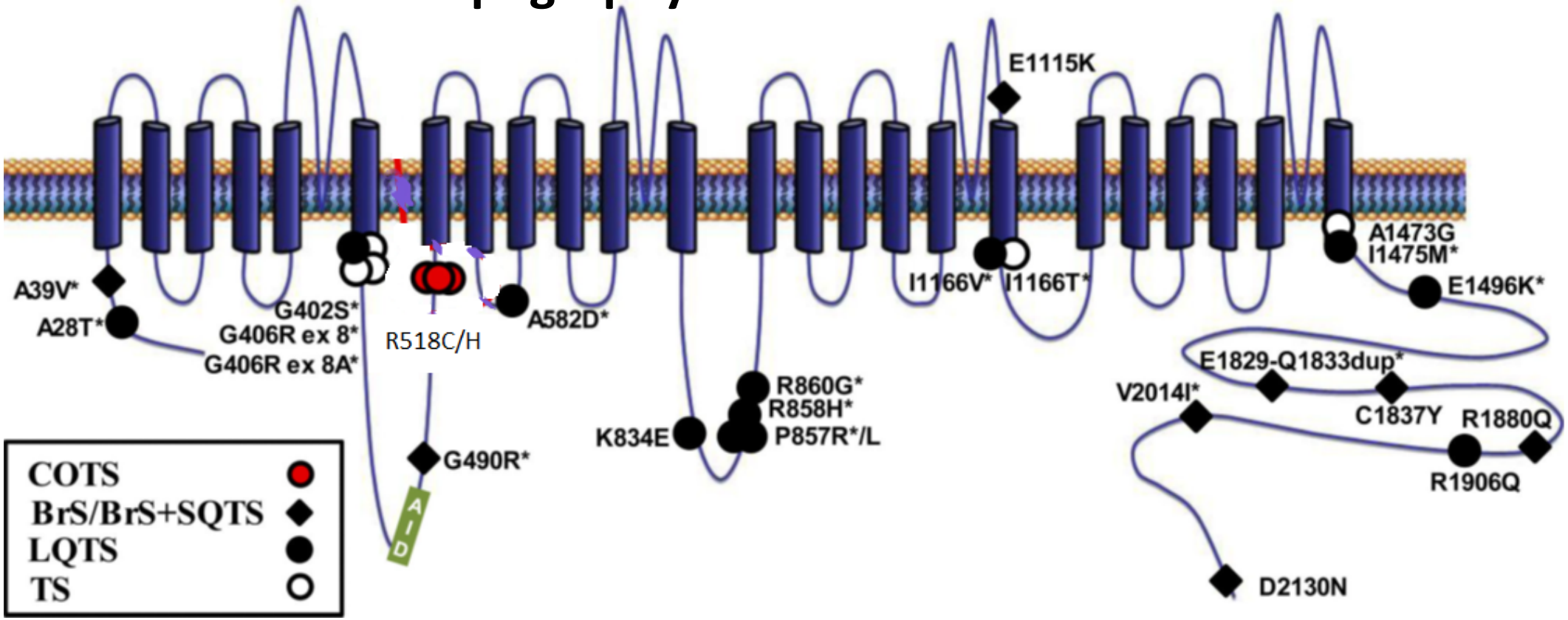
CACNA1C Topography



Cardiomyopathy & CACNA1C mutations:

G406R E8[Splawski 2005; Lo-A-Njoe 2005; Kawaida 2016 and our patient]

G402S [Splawski 2005]

G490R & E771G [D'Argenio 2014]

I1166T [Wemhoner, 2015]

R518C/H [Boczek, 2015]

**LQTS + Syndactyly: mild HCMP + endocardial fibroelastosis [Marks 1995]

Boczek et al., 2015

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Ospedale Pediatrico

Take home message:

Think of CACNA1C!!!!

Individual or intrafamilial recurrence of:

- ✓ LQTS, ventricular tachyarrhythmias, 2:1 AV block (functional);
- ✓ Congenital Heart defects;
- ✓ Cardiomyopathy;
- ✓ Sudden cardiac death.

Even in the absence of extracardiological involvement.

There is no strict genotype – phenotype correlation -> better complete gene coverage and not only hotspot screening.

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Ospedale Pediatrico

www.EPteachingAEPC2017.it

First Announcement

PAEDIATRIC ARRHYTHMIAS

6th TEACHING COURSE OF THE ASSOCIATION FOR EUROPEAN PAEDIATRIC AND CONGENITAL CARDIOLOGY

September 22/23, 2017

Bambino Gesù
Ospedale Pediatrico

Thank you for your attention!

Bambino Gesù
Ospedale Pediatrico