Long QT Syndrome

Lia Crotti

Rome Cardiology Forum 2014

31st January

University of Pavia,

IRCCS Istituto Auxologico Italiano, Milan, Italy

Institute of Human Genetics, HelmholtzZentrum Munchen, Neuherberg, Germany

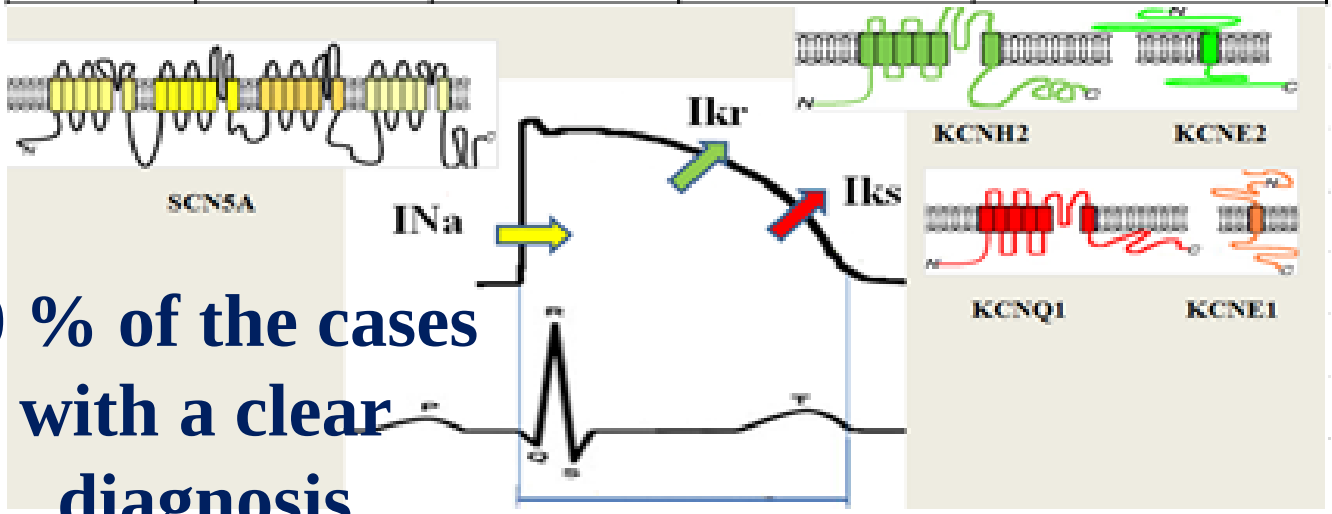
Congenital Long QT Syndrome

- ✓ Genetically transmitted
- ✓ Manifests in young age
- ✓ Prolonged QT interval
- ✓ Frequent syncope or cardiac arrest during emotional or physical stress
- ✓ High mortality among symptomatic and untreated patients

Long QT Syndrome: genetic basis

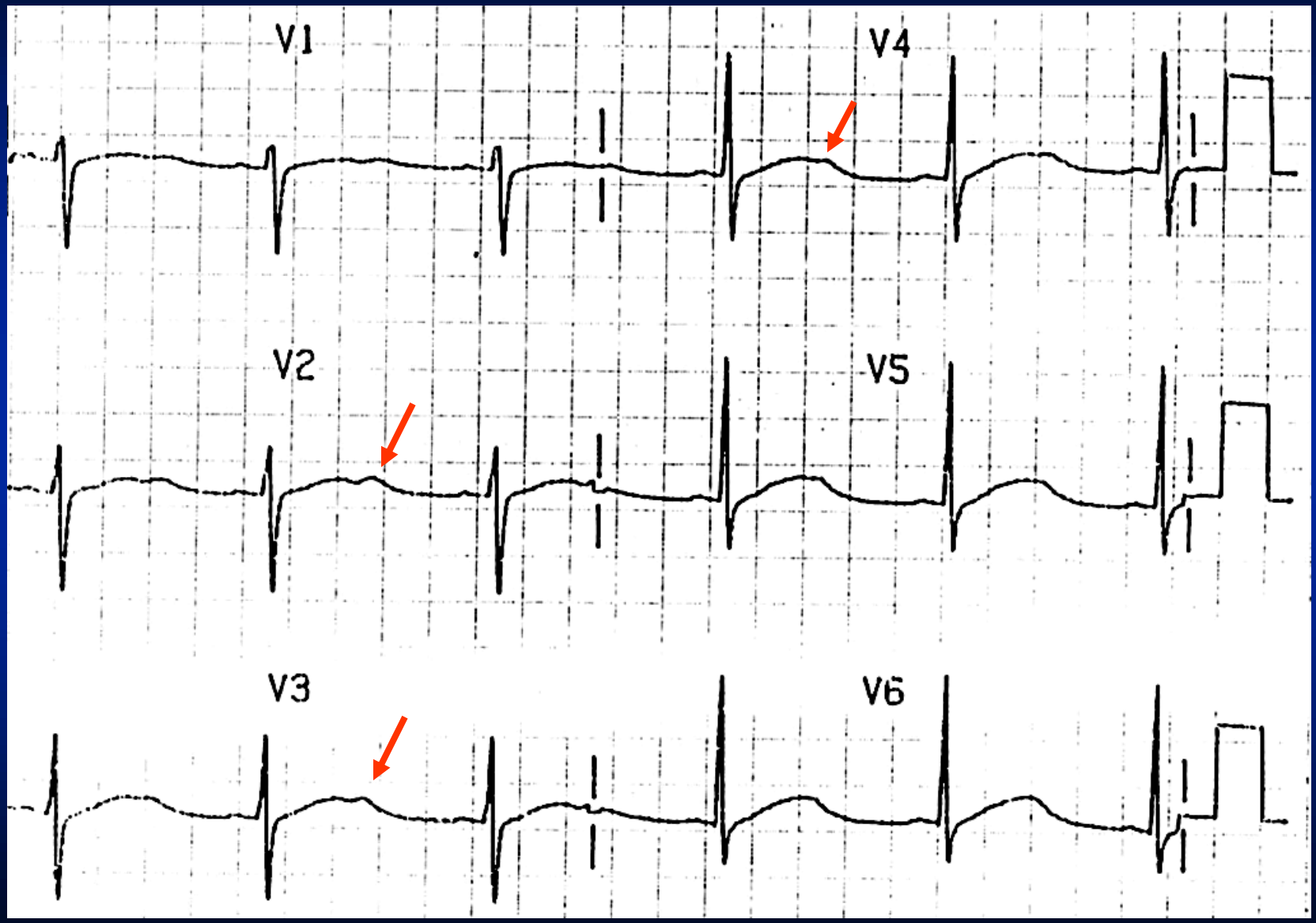
LQTS Genes

LQTS	GENE	POSITION	PREVALENCE	IONIC CHANNEL
LQT1	KCNQ1	11p15.5	45-50%	Iks
LQT2	KCNH2	7q35-36	40-45%	Ikr
LQT3	SCN5A	3p21-24	5%	INa
LQT5	KCNE1	21q22.1	<1%	Iks
LQT6	KCNE2	21q22.1	<1%	Ikr



80 % of the cases with a clear diagnosis

MP, 18 yrs, male SD QTc V2 621 ms QTc V5 595 ms



DIAGNOSIS

- Easy in typical cases presenting with QT prolongation and arrhythmic events

- In borderline cases diagnostic criteria were proposed to support the diagnostic process.

The idiopathic long QT syndrome: pathogenetic mechanisms and therapy

P. J. SCHWARTZ AND E. LOCATI

Eur Heart J 1985

QTc Behavior During Exercise and Genetic Testing for the Long-QT Syndrome

Peter J. Schwartz, MD; Lia Crotti, MD, PhD

ELECTROCARDIOGRAPHIC FINDINGS			
A	QTc	> 480 ms	3
		460 – 479 ms	2
		450 – 459 (male) ms	1
B	QTc 4th minute of recovery from exercise stress test ≥ 480 ms		1
C	TORSADE DE POINTES		2
D	T WAVE ALTERNANS		1
E	NOTCHED T WAVE IN 3 LEADS		1
F	LOW HEART RATE FOR AGE		0.5
CLINICAL HISTORY			
A	SYNCOPE	WITH STRESS	2
		WITHOUT STRESS	1
B	CONGENITAL DEAFNESS		0.5
FAMILY HISTORY			
A	FAMILY MEMBERS WITH DEFINITE LQTS		1
B	UNEXPLAINED SUDDEN CARDIAC DEATH BELOW AGE 30 AMONG IMMEDIATE FAMILY MEMBERS		0.5

SCHWARTZ SCORE

≤ 1 point
low probability of LQTS

1.5 to 3 points
Intermediate probability of LQTS

≥ 3.5 points
high probability of LQTS

Circulation 2011

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

Silvia G. Priori, MD, PhD, (HRS Chairperson)[1], Arthur A. Wilde, MD, PhD, (EHRA Chairperson)[2], Minoru Horie, MD, PhD, (APHRS Chairperson)[3], Yongkeun Cho, MD, PhD, (APHRS Chairperson)[4], Elijah R. Behr, MA, MBBS, MD, FRCP[5], Charles Berul, MD, FHRS, CCDS[6], Nico Blom, MD, PhD[7,*], Josep Brugada, MD, PhD[8], Chern-En Chiang, MD, PhD[9], Heikki Huikuri, MD[10], Prince Kannankeril, MD[11,‡], Andrew Krahn, MD, FHRS[12], Antoine Leenhardt, MD[13], Arthur Moss, MD[14], Peter J. Schwartz, MD[15], Wataru Shimizu, MD, PhD[16], Gordon Tomaselli, MD, FHRS[17,†], Cynthia Tracy, MD[18,%]

Heart Rhythm, Vol 10, No 12, December 2013

Expert Consensus Recommendations on ***LQTS Therapeutic Interventions***

Class I

1. The following lifestyle changes **are recommended** in all patients with a diagnosis of LQTS:
   a) Avoidance of QT-prolonging drugs (www.qtdrugs.org)
   b) Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss.
2. Beta-blockers **are recommended** for patients with a diagnosis of LQTS who are:
   a) Asymptomatic with QTc ≥470 ms *and/or*
   b) Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF).
3. Left cardiac sympathetic denervation (LCSD) **is recommended** for high-risk patients with a diagnosis of LQTS in whom:
   a) Implantable cardioverter defibrillator (ICD) therapy is contraindicated or refused *and/or*
   b) Beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated.
4. ICD implantation **is recommended** for patients with a diagnosis of LQTS who are survivors of a cardiac arrest.
5. All LQTS patients who wish to engage in competitive sports **should be** referred to a clinical expert for evaluation of risk.

Class IIa

6. Beta-blockers **can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.
7. ICD implantation **can be useful** in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.
8. LCSD **can be useful** in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.
9. Sodium channel blockers **can be useful**, as add-on therapy, for LQT3 patients with a QTc >500 ms who shorten their QTc by >40 ms following an acute oral drug test with one of these compounds.

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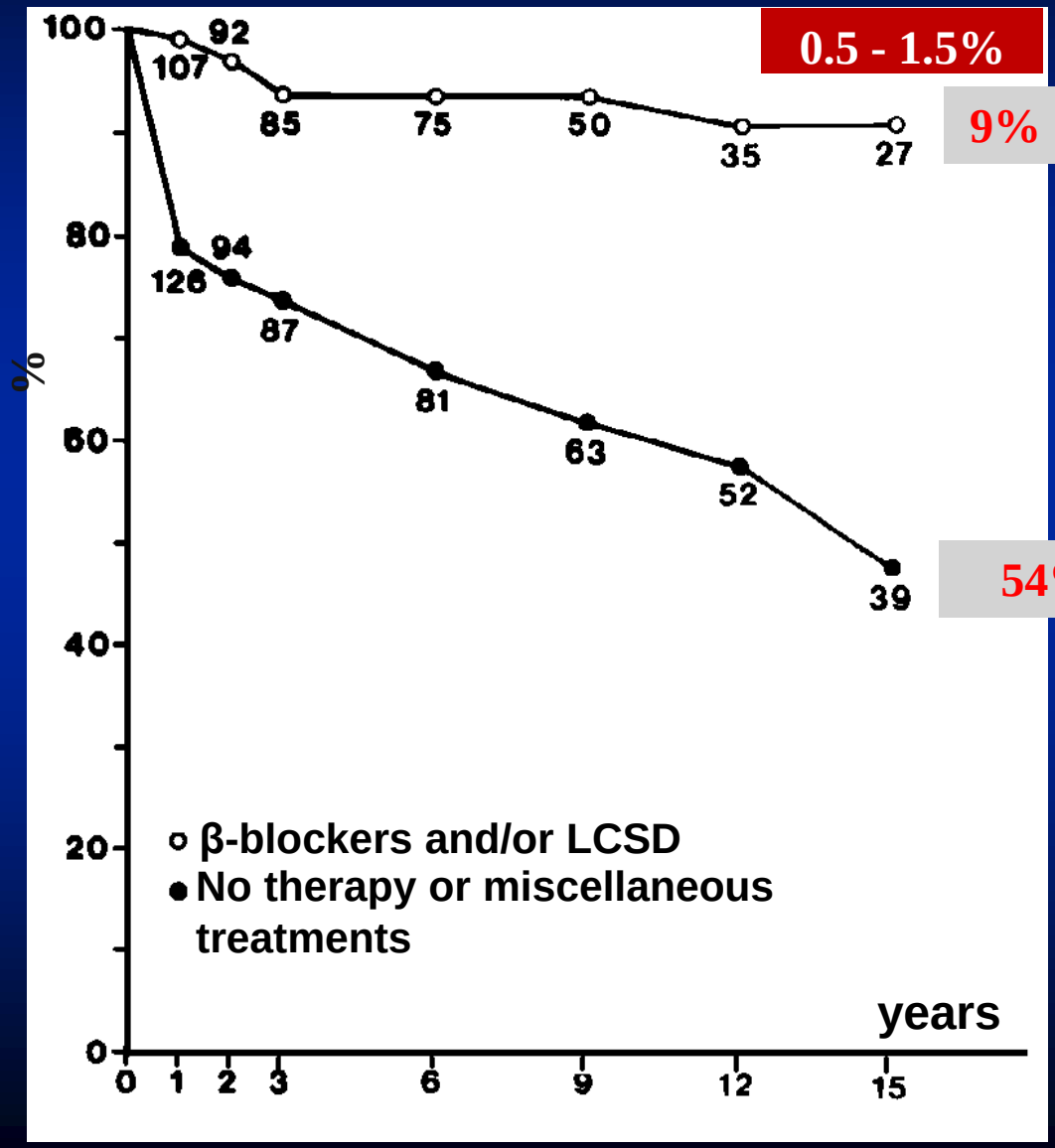
THERAPY



0.5 - 1.5%

9%

54%

2013

Survival after the first syncope in 233 LQTS patients

Schwartz PJ, AHJ 1985

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Heart Rhythm, Vol 10, No 12, December 2013

Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

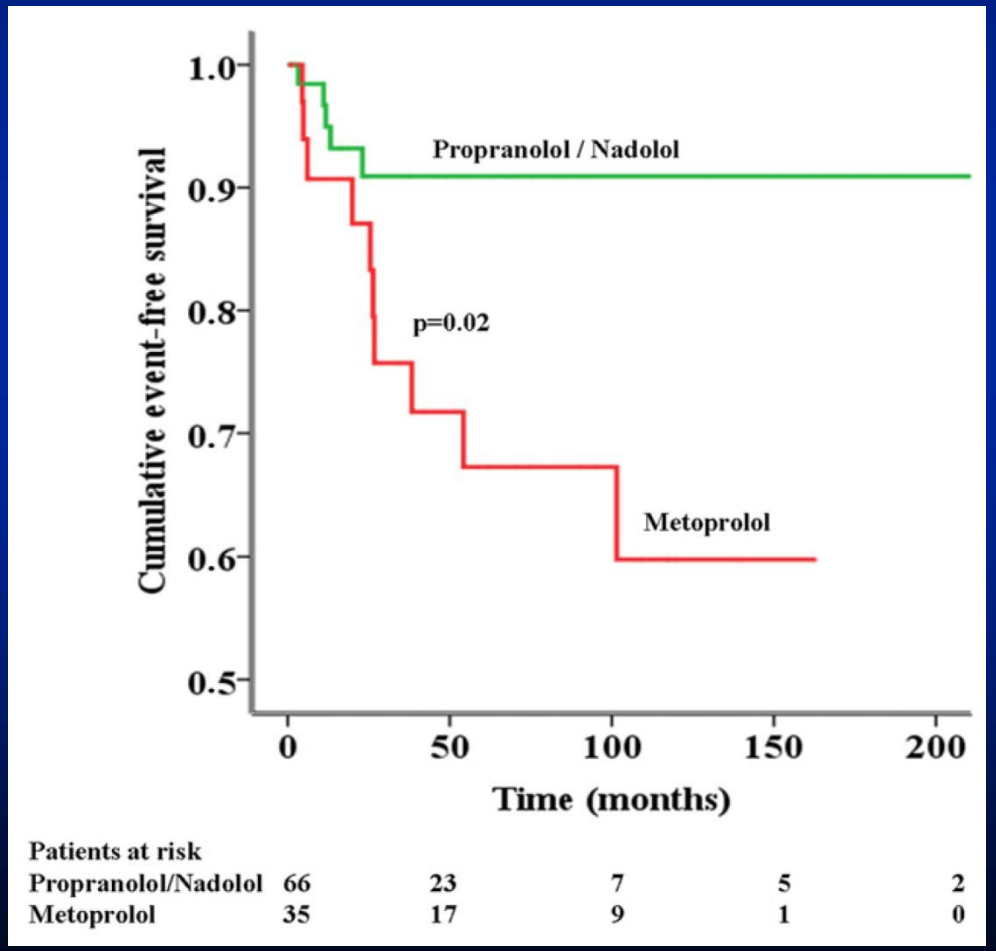
Higher Recurrence of Events Under Metoprolol

Priya Chockalingam, MBBS, PHD,*† Lia Crotti, MD, PHD,‡|| Giulia Girardengo, MD,‡
Jonathan N. Johnson, MD,¶ Katy M. Harris, MS, RN,¶ Jeroen F. van der Heijden, MD, PHD,#
Richard N. W. Hauer, MD, PHD,# Britt M. Beckmann, MD,** Carla Spazzolini, DVM, MS,‡
Roberto Rordorf, MD,§ Annika Rydberg, MD, PHD,†† Sally-Ann B. Clur, MBBCH, MSC (MED), PHD,†
Markus Fischer, MD,‡‡ Freek van den Heuvel, MD, PHD,§§ Stefan Kääb MD, PHD,**
Nico A. Blom, MD, PHD,†||| Michael J. Ackerman, MD, PHD,¶ Peter J. Schwartz, MD,‡¶¶##
Arthur A. M. Wilde, MD, PHD*

(J Am Coll Cardiol 2012;60:2092–9)

383 LQT1/LQT2 ptz

27% symptomatic



CA/SD despite BB therapy

271 ptz. LQTS – all symptomatic

LQT1	4%
LQT2	4%
LQT3	17%

Schwartz et al., 2001

Genetic Testing and ICD Implants

Long QT Syndrome in Children in the Era of Implantable Defibrillators

Susan P. Etheridge, MD, FACC,* Shubhayan Sanatani, MD,† Mitchell I. Cohen, MD, FACC,‡
Cecilia A. Albaro, MD,* Elizabeth V. Saarel, MD, FACC,* David J. Bradley, MD, FACC*

Salt Lake City, Utah; Vancouver, British Columbia, Canada; and Phoenix, Arizona

"All 3 centers recommended implantation for …. identification of an *SCN5A* mutation."

"No one with a known *SCN5A* mutation has had an appropriate ICD discharge"

Who Are the Long-QT Syndrome Patients Who Receive an Implantable Cardioverter-Defibrillator and What Happens to Them?

Data From the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry

Peter J. Schwartz, MD; Carla Spazzolini, DVM; Silvia G. Priori, MD, PhD; Lia Crotti, MD, PhD; Alessandro Vicentini, MD; Maurizio Landolina, MD; Maurizio Gasparini, MD; Arthur A.M. Wilde, MD; Reinoud E. Knops, MD; Isabelle Denjoy, MD; Lauri Toivonen, MD; Gerold Mönnig, MD; Majid Al-Fayyadh, MD; Luc Jordaens, MD; Martin Borggrefe, MD; Christina Holmgren, MD; Pedro Brugada, MD, FAHA; Luc De Roy, MD; Stefan H. Hohnloser, MD; Paul A. Brink, MD

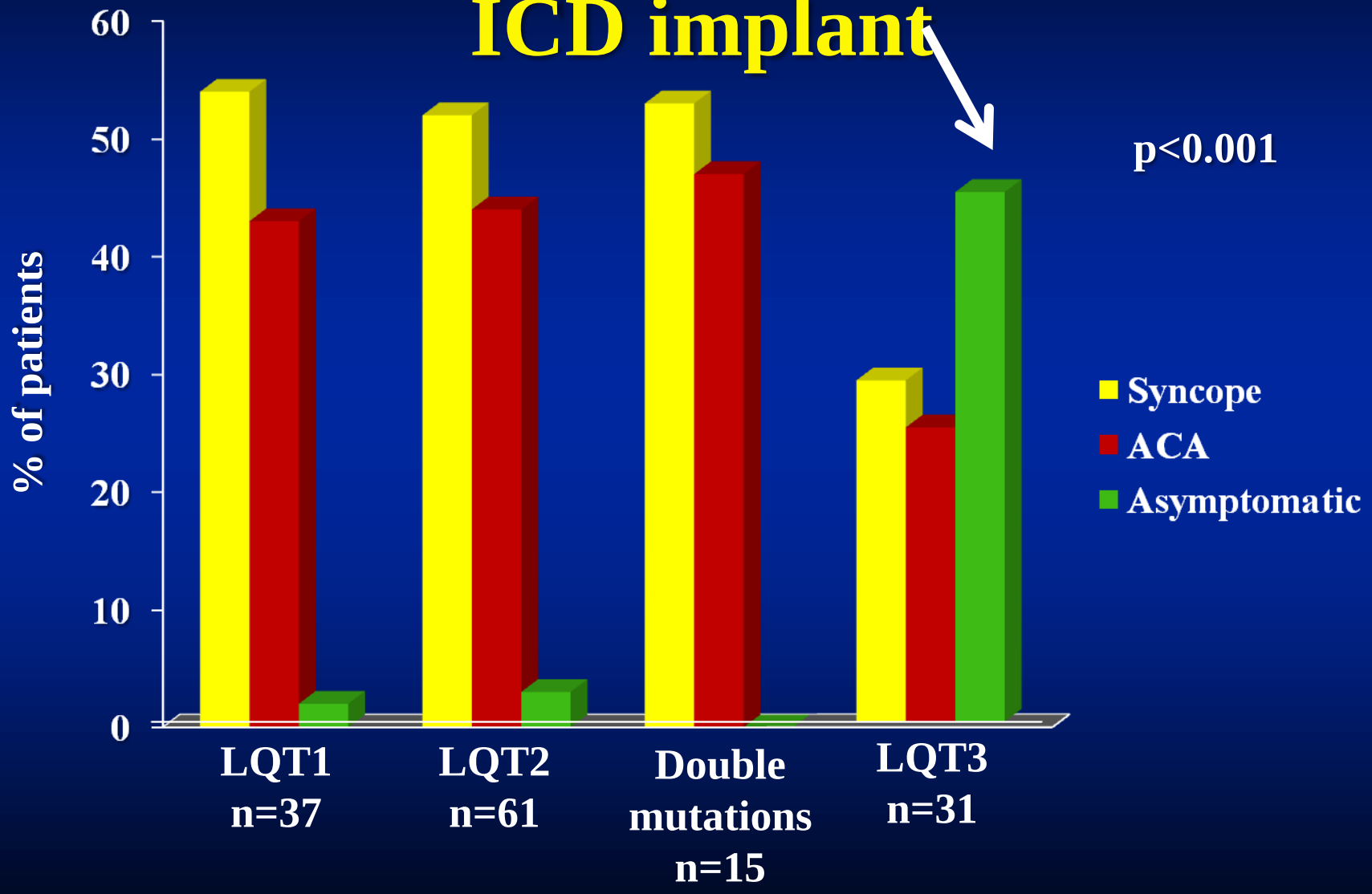
Population Under Study

- **Patients 233**
- **Follow-up 5 years**
- **9% asymptomatic**

(*Circulation*. 2010;122:1272-1282.)

European Registry ICD & LQTS

Genotype and cardiac events before ICD implant



All LQT3 patients need an ICD: True or false?

Peter J. Schwartz, MD, FHRS,*†‡§#¶ Carla Spazzolini, DVM, MS,† Lia Crotti, MD, PhD*†‡

(Heart Rhythm 2009;6:113–120)

Cardiac Events in LQT3 patients on BB therapy.

Mean FU 9 years

Events in the first year of life (4/22, 18%)

Sudden Death (SD)	**3 (14%)**	**βB; βB; βB +Mexiletine**
Cardiac Arrest (CA)	**1 (4.5%)**	**βB+PM+Mexiletine**

NO events in the first year of life (18/22, 82%)

SD/CA	**0**	
Syncope	**2 (11%)**	**LCSD; βB**
No symptoms	**16 (89%)**	**βB and/or LCSD**

Propranolol prevents life-threatening arrhythmias in LQT3 transgenic mice: Implications for the clinical management of LQT3 patients

Laura Calvillo, PhD,[*] Carla Spazzolini, DMV, MS,[†] Eleonora Vullo, MD,[†‡] Roberto Insolia, PhD,[‡] Lia Crotti, MD, PhD,[¶‡§] Peter J. Schwartz, MD, FHRS[*‡¶‖**††]

Heart Rhythm 2014; 11:126-132

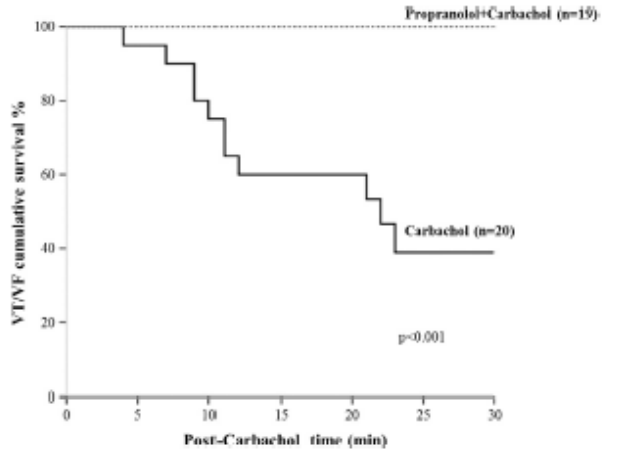


Figure 4 Cumulative survival to major arrhythmias (ventricular tachycardia/ventricular fibrillation [VT/VF]) in transgenic mice according to protocol treatment.

In TG DeltaKPQ-SCN5A mice, drug-induced life-threatening arrhytmias were observed in 55% of the mice. By contrast, none of the mice pre-treated with propranolol developed malignant arrhythmias.

Sodium Channel Mutations and Risk of Cardiac Events in Long QT Syndrome Type 3

Wilde AM, AJ Moss, MJ Ackerman, PJ Schwartz et al – In preparation

- 407 LQT3 pts
- 107 pts on β-blocker therapy
- 7 deaths (4 with CA in the 1st year of life)

Mortality for pts on β-blocker therapy w/out events in the 1st year of life:

2.8%

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Heart Rhythm, Vol 10, No 12, December 2013

Clinical Implications for Patients With Long QT Syndrome Who Experience a Cardiac Event During Infancy

Carla Spazzolini, DVM,* Jamie Mullally, BS,† Arthur J. Moss, MD,† Peter J. Schwartz, MD,*§ Scott McNitt, MS,† Gregory Ouellet, BS,† Thomas Fugate, BS,† Ilan Goldenberg, MD,† Christian Jons, MD,† Wojciech Zareba, MD, PHD,† Jennifer L. Robinson, MS,† Michael J. Ackerman, MD, PHD,‖ Jesaia Benhorin, MD,¶ Lia Crotti, MD, PHD,* Elizabeth S. Kaufman, MD,# Emanuela H. Locati, MD, PHD,** Ming Qi, PHD,‡ Carlo Napolitano, MD,†† Silvia G. Priori, MD, PHD,†† Jeffrey A. Towbin, MD,‡‡ G. Michael Vincent, MD§§

Pavia and Milan, Italy; Rochester, New York; Rochester, Minnesota; Jerusalem, Israel; Cleveland and Cincinnati, Ohio; and Salt Lake City, Utah

LQTS patients with a CA in the first year of life are a small (<2%) but very-high risk group for subsequent near-fatal and fatal cardiac events during the first decade of life

JACC 2009

An ACA in the first year of life was associated with an HR of 23.4 (p 0.01) for a subsequent ACA/LQTS-related SCD during the 1- to 10-year period

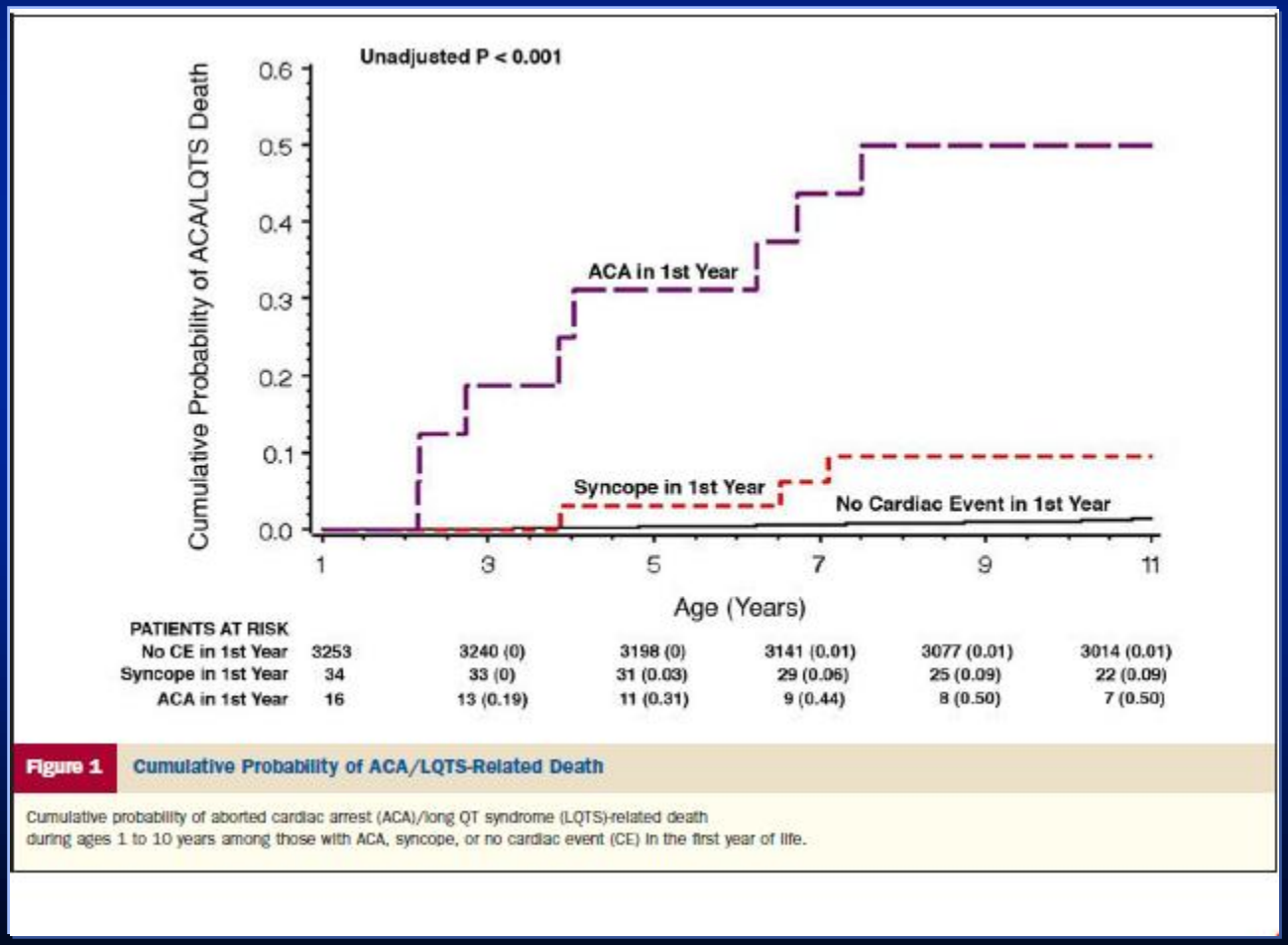


Figure 1 Cumulative Probability of ACA/LQTS-Related Death

Cumulative probability of aborted cardiac arrest (ACA)/long QT syndrome (LQTS)-related death during ages 1 to 10 years among those with ACA, syncope, or no cardiac event (CE) in the first year of life.

Prevalence of Long-QT Syndrome Gene Variants in Sudden Infant Death Syndrome

Marianne Arnestad, MD*; Lia Crotti MD*; Torleiv O. Rognum, MD; Roberto Insolia, BSc; Matteo Pedrazzini, BSc; Chiara Ferrandi, BSc; Ashild Vege, MD; Dao W. Wang, MD; Troy E. Rhodes, MD, PhD; Alfred L. George, Jr, MD; Peter J. Schwartz, MD

(*Circulation*. 2007;115:361-367.)

201 SIDS cases
227 controls

A functional mutation in LQTS genes was identified in:

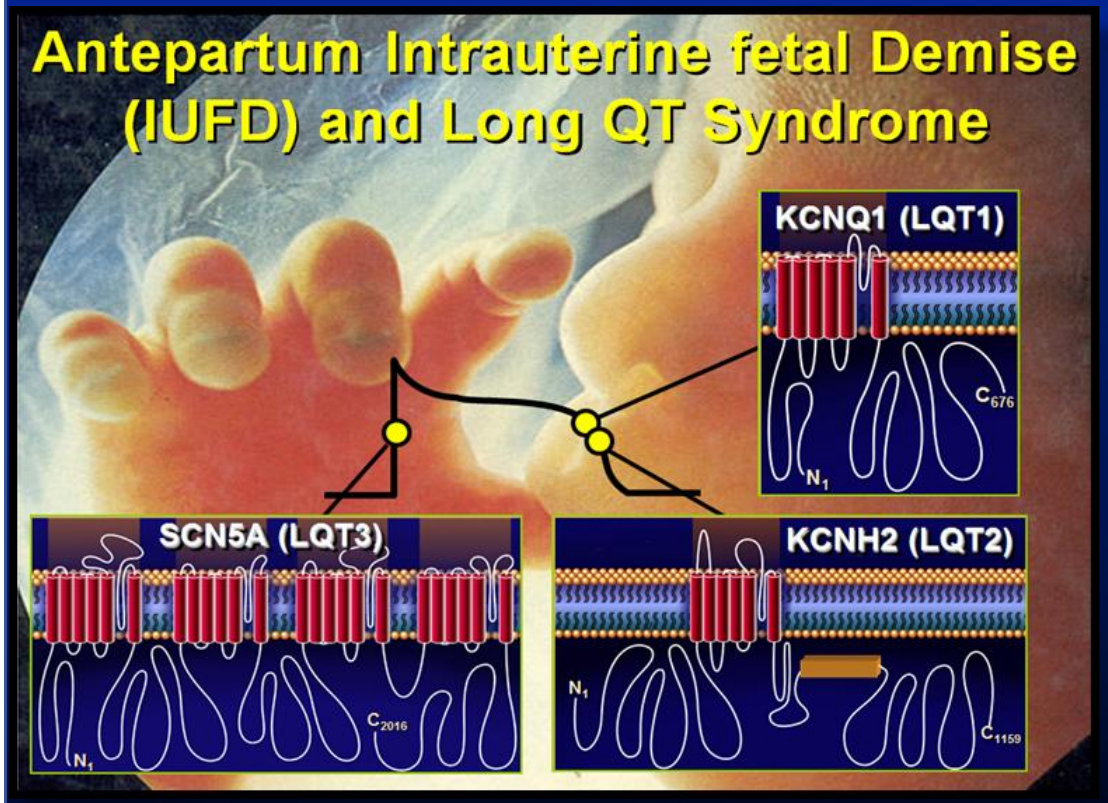
19/201 (9.5%)

95% C.I. 5.8-14.4%

Long QT Syndrome–Associated Mutations in Intrauterine Fetal Death

Lia Crotti, MD, PhD
David J. Tester, BS
Wendy M. White, MD
Daniel C. Bartos, BS
Roberto Insolia, PhD
Alessandra Besana, PhD
Jennifer D. Kunic, BS
Melissa L. Will, BS
Ellyn J. Velasco, BS
Jennifer J. Bair, BS
Alice Ghidoni, BS
Irene Cetin, MD
Daniel L. Van Dyke, PhD
Myra J. Wick, MD, PhD
Brian Brost, MD
Brian P. Delisle, PhD
Fabio Facchinetti, MD
Alfred L. George Jr, MD
Peter J. Schwartz, MD
Michael J. Ackerman, MD, PhD

91 cases with unexplained IUFD



JAMA 2013

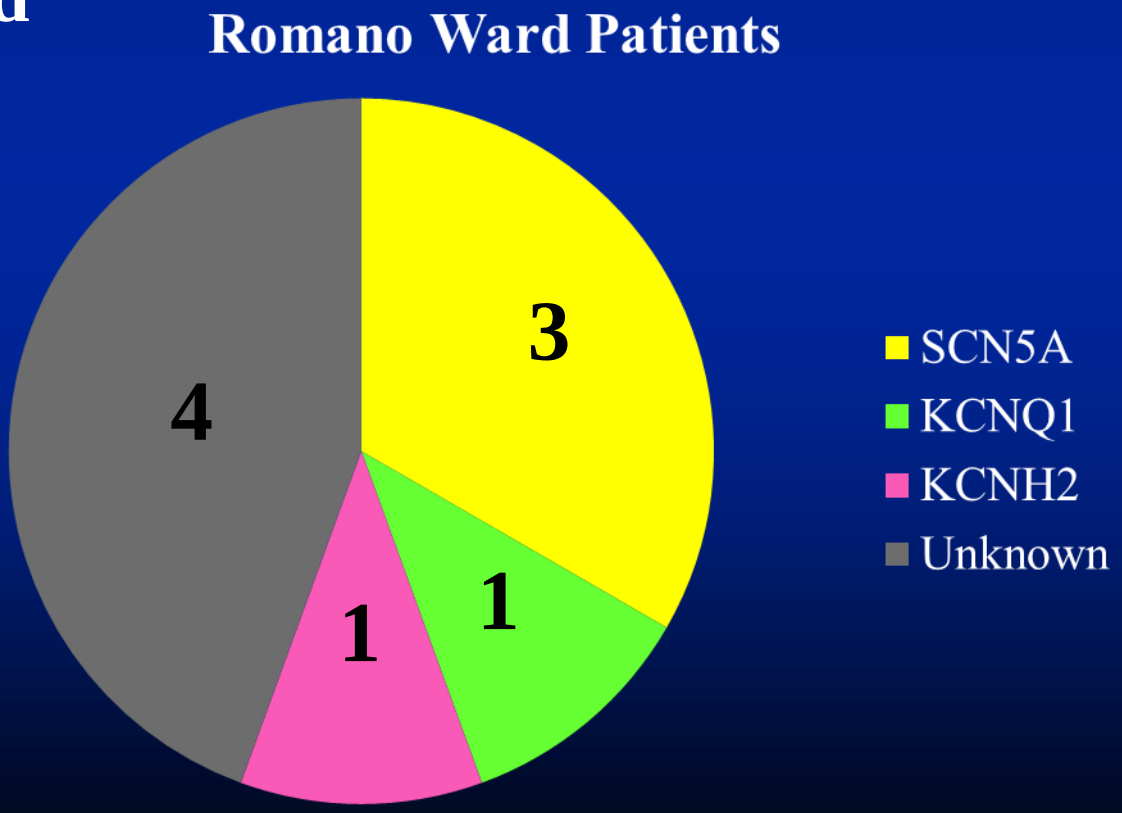
Malignant LQTS causing life-threatening arrhythmias during the perinatal period

- Life-threatening arrhythmias starting in utero and/or during the first months of life
- ECG signs of severe electrical instability: 2:1 functional AV block, T-wave alternans
- SCD could be the first manifestation of the disease: diagnosis only through molecular autopsy

Life-threatening arrhythmias in the first year of life in the Pavia's database:

TOT 12:

- **3 Jervell Lange-Nielsen (double KCNQ1 mutation)**
- **9 Romano Ward**



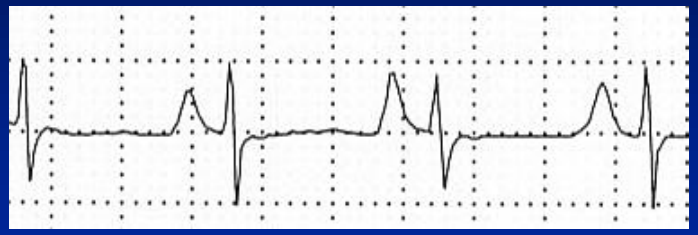
Proband 1

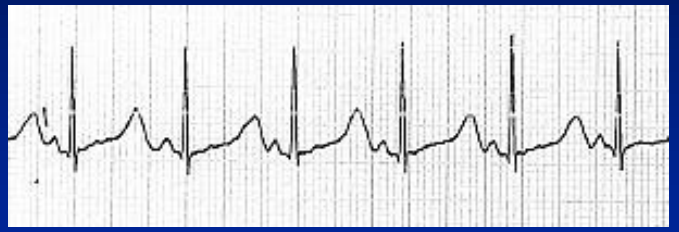
Presentation

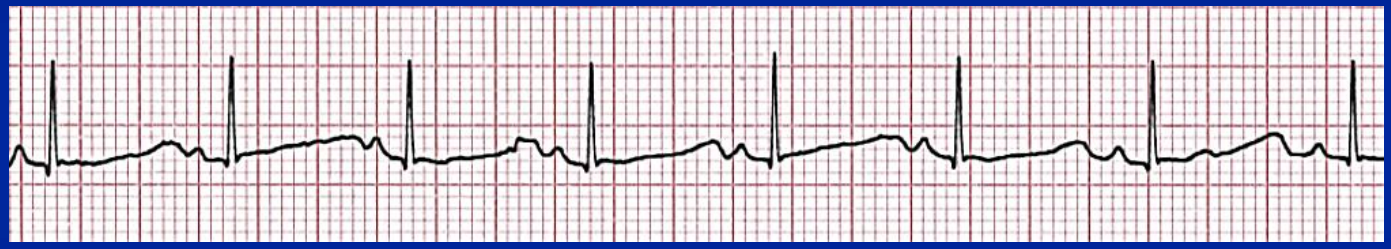
- VF at 6 month (16 VF in the first 2 years of life)
- QTc 630 ms
- T wave alternans (TWA)
- Intermittent 2:1 AV block → ICD

Proband 1

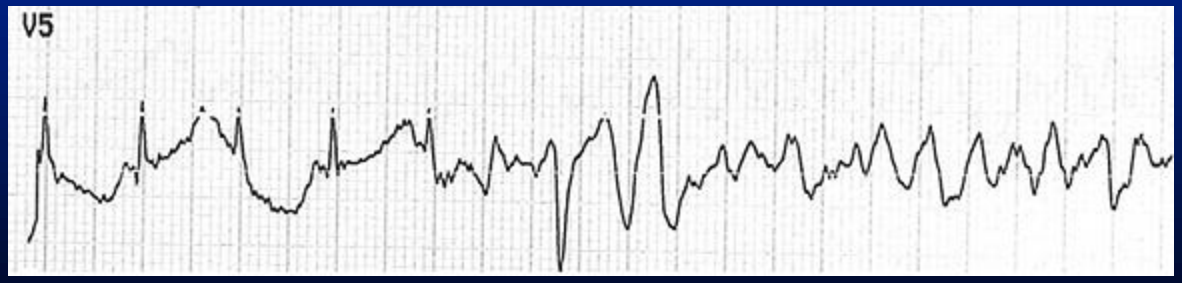
Basal ECGs





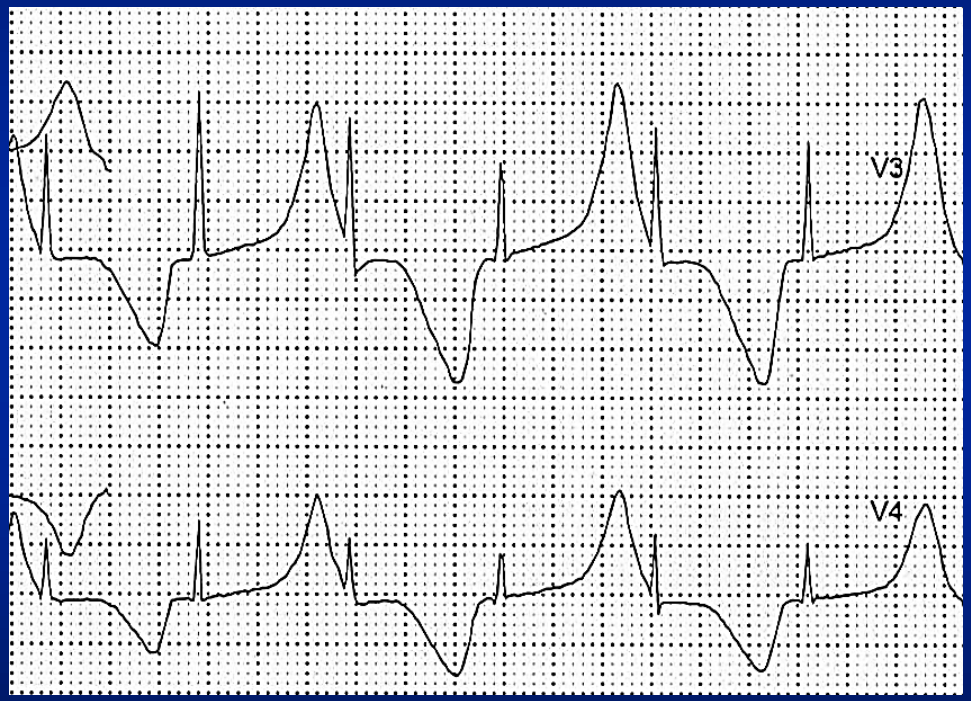


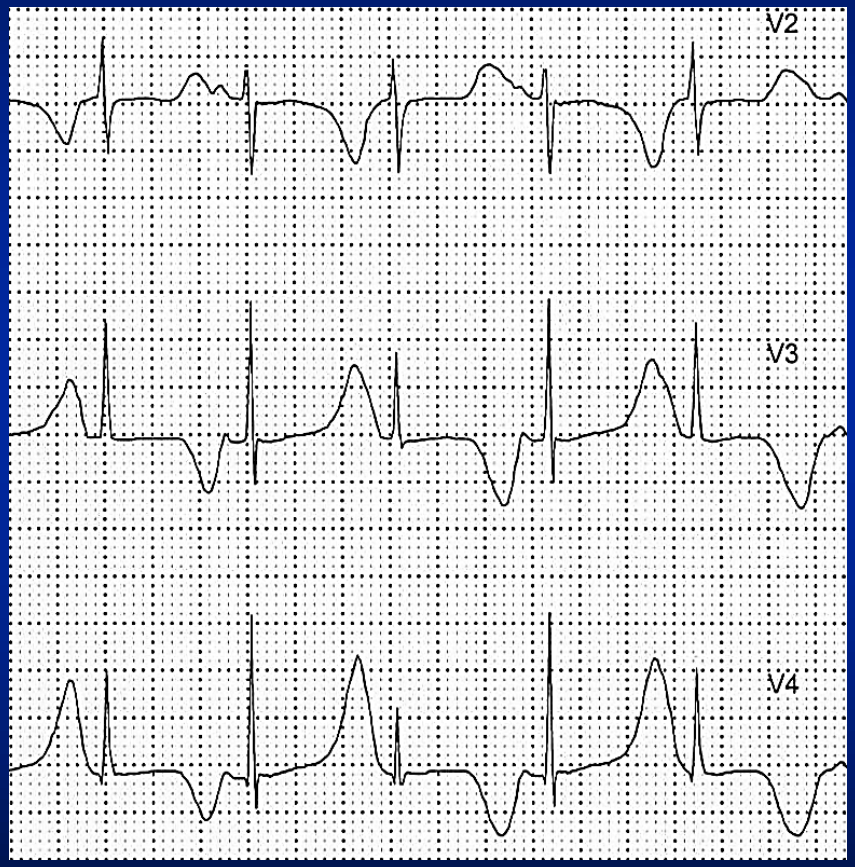
TdP / VF onset



Proband 1

T Wave Alternans



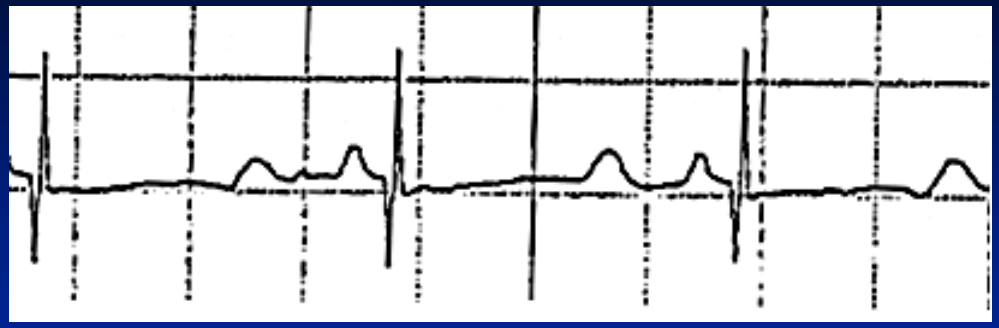


Proband 2

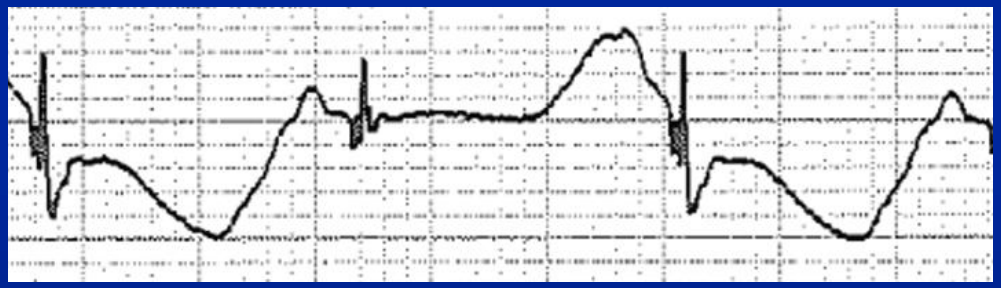
Presentation

- Fetal bradycardia at 21 weeks gestation
- First VF at 3 weeks and then recurrent episodes
- bradycardia, QTc 690 ms, 2:1 AV block, T-wave alternans
- Right parietal lobe cerebral infarction
- Developmental delay

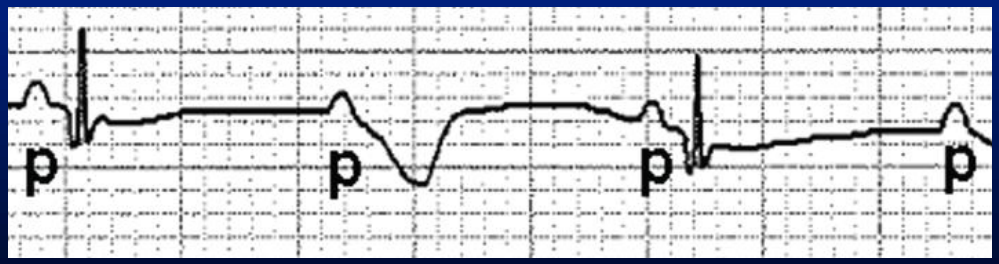
Proband 2



Basal ECG at birth



T-wave alternans

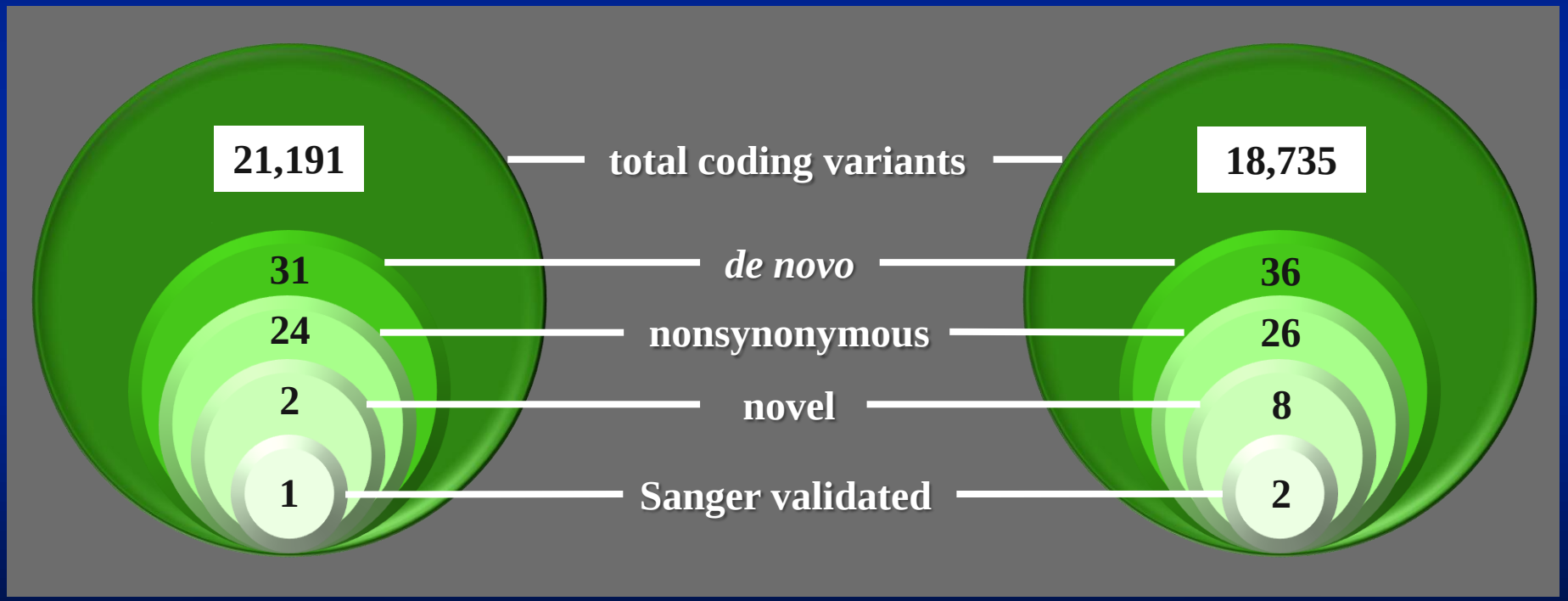


2:1 AV block

Whole Exome Sequencing

- Performed on the 2 probands and their parents
- Searched for novel variants
  1. Not inherited (de novo)
  2. Predicted to have deleterious effects

Whole Exome Sequencing



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Calmodulin Mutations Associated with Recurrent Cardiac Arrest in Infants

Lia Crotti, Christopher N. Johnson, Elisabeth Graf, Gaetano M. De Ferrari, Bettina F. Cuneo, Marc Ovadia, John Papagiannis, Michael D. Feldkamp, Subodh G. Rathi, Jennifer D. Kunic, Matteo Pedrazzini, Thomas Wieland, Peter Lichtner, Britt-Maria Beckmann, Travis Clark, Christian Shaffer, D. Woodrow Benson, Stefan Kääb, Thomas Meitinger, Tim M. Strom, Walter J. Chazin, Peter J. Schwartz and Alfred L. George, Jr.

Circulation. published online February 6, 2013;

Calmodulin Mutations

Potential Mechanisms

- Calmodulin serves for Ca^{2+}-dependent inactivation of L-type Ca^{2+} channels.
- Calmodulin is required for Iks activation during sympathetic activation
- Calmodulin is involved in INa inactivation

Calmodulin Mutation Associated with Neonatal Long-QT Syndrome Evokes Increased Persistent Sodium Current from a Fetal $Na_V1.5$ Splice Variant

Lisa L. Murphy, Courtney M. Campbell, Lia Crotti, Christopher N. Johnson, Jennifer D. Kunic, Peter J. Schwartz, Walter J. Chazin, Alfred L. George, Jr.

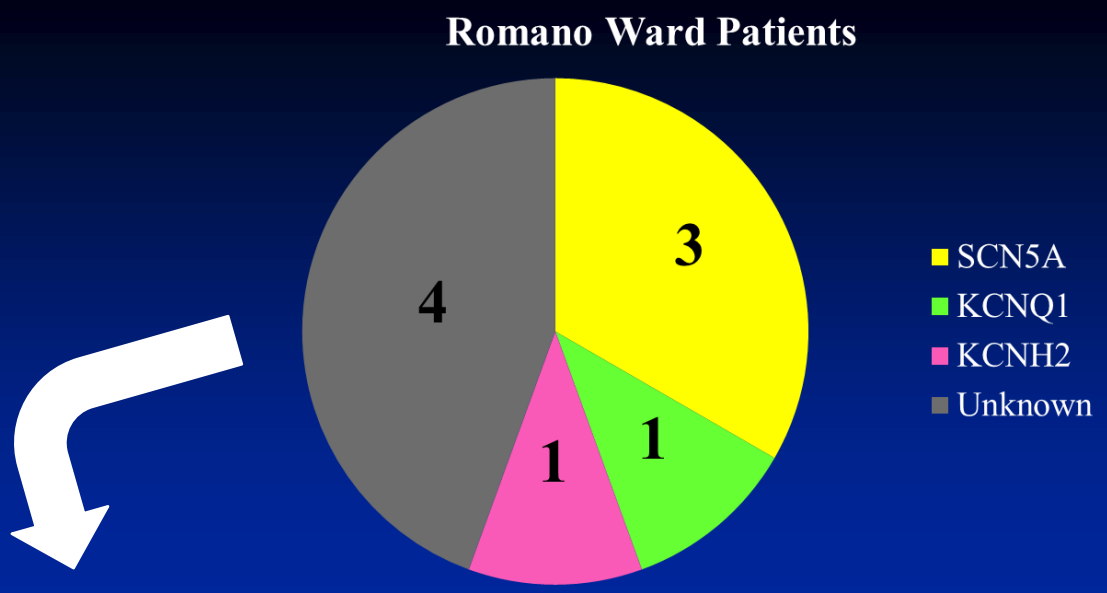
Circulation 2013; 128: A14999

D130 G, a *CALM 1* mutation identified in 2 of our patients, when expressed in a fetal isoform evokes a persistent I_{Na} significantly larger compared to that of wild-type $Na_v1.5$.

The preferential effect of CaM-D130G on fetal $Na_V1.5$ helps explain the early onset of arrhythmia.

VALIDATION

- **Cohort of 82 LQTS patients genotype-negative / phenotype-positive**
- **Direct search for mutations in *CALM1, CALM2, CALM3***
- ***CALM1* mutations discovered in 2 subjects**



In our LQTS cohort of genotype-negative/phenotype-positive patients only four had extremely malignant arrhythmias with onset in infancy.

In three of these four we found calmodulin mutations.

Subject	Sex	Age at diagnosis	VF	QTc	TWA	2:1 AVB	Seizures	Developmental delay
Proband 1	F	6 months	+	630 ms	+	+	-	+/-
Proband 2	F	prenatal	+	690 ms	+	+	+	+
Case 3	M	1 month	+	610 ms	+	+	+	+
Case 4	M	? neonatal	+	>600 ms	+	-?	+	+

Subject	Treatments	Mutation
Proband 1	βB, MEX, VER, FLEC, LCSD, RCSD, ICD	*CALM*1-D130G
Proband 2	βB, MEX, ICD	*CALM*2-D96V
Case 3	βB, MEX, ICD	*CALM*1-D130G
Case 4	βB, MEX, LCSD, ICD	*CALM*1-F142L

Clinical implications

- **Patients with life-threatening arrhythmias in the first year of life are usually not fully responders to anti-adrenergic therapy and also to association of therapies.**

- **Despite the young age and the potential complications associated with device implantation in small subjects, an ICD should be carefully evaluated**

Who Are the Long-QT Syndrome Patients Who Receive an Implantable Cardioverter-Defibrillator and What Happens to Them?

Data From the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry

Peter J. Schwartz, MD; Carla Spazzolini, DVM; Silvia G. Priori, MD, PhD; Lia Crotti, MD, PhD; Alessandro Vicentini, MD; Maurizio Landolina, MD; Maurizio Gasparini, MD; Arthur A.M. Wilde, MD; Reinoud E. Knops, MD; Isabelle Denjoy, MD; Lauri Toivonen, MD; Gerold Mönnig, MD; Majid Al-Fayyadh, MD; Luc Jordaens, MD; Martin Borggrefe, MD; Christina Holmgren, MD; Pedro Brugada, MD, FAHA; Luc De Roy, MD; Stefan H. Hohnloser, MD; Paul A. Brink, MD

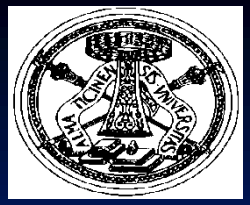
Population Under Study

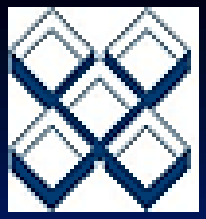
- **Patients 233**
- **Follow-up 5 years**
- **9% asymptomatic**

(*Circulation*. 2010;122:1272-1282.)

Indications at ICD implants

- Previous cardiac arrest
- Syncopal events despite full antiadrenergic therapy (possibly including LCSD)
- Asymptomatic patients with QTc>550msec, with signs of high electrical instability (i.e. T wave alternans, 2:1 AV block) or other evidence of being at very high risk (i.e. very long sinus pauses that might favour EAD)





HelmholtzZentrum münchen
German Research Center for Environmental Health

Peter J. Schwartz

Matteo Pedrazzini

Federica Dagradi

Margherita Torchio

Alice Ghidoni

Roberto Insolia

Christina Kotta

Thomas Meitinger

Tim M. Strom

Peter Lichtner

Elisa Mastantuono

Thomas Wieland

liacrotti@yahoo.it

lia.crotti@unipv.it

THANK YOU

Expert Consensus Recommendations on ***LQTS Therapeutic Interventions***

Class I

1. The following lifestyle changes **are recommended** in all patients with a diagnosis of LQTS:
   a) Avoidance of QT-prolonging drugs (www.qtdrugs.org)
   b) Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss.
2. Beta-blockers **are recommended** for patients with a diagnosis of LQTS who are:
   a) Asymptomatic with QTc ≥470 ms *and/or*
   b) Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF).
3. Left cardiac sympathetic denervation (LCSD) **is recommended** for high-risk patients with a diagnosis of LQTS in whom:
   a) Implantable cardioverter defibrillator (ICD) therapy is contraindicated or refused *and/or*
   b) Beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated.
4. ICD implantation **is recommended** for patients with a diagnosis of LQTS who are survivors of a cardiac arrest.
5. All LQTS patients who wish to engage in competitive sports **should be** referred to a clinical expert for evaluation of risk.

Class IIa

6. Beta-blockers **can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.
7. ICD implantation **can be useful** in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.
8. LCSD **can be useful** in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.
9. Sodium channel blockers **can be useful**, as add-on therapy, for LQT3 patients with a QTc >500 ms who shorten their QTc by >40 ms following an acute oral drug test with one of these compounds.

Heart Rhythm, Vol 10, No 12, December 2013

CALM Mutations and Life-Threatening Arrhythmias

Mutations in Calmodulin Cause Ventricular Tachycardia and Sudden Cardiac Death

Mette Nyegaard,[1,8,*] Michael T. Overgaard,[2,8] Mads T. Søndergaard,[2] Marta Vranas,[1] Elijah R. Behr,[3] Lasse L. Hildebrandt,[2] Jacob Lund,[2] Paula L. Hedley,[4,5] A. John Camm,[3] Göran Wettrell,[6] Inger Fosdal,[7] Michael Christiansen,[4] and Anders D. Børglum[1,*]

The American Journal of Human Genetics *91*, 703–712, October 5, 2012 703

Gene: ***CALM1***

Population: **1) a large Swedish family with a severe dominantly inherited form of CPVT-like arrhythmia**

2) a man of Iraqi origin with a *de novo* mutation

CALM Mutations and Life-Threatening Arrhythmias

A mutation in *CALM1* encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence

Roos F. Marsman, MSc[1*], Julien Barc, PhD[1,2*], Leander Beekman, BSc[1], Marielle Alders, PhD[3], Dennis Dooijes, PhD[4], Arthur van den Wijngaard[5], PhD, Ilham Ratbi[6], MD, Abdelaziz Sefiani, MD, PhD[6], Zahurul A. Bhuiyan, MD, PhD[3,7], Arthur A.M. Wilde, MD, PhD[1,8], Connie R. Bezzina, PhD[1]

J Am Coll Cardiol 2013 doi:10.1016/j.jacc.2013.07.091.

Gene: *CALM1*

Population: a Moroccan family:
- 4 siblings CA/SCD
- mother and a sibling are asymptomatic mutation carriers

CALM Mutations and Life-Threatening Arrhythmias

***CALM2* Mutations Associated with Atypical Juvenile Long QT Syndrome**

Naomasa Makita, Nobue Yagihara, Lia Crotti, Christopher N. Johnson, Britt-Marie Beckermann, Daichi Shigemizu, Hiroshi Watanabe, Taisuke Ishikawa, Takeshi Aiba, Elisa Mastantuono, Tatsuhiko Tsunoda, Hidewaki Nakagawa, Yukiomi Tsuji, Takeshi Tsuchiya, Hirokazu Yamamoto, Yoshihiro Miyamoto, Naoto Endo, Akinori Kimura, Kouichi Ozaki, Hideki Motomura, Kenji Suda, Toshihiro Tanaka, Peter J Schwartz, Thomas Meitinger, Stefan Kääb, Wataru Shimizu, Walter Chazin, Alfred L George Jr,

Circulation 2013;128:A13371

Gene: *CALM2*

Population: **12 Japanese probands** (mutation identified in a 19 months girl with syncope and CA)

190 genotype-negative Japanese LQTS probands (mutation identified in a 5 yrs boy with episodes of exercise-induced syncope)

98 genotype-negative Caucasian LQTS probands (mutation identified in an adult female with history of neonatal LQTS and subsequent features consistent with CPVT)