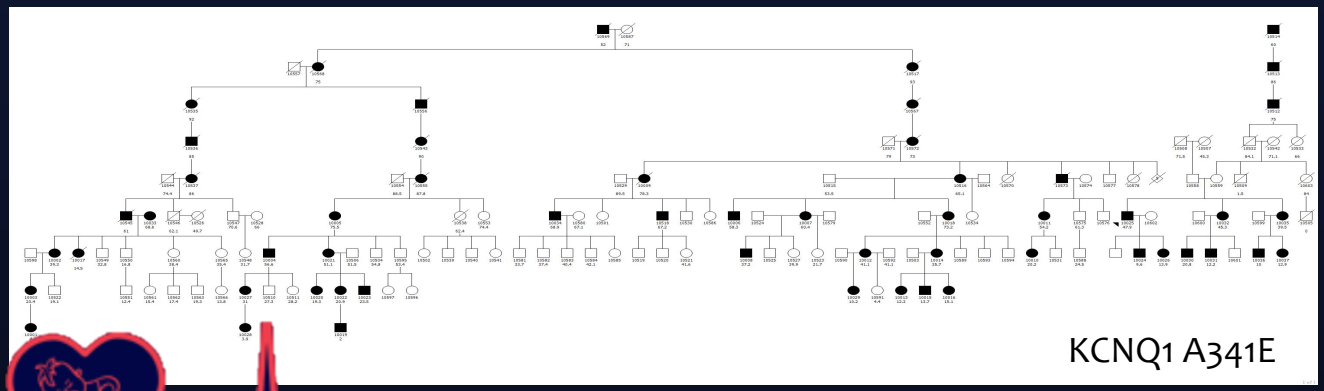
Inherited Arrhythmia Syndromes: How To Manage Affected Family Members

Susan P. Etheridge, MD
University of Utah



PedIRhYtHm

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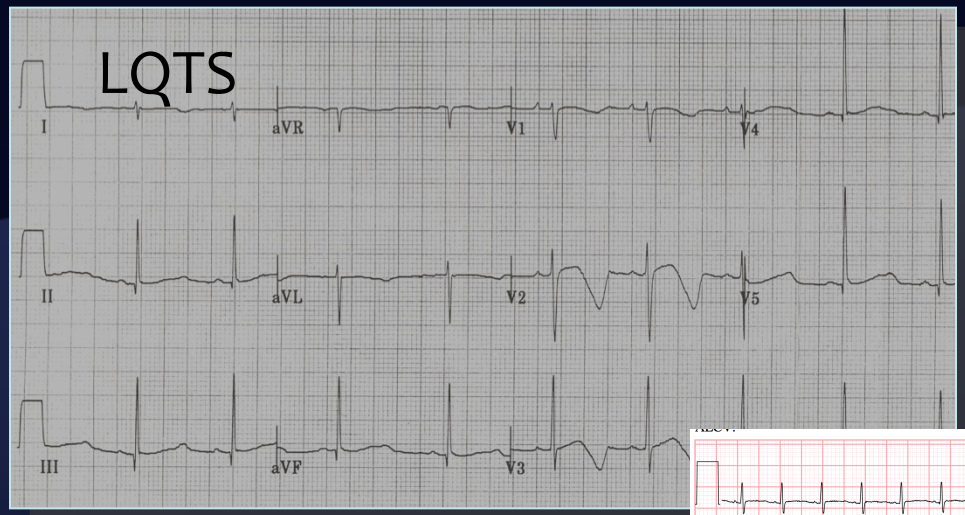
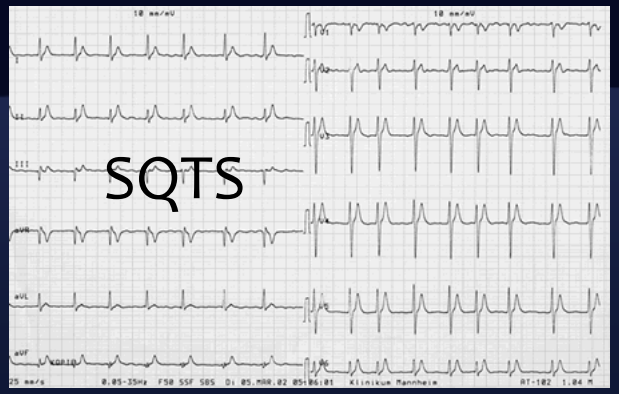
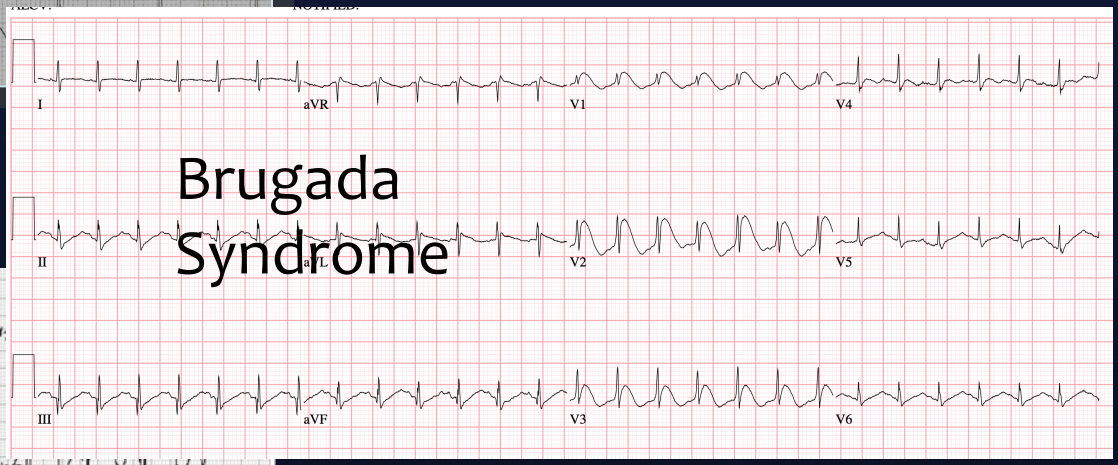
Goals

- Identify proband (index case) ✅
- Cascade screening family ✅
- Managing affected family members


LQTS
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3


SQTS


Brugada
Syndrome
I
aVR
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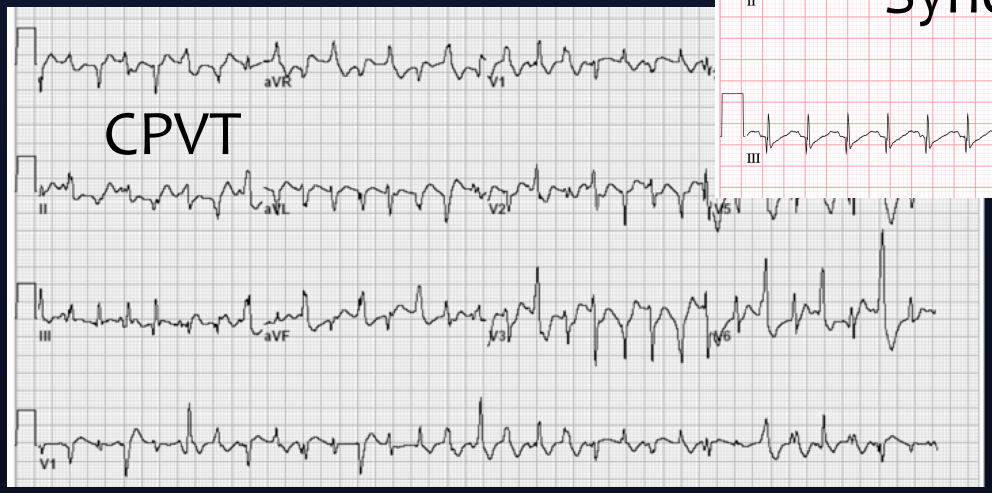
V5
III
aVF
V3
V6


CPVT
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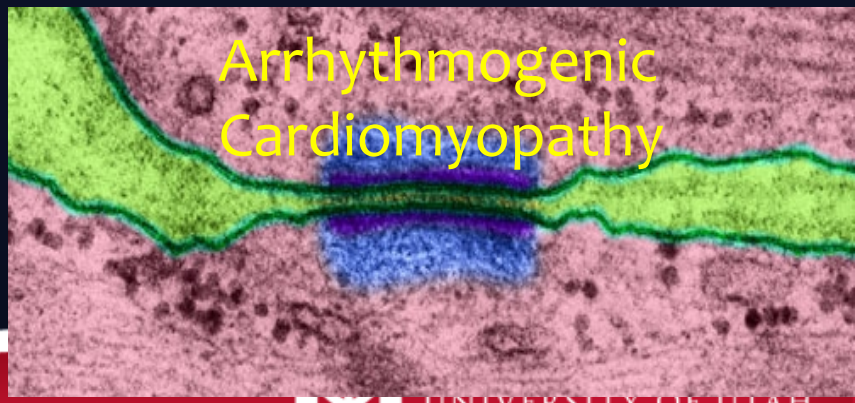
V1

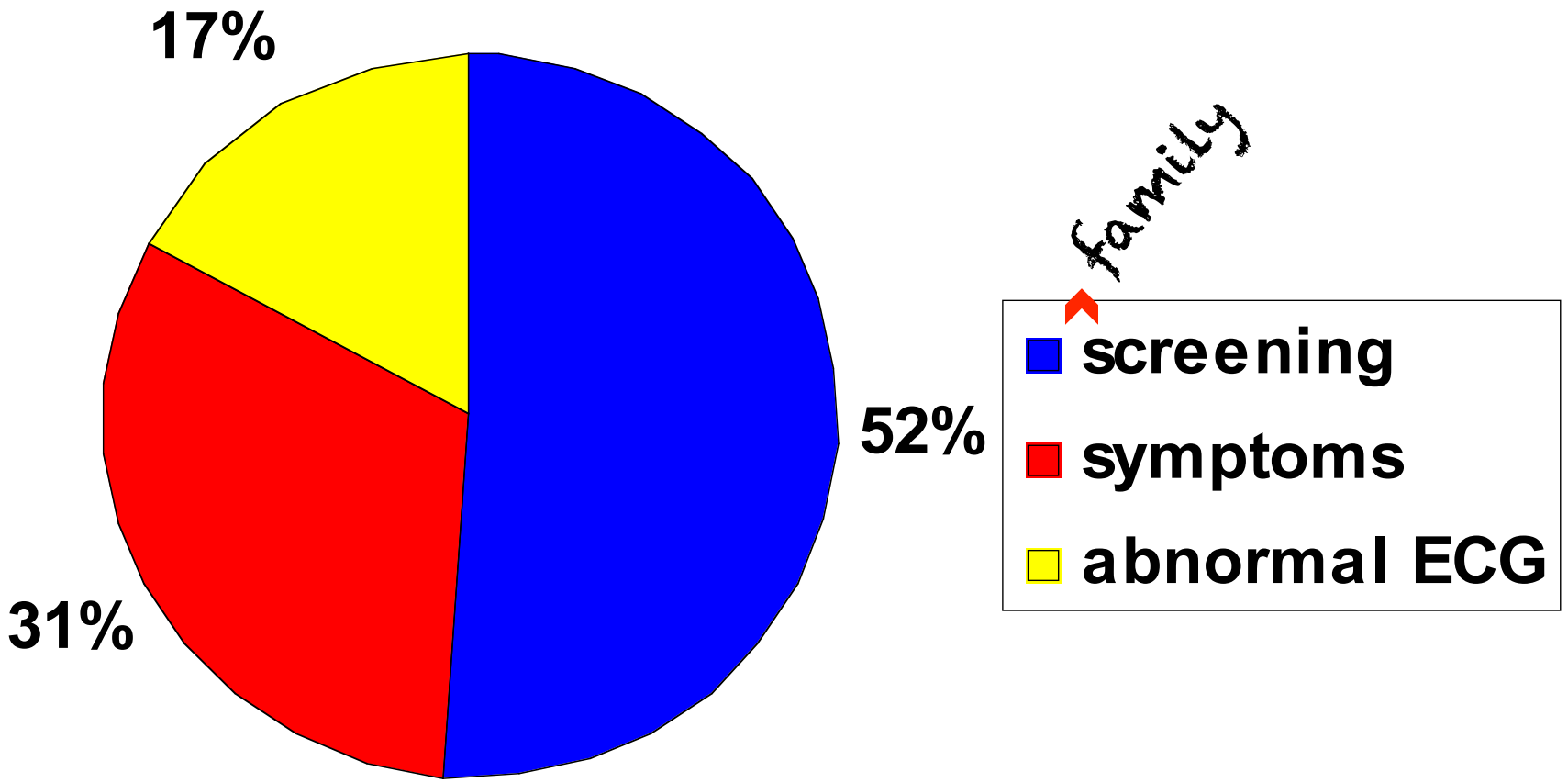

Arrhythmogenic
Cardiomyopathy

KCNQ1 V254

Inherited Arrhythmia Syndrome Characteristics

- Autosomal dominant inheritance
- More affected family members than probands
- Incomplete penetrance and variable expressivity
- Spectrum of phenotypes
  - Lifelong asymptomatic state to sudden death in infancy
- Clinical course affected by age, sex, genotype, environmental factors, therapy or modifier genes

LQTS Patient Identification



Etheridge JACC 2007

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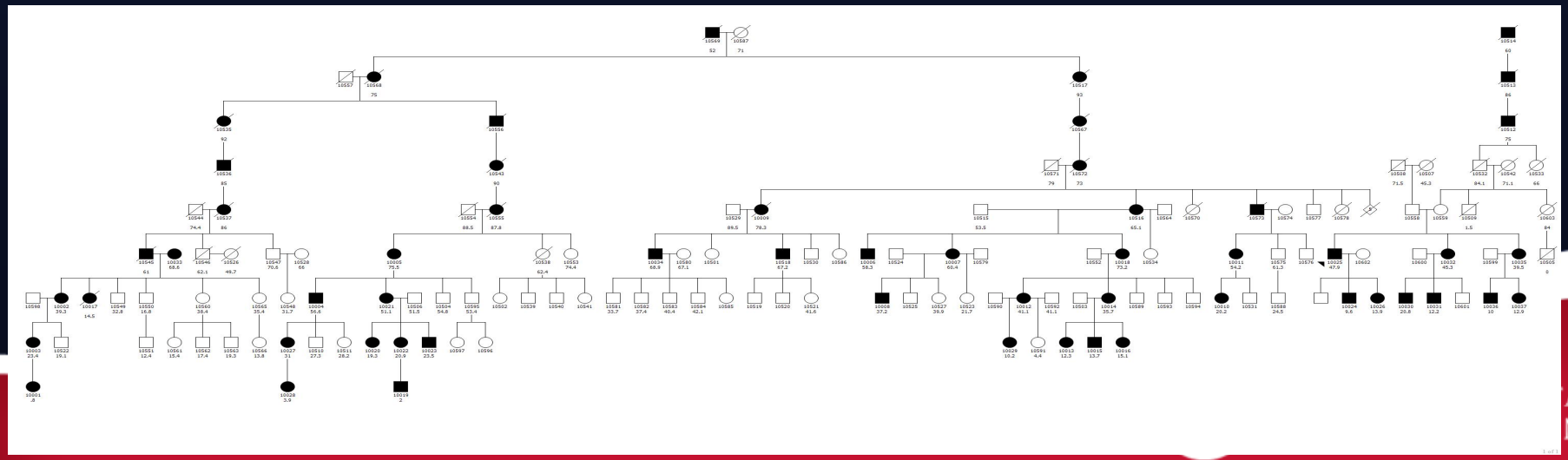
Serious diseases of syncope and sudden death

Minimally symptomatic and asymptomatic affected family members of probands

- Genetic data routine part of identifying affected family members
- Must not forget about the phenotype
- Meticulous interrogation of each patient and each event
- Every "spell" should be assessed as to likelihood of being disease-related event
- Testing varies based on disease

LQTS

- Channelopathy about which we have most proband and nonproband data
- Screening will identify family members before symptoms
- Can prevent sudden death



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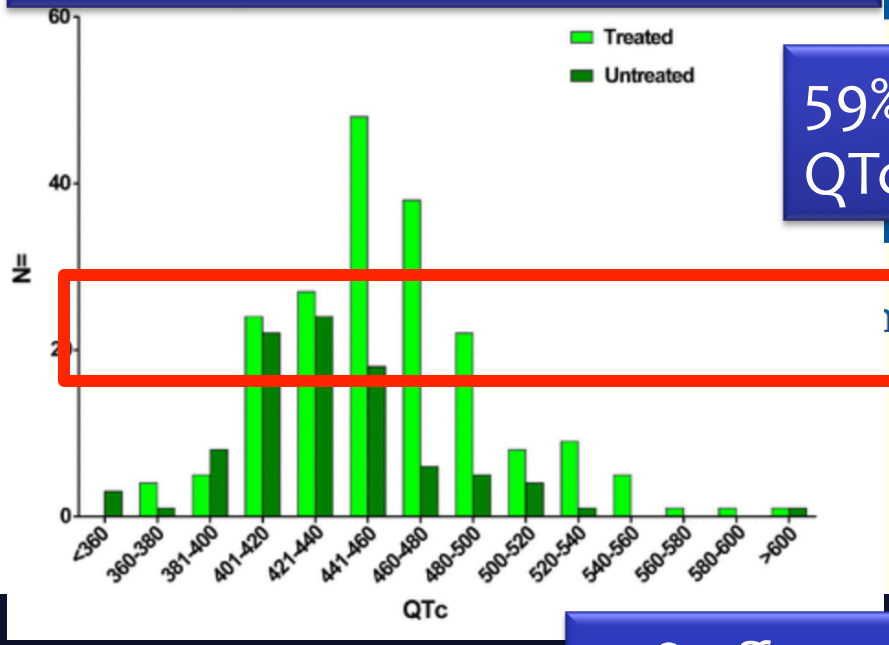
doi:10.1016/j.jacc.2009.12.063

QTc longer in treated patients



59% of treated patients
QTc < 460 ms

ıla Syndromes

nent?

PHD,† Marielle Alders, PHD,*
M. Wilde, MD, PHD†

308 affected family members of probands

- 65% treated
- Treatment based on
  - Symptoms
  - QTc
  - Family history

Mutation-Specific Recommendations

All affected patients

- Avoid circumstances that reduce K+ levels (diarrhea, vomiting)
- Medications to avoid (www.qtdrugs.org)

Hofman JACC 2010

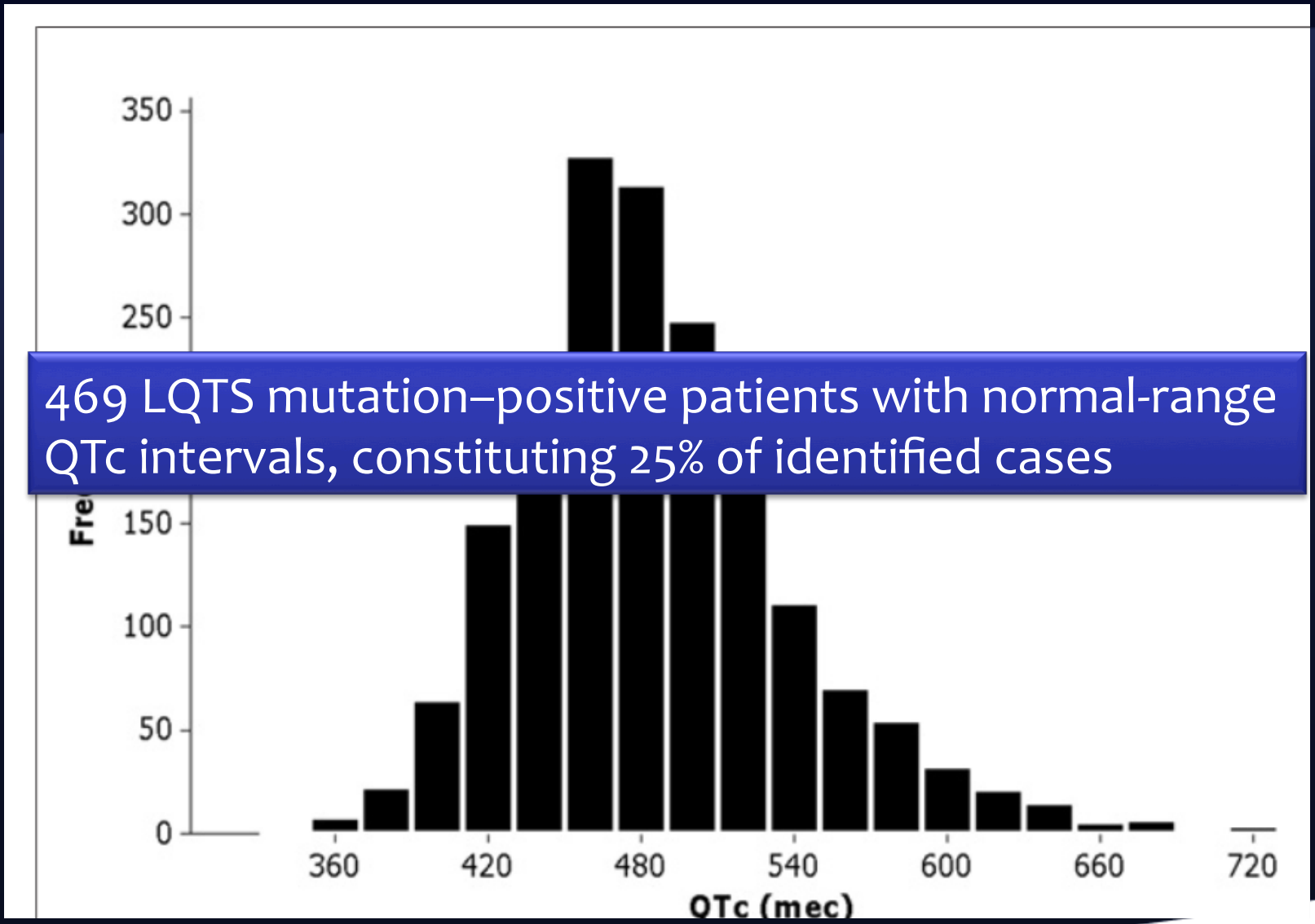
Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

JACC 2012

Ilan Goldenberg, MD,* Samuel Horr, MA,* Arthur J. Moss, MD,* Coeli M. Lopes, PHD,†
Alon Barsheshet, MD,* Scott McNitt, MS,* Wojciech Zareba, MD, PHD,* Mark L. Andrews, BBA,*
Jennifer L. Robinson, MS,* Emanuela H. Locati, MD,§ Michael J. Ackerman, MD, PHD,¶
Jesaia Benhorin, MD,‖ Elizabeth S. Kaufman, MD,# Carlo Napolitano, MD,**††
Pyotr G. Platonov, MD, PHD,§§ Silvia G. Priori, MD, PHD,**†† Ming Qi, MD,‡
Peter J. Schwartz, MD,‡‡ Wataru Shimizu, MD, PHD,‖‖ Jeffrey A. Towbin, MD,¶¶
G. Michael Vincent, MD,*** Arthur A. M. Wilde, MD, PHD,## Li Zhang, MD***

Rochester and New York, New York; Milan and Pavia, Italy; Tel Aviv, Israel; Rochester, Minnesota; Cleveland, Ohio; Lund, Sweden; Suita, Japan; Houston, Texas; Amsterdam, the Netherlands; and Salt Lake City, Utah

- Compare clinical courses of patients:
  - LQTS and normal QTc intervals to
  - LQTS and prolonged QTc intervals and
  - Genotype-negative unaffected family members
- Identify specific clinical and genetic risk factors for life-threatening cardiac events

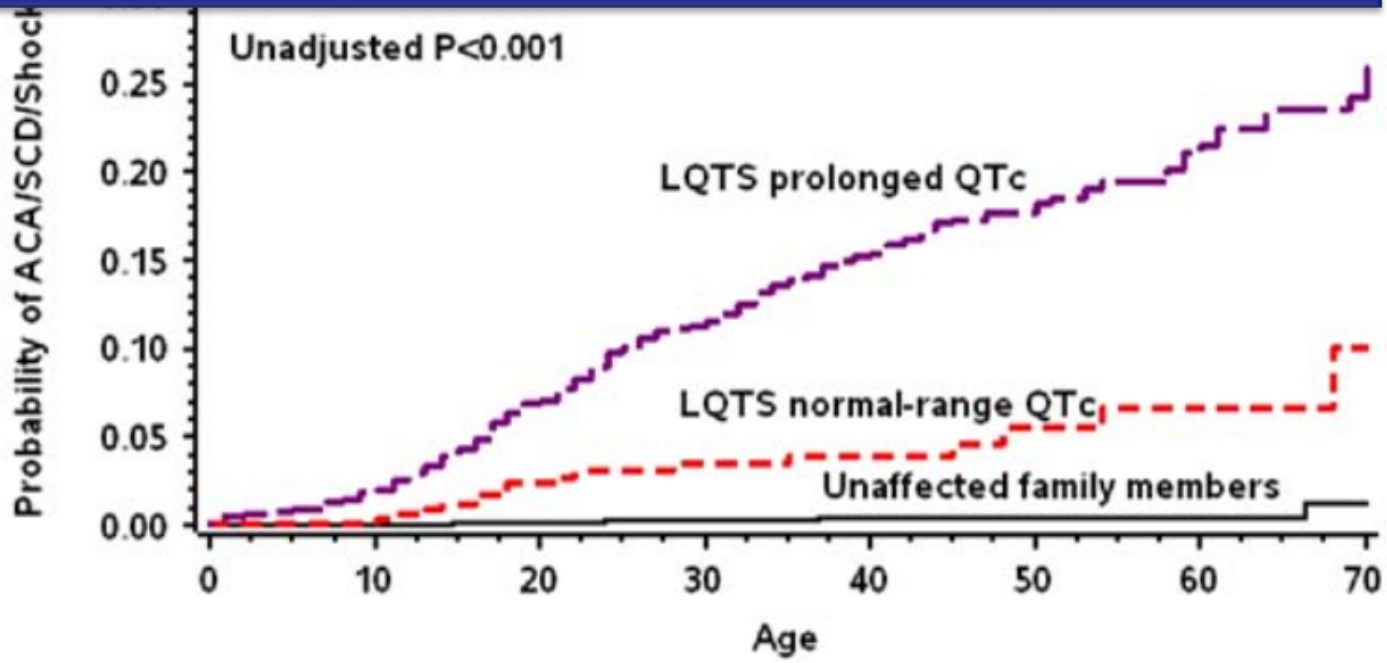


469 LQTS mutation–positive patients with normal-range QTc intervals, constituting 25% of identified cases

Wide QTc interval distribution 350 ms - 800 ms (mean 450 ms)

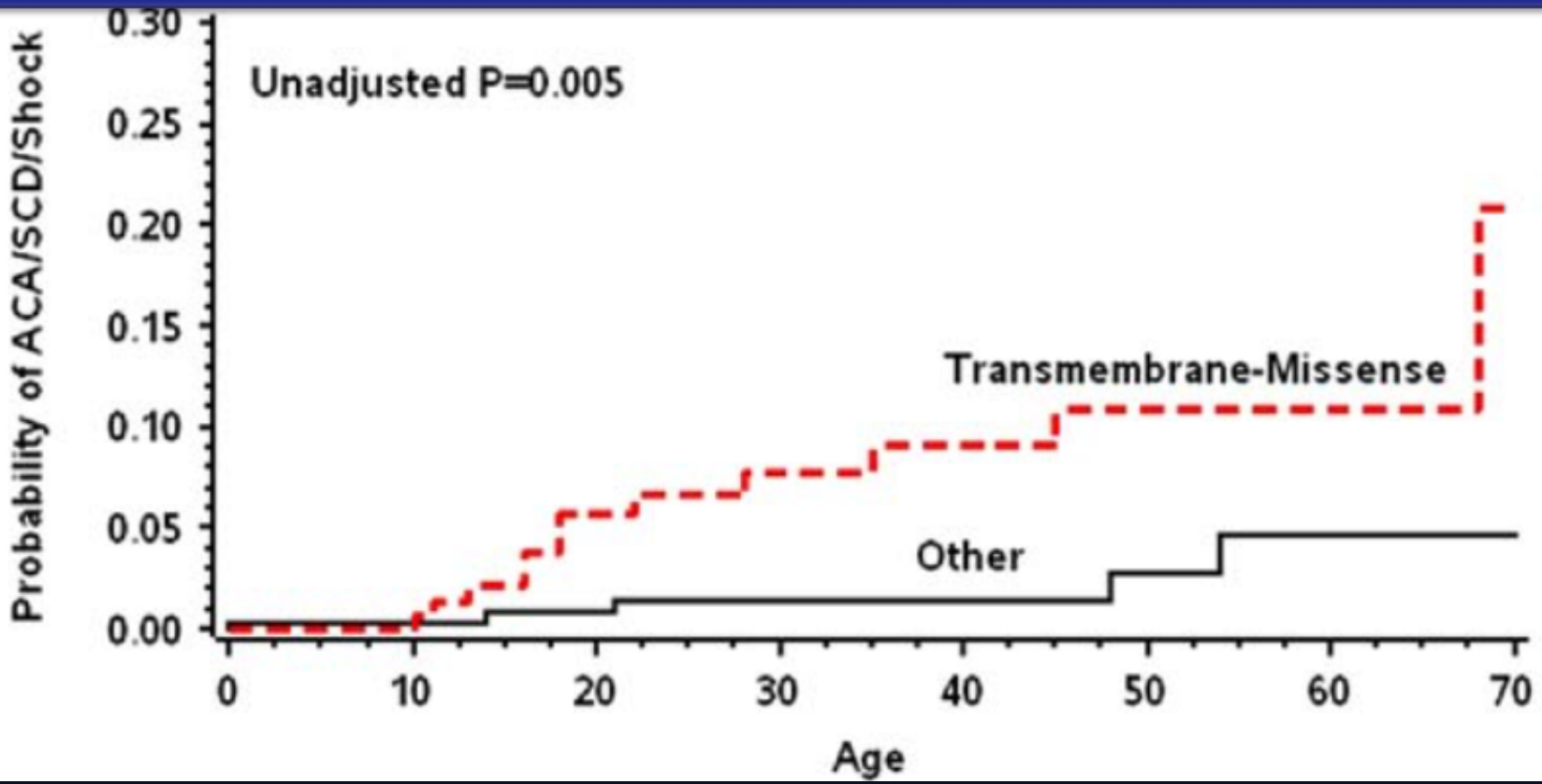
Gene (+) Normal QT Event Rate 4% (birth-40 y)

But 10 times higher than unaffected family members



Patients at Risk					
Gen-/Phen-	1525	1377 (0)	728 (0)	348 (0)	92 (0.01)
Gen+/Phen-	469	406 (0)	236 (0.04)	97 (0.06)	20 (0.10)
Gen+/Phen+	1392	1235 (0.02)	729 (0.11)	334 (0.18)	94 (0.24)

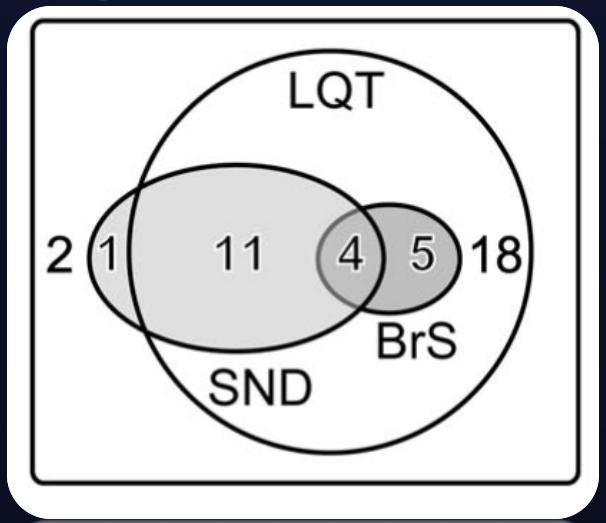
Transmembrane – missense mutations > 6 fold increased risk in normal QT patients



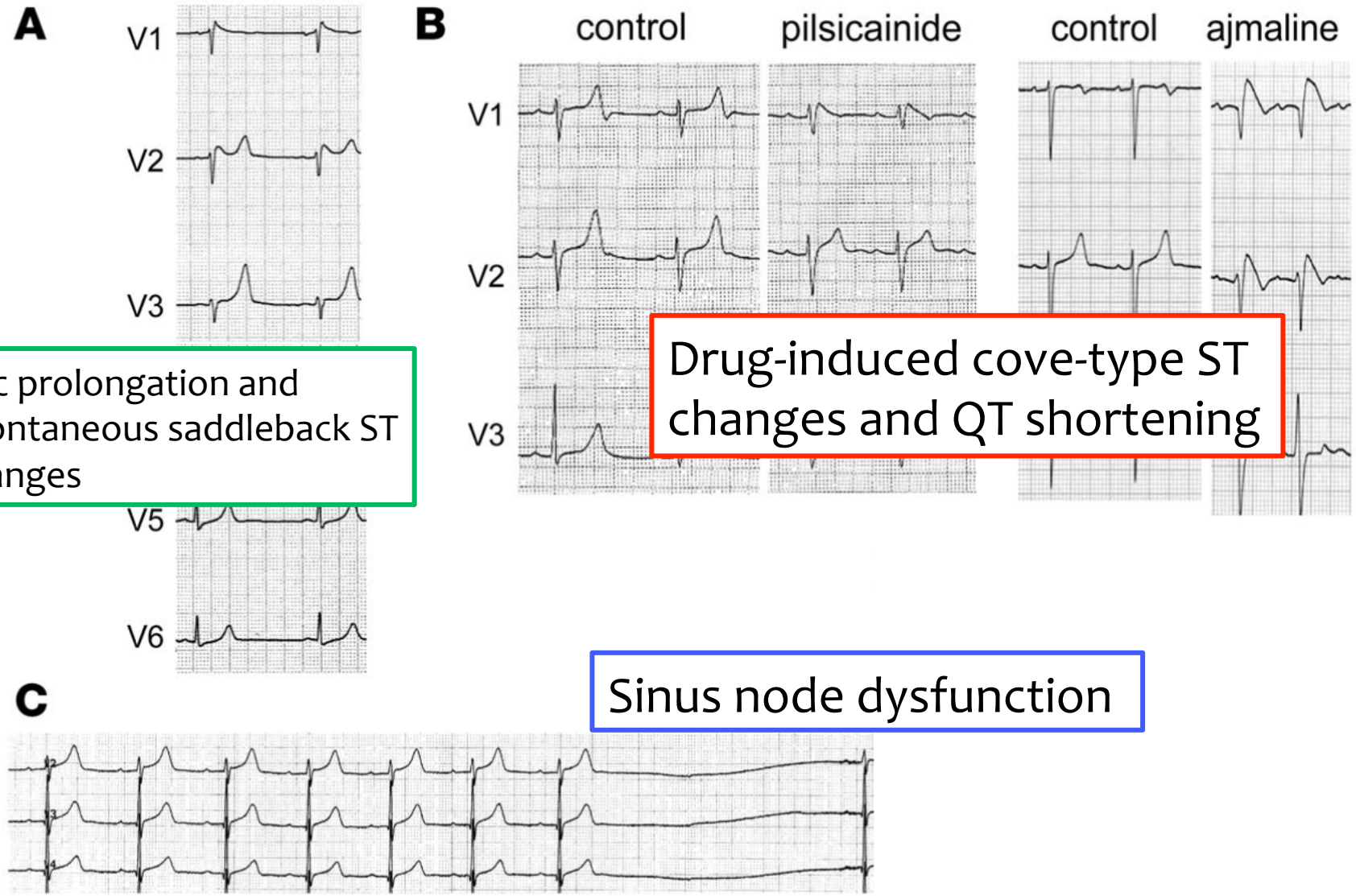
Transmembrane region responsible for forming the ion channel

Phenotype Variability SCN5A Mutations

- Overlapping features
  - LQT3, Brugada syndrome, sick sinus syndrome, cardiomyopathy and cardiac conduction disease
- Biophysical properties of mutant channel



Makita J Clin Invest 2008



QTc prolongation and spontaneous saddleback ST changes

Drug-induced cove-type ST changes and QT shortening

Sinus node dysfunction

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis

Class I Recommendations

The following **lifestyle changes are recommended in all**

Beta-Blocker treatment should be initiated in all patients including asymptomatic because

- 10% to 12% of LQTS the 1st clinical manifestation is sudden death

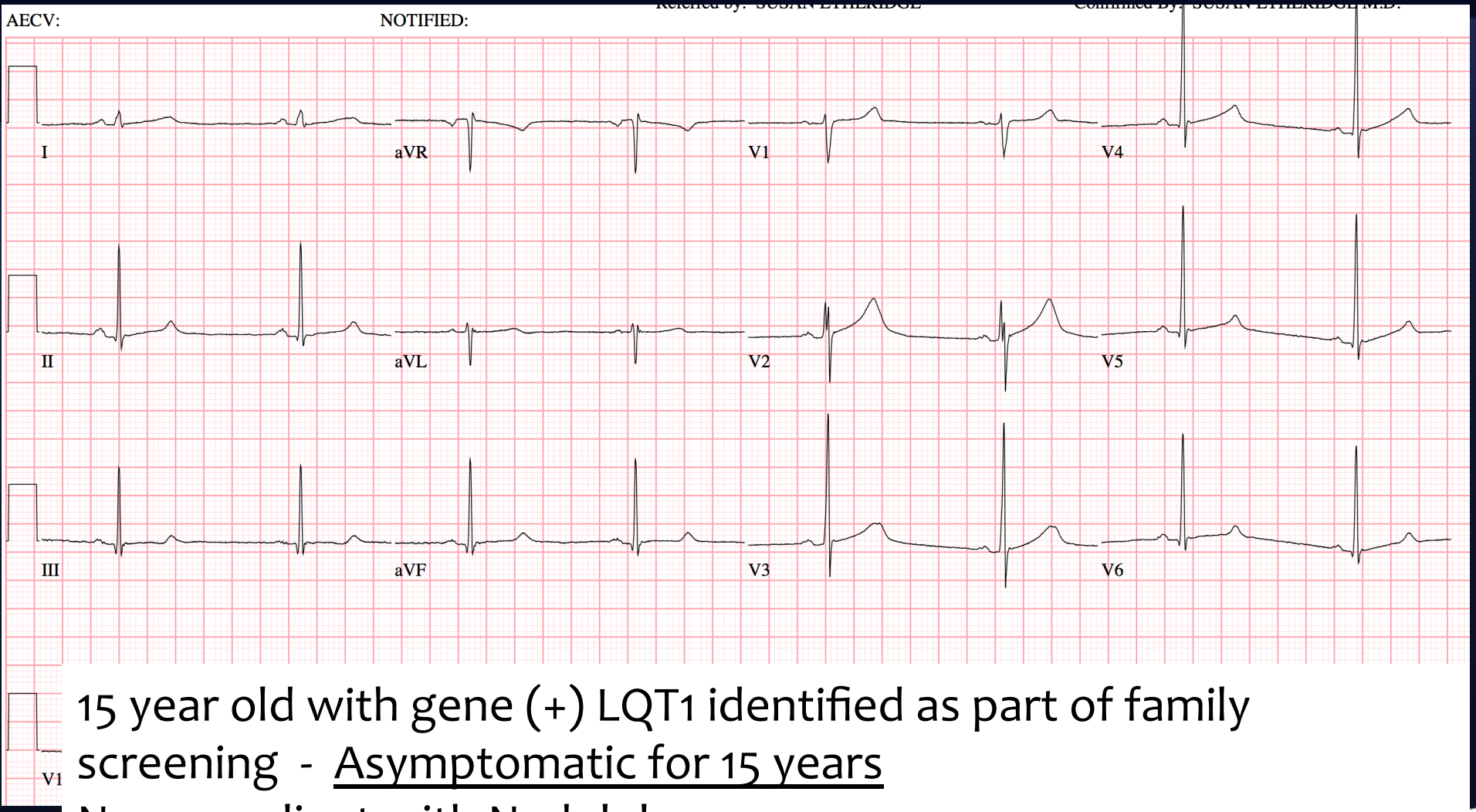
Reasonable exceptions

- LQT1 men >40 yr, they seldom have a 1st event after this age
- Individuals aged >50 yrs with a QTc <480 ms

LQT2 women remain at risk throughout life, and it is wise to always treat them, with few exceptions

Schwartz Circ A/E 2012

Beta-blockers can be useful EVEN in patients who are asymptomatic with QTc < 470ms



15 year old with gene (+) LQT1 identified as part of family screening - <u>Asymptomatic for 15 years</u>

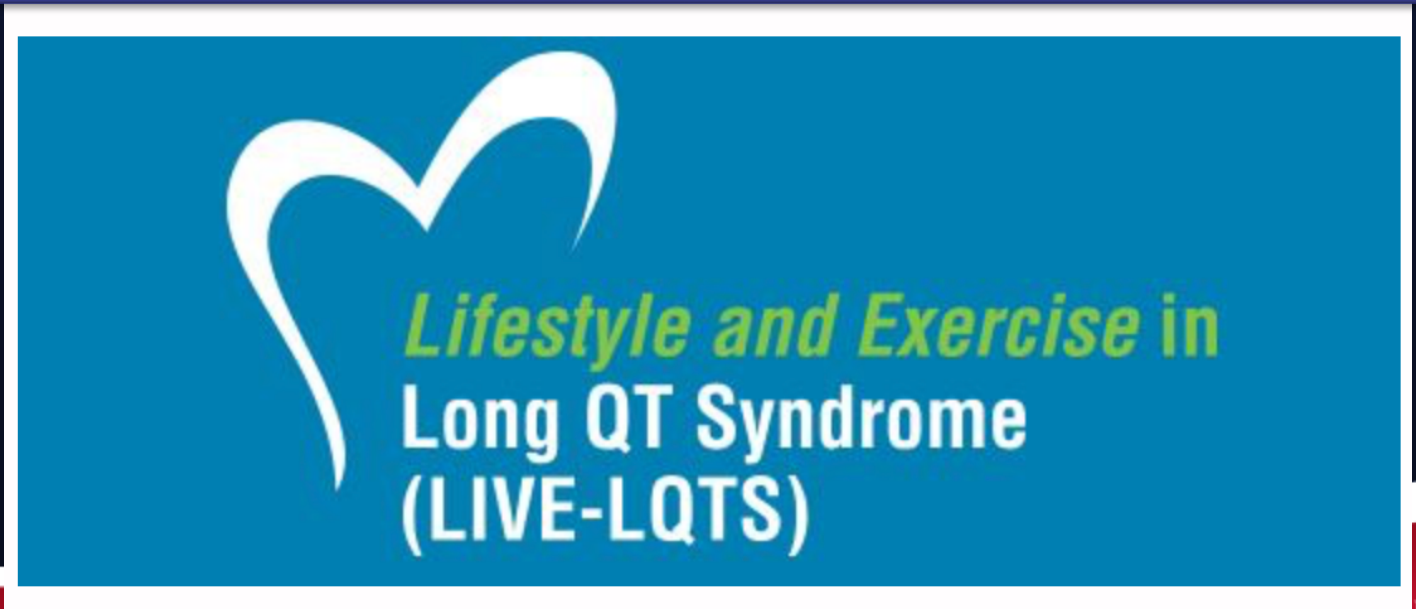
Noncompliant with Nadolol

Near-drowning event after jumping off a bridge into a cold river

VF upon arrival of EMS

Lifestyle Modifications

- 2 events in 1 noncompliant LQT1 boy
- 650 athlete-years follow-up in 60 appropriately counseled and treated LQTS patients
- 12±7 years; QTc 501±46 ms
- Patient/familial autonomy and self-determination after detailed clinical assessment and counseling

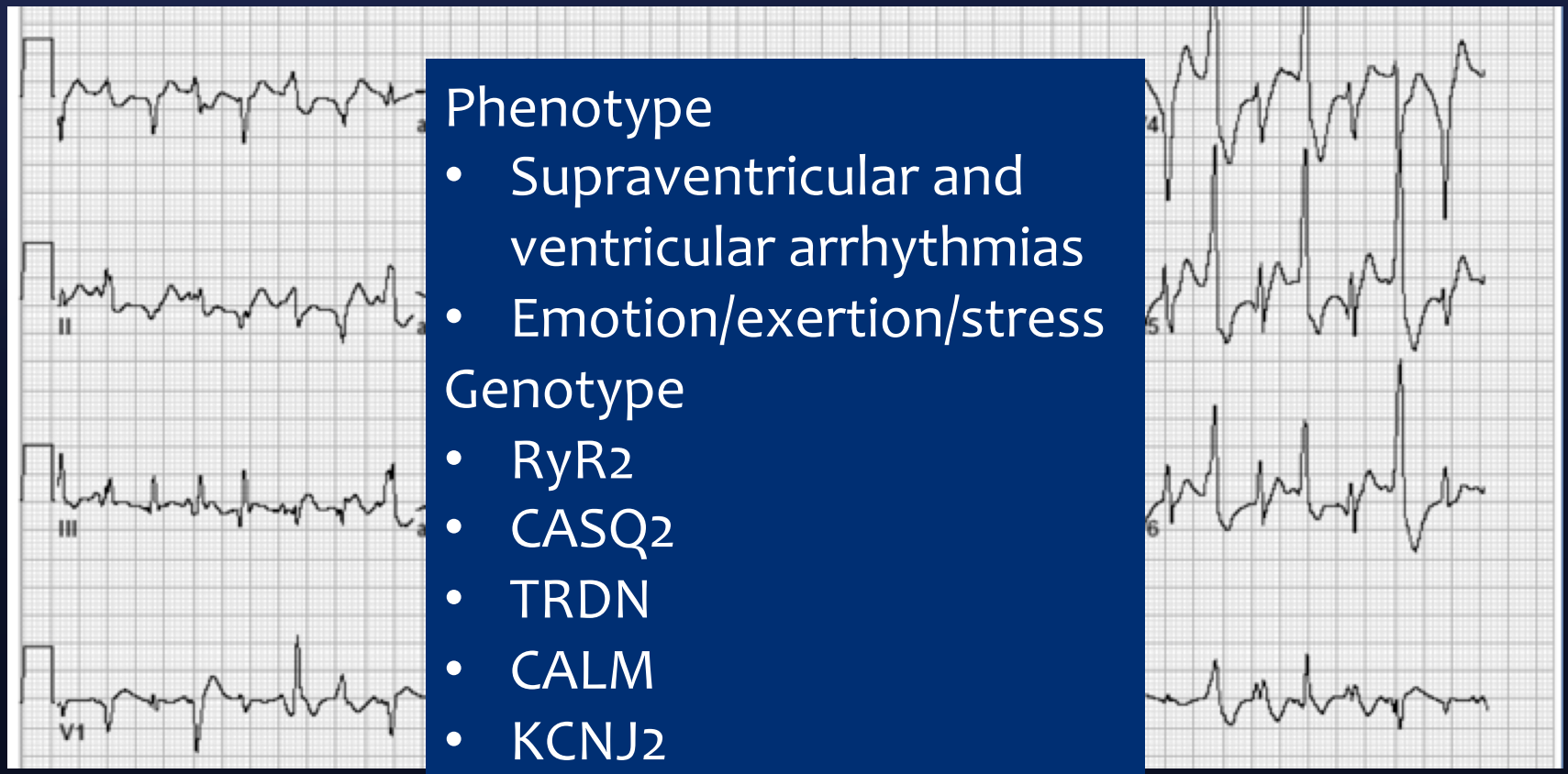


Johnson *Br J Sports Med* 2013

LQTS: Management of Affected Family Members

- Children with LQTS should be treated unless compelling reason not to
  - Beta-blockers (nadolol/propranolol)
- Consideration of mutation location and function
  - Age of therapy initiation may vary - although easier to start beta-blockers in a child
- QTc intervals can vary over time
- QTc intervals can be hard to measure
- Children have yet to prove survivorship
- Lifestyle modifications and follow-up

Catecholaminergic Polymorphic VT



Phenotype

- Supraventricular and ventricular arrhythmias
- Emotion/exertion/stress

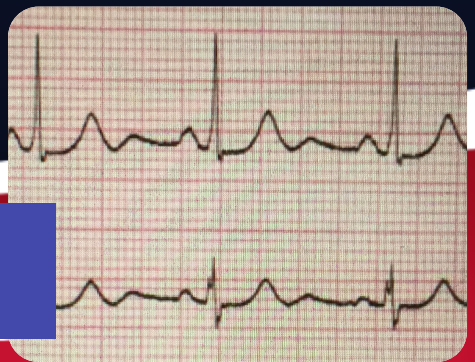
Genotype

- RyR2
- CASQ2
- TRDN
- CALM
- KCNJ2
- TERCL

CPVT

- Important cause of juvenile sudden death
- 30% lethal arrhythmia as 1st symptom
- Effective treatment available
- Highly penetrant
- Hard to identify with clinical screening
  - Normal ECG, echo
  - Treadmill with atrial and ventricular arrhythmias (BiVT, polymorphic VT, VF)
- Genetic screening important

BB and flecainide are effective as long as patients take them



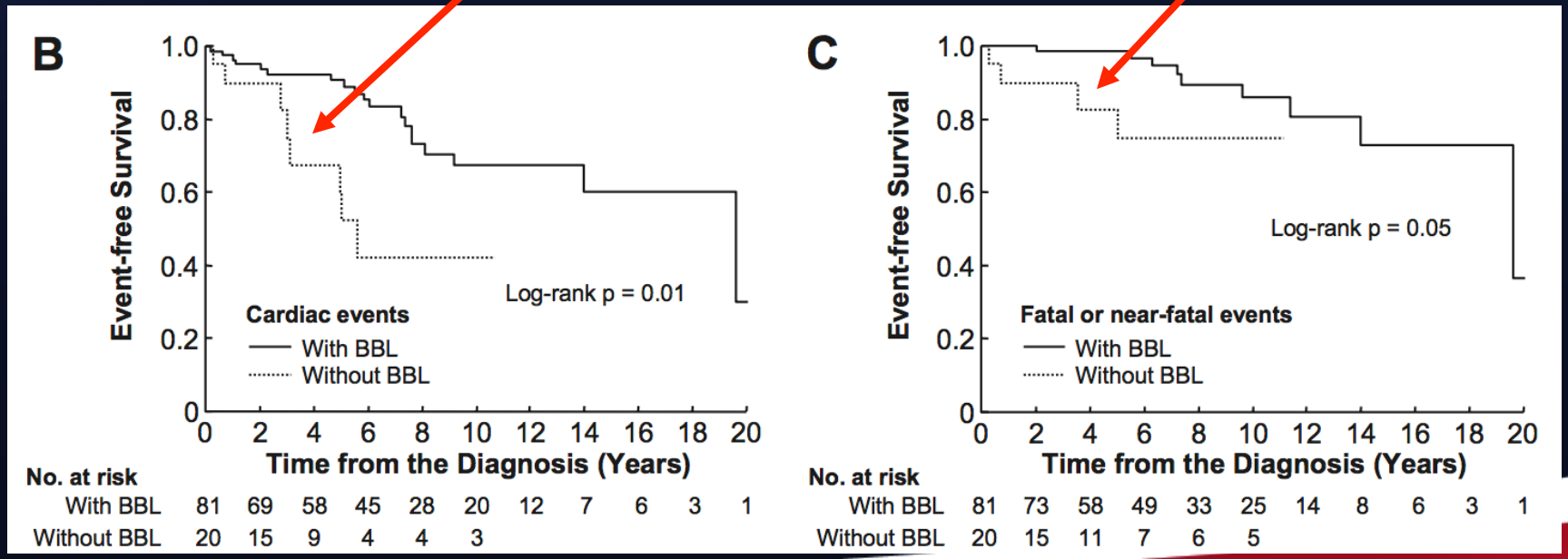
Sometimes U wave
Rest and after exercise

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

101 patients

- Risk: young age and no beta-blockers
- Follow-up of 7.9 yrs
- Cardiac events in 27 patients, including 2

Fine at birth then a precipitous decline in event-free survival



Hayashi Circ 2009

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Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

Meiso Hayashi, MD; Isabelle Denjoy, MD; Fabrice Extramiana, MD, PhD; Alice Maltret, MD; Nathalie Roux Buisson, MD; Jean-Marc Lupoglazoff, MD, PhD; Didier Klug, MD; Miyuki Hayashi, MD; Seiji Takatsuki, MD; Elisabeth Villain, MD; Joël Kamblock, MD; Anne Messali, MD; Pascale Guicheney, PhD; Joël Lunardi, MD, PhD; Antoine Leenhardt, MD

Cardiac events occurred in silent genetic mutation carriers with normal exercise stress tests

Importance of family screening including genetic testing

Genetically positive family members should receive beta-blockers even after a negative exercise test

Hayashi Circ 2009

Familial Evaluation in Catecholaminergic

Optimally treated relatives carrying a mutation have low risk of fatal events

Underscores the importance of treating all mutation carriers until risk stratification tools are available

Chri MSc;

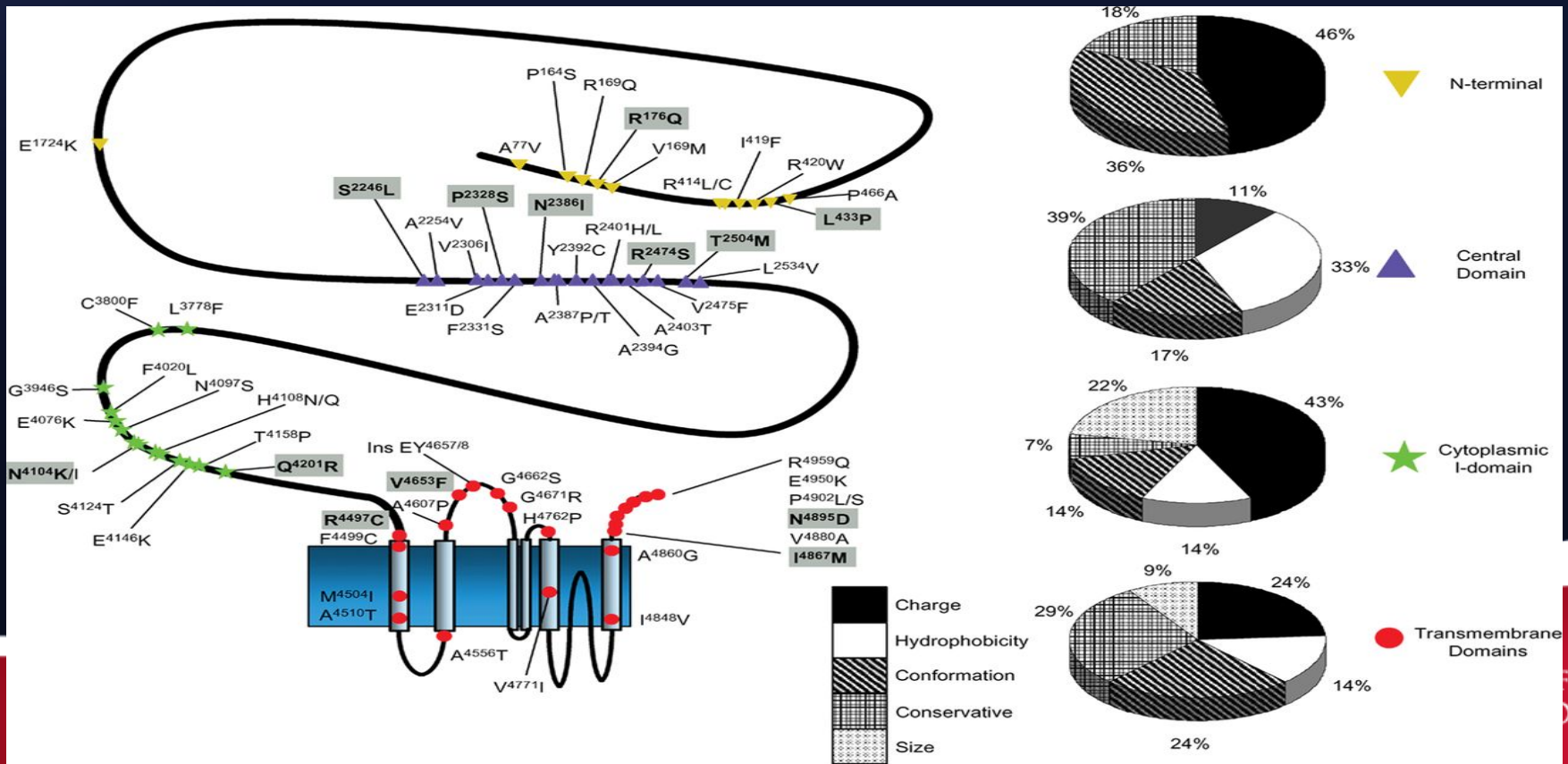
Zahurul A. Bhuiyan, MD, PhD; Maarten P. van den Berg, MD, PhD; Arthur A.M. Wilde, MD, PhD

Circ A/E 2012

- RyR2 mutation (+) cohort
  - 24 probands (6 deceased)
  - 116 relatives (15 families) identified by screening
- 50% family - CPVT phenotype increased to 63% with follow-up (on therapy)

Affected Family in CPVT

- Possibly increased VT in relatives carrying <u>C-terminal</u> compared with N-terminal and central mutations



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

Class I Recommendations

Beta-blockers **recommended** in all with clinical CPVT based on spontaneous or stress-induced ventricular arrhythmias

Class IIa Recommendations

Beta-blockers **should be considered** in gene (+) family members even if negative exercise test

ESC 2015 guidelines (Priori 2015 Eur H J)

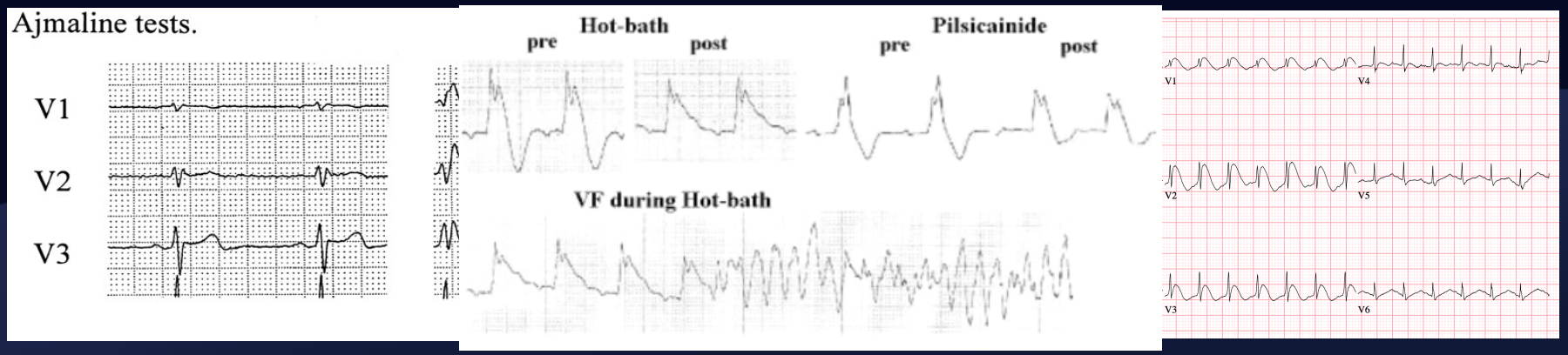
Class I

Beta-blockers are recommended in all patients with a clinical diagnosis of CPVT, based on presence of documented spontaneous or stress-induced ventricular arrhythmias

CPVT: Management of Affected Family members

- Beta-blockers for all affected
  - Even when exercise test (-)
  - Nadolol - monitor efficacy with exercise testing
- Add flecainide early
- Regular re-evaluation
- Gene (-) proband - clinical evaluation should be undertaken in 1st degree relatives (Holter, exercise test)

Brugada Syndrome

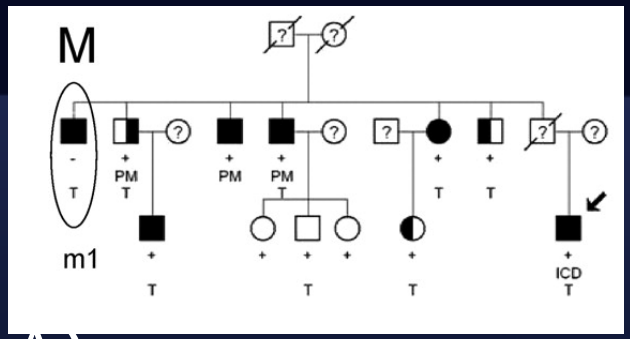


  - ECG pattern and arrhythmia may be provoked by drugs or heat
- ECG findings mimic other diseases
- > 1/3 cases now identified by family screening

Since the first reporting, the reported annual rate of events has decreased.[70,72–78] The change probably reflects the inherent bias during the first years following the description of a novel disease, in which particularly severe forms of the disease are most likely to be diagnosed.

Gourrard Front CV Med 2015, Juang. J of Arrhythmias 2016

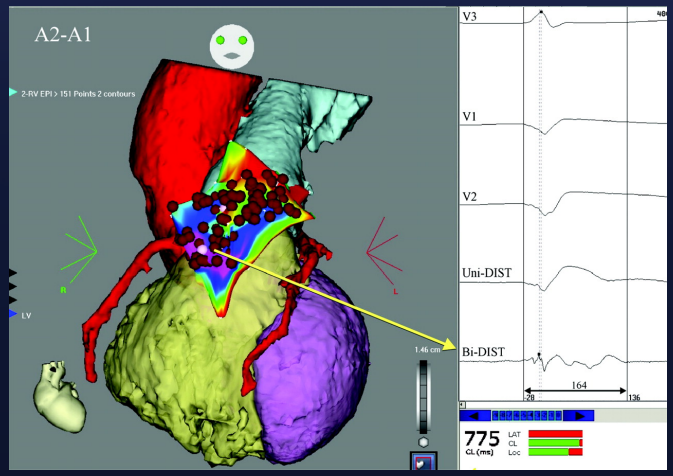
BrS is Difficult



- Difficult genetics
  - Numerous gene types (20-25% SCN5A)
    - Mutations effect Na^+, K^+ and Ca^{2+} current
  - 65-70% genetically elusive
  - Variable penetrance (lower than LQTS/CPVT) and expressivity
  - Variable phenotype associated with same mutation
  - Age (mean age 45 y) and sex variability (males 3-4x)
  - ? Mono vs oligogenic disease
  - Possibly a disease of RVOT

Probst Circ CV Genet 2009

BrS is Difficult



- Treatment is difficult
  - ICD/quinidine
  - ablation RVOT epicardium
- Risk stratification is difficult
  - Symptoms and spontaneous ECG pattern
  - Uncertain contribution of genetics to risk

Unresolved Questions in BrS

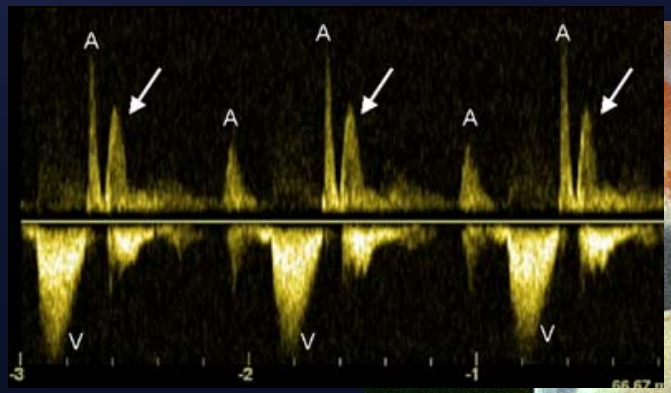
- Complete genetic architecture
- Role of polymorphisms/gene modifiers
- Role of environmental modifiers
- How to apply genetics as a diagnostic tool

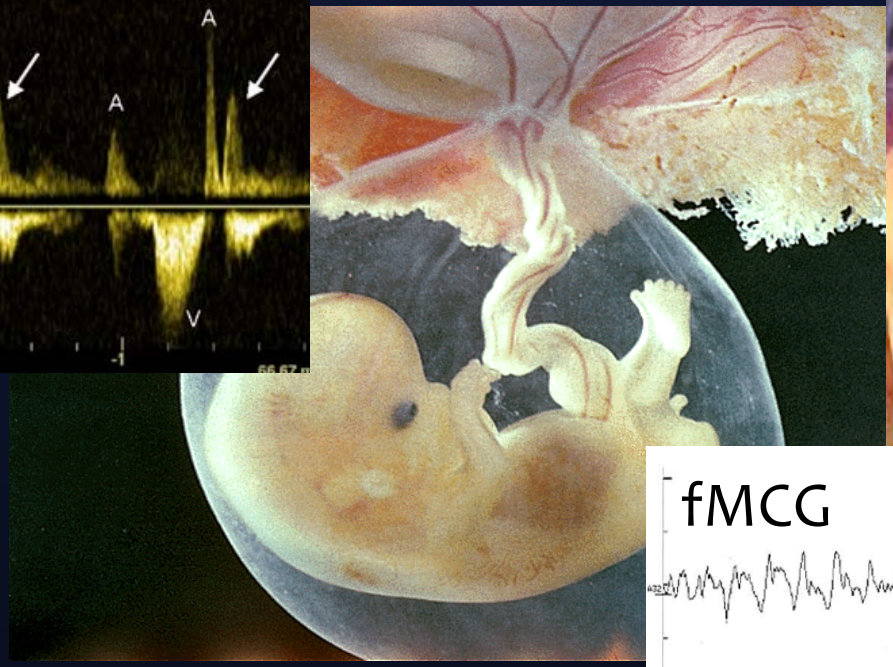
BrS: Managing Affected Family Members

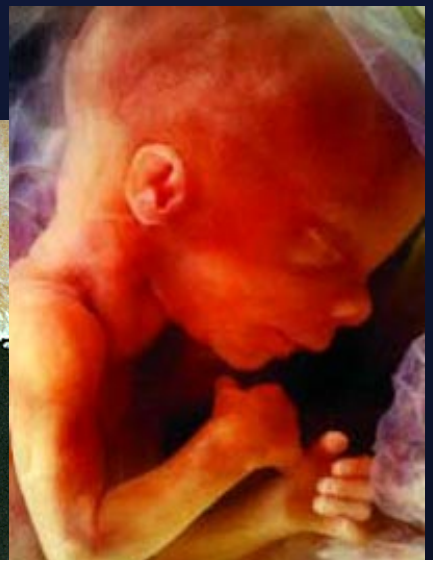
- Making diagnosis
- In proven disease
  - Lifestyle modifications/drug restrictions in asymptomatic
  - Symptoms, spontaneous BrS ECG- all we really have is an ICD
- Aggressive fever control/monitoring during fever (ECG with fever)
- Follow-up

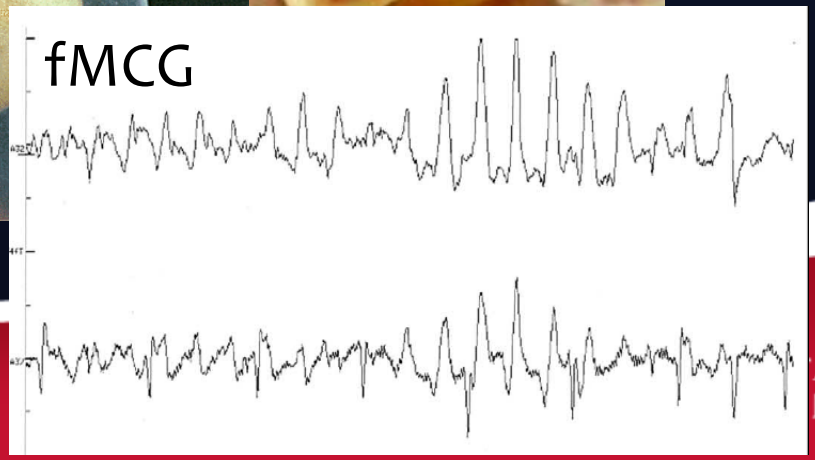
The Fetus is part of the family

- Fetal loss, bradycardia (sinus and AVB) and ventricular arrhythmias





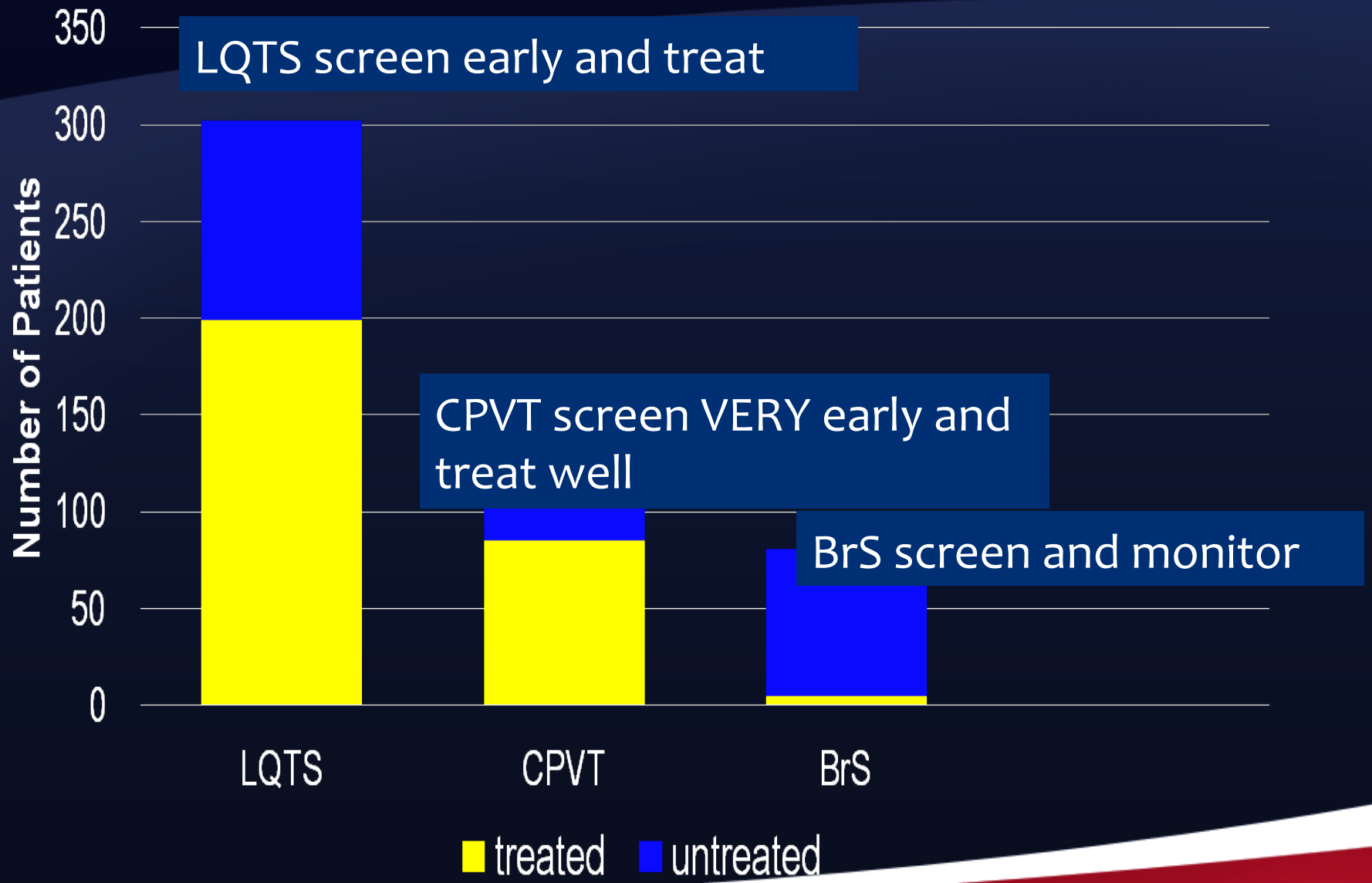




Just w… to not cons… Mosaic

- Mutati…m cell or very early in…
- May pla…an diseases includin…
- Mutatic… commercial testing…
- Risk of …n

Rogue DNA in Parents Can Lead to Genetic Disease in Their Children



Hofman JACC 2010

Conclusions

- Managing the affected family members has become a large part of our practice
- Management depends on disease, phenotype
- Presymptomatic treatment in most LQTS and CPVT and monitoring in BrS
- Lifestyle modifications in all
- Ongoing follow-up in all
- Aim of preventing serious arrhythmias and sudden cardiac death in all