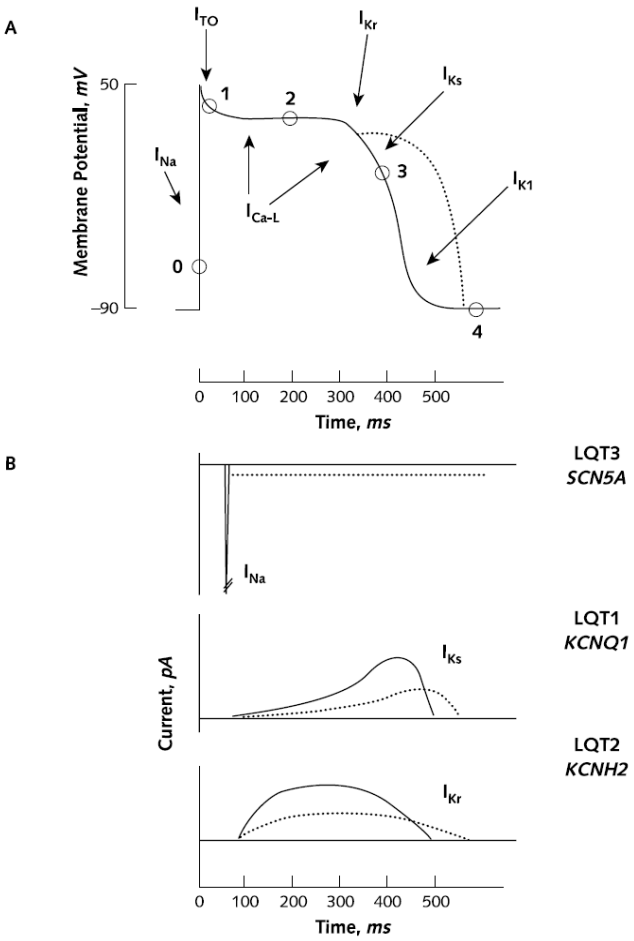
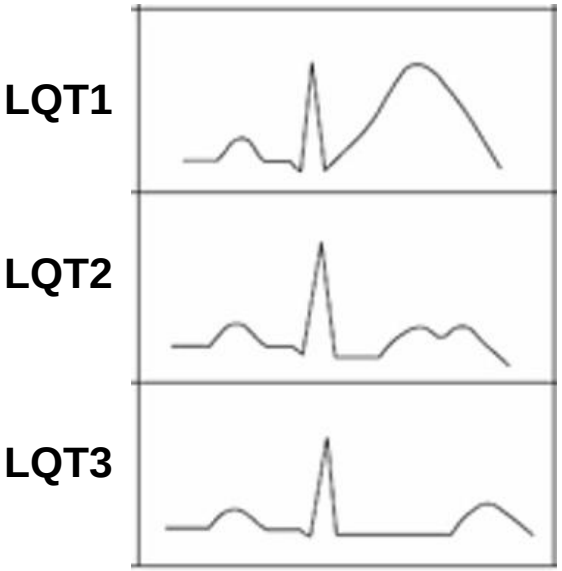
SEVERANCE

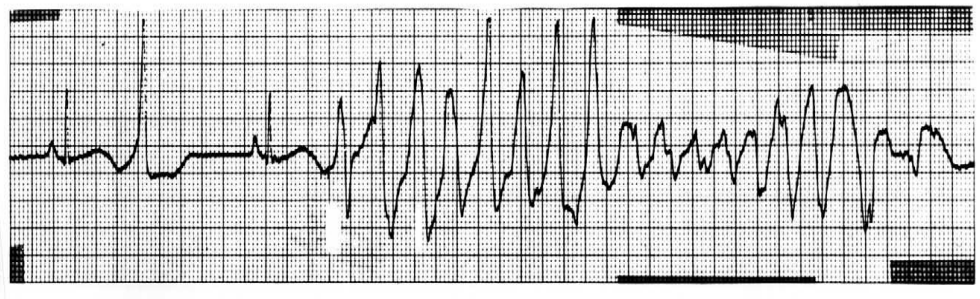
Asymptomatic QT prolongation: Needs Gene Study?

Boyoung Joung, MD, PhD
Professor
Director of Electrophysiology Laboratory
Division of Cardiology, Department of Internal Medicine
Severance Cardiovascular Hospital
Yonsei University College of Medicine

Long QT syndrome (LQTS)
Prolonged QT, abnormal T waves, Tdp



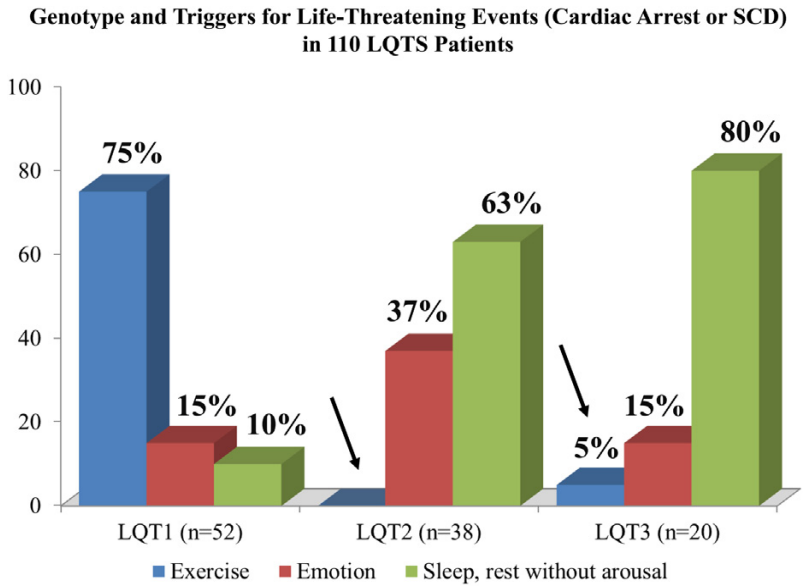




Key Genes in LQTS

- **Mutations in 13 gens associated with LQTS.**
- **Pathogenic mutations identified in 75% of cases.**
- **Three main genes account for 90% of genotyped cases.**

Gene	Locus	Protein	Frequency
KCNQ1 (LQT1)	11p15.5	I_{ks} potassium channel alpha subunit (Kv7.1)	30-35%
KCNH2 (LQT2)	7q35-q36	I_{kr} potassium channel alpha subunit (Kv11.1)	25-40%
SCN5A (LQT3)	3q21	Cardiac sodium channel alpha subunit (NaV1.5)	5-10%



Ackerman MJ, e t al. Europace 2011

Long QT syndrome: Diagnosis

Diagnosis of Long QT Syndrome (in the absence of secondary causes for QT prolongation)

Recommendations	Class	Level
LQTS is diagnosed with either – QTc ≥480 ms in repeated 12-lead ECGs or – LQTS risk score > 3	I	C
LQTS is diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration.	I	C
ECG diagnosis of LQTS should be considered in the presence of a QTc ≥460 ms in repeated 12-lead ECGs in patients with an unexplained syncopal episode in the absence of secondary causes for QT prolongation.	IIa	C

2015 Guidelines management of VA and Prevention of SCD

Asymptomatic patients

- **Every patient is asymptomatic… until he/she experience the first event (which may be a cardiac arrest!)**

- **Risk stratification should be performed based on the QT interval duration, family history, life-style**

Risk stratification in asymptomatic Pts

- **The risk of life-threatening arrhythmic events should be assessed in all asymptomatic patients.**
- **Life style adjustments are the first message to be conveyed to the patient**
- **Decision of required therapy should be made with the patient discussing the individual risk profile.**

LQTS: Lifestyle modifications for all patients (class I): May they be the only approach in “asymptomatic LQT”?

- **Avoidance of QT prolonging drugs:**
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- **Correction of electrolyte abnormalities:**

- **Avoidance of genotype-specific triggers for arrhythmia:**

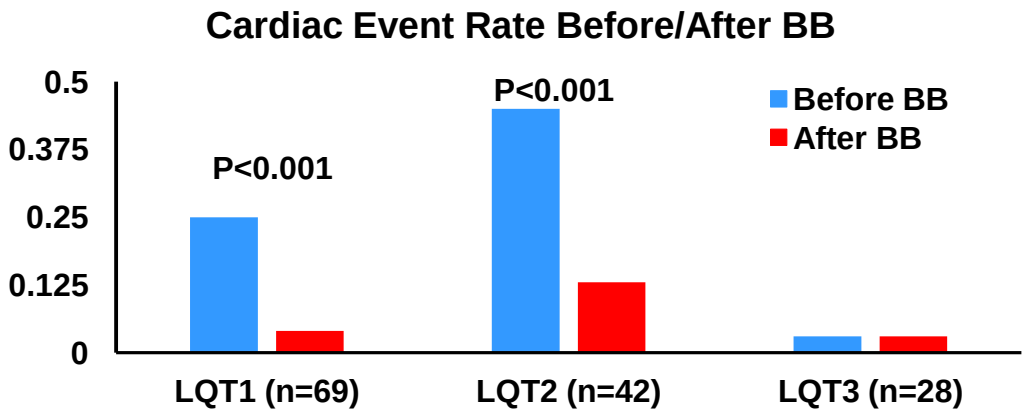
LQT1

LQT2

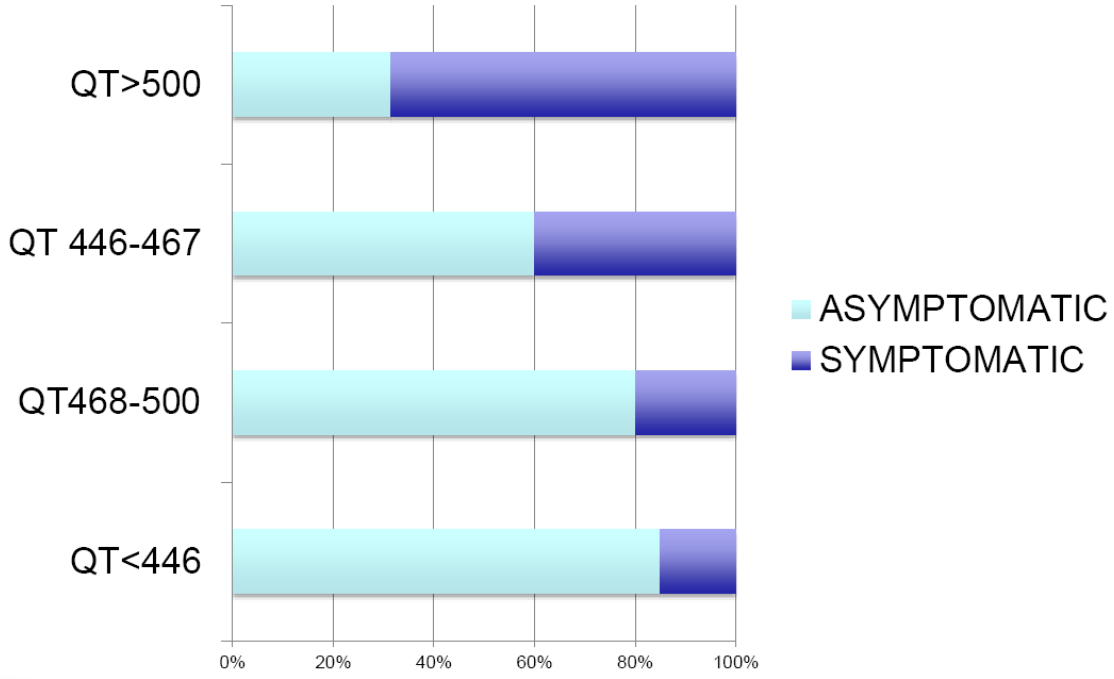
The consensus is to treat also asymptomatic LQT pts

2015 ESC VA and SCD Guidelines

Recommendations	Class	Level
Beta-blockers are recommended in patients with a clinical diagnosis of LQTS	**I**	**B**
Beta-blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.	**IIa**	**B**

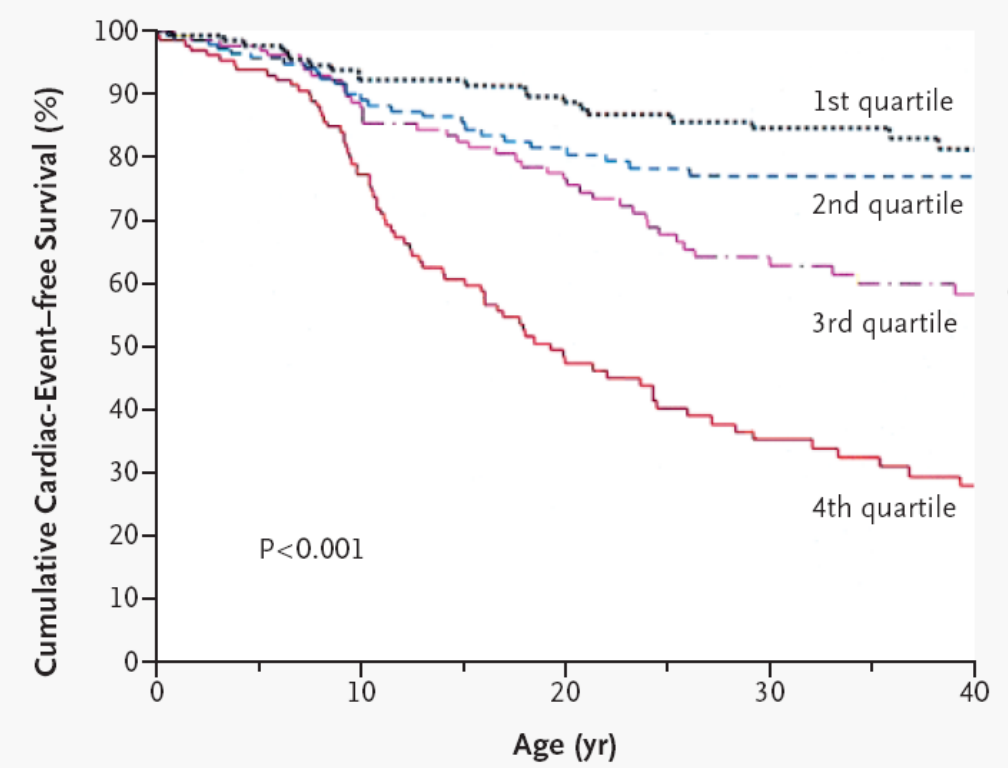


QTc duration as a key indicator of risk



Priori SG et al. NEJM 2003

Event-free survival to QTc



QTc < 446

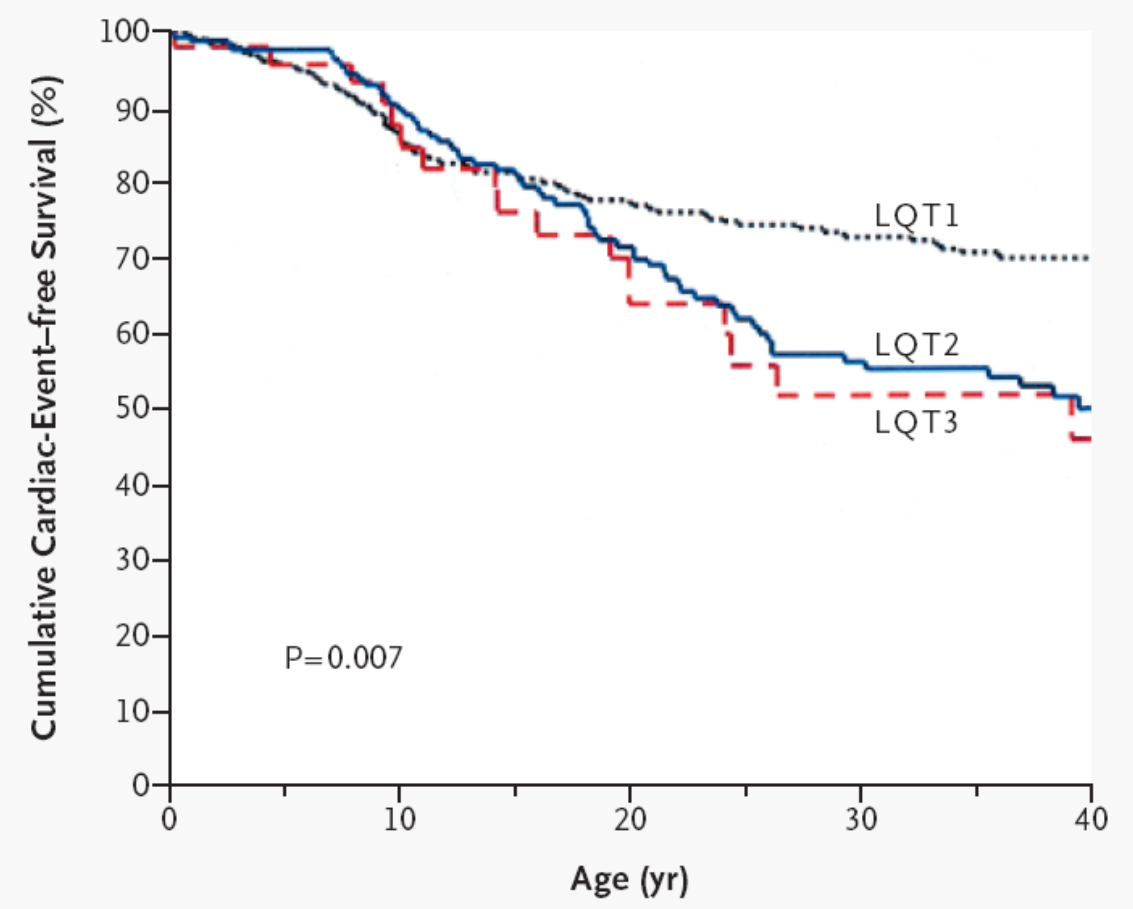
QTc 446-467

QTc 468-500

QTc > 500

Priori SG et al. NEJM 2003

Survival according to gentype

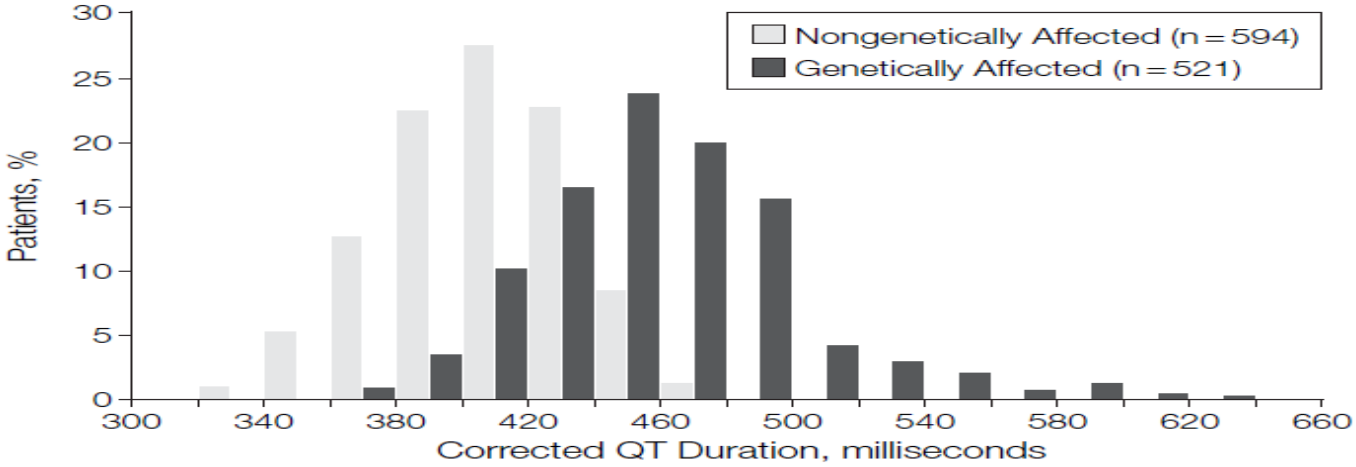


Priori SG et al. NEJM 2003

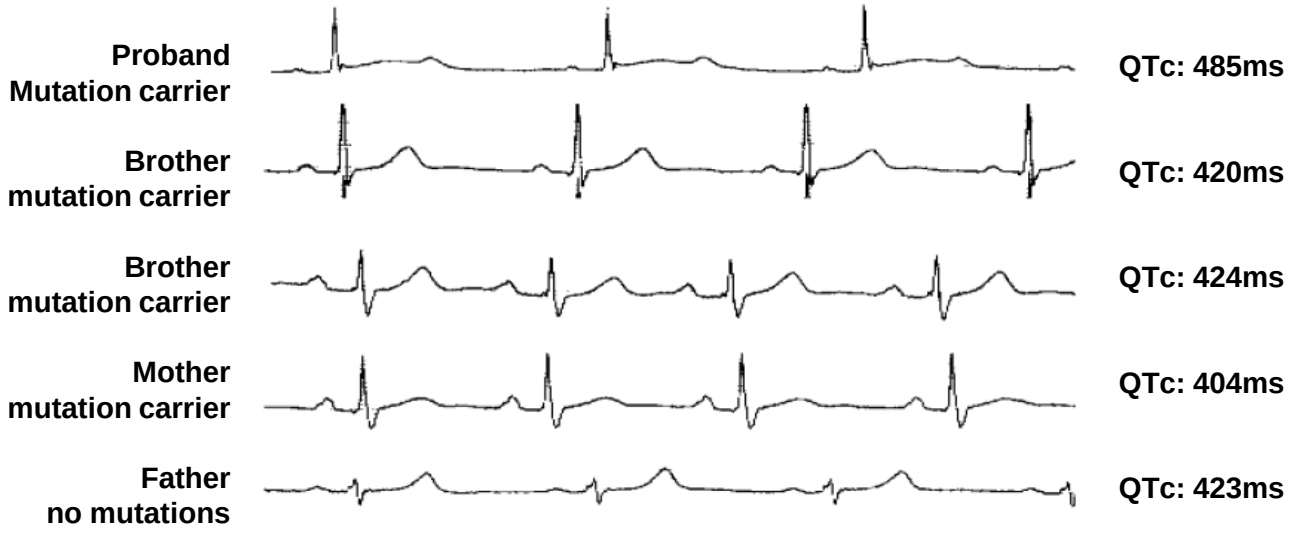
Gender and risk stratification of LQT1

- **Asymptomatic LQT1 male patients who have remained asymptomatic until age 15 have a lower probability of experiencing a first cardiac event.**

Same family but… different risk

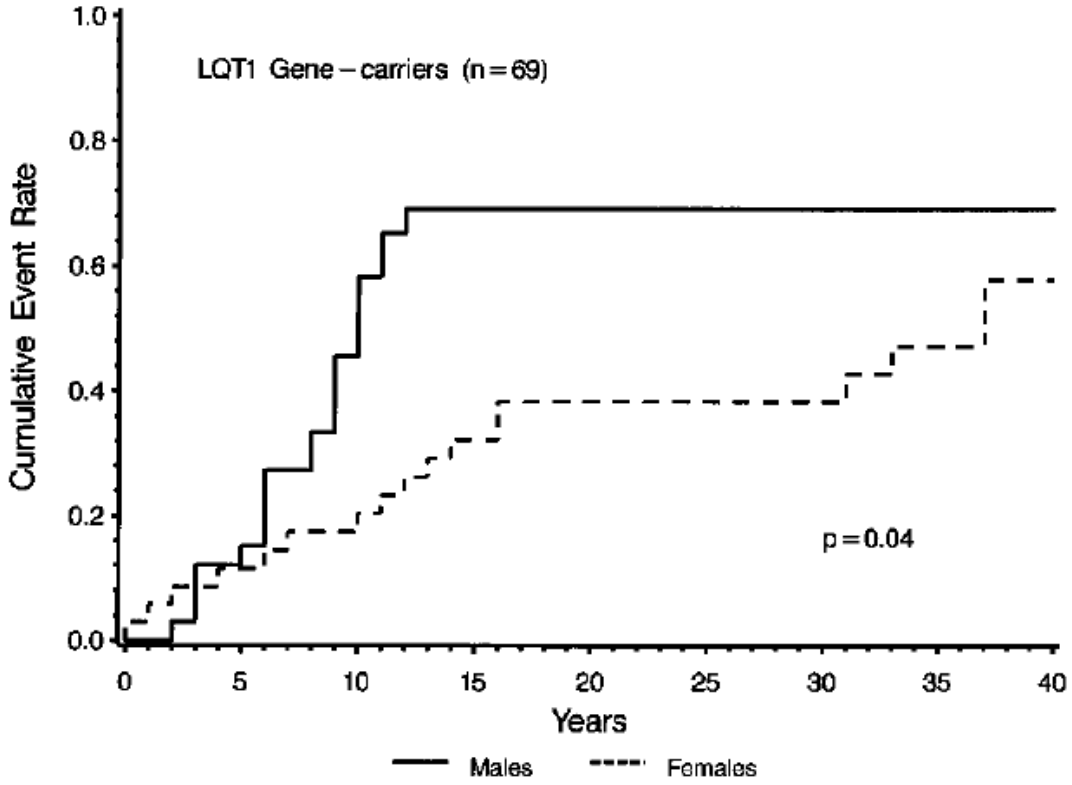


KCNH2 A512V



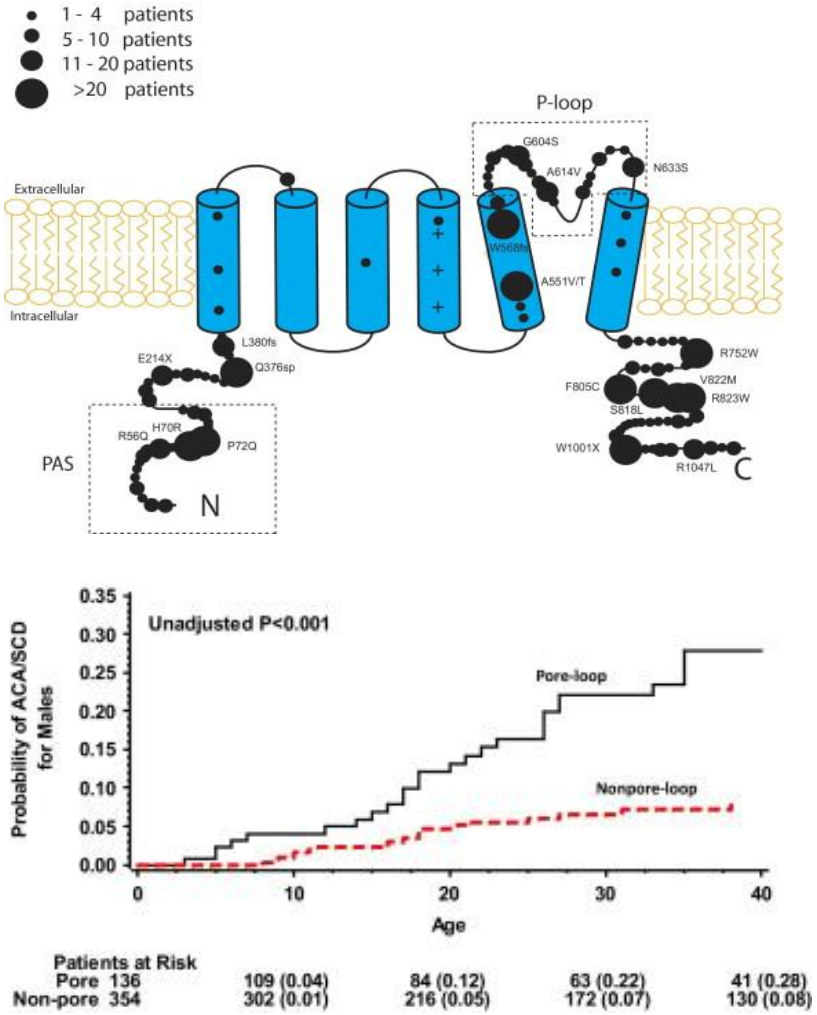
Napolitano C, et al. JAMA 2005

Gender effect in LQT1



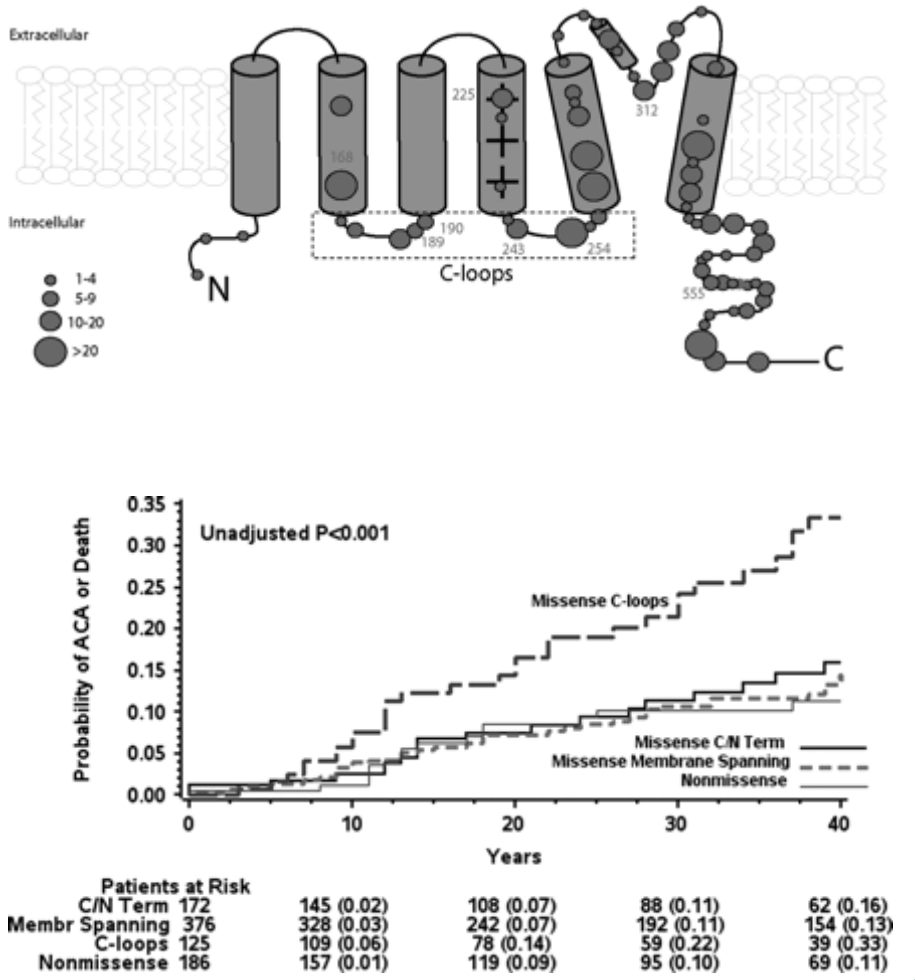
Locati et al. Circulation 1998;97:2237-44

KCNH2 (LQT2) PORE Region



Migdalovich D et al. Heart rhythm 2011

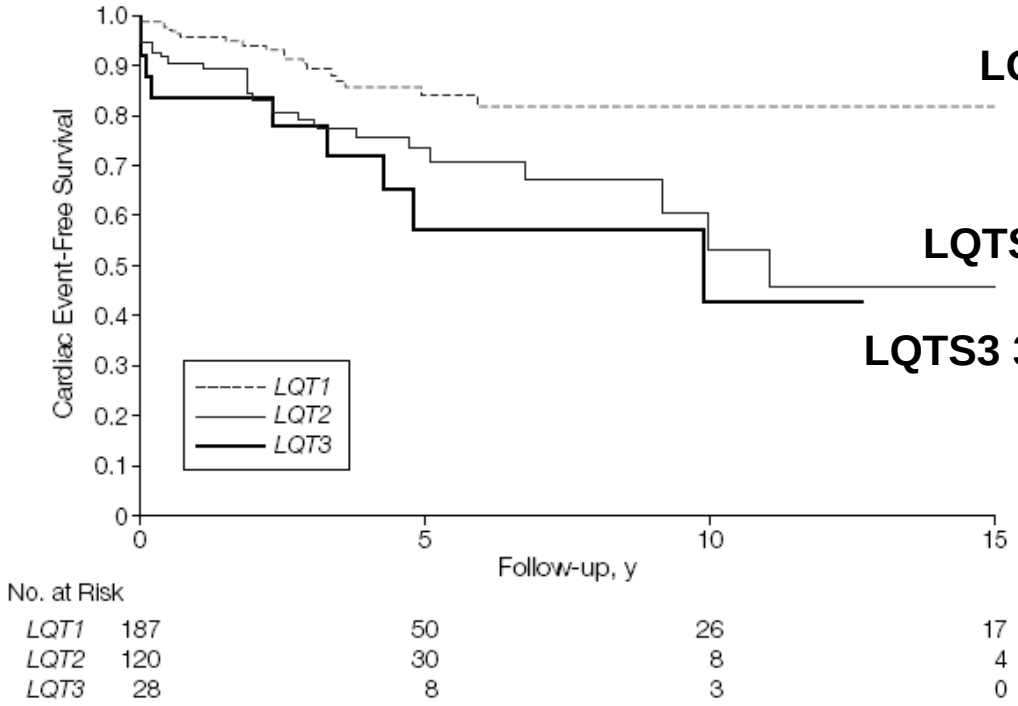
KCNQ1 (LQT1) C-loop Region



Barheshet A et al. Circulation 2012

Different effects of beta-blocker among LQTs

Consecutive LQT-genotyped patients (n=335) in Italy treated with beta-blockers for an average of 5 years



LQTS1 10%

LQTS2 23%

LQTS3 32%

Priory S, JAMA 2004

Predictors of cardiac events on beta-blockers

Significant Predictors of Cardiac Events and Cardiac Arrest for Patients Receiving Therapy (N = 335)

Predictors of Cardiac Events	Relative Risk (95% CI)	*P* Value
First cardiac event before therapy in early childhood (7 y)	4.34 (2.35-8.03)	<.001
QTc 500 ms while receiving therapy	2.01 (1.16-3.51)	.01
Genetic locus		
LQT2 vs *LQT1*	2.81 (1.50-5.27)	.001
LQT3 vs *LQT1*	4.00 (2.45-8.03)	.001

Priori et al. JAMA 2004

How to put it all together?

- **The QTc duration**
- **The gene in which a mutation is present**
- **The location of the mutation**
- **The gender**

A single parameter is not sufficient to decide the risk, it is the composite picture that defines the probability of cardiac events. The most important element however is the duration of QT interval.

Expert Consensus Recommendations of genetic testing in LQTS

STATE OF GENETIC TESTING FOR LONG QT SYNDROME (LQTS)

Class I (is recommended)

- Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for
  - any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.
  - **any asymptomatic patient with QT prolongation** in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc 480 ms (prepuberty) or 500 ms (adults).
- Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

HRS/EHRA Expert Consensus Statement. Heart Rhythm 2011; 8:1308 –1339

Thank you for your attention!

해결해야 할점?

- 유전자 검사의 보험
- **LQT 1-3**는 이미 치료, 에 후에 모두 중요함

Long term impact of LQTS predictive testing in childhood

TABLE 3: ADULT PSYCHOSOCIAL WELL-BEING BY CHILDHOOD GENETIC STATUS GROUP

	Genetic Testing Status By Age 18				
	Negative (n = 8)	Positive (n = 8)	Uncertain (n = 24)	**p Value**	
Psychological Measures					
State anxiety (20-80)	39.58	34.25	34.21	**0.567**	**N.S.**
Trait anxiety (20-80)	42.25	32.02	32.91	**0.086**	**N.S.**
Depression (0-63)	7.50	3.77	3.73	**0.352**	**N.S.**
Self esteem (0-30)	20.13	24.67	25.78	**0.065**	**N.S.**
Disease-related distress (0-75)	24.75	15.38	13.50	**0.229**	**N.S.**
Adaptation (20-100)	80.25	84.35	80.16	**0.816**	**N.S.**

N.S.=Not significant; cutoff for statistical significance: $p < 0.05$

For all psychosocial variables, we created a general linear model with gender and genetic status as predictors.

Shown here are final adjusted group mean scores after adjusting for the effect of gender.

Dunn et al

Benefits of early risk awareness

TABLE 4: ASSOCIATION BETWEEN ADULT PSYCHOSOCIAL WELL-BEING AND YEARS SINCE FIRST LEARNED LQTS WAS IN THE FAMILY (n = 40)

	$\hat{\beta}$	Direction of Association	**p Value**	
Psychological Measures				
State anxiety	-0.9373	Negative	**0.002**	**
Trait anxiety	-0.6236	Negative	**0.023**	*
Depression	-0.2552	Negative	**0.122**	**N.S.**
Self-esteem	0.3959	Positive	**0.010**	**
Disease-related distress	-0.8392	Negative	**0.037**	*
Adaptation	1.2090	Positive	**0.002**	**

N.S.=Not significant; *$p < 0.05$, **$p \leq 0.01$

For all psychosocial variables, we created a general linear model with gender and years since first learning LQTS was in the family as predictors.

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