Inherited Long QT Syndrome: Recent Advances

Prof Pascal McKeown

4 November 2024

Outline

- What is Long QT (LQT) Syndrome
- Genetics of LQT
- Investigation and Management
- Some novel insights

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Background

ervell A, Lange-Nielsen F.
Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden eath. Am Heart J 1957;54:59-68

Romano C, Gemme G, Pongiglione R.
Aritmiecardiache rare dell'eta pediatrica, II: ccessi sincopali per fibrillazione ventricolare arossitica. Clin Pediatr. 1963;45:656–683.

Ward OC. A new familial cardiac syndrome in hildren. J Ir Med Assoc. 1964;54:103–106.

- Estimated prevalence is 1 in 2,000
- Accurate measurement of QT interval is very important – usually lead II or V5
- Correction for heart rate: Bazett, Fridericia, linear regression models
- QTc measurements - resting, ambulatory and exercise
- What is 'abnormal' QTc?
  - >450ms (male), >460 ms (female)?

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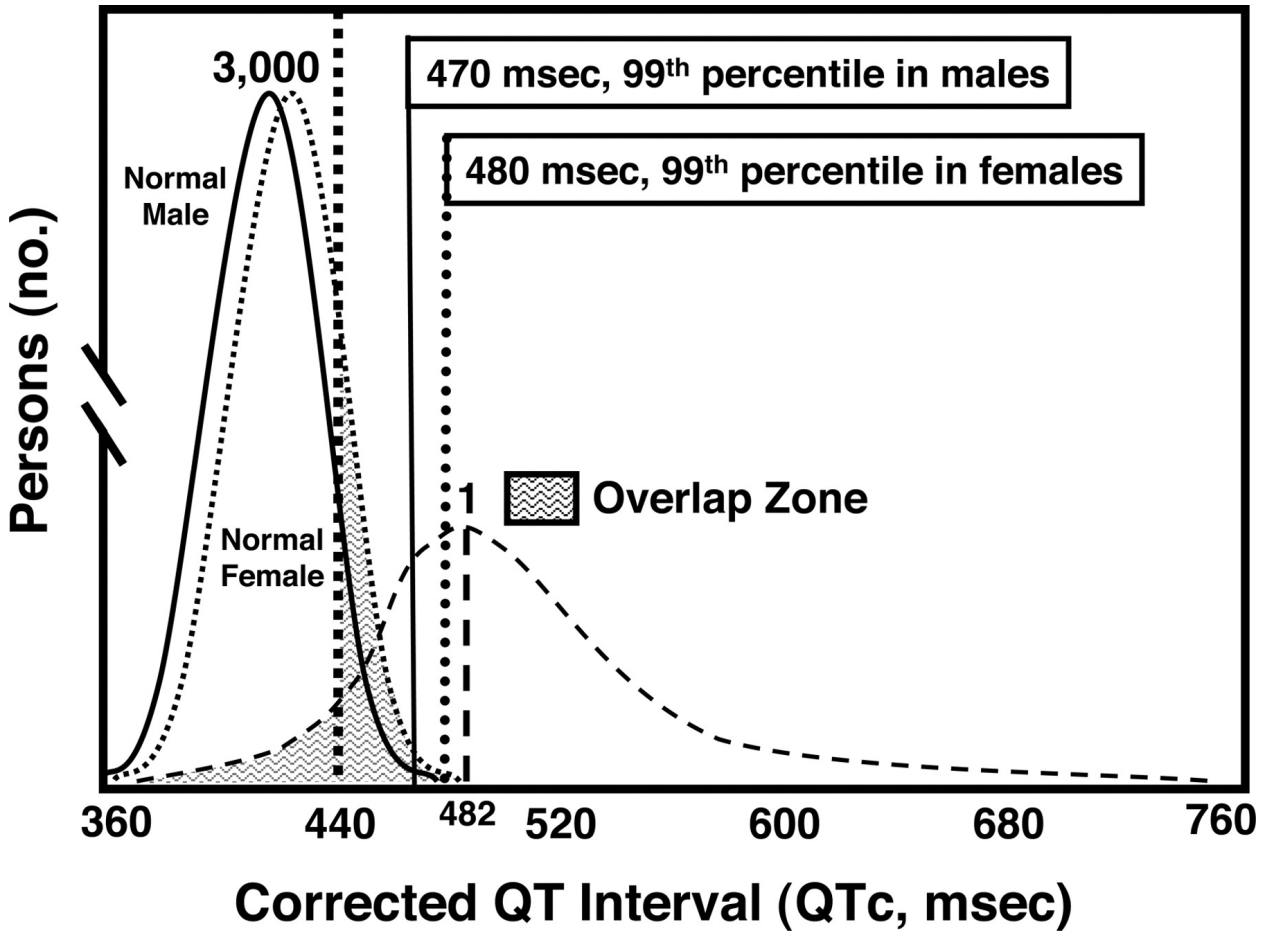
Tc values in normal population and patients with LQT



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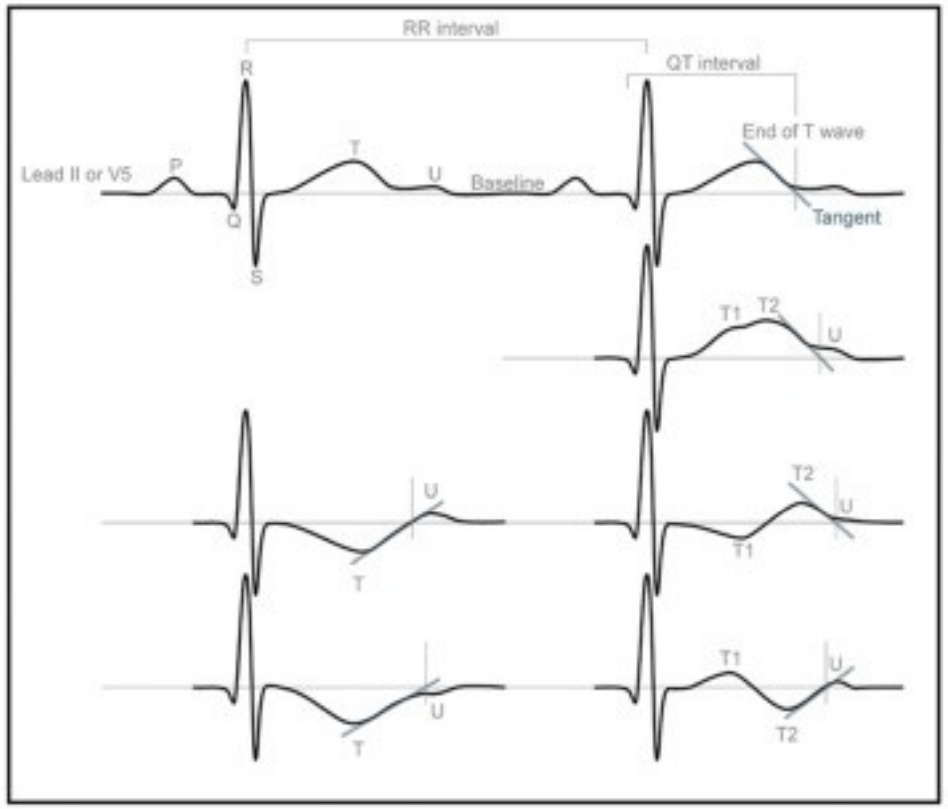
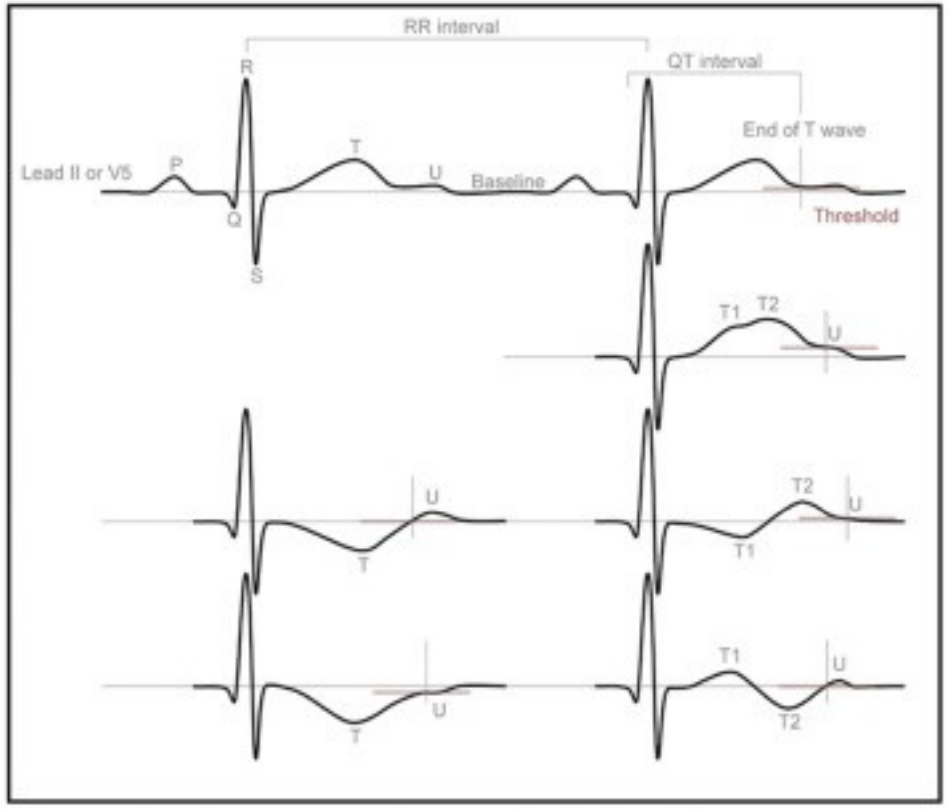
Taggart et al. Circulation 2007;115:2613–2620

Measuring the QT interval



Tangent technique: the end of the T-wave is the point where the tangent to the steepest point of the terminal limb of the T-wave intersects with the isoelectric baseline.



Threshold technique: the end of the T-wave is the intersection of the terminal limb of the T-wave with the isoelectric baseline; when interrupted by a U-wave, it was defined as the nadir between the T- and U-wave.

Krahn AD et al. *J Am Coll Cardiol EP* 2022;8:687-706.

JAC Clinical Electrop

HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Expert Consensus Recommendations on LQTS Diagnosis
1. LQTS is diagnosed:
a. In the presence of an LQTS risk score ≥3.5 in the absence of a secondary cause for QT prolongation *and/or*
b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes *or*
c. In the presence of a corrected QT interval for heart rate using Bazett's formula (QTc) ≥500 ms in repeated 12- lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.
2. LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.

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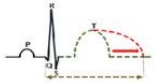
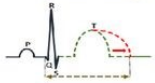
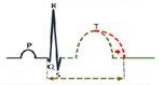
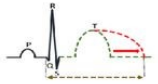
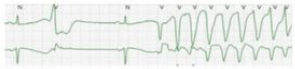
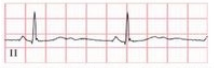
EP Europace 2013;15:1389–140

Schwartz Score

		Points
Electrocardiographic findings *(in absence of acquired causes)*		
QTc duration *(calculated by Bazett formula)*	≥ 480 msec 	3
	460-479 msec 	2
	450-459 msec *(men)* 	1
QTc 4th minute of recovery from exercise test	≥ 480 msec 	1
Torsades de Pointes* *(mutually exclusive)*		2
T-wave alternans		1
Notched T wave in 3 leads		1
Low resting heart rate	Below the 2nd percentile for age	0.5
Clinical history		
Syncope* *(mutually exclusive)*	With stress 	2
	Without stress 	1
Congenital deafness		0.5
Family history *(the same family member cannot be counted twice for the rows below)*		
Family members with definite LQTS	Index → 	1
Unexplained SCD <30 years among immediate family members	Index → 	0.5

Definite LQTS is defined by an LQTS sc
≥3.5 points
Intermediate probability of LQTS by an
LQTS score of <3.5 and >1
Low probability of LQTS by ≤1 point.
In the family history rows, the same fami
member cannot be counted in both
categories.

Wilde AA et al. Heart 2022;108:332-338

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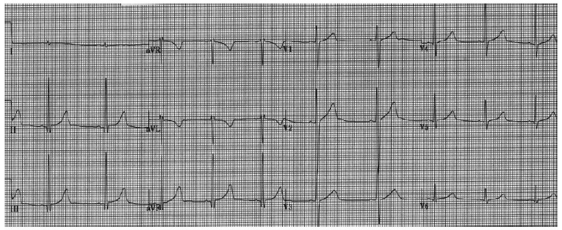
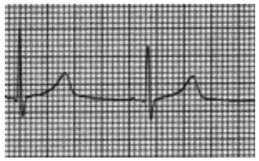
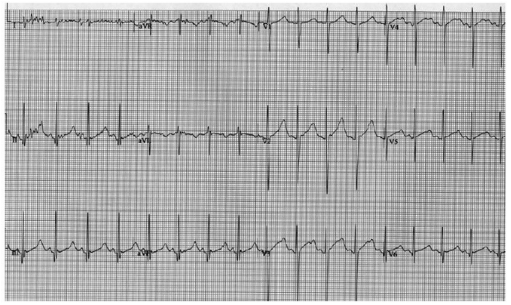
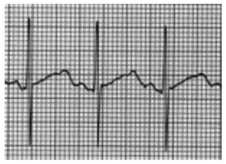
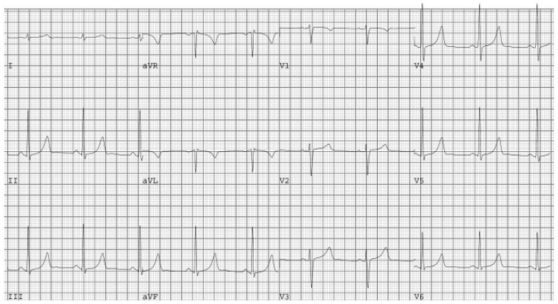
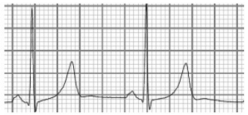
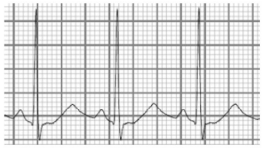
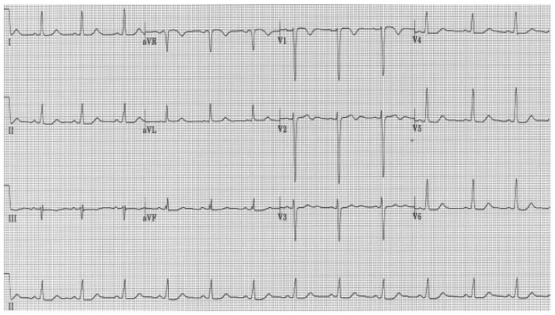
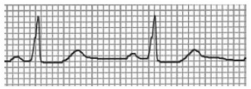
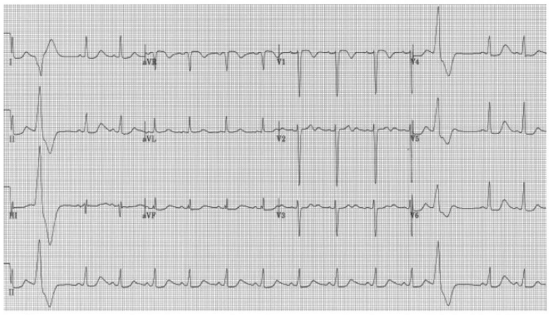
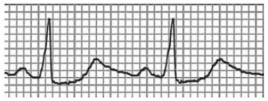
EP Europace 2013;15:1389–140

Provocation Tests

	Baseline		Provocation	
Stand-up Test		 QT=440ms, RR=920ms **QTc=459ms**		 QT=420ms, RR=580ms **QTc=551ms**
Exercise Test*		 QT=450ms, RR=1020ms **QTc=446ms**		 QT=460ms, RR=680ms **QTc=558ms**
Epinephrine Challenge		 QT=420ms, RR=820ms **QTc=464ms**		 QT=450ms, RR=680ms **QTc=546ms**

Krahn AD et al. *J Am Coll Cardiol EP* 2022;8:687-706.

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Clinical Genome Resource curated gene panels for LQT

Entity	Genetic evidence strong/moderate for causation		Genetic evidence weak/disputed for causation	
LQTS	*KCNQ1* (AD/AR)	(LQT1/JLNS)	*ANK2*	(LQT4)
	KCNH2	(LQT2)	*KCNE1** (AD/AR)	(LQT5/JLNS)
	SCN5A	(LQT3)	*KCNE2*	(LQT6)
	CALM1		*CAV3*	(LQT9)
	CALM2		*SCN4B*	(LQT10)
	CALM3		*AKAP9*	(LQT11)
	TRDN (AR)		*SNTA1*	(LQT12)
	KCNJ2	(LQT7 Andersen-Tawil Syndrome)	*KCNJ5*	(LQT13)
	CACNA1C	(LQT8 Timothy syndrome)		

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Autosomal dominant inheritance unless stated.
*May be considered a milder or modifying form of LQTS that in autosomal recessive form can cause a milder form of JLNS.

Specterman and Behr. Heart 2023;109:434-

Interpretation of Genetic Variants

Pathogenic
Likely pathogenic
Variant of uncertain significance (VUS)
Likely benign
Benign

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

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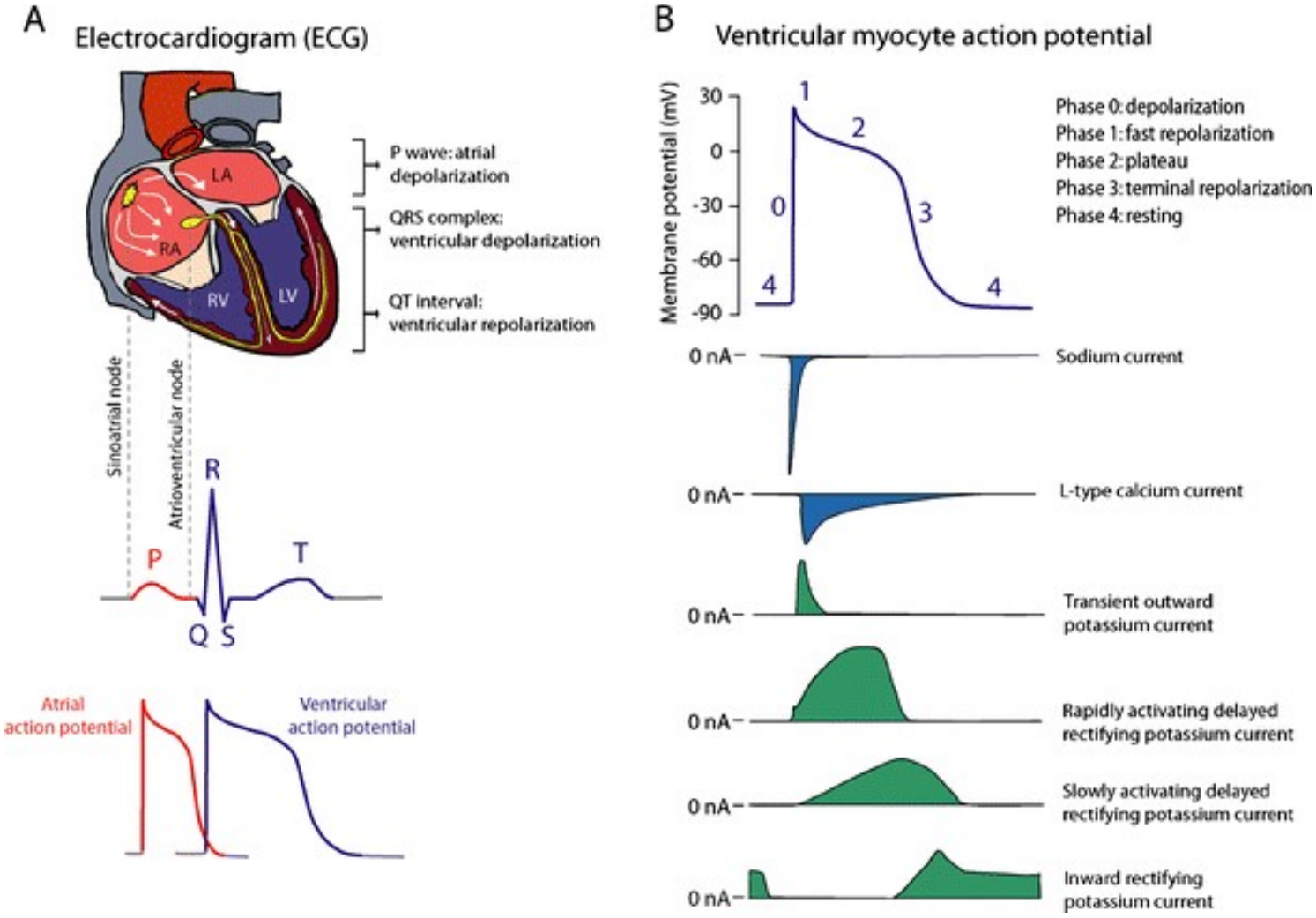
https://www.nature.com/articles/gim2

Action Potential and Ion Currents



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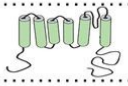
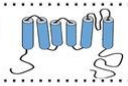
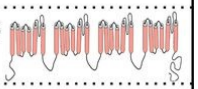
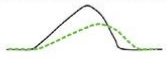
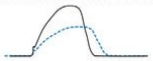
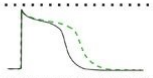
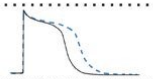
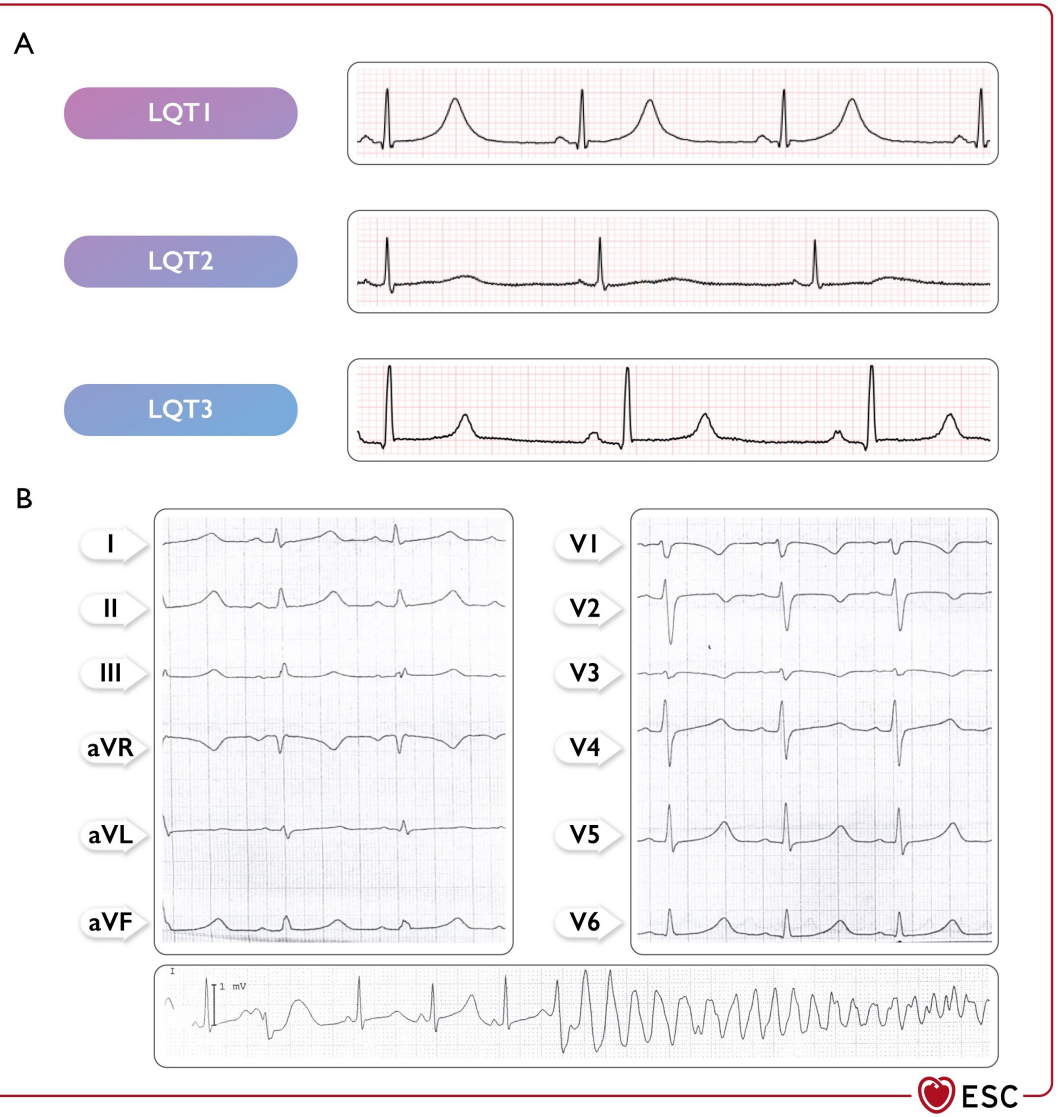
https://link.springer.com/article/10.1007/s00424-009-0761-0/figures/1

Genotype–phenotype relationship for the three most important subtypes

	Type 1	Type 2	Type 3
Gene	*KCNQ1*	*KCNH2*	*SCN5a*
Protein	$K_v7.1$ 	$K_v11.1$ 	$Na_v1.5$ 
Effect on current	$I_{Ks}\downarrow$ 	$I_{Kr}\downarrow$ 	$I_{Na,L}\uparrow$ 
Effect on action potential			
Frequency among LQTS	± 35% 	± 30% 	≤ 10% 
Penetrance	± 65% 	± 80% 	± 90% 
Typical resting ECG (V_5)			
QT change with exercise	Failure to shorten	Normal	Supranormal
Main trigger of events	Exercise *(swimming)* 	Arousal 	Rest 
Age of onset arrhythmias	Childhood 	Puberty 	Puberty 
Gender most at risk	♂	♀	♀
Onset of arrhythmias	 *Not pause-dependent*	 *Pause-dependent*	At lower heart rates
Therapy	Beta-blockers (+++) Left stellectomy	Beta-blockers (++) Left stellectomy Potassium suppletion	Beta-blockers (++) Sodium channel blocker Pacemaker

Wilde AA et al. Heart 2022;108:33

Gene-specific Long QT syndrome electrocardiograms and torsade-de-pointes

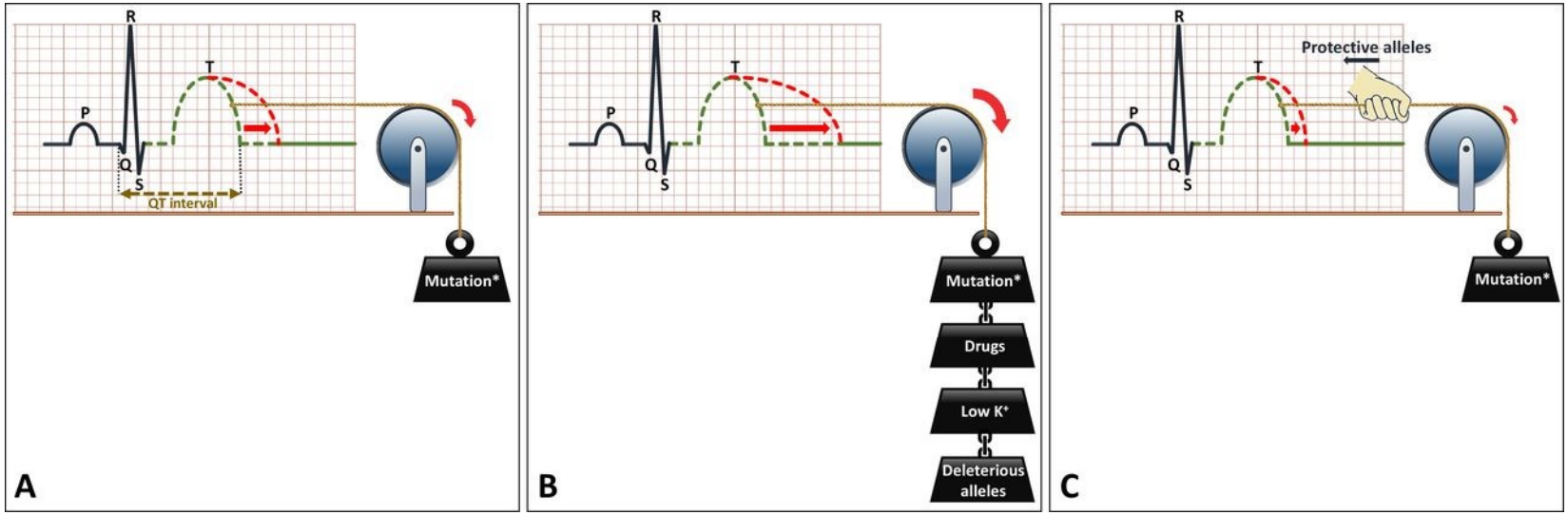


(A) ECG characteristics in the three major LQTS phenotypes.

(B) Example of Torsade-de-pointes in a male patient with a *SCN5A* (c.1238C>A, p.A413E) mutation.

Eur Heart J, Volume 43, Issue 40, 21 October 2022, Pages 3997–4126, https://doi.org/10.1093/eurheartj/ehac262.

Schematic representation of the effects of genetic and environmental factors in LQTS



(A) LQTS-associated mutation causes prolongation of the QT interval on the ECG.
(B) Environmental factors such as certain drugs (which decrease repolarisation reserve) or hypokalaemia, or genetic factors (ie, deleterious alleles) act in a conjoint manner with the LQTS-associated mutation to further prolong the QT interval.
(C) Protective alleles counteract the effects of the mutation and may reduce the QT prolongation.

Wilde AA et al. Heart 2022;108:332-338

Heart

nternational Consensus Standards for ECG Interpretation in Athletes

Abnormal ECG findings are unrelated to regular training or expected physiologic adaptation to exercise, may suggest the presence of pathologic cardiovascular disease, and require further diagnostic investigation

Prolonged QT interval

- QTc ≥ 470 ms (male)
- QTc ≥ 480 ms (female)
- QTc ≥ 500 ms (marked QT prolongation)

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European Heart Journal (2018) 39, 1466–1480

Management Options

- *Avoid electrolyte issues, such as hypokalaemia*

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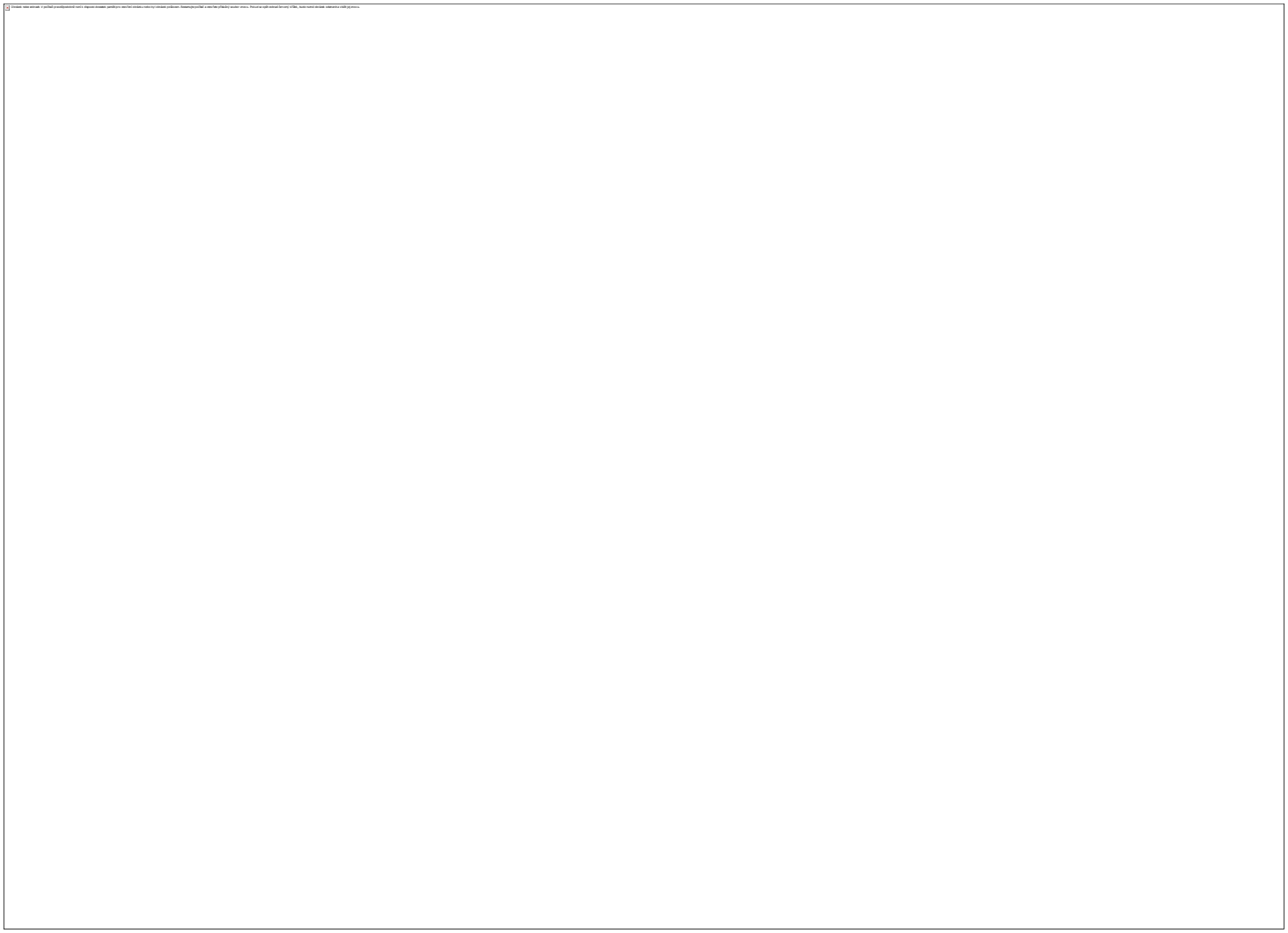
Management Options

- *Avoid electrolyte issues, such as hypokalaemia*
- Advice about participation in sports, although guidelines now less restrictive

Vigorous Exercise (>6 METS for >60hr / year) Study



N=1,413

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Lampert R et al. Circulation 2024;150:516-

Management Options

- *Advice about participation in sports*
- Avoidance of certain medications
- https://crediblemeds.org/login

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Management Options

- *Advice about participation in sports*
- *Avoidance of certain medications*

- Medication
  - beta-blockers (ideally, nadolol / propranolol)
  - Mexiletine (LQT3 and some evidence for LQT2)
- Devices
  - Pacemaker
  - ICD
- Left cardiac sympathetic denervation

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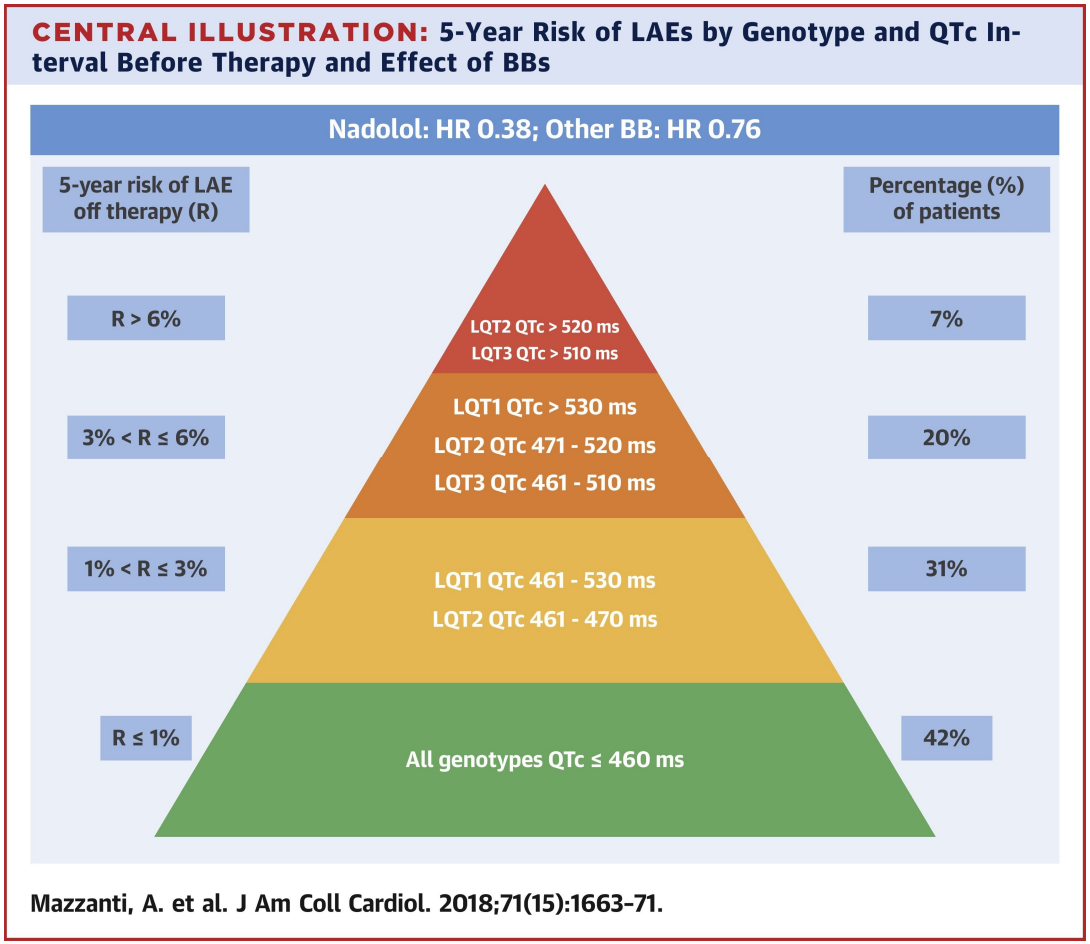
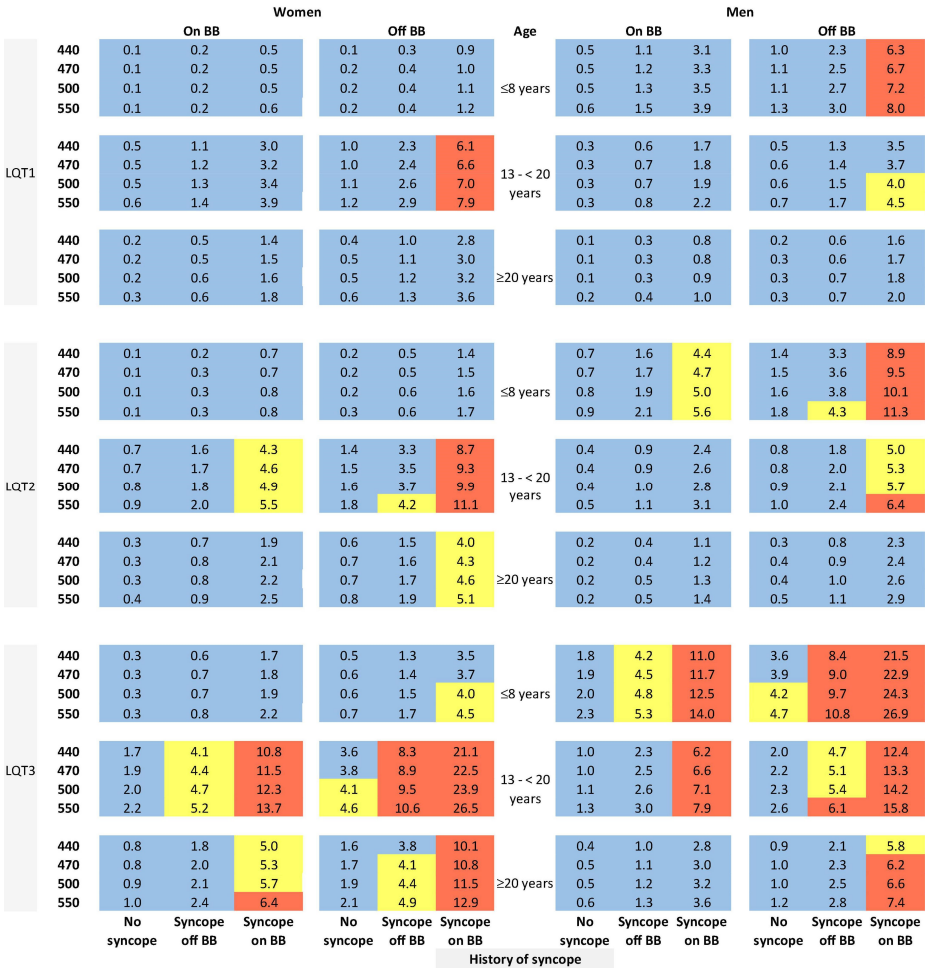
5-year risk models

Mazzanti vs Rochester





		Women						Age	Men					
		On BB			Off BB				On BB			Off BB		
	440	0.1	0.2	0.5	0.1	0.3	0.9		0.5	1.1	3.1	1.0	2.3	6.3
	470	0.1	0.2	0.5	0.2	0.4	1.0		0.5	1.2	3.3	1.1	2.5	6.7
	500	0.1	0.2	0.5	0.2	0.4	1.1	≤8 years	0.5	1.3	3.5	1.1	2.7	7.2
	550	0.1	0.2	0.6	0.2	0.4	1.2		0.6	1.5	3.9	1.3	3.0	8.0
LQT1	440	0.5	1.1	3.0	1.0	2.3	6.1		0.3	0.6	1.7	0.5	1.3	3.5
	470	0.5	1.2	3.2	1.0	2.4	6.6		0.3	0.7	1.8	0.6	1.4	3.7
	500	0.5	1.3	3.4	1.1	2.6	7.0	13 - < 20 years	0.3	0.7	1.9	0.6	1.5	4.0
	550	0.6	1.4	3.9	1.2	2.9	7.9		0.3	0.8	2.2	0.7	1.7	4.5
	440	0.2	0.5	1.4	0.4	1.0	2.8		0.1	0.3	0.8	0.2	0.6	1.6
	470	0.2	0.5	1.5	0.5	1.1	3.0		0.1	0.3	0.8	0.3	0.6	1.7
	500	0.2	0.6	1.6	0.5	1.2	3.2	≥20 years	0.1	0.3	0.9	0.3	0.7	1.8
	550	0.3	0.6	1.8	0.6	1.3	3.6		0.2	0.4	1.0	0.3	0.7	2.0
	440	0.1	0.2	0.7	0.2	0.5	1.4		0.7	1.6	4.4	1.4	3.3	8.9
	470	0.1	0.3	0.7	0.2	0.5	1.5		0.7	1.7	4.7	1.5	3.6	9.5
	500	0.1	0.3	0.8	0.2	0.6	1.6	≤8 years	0.8	1.9	5.0	1.6	3.8	10.1
	550	0.1	0.3	0.8	0.3	0.6	1.7		0.9	2.1	5.6	1.8	4.3	11.3
LQT2	440	0.7	1.6	4.3	1.4	3.3	8.7		0.4	0.9	2.4	0.8	1.8	5.0
	470	0.7	1.7	4.6	1.5	3.5	9.3		0.4	0.9	2.6	0.8	2.0	5.3
	500	0.8	1.8	4.9	1.6	3.7	9.9	13 - < 20 years	0.4	1.0	2.8	0.9	2.1	5.7
	550	0.9	2.0	5.5	1.8	4.2	11.1		0.5	1.1	3.1	1.0	2.4	6.4
	440	0.3	0.7	1.9	0.6	1.5	4.0		0.2	0.4	1.1	0.3	0.8	2.3
	470	0.3	0.8	2.1	0.7	1.6	4.3		0.2	0.4	1.2	0.4	0.9	2.4
	500	0.3	0.8	2.2	0.7	1.7	4.6	≥20 years	0.2	0.5	1.3	0.4	1.0	2.6
	550	0.4	0.9	2.5	0.8	1.9	5.1		0.2	0.5	1.4	0.5	1.1	2.9
	440	0.3	0.6	1.7	0.5	1.3	3.5		1.8	4.2	11.0	3.6	8.4	21.5
	470	0.3	0.7	1.8	0.6	1.4	3.7		1.9	4.5	11.7	3.9	9.0	22.9
	500	0.3	0.7	1.9	0.6	1.5	4.0	≤8 years	2.0	4.8	12.5	4.2	9.7	24.3
	550	0.3	0.8	2.2	0.7	1.7	4.5		2.3	5.3	14.0	4.7	10.8	26.9
LQT3	440	1.7	4.1	10.8	3.6	8.3	21.1		1.0	2.3	6.2	2.0	4.7	12.4
	470	1.9	4.4	11.5	3.8	8.9	22.5		1.0	2.5	6.6	2.2	5.1	13.3
	500	2.0	4.7	12.3	4.1	9.5	23.9	13 - < 20 years	1.1	2.6	7.1	2.3	5.4	14.2
	550	2.2	5.2	13.7	4.6	10.6	26.5		1.3	3.0	7.9	2.6	6.1	15.8
	440	0.8	1.8	5.0	1.6	3.8	10.1		0.4	1.0	2.8	0.9	2.1	5.8
	470	0.8	2.0	5.3	1.7	4.1	10.8		0.5	1.1	3.0	1.0	2.3	6.2
	500	0.9	2.1	5.7	1.9	4.4	11.5	≥20 years	0.5	1.2	3.2	1.0	2.5	6.6
	550	1.0	2.4	6.4	2.1	4.9	12.9		0.6	1.3	3.6	1.2	2.8	7.4
		No syncope	Syncope off BB	Syncope on BB	No syncope	Syncope off BB	Syncope on BB	History of syncope	No syncope	Syncope off BB	Syncope on BB	No syncope	Syncope off BB	Syncope on BB

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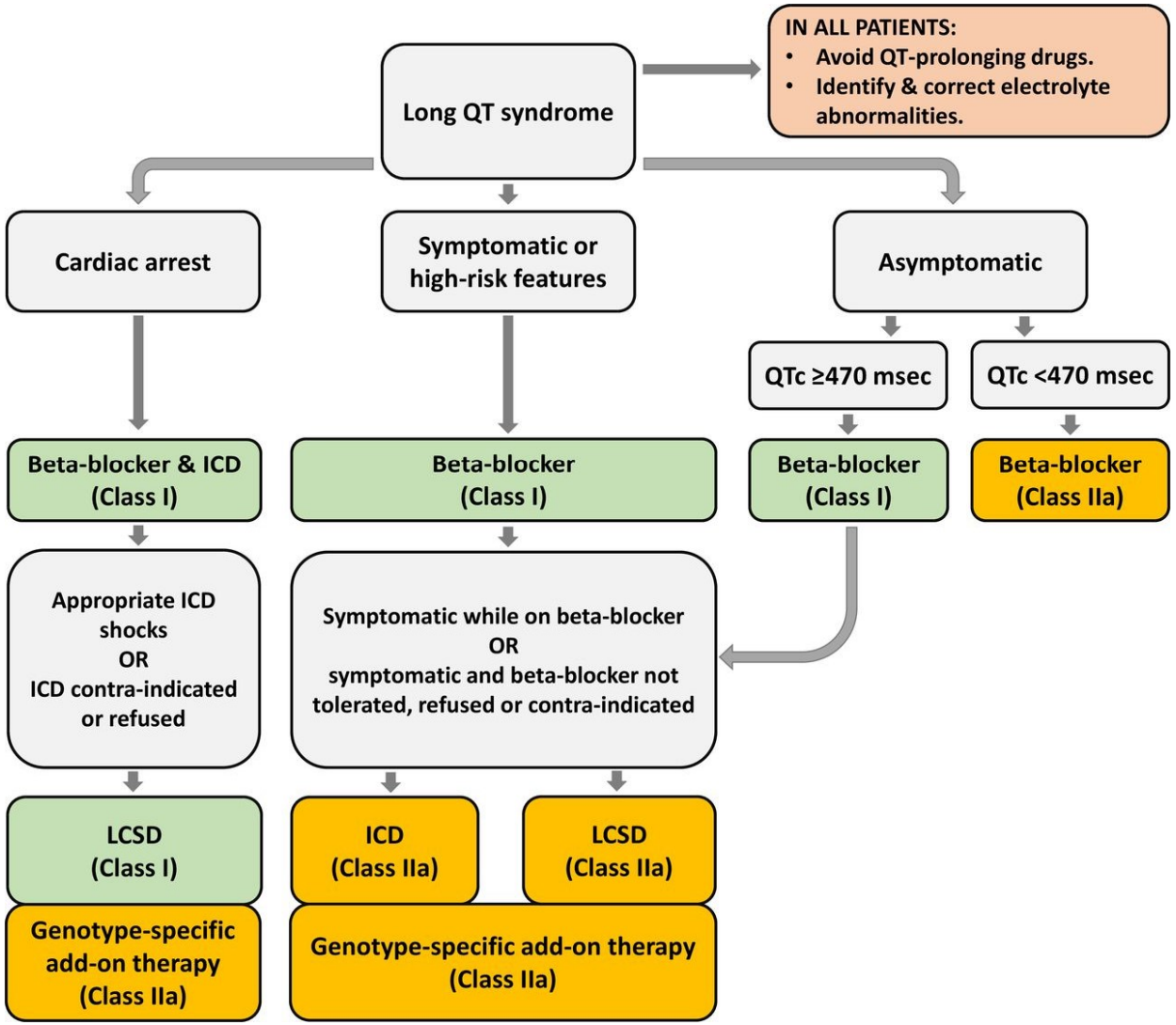
LAE – life-threatening arrhythmic events; n=1,710

Predicted 5-year risk of life-threatening arrhythmic events (ACA, SCD, or approp shocks) for patients with a single mutation in LQT1, LQT2, or LQT3. Blue colour i a predicted 5-year risk of <4%, yellow colour 4% to < 6%, and red colour ≥ 6%. N in this figure are percentage. Wang et al. Front CV Med 2022

Schematic flow chart for the therapeutic choices in LQTS



Wilde AA et al. Heart 2022;108:332-338

Long QT Syndrome: importance of reassessing arrhythmic risk after treatment initiation

ey Question

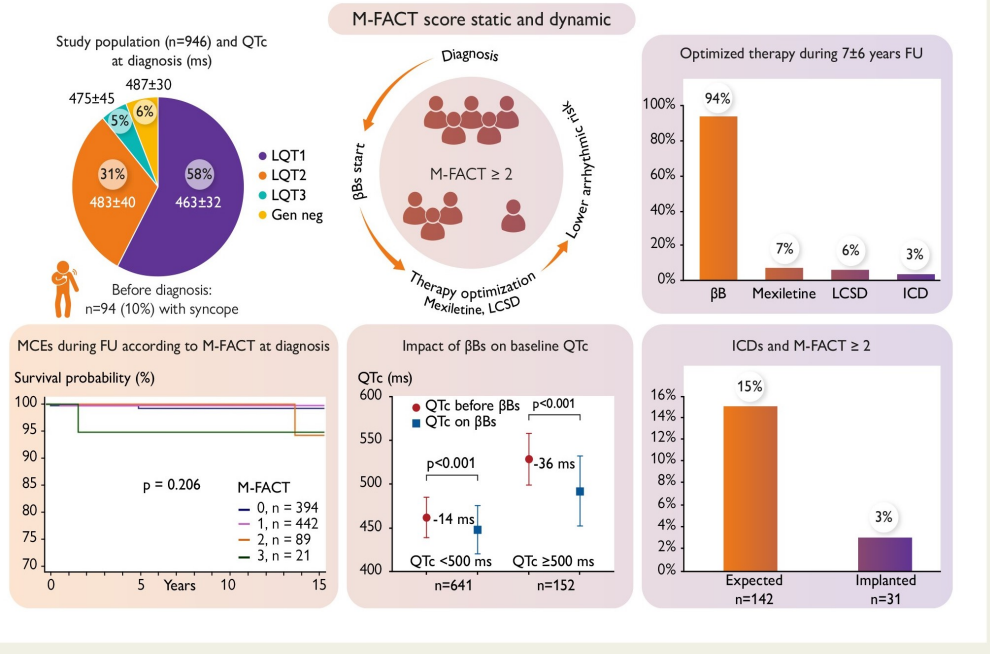
oes an M-FACT score ≥2 in long QT syndrome (LQTS), previously proposed as a cut-off for the implant of the implantable rdioverter defibrillator (ICD), effectively identify high-risk patients? Can therapy modify parameters critical for risk assessment, thus ducing the predicted arrhythmic risk? Does dynamic risk reassessment outperform a single assessment at first visit?

ey Finding

946 patients with LQTS, none died during 7±6 year follow-up. Beta-blockers, often accompanied by mexiletine and left cardiac mpathetic denervation, shortened QTc, a parameter pivotal for risk stratification, thus voiding its predictive value. Dynamic risk essment with timely therapeutic optimization significantly decreased the number of ICDs which would have been implanted based on seline M-FACT score without enhancing risk of life-threatening events.

ke Home Message

LQTS patients a single risk prediction made at diagnosis, prior to therapeutic optimization, is likely to overestimate risk and to result in necessary ICD implantations, with a negative impact on quality of life.



M-FACT Risk Score for evaluating risk of appropriate ICD therapy

	−1 Point	0 Points	1 Point	2 Point
Event free on therapy for >10 y	Yes	—	—	—
QTc (ms)	—	≤500	>501–≤550	≥551
Prior SCA	—	No	Yes	—
Events on therapy	—	No	Yes	—
Age at implantation (y)	—	>20	≤20	—

Adapted from Schwartz PJ, Spazzolini C, Priori SG, et al. 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 Implanted Cardioverter-Defibrillator (LQTS ICD) Registry. Circulation 2010;122:1278; with permission.

M (minus 1 point), F (500, 550 ms), A (age), C (cardiac arrest), T (events on therapy)

N=946, no history of aborted cardiac arrest before diagnosis or cardiac events below age 1 yr

M-FACT score ≥ 2

LQT 1,2,3 and genotype-negative patients included

Dusi et al. Eur Heart J 2024;45:2647-2656

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Inherited Cardiac Diseases Clinic

- Multi-disciplinary
  - Cardiologists (adult and paediatric), specialist nurses, geneticists
  - Liaison with forensic staff, genetics counsellors, psychologists
- Detailed personal and family history
- Previous cardiac investigations
- Protocols for investigation
- Genetic testing, where appropriate, which may facilitate cascade screening
- Provision of information (verbal and written)

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Novel Insights

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KCNQ1 suppression-replacement gene therapy in transgenic rabbits with type 1 long QT syndro

Key Question

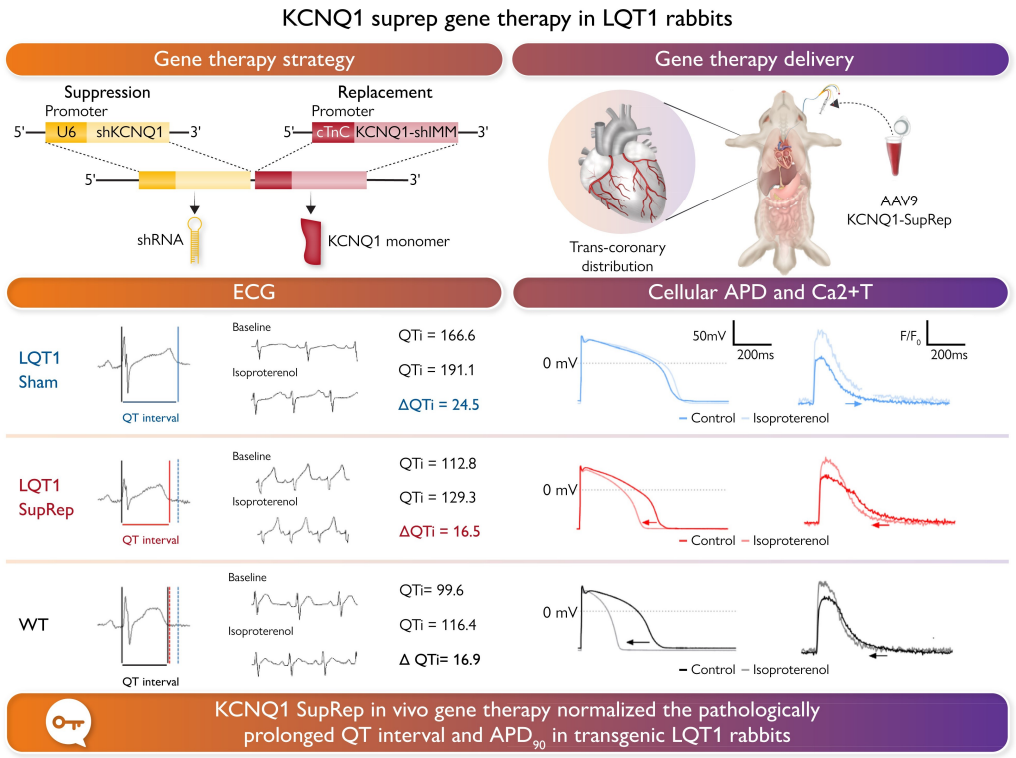
Can AAV9-mediated KCNQ1 suppression-replacement (SupRep) gene therapy restore physiological KCNQ1 function and rescue the diseased phenotype in transgenic LQT1 rabbits?

Key Finding

Treatment of LQT1 rabbits with AAV9-KCNQ1-SupRep gene therapy, delivered via targeted intra-aortic root injections, resulted in significant shortening of the pathologically prolonged QTi and cellular APD_{90} towards those observed in wild type (WT) rabbits. SupRep treated LQT1 rabbits demonstrated a physiological behavior under β-adrenergic stimulation.

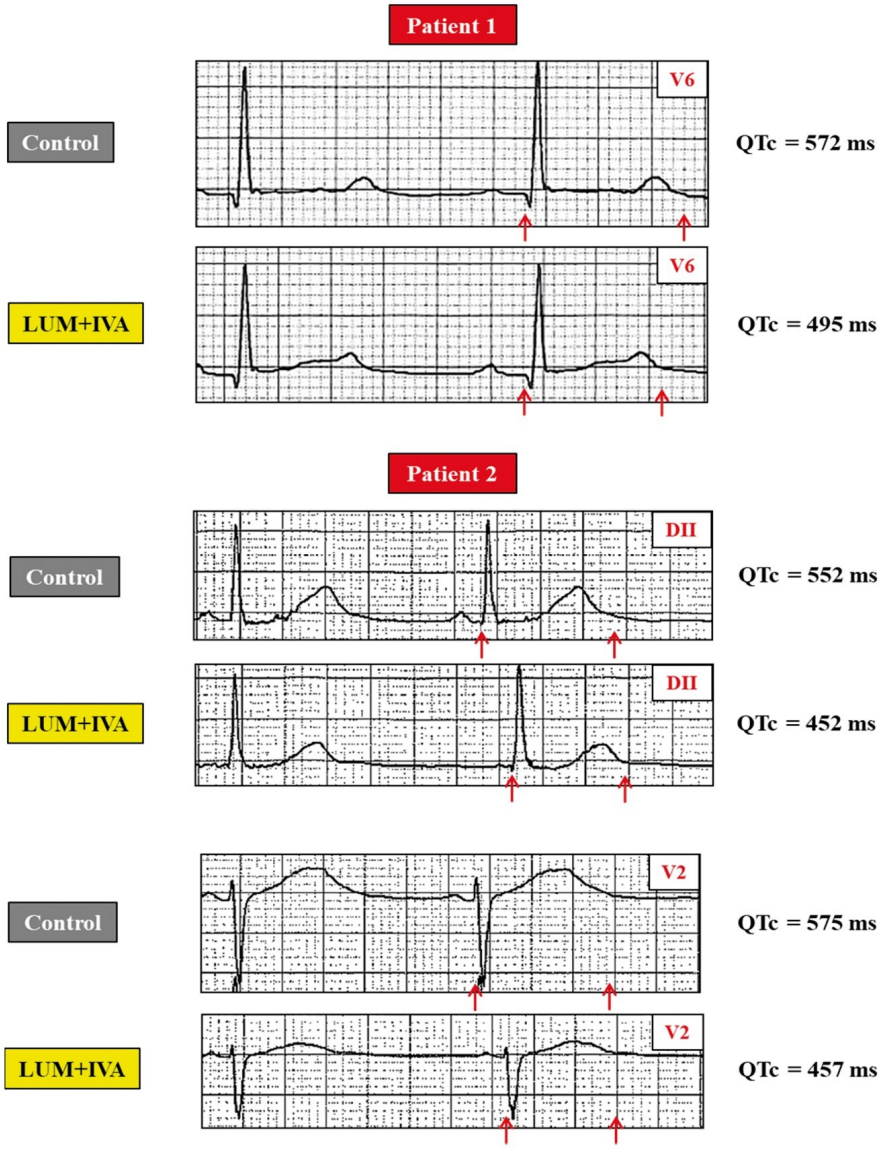
Take Home Message

In vivo KCNQ1-SupRep gene therapy rescues the physiological QTi and APD_{90} to those observed in WT rabbits both at baseline and after provocation with isoproterenol. This translational study might impact future LQT1 treatment.



Bains S et al. Eur Heart J 2024;45:3751-3763

om patient-specific induced pluripotent stem cells to clinical translation - lumacaf

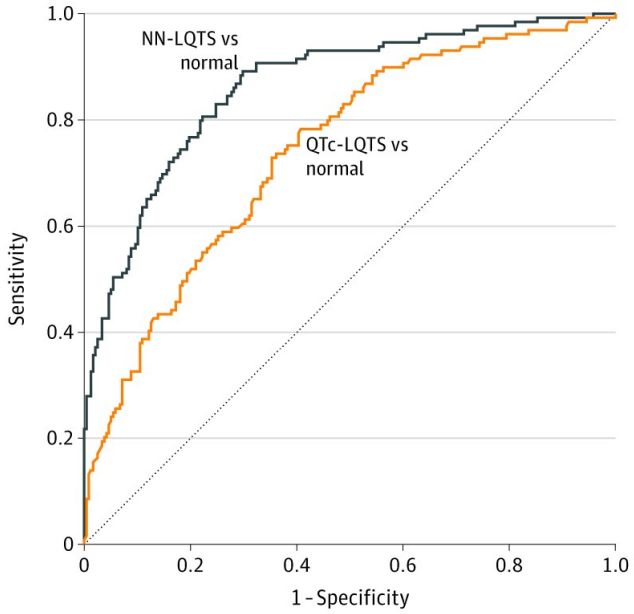


Schwartz P et al. Eur Heart J 2019;40:1832-1836

JAMA Network™

From: **Use of Artificial Intelligence and Deep Neural Networks in Evaluation of Patients With Electrocardiographically Concealed Long QT Syndrome From the Surface 12-Lead Electrocardiogram**

JAMA Cardiol. 2021;6(5):532-538. doi:10.1001/jamacardio.2020.7422



QTc-LQTS vs normal

	Estimated negative	Estimated positive
Real negative	154	84
Real positive	35	94

NN-LQTS vs normal

	Estimated negative	Estimated positive
Real negative	185	53
Real positive	25	104

Performance of Convolutional Neural Network (CNN) in Concealed Long QT Syndrome (LQTS) Detection Receiver operating characteristics curve and confusion matrix showing performance of the CNN to distinguish patients with concealed LQTS (corrected QT [QTc] ≤450 milliseconds) from those dismissed normal. NN indicates neural network.

Summary

- LQT affects ~1 in 2,000 of the population
- Multi-disciplinary team approach essential
- Accurate measurement of QTc interval and calculation of Schwartz score
- Genetics offer diagnostic and, on occasions, prognostic and therapeutic options; cascade screening available when genotype identified
- Risk stratification important – dynamic process
- Increasing patient expectations about personalised medicine. Shared decision making very important. Optimisation of therapeutic options of clear benefit.

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