Long QT Syndromes
An Update

Channelopathies and Hearts too Good to Die

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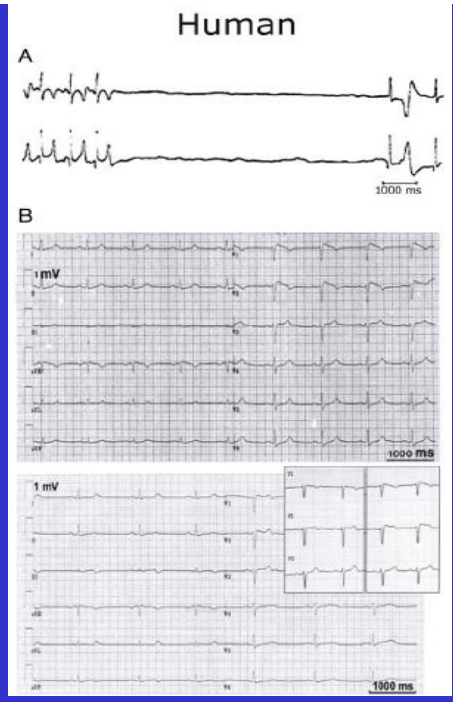
Long QT Syndromes
A Component of Cardiac Ion Channelopathies

- Mutations of specific genes encoding components of cardiac ion channels, cardiac membrane, and regulatory proteins, have been shown in the last decade to result in a variety of cardiac arrhythmias including sinus node disease, atrial standstill, atrial fibrillation, and conduction disorders.
- The most serious channelopathies are associated with ventricular tachyarrhythmias and sudden cardiac death. The four major syndromes in this group are: the Long QT syndrome (LQTS), the Brugada syndrome (BS), the short QT syndrome (SQTS), and the Catecholaminergic polymorphic ventricular tachycardia (CPVT).

Sinus Arrest

Brugada Syndrome

Long QT3

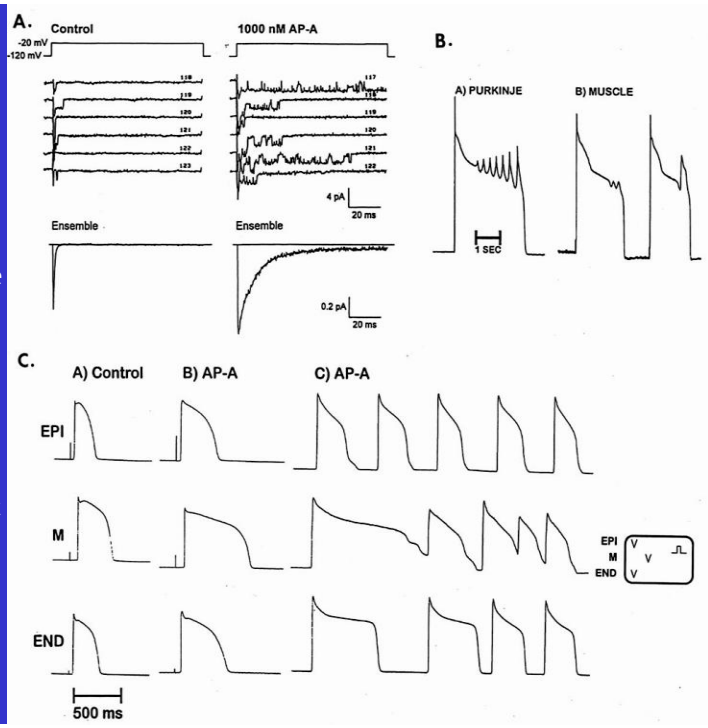


Cardiac Sodium Channel Overlap Syndromes

Trends Cardiovasc Med 2008

In 1988 El-Sherif et al described an Experimental model Of TdP using the Neurotoxin AP-A, Today considered the Perfect surrogate Model of LQT3

The model was Described 7 years Before the first patient With LQT3 was reported



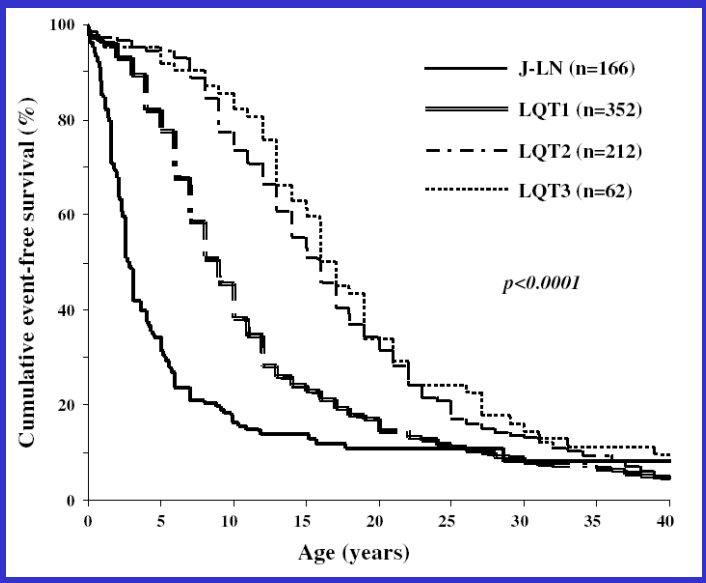
IONIC BASIS OF CONGENITAL AND ACQUIRED LQTS.

- **INCREASE OF INWARD CURRENTS: $I_{NA\text{-}SLOW}$, $I_{CA\text{-}L/CA\ WINDOW\ CURRENT}$, $I_{Na/Ca}$.**
- **DECREASE OF OUTWARD CURRENTS: I_{kr}. I_{ks}. I_{K1}, I_{to}, I_p**

Table 1. LQTS Genes

Gene	Syndrome	Frequency	Locus	Protein (Functional Effect)
KCNQ1 (LQT1)	RWS, JLNS	40–55	11p15.5	Kv7.1 (↓)
KCNH2 (LQT2)	RWS	30–45	7q35–36	Kv11.1 (↓)
SCN5A (LQT3)	RWS	5–10	3p21–p24	NaV1.5 (↑)
ANKB (LQT4)	RWS	<1%	4q25–q27	Ankyrin B (↓)
KCNE1 (LQT5)	RWS, JLNS	<1%	21q22.1	MinK (↓)
KCNE2 (LQT6)	RWS	<1%	21q22.1	MiRP1 (↓)
KCNJ2 (LQT7)	AS	<1%	17q23	Kir2.1 (↓)
CACNA1C (LQT8)	TS	<1%	12p13.3	L-type calcium channel (↑)
CAV3 (LQT9)	RWS	<1%	3p25	Caveolin 3 (↓)
SCN4B (LQT10)	RWS	<1%	11q23.3	Sodium channel-β4 (↓)
AKAP9 (LQT11)	RWS	<1%	7q21–q22	Yotiao (↓)
SNTA1 (LQT12)	RWS	<1%	20q11.2	Syntrophin α1 (↓)
KCNJ5 (LQT13)	RWS	<1%	11q24	Kir3.4 (↓)

Event=free survival comparing J-LN patients with Patients with LQT1, LQT2. and LQT3



Schwatz et al, Circ Arrhythm Electrophysiol, 2012

Long QT Syndromes
ROLE OF MODIFIER GENES

- Modifier genes are genes that are not involved in the genesis of the disease, but modify the severity of the phenotypic expression.
- The final phenotype is the result of interaction between the causal genes, genetic background (modifier genes), and inviromental factors.
- Identification of modifier genes could help implement preventive and therapeutic measures in patients susceptible to drug-induced LQTS/TdP

A perfect example of how modifier genes are discovered and reporeted

Genetic variation of nitric oxide synthase 1 adaptor protein (NOS-1 AP).

- A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. Arkin et al, Nature Genetics 2006.

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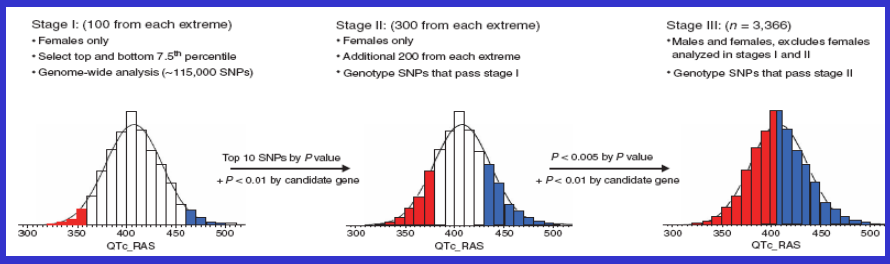

Genome-wide Association Study (GWAS) of the QT Interval

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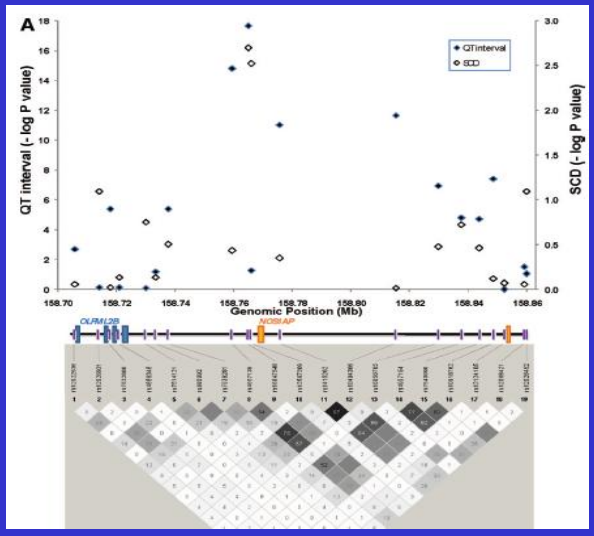

Plots of association for both QT interval and SCD in whites

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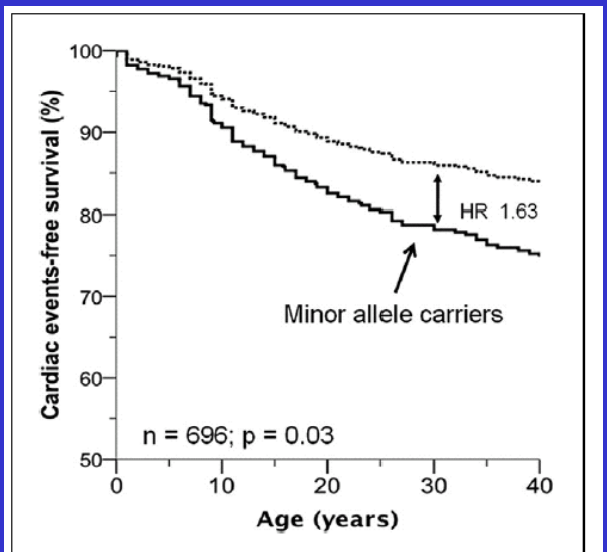

Figure 2 Effect of rs10494366 Minor Allele in LQTS With QTc <500 ms

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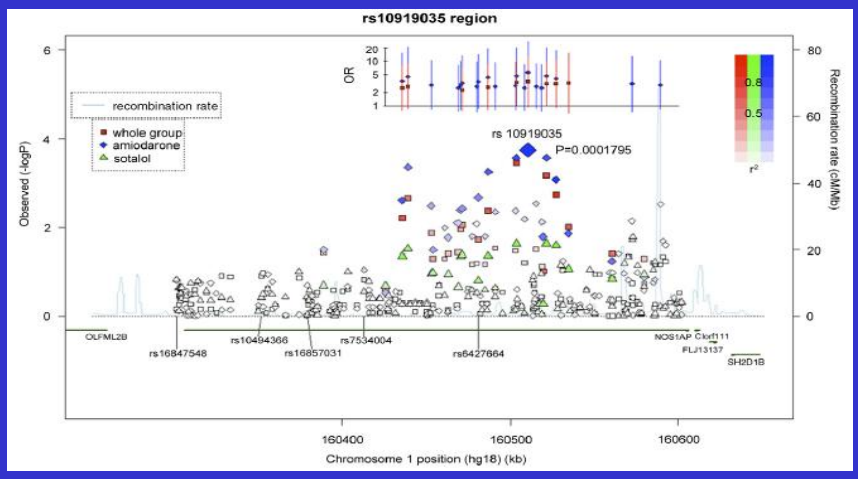
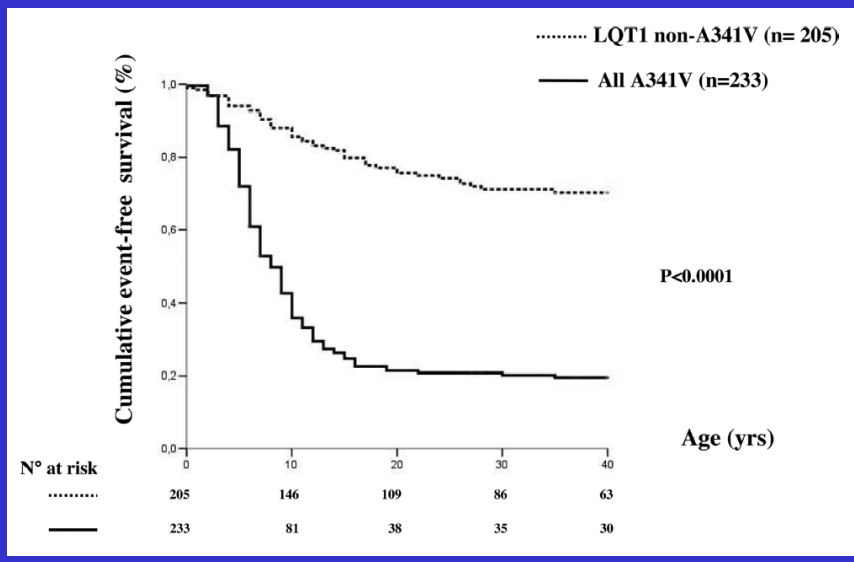
Jamshidi et al, J Am Coll cardiol 2012



Regional Association Plot for NOS1AP SNPs

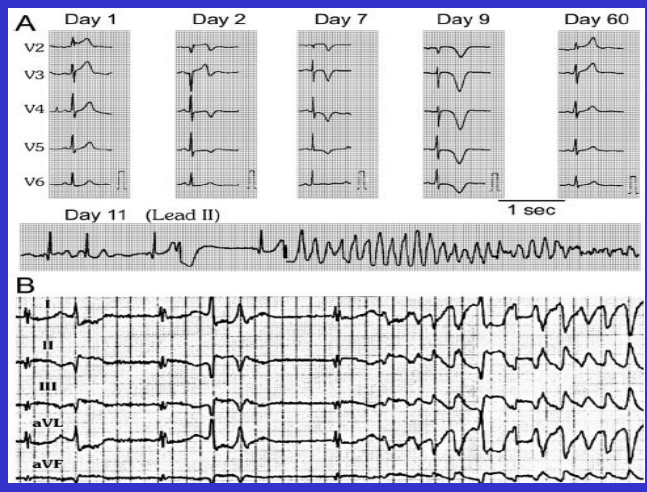
The Common Long-QT Syndrome Mutation KCNQ1/A341VCauses Unusually Severe Clinical Manifestations in Patients With Different Ethnic Backgrounds

Crotti et al, Circulation 2007



Torsade de Pointes following acute myocardial infarction: Evidence of a deadly link with a common genetic variant

Crotti et al, Heart Rhythm 2012;9:1104-12



A common KCNH2-K897T polymorphism is associated with increased risk of TdP in the subacute phase of myocardial infarction

Management options in Long QT Syndrome

- The AICD
- Drugs, primarily Beta Blockers
- High dose Beta Blockers + Anti-Bradycardia Pacemaker
- Cervico-dorsal Sympathectomy

Long QT Syndrome From Genetics to Management

Schwartz et al
Circ Arrhythmia Electrophysiol 2012

Table 2. LQTS Diagnostic Criteria of 1993 to 2011

		Points
Electrocardiographic findings		
A	QTc,* ms	
	≥480	3
	460–479	2
	450–459 (men)	1
B	QTc* 4th minute of recovery from exercise stress test ≥480 ms	1
C	Torsades-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 younger than age 30 among immediate family members§	0.5

Hearts too Good to Die

Q: Why as an Internist one should care about a bunch of EXOTIC syndromes that only account for a small percentage of SCD victims?

A: The majority are young individuals with structurally normal hearts. To be able to make the diagnosis, followed by appropriate management to save one life, ought to be one of the most rewarding experience for an internist (not to mention a Cardiologist)

El-Sherif, Turitto: The Long QT Syndrome and TdP, Pacing and Clinical Electrophysiology, 1999 (figure 1)


THANK YOU
NABIL EL-SHERIF