Ion channel Genes and Propensity to TdP

Silvia Priori, MD PhD

FSM- Molecular Cardiology

QT INTERVAL

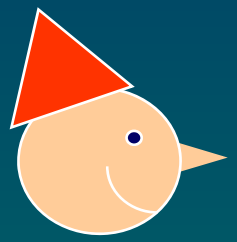
LONG

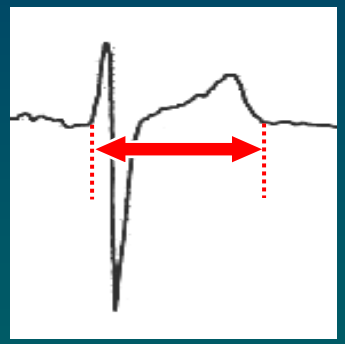
NORMAL

SHORT

QT INTERVAL

LONG





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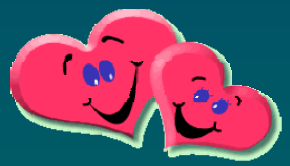
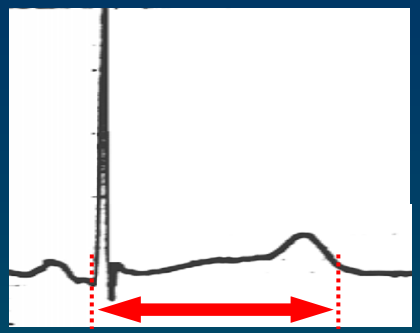
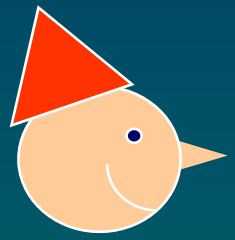


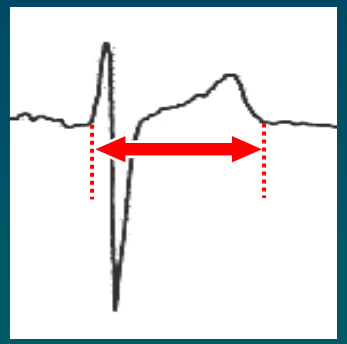
SHORT

QT INTERVAL



LONG





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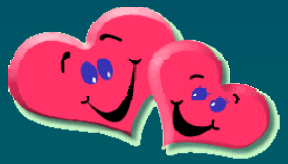
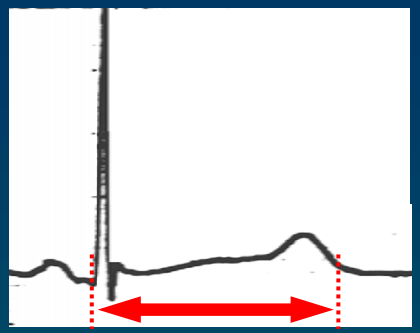
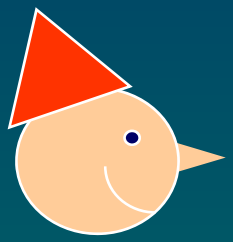


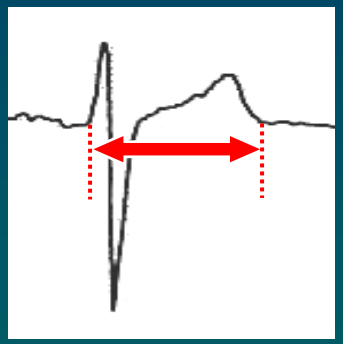
SHORT

QT INTERVAL



LONG





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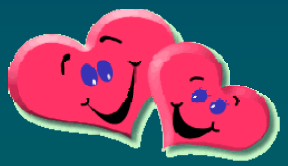
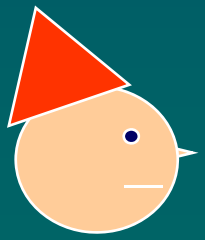
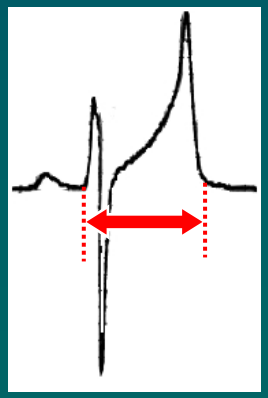
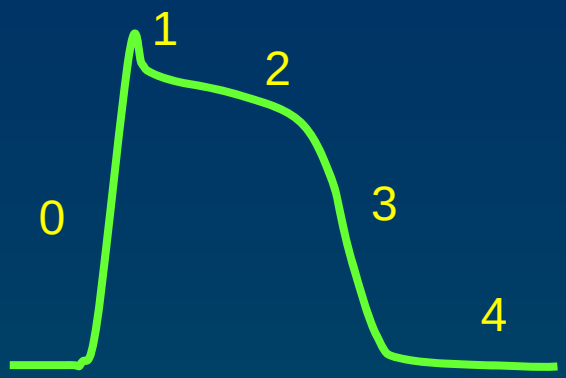






SHORT

What determines the duration of QT interval?

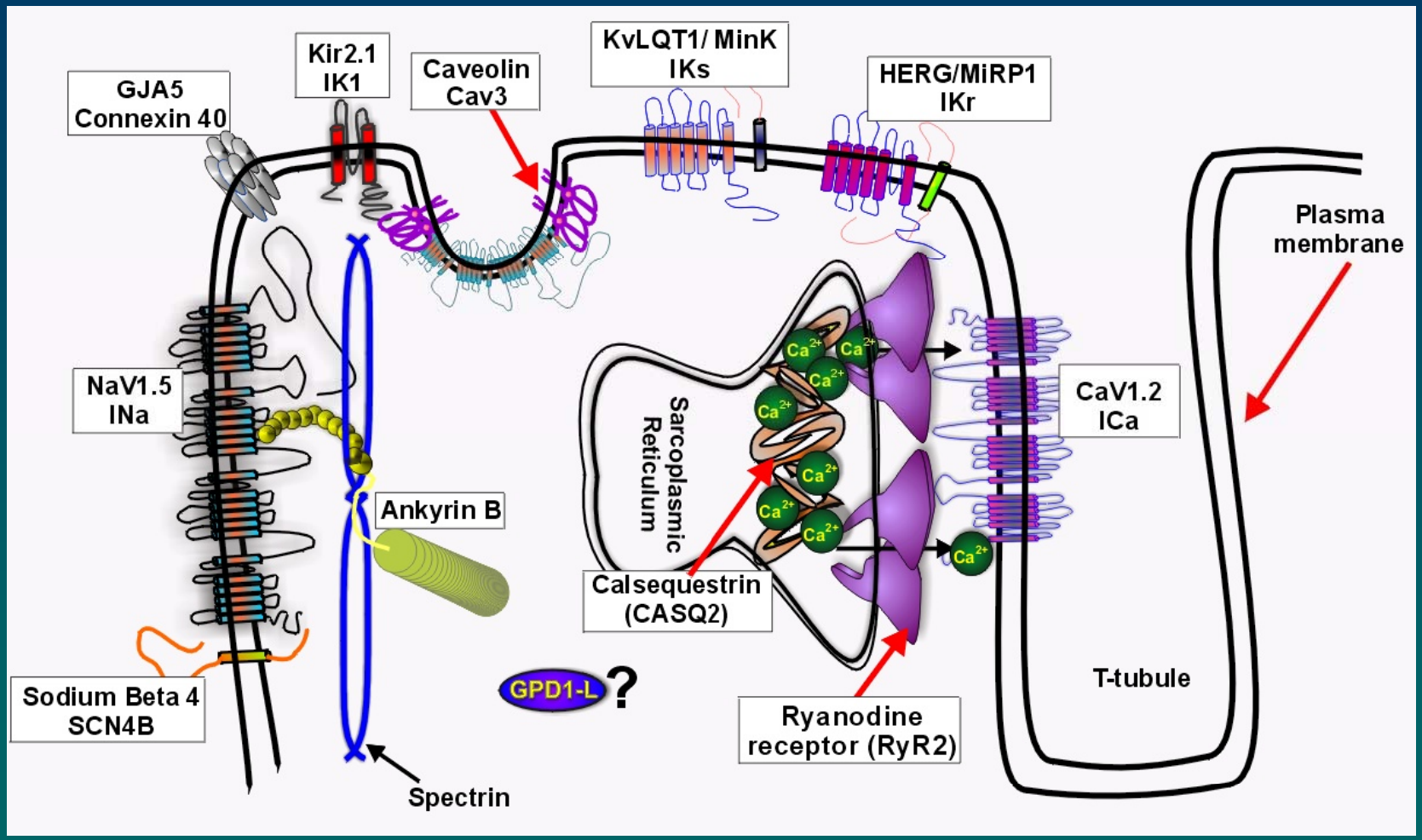


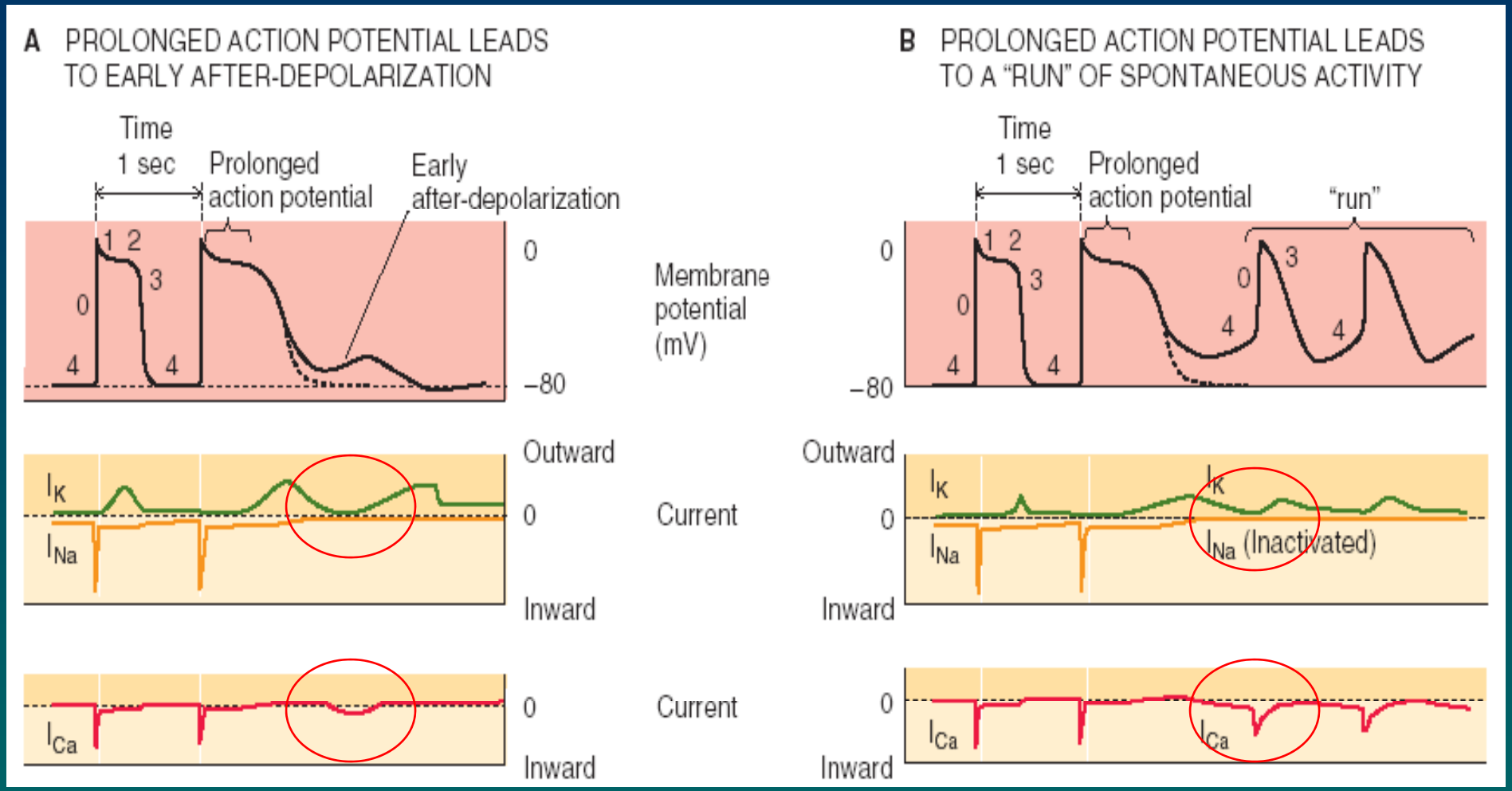
Action Potential Phases

0 = depolarization
1 = fast repolarization
2 = plateau
3 = terminal repolarization
4 = resting

Current		Protein	Gene
Sodium current (I_{Na})		Nav 1.5	*SCN5A*
Calcium current (I_{Ca})		Cav 1.2	*CACNA1C*
Na-Ca exchanger (I_{ti})		NCX1	*SLC8A1*
Transient Outward (I_{To})		Kv4.2/Kv4.3	*KCND2/KCND3*
Delayed Rectifier Slow (I_{Ks})		KvLQT1/minK	*KCNQ1/KCNE1*
Delayed Rectifier Fast (I_{Kr})		HERG/MiRP	*KCNH2/KCNE2*
Inward Rectifier Slow (I_{K1})		Kir2.1	*KCNJ2*
Pace maker current (I_f)		hHCN4	*HCN4*

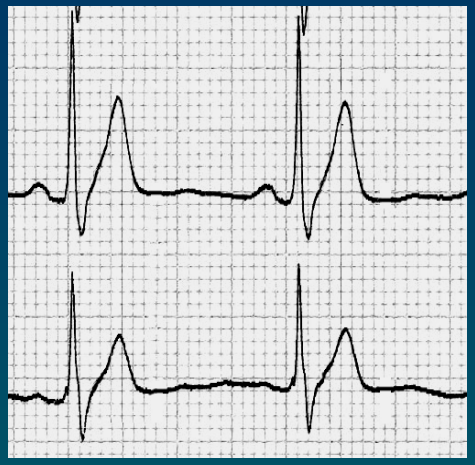
Genes involved in QT abnormalities

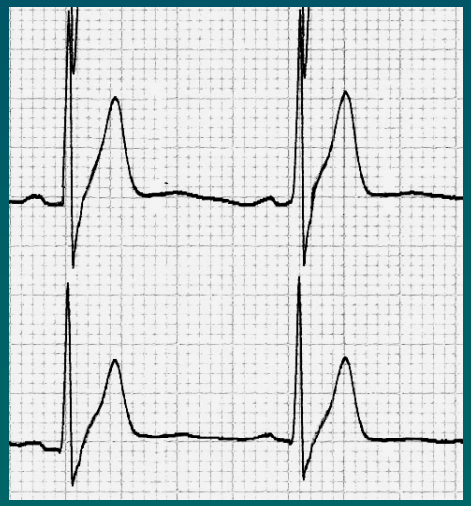




Extended phase two cause long QT syndrome.

SHORT QT SYNDROME



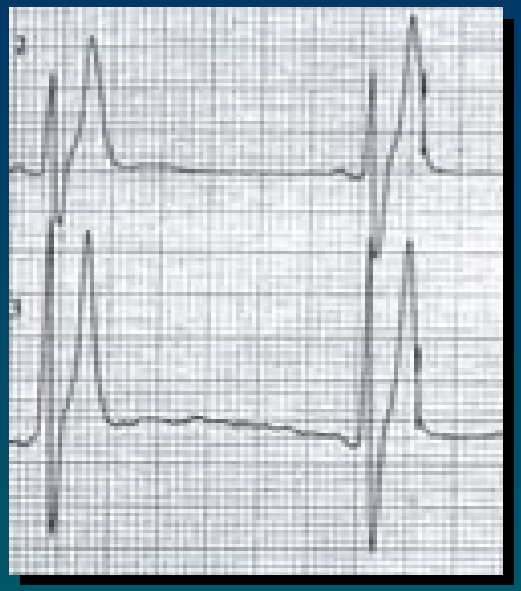


- **QTc interval < 320 msec;**
- **tall peaked T waves**
- **Autosomal dominant**

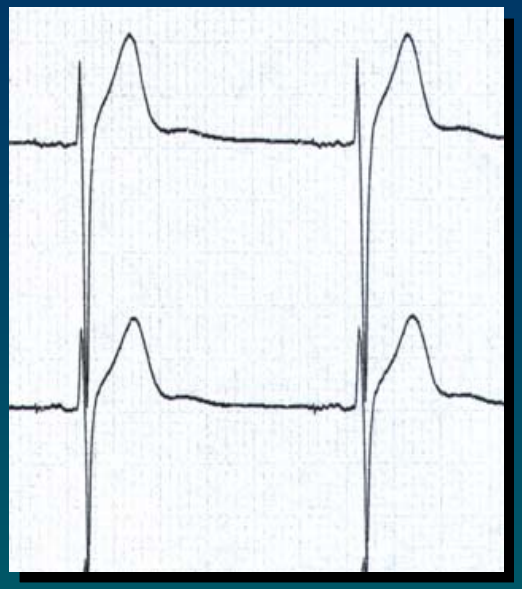
SQTS1: *KCNH2*
SQTS2: *KCNQ1*
SQTS3: *KCNJ2*

<u>OPEN ISSUES</u>
- **Prevalence (probably low)**
- **What is Short QT?**

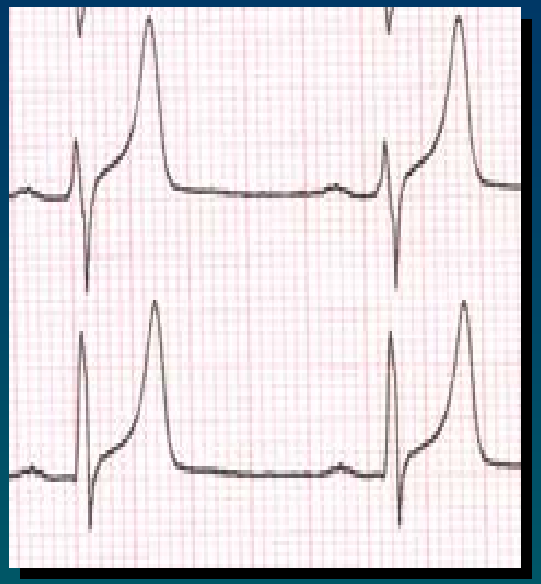
Gain of function of K^+ channels and ECG



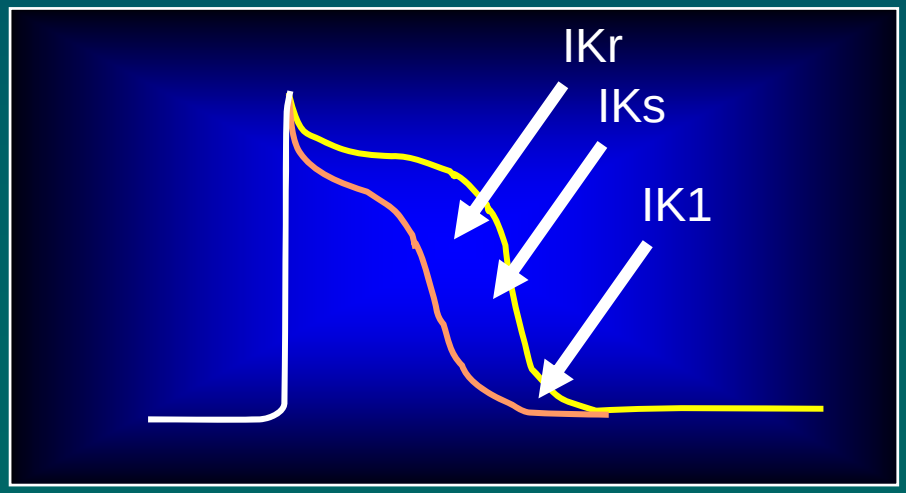
SQTS1



SQTS2

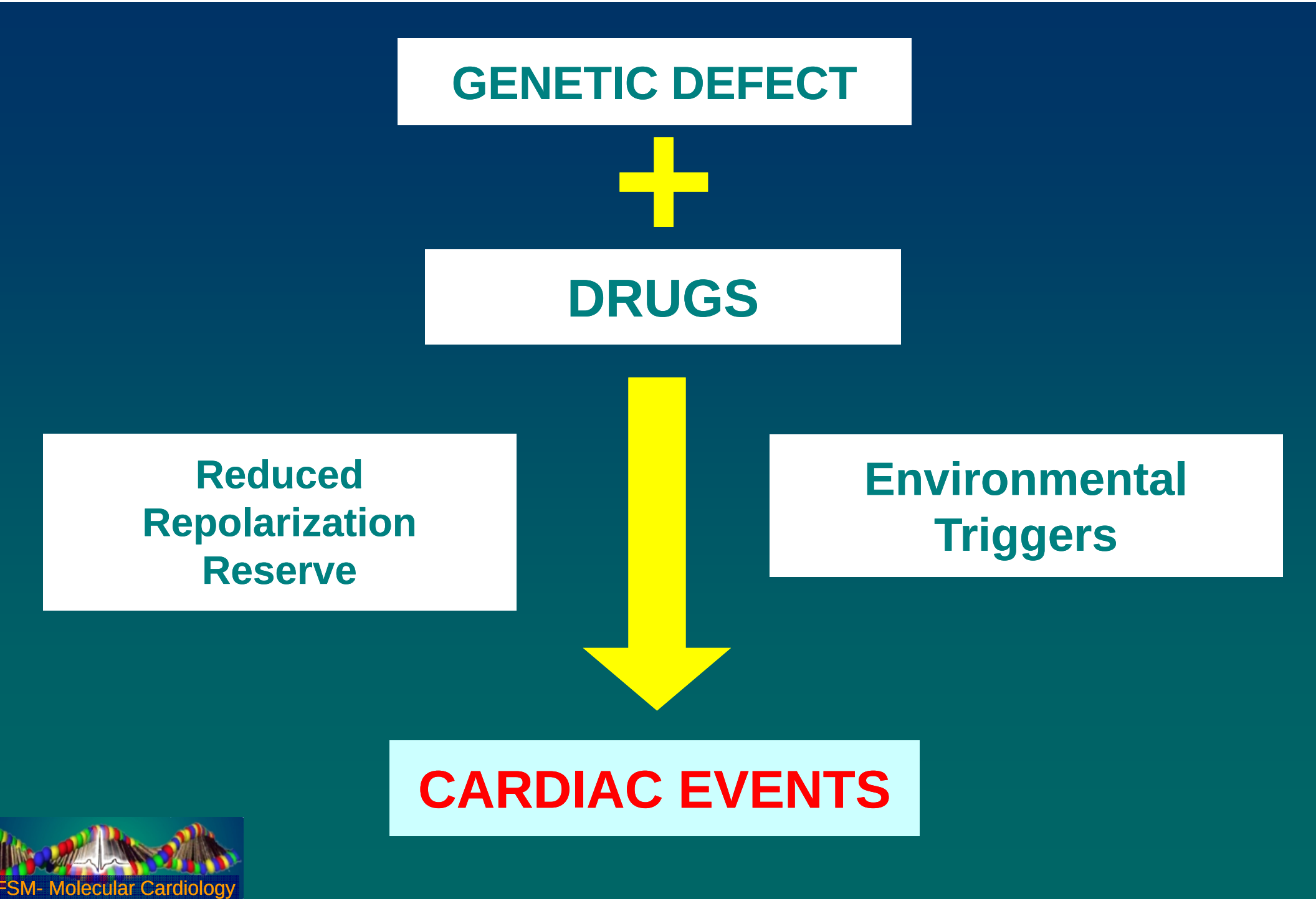


SQTS3



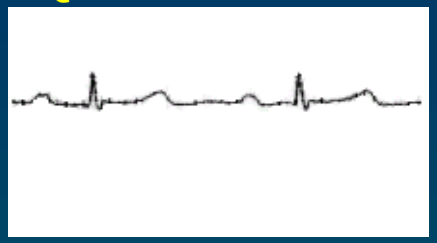
1.

“Mild” genetic defects or incompletely penetrant forms of LQTS predisposing to TdP

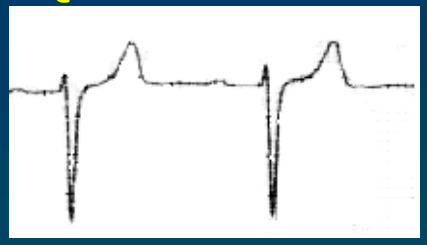

GENETIC DEFECT
+
DRUGS
Reduced Repolarization Reserve
Environmental Triggers
CARDIAC EVENTS

Control – Pre Treatment

QTc 430ms

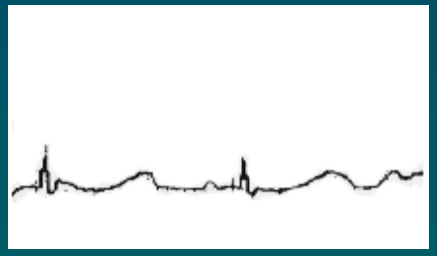


QTc 437ms

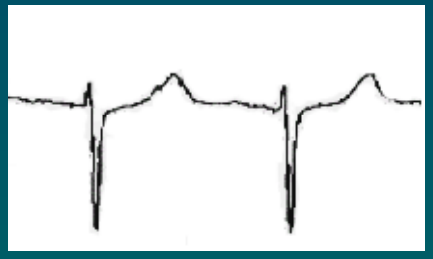


Cisapride 30mg

QTc 523ms



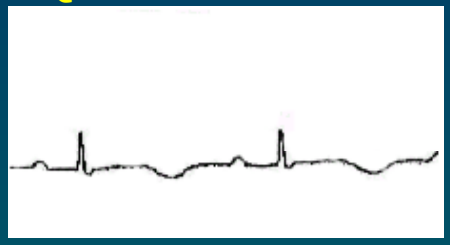
QTc 530ms



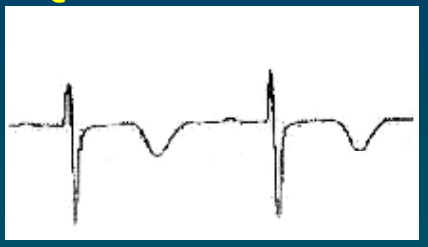
VF

Cisapride 30mg

QTc 595ms

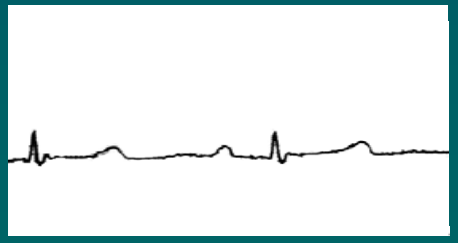


QTc 590ms

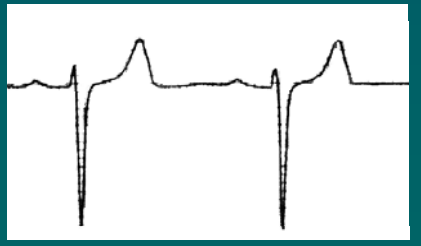


After Cisapride Withdrawal

QTc 430ms



QTc 428ms



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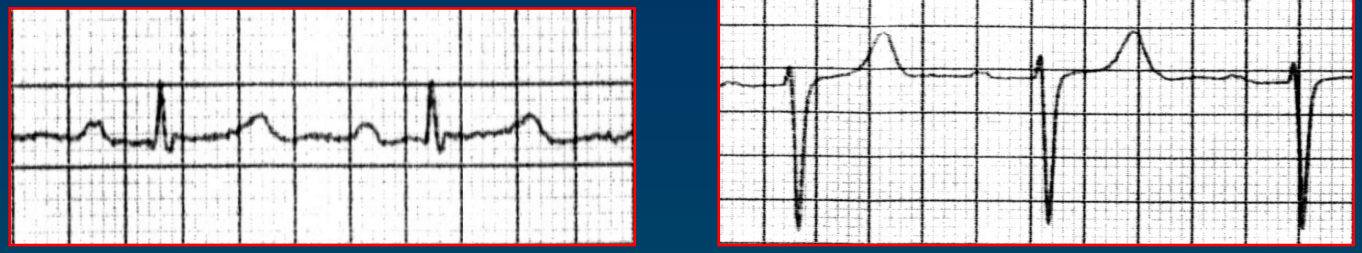
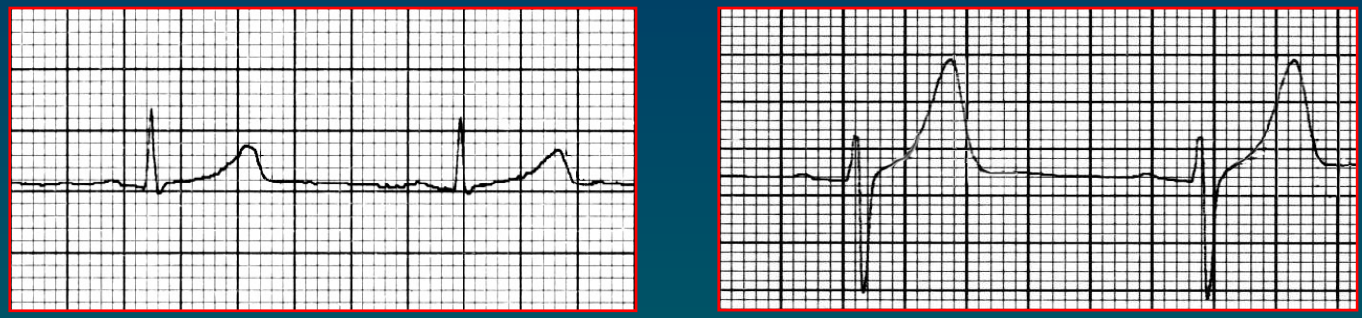
Napolitano C et al. JCE, 2000

Kindred: MA012: Mutation in *KvLQT1* gene

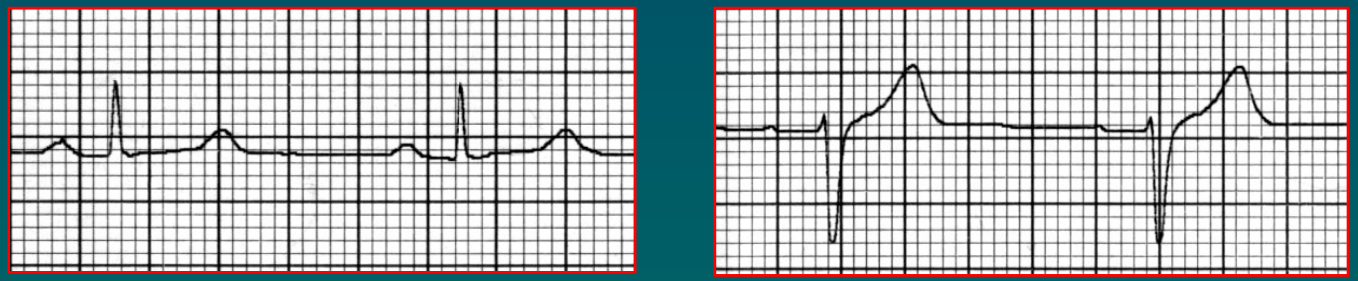
Proband: 69 yrs,
QTc: 445 ms
Gene Carrier



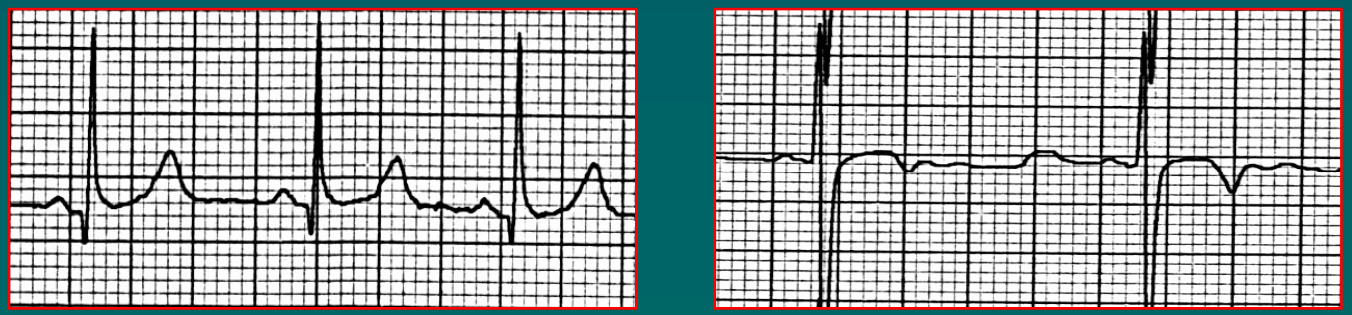
Son: 50 yrs,
QTc: 430 ms
Gene Carrier



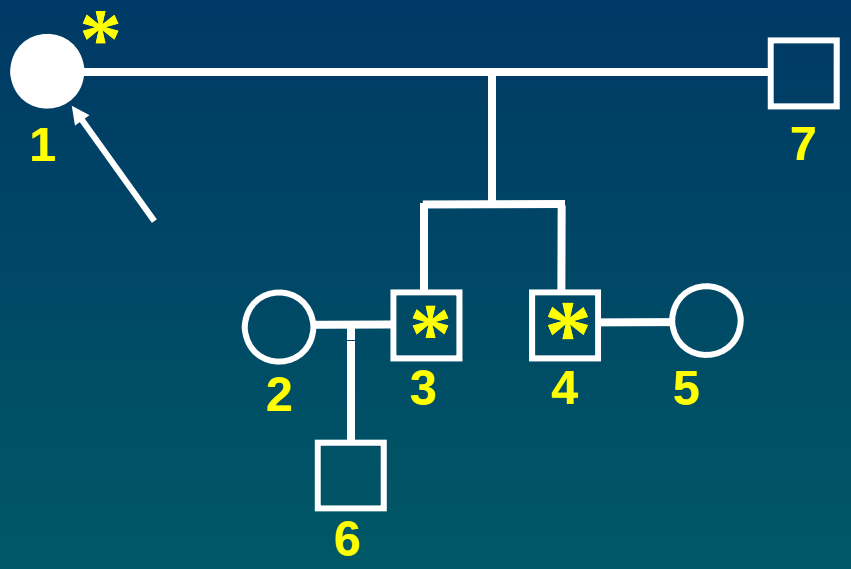
Son: 44 yrs,
QTc: 398 ms
Gene Carrier

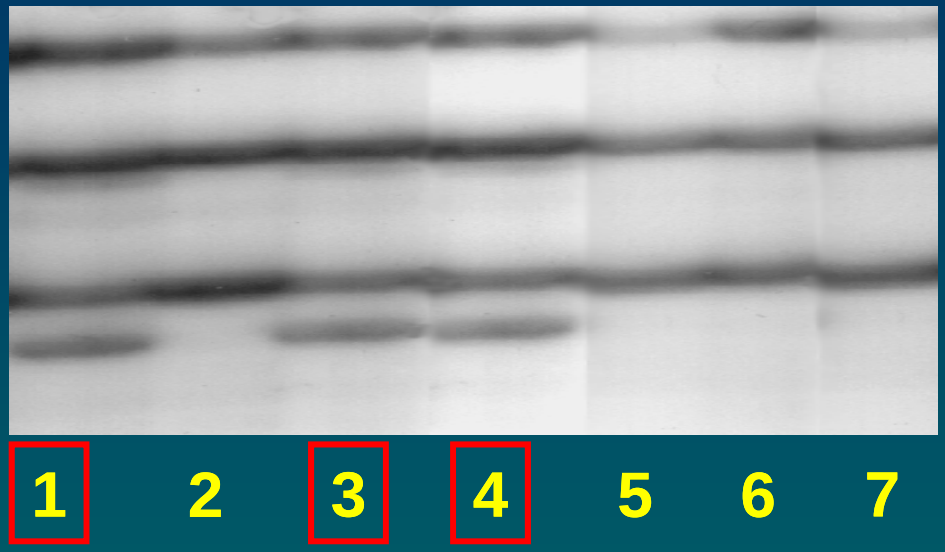


Nephew: 9 yrs,
QTc: 392 ms
Non Gene Carrier



Drug-Induced TdP: KCNQ1 mutation





Y315C

KvLQT1-Hu:	V	V	T	V	T	T	I	G	Y	G	D	K	V	P	Q	T	W	V	G	K
KvLQT1-RN:	V	V	T	V	T	T	I	G	Y	G	D	K	V	P	R	-	-	-	-	-
KvLQT1-CE:	V	V	T	V	M	T	V	G	Y	G	D	I	Y	P	V	G	A	L	T	K
KvLQT1-XL:	V	V	T	V	T	T	I	G	Y	G	D	K	V	P	Q	T	W	I	G	K

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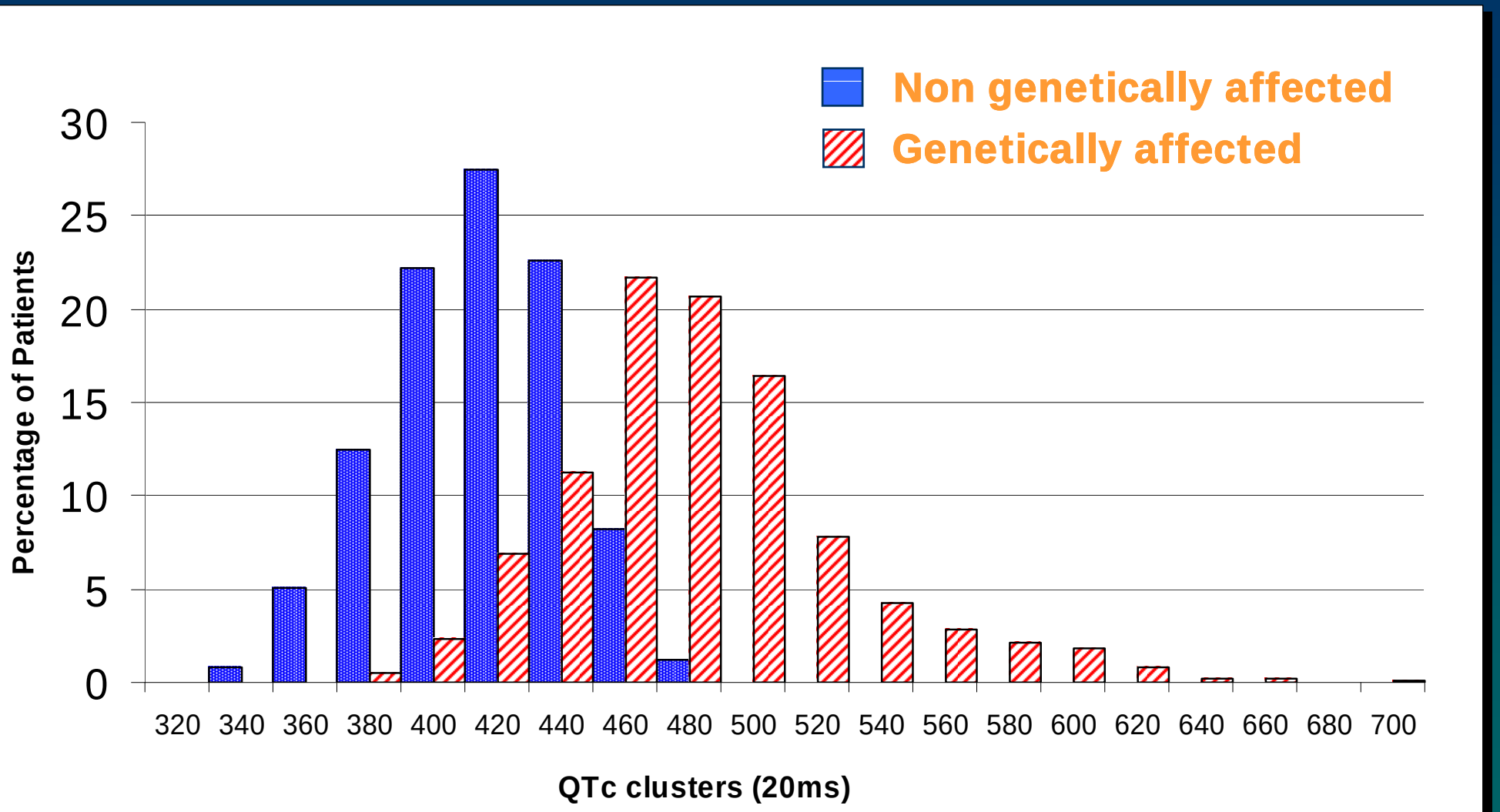
Napolitano C et al. JCE, 2000



Mutation carriers with normal QT interval:
12% incidence of syncope – 4% incidence of cardiac arrest

Napolitano et al JAMA 2005

2.

Common variants of genes called SNPs may predispose to TdP

Suceptibility SNP's

+

DRUGS

Reduced Repolarization Reserve

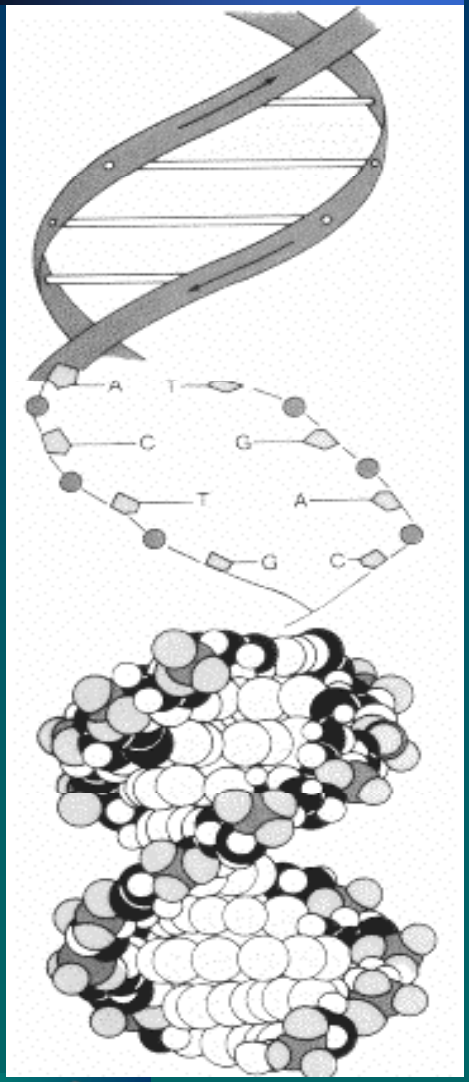
Environmental Triggers

CARDIAC EVENTS

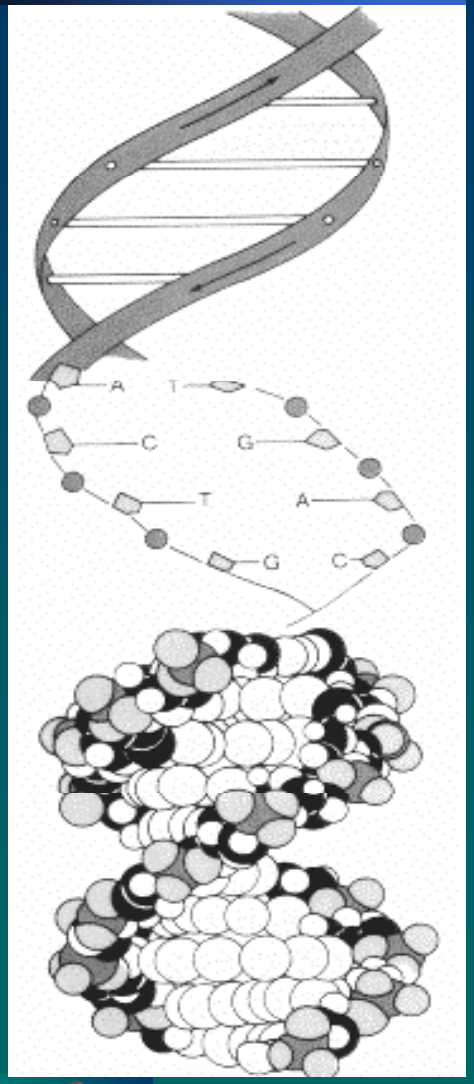
Genetic variation: 0.3 %

(~10 mill SNPs)

DNA

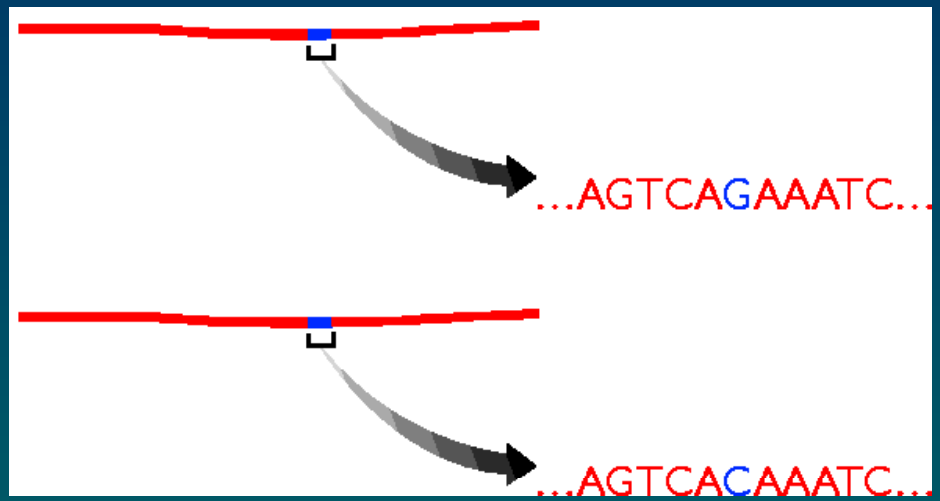


DNA

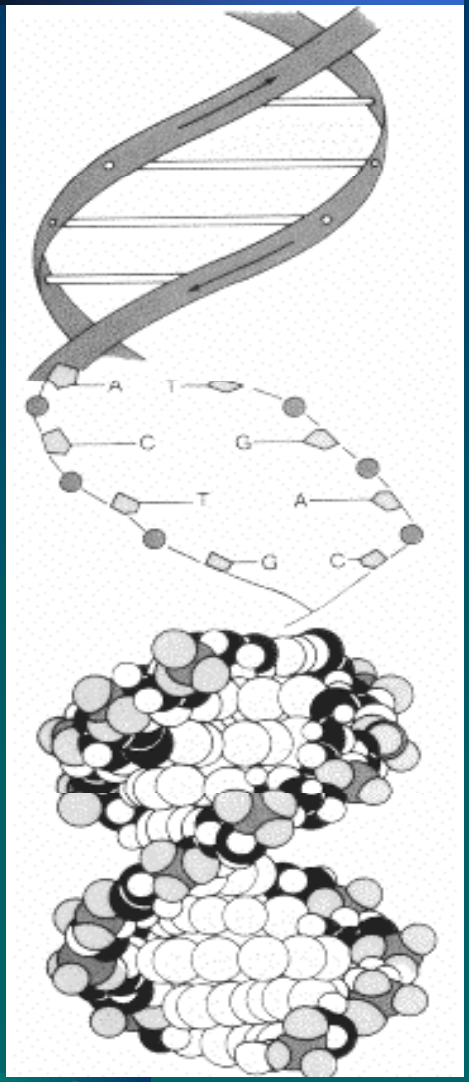


SNPs

Single Nucleotide Polymorphisms

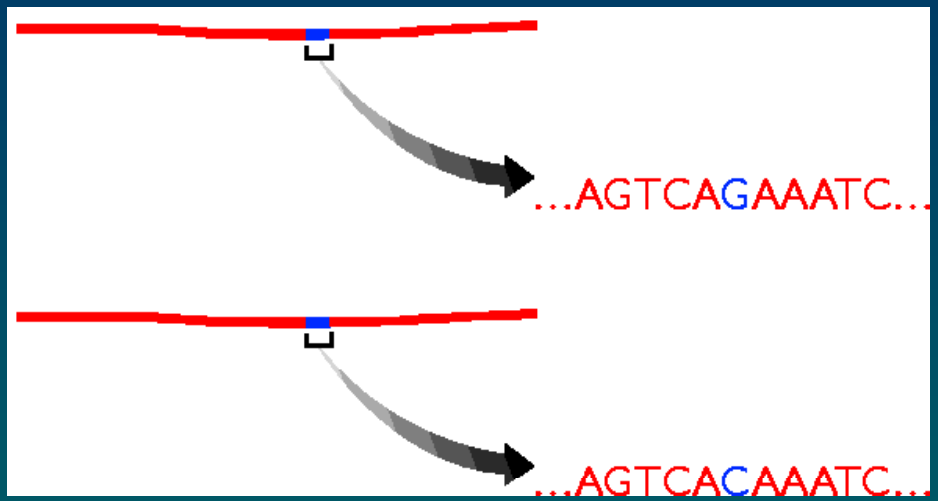


DNA



SNPs

Single Nucleotide Polymorphisms



- ✓ Frequent
- ✓ Well distributed
- ✓ Stable
- ✓ Functional?

Nitric oxyde synthase and QT interval

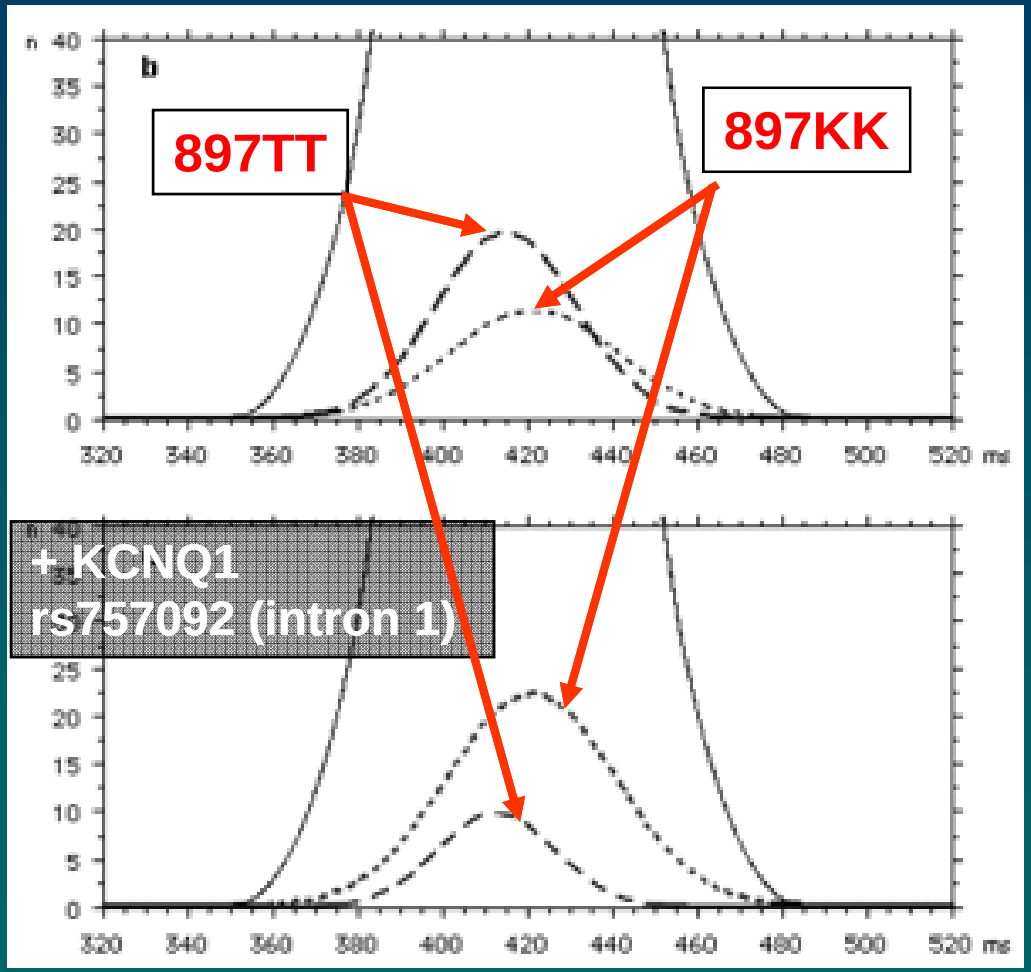
- ✓ Genome-wide association study on 200 subjects at the extremes of a population-based QT interval distribution of 3,966 subjects from the KORA cohort in Germany
- ✓ Validated cohort in two independent samples of 2,646 subjects from Germany and 1,805 subjects from the US Framingham Heart Study.
- ✓ This genome-wide study identified NOS1AP (CAPON), a regulator of neuronal nitric oxide synthase, as a new target that modulates cardiac repolarization.
- ✓ **The minor allele of the NOS1AP genetic variant explains up to 1.5% of QT interval variation.**

Arking DE et al. Nat Genet 2006

Polymorphisms in LQTS genes and QT interval

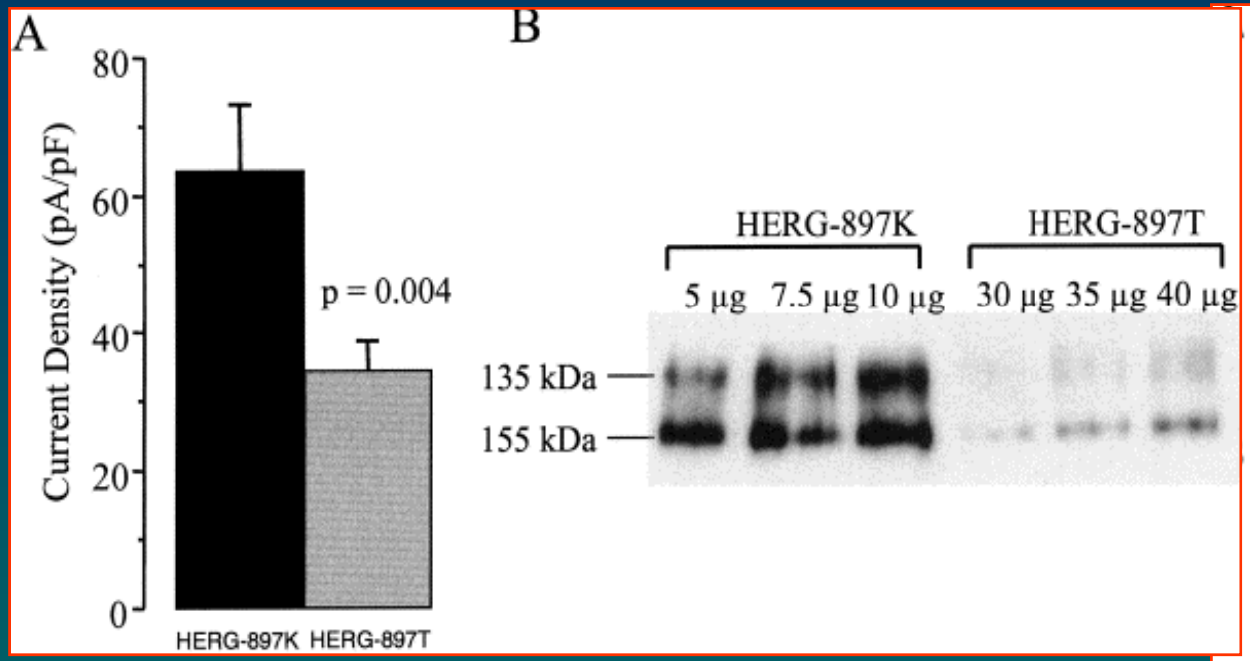
- ✓ The analysis of additive effects by an allelic score explained a 10.5 ms difference in QTc between extreme groups and 0.95% of trait variance (*P*<0.00005).

Samples from the KORA study

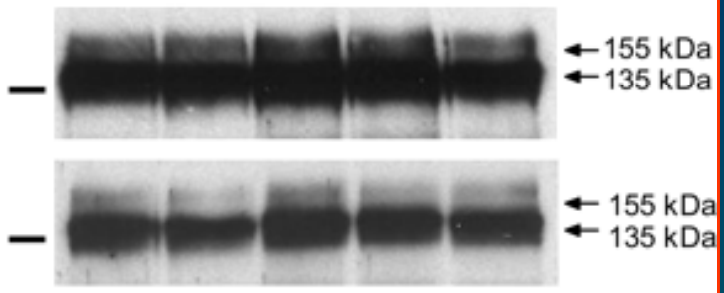


Pfeufer, A. et al. Circ Res 2005;96:693-701

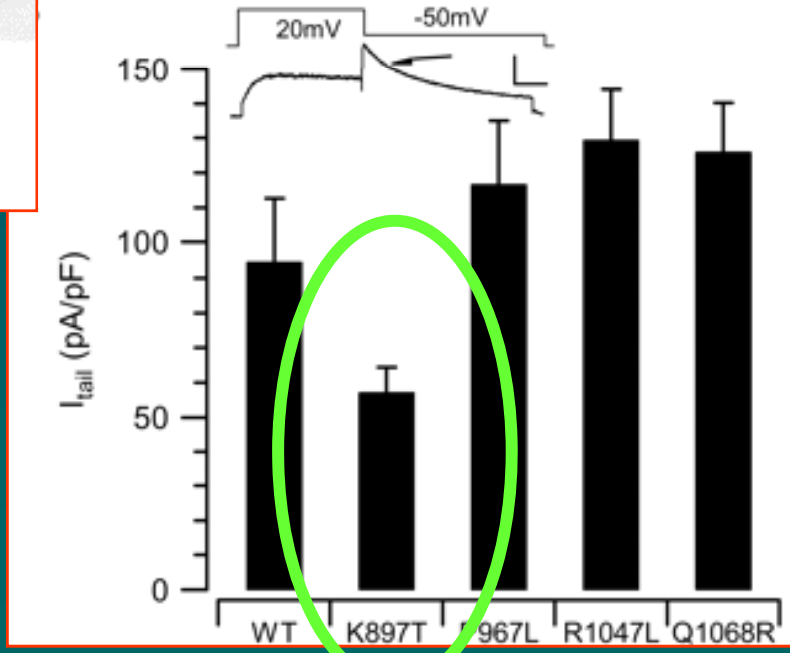
KCNH2 K897T polymorphism is functionally active



Paavonen et al. Cardiovascular Research 2003;59:603-611



Ansen et al. AJP 2004;286:H2434-H2441



Allelic variants and TdP: how often?

“DNA variants in the coding regions of congenital long-QT disease genes predisposing to aLQTS can be identified in 10% to 15% of affected subjects, predominantly in genes encoding ancillary subunits.“

Yang et al Ciculation 2002

Genetic variants that modify drug metabolism of QT prolonging drugs.

- ✓ Genetic factors may play a very important role in inlfuencing the eficiency of metabolism of QT prolonging drugs.
- ✓ Genetic variants of the gene for CYP2D6 are present in poor metabolizers who are more prone to accumulation of compounds.

Conclusions

- ✓ Beside gender, drugs and metabolic abnormalities may rpedispose to TdP
- ✓ “Forme fruste” of LQTS cause approximately 8% of drug induced TdP (Circulation 2002)
- ✓ SNPs of genes that regulate QT durations (increase or decrease) are likely to contribute to TdP susceptibility
- ✓ SNPs of genes that regulate metabolism of drugs that affect repolarization are likely to play a role in TdP