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Schleswig-
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Essen
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Augsburg
Baden-
Württemberg
Freiburg
München
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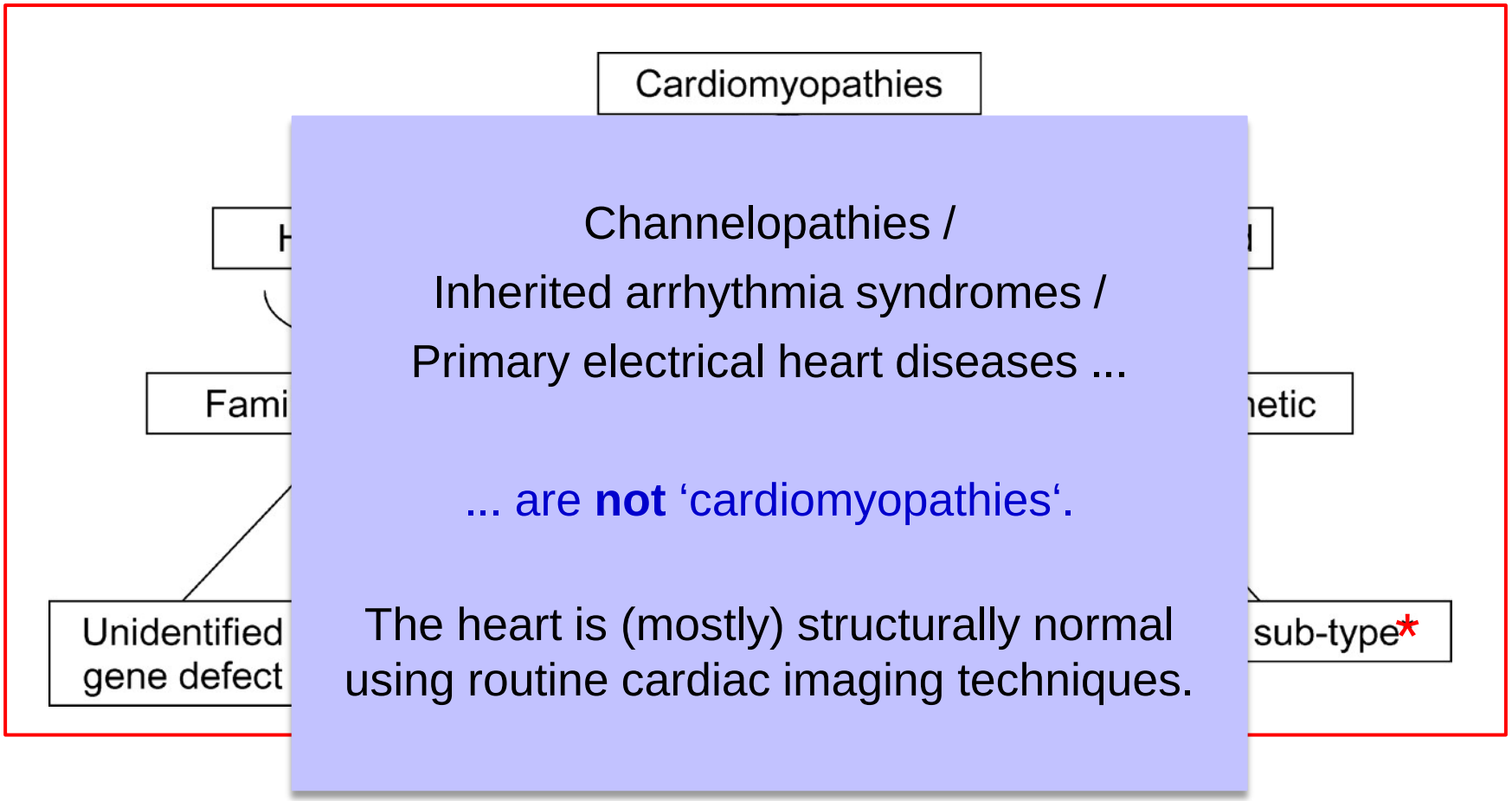
ESC Classification of Cardiomyopathies (morphological)



Elliott et al. (2008) Eur. Heart J. 29: 270-276

Cardiac Ion Channel Disorders
(Primary Electrical Heart Diseases)

Ventricular	**Supraventricular**
Long-QT syndrome (LQTS)	Sinus node dysfunction*
Short-QT syndrome (SQTS)	Atrial fibrillation*
Brugada syndrome*	AV block*
Polymorphic VT/VF (CPVT)	RBBB, LBBB, ...*
Early Repolarisation (ERS)*	WPW (+HCM)

(Idiopathic VF)
(drug-induced LQTS)
(SIDS, SUDS/SADS, drowning/sport victims, …)

*: exclude phenocopies (mimicking conditions),
consider genetics if familial or unexplained/idiopathic case

DGK / DGPK Expert Consensus Statement

Molecular Diagnostics of Cardiovascular Diseases

Arrhythmias

- Long-QT syndrome (LQTS)
- Catecholam. polymorphic VT (CPVT)
- Syndromic: JLNS, Timothy, Andersen **1**

Brugada syndrome (BrS) **2A**

- Others: IVF, early repolarisation, Short-QT (SQTS), drug-induced forms, … **2B**

SNPs / Polymorphisms **3**

- Diagnostics
- Therapy
- Prognosis

Schulze-Bahr et al. (2015) Kardiol. online
Pocket guidelines
International version in prep.

DGK / DGPK Expert Consensus Statement

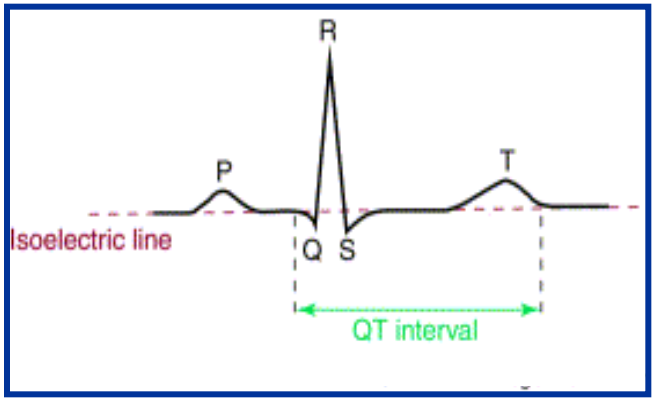
Molecular Diagnostics of Cardiovascular Diseases

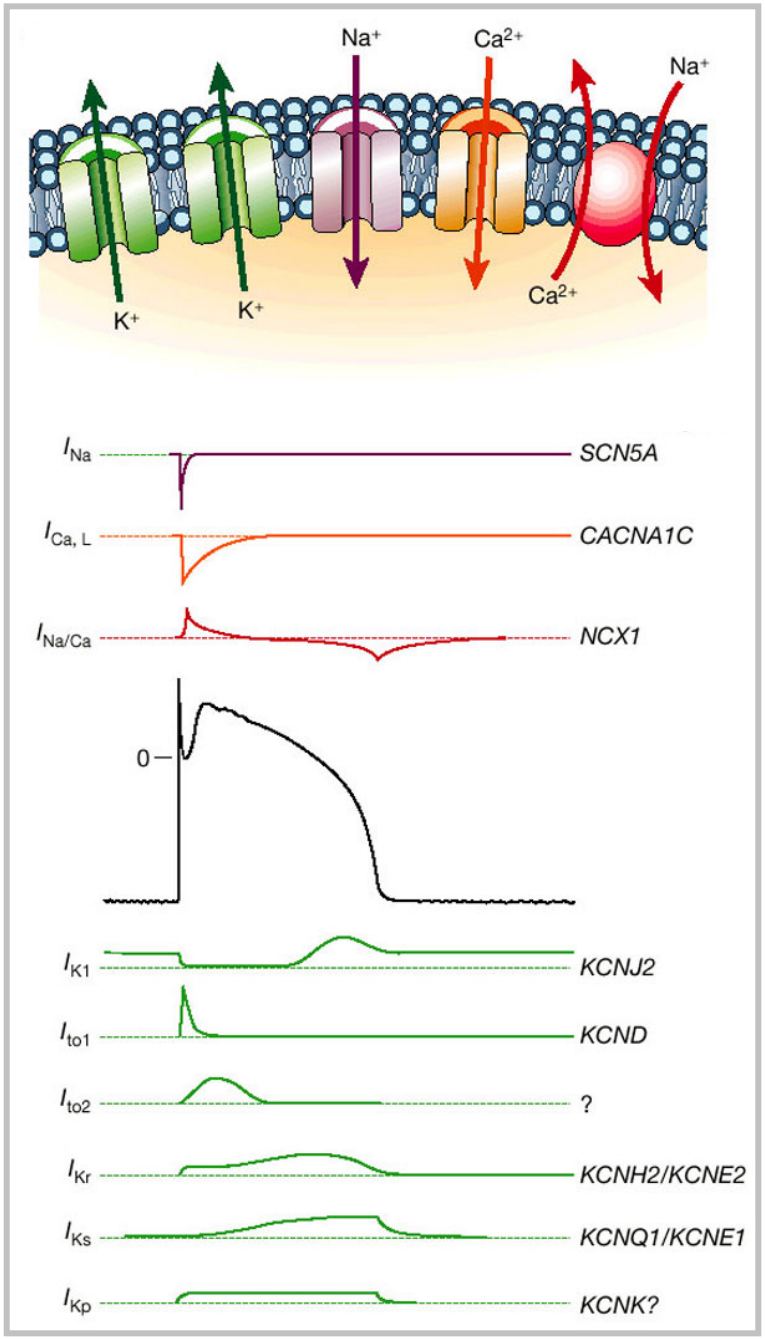
Indications for Molecular Diagnostics

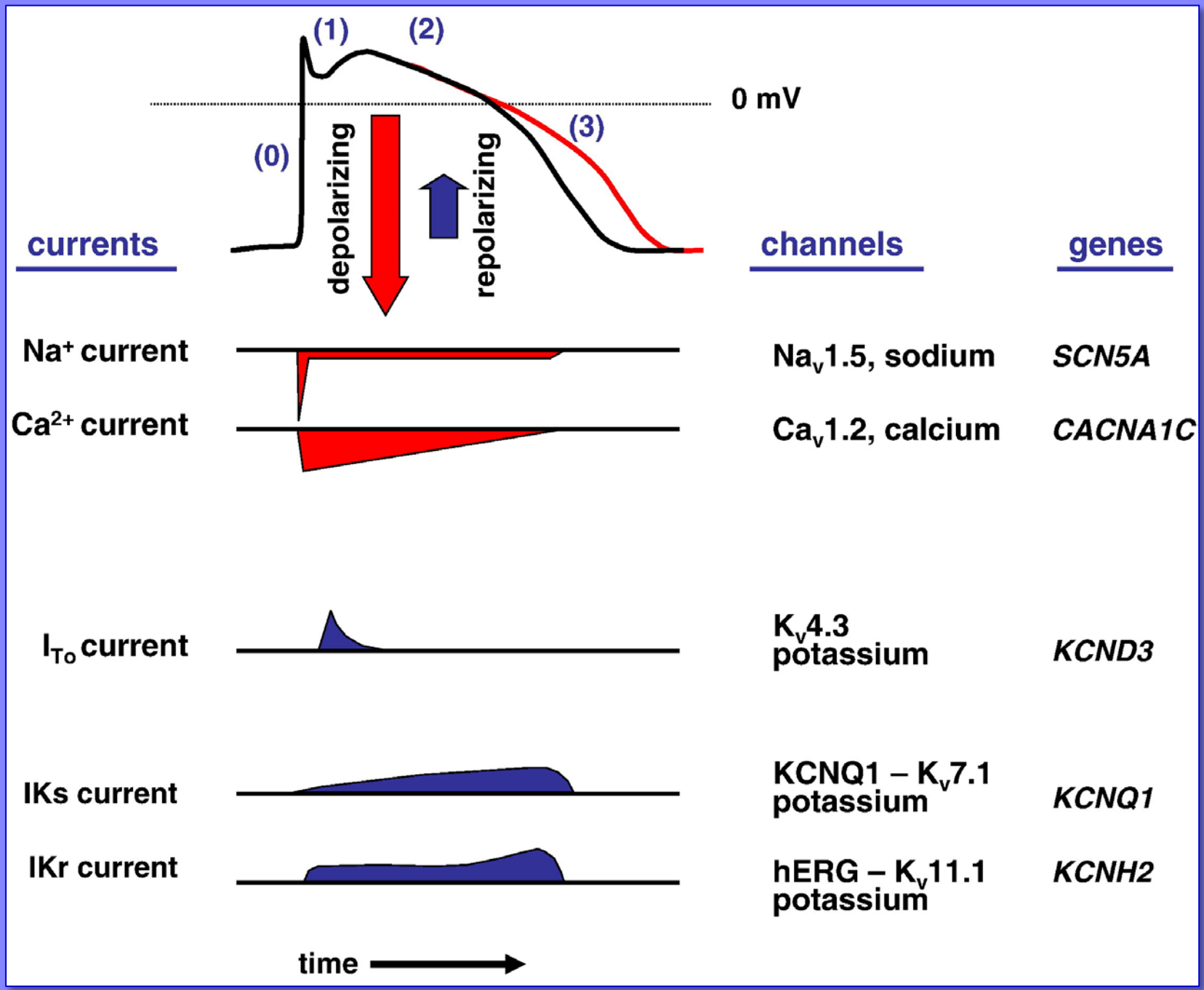
Disease:	Sensitivity >30%	
Gene:	Sensitivity >10%	**1**
Disease:	Sensitivity 10-30%	
Gene:	Sensitivity 1-10%	**2A**
Disease:	Sensitivity <10%	
Gene:	Sensitivity <1%	**2B**
Disease w/o genetic basis		
Gene w/o known relation with disease		**3**

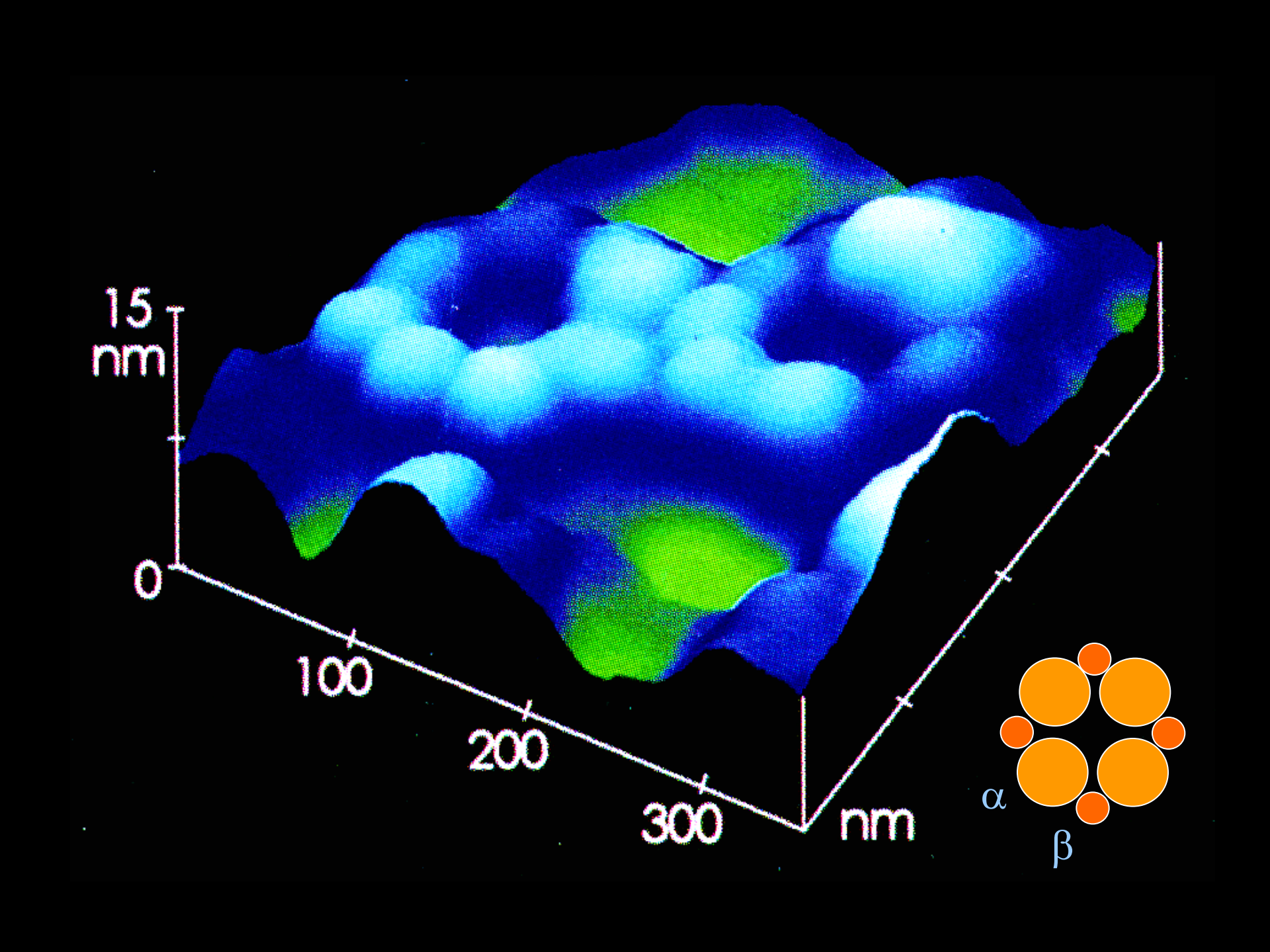
- Diagnostics
- Therapy
- Prognosis

Schulze-Bahr et al. (2015) Kardiol. online
Pocket guidelines
International version in prep.

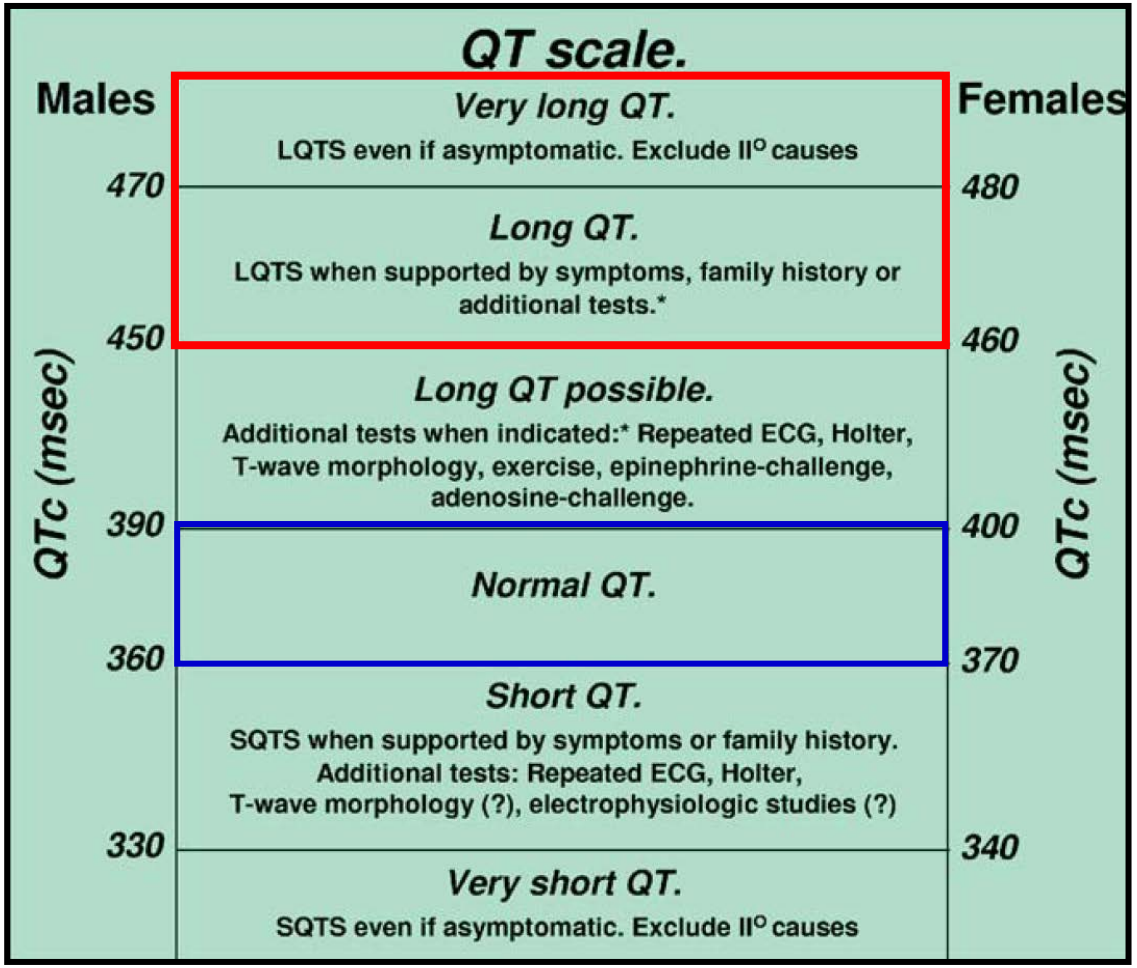

R
P
T
Isoelectric line
Q
S
QT interval


Na+
Ca2+
Na+
K+
K+
Ca2+
INa
SCN5A
ICa, L
CACNA1C
INa/Ca
NCX1
0
IK1
KCNJ2
Ito1
KCND
Ito2
?
IKr
KCNH2/KCNE2
IKs
KCNQ1/KCNE1
IKp
KCNK?

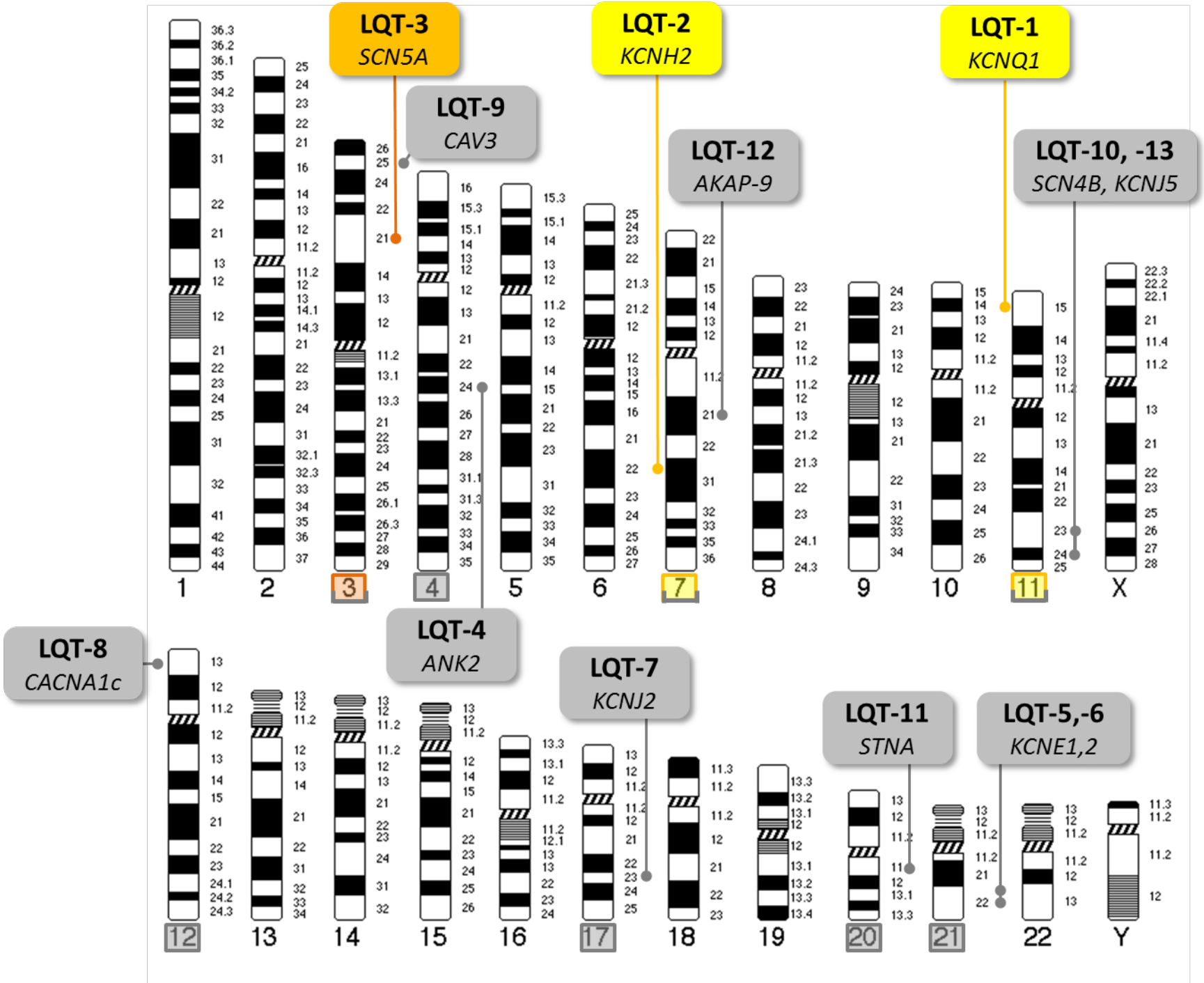

(1)
(2)
0 mV
(3)
(0)
depolarizing
repolarizing
currents
channels
genes
Na+ current
Nav1.5, sodium
SCN5A
Ca2+ current
Cav1.2, calcium
CACNA1C
ITo current
Kv4.3
potassium
KCND3
IKs current
KCNQ1 – Kv7.1
potassium
KCNQ1
IKr current
hERG – Kv11.1
potassium
KCNH2
time


15
nm
0
100
200
300
nm
α
β

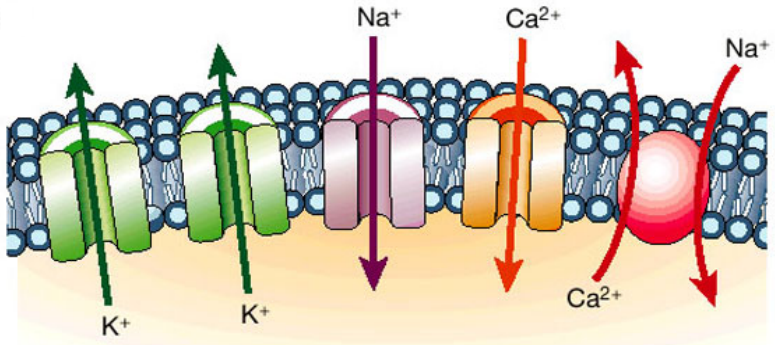
Heart-rate corrected QT Interval (QTc; Bazett‘s method)

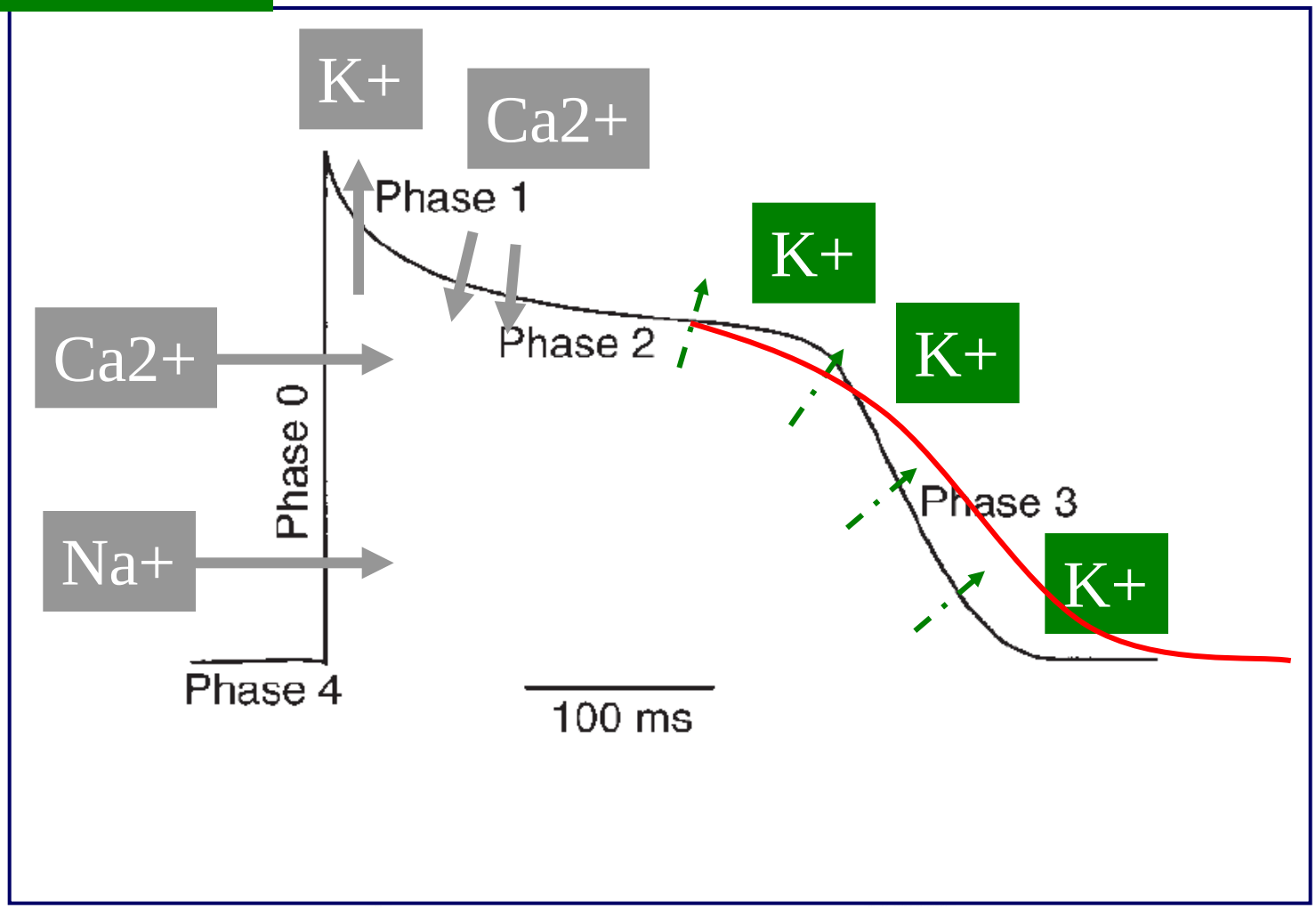


Viskin. Heart Rhythm 2009; 6: 711-715

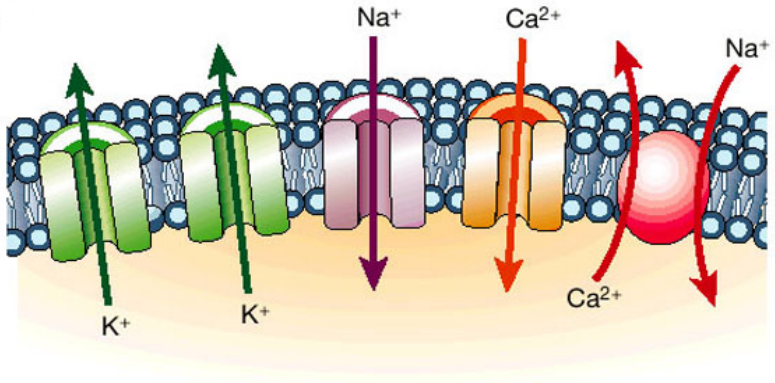

LQT-3
SCN5A
LQT-2
KCNH2
LQT-1
KCNQ1
LQT-9
CAV3
LQT-12
AKAP-9
LQT-10, -13
SCN4B, KCNJ5
LQT-8
CACNA1c
LQT-4
ANK2
LQT-7
KCNJ2
LQT-11
STNA
LQT-5,-6
KCNE1,2
1
2
3
4
5
6
7
8
9
10
11
X
12
13
14
15
16
17
18
19
20
21
22
Y

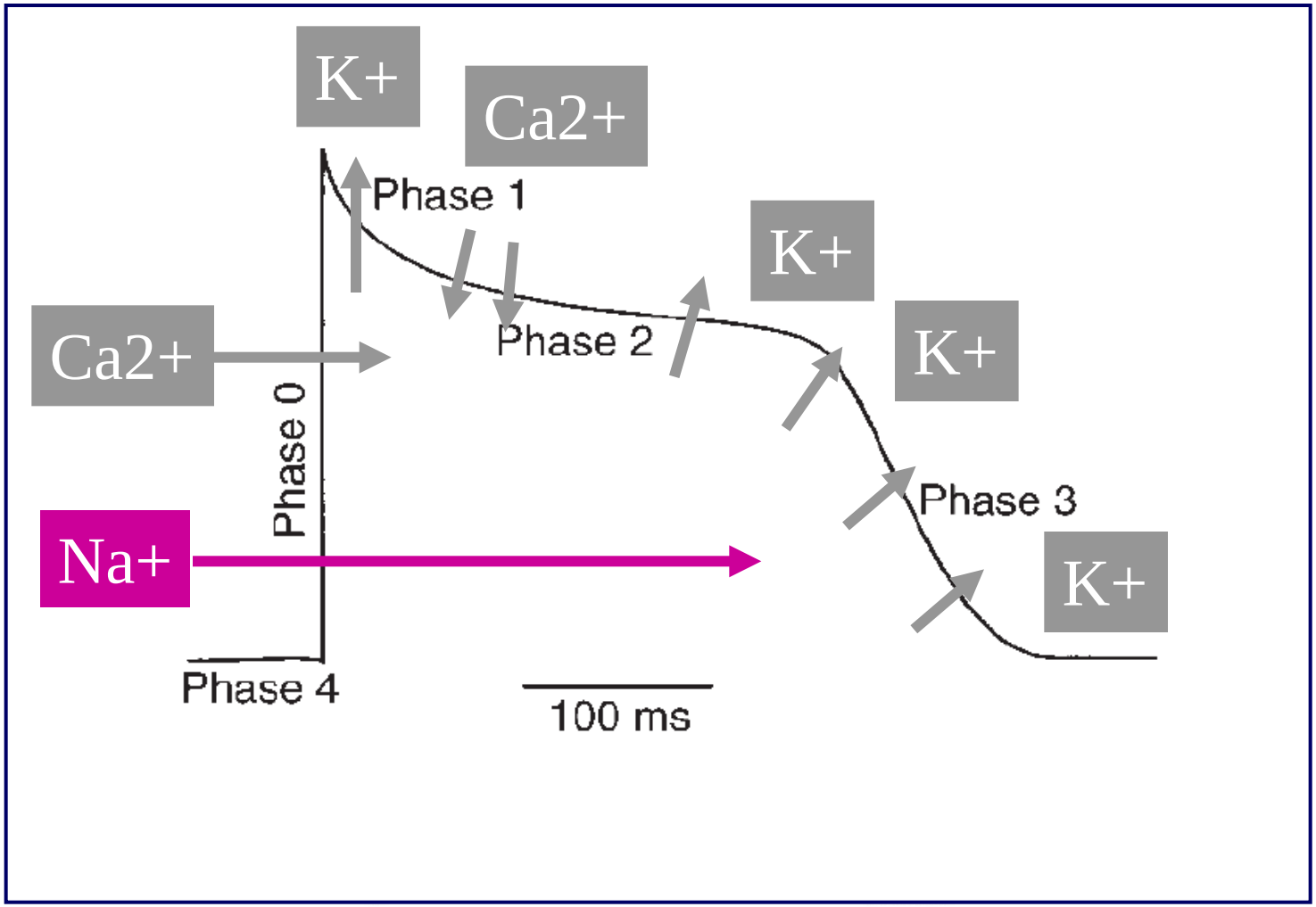
LQTS
K⁺-Channel-Type
(LQT 1,2, 5-7
[Andersen])



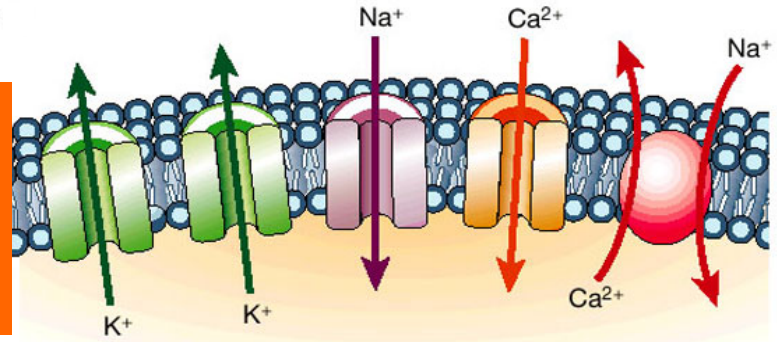


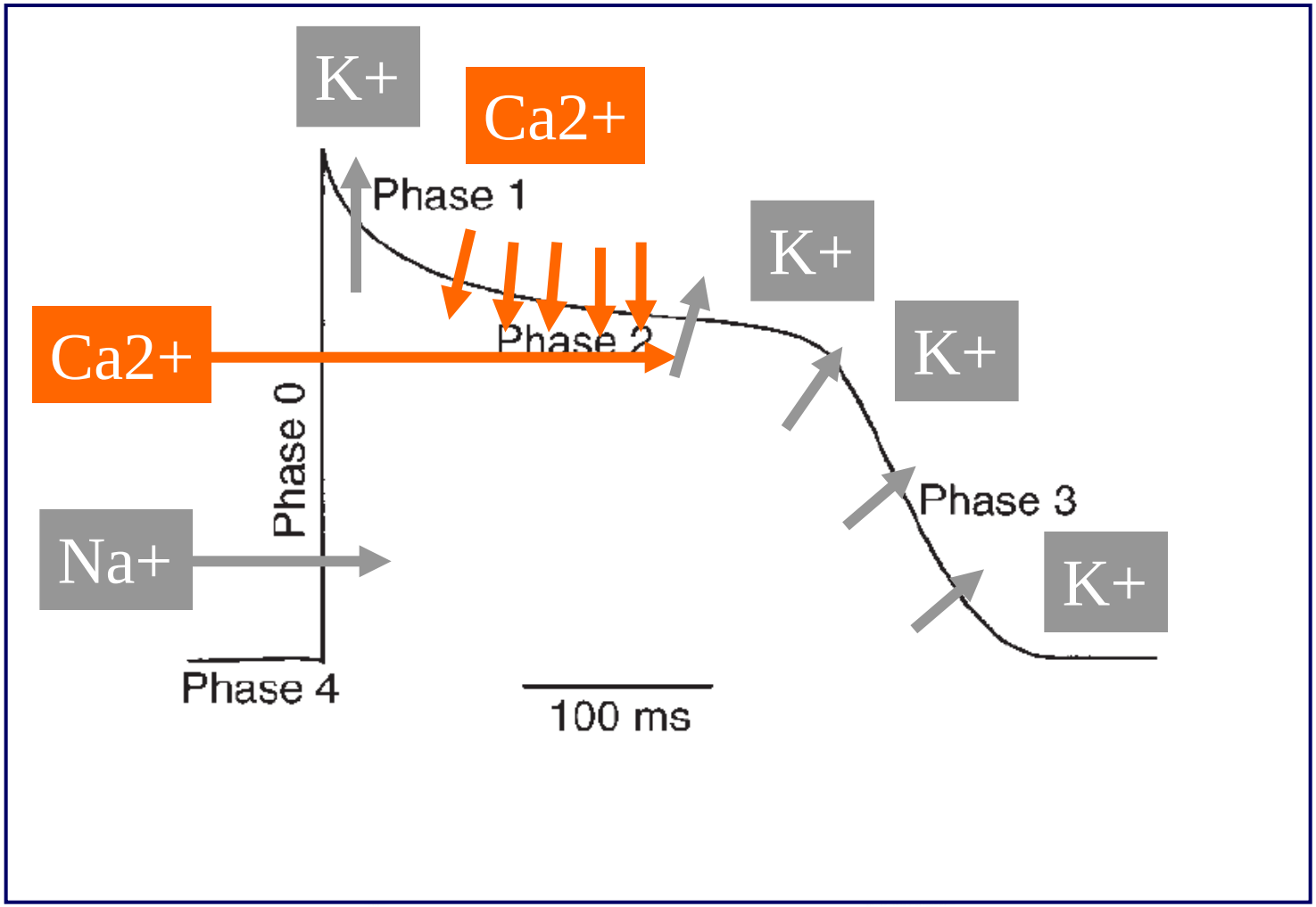
LQTS
Na⁺-Channel-Type
(LQT3, 9, 10)



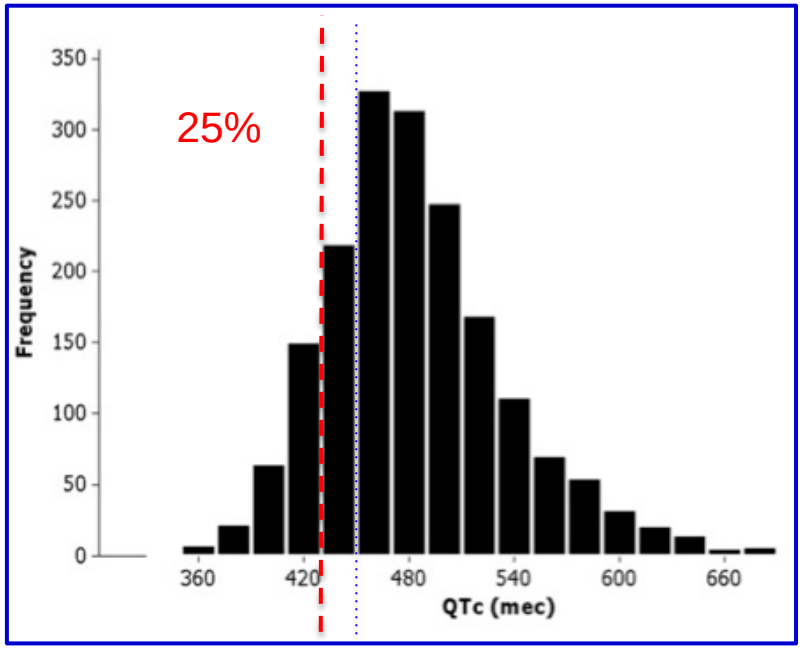


LQTS
Ca^{2+}-Channel-Type (LQT8, Timothy)





LQTS Genotype (+): Normal baseline QT Interval (at rest)



n=469
419 ± 20 ms

n=1,392
501 ± 48 ms

Non-LQTS:
n=1,525
412 ± 22 ms

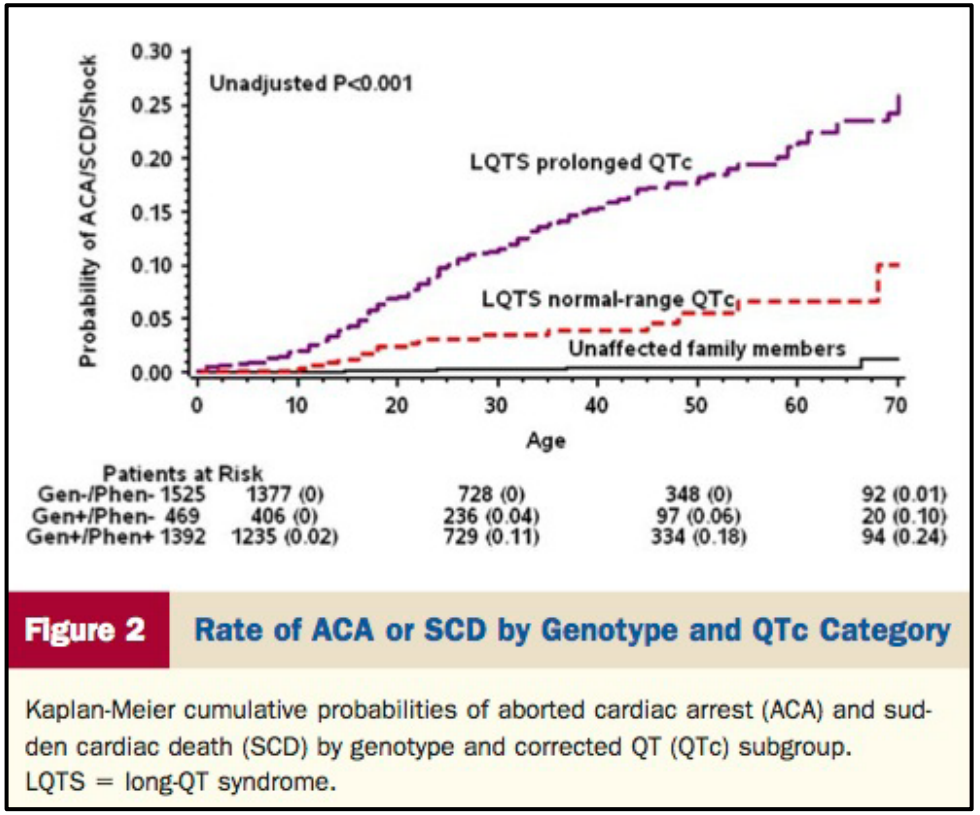


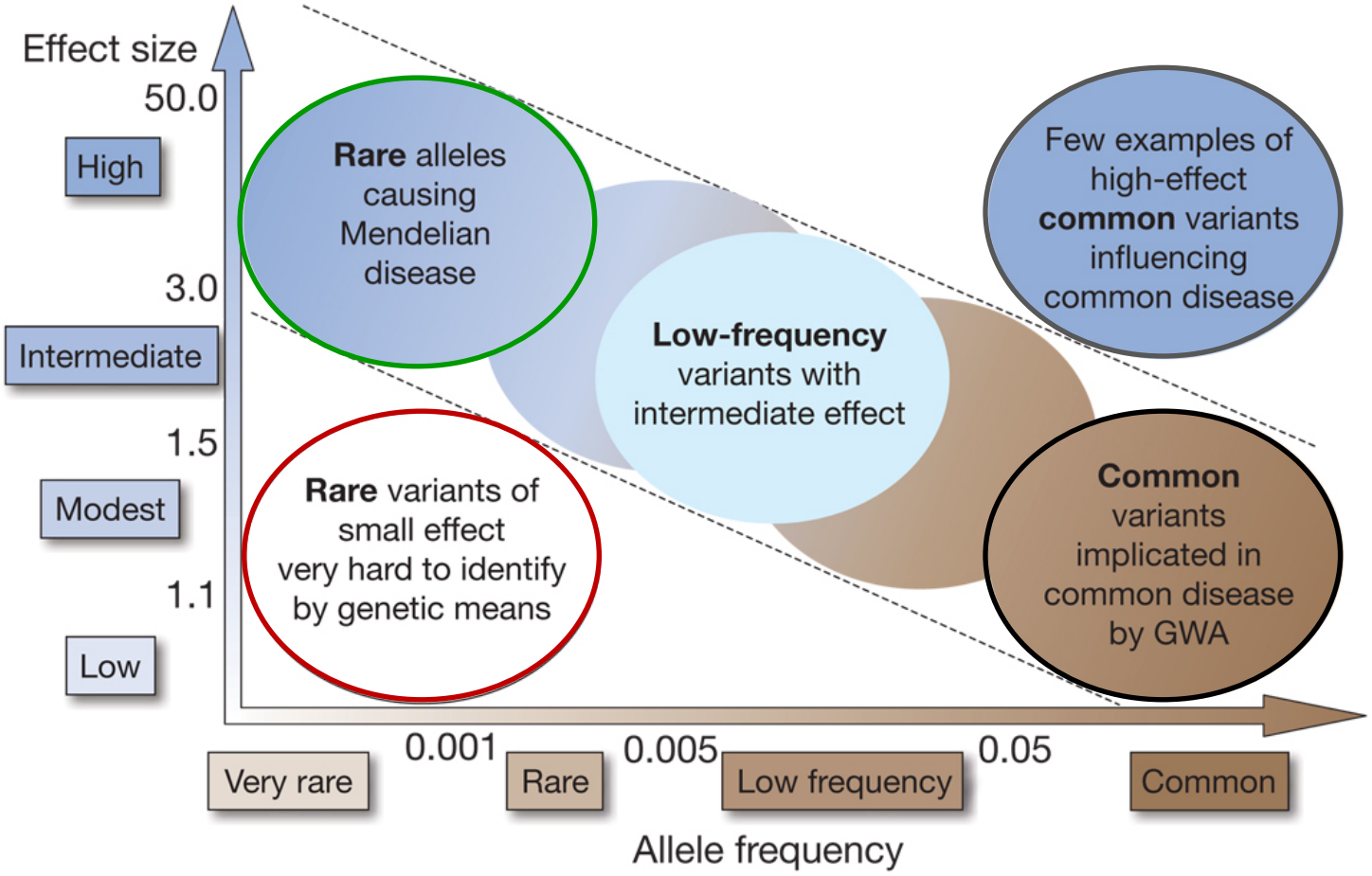
Figure 2 **Rate of ACA or SCD by Genotype and QTc Category**

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by genotype and corrected QT (QTc) subgroup. LQTS = long-QT syndrome.

Syncope	40%	21%	(10%)
ACA/SCD	11%	2.3%	(0.8%)

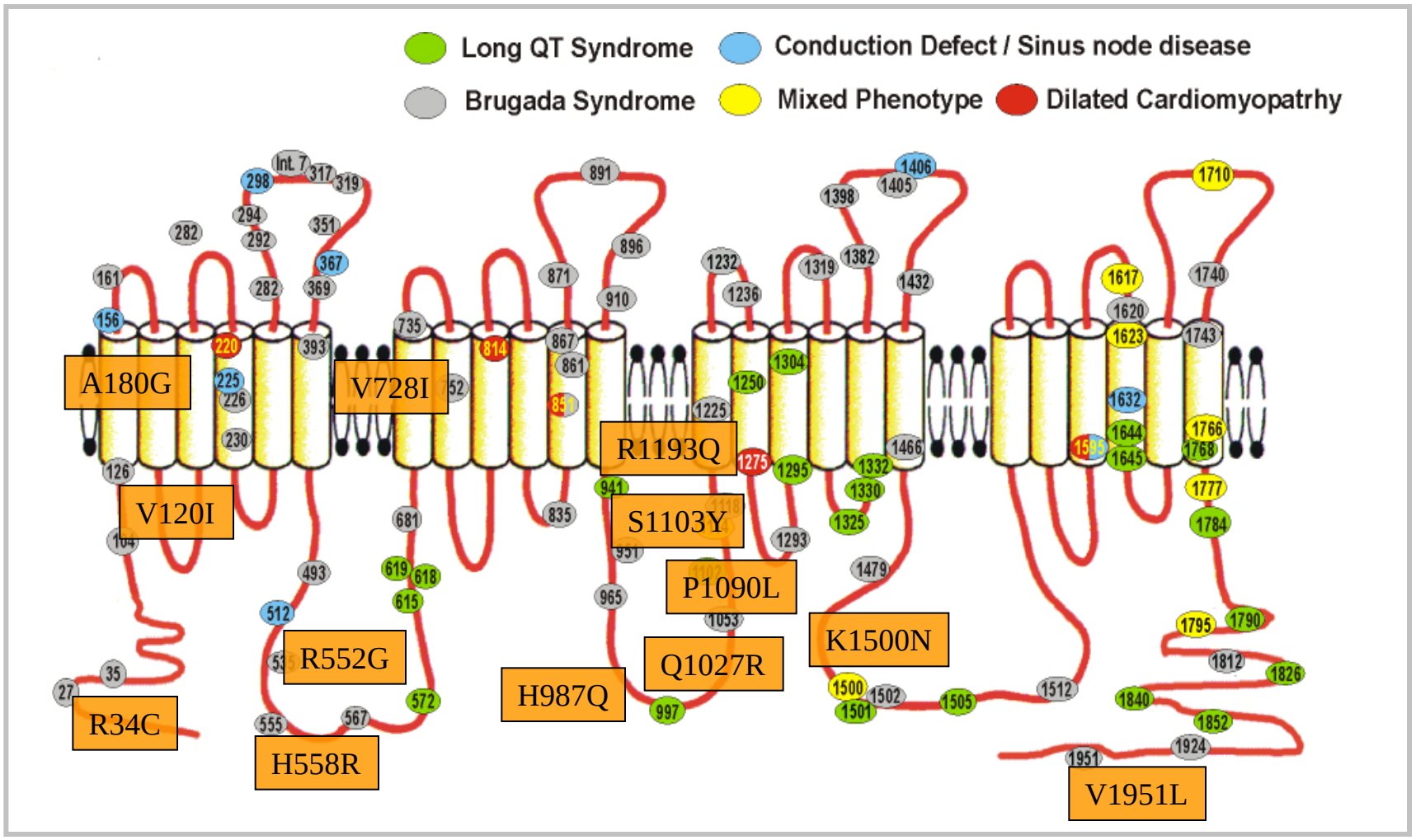
Goldenberg et al. (2011) JACC. 57: 51-59

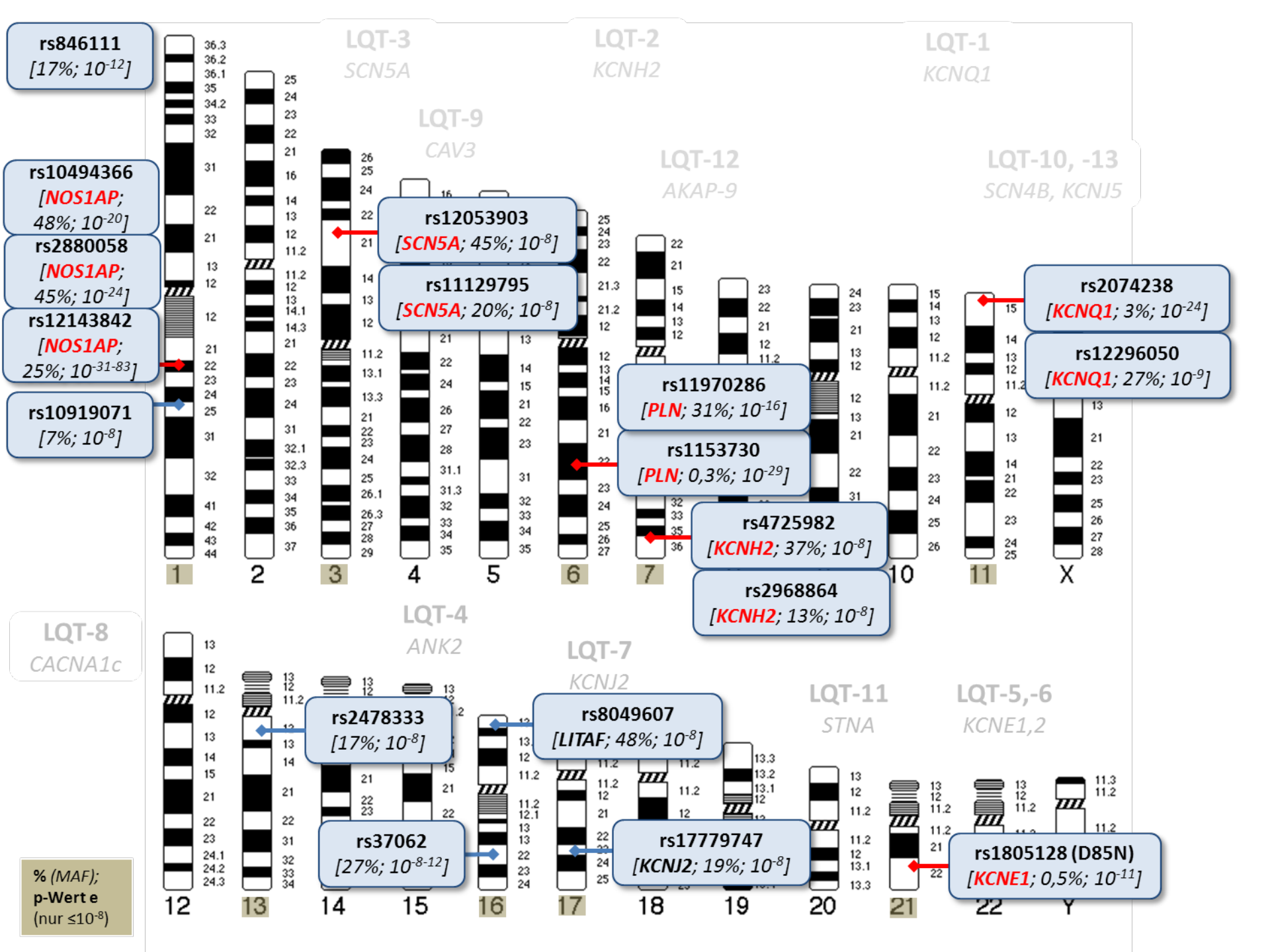
“Finding the missing heritability of complex diseases“



Manolio et al. Nat. Genet. (2009) 461: 747-753

SCN5A Gene Alterations: Phenotype vs. Common Variation



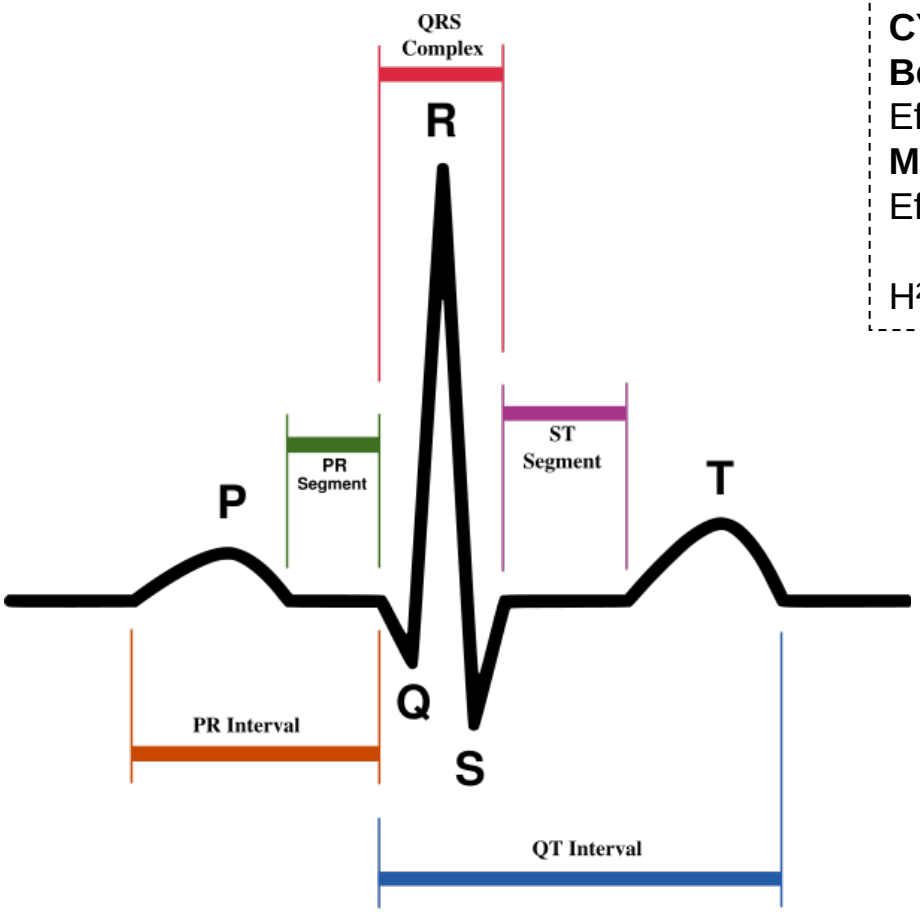

rs846111
[17%; 10-12]
LQT-3
SCN5A
LQT-2
KCNH2
LQT-1
KCNQ1
LQT-9
CAV3
LQT-12
AKAP-9
LQT-10, -13
SCN4B, KCNJ5
rs10494366
[NOS1AP; 48%; 10-20]
rs2880058
[NOS1AP; 45%; 10-24]
rs12143842
[NOS1AP; 25%; 10-31-83]
rs10919071
[7%; 10-8]
rs12053903
[SCN5A; 45%; 10-8]
rs11129795
[SCN5A; 20%; 10-8]
rs11970286
[PLN; 31%; 10-16]
rs1153730
[PLN; 0,3%; 10-29]
rs4725982
[KCNH2; 37%; 10-8]
rs2968864
[KCNH2; 13%; 10-8]
rs2074238
[KCNQ1; 3%; 10-24]
rs12296050
[KCNQ1; 27%; 10-9]
LQT-8
CACNA1c
LQT-4
ANK2
LQT-7
KCNJ2
LQT-11
STNA
LQT-5,-6
KCNE1,2
rs2478333
[17%; 10-8]
rs37062
[27%; 10-8-12]
rs8049607
[LITAF; 48%; 10-8]
rs17779747
[KCNJ2; 19%; 10-8]
rs1805128 (D85N)
[KCNE1; 0,5%; 10-11]
% (MAF);
p-Wert e
(nur ≤10-8)

ECG Parameters - Quantitative Traits

(GWAS; H^2: heritability estimates)

TBX5, SCN10A
6p21, 10q21
Effect: 5-7%

H^2: 0-36%



CYP2D6 *4/*4 PMs + Betablocker treatment:
Effect HR -8.5/min
MYH6
Effect 5.7% of HR

H^2: 29-77%

SCN10A, SCN5A
CAV1-CAV2, NKX2-5, SOX5, WNT11, MEIS1, TBX5, -3
Effect: 1-3 ms
SCN10A
Effect: 1-3 ms

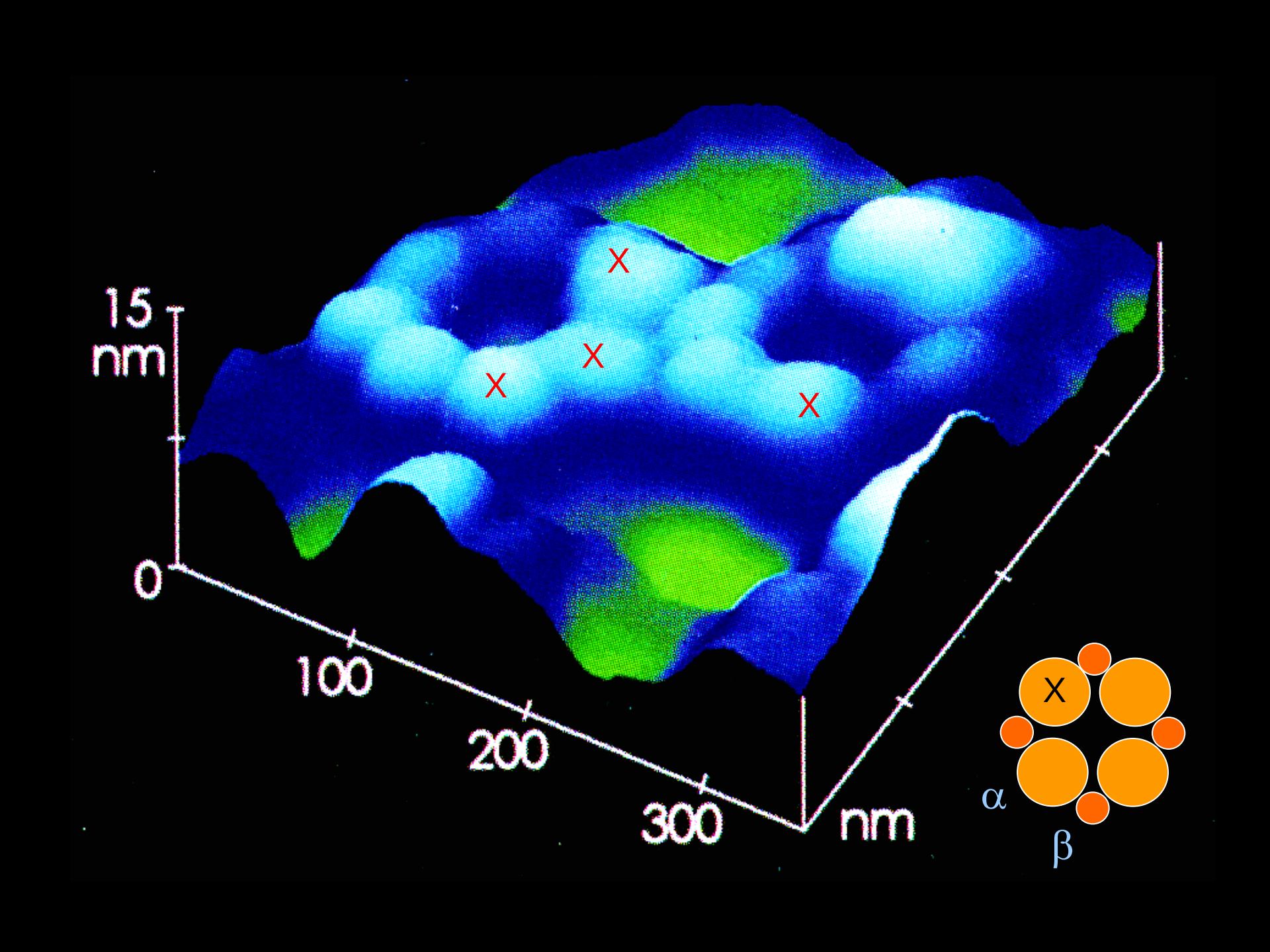
H^2: ~34%

NOSAP1-rs10494366, NOSAP1-rs2880058
Effect: 3-7 ms
ANK-B (LQT4)
2-3 ms
KCNE1_D85N (LQT5)
Effect: ~10 ms
KCNH2 K897T (LQT2)
Effect: 3-4 ms

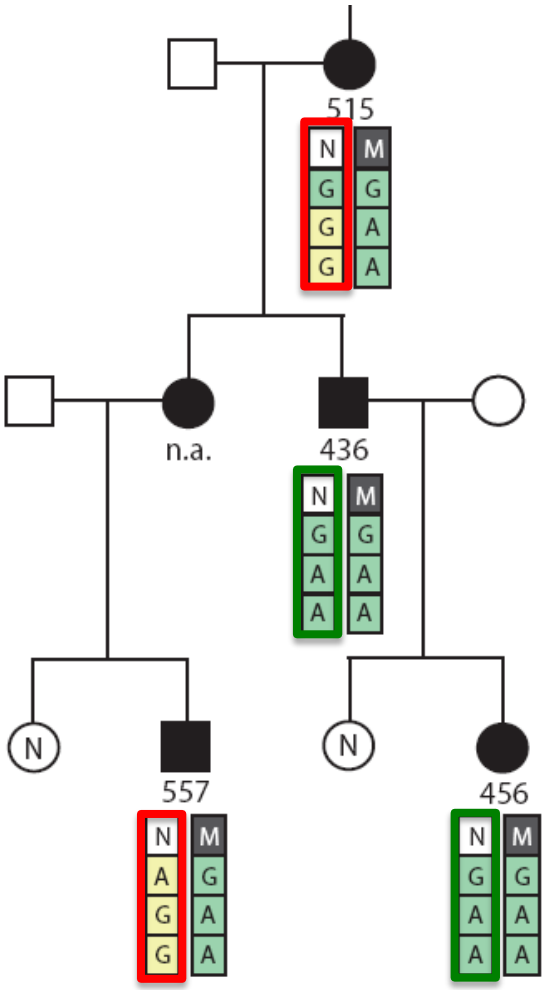
<1% of variance explained
H^2: 29-77%

KCNH2
K897T

0.84/0.16	Fins ($n=415$)	*Rattus norvegicus* (c)	**897T**: female carriers had ↑ repolarization parameters; no isoform-associated effect in males
0.76/0.24	Caucasians ($n=1030$)	*Mus musculus* (c) *Oryctolagus cuniculus* (c) *Canis familiaris* (nc, R)	**897T**: ↑ current activation (−7mV shift) and deactivation (HEK 293), ↑ I_{Kr} current.
#	Twins ($n=236$)		**897T** carriers ($n=58$) had a shorter QT interval than 897K carriers (females>males, twins: males>females)
	aLQTS ($n=1$)		**897T**: I_{Kr} currents comparable with wild-type (±MirP) (Xenopus oocytes)
#	LQT1-Fins ($n=261$)		**897T**: no gender-related differences in baseline QTc, but increased QTc during exercise.
			897T: I_{Kr} channel activation comparable with wild type, reduced protein level (Western), ↓ deactivation and inactivation, hyperpolarizing shift in steady-state inactivation, decrease of I_{Kr} (HEK 293)
0.87/0.13	US citizens ($n=90$)		Allele frequencies: aLQTS ($n=98$) ~ controls
#	LQT1-Fins ($n=261$)		**897T**: changes in I_{Kr} channel kinetics, PKA modulation similar to wild-type: ↓ I_{Kr} current density, ↓ deactivation time constants, ↓ inactivation (HEK 293). LQT1 (589D)+ 897T carriers ($n=39$) had a longer QT interval than 897K carriers.
§	Different ethnic populations		**Heterozygous genotype**: 8.2% US-Blacks ($n=305$ total), 33.1% US-Caucasians ($n=187$), 7.5% US-Asians ($n=134$), 6.8% Hispanics ($n=118$)
0.98/0.02	Japanese ($n=50$)		n.d.
0.84/0.16	Caucasians ($n=100$)		n.d.
0.76/0.24	US-Caucasians ($n=100$)		**897T**: ↓ I_{Kr} current density, −5 mV shift of activation, ↑ inactivation and recovery; normal protein levels (Western)
0.96/0.04	African Americans ($n=100$)		


15
nm
0
100
200
300
nm
X
X
X
X
α
β

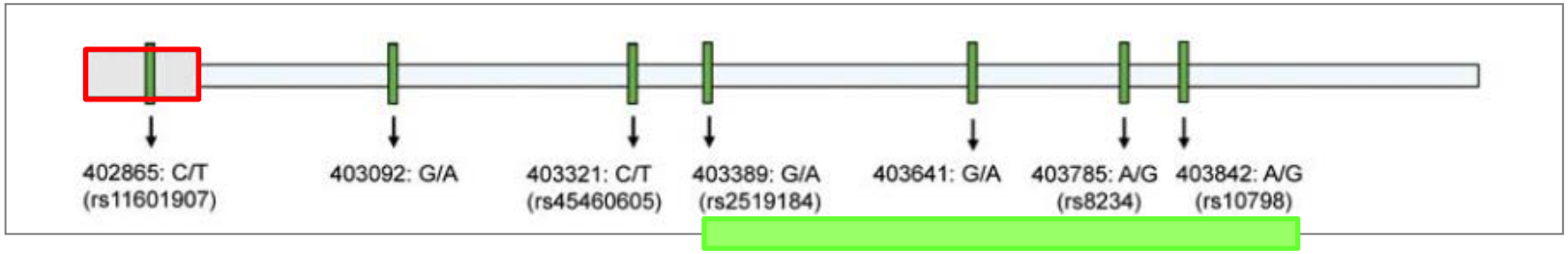
Disease Severity: Balancing the Protein between Normal and Mutant ?!



- Concept of ‘Genomic Convergence‘
- Disease expression of a (mutant) haplotype **M*-G-A-A** depends on the second allele
- Wild-type N-**x-x-x** haplotype might have a different, intrinsic allele expression

(adapted from Amin et al., EHJ 2012)

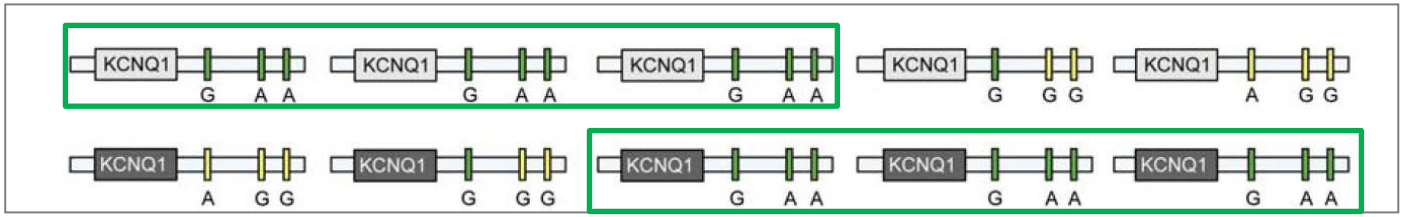
Evidence of Polymorphic Sites within the 3‘-UTR of LQT-1 (*KCNQ1*)



◄ … KCNQ1

Ancestral haplotype:

G A A

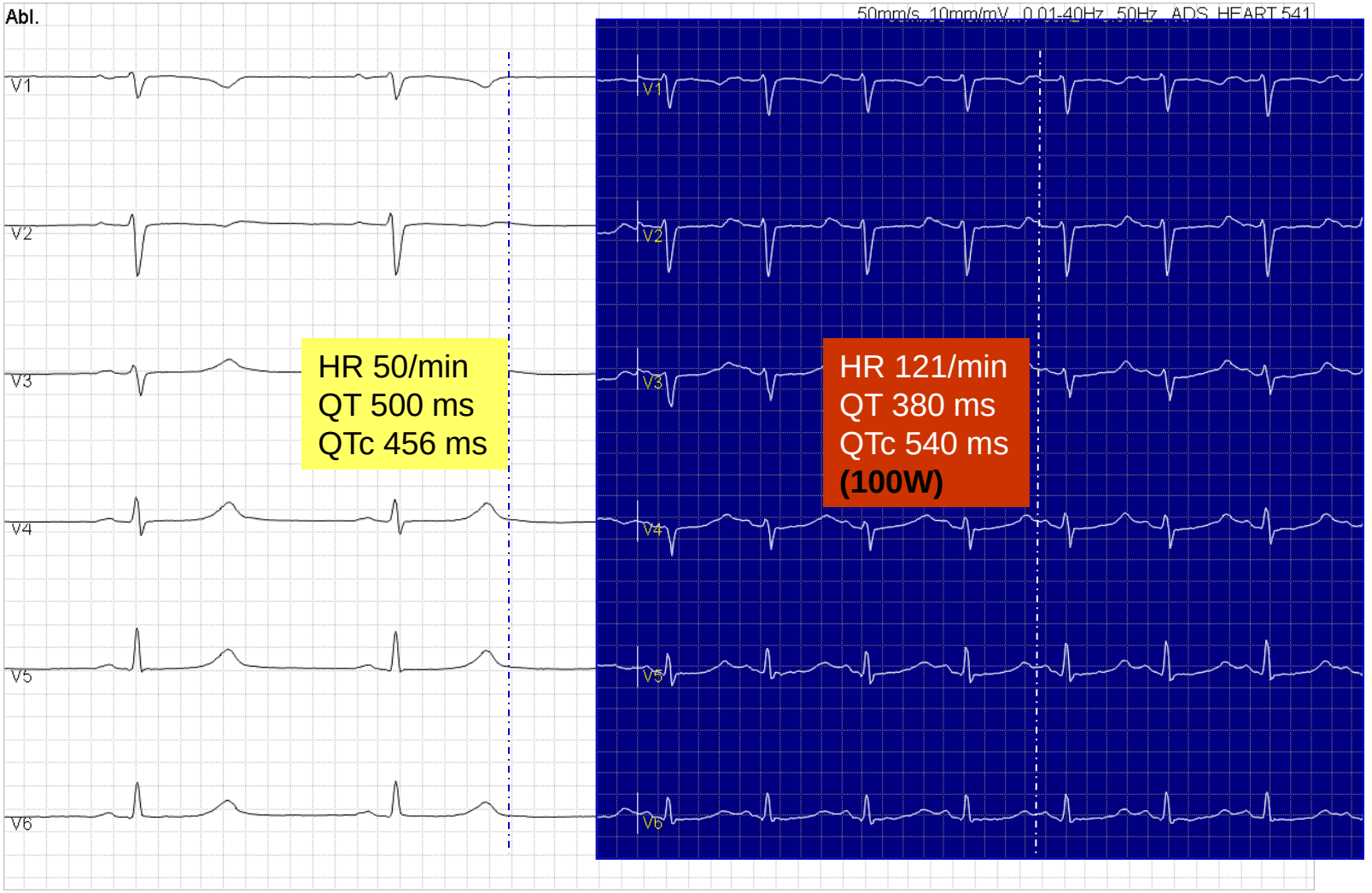


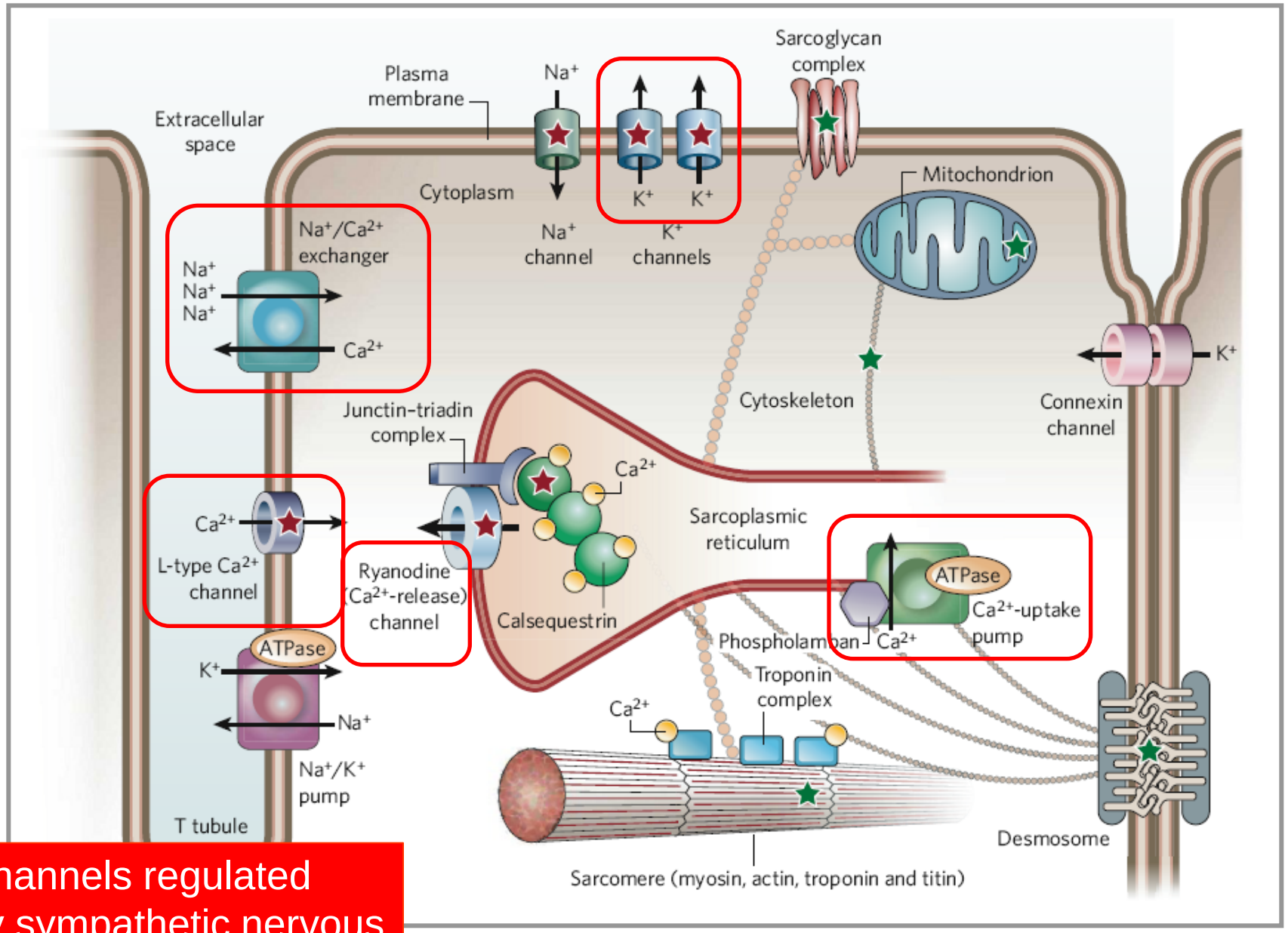
QTc	**430**	**440**	**450**	**470**	**520**
N	26	1	31	17	3

Amin et al. EurHJ (2012) 33: 714-723

ECG of a young female

"Asymptomatic", National Team Player (Basketball)





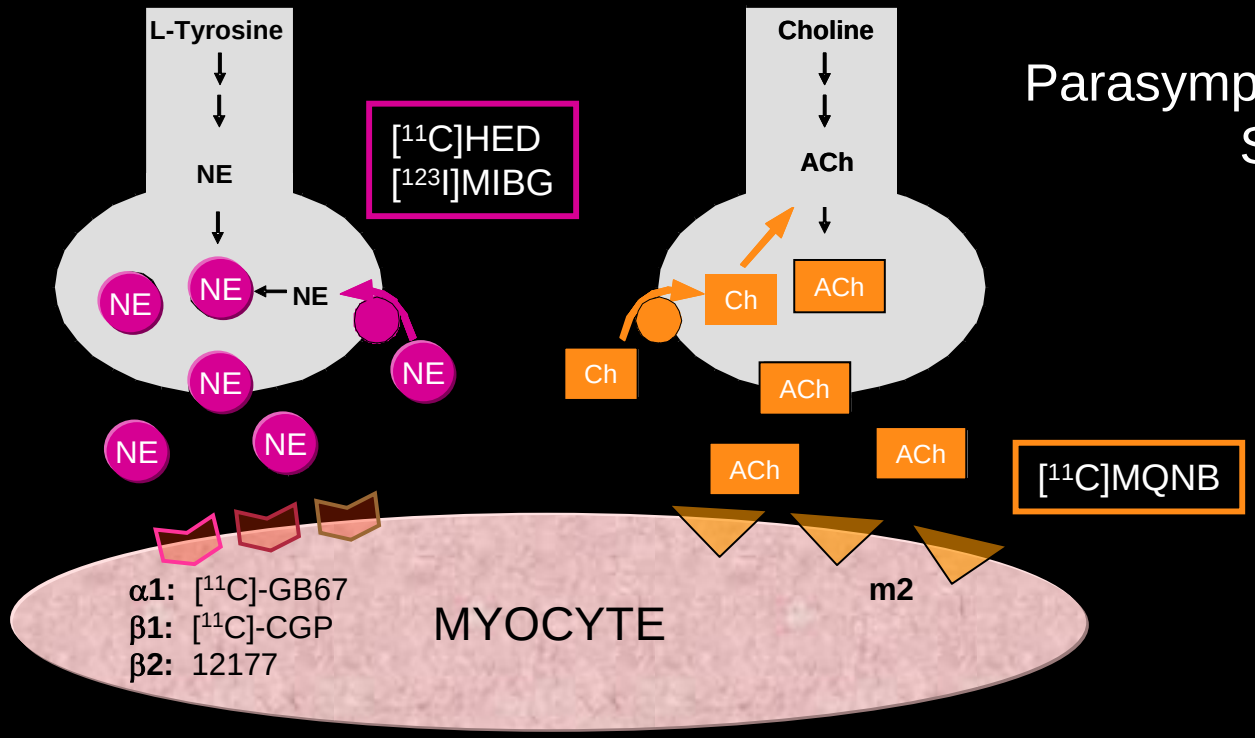
Channels regulated by sympathetic nervous system (cAMP)

Knöllmann and Roden (2008) Nature 451: 929-936

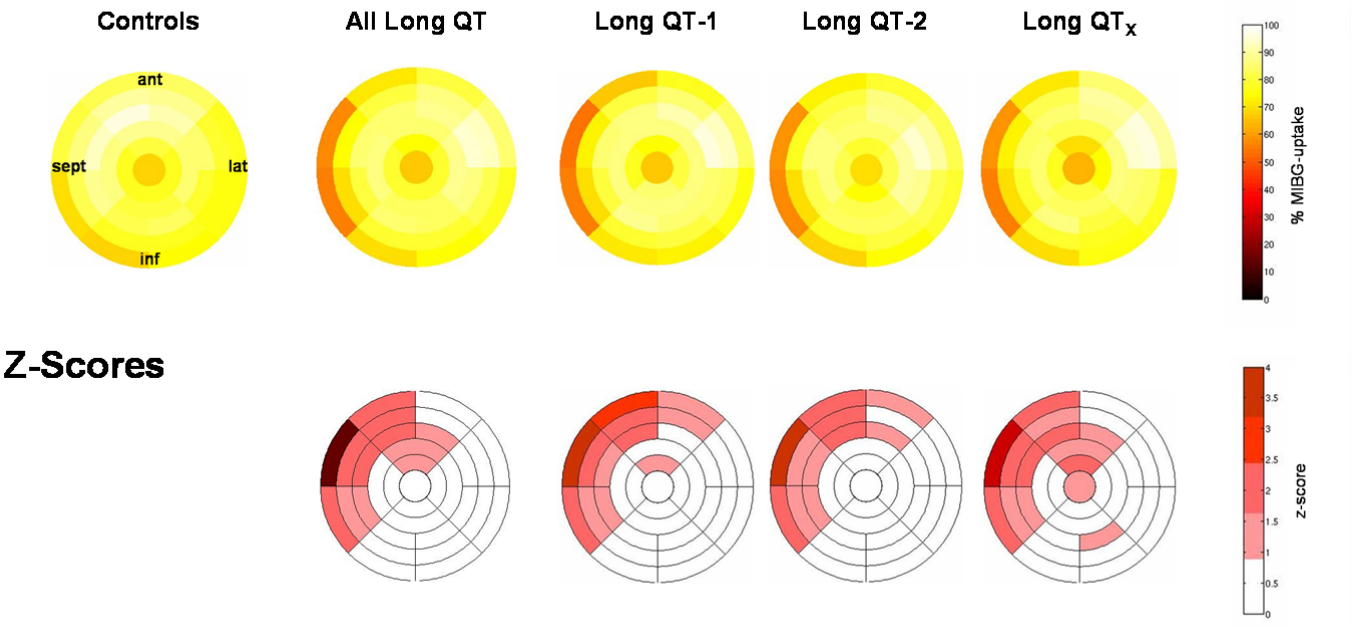
Imaging of Myocardial Innervation
Radioactive Tracer Activity

Sympathetic System

Parasympathetic System



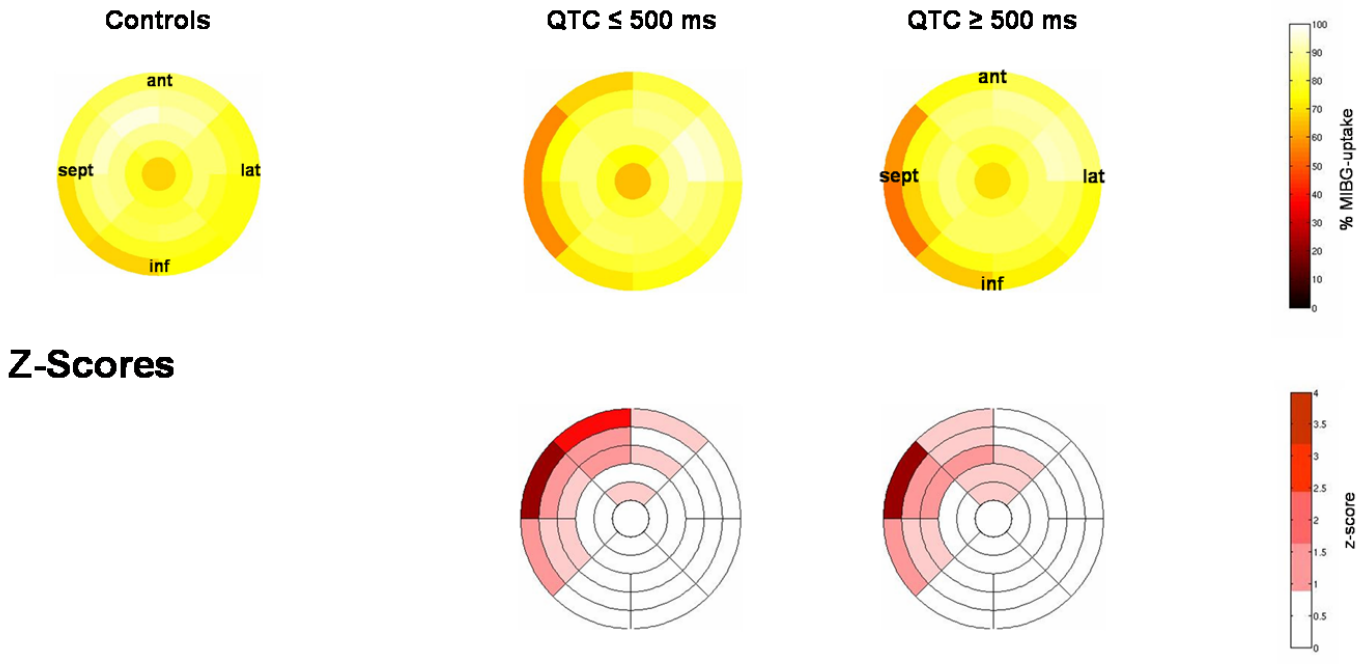
Sympathetic cardiac innervation: 28 symptomatic LQTS pts. (MIBG-SPECT)



N:	**10**	**28**	7	12	9
QTc (ms)		**501±69**	481±69	508±81	508±54
Abnormal MIBG:		17	5	7	5
Segm. with tracer ↓:			5	6	4

Kies et al. (2013) Eur. J. Nucl. Med.

MIBG-SPECT and QT Prolongation: 28 symptomatic LQTS pts.



N:	**28**	18	10
QTc (ms)	**501±69**	468	543
Syncope/VF	**18/10**	7/0	5/7
Abnormal MIBG:	17 (61%)	10 (56%)	7 (70%)

Kies et al. (2013) Eur. J. Nucl. Med.

Therapy LQTS

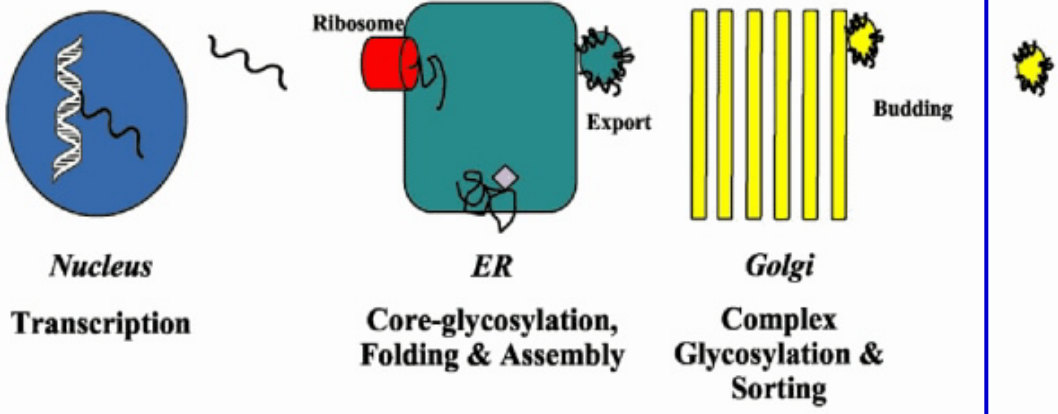
- Depends on symptoms and QTc duration

  (i) BB
  (ii) BB and ICD, if BB is not tolerated
  or QTc ⇑⇑
  or symptoms during BB
  (iii) ICD for secondary prophylaxis (or class IIB)
  (iv) class IB antiarrhythmics for LQT3

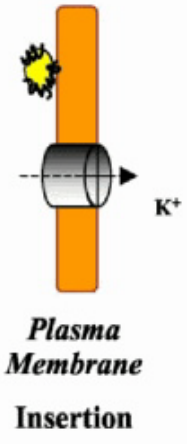
- Avoid QT-prolonging agents, serum ⇓ K+
- Avoid genotype-specific triggers, modify life style to genotype

Strategies to Restore Ion Channel Dysfunction

Class 1	Abnormal protein synthesis (altered transcription or translation)
Class 2	Defective protein processing/trafficking.
Class 3	Abnormal gating/kinetics
Class 4	Altered or no permeability

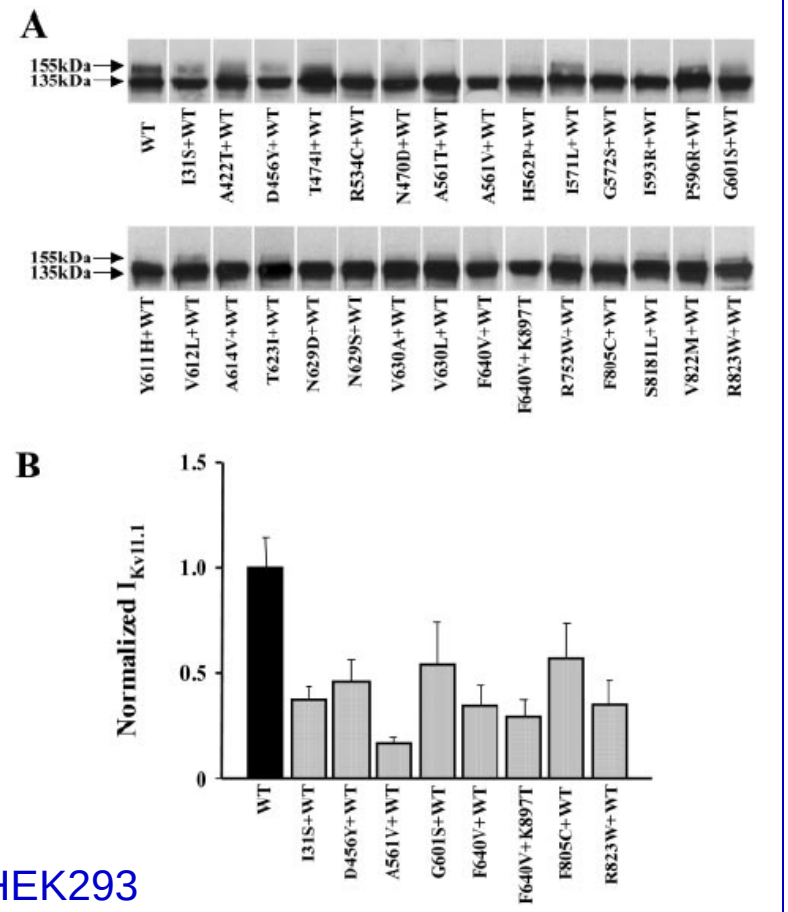


Increase number of functional (WT) channels

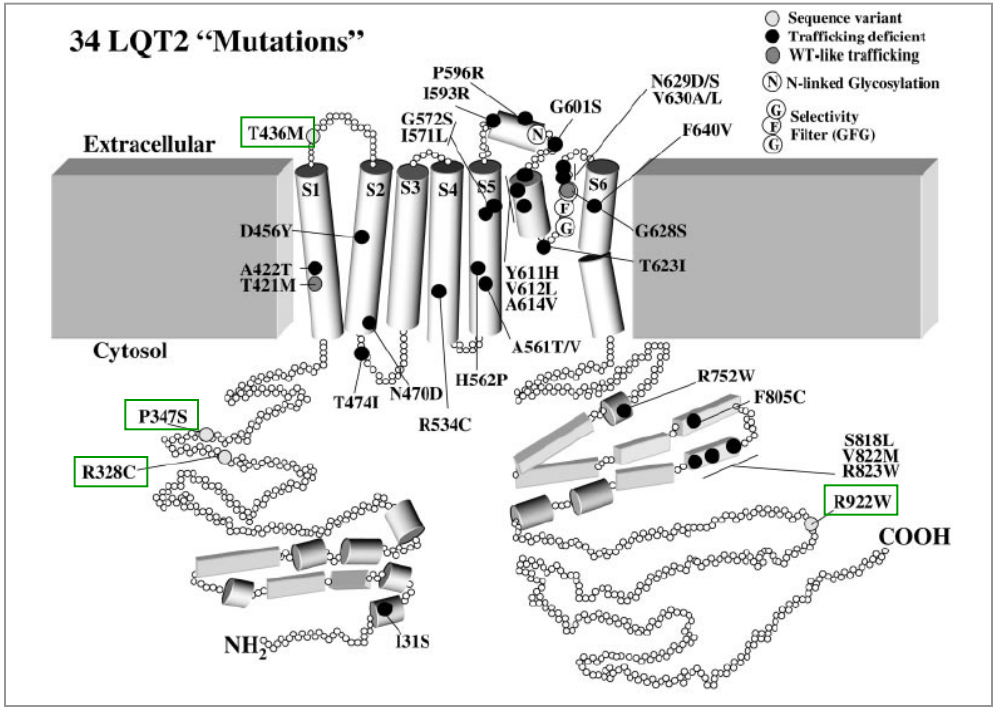


Modulate dysfunc-tional channels

Loss of Functional HERG Channels: Key Mechanism for LQT-2 (I_{Kr} ⇓)



155 kDa: Mature HERG protein
135 kDa: Immature HERG protein



28/34 Missense mutations were trafficking-deficient" (Western blot: 135 kDa)

4/6 Missense mutations (R328C, P347S T436M, R922W) had wild-type like I_{Kr}

Anderson et al. (2006) Circulation 113: 365-373

Ranolazine Effects on Ventricular Repolarisation (rabbit hearts, in vivo)

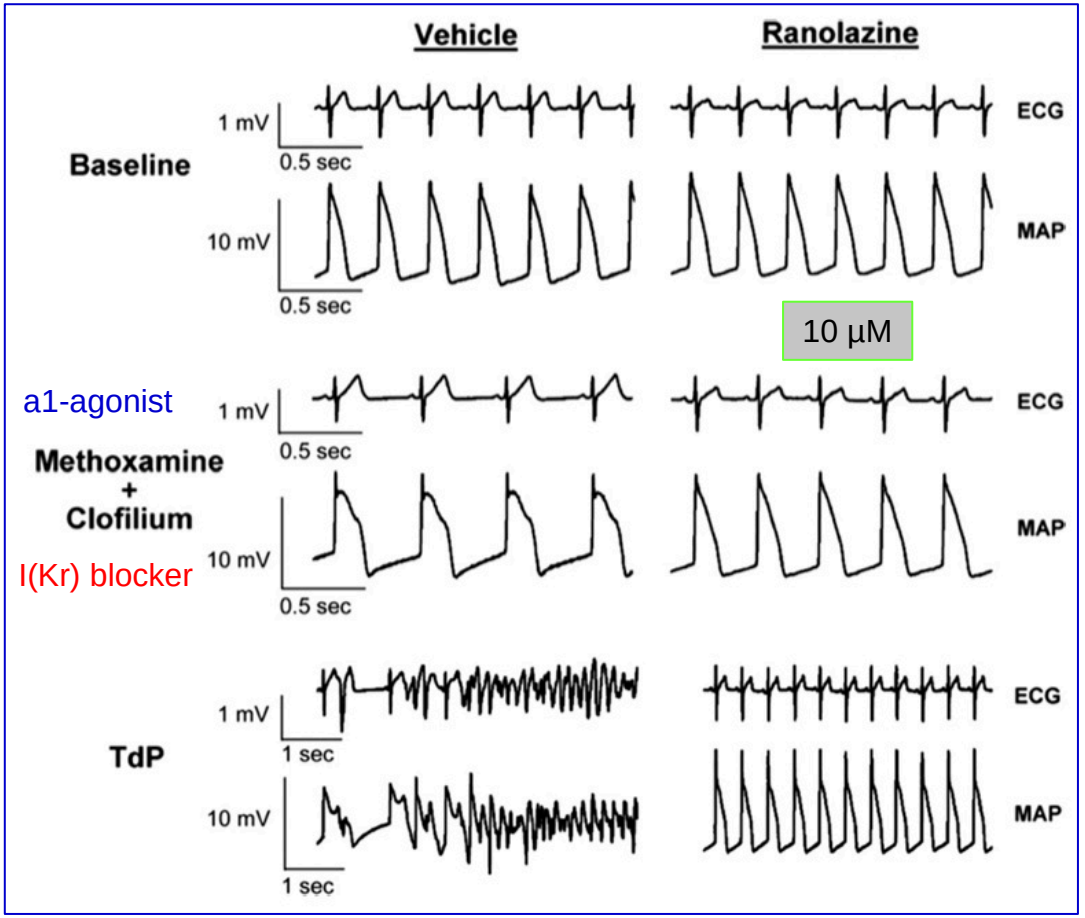
Table 1 Summary of ranolazine potency in inhibiting cardiac ion channel currents in canine left ventricular myocytes

Ion currents	IC_{50} values (μM)
A. Inward	
Peak I_{Na}	294
Late I_{Na}	5.9
Peak $I_{Ca,L}$	296
I_{Na-Ca}	91
B. Outward	
I_{Kr}	11.5
I_{Ks}	17% at 30 μM
I_{K1}	No effect
I_{To}	No effect

All data from Antzelevitch et al,[1] except peak I_{Na}, which is from Undrovinas et al.[3]

Note: The magnitude of effect of ranolazine on peak and late I_{Na} is voltage, frequency, and tissue dependent (see text for details).

IC_{50} = concentration of ranolazine that causes 50% inhibition (potency).

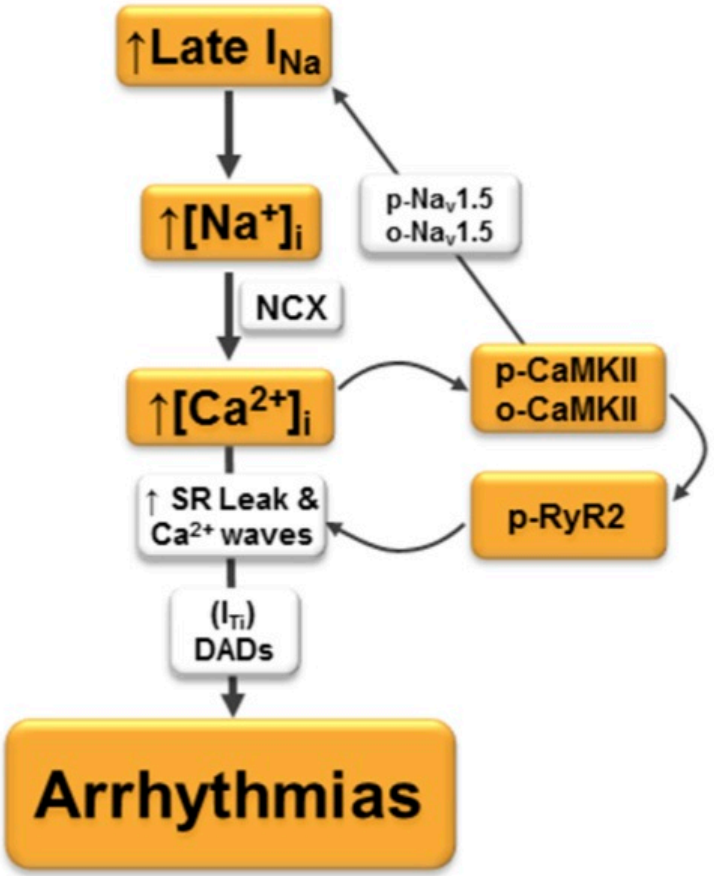


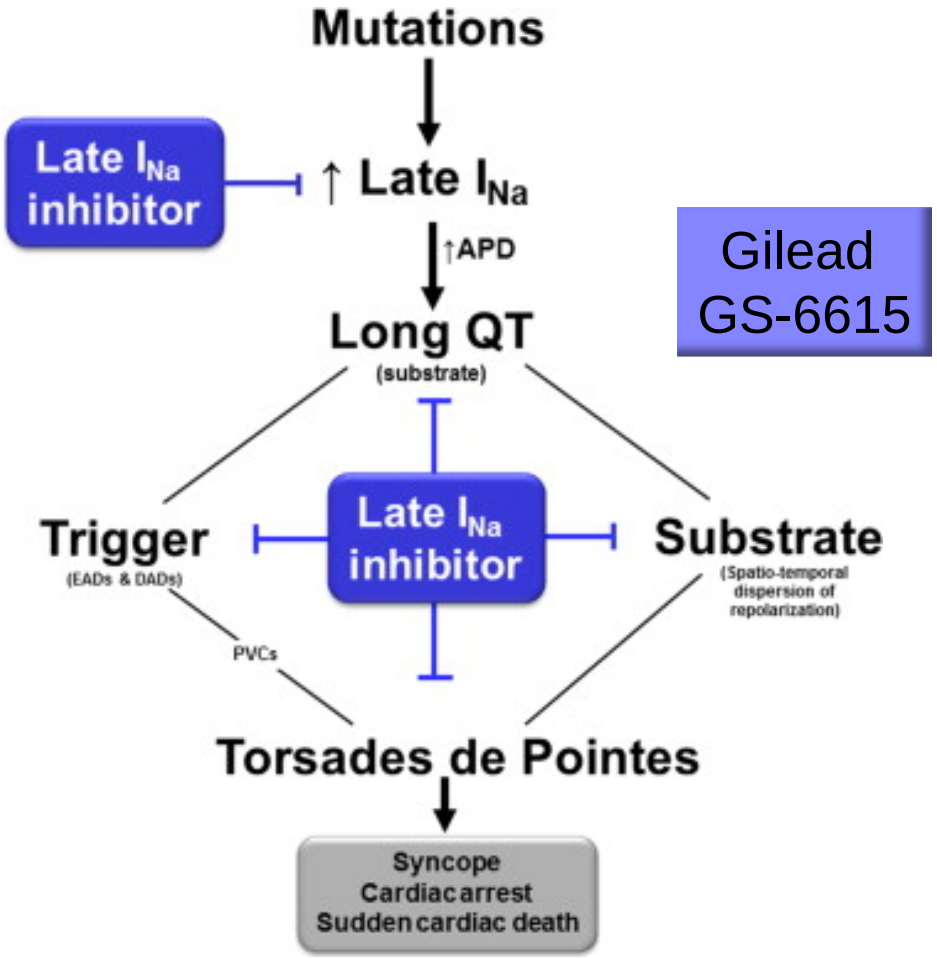
Reduction of

- APD and TDR in M and Purkinje cells (lower HR) at the ventricular level

Antzelevitch et al. (2011) Heart Rhythm 8: 1281-90

Late I(Na) current: A substrate to maintain repolarization



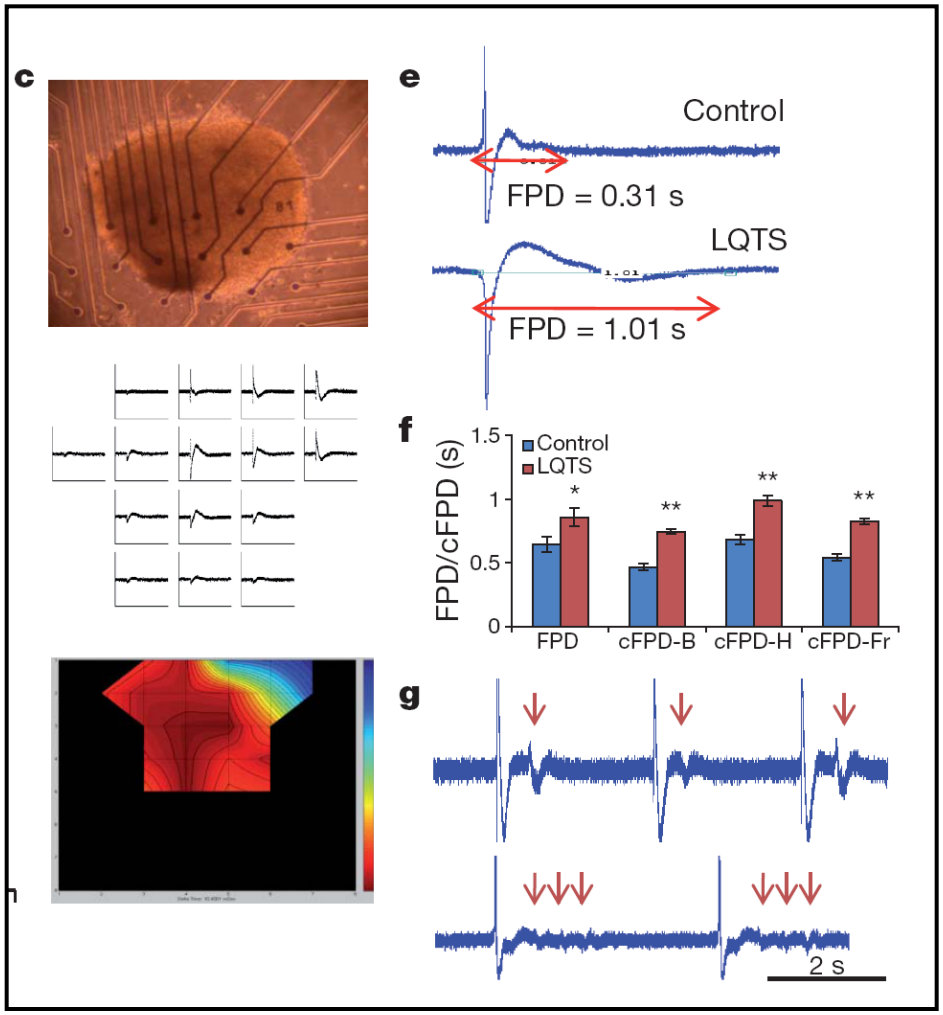


p-, phosphorylated
o-, oxidized

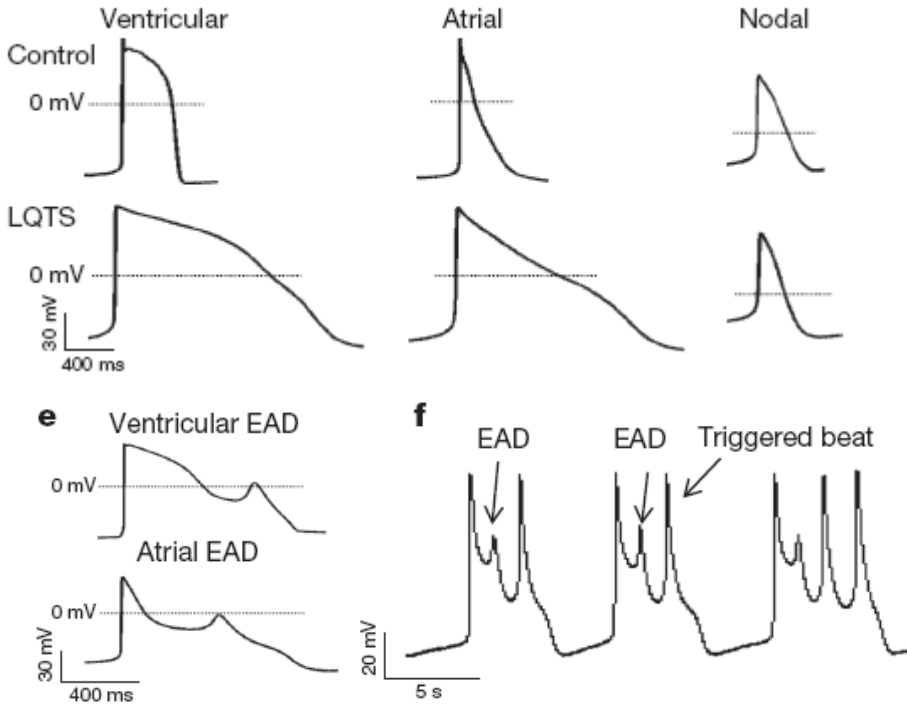
Bernadinelli et al. Heart Rhythm (2015) 12: 440-448

Cardiac-like Myocytes

(from human induced, pluripotent stem cells; hiPSCs, LQT-2)



FPD: field potential duration



EAD suppression with nifedipin (I(Ca2+) block), Pinacidil (I(K-ATP) opener), ranolazine (I(Na(Kr) block)

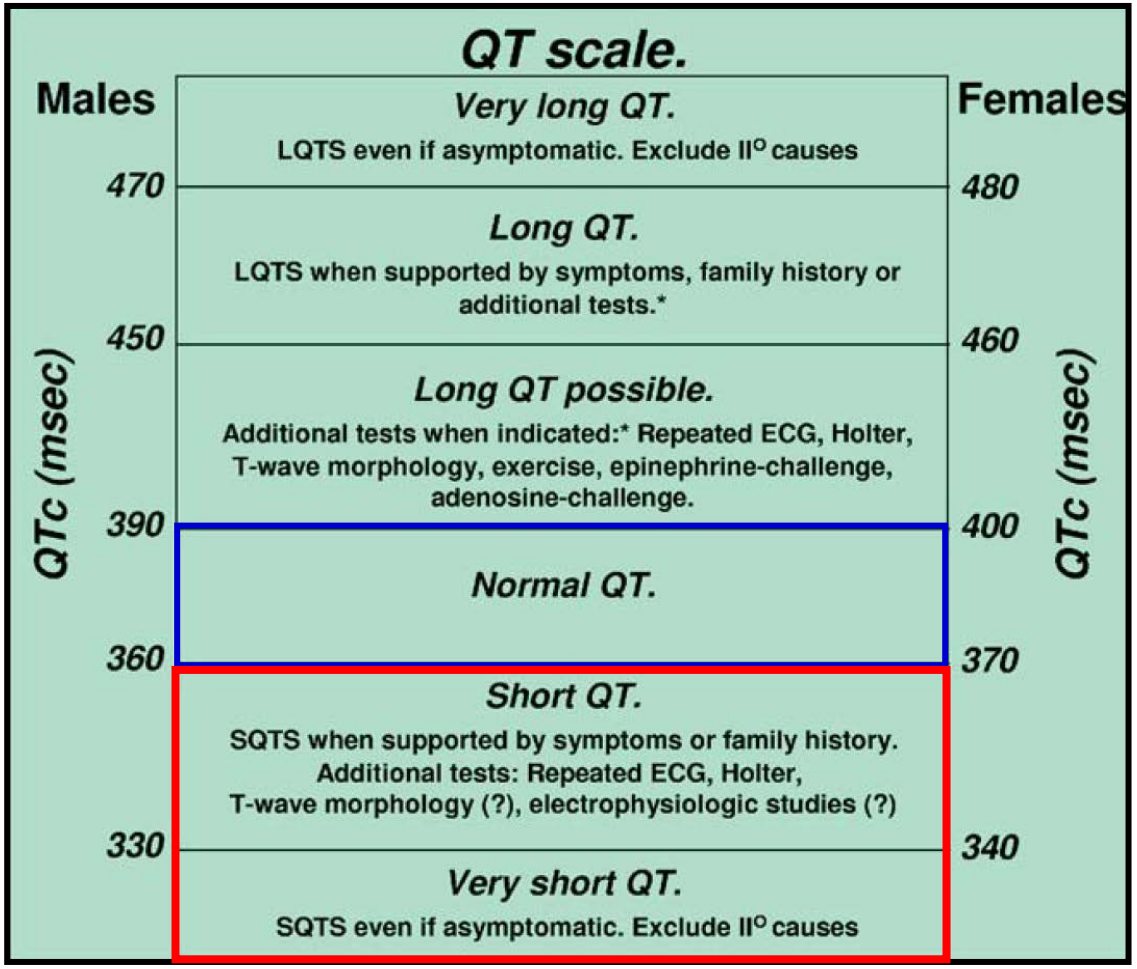
Modelling the long QT syndrome with induced pluripotent stem cell
Izhaki et al. Nature Feb. 2010 epub

UKM
Universitätsklinikum
Münster

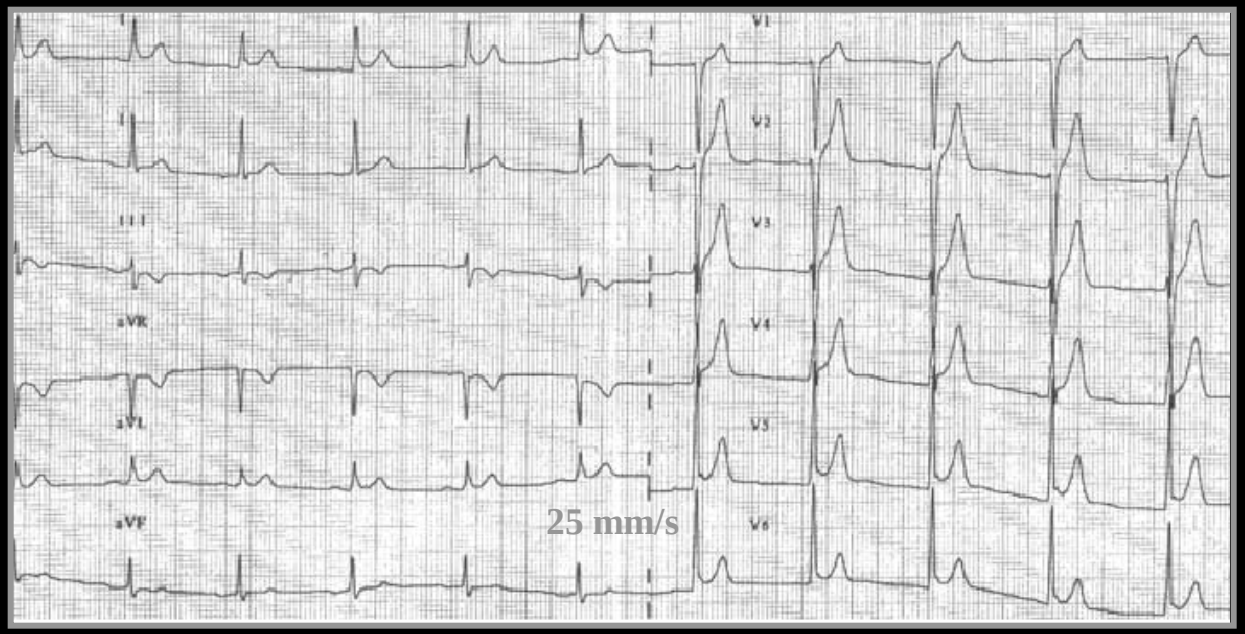
Repolarisation:

Respect also the short (SQTS).

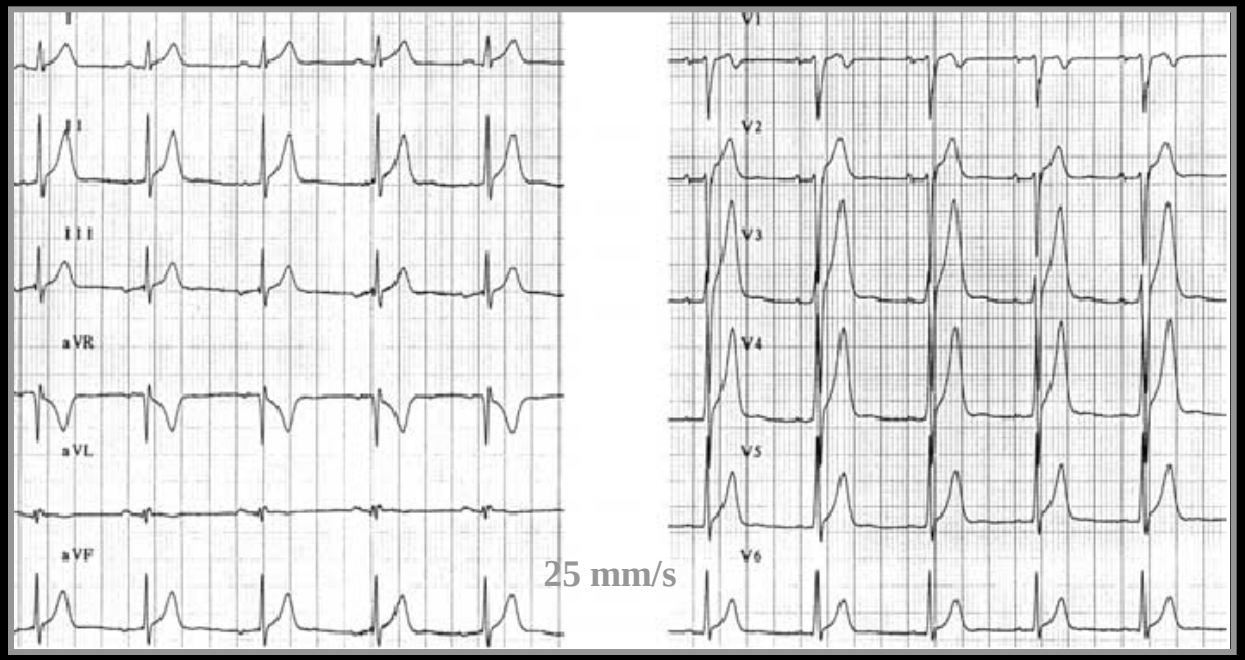
Heart-rate corrected QT Interval (QTc; Bazett‘s method)



Viskin. Heart Rhythm 2009; 6: 711-715



Brother:
QT: 300 ms
QTc: 335 ms
QTp: 80%

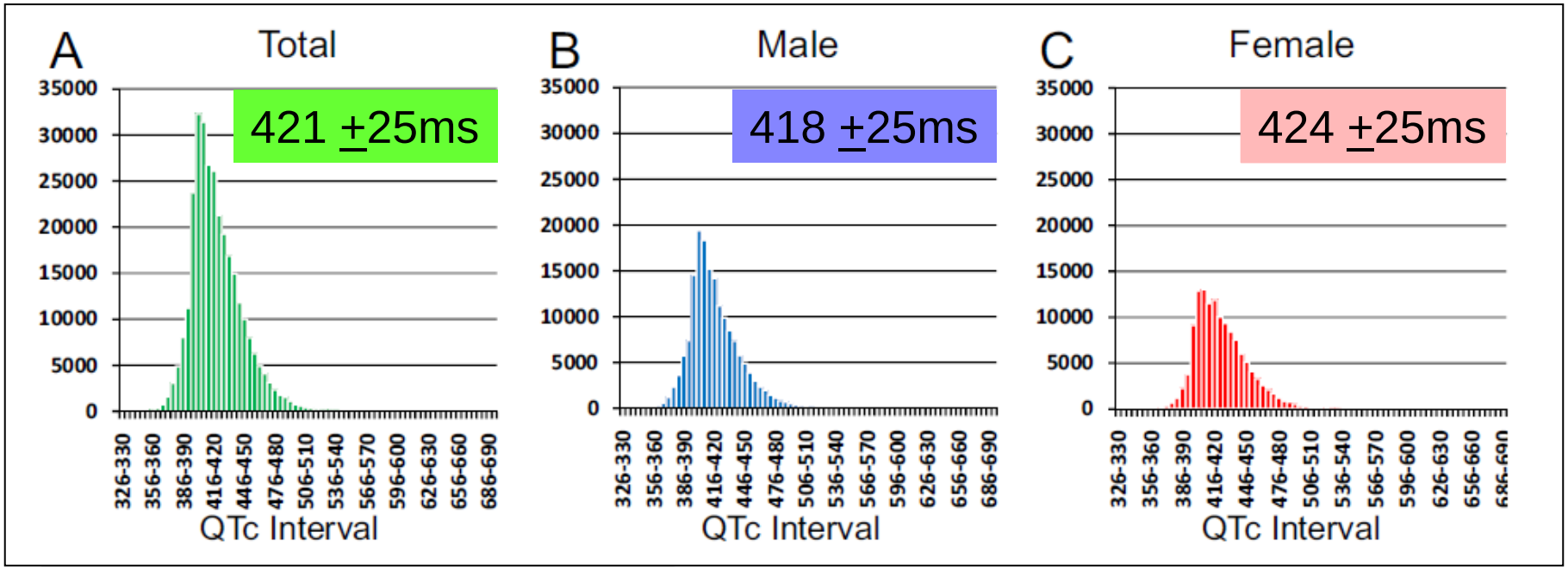


Proband:
QT: 300
QTc: 335 ms
QTp: 78%

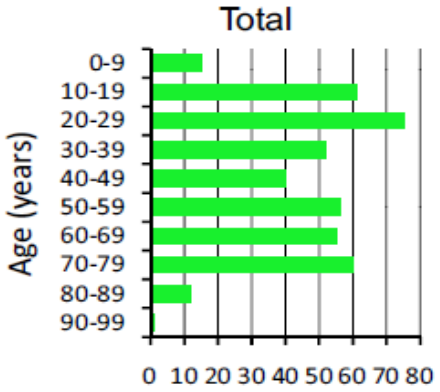
HR 2005; 2: 1136

(Short) QT Intervals: The Range

(Japan, >110,000 In-hospitals)



	Bazett QTc interval (ms)	
Percentile	Male	Female
2.5	380.0	387.0
2.0	378.0	386.0
1.0	373.0	381.0
0.5	369.0	376.0
0.15	362.0	369.0
0.1	361.0	367.0
0.0	331.0	329.0

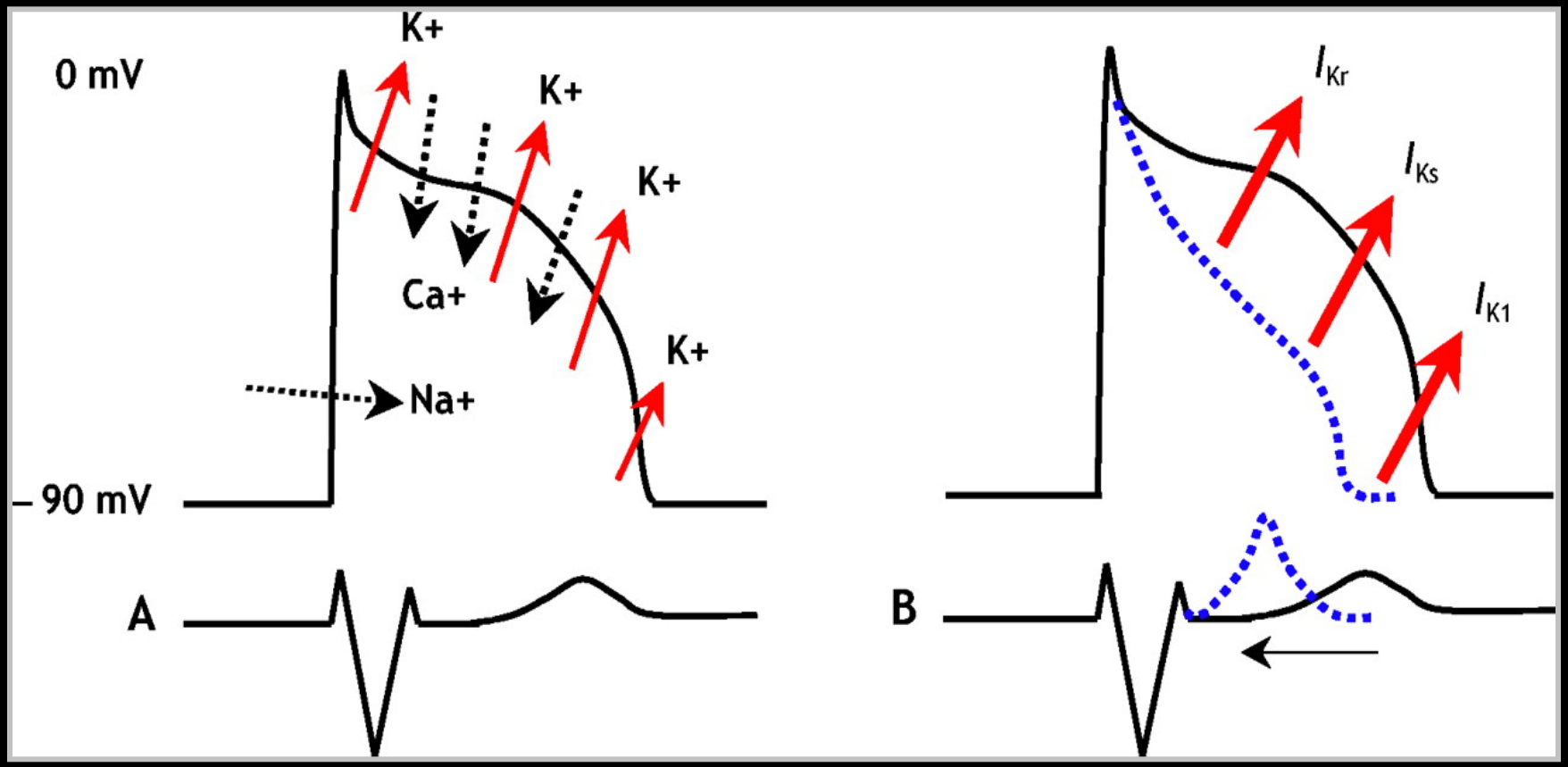


N=427 — 234

193

Heart Rhythm (2012) 9: 66-72

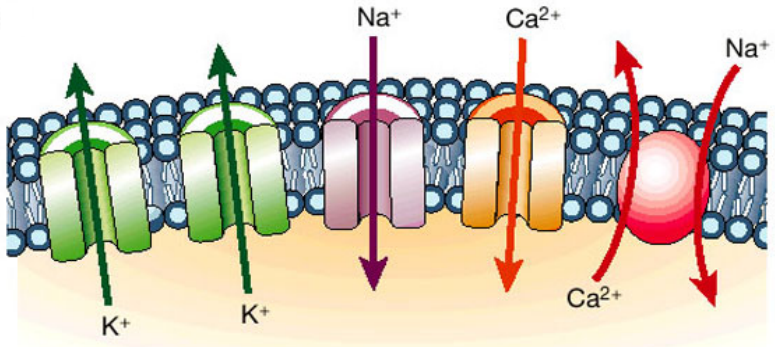
Shortened AP/Repolarization and K+ Currents (I_K): SQT1-3

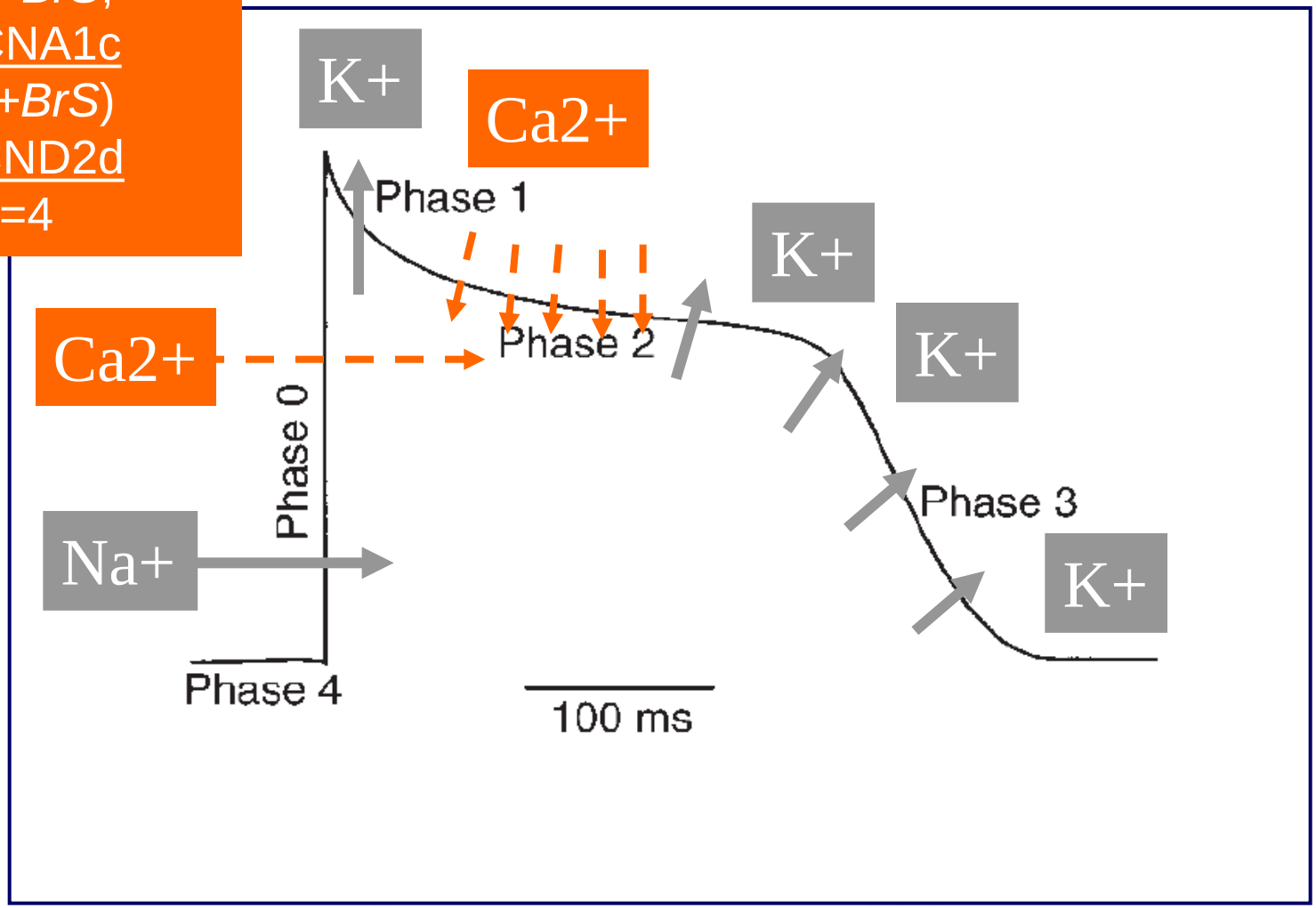


SQTS

Ca^{2+}-Channel Types

(CACNB2b *n=1+BrS*, CACNA1c *n=4+BrS*) CACND2d n=4





HRS/EHRA [2013] Expert Consensus Statement: **SQTS**

Expert Consensus Recommendations on ***Short QT Syndrome Therapeutic Interventions***

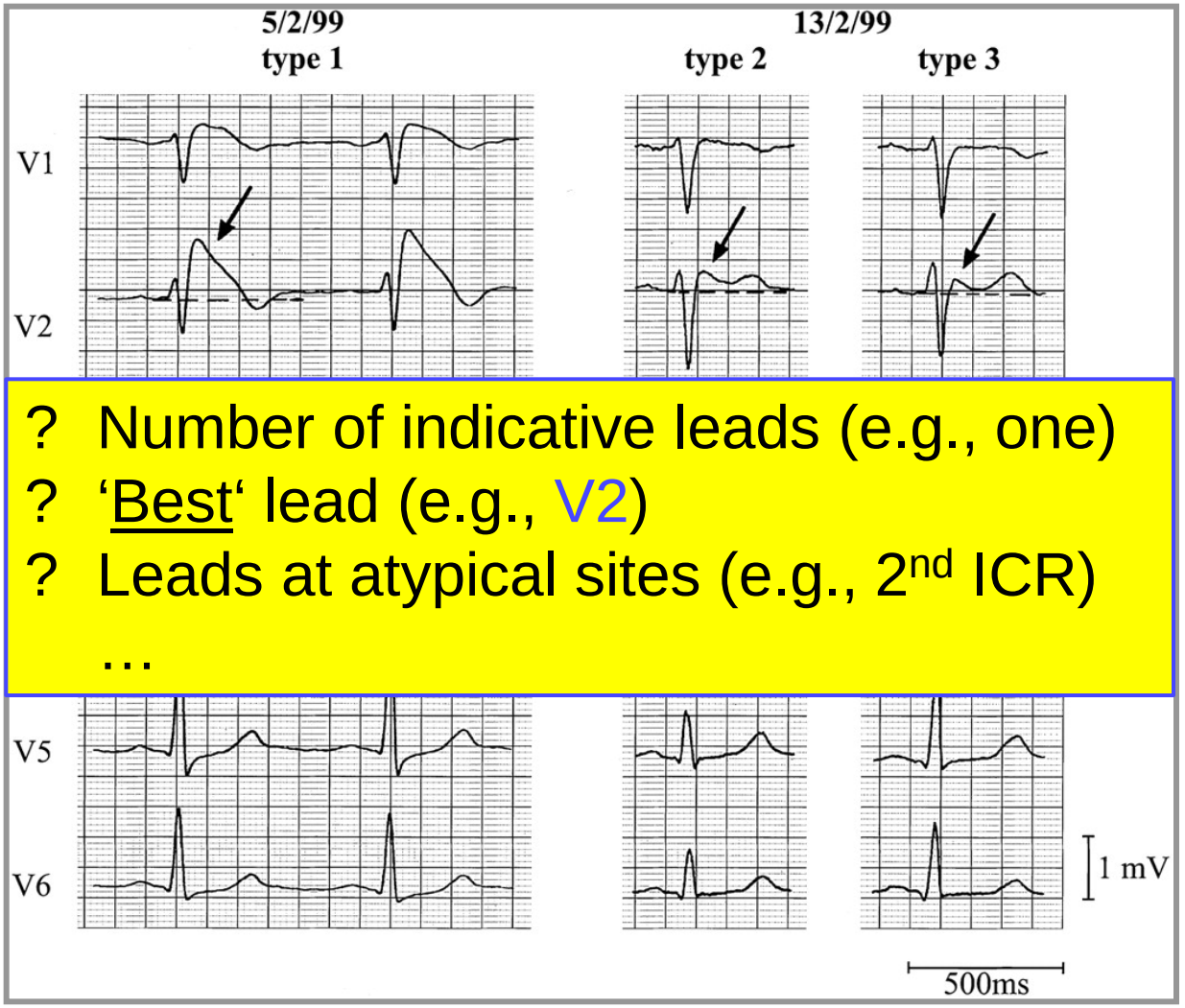
Class I	1. ICD implantation ***is recommended*** in symptomatic patients with a diagnosis of SQTS who a. Are survivors of a cardiac arrest *and/or* b. Have documented spontaneous sustained VT with or without syncope.
Class IIb	2. ICD implantation ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. 3. Quinidine ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. 4. Sotalol ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.

(... disopyramide, flecainide, ibutilide, nifekalant, ...)

Heart Rhythm (2013), in press (ePUB)
Europace (2013), in press

Brugada Syndrome
(BRGDA / BrS)

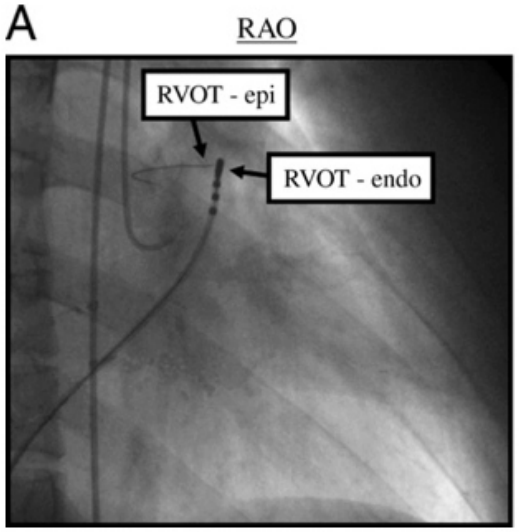
Brugada Syndrome (BrS): Indicative ECGs



? Number of indicative leads (e.g., one)
? ‘Best‘ lead (e.g., V2)
? Leads at atypical sites (e.g., 2nd ICR)
…

- BrS Type 1-ECG only diagnostic at rest, after provocation, after conversion of BrS Type 2/3
- J-point / ST ⇑ of more than 2 mm in two or more right precordial leads
- Exclusion of other causes (phenocopying conditions)

Brugada Syndrome (BrS): Epicardial APD Prolongation



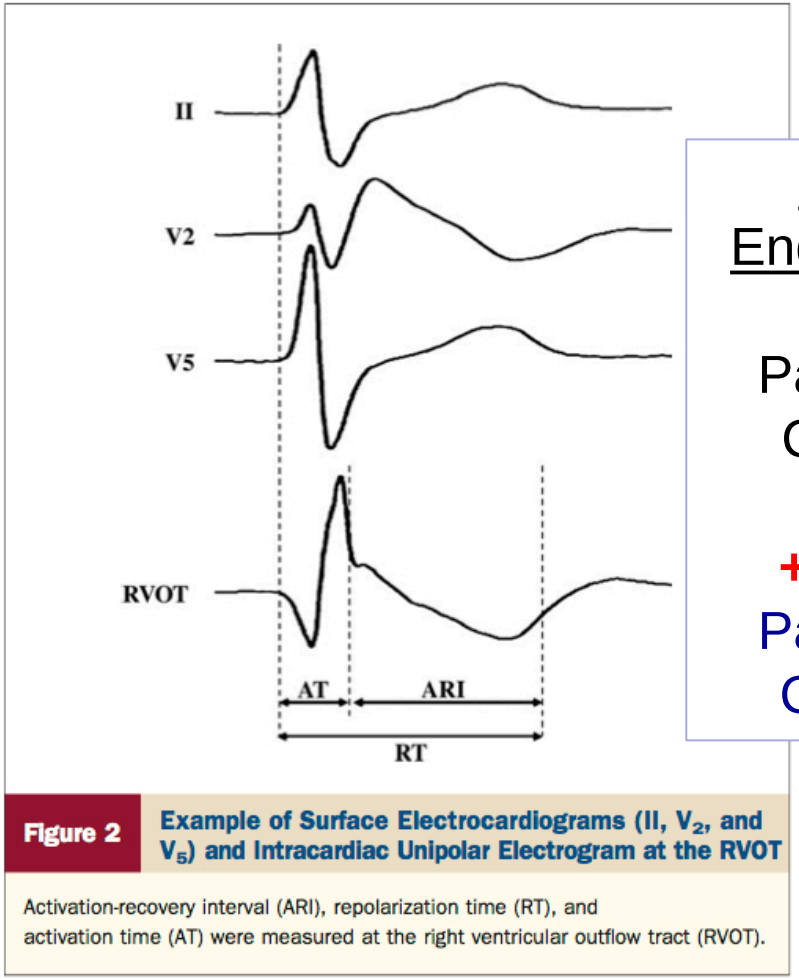


Figure 2 Example of Surface Electrocardiograms (II, V_2, and V_5) and Intracardiac Unipolar Electrogram at the RVOT

Activation-recovery interval (ARI), repolarization time (RT), and activation time (AT) were measured at the right ventricular outflow tract (RVOT).

Epicardial vs. Endocardial MAPs:

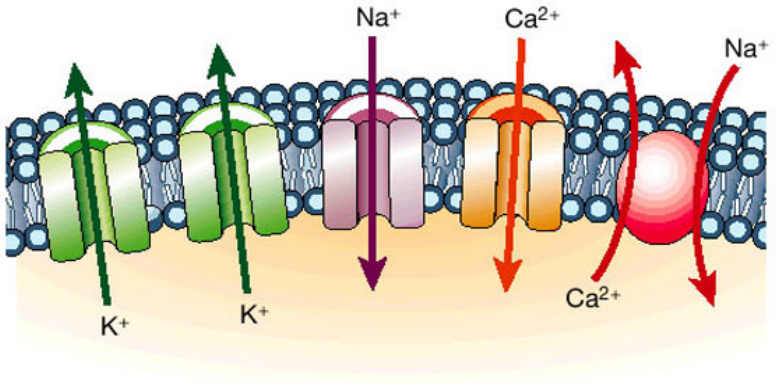
Patients +15 ms
Control -11 ms

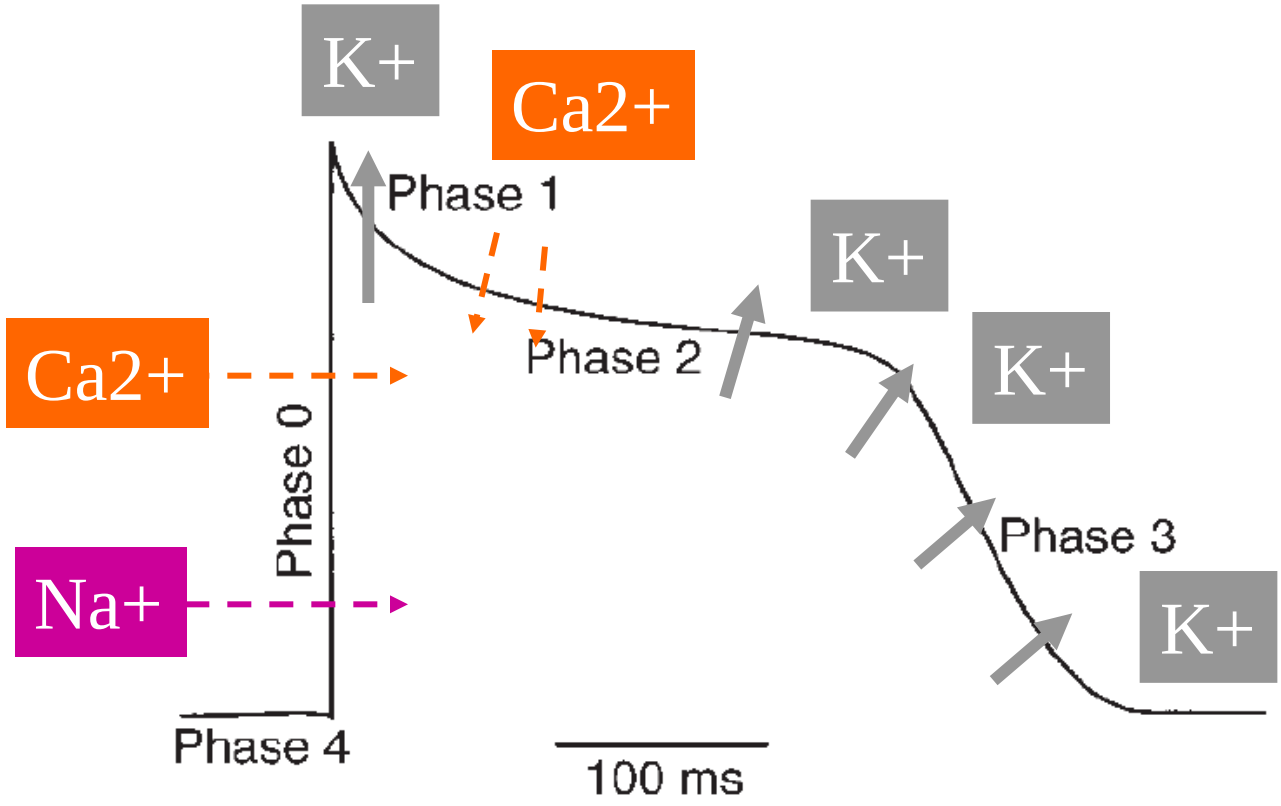
+ Pilsicainide:
Patients +34 ms
Control -14 ms

Nagase et al. (2008) JACC 51: 1154-1160v

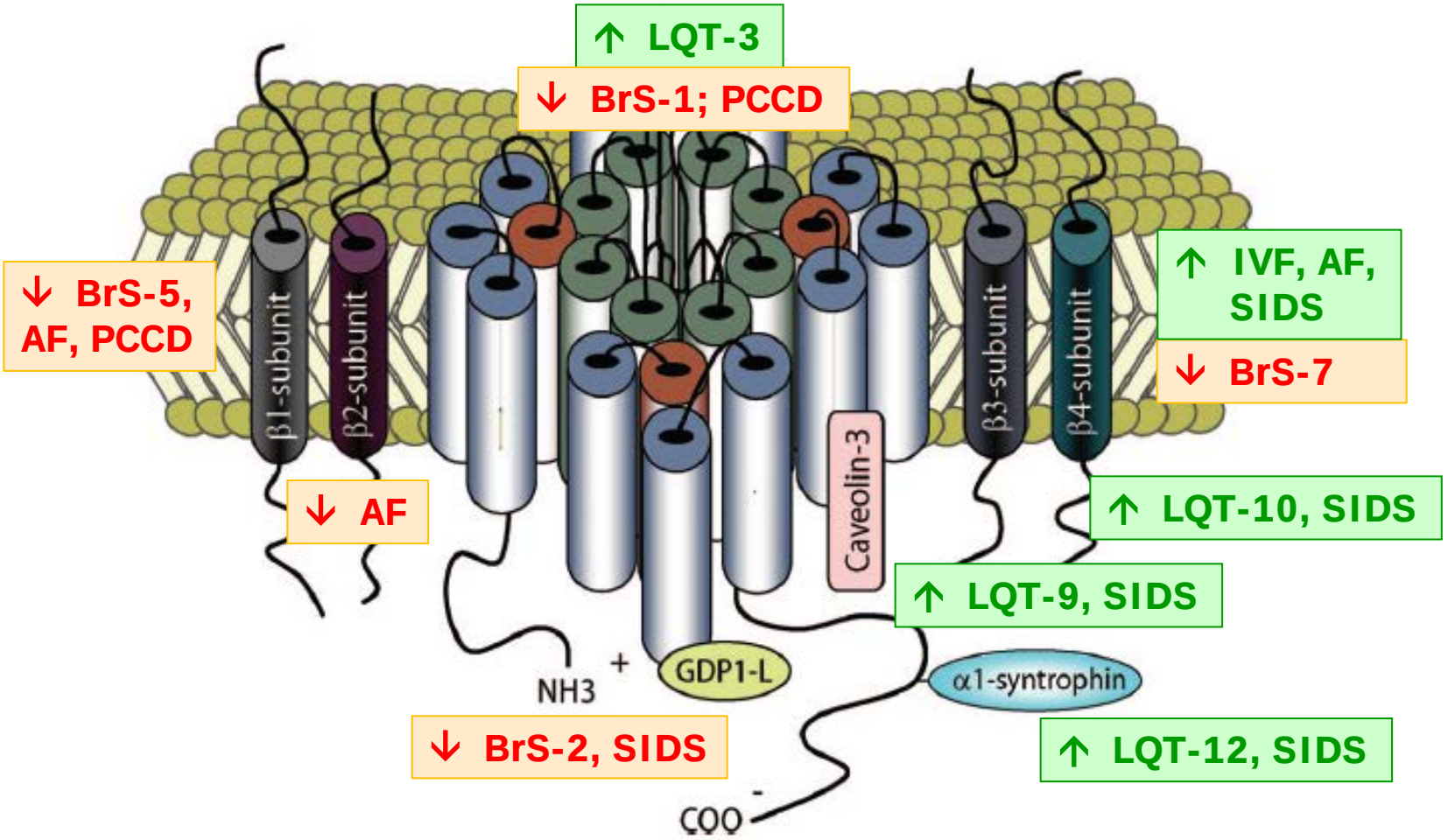
Brugada
Na^+ Channel
(BrS-1,-2,-5)

Brugada
Ca^{++} Channel
(BrS-3,-4)



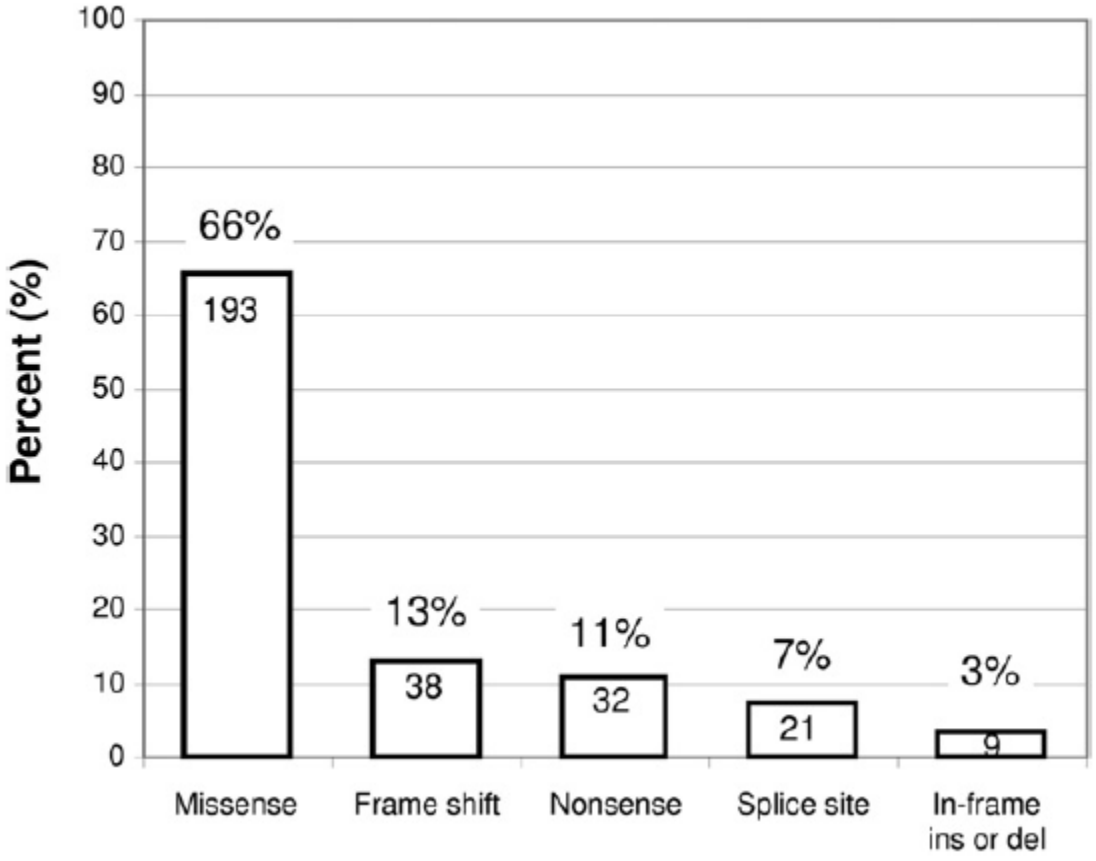


Cardiac Sodium Channelopathies (I_{Na})



Wilde et al. Circ. Res. (2011) 108: 884-897

Brugada Syndrome: Mutational Spectrum (n=2,111 probands)

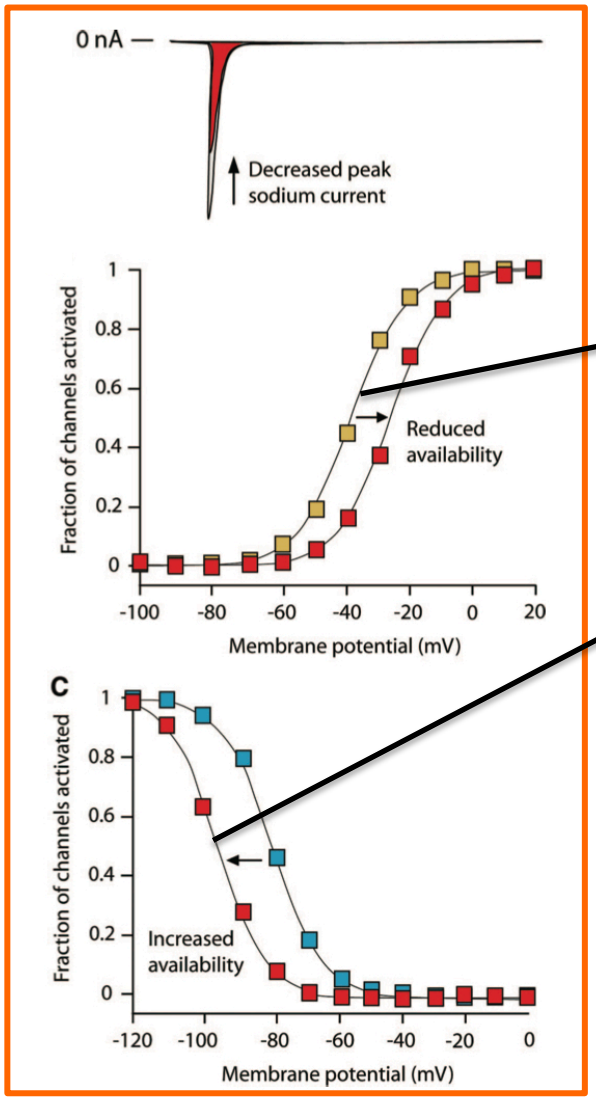


In average, 21% SCN5A+

All mutations are ‚private', no gene hot spots.

Heart Rhythm 2010: 7: 33-46

Brugada Syndrome (BrS):
The decrease in I(Na) peak current



Shift of voltage dependence of steady-state activation towards more depolarized membrane potentials

Hyperpolarizing shift of the voltage dependence of steady-state inactivation curve will lead to fewer sodium channels at RMP.

Slower recovery from channel inactivation has also been described for BrS-associated SCN5A mutations.

Wilde et al. (2011) Circ Res 108: 884-890

HRS/EHRA [2013] Expert Consensus Statement: **Brugada**

Expert Consensus Recommendations on ***Brugada Syndrome Therapeutic Interventions***

Class I	1. The following lifestyle changes ***are recommended*** in all patients with diagnosis of BrS: a) Avoidance of drugs that may induce or aggravate ST segment elevation in right precordial leads (for example, visit Brugadadrugs.org), b) Avoidance of excessive alcohol intake, c) Immediate treatment of fever with antipyretic drugs. 2. ICD implantation ***is recommended*** in patients with a diagnosis of BrS who: a) Are survivors of a cardiac arrest, and/or b) Have documented spontaneous sustained VT with or without syncope.

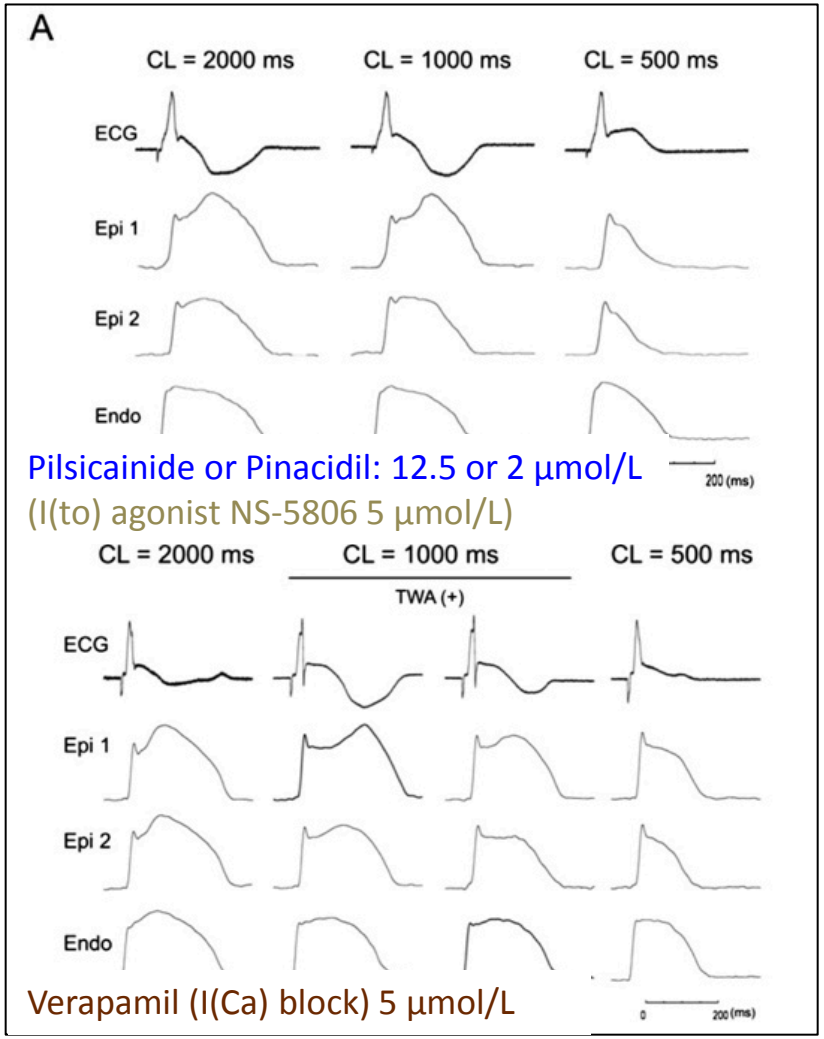
Heart Rhythm (2013), in press (ePUB)
Europace (2013), in press

HRS/EHRA [2013] Expert Consensus Statement: **Brugada**

Class IIa	3. ICD implantation ***can be useful*** in patients with a spontaneous diagnostic Type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias. 4. Quinidine ***can be useful*** in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours. 5. Quinidine ***can be useful*** in patients with a diagnosis of BrS: a) Who qualify for an ICD but present a contraindication to the ICD or refuse it, *and/or* b) Have a history of documented supraventricular arrhythmias that require treatment. 6. Isoproterenol infusion **can be useful** in suppressing arrhythmic storms in BrS patients.
Class IIb	7. ICD implantation ***may be considered*** in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients). 8. Quinidine ***may be considered*** in asymptomatic patients with a diagnosis of BrS with a spontaneous type 1 ECG. 9. Catheter ablation ***may be considered*** in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.
Class III	10. ICD Implantation **is not indicated** in asymptomatic BrS patients with a drug induced type 1 ECG and on the basis of a family history of SCD alone.

Heart Rhythm (2013), in press (ePUB)
Europace (2013), in press

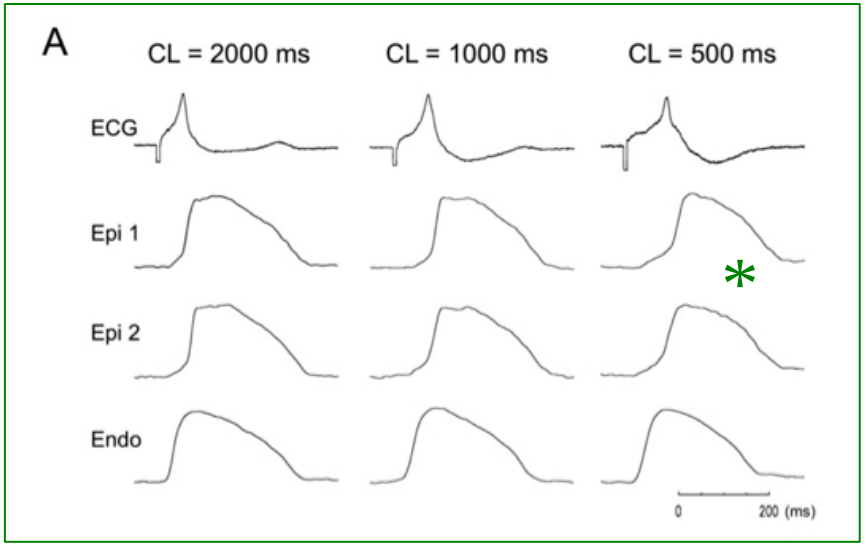
Brugada Models (cor.-art. perf. RV canine wedge) and Effect of Quinidine



Pilsicainide or Pinacidil: 12.5 or 2 µmol/L

(I(to) agonist NS-5806 5 µmol/L)

Verapamil (I(Ca) block) 5 µmol/L

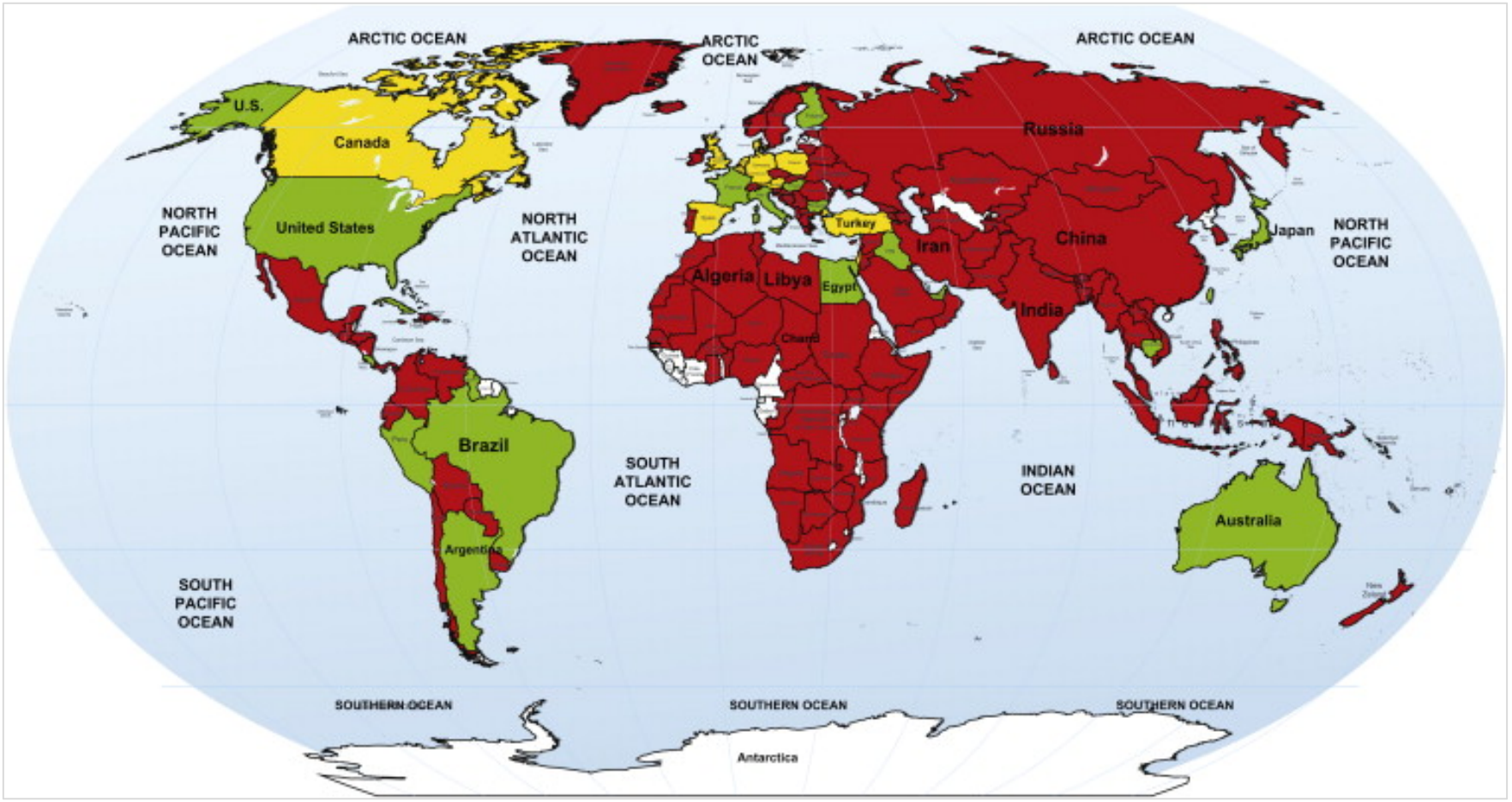


Pilsicainide/Pinacidil + Quinidine 5 µmol/L

(blocks: I(Na_TTX+), I(to), I(Ks), I(Kr), I(K1), I(K-ATP))

Reduced epicardial dispersion of repolarisation
Reduced TDR (epi-endocardial)
Restored epicardial notch

Morita et al. (2010) Heart Rhythm 7: 820-828



(Non-) Availability of quinidine:

Green = available

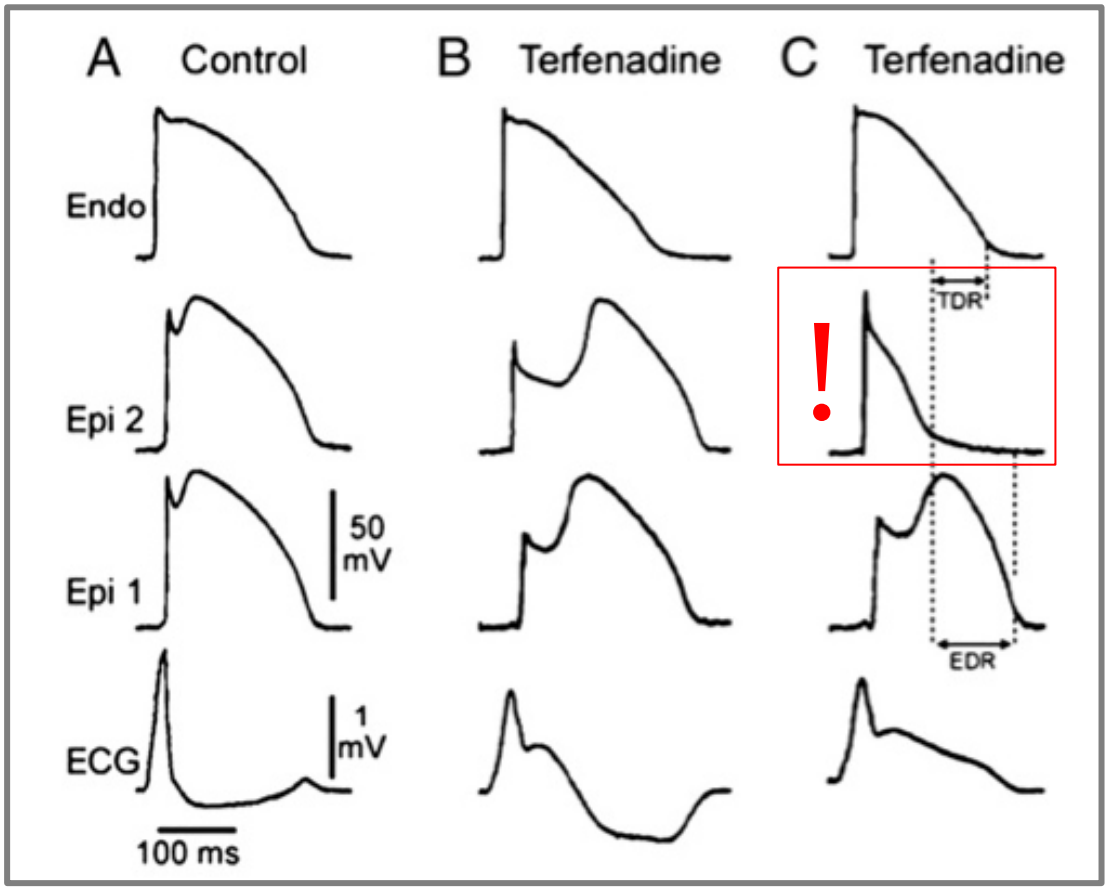
Red = not available

Yellow = available with restrictions

White = no data

JACC (2013) 61: 2383-2387

Novel Approaches in Brugada syndrome Models

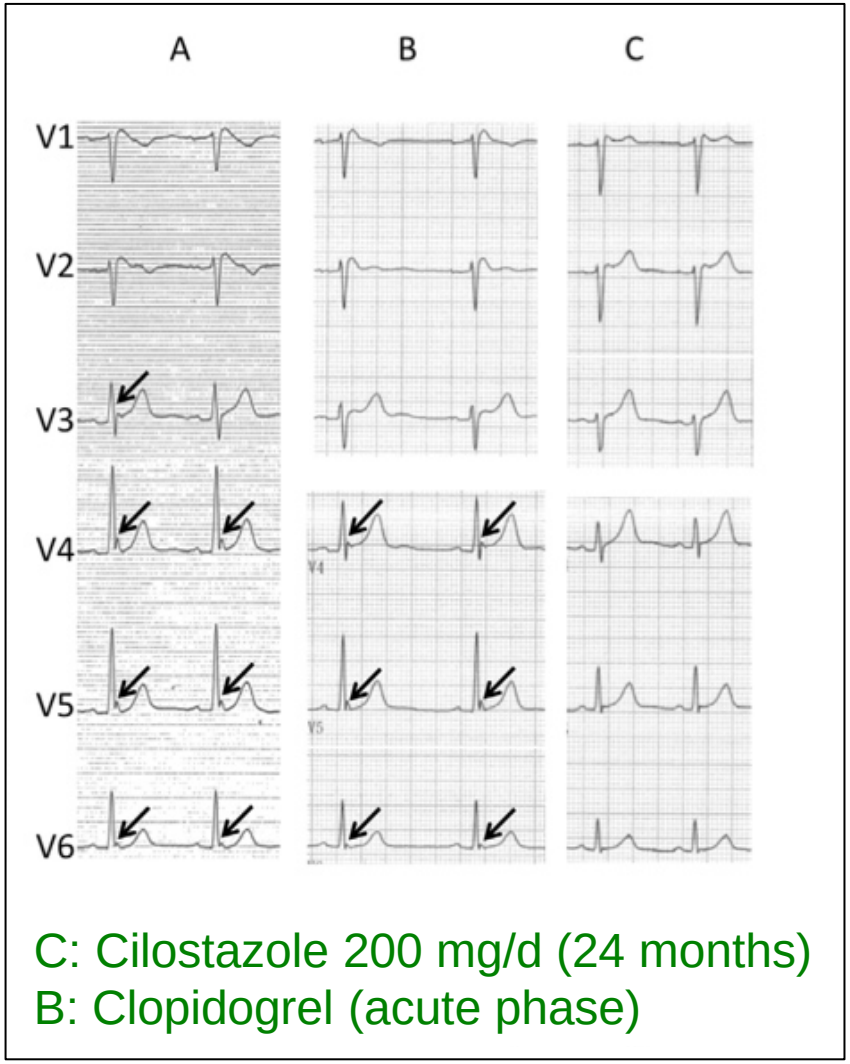


Terfenadine
(blocks: I(Na) and I(Ca))

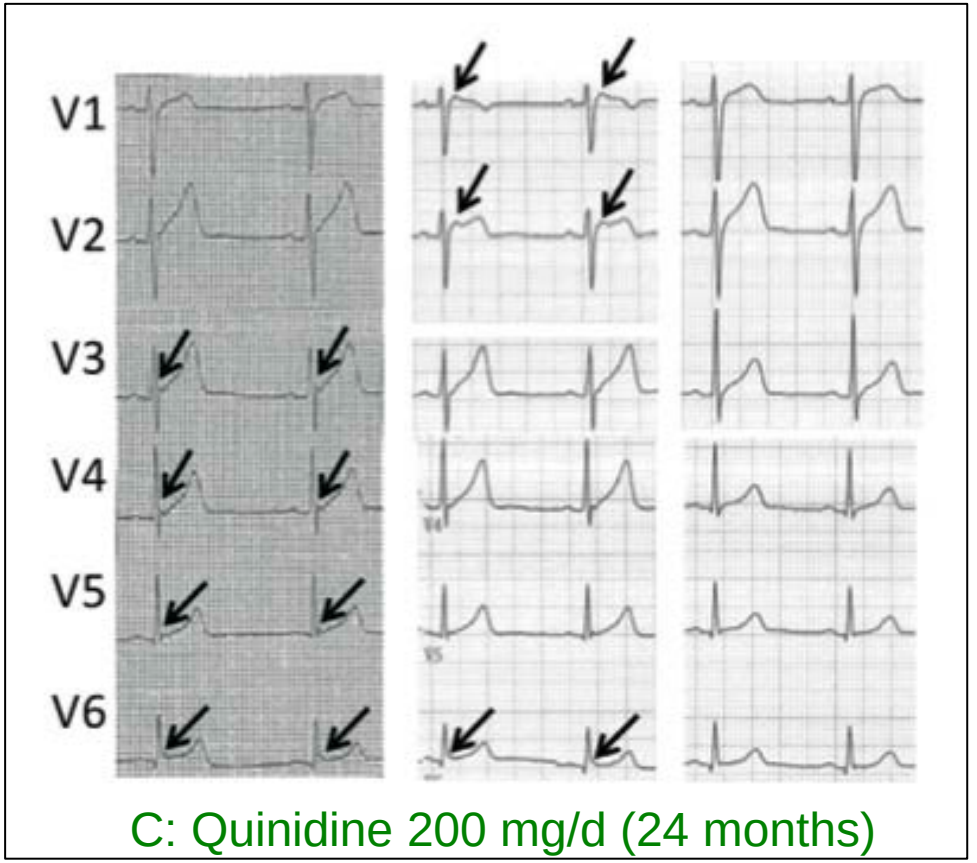
- PDE-III inhibitors (2-10 µmol/L):
  Milrinone, Cilastazol
  > cAMP ↑, I(L-Ca) ↑
- I(to) blockers/regulators:
  4-AP (4‘ aminopyridine)
  Semaphorin / *SEMA3A*
  CRIP (cold-inducible RNA-binding protein for I(to))

Szel et al. (2013) Heart Rhythm 10: 1720–1727
Boczek at al. (2014) Circ Res.115: 460-469

Long-term Suppression of J-wave in Brugada syndrome



C: Cilostazole 200 mg/d (24 months)
B: Clopidogrel (acute phase)



C: Quinidine 200 mg/d (24 months)

Szel et al. (2013) Heart Rhythm 10: 1720–1727
Boczek at al. (2014) Circ Res.115: 460-469

Novel Approaches in Brugada syndrome Models

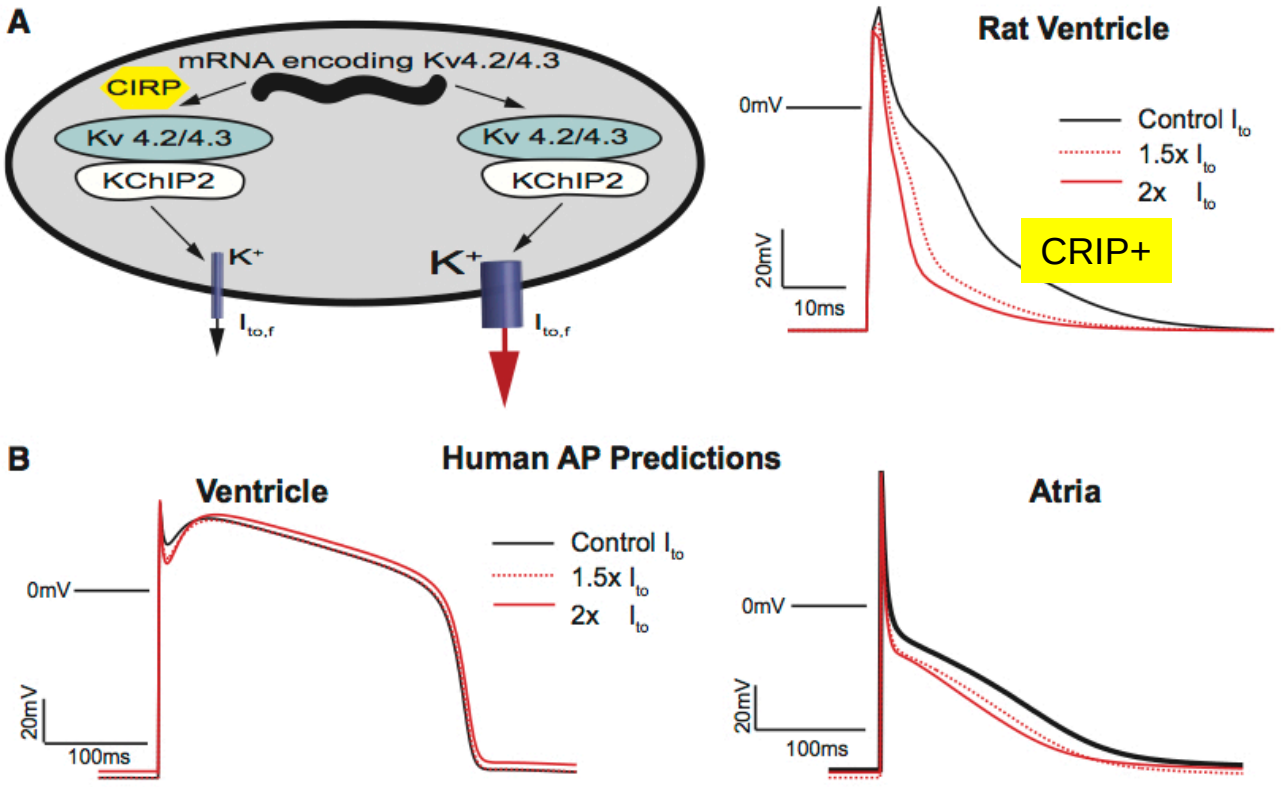


Figure. Computational modeling of impact of cold-inducible RNA-binding protein (CIRP) I_{to} downregulation in rat and human cardiomyocytes. A, Schematic of CIRP regulation in the rat cardiomyocyte (**left**), where the absence of CIRP leads to greater I_{to} density and a shortened action potential (AP) duration (**right**). **B**, Computational modeling of human AP waveforms in ventricular (**left**) and atrial (**right**) myocytes reveals expected tissue-specific effects when increasing I_{to} current density.

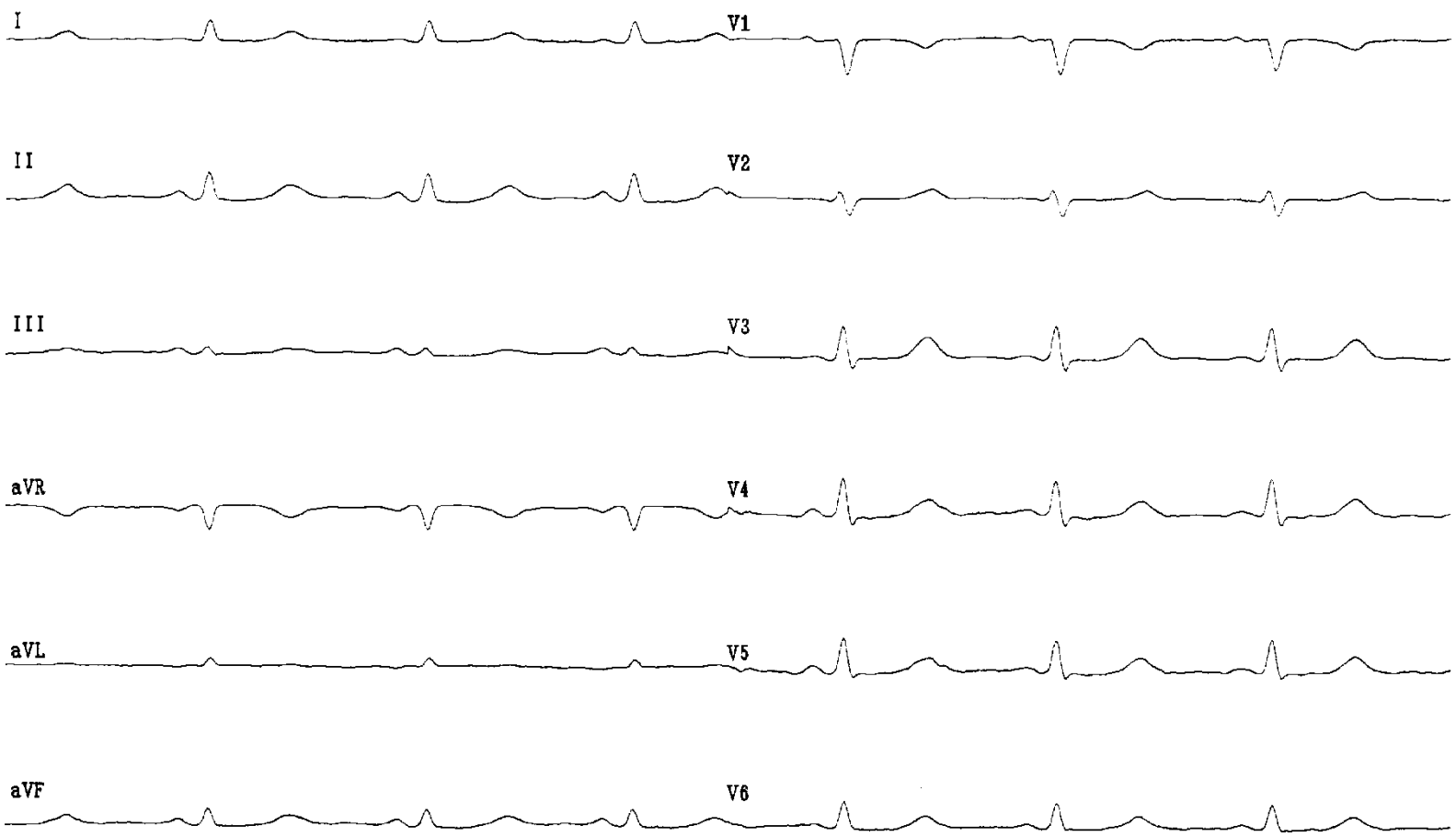
Editorial by Bohnen et al. (2015) Circ Res. 116:1633-1635

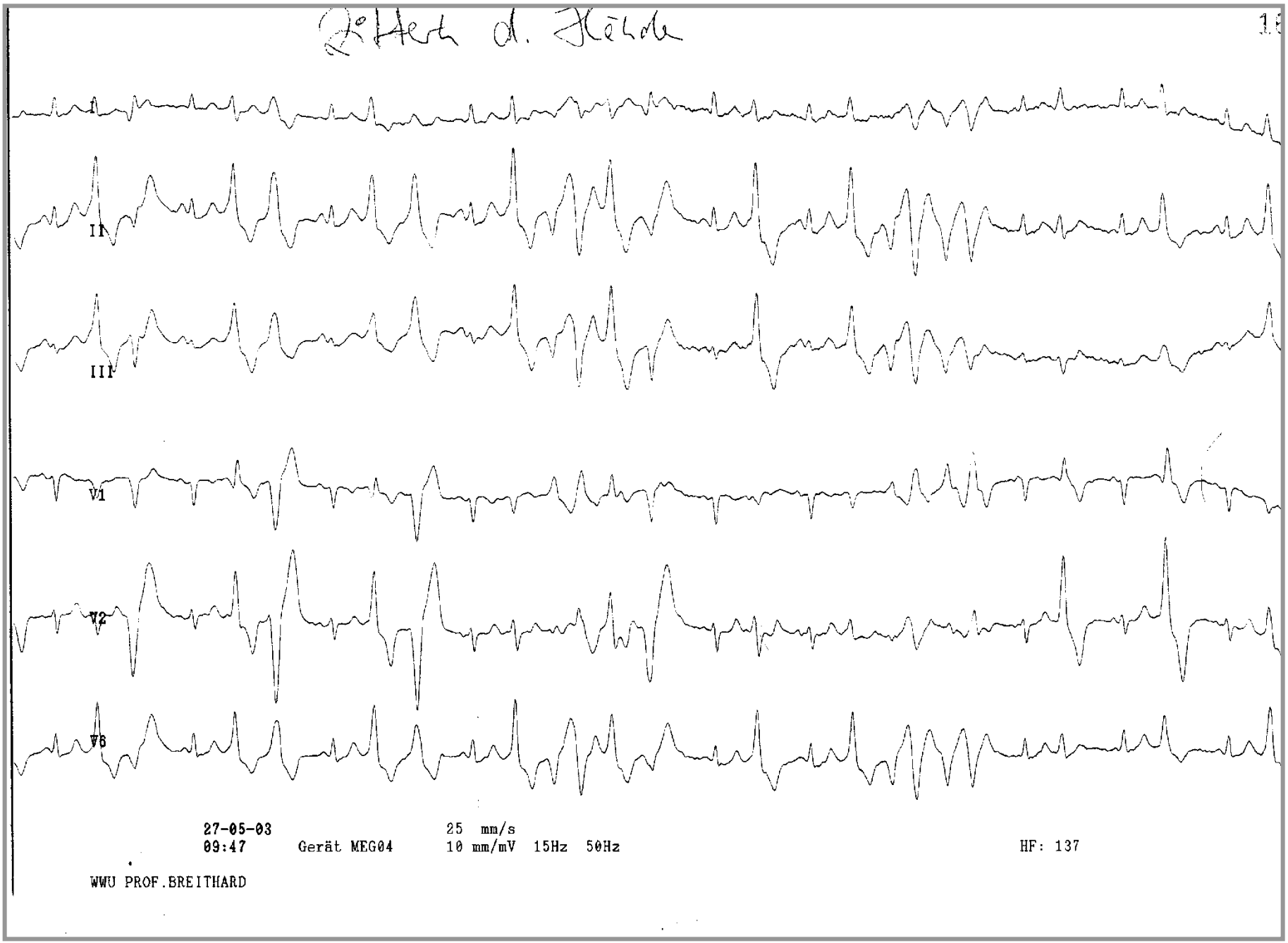
Li et al. (2015) “Cold-inducible RNA-binding protein regulates cardiac repolarization by targeting transient outward potassium channels.” Circ Res. 2015;116:1655–1659

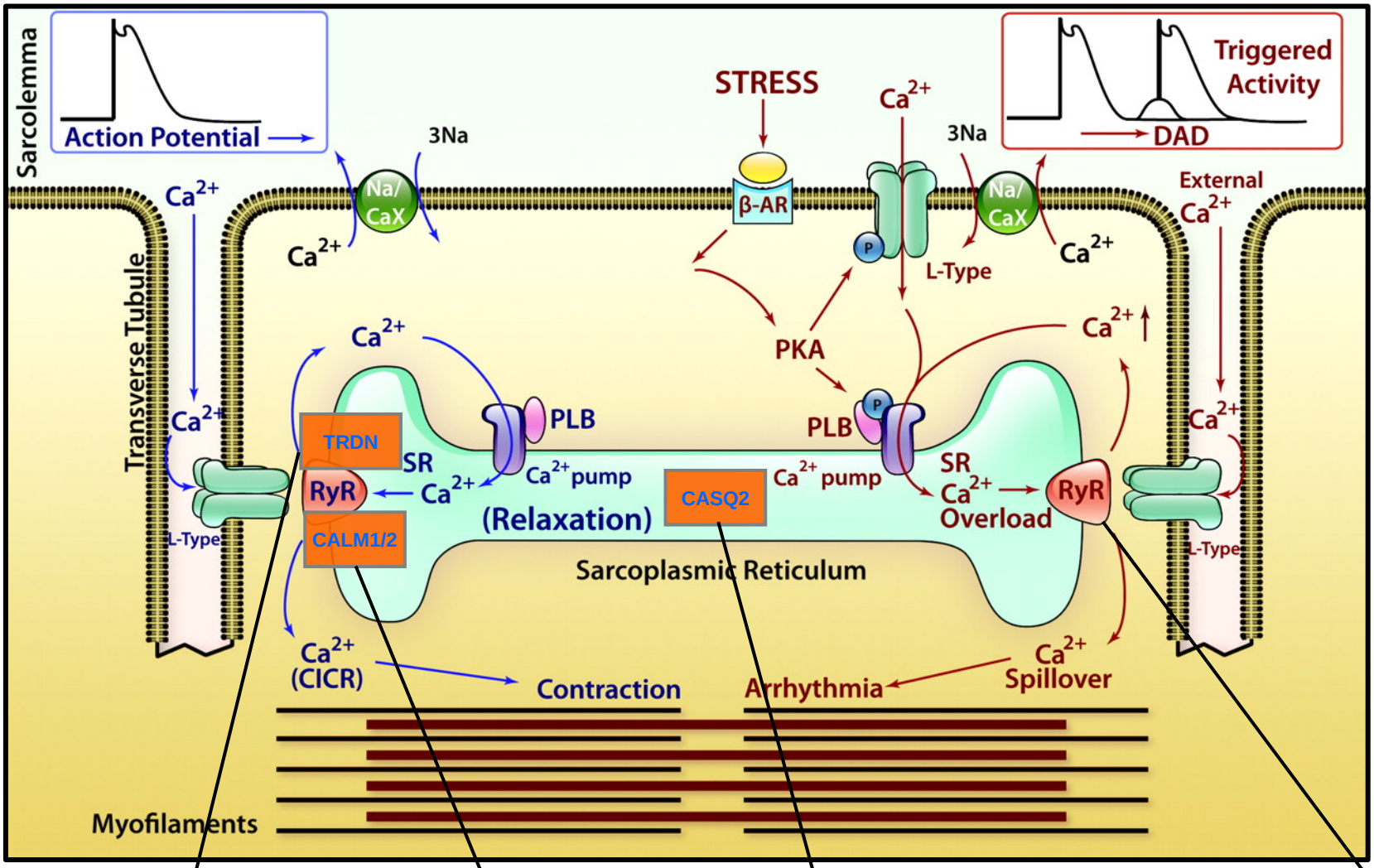
CPVT

(catecholaminergic polymorphic ventricular tachycardia)

ID:	Phase:	**Ruhe**	HF:	**80**	Datum: **27-05-03**
Nachname:	Phasendauer:	**00:31**	RR:	**125/80**	Zeit: **09:41**
Vorname:					Gerät **MEG04**
					Standort: **EKG MED-C**
	Belastung:	**0 W**			Ort: **UNIV. MS**
	Protokoll:	**Standard**			




I
II
III
V1
V2
V6
27-05-03
09:47
Gerät MEG04
25 mm/s
10 mm/mV 15Hz 50Hz
HF: 137
WWU PROF.BREITHARD



CPVT5 (<1%) ↓

CPVT4 (1-5%) ↓

CPVT2 (<1%) ↓

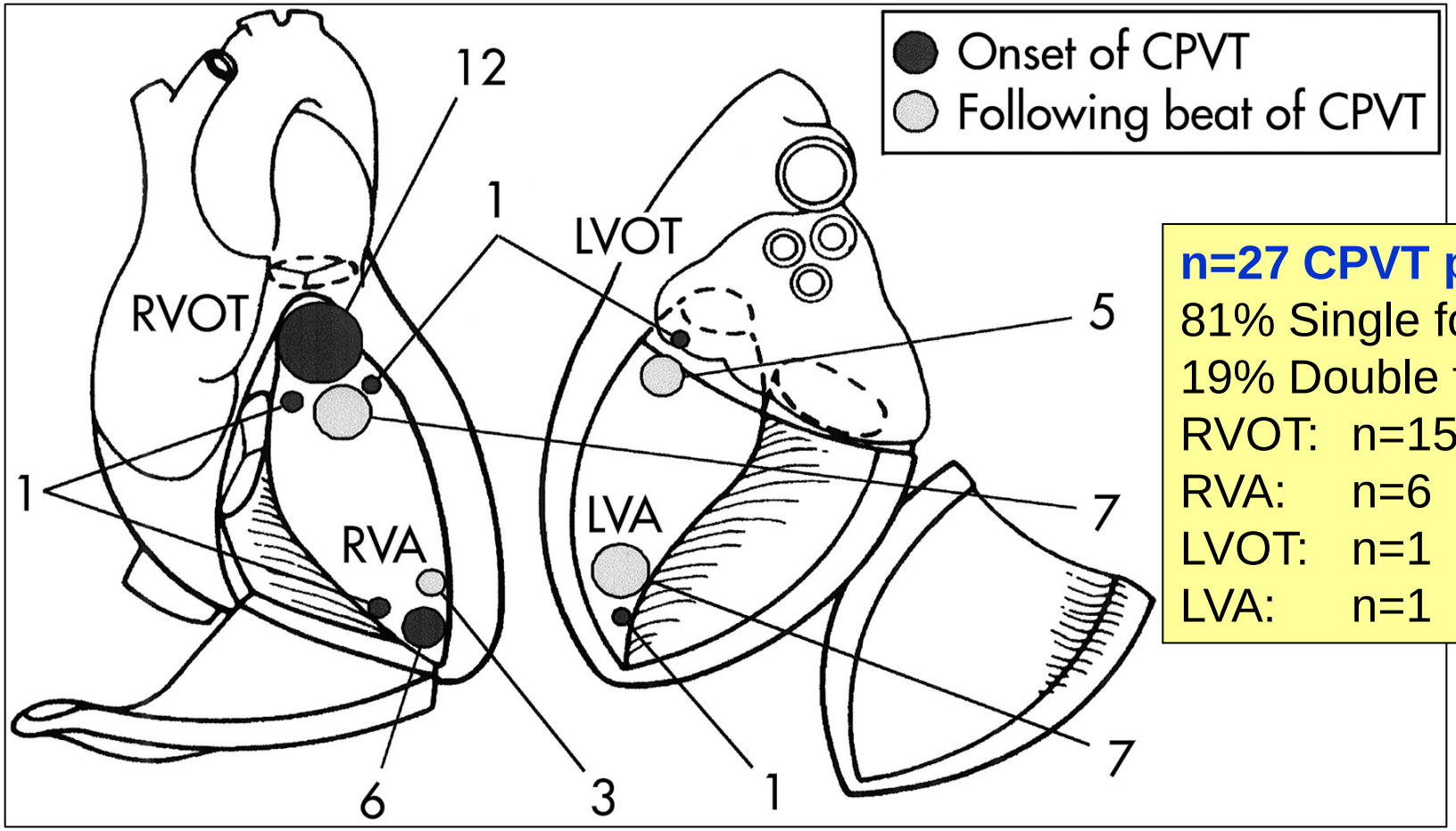
CPVT1 (>60%) ↑

Priori et al. (2011) Circ Res 108: 871-883

CPVT:
Treatment Options

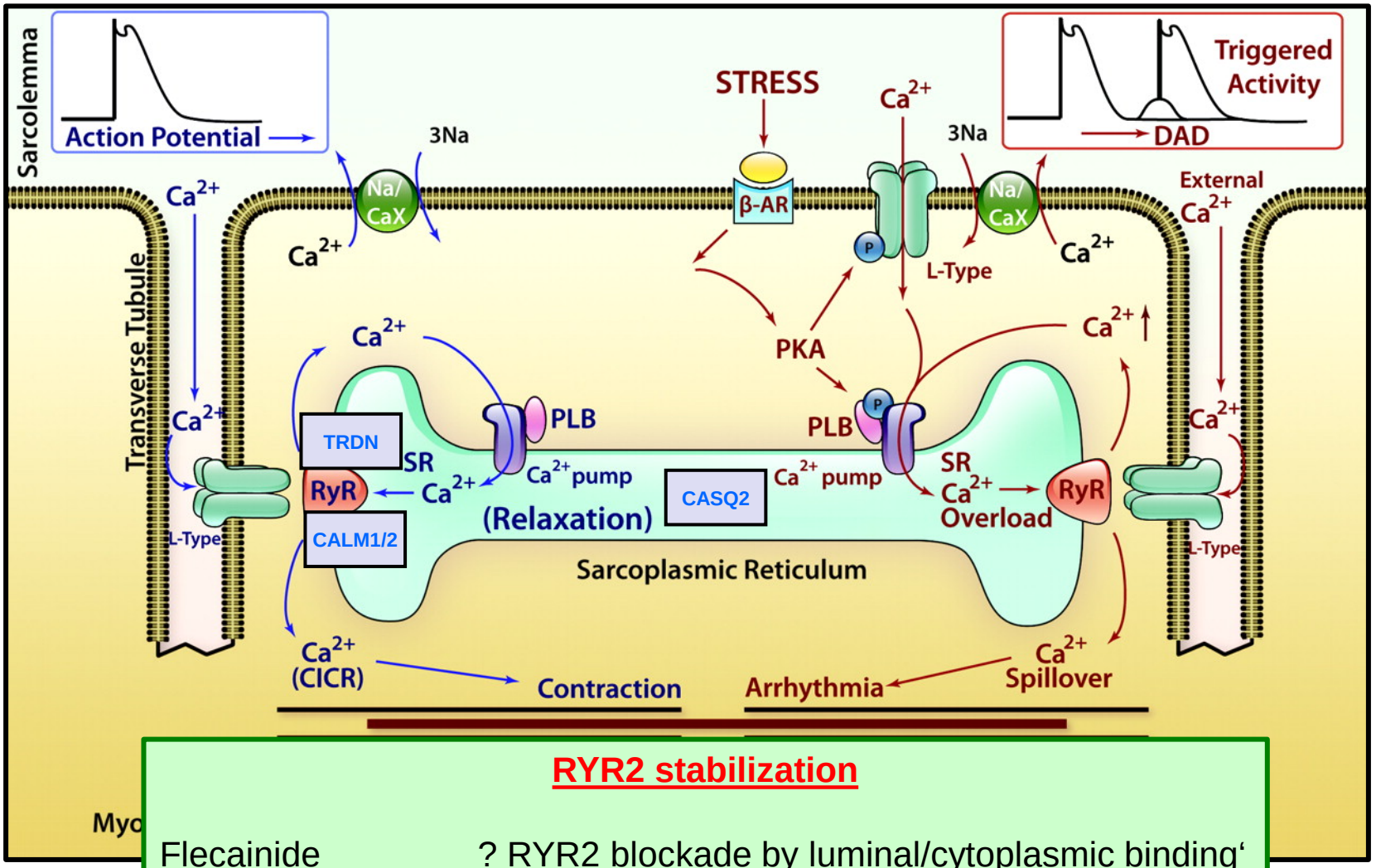
- Due to severe clinical course, treatment is considered a priori in ‚affected' individuals
- Suggestive indicators for therapeutic effectiveness are the reduction of VES/VT and symptoms
- Treatment options include:
  - **Life style modification** !
  - Drugs (BB +/- verapamil +/- flecainide)
  - ICD implantation
  - Left sympathetic cardiac denervation (LSCD)

CPVT:
First and Second Focus



n=27 CPVT pts.
81% Single focus
19% Double focus
RVOT: n=15
RVA: n=6
LVOT: n=1
LVA: n=1

Sumitomo et al. (2003) Heart 89: 66-70



RYR2 stabilization

Flecainide	? RYR2 blockade by luminal/cytoplasmic binding‘
	? I(Na) blockade
KN-93 (1µM)	CamKII inhibition – less phosphorylation
Dantrolene	RYR2 binding (effective in MHH/RYR1)
Ranolazine (10µM)	reduces P_o of RYR2 receptors

Priori et al. (2011) Circ Res 108: 871-883

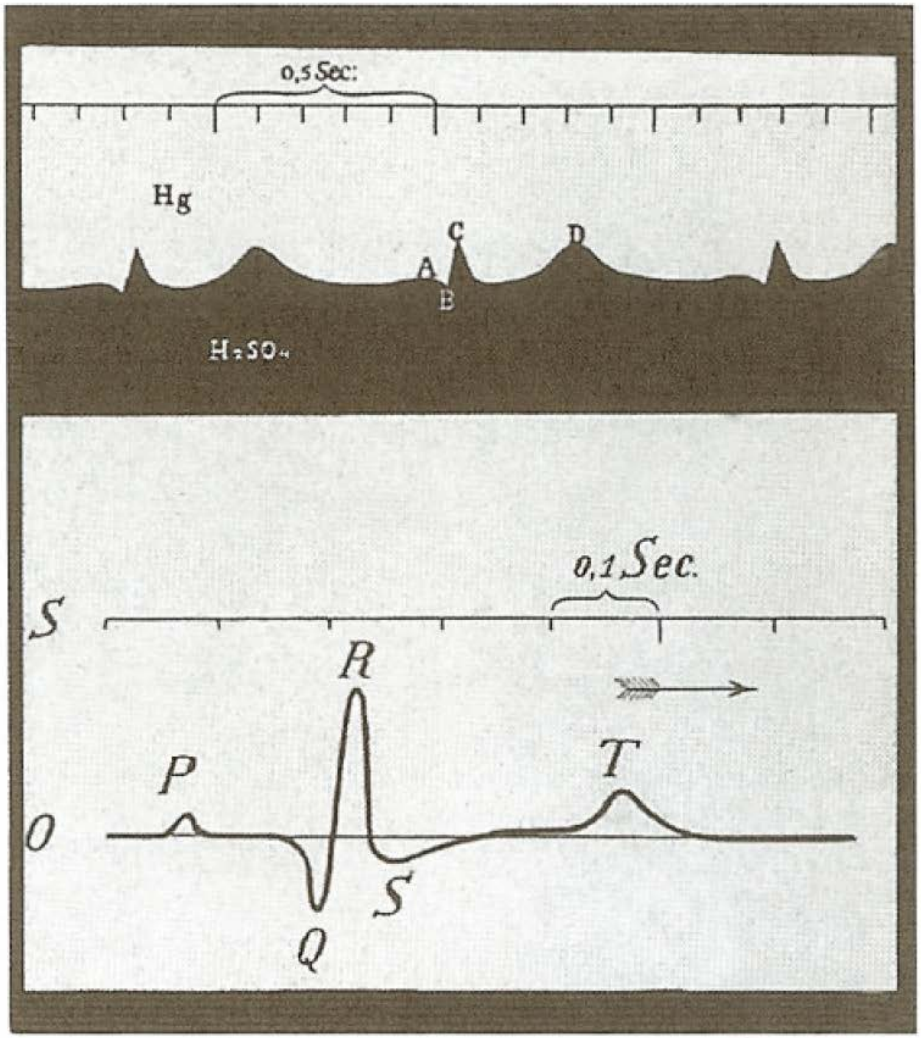


Fig. 4. Einthoven's first ECG tracings. Recording of an ECG with A, B, C and D wave using a capillary electrometer (upper registration). The lower ECG registration is Einthoven's first published electrocardiographic tracing using a string galvanometer and a different nomenclature with P, Q, R, S, and T wave.

Eric Schulze-Bahr

Institute for Genetics of Heart Diseases
Department for Cardiology and Angiology
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Uses of Genetic Testing in Cardiovascular Diseases

- Diagnostic and/or predictive testing (for monogenic traits)
- Pharmacogenomic testing (CYP450, e.g. -2C9, -2D6)
- Postmortem testing ('Molecular Autopsy')

- Risk prediction testing, uses genome information (QTLs) from GWAS to assess individual relative risk for common cardiovascular disorders

- Direct-to-consumer testing, commercial service without professional medical consultation
- Pre-implantation testing (selection during fertilization)