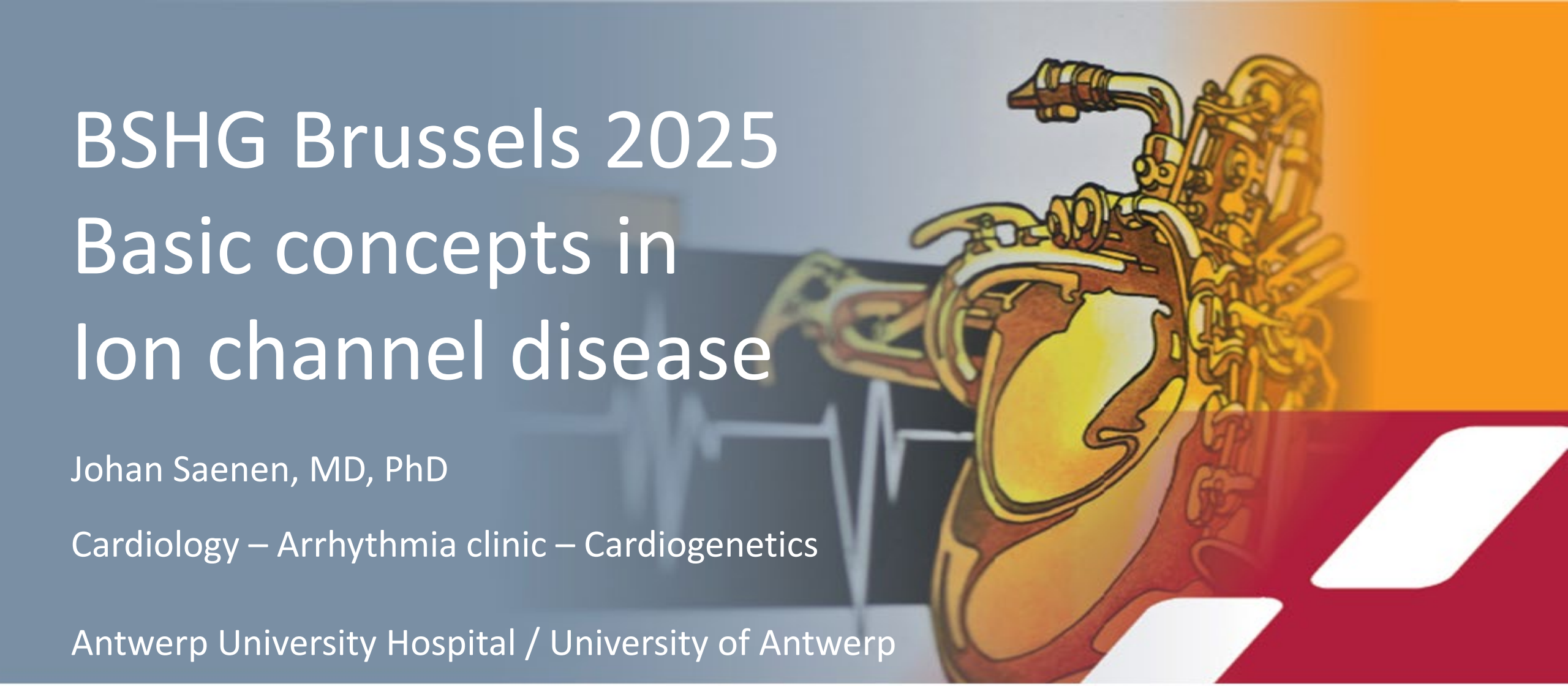
BSHG Brussels 2025
Basic concepts in Ion channel disease



Johan Saenen, MD, PhD

Cardiology – Arrhythmia clinic – Cardiogenetics

Antwerp University Hospital / University of Antwerp

Kennis / Ervaring / Zorg

Universiteit Antwerpen / UZA

The normal heart

Arrhythmogenesis

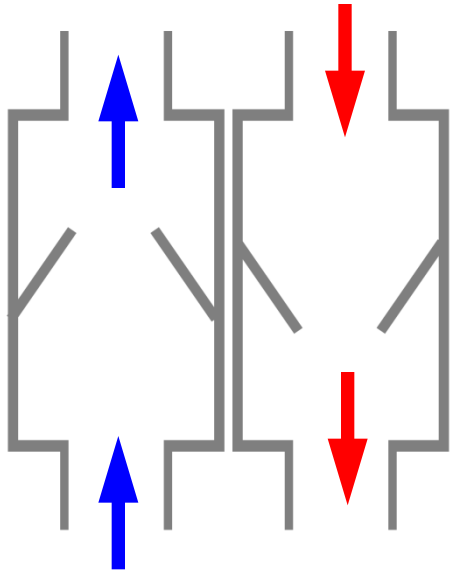
What causes APD changes ?

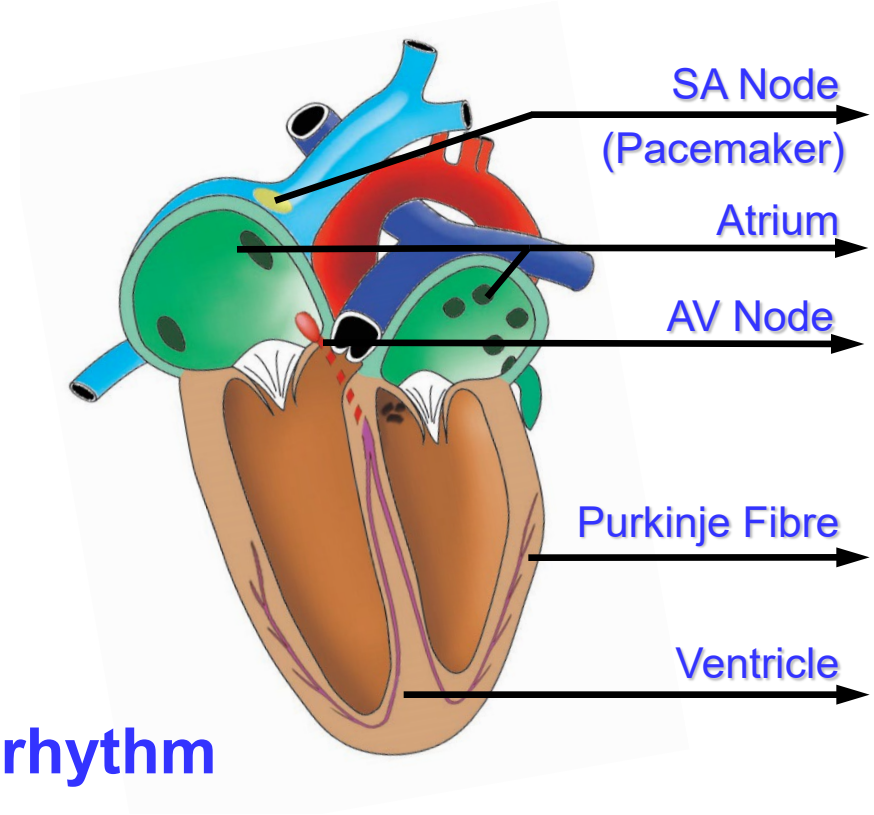
Hereditary Arrhythmia Syndromes

Conclusion

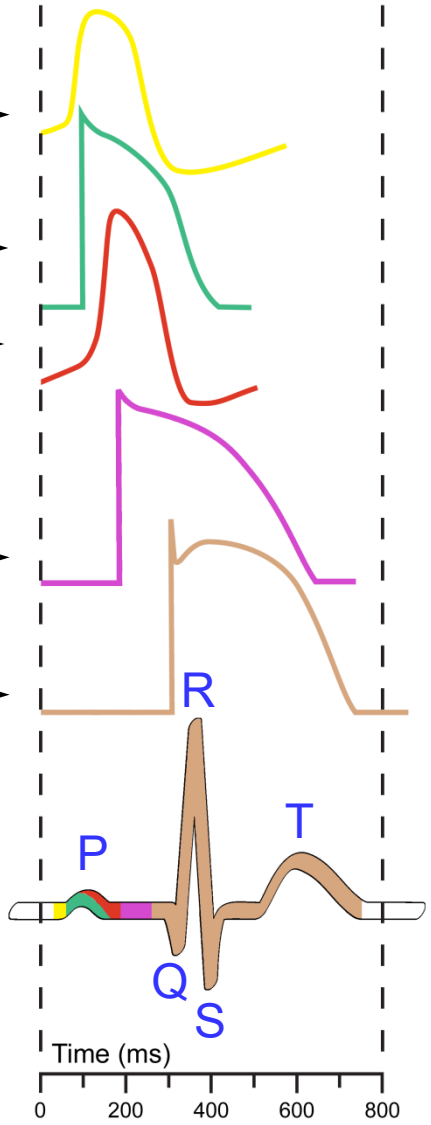
The normal heart

Electrical functioning of the normal heart

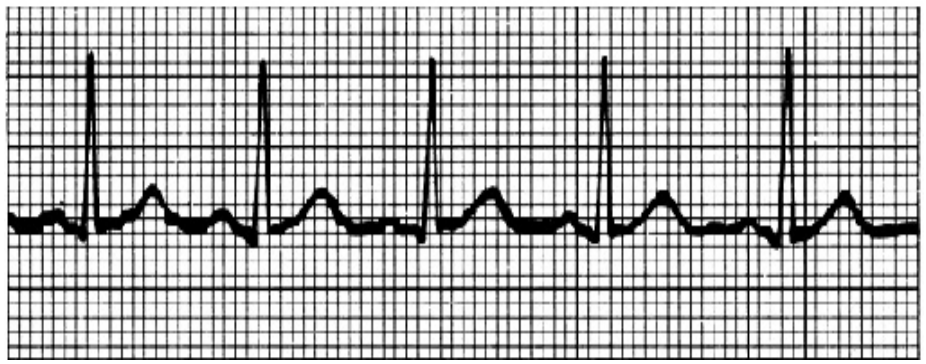




Action potential (AP)



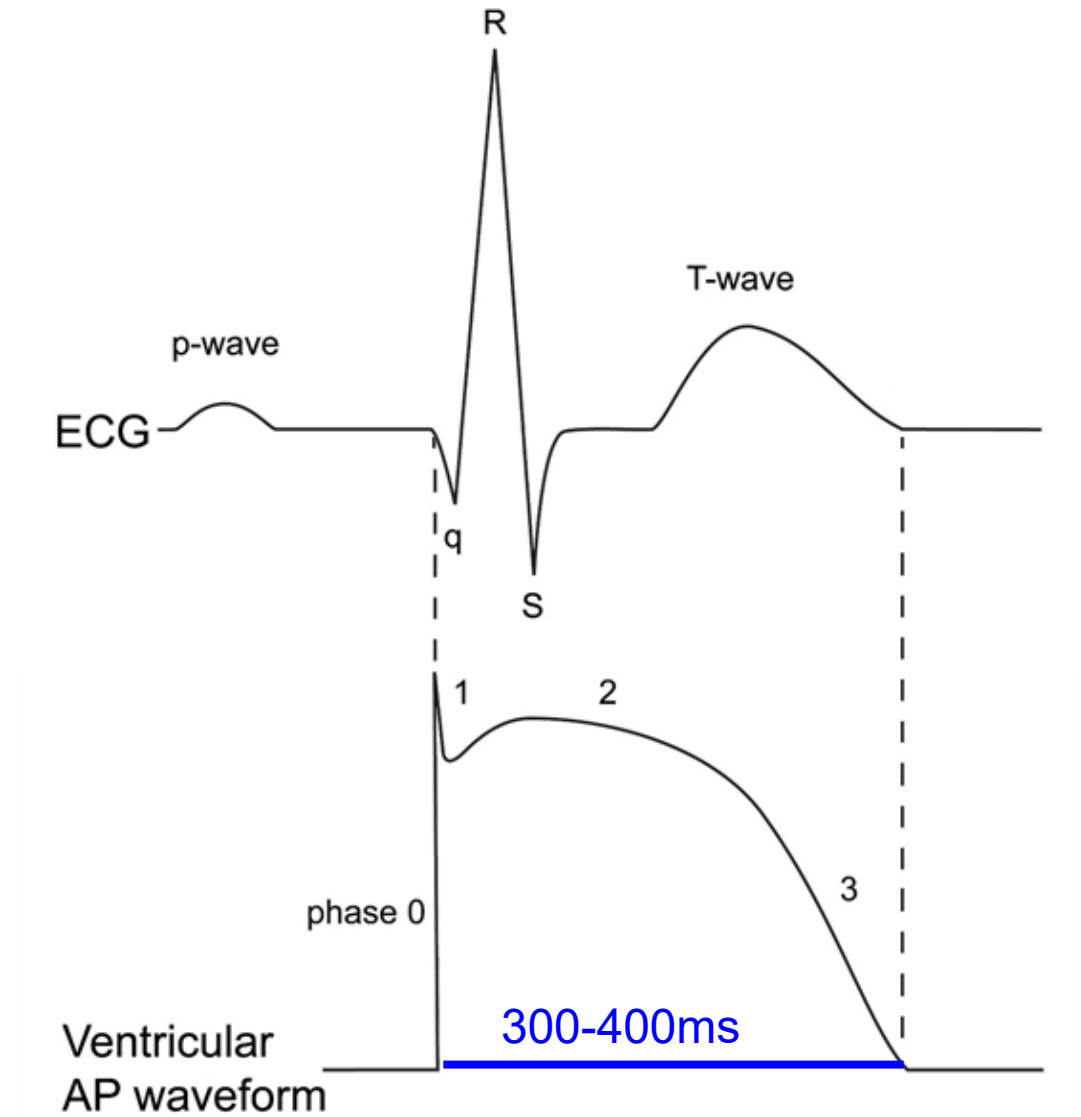
Sinus rhythm



Surface ECG

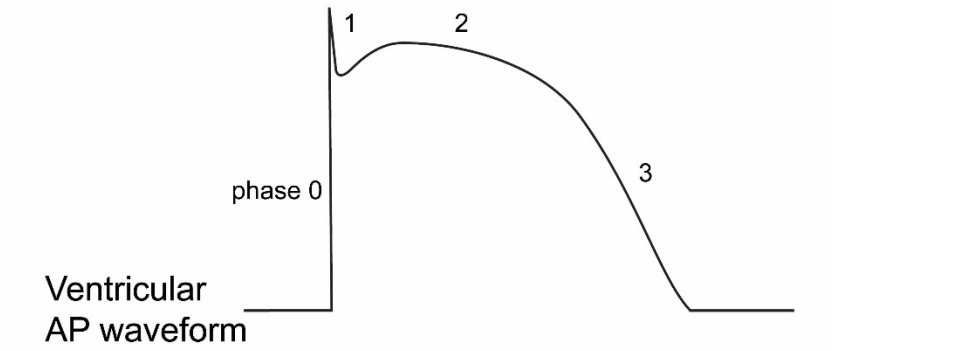
1 beat

Electrical functioning of the normal heart



Electrical functioning of the normal heart

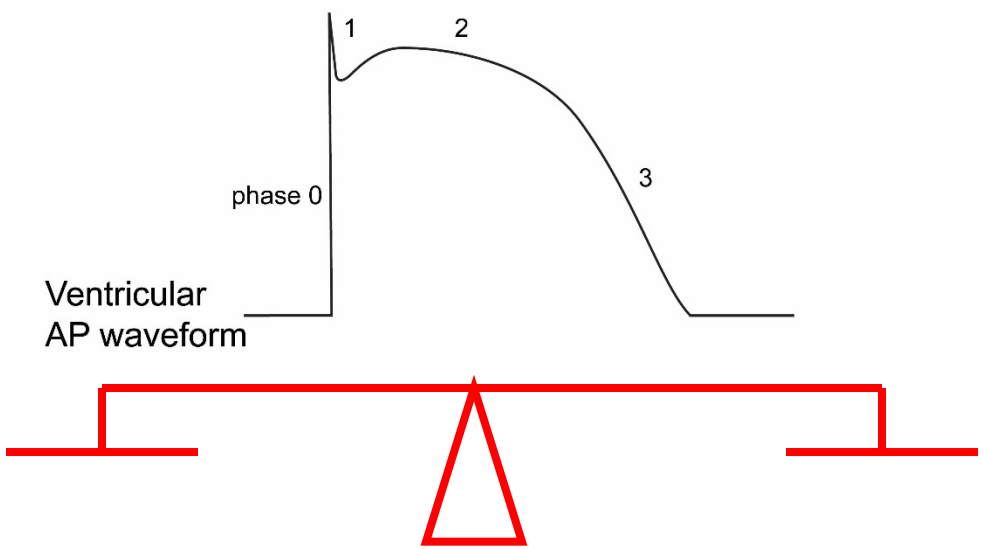
The cardiac action potential (AP)



Ion channel Gene	Ionic current
SCN5A	Nav1.5 / I_{Na}
CACNA1C	Cav1.2 / L-type I_{Ca}
CACNA1G *CACNA1H*	Cav3.1 / T-type I_{Ca} Cav3.2 / T-type I_{Ca}
NCX1	Na/Ca exchanger
KCND2/KCND3	Kv4.2/Kv4.3 / $I_{to,1}$
?	-- / $I_{to,2}$
KCNQ1	KvLQT1 / I_{Ks}
KCNH2	hERG / I_{Kr}
KCNA5	Kv1.5 / I_{Kur} or I_{Kq}
CFTR,CLC2/3 ? *KCNK2*	I_{Cl} TREK-1 / I_{ss}
KCNJ2/KCNJ12	Kir2.1/Kir2.2 / I_{K1}
KCNJ3/KCNJ5 *KCNJ11*	Kir3.1/Kir3.4 / I_{KACh} Kir6.2 / I_{KATP}
HCN1,2,4	I_f

Electrical functioning of the normal heart

The cardiac action potential (AP)



Depolarization

I_{Na+} (SCN5A)

I_{Ca2+} (α_{1c}, α_{1H}, Exch.)

Repolarization

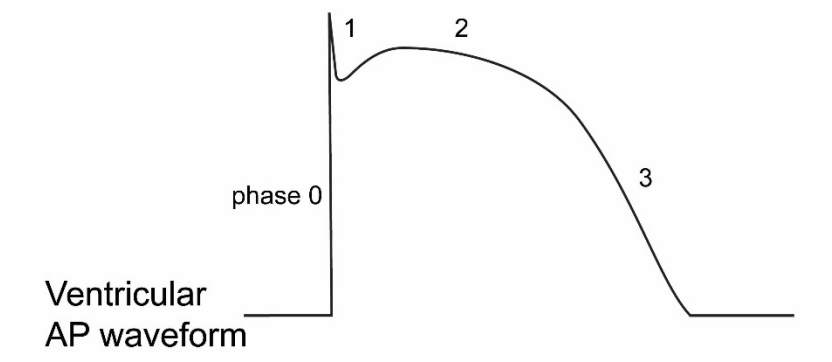
I_{to} (Kv4.2/4.3)

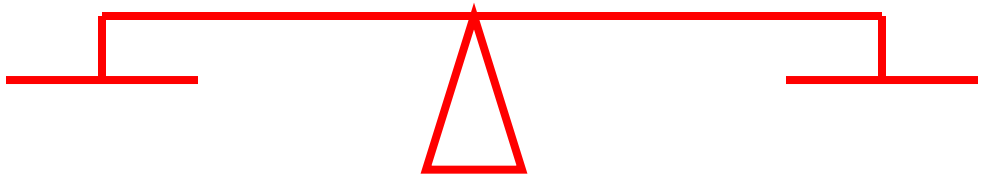
I_{Kr}, I_{Ks} (KvLQT1,hERG)

I_{K1} (Kir 2.1)

Electrical functioning of the normal heart

The cardiac action potential (AP)





Depolarization

Na^+/Ca^{2+}

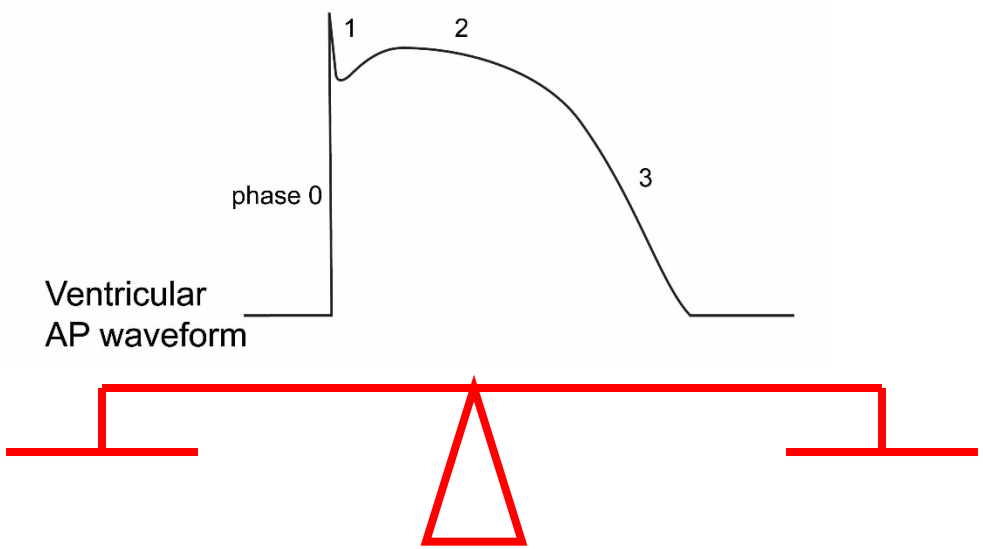
Repolarization

K^+

Arrhythmogenesis

Arrhythmogenesis

The cardiac action potential (AP)



Depolarization

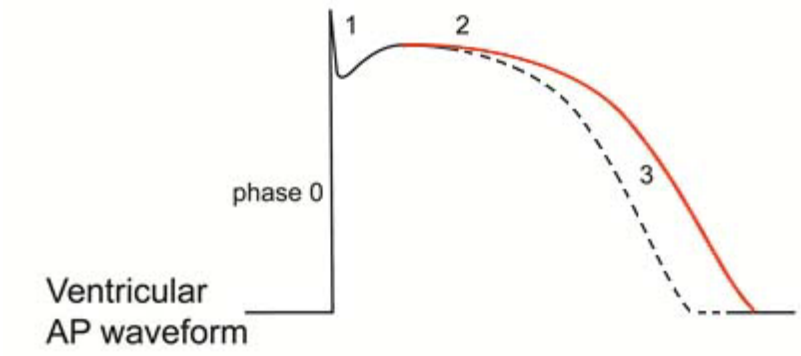
Na^+/Ca^{2+}

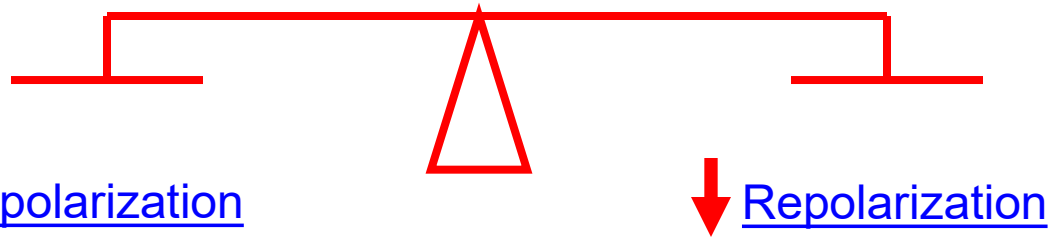
Repolarization

K^+

Arrhythmogenesis
Long QT Syndrome

The cardiac action potential (AP)





Depolarization

Na^+/Ca^{2+}

“Gain of functional expression”

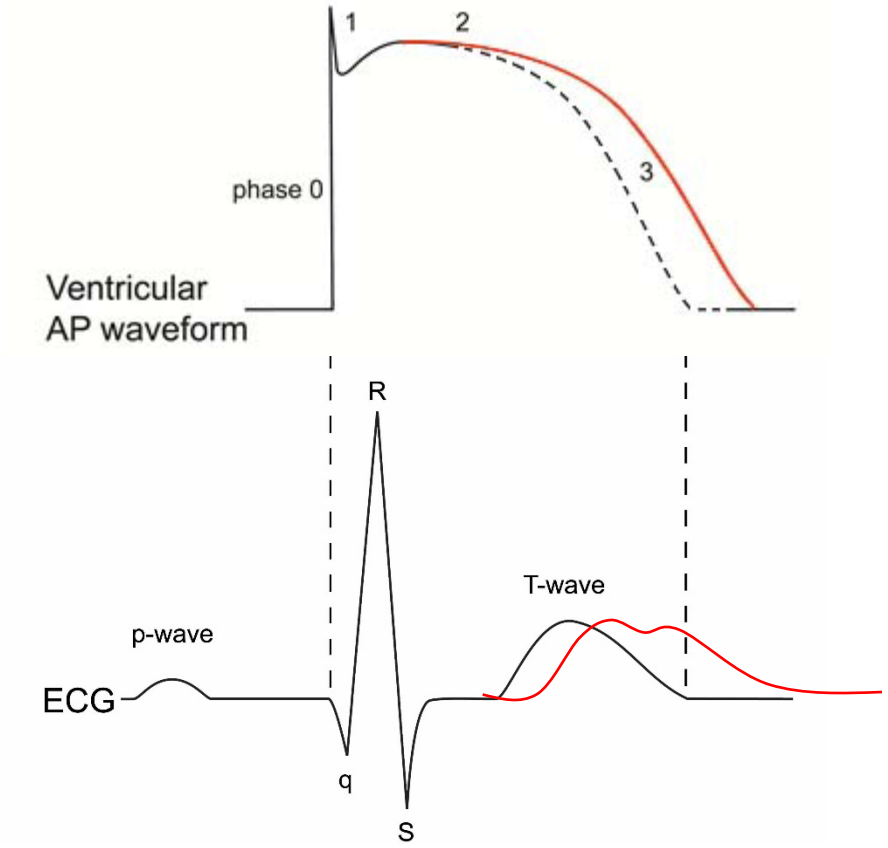
Repolarization

K^+

“Loss of functional expression”

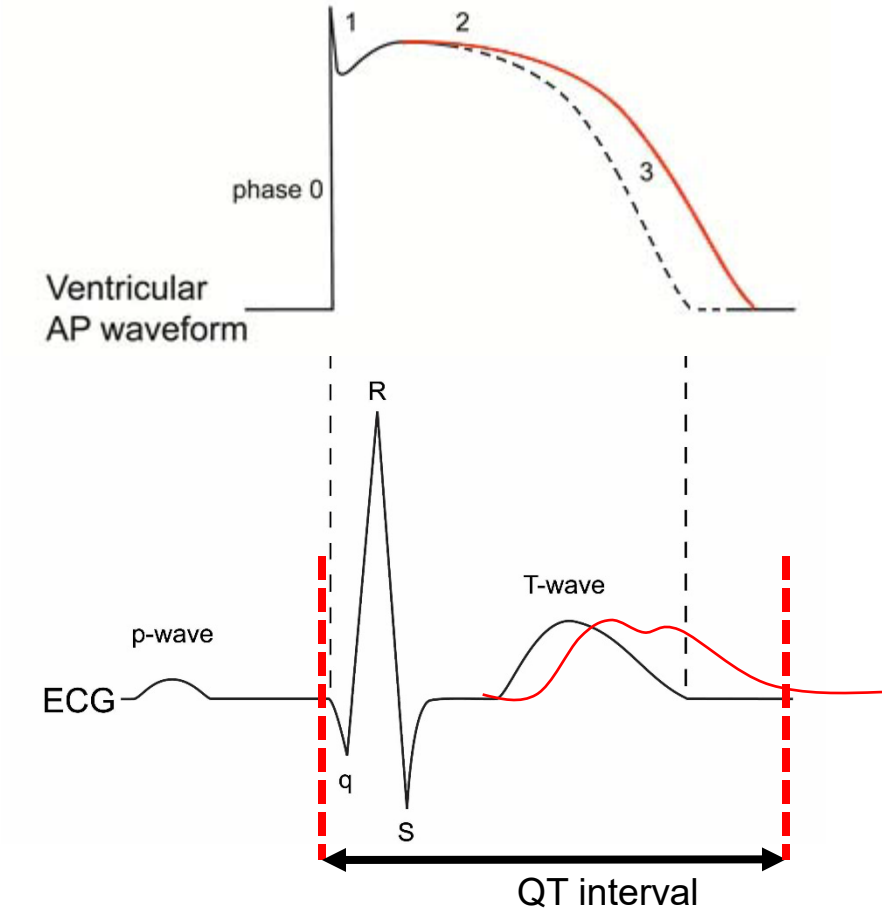
Arrhythmogenesis
Long QT Syndrome

The cardiac action potential (AP)

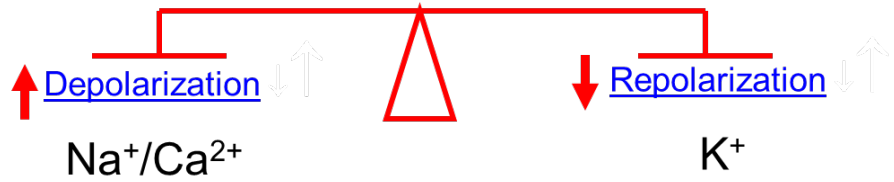


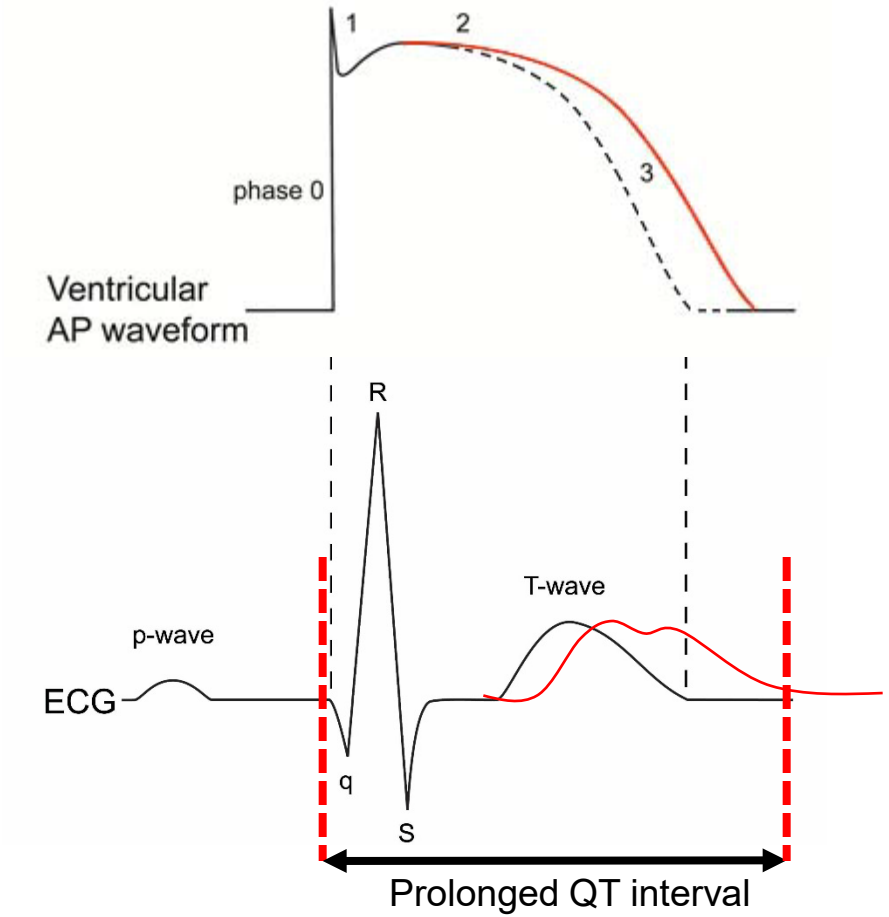
Arrhythmogenesis
Long QT Syndrome

The cardiac action potential (AP)

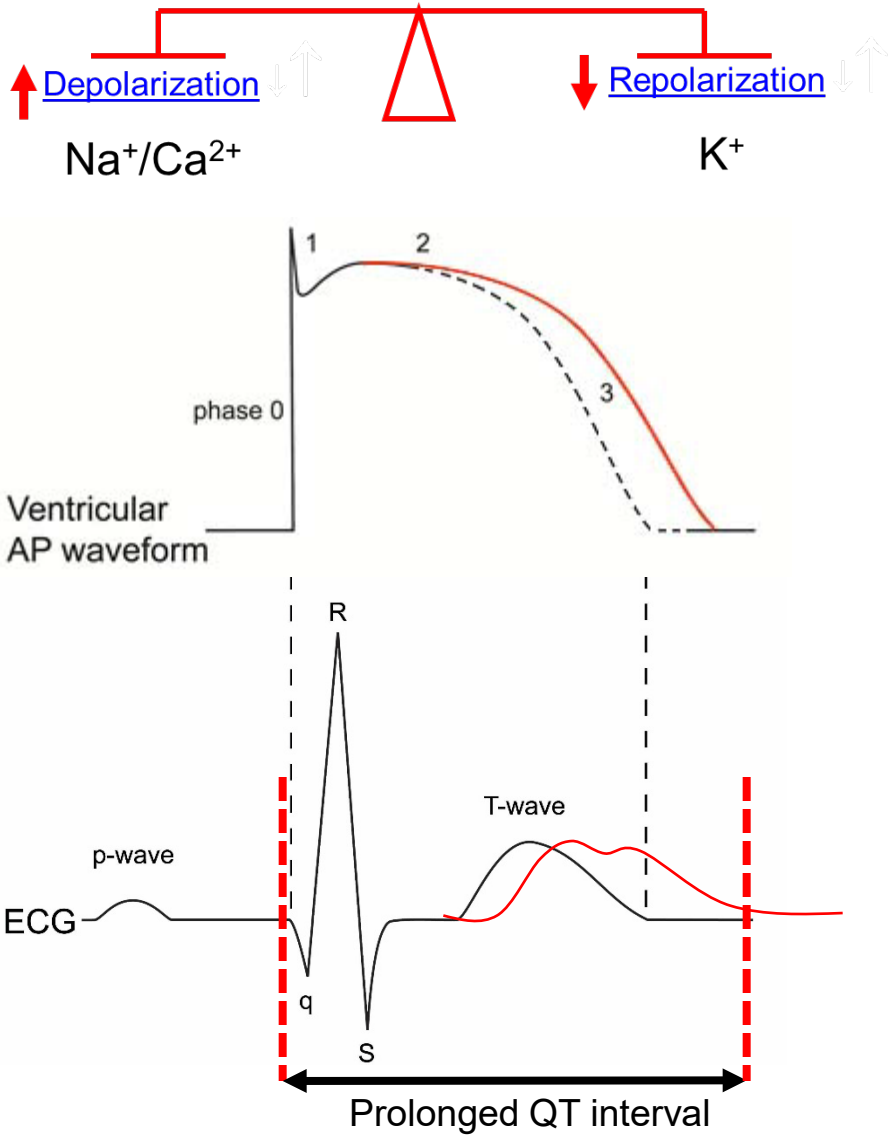


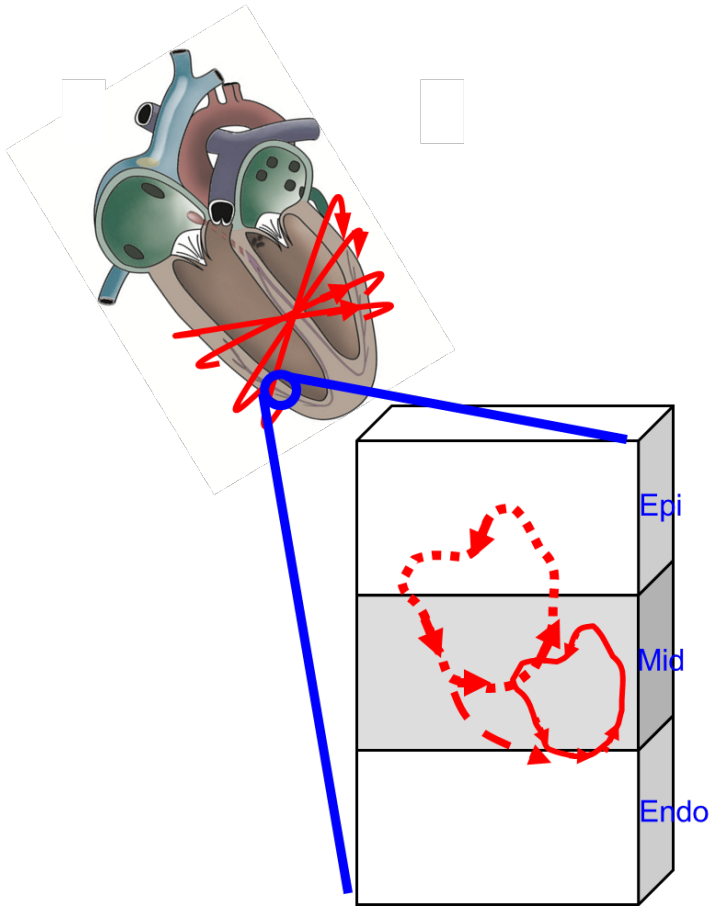
Arrhythmogenesis
Long QT Syndrome



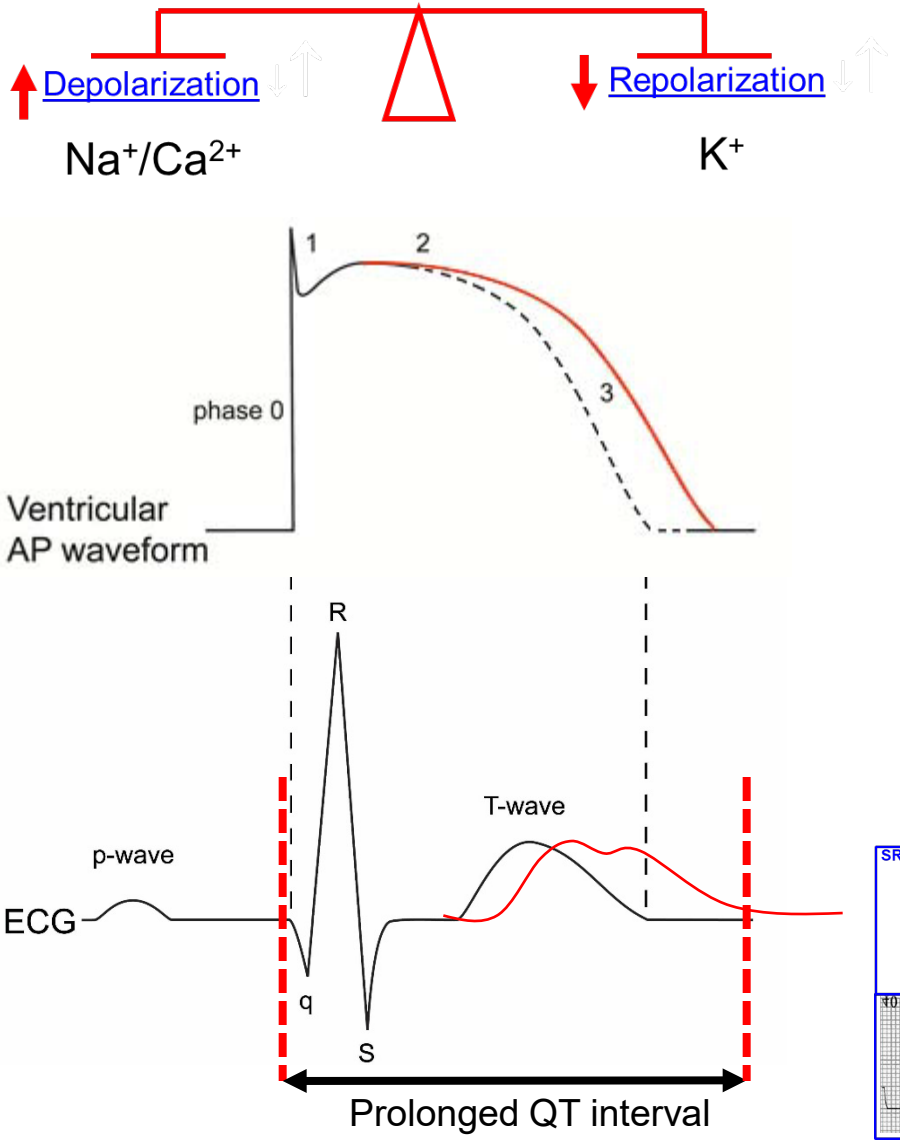


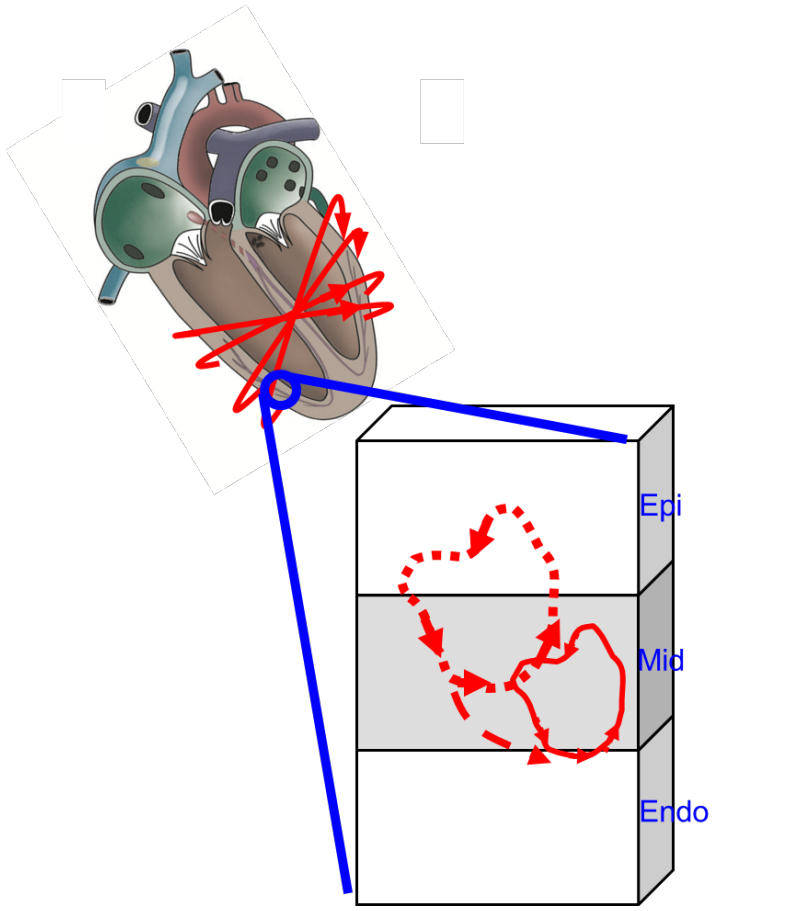
Arrhythmogenesis
Long QT Syndrome

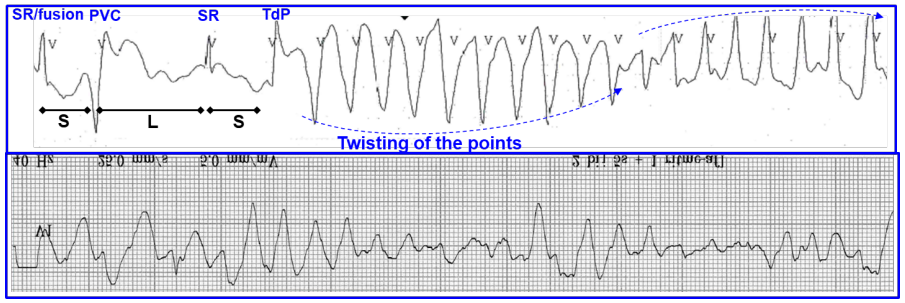




Arrhythmogenesis
Long QT Syndrome

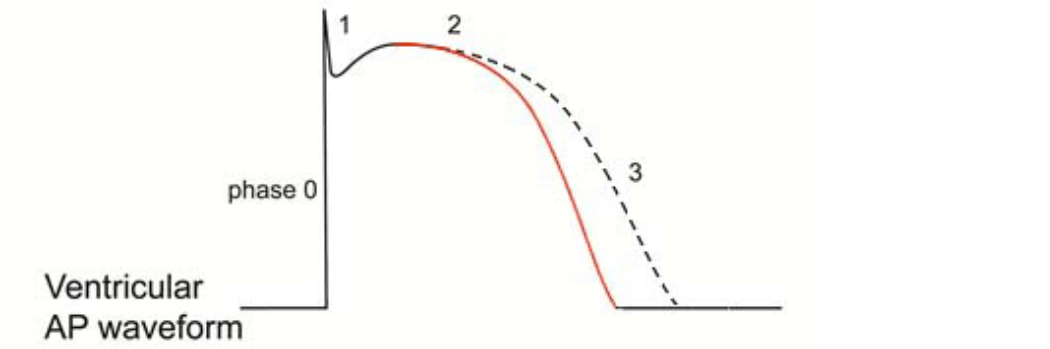


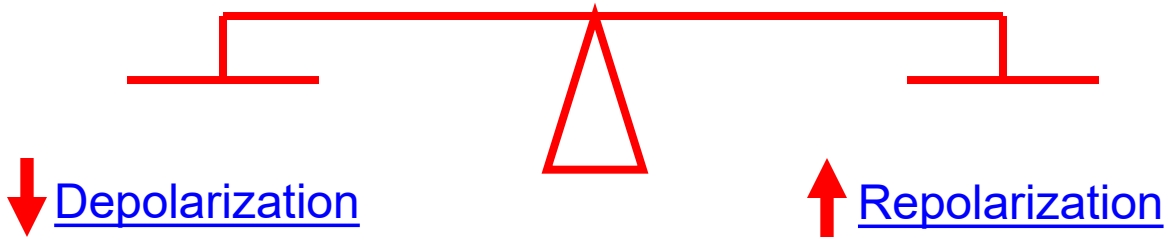




Arrhythmogenesis
Short QT Syndrome

The cardiac action potential (AP)





Depolarization

Na^+/Ca^{2+}

“Loss of functional expression”

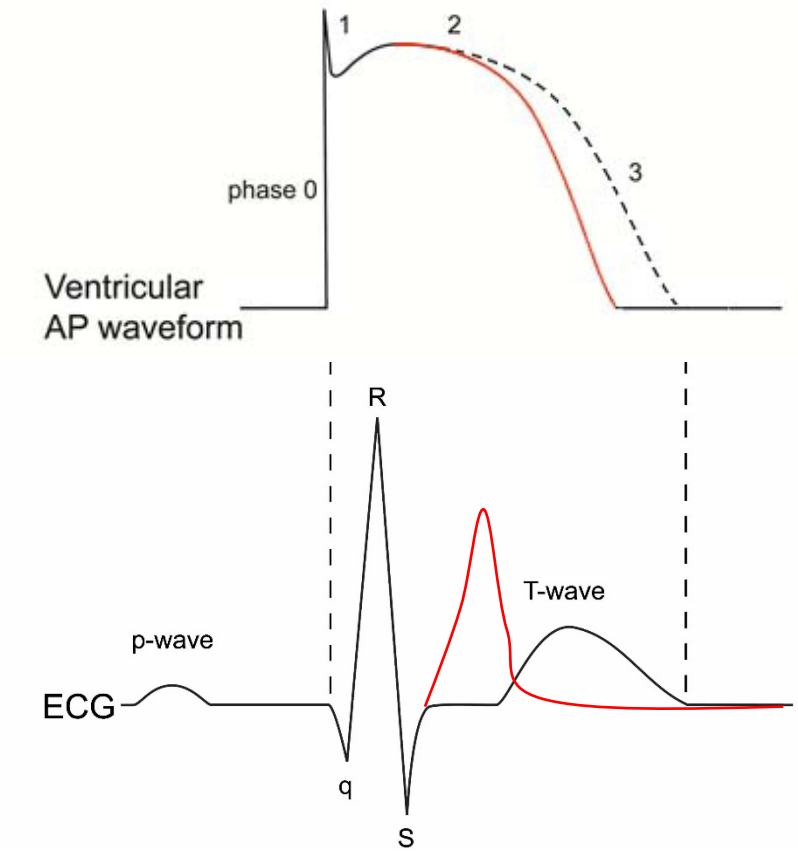
Repolarization

K^+

“Gain of functional expression”

Arrhythmogenesis
Short QT Syndrome

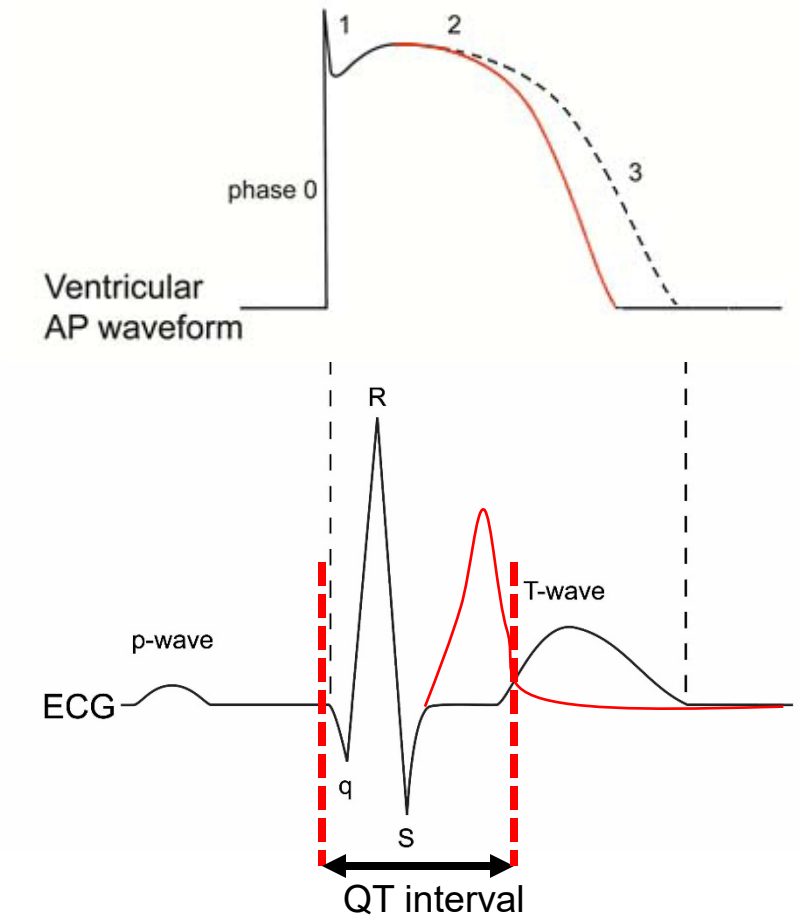
The cardiac action potential (AP)



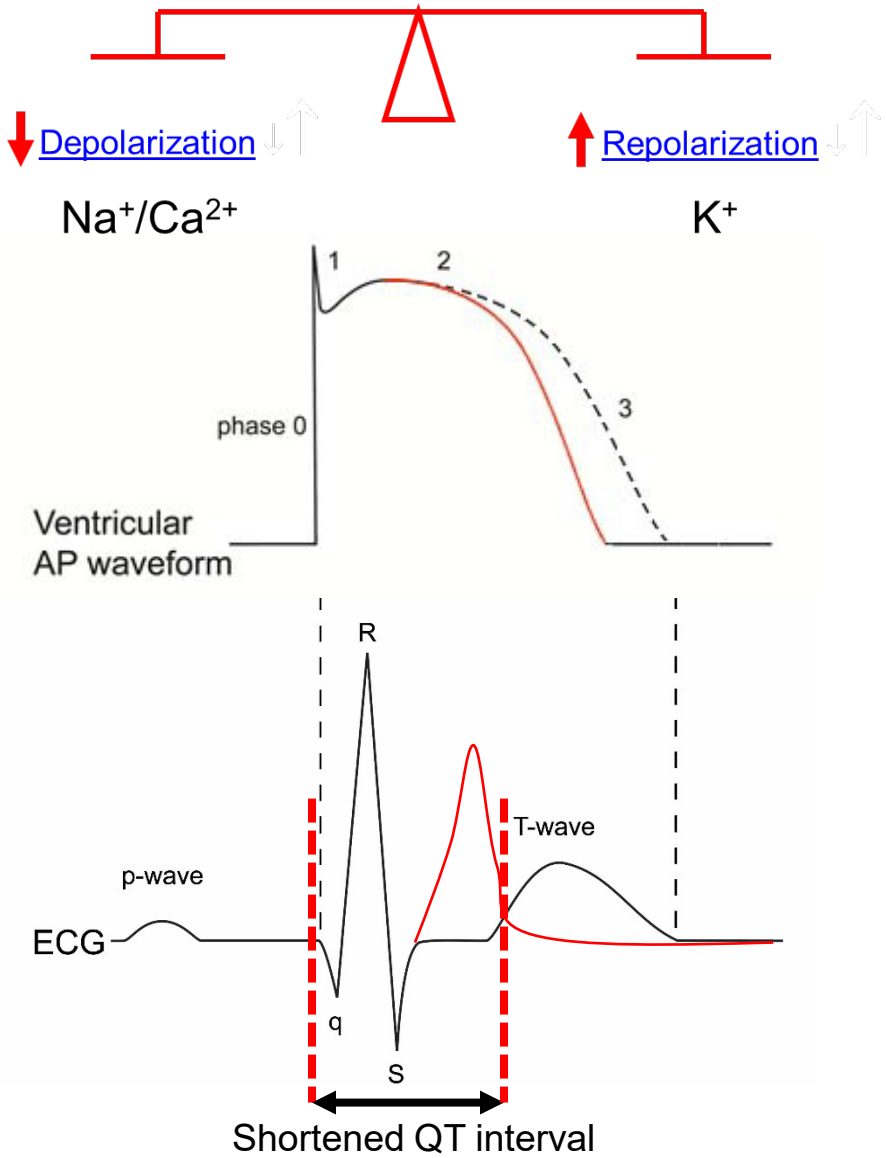
QT interval

Arrhythmogenesis
Short QT Syndrome

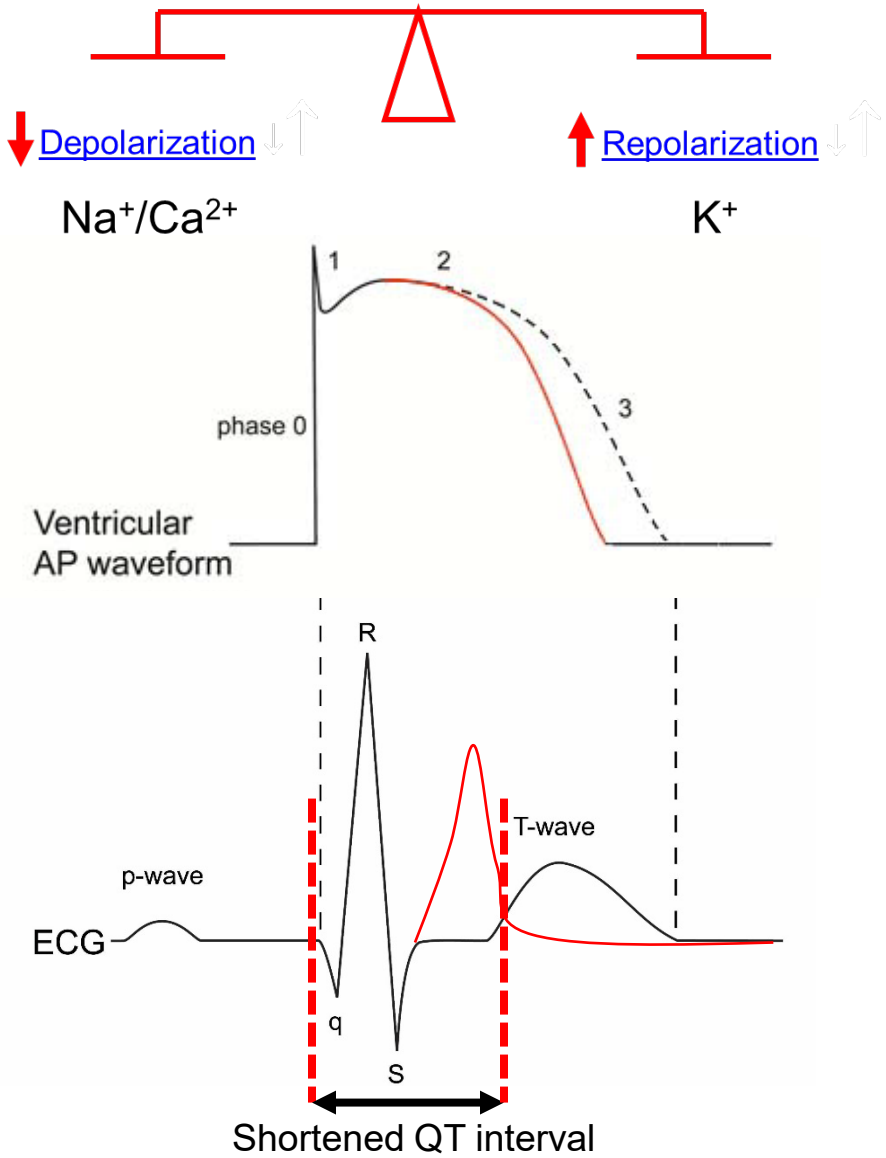
The cardiac action potential (AP)

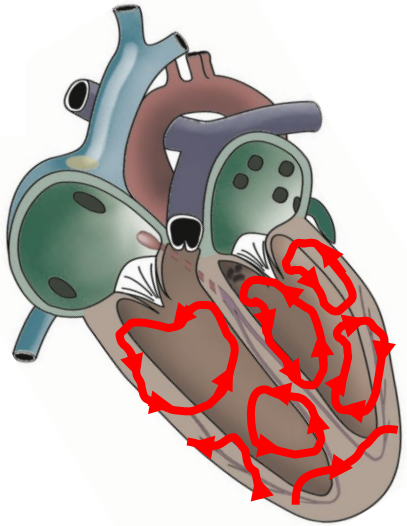


Arrhythmogenesis
Short QT Syndrome

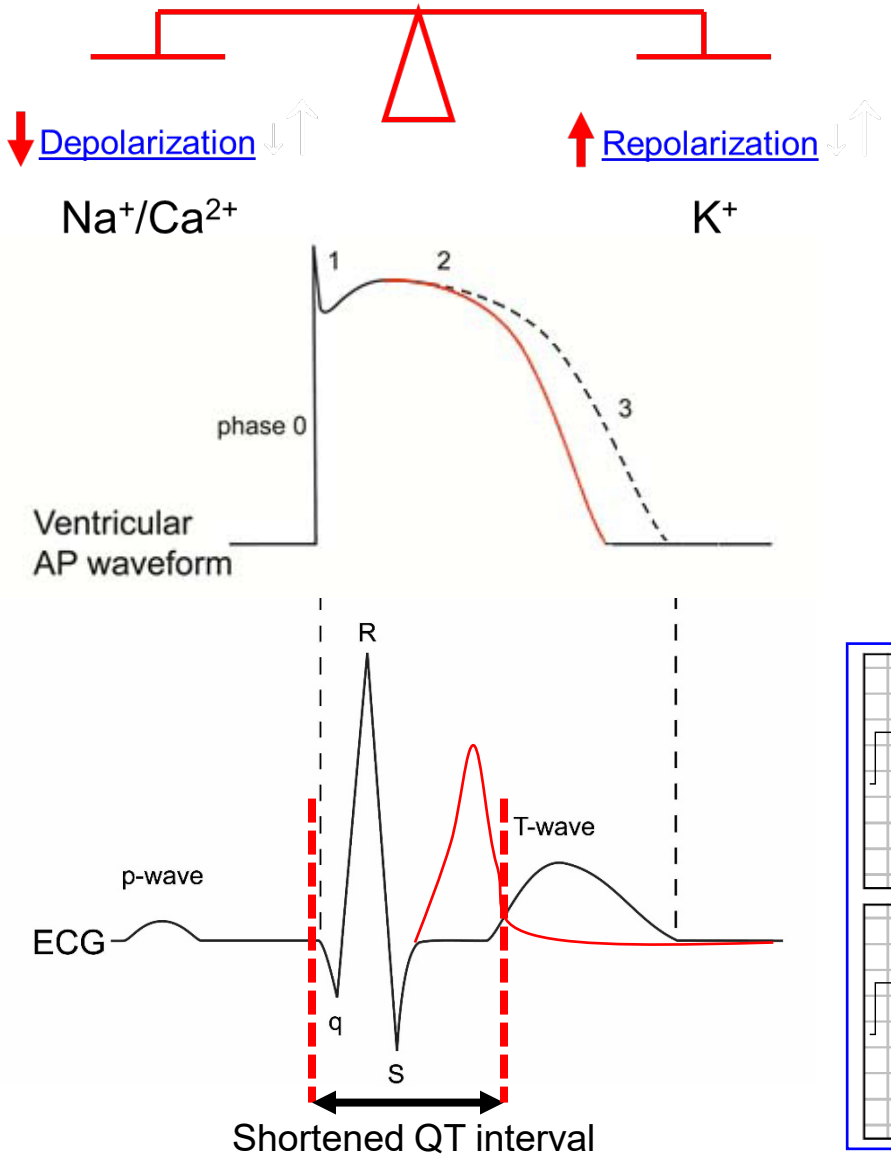


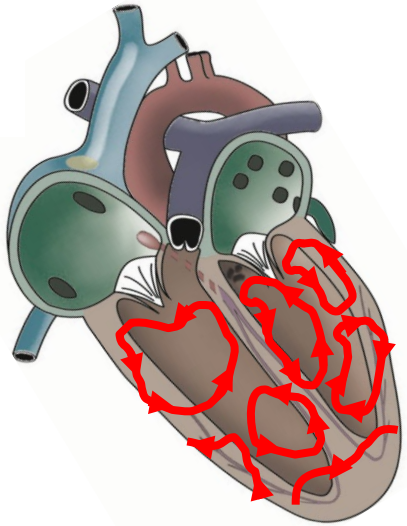
Arrhythmogenesis
Short QT Syndrome

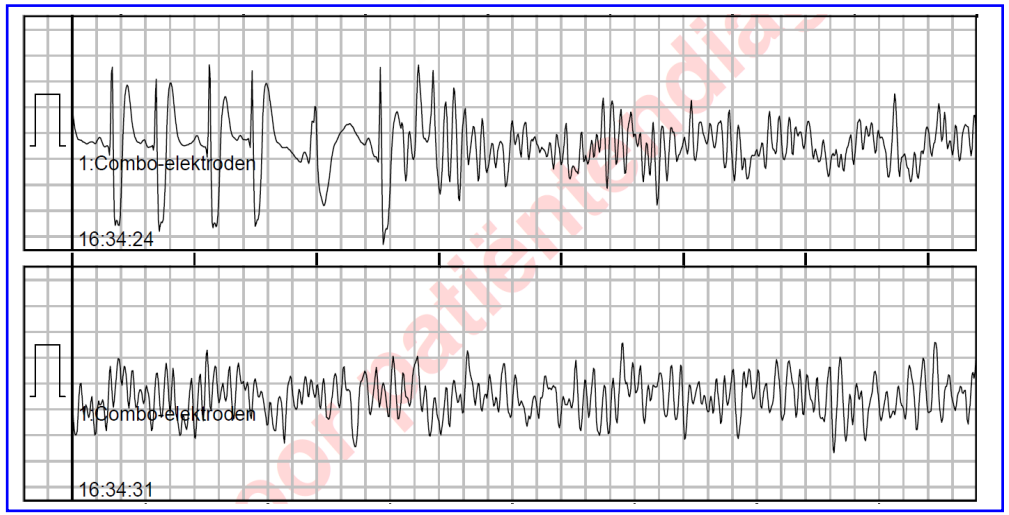




Arrhythmogenesis
Short QT Syndrome

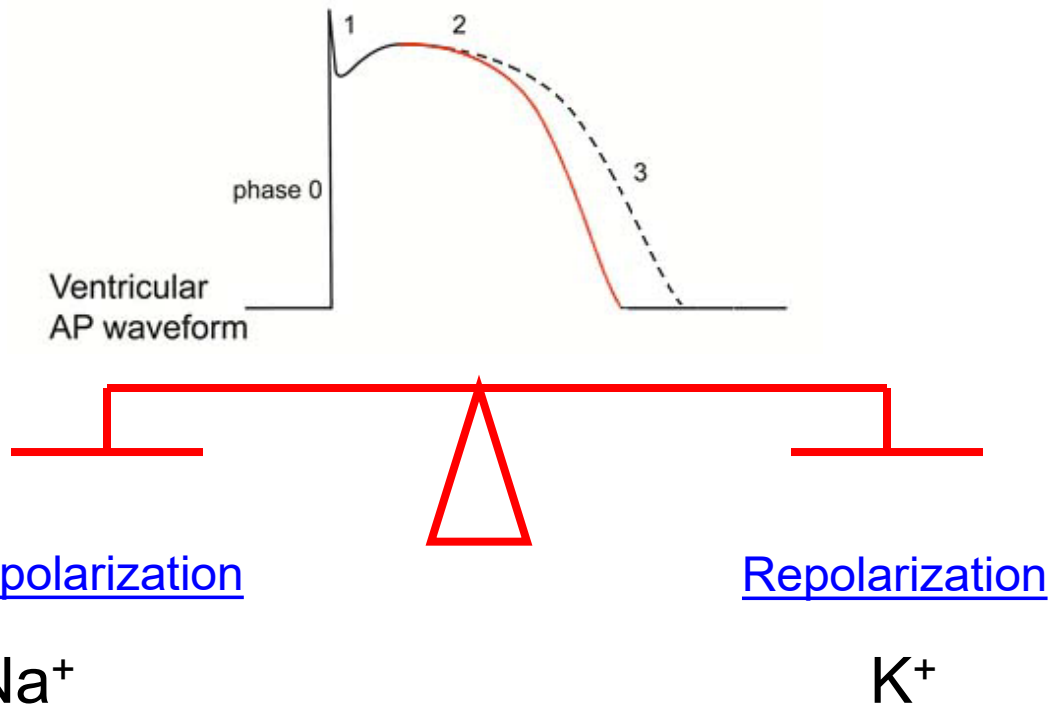






Arrhythmogenesis
Brugada QT Syndrome / J-wave Syndromes

The cardiac action potential (AP)

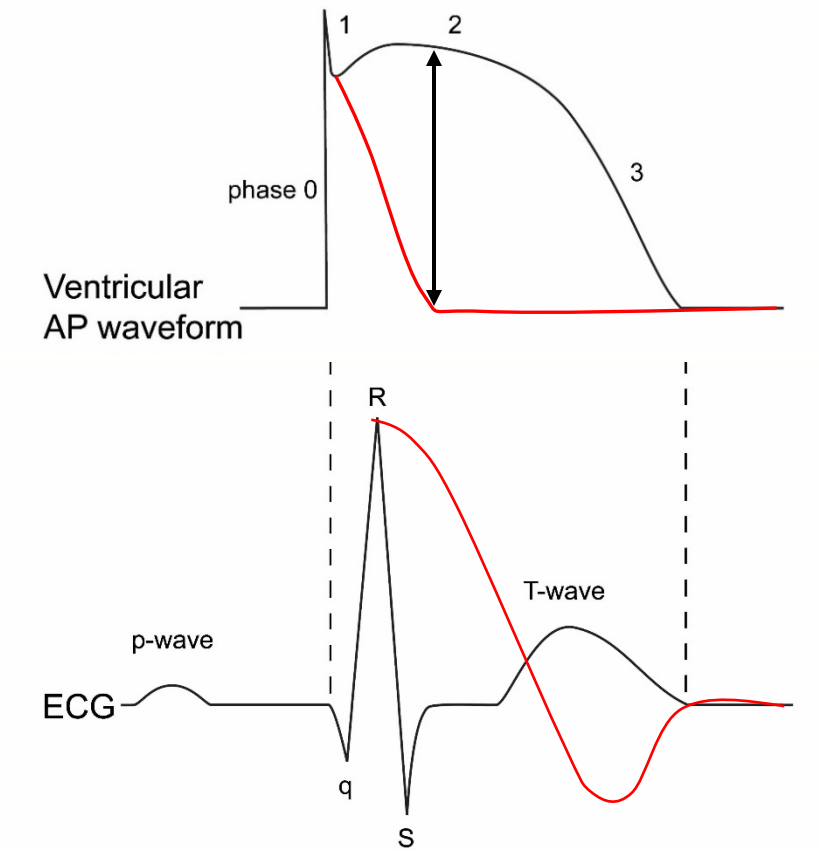


"Loss of functional expression"

Arrhythmogenesis

Brugada QT Syndrome / J-wave Syndromes

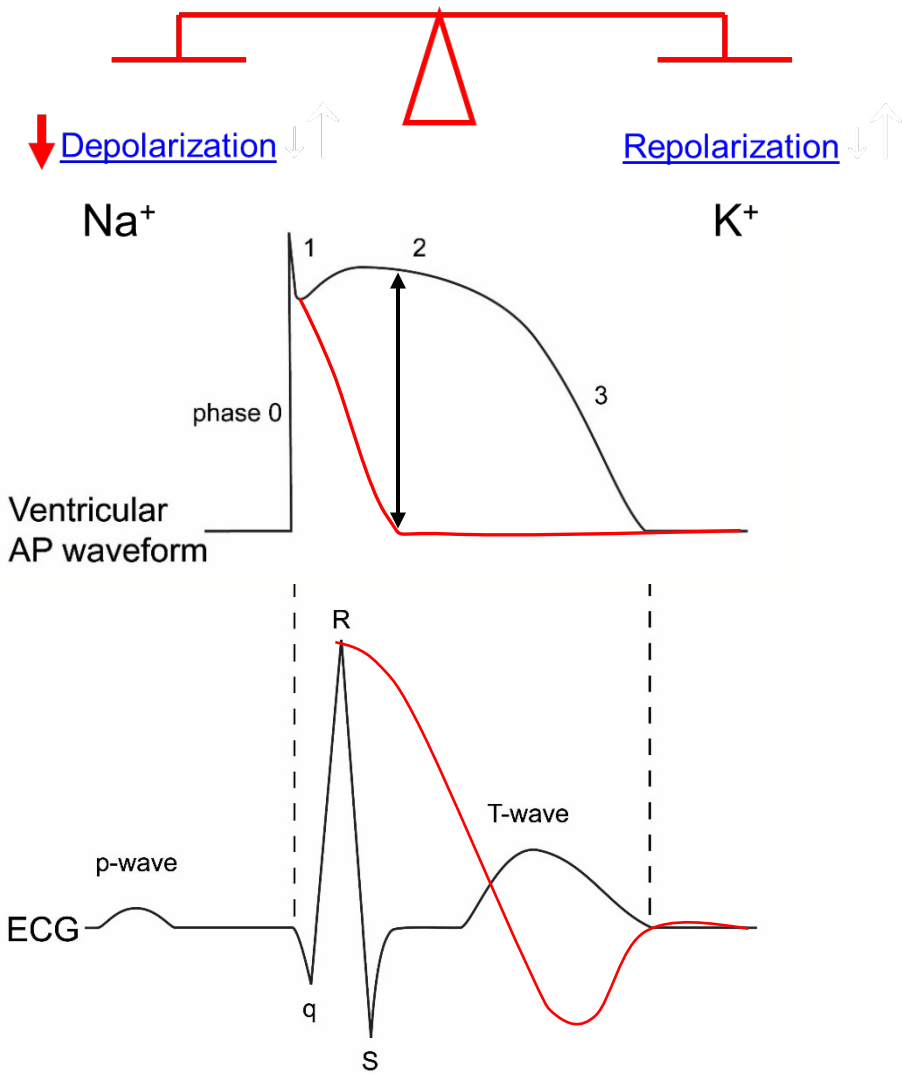
The cardiac action potential (AP)



Type-1 pattern

Arrhythmogenesis

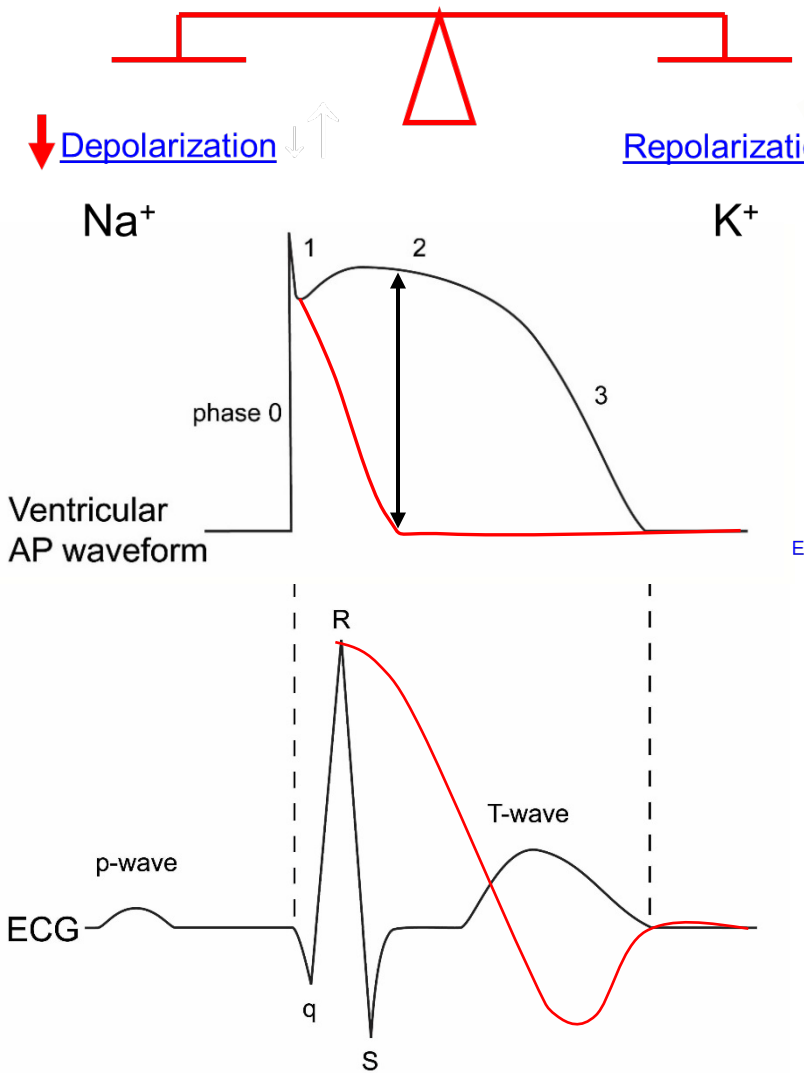
Brugada QT Syndrome / J-wave Syndromes

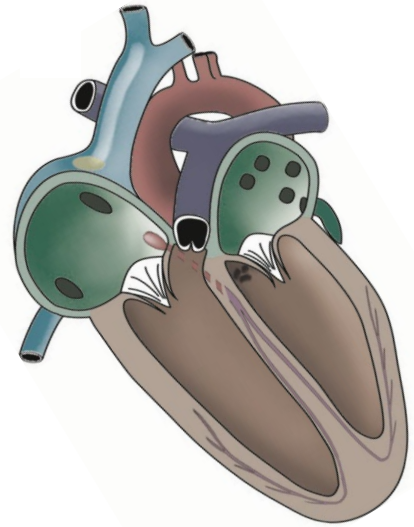


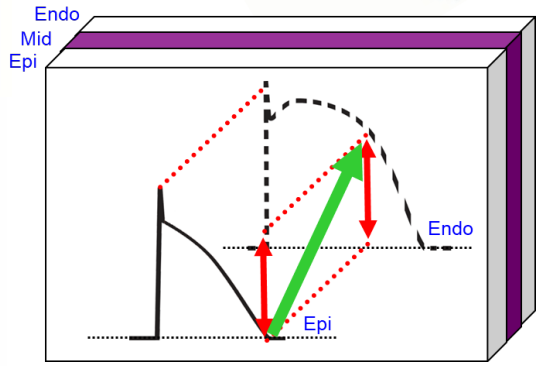
Type-1 pattern

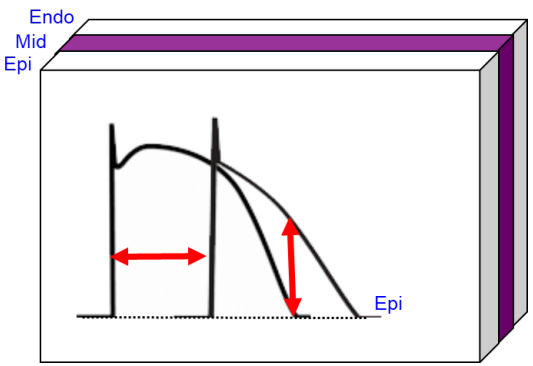
Arrhythmogenesis

Brugada QT Syndrome / J-wave Syndromes





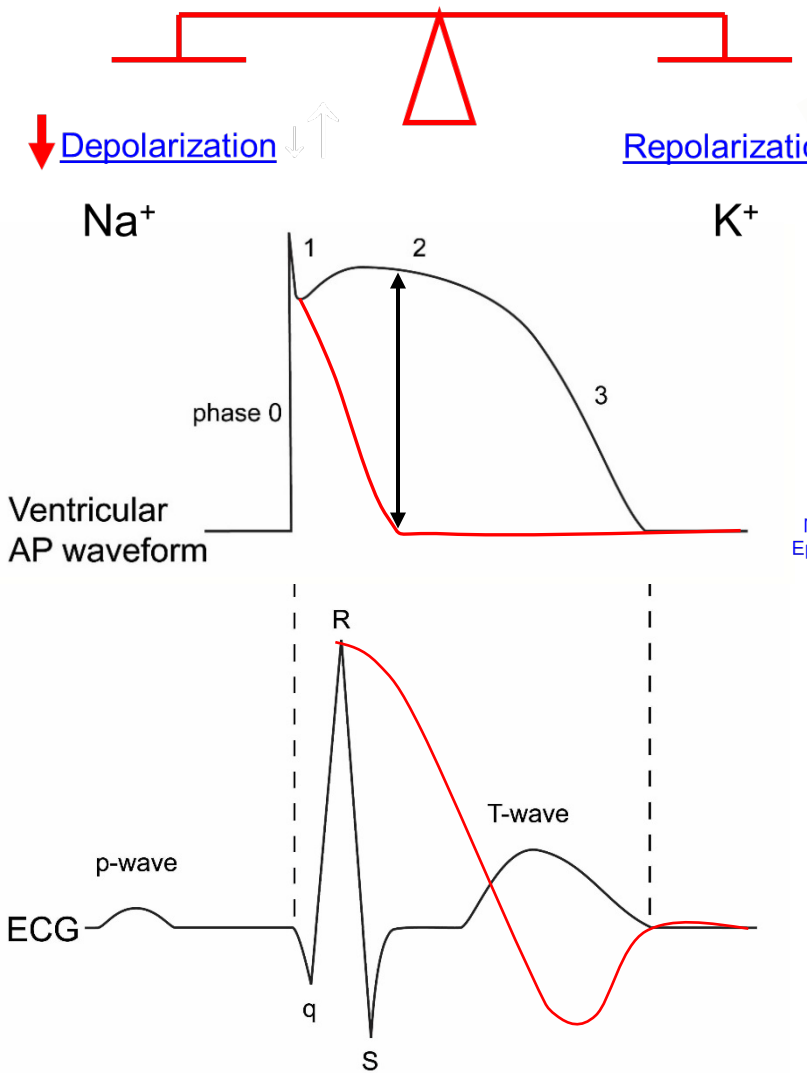




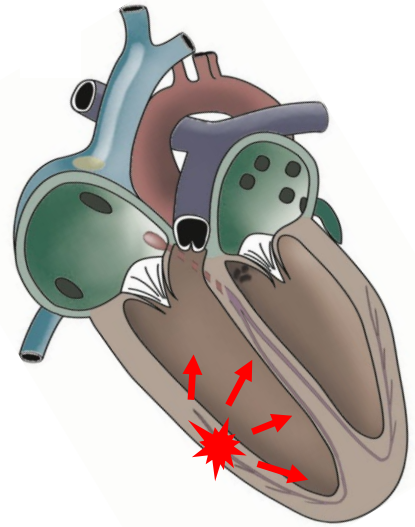
Type-1 pattern

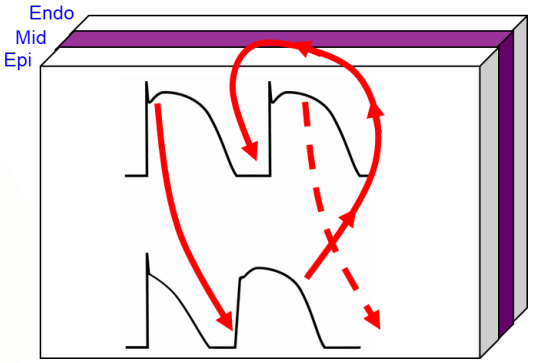
Arrhythmogenesis

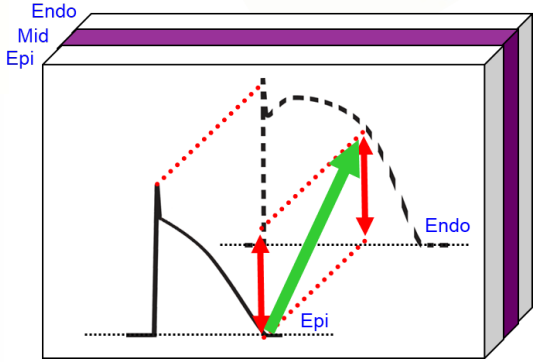
Brugada QT Syndrome / J-wave Syndromes

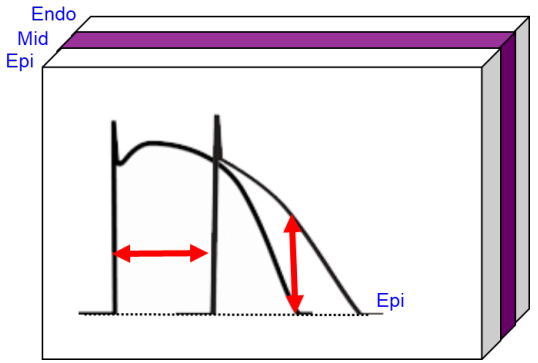


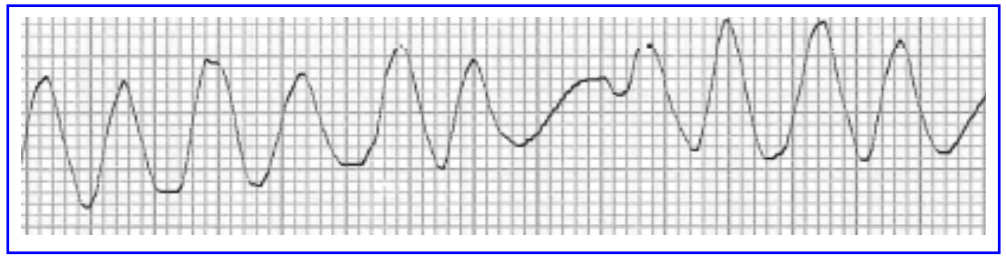
Type-1 pattern





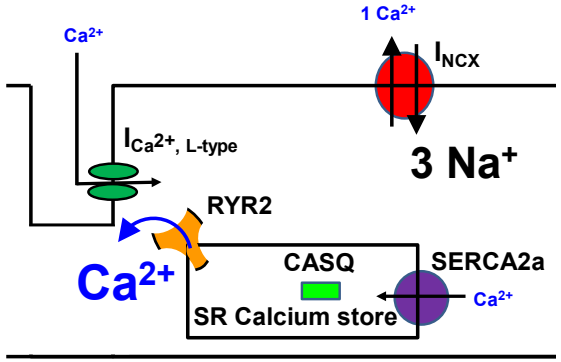






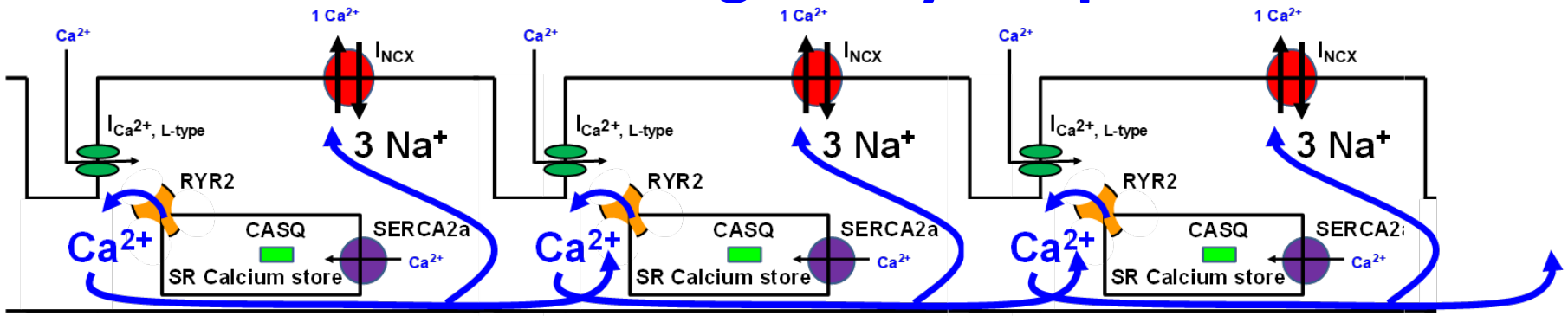
Arrhythmogenesis

Catecholaminergic Polymorphic VT



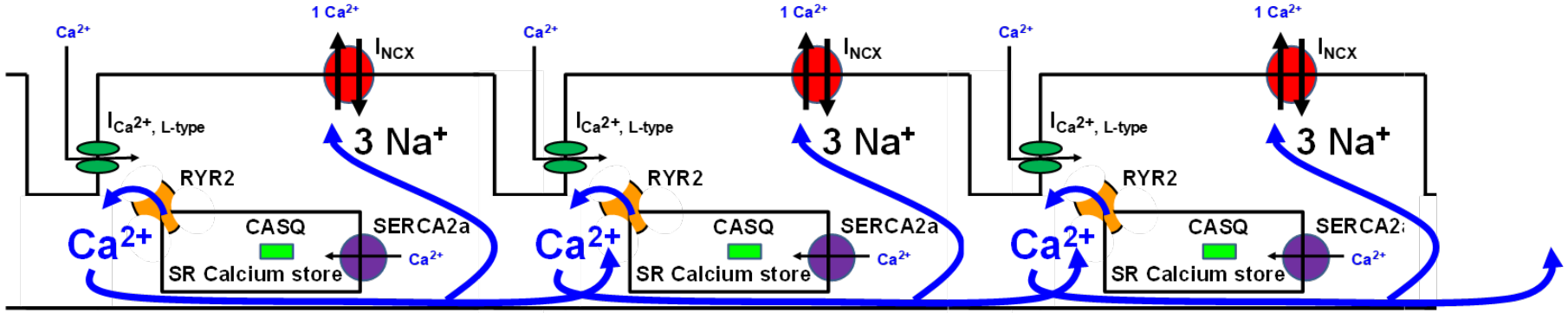
Arrhythmogenesis

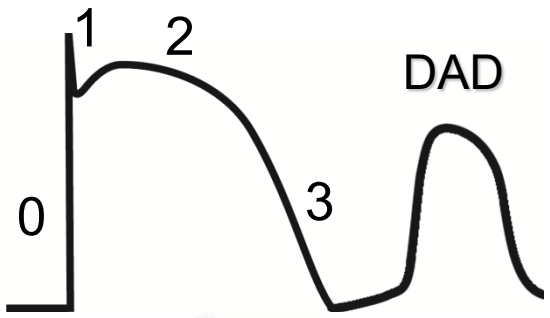
Catecholaminergic Polymorphic VT

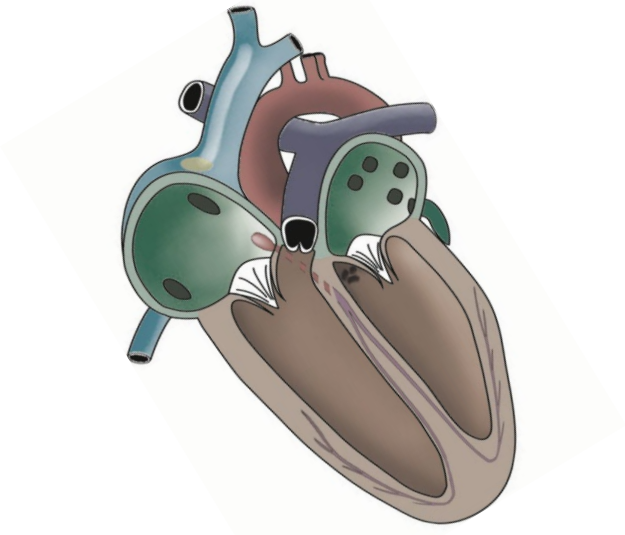


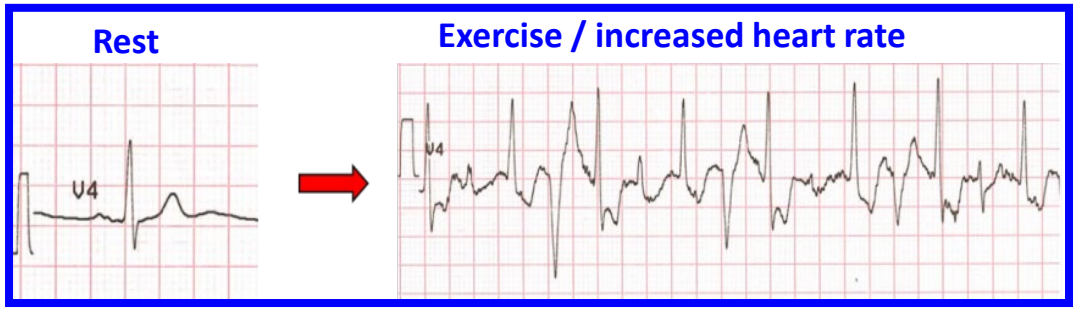
Arrhythmogenesis

Catecholaminergic Polymorphic VT



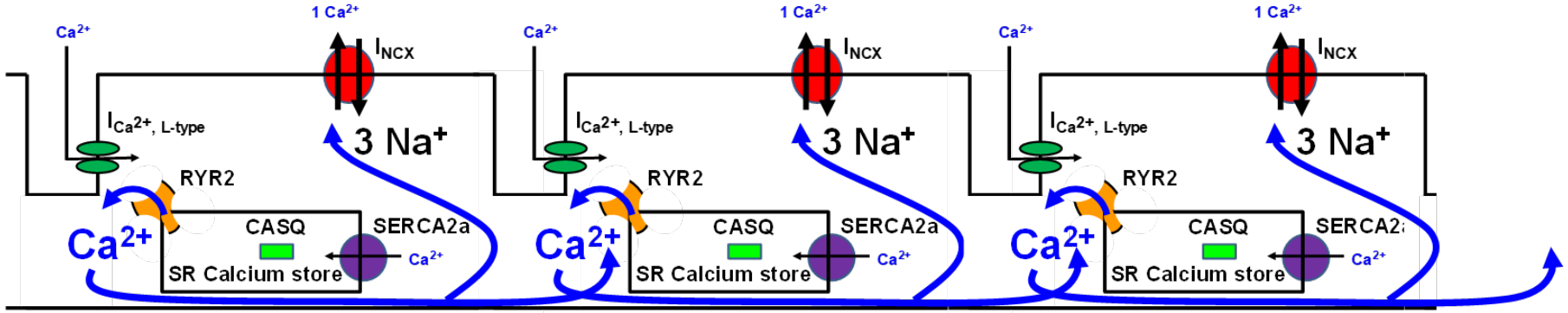


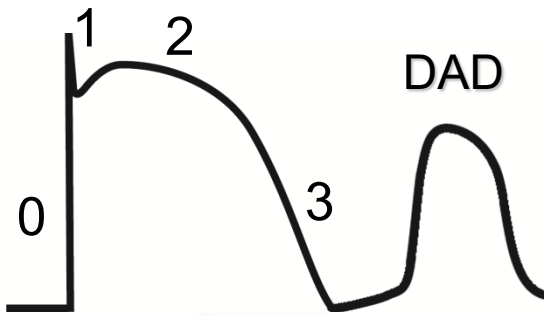


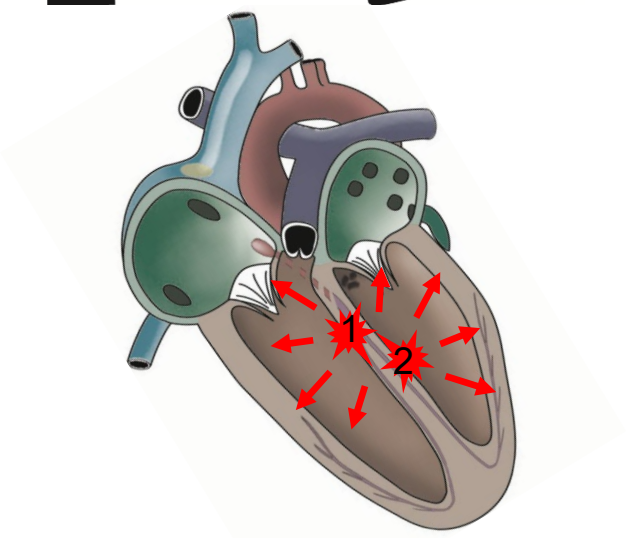


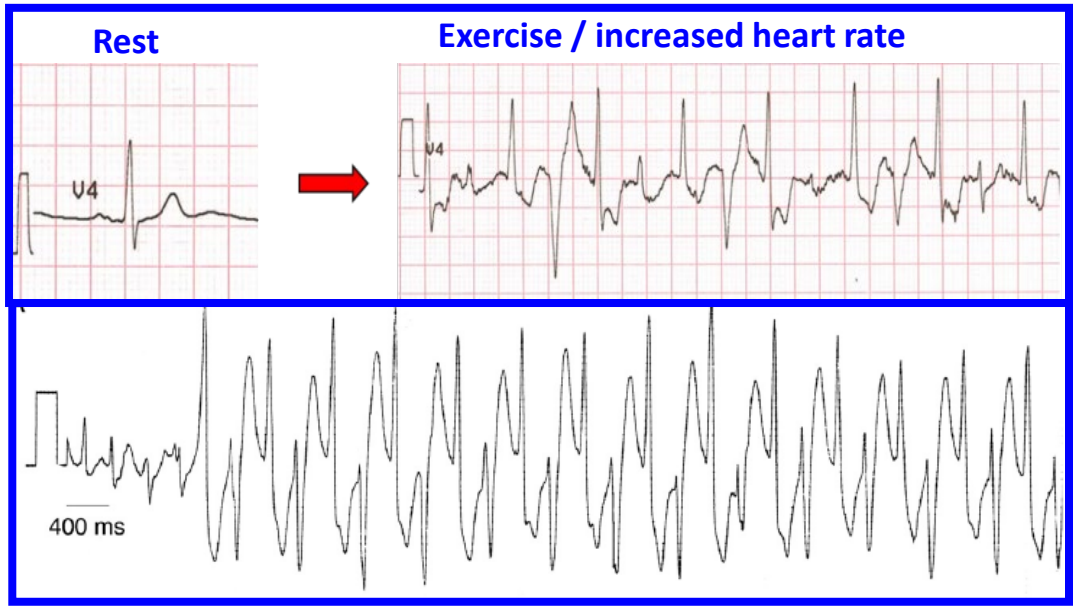
Arrhythmogenesis

Catecholaminergic Polymorphic VT

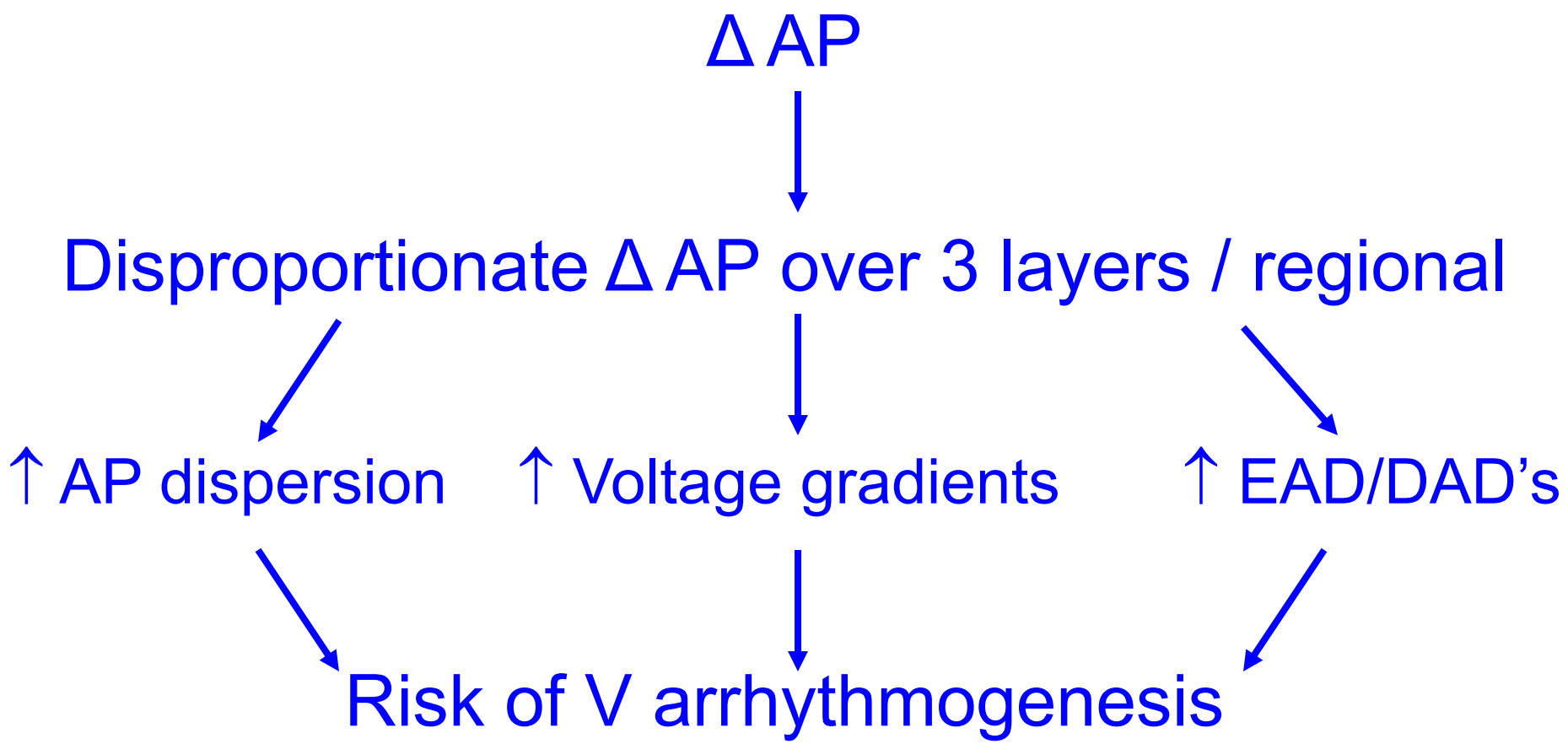




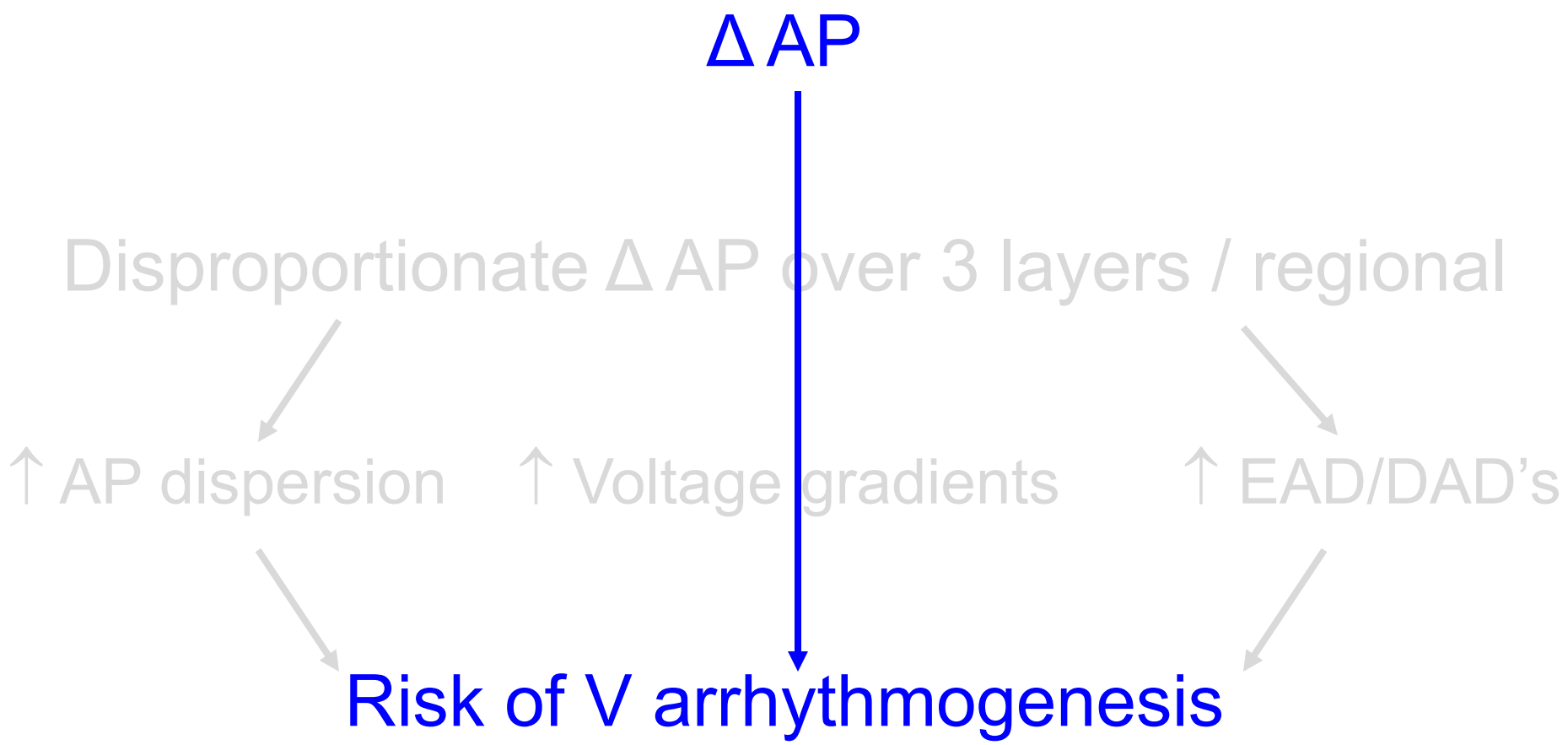




Ventricular arrhythmogenesis
A common pathway



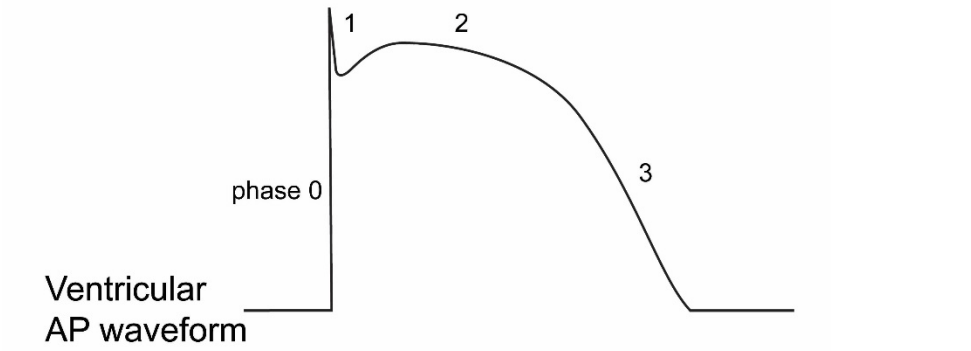
Ventricular arrhythmogenesis
A common pathway



What causes APD changes ?

Electrical functioning of the normal heart

The cardiac action potential (AP)



Ion channel Gene	Ionic current
SCN5A	Nav1.5 / I_{Na}
CACNA1C	Cav1.2 / L-type I_{Ca}
CACNA1G *CACNA1H*	Cav3.1 / T-type I_{Ca} Cav3.2 / T-type I_{Ca}
NCX1	Na/Ca exchanger
KCND2/KCND3	Kv4.2/Kv4.3 / $I_{to,1}$
?	-- / $I_{to,2}$
KCNQ1	KvLQT1 / I_{Ks}
KCNH2	hERG / I_{Kr}
KCNA5	Kv1.5 / I_{Kur} or I_{Kq}
CFTR,CLC2/3 ? *KCNK2*	I_{Cl} TREK-1 / I_{ss}
KCNJ2/KCNJ12	Kir2.1/Kir2.2 / I_{K1}
KCNJ3/KCNJ5 *KCNJ11*	Kir3.1/Kir3.4 / I_{KACh} Kir6.2 / I_{KATP}
HCN1,2,4	I_f

Mechanisms of ion channel function alteration

1. Modified Expression Level

   Changes in the amount of functional channels

   in the myocyt cell membrane

2. Altered channel function

   Changes in voltage-dependence, kinetics, leaky channel

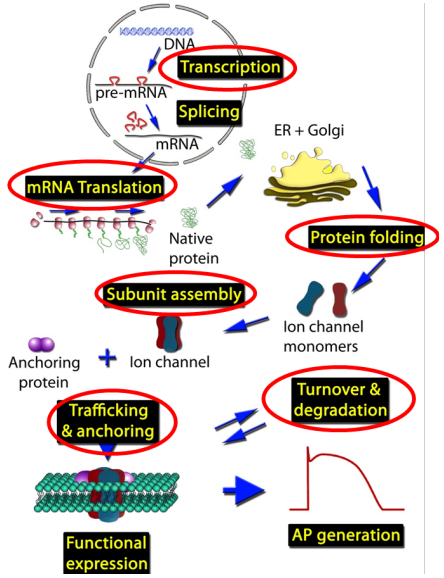
3. Pharmacological modification

   Drug blocks the channel pore

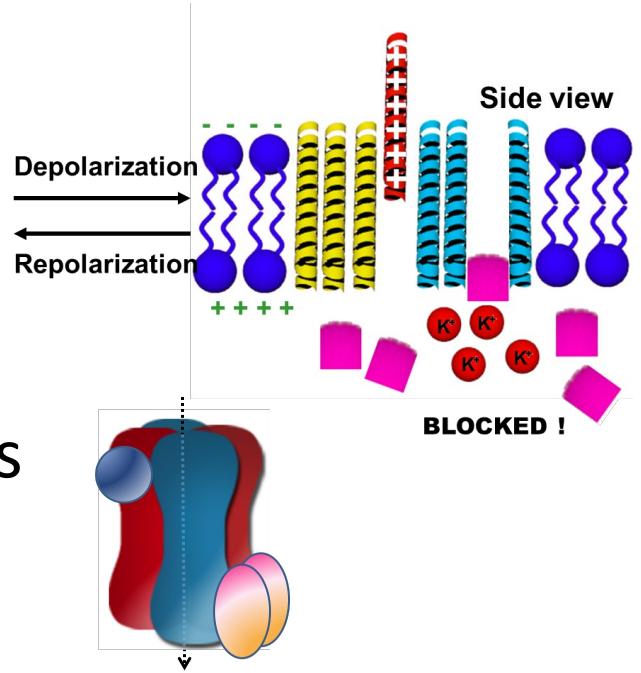
   Drug enhances channel function

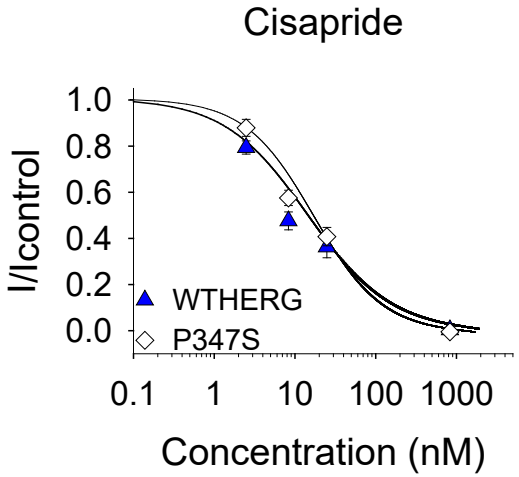
4. Modulation by accessory proteins

   β-subunits, KChips, KChaps,…



Saenen et al. Journal of Molecular and Cellular Cardiology. 2008;44:633-646





Saenen et al. Journal of Molecular and Cellular Cardiology. 2007;43(1):63-72 supplemental data

Hereditary arrhythmia syndromes

Long QT Syndrome (LQTS)
Short QT Syndrome (SQTS)

Brugada Syndrome (BS)
Early Repolarization Syndrome (ERS)

Catecholaminergic Polymorphic VT (CPVT)
Calcium Release Deficiency Syndrome (CRDS)

Progressive Cardiac Conduction Defect (PCCD)
Familial Wolff-Parkinson-White (WPW)
Familial Idiopathic VF (IVF)
Multifocal Ectopic Purkinje-Related Premature Contractions (MEPPC)

Long QT Syndrome
LQTS

The Long QT Syndrome
At a glance

LQTS is an electrical disease of the heart

1/2000

No detectable structural abnormalities

Clinical features

Abnormal QTc porlongation

Unexplained syncope

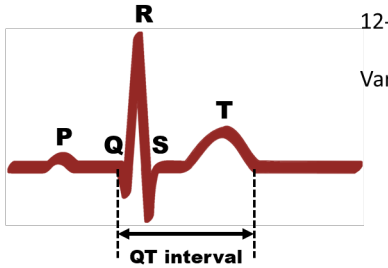
SCD at young age

Commonly used QTc ranges

Rating	1–15 yrs	Adult Male	Adult Female
Normal	<440	<430	<450
Borderline	440–460	430–450	450–470
Prolonged	>460	>450	>470

JACC 2008;51:2291-300

The QT interval

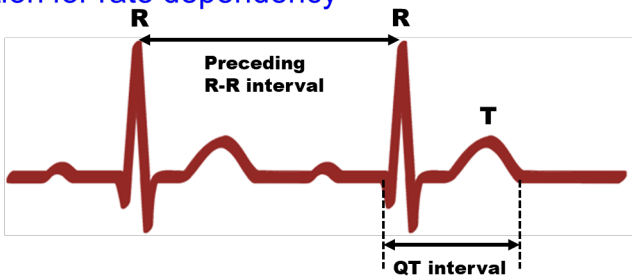


12-lead surface ECG: II, V5

Variation: Heart rate
Time
Gender/puberty

Bazzet's QT correction for rate dependency

$$QT_c = \frac{QT(ms)}{\sqrt{RR(s)}}$$



The Long QT Syndrome
Genetic aspects

Type	Locus	Gene	Protein	Ionic current	Transmission
Romano-Ward syndrome					
LQT1	11p15.5	*KCNQ1*	KvLQT1	I_{Ks}	AD
LQT2	7q35-36	*KCNH2*	hERG	I_{Kr}	AD
LQT3	3p21-p24	*SCN5A*	Nav1.5	I_{Na}	AD
LQT4	4q25-27	*ANK2*	Ankyrin-B		AD
(LQT4 = 'Ankyrin-B syndrome')					
LQT5	21q22.1	*KCNE1*	MinK	I_{Ks}	AD
LQT6	21q22.1	*KCNE2*	MiRP1	I_{Kr}	AD
Jervell Lange-Nielsen syndrome					
JLN1	11p15.5	*KCNQ1*	KvLQT1	I_{Ks}	AR
JLN2	21q22.1	*KCNE1*	MinK	I_{Ks}	AR
Andersen-Tawil syndrome					
LQT7	17q23	*KCNJ2*	Kir2.1	I_{K1}	AD
Timothy syndrome					
LQT8	12p13	*CACNA1C*	Cav1.2	I_{Ca}	ND
Recently found					
LQT9	3p25	*CAV3*	Caveolin-3	auxiliary to I_{Na}	ND
LQT10	11q24	*SCN4B*	Navβ4	β-subunit of I_{Na}	AD
LQT11	7q21.2	*AKAP-9*	AKAP-9	modifies I_{Na}	ND
LQT12	20q11.2	*SNTA-1*	α-1 Syntrophin	modifies I_{Ks}	ND
LQT13	11q23.3	*KCNJ5*	Kir3.4/GIRK4	$I_{K,ATP1}$	AD
LQT14	14q32.11	*CALM1*	Calmodulin 1	Signaling protein	AD
LQT15	2q21	*CALM2*	Calmodulin 2	Signaling protein	AD
LQT16	19q13	*CALM3*	Calmodulin 3	Signaling protein	AD
LQT17	6q21.31	*TRDN*	Triadin	Calcium handling	AR
LQTS-associated		*RYR2*			
LQTS-associated		*SCN10A*			

LQT = Long QT Syndrome; JLN = Jervell, Lange-Nielsen; AD = Autosomal dominant;
AR = Autosomal recessive; ND = Not determined.

The Long QT Syndrome
Genetic aspects

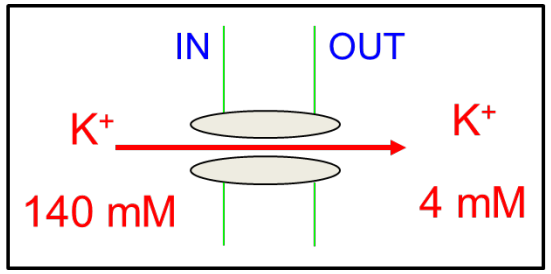
75-85%

Type	Locus	Gene	Protein	Ionic current	Transmission
Romano-Ward syndrome					
LQT1	11p15.5	*KCNQ1*	KvLQT1	I_{Ks}	AD
LQT2	7q35-36	*KCNH2*	hERG	I_{Kr}	AD
LQT3	3p21-p24	*SCN5A*	Nav1.5	I_{Na}	AD
LQT4	4q25-27	*ANK2*	Ankyrin-B		AD
(LQT4 = 'Ankyrin-B syndrome')					
LQT5	21q22.1	*KCNE1*	MinK	I_{Ks}	AD
LQT6	21q22.1	*KCNE2*	MiRP1	I_{Kr}	AD
Jervell Lange-Nielsen syndrome					
JLN1	11p15.5	*KCNQ1*	KvLQT1	I_{Ks}	AR
JLN2	21q22.1	*KCNE1*	MinK	I_{Ks}	AR
Andersen-Tawil syndrome					
LQT7	17q23	*KCNJ2*	Kir2.1	I_{K1}	AD
Timothy syndrome					
LQT8	12p13	*CACNA1C*	Cav1.2	I_{Ca}	ND
Recently found					
LQT9	3p25	*CAV3*	Caveolin-3	auxiliary to I_{Na}	ND
LQT10	11q24	*SCN4B*	Navβ4	β-subunit of I_{Na}	AD
LQT11	7q21.2	*AKAP-9*	AKAP-9	modifies I_{Na}	ND
LQT12	20q11.2	*SNTA-1*	α-1 Syntrophin	modifies I_{Ks}	ND
LQT13	11q23.3	*KCNJ5*	Kir3.4/GIRK4	$I_{K,ATP1}$	AD
LQT14	14q32.11	*CALM1*	Calmodulin 1	Signaling protein	AD
LQT15	2q21	*CALM2*	Calmodulin 2	Signaling protein	AD
LQT16	19q13	*CALM3*	Calmodulin 3	Signaling protein	AD
LQT17	6q21.31	*TRDN*	Triadin	Calcium handling	AR
LQTS-associated		*RYR2*			
LQTS-associated		*SCN10A*			

LQT = Long QT Syndrome; JLN = Jervell, Lange-Nielsen; AD = Autosomal dominant;
AR = Autosomal recessive; ND = Not determined.

The Long QT Syndrome
Acquired aspects

Electrolyte Balance Disturbances



hyperK^{+}
hypoK^{+}
hypoMg^{2+}
hypoCa^{2+}

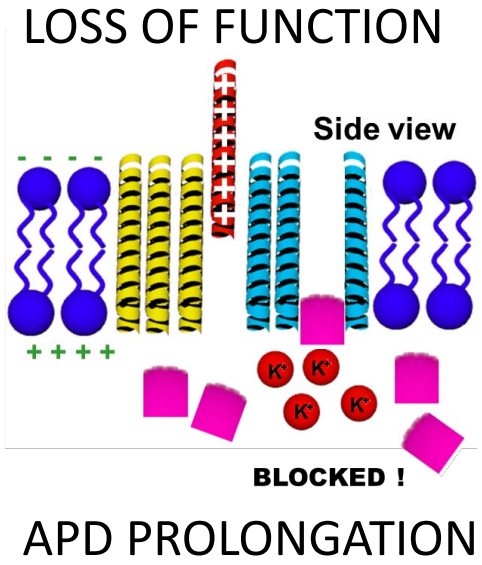
QT PROLONGATION

Hypothyroidism

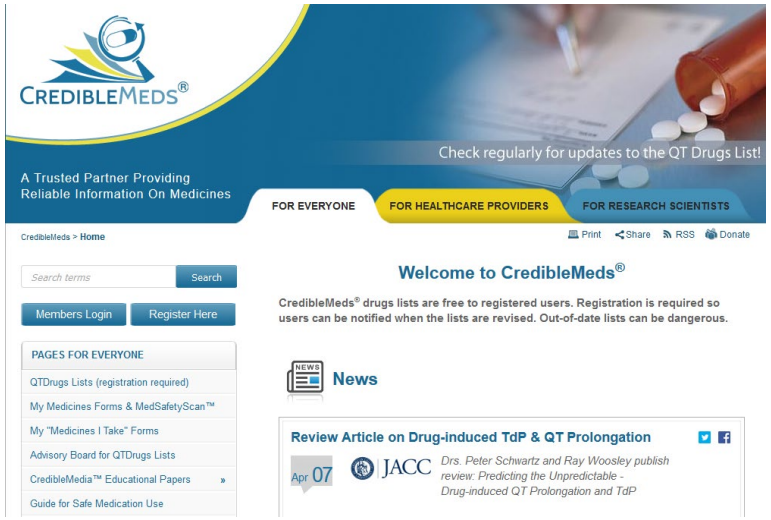
The Long QT Syndrome
Acquired aspects

Pharmacological interaction

All antidepressants
Neuroleptica
Antibiotics
Anti arrhythmic drugs
Inotropica
Methadone
Morphine
Cocaine
Alcohol



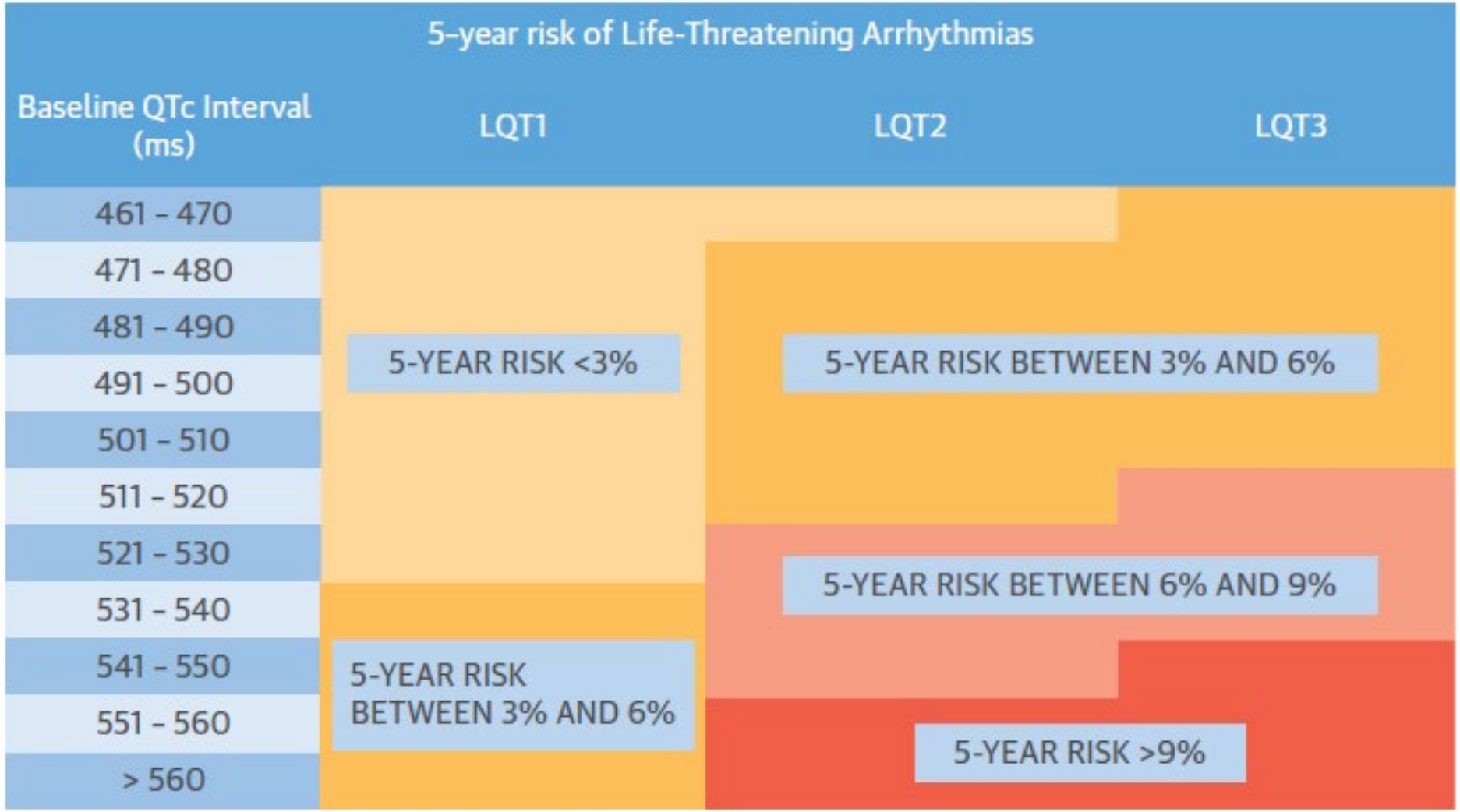
www.Crediblemeds.org



Pharmacogenetic disease - Interplay with genetic variation

Drug-induced LQTS ≈ 10-15% genetic predisposition

The Long QT Syndrome
Gene-specific risk stratification

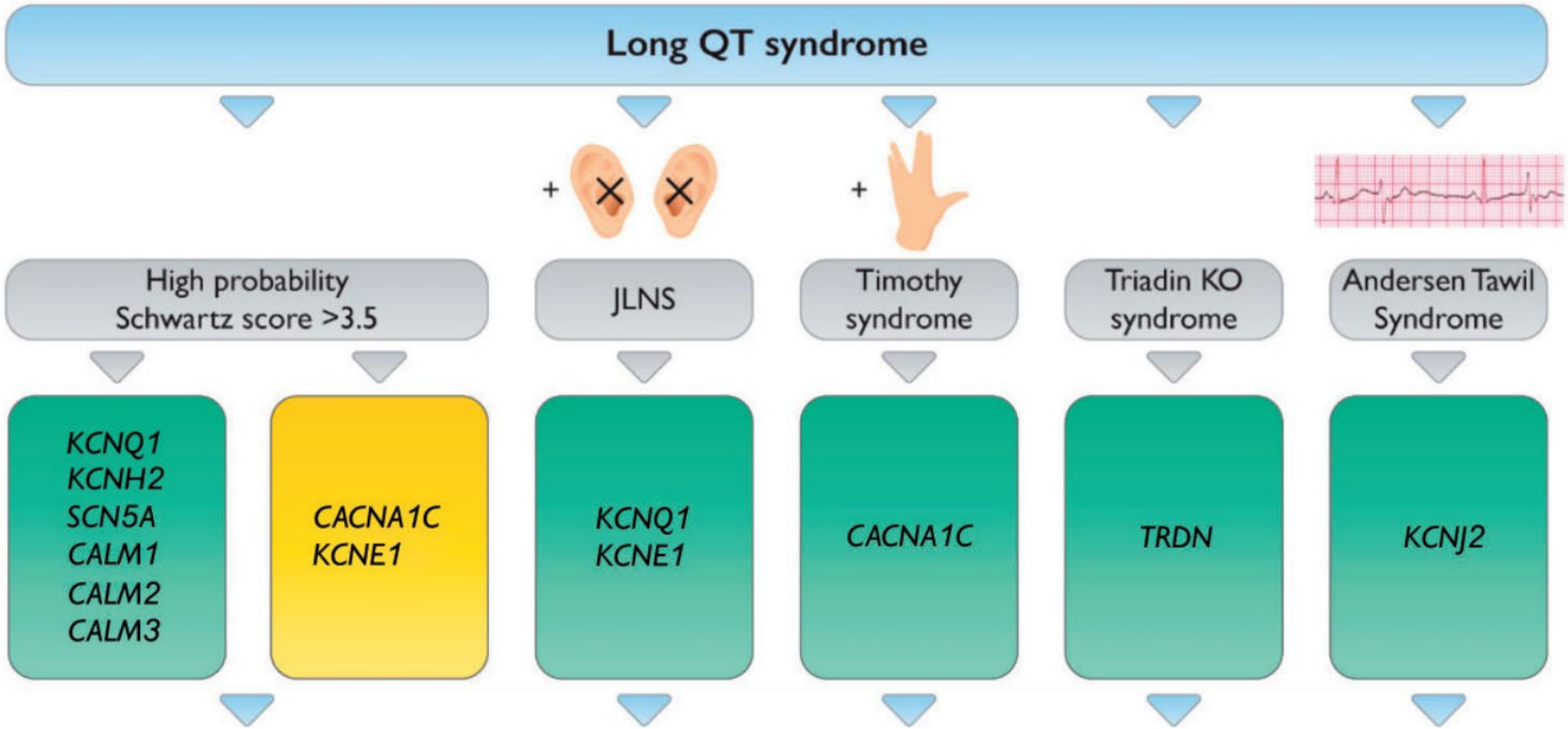


Mazzanti et al. JACC 2018;71(15):1663-71

The Long QT Syndrome

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
LQTS	+++	+++	+++



CASCADE SCREENING OF FDR'S

Adapted from Wilde AAM et al, Europace. 2022 Sep 1;24(8):1307-1367.

Short QT Syndrome
SQTS

The Short QT Syndrome
At a glance

SQTS is an electrical disease of the heart

Very rare

No structural abnormalities

Mirror image of LQTS

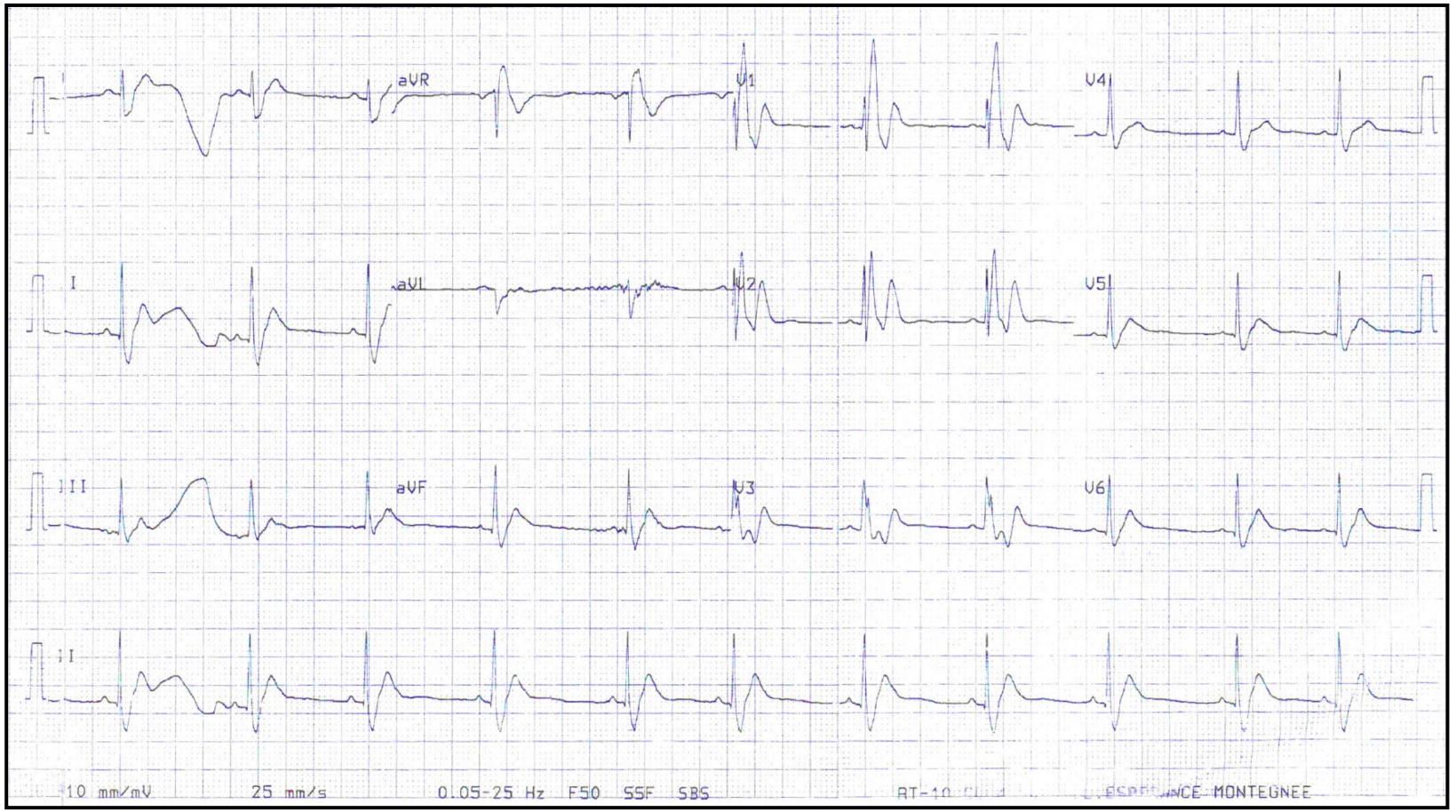
Clinical features

Abnormal QTc ≤340ms

Abnormal QT adaptation

Unexplained syncope

SCD at young age



The Short QT Syndrome
Genetic aspects

Type	Locus	Gene	Protein	Ionic current
SQTS1	7q35-36	*KCNH2*	hERG	I_{kr}
SQTS2	11p15.5	*KCNQ1*	KvLQT1	I_{ks}
SQTS3	17q23.1-24.2	*KCNJ2*	Kir2.1	I_{K1}
SQTS4	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}
SQTS5	10p12	*CACNB2*	Cavβ2	I_{Ca} β-subunit
SQTS6	7q21.11	*CACN2D1*	Cav2δ1	I_{Ca} δ-subunit
SQTS7	2q35	*SLC4A3*	AE3	Cl/HCO3exchanger

Acquired aspects

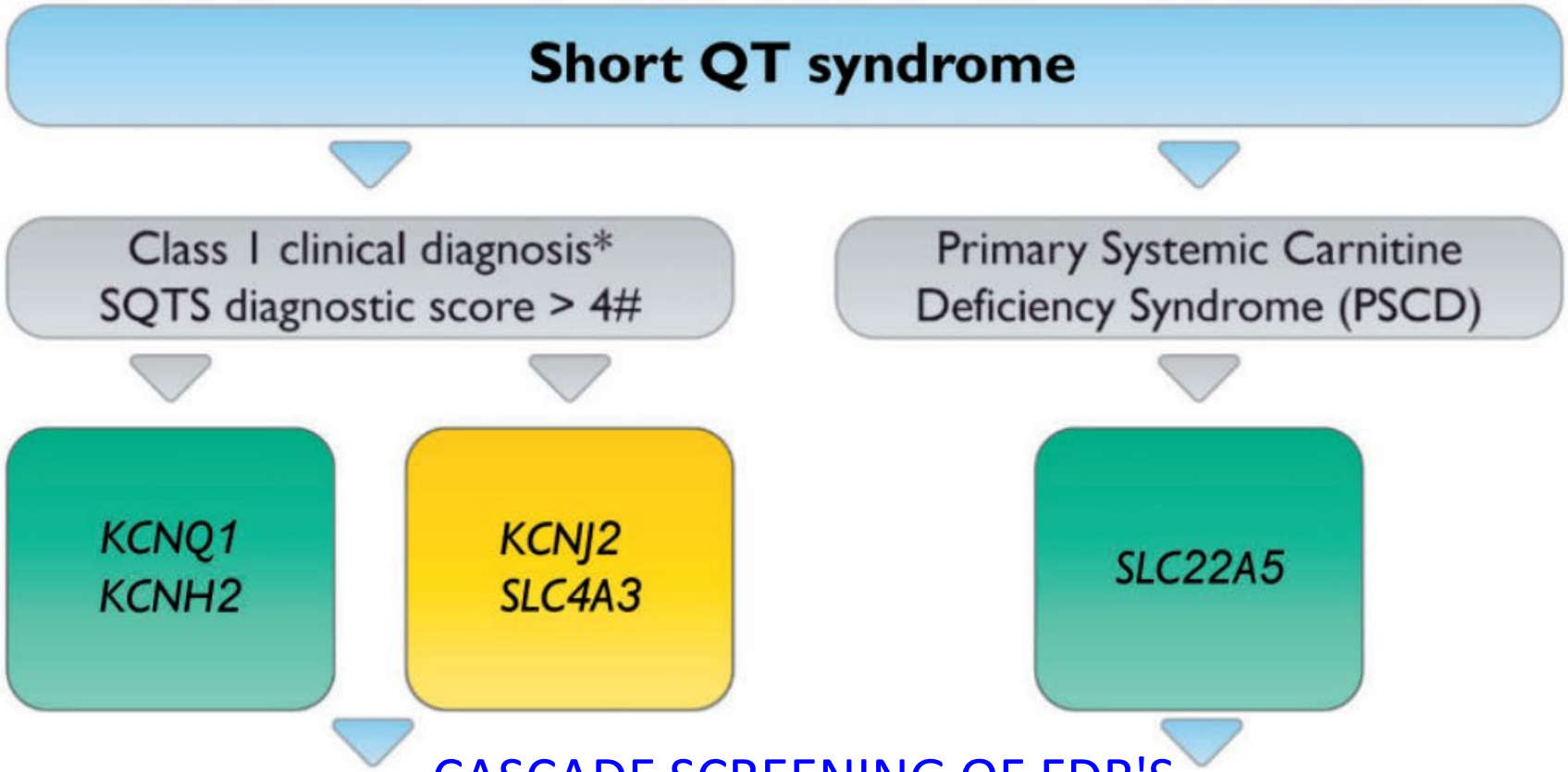
HyperCa^{2+}

- Shortening of QT / QTc
- Arrhythmogenic potential uncertain

The Short QT Syndrome

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
SQTS	+	+	+



CASCADE SCREENING OF FDR'S

Adapted from Wilde AAM et al, Europace. 2022 Sep 1;24(8):1307-1367.

Brugada Syndrome
BrS

The Brugada Syndrome
At a glance

BrS is an electrical disease with discrete structural abnormalities

1:2000

Subtle structural abnormalities RVOT epicardium

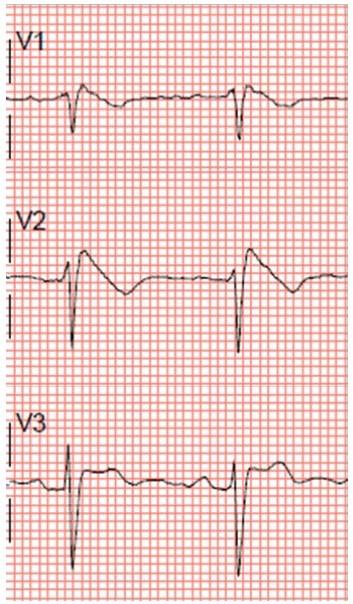
Clinical features

Type-1 ECG

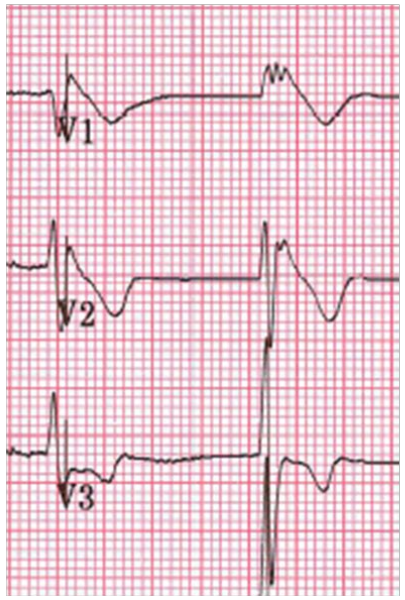
Unexplained syncope

SCD during sleep

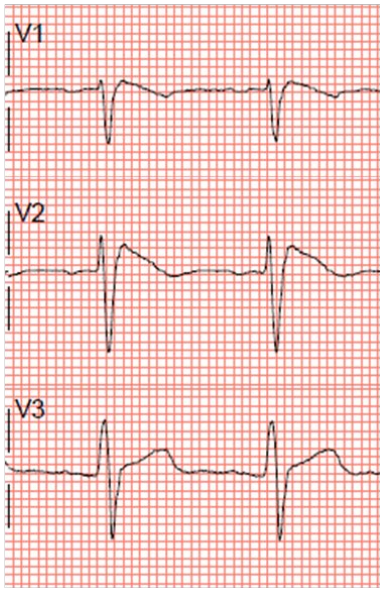
SPONTANEOUS



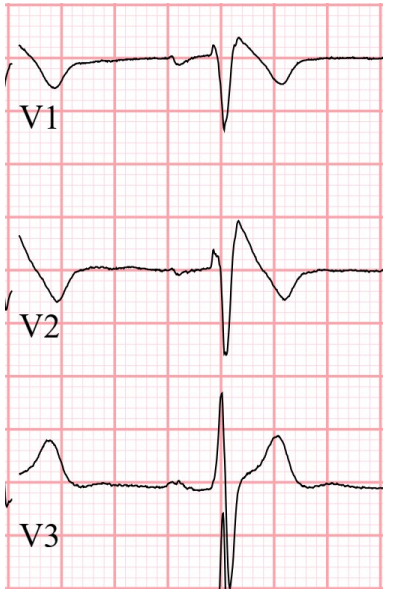
FEVER INDUCED



AJMALIN INDUCED



LAMOTRIGIN INDUCED



The Brugada Syndrome
Genetic aspects

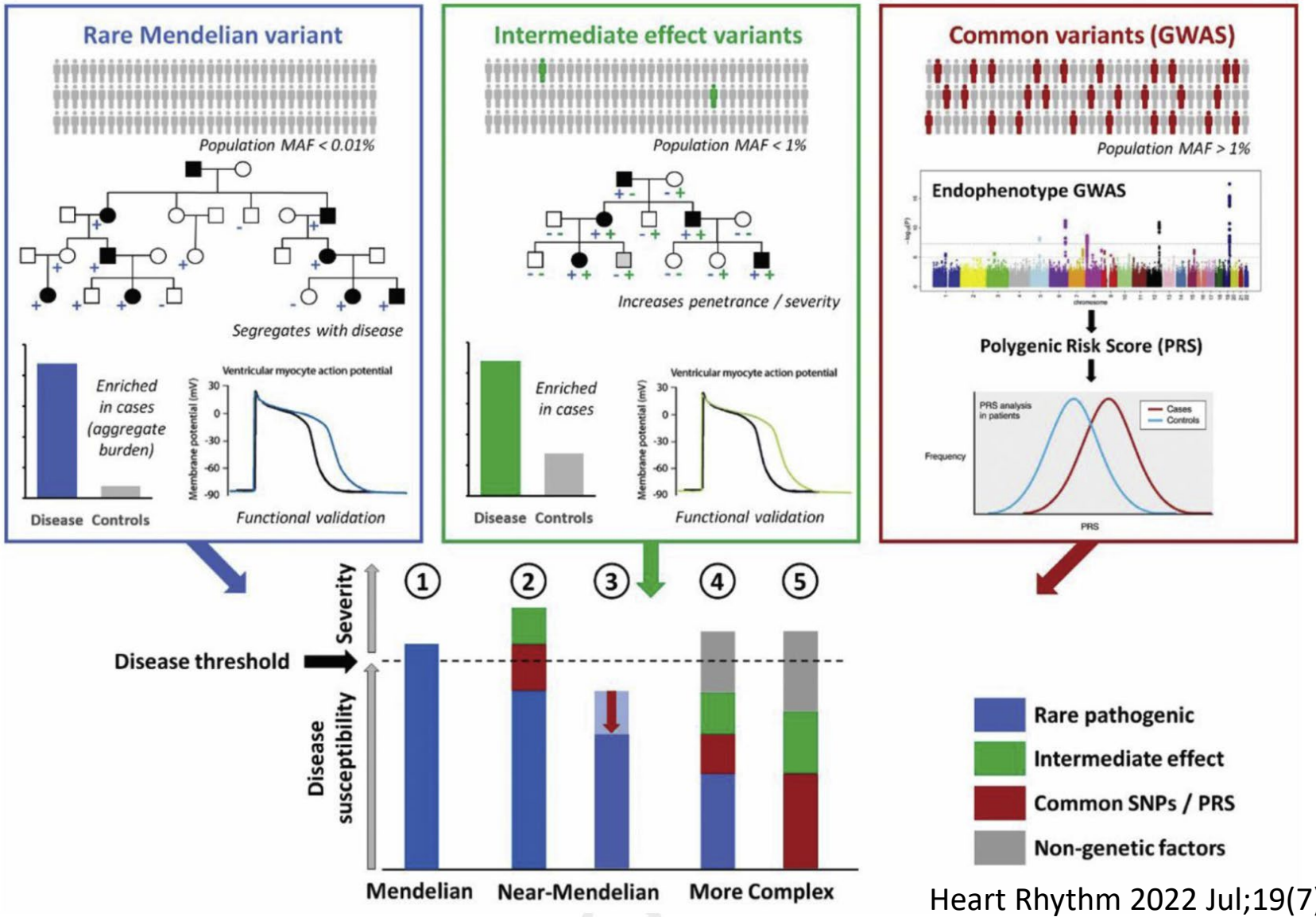
Type	Locus	Gene	Protein	Ionic current	Transmission
BrS1	3p21	*SCN5A*	Nav1.5	I_{Na}	AD
BrS2	3p22.3	*GPD1L*			AD
BrS3	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	AD
BrS4	10p12.33	*CACNB2b*	Cavβ2b	I_{Ca} β-subunit	AD
BrS5	19q13.1	*SCN1B*	SCNβ1	I_{Na} β1-subunit	AD
BrS6	11q13.4	*KCNE3*	MiRP2	I_{K} β-subunit	AD
BrS7	11q24.1	*SCN3B*	SCNβ3	I_{Na} β3-subunit	AD
BrS8	15q24.1	*HCN4*	HCN4	I_{f}	AD
BrS9	1p13.2	*KCND2/KCND3*	Kv4.2 /Kv4.3	$I_{To,1}$	AD
BrS10	7q21.11	*CACNA2D1*	Cav2δ1	I_{Ca} δ-subunit	AD
BrS11	12p11.23	*KCNJ8*	Kir6.1	$I_{K,ATP}$	AD
BrS12	17p13.1	*RANGRF/MOG1*	Ran Guanine Nucleotide Release Factor	Nav1.5 modulator	AD
BrS13	3p14.3	*SLMAP*	Sarcolemmal Associated Protein	Nav1.5 modulator	AD
BrS14	12p12.1	*ABCC9*	ATP binding cassette		AD
BrS15	11q23.3	*SCN2B*	SCNβ2	I_{Na} β2-subunit	AD
BrS16	12p11.21	*PKP2*	Plakophilin	Cell adhesion	AD
BrS17	3q28	*FGF12, FHAF1*	Fibroblast Growth Factor 12	Nav1.5 modulator	
BrS18	3p22.2	*SCN10A*	Nav1.8	I_{Na}	AD
BrS19	6q	*HEY2*	Transcriptional factor	Nav1.5 modulator	
BrS20	19q13.33	*TRPM4*	Transient Receptor Potential Cation Channel M4	Nav1.5 modulator	AD
BrS21	7q36.1	*KCNH2*	hERG	I_{Kr}	AD
BrS22	Xq22.3	*KCNE5*	KCNE1-Like protein / MiRP4	$I_{To,1}$ modulator	AD
BrS23	4q25-27	*Ank2*	Ankyrin-B	Anchoring protein	AD

The Brugada Syndrome
Genetic aspects

Type	Locus	Gene	Protein	Ionic current	Transmission
BrS1	3p21	*SCN5A*	Nav1.5	I_{Na}	AD
BrS2	3p22.3	*GPD1L*			AD
BrS3	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	AD
BrS4	10p12.33	*CACNB2b*	Cavβ2b	I_{Ca} β-subunit	AD
BrS5	19q13.1	*SCN1B*	SCNβ1	I_{Na} β1-subunit	AD
BrS6	11q13.4	*KCNE3*	MiRP2	I_K β-subunit	AD
BrS7	11q24.1	*SCN3B*	SCNβ3	I_{Na} β3-subunit	AD
BrS8	15q24.1	*HCN4*	HCN4	I_f	AD
BrS9	1p13.2	*KCND2/KCND3*	Kv4.2 /Kv4.3	$I_{To,1}$	AD
BrS10	7q21.11	*CACNA2D1*	Cavδ1	I_{Ca} δ-subunit	AD
BrS11	12p11.23	*KCNJ8*	Kir6.1	$I_{K,ATP}$	AD
BrS12	17p13.1	*RANGRF/MOG1*	Ran Guanine Nucleotide Release Factor	Nav1.5 modulator	AD
BrS13	3p14.3	*SLMAP*	Sarcolemmal Associated Protein	Nav1.5 modulator	AD
BrS14	12p12.1	*ABCC9*	ATP binding cassette		AD
BrS15	11q23.3	*SCN2B*	SCNβ2	I_{Na} β2-subunit	AD
BrS16	12p11.21	*PKP2*	Plakophilin	Cell adhesion	AD
BrS17	3q28	*FGF12, FHAF1*	Fibroblast Growth Factor 12	Nav1.5 modulator	
BrS18	3p22.2	*SCN10A*	Nav1.8	I_{Na}	AD
BrS19	6q	*HEY2*	Transcriptional factor	Nav1.5 modulator	
BrS20	19q13.33	*TRPM4*	Transient Receptor Potential Cation Channel M4	Nav1.5 modulator	AD
BrS21	7q36.1	*KCNH2*	hERG	I_{Kr}	AD
BrS22	Xq22.3	*KCNE5*	KCNE1-Like protein / MiRP4	$I_{To,1}$ modulator	AD
BrS23	4q25-27	*Ank2*	Ankyrin-B	Anchoring protein	AD

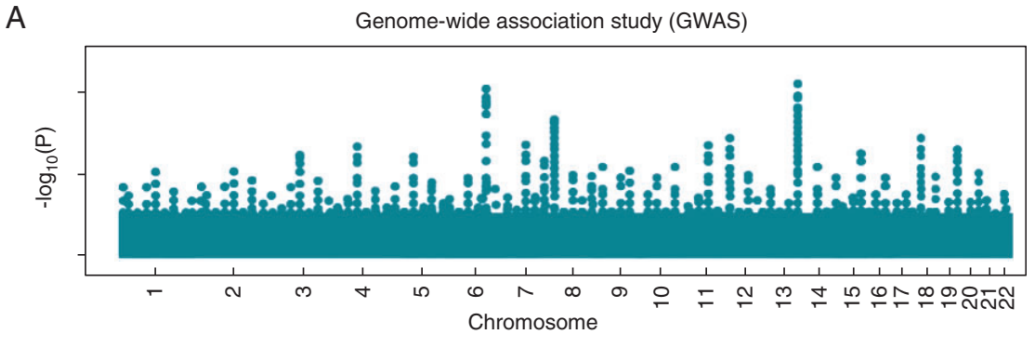
Causality ??

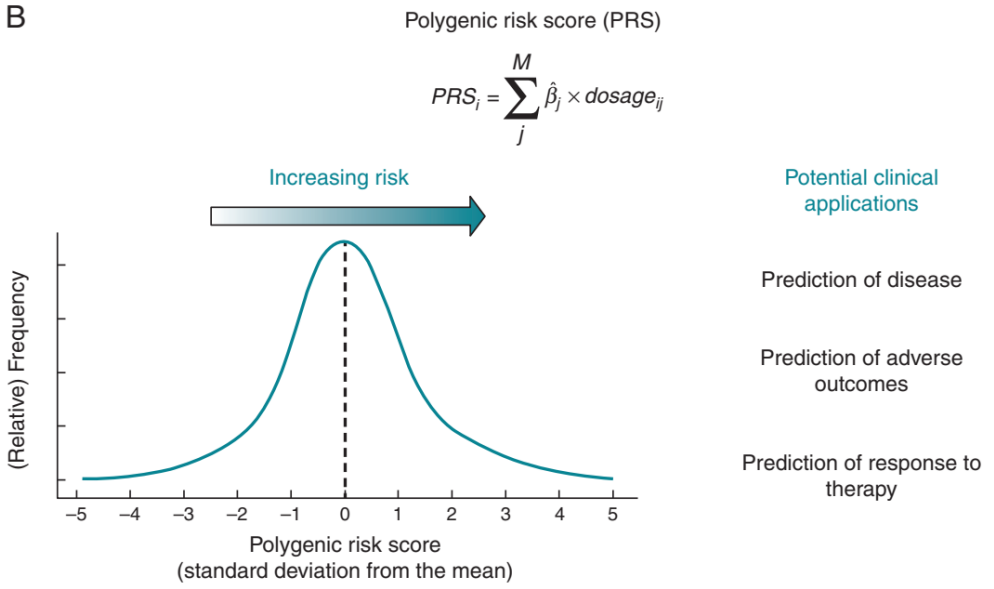
The Brugada Syndrome
The concept of complex genetic architecture



Heart Rhythm 2022 Jul;19(7):e1-e60

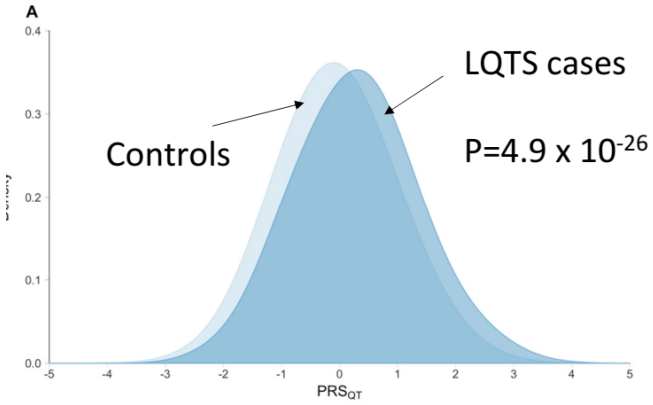
The Brugada Syndrome
Polygenic Risk Scores to predict individual genotype-phenotype expression ?

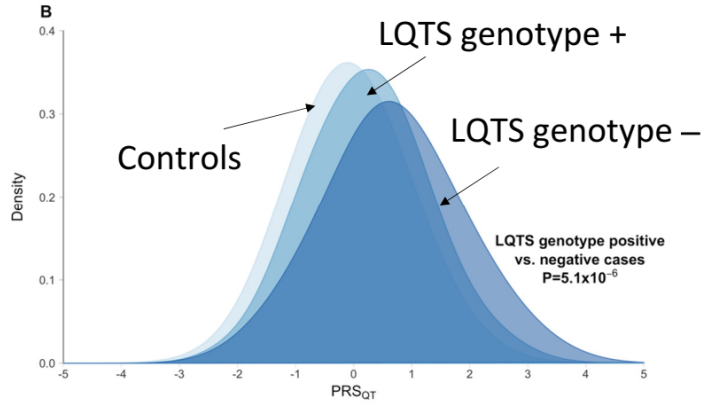




Proof-of-concept **BUT**
significant overlap between controls and pts.

genotype + vs. Genotype -
$P=5.1x10^{-6}$





Lahrouchi et al., Circulation 2020

The Brugada Syndrome

4 Important implications for the cardiogenetic practise

1/ Genotyping YES,
BUT oligogenic achitecture = unpredictable genotype-phenotype correlation

2/ Too early for PRS in routine clinical practise

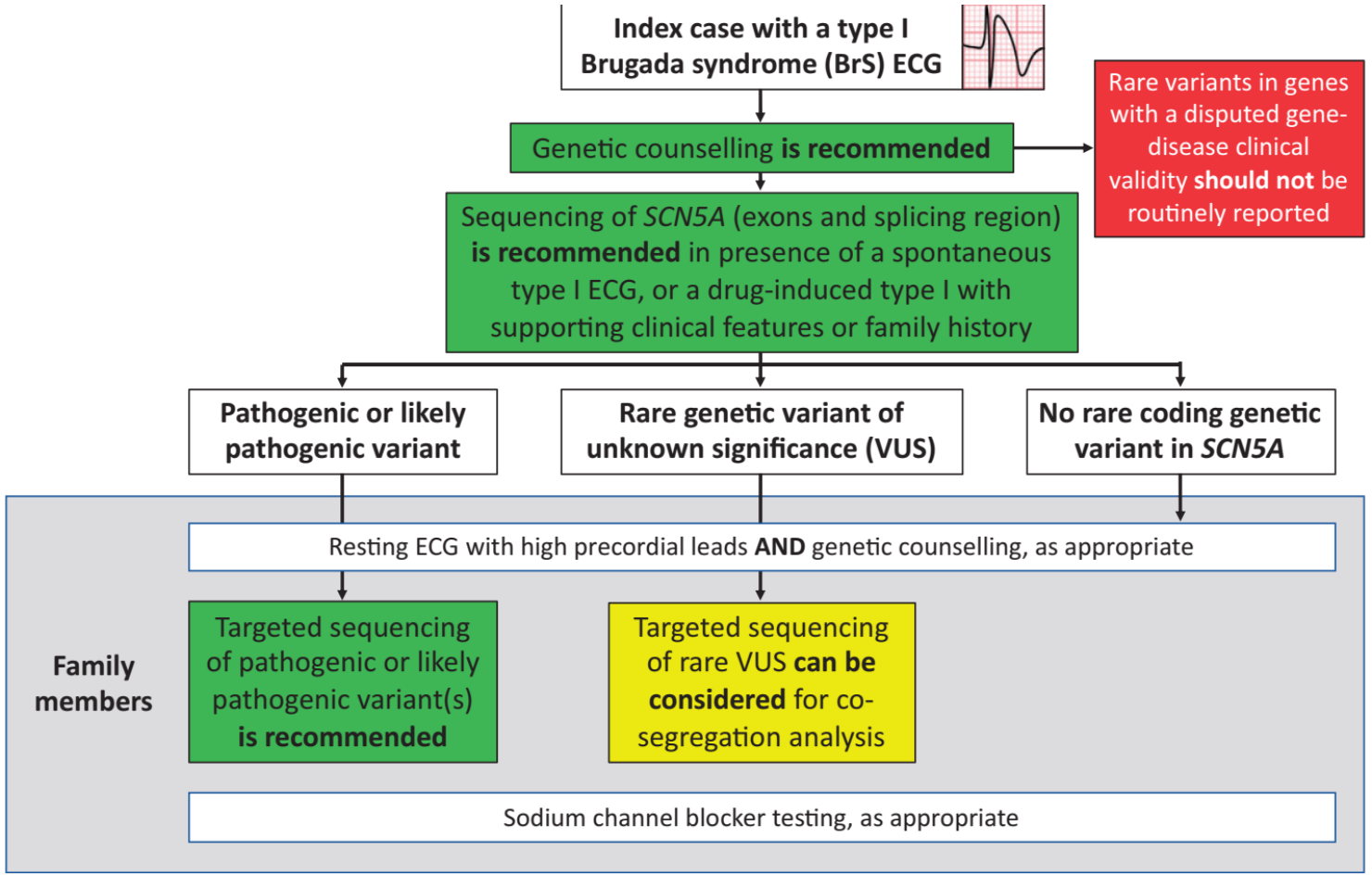
3/ Phenotype-based management remains important
Despite the low event rate
Let's not be afraid of ajmalin testing

4/ BUT Correct interpretation and counseling of results is crucial

The Brugada Syndrome

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
Brugada syndrome	+	+	+

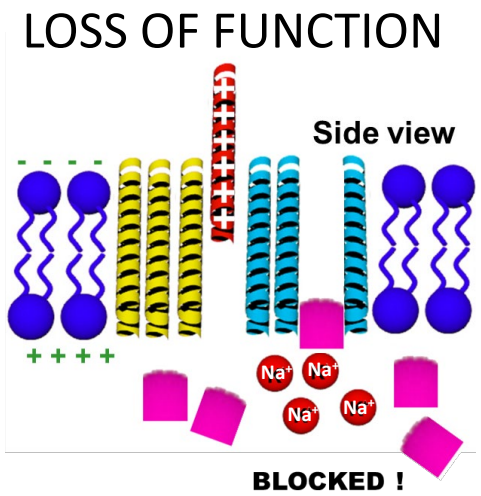


Wilde AAM et al, Europace. 2022 Sep 1;24(8):1307-1367.

The Brugada Syndrome
Acquired aspects

Pharmacological interaction

Anti arrhythmic drugs
Psychotropis drugs
Anesthecis
Analgesics
Acetylcholine
Cocaine
Alcohol



TYPE-1 ECG

www.BrugadaDrugs.org

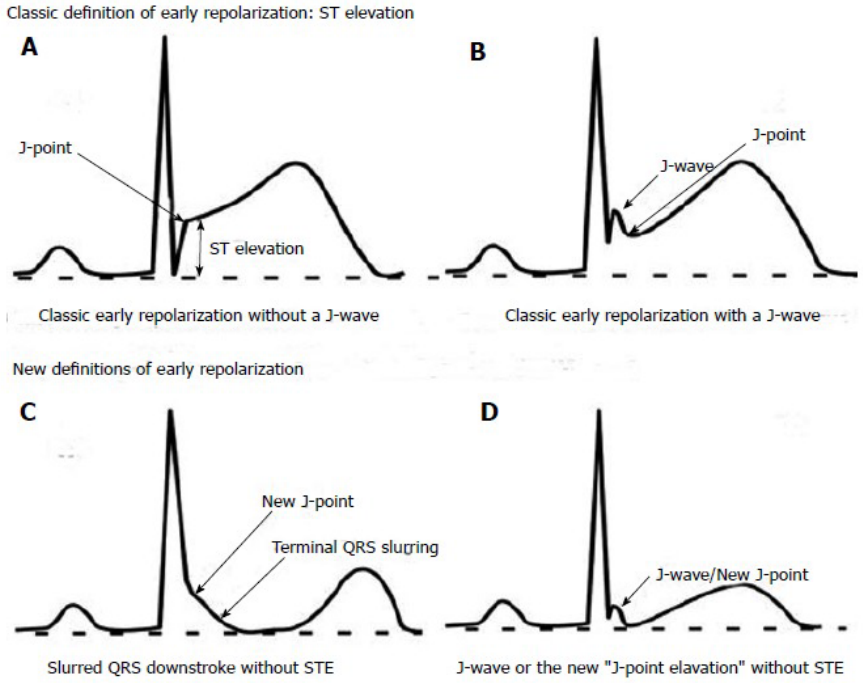
Early Repolarisation Syndrome
ERS

Early Repolarisation Syndrome

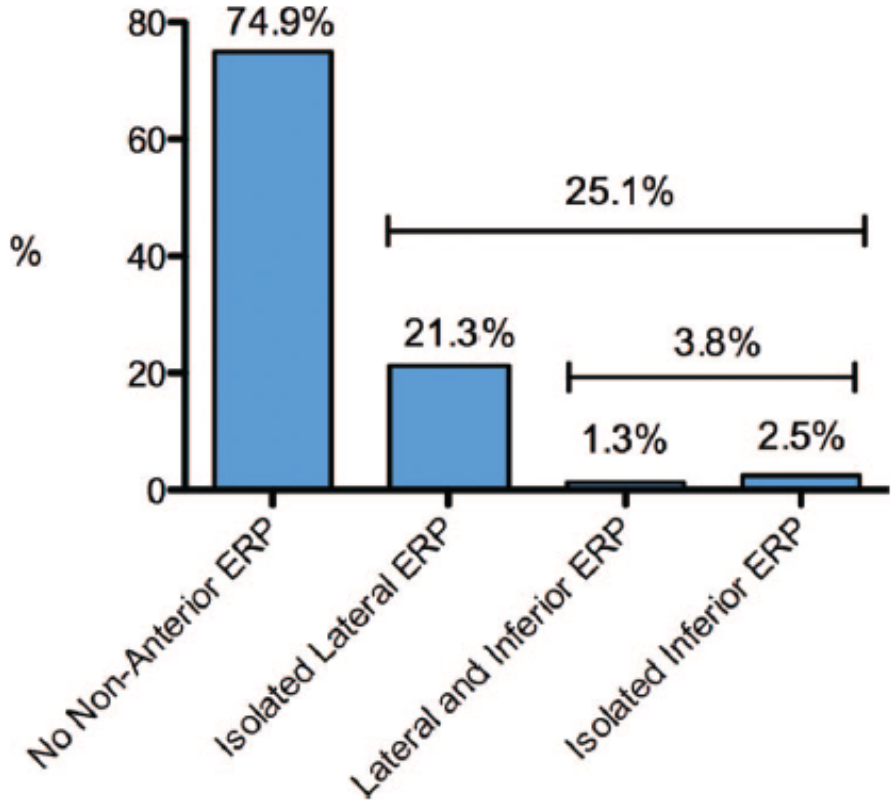
Mostly benign ECG trait

Frequent finding 1-5%

Up to 25% in athletes



World J Cardiol. 2015; 7(8): 466–475.



Circ Arrhythm Electrophysiol. 2011;4:432-440

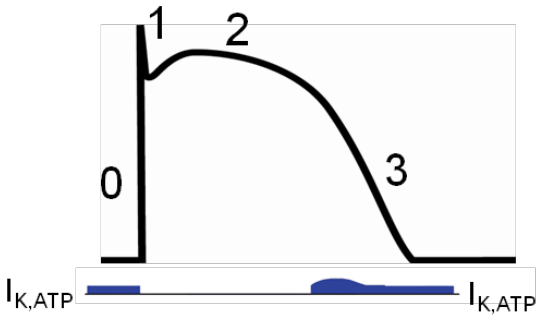
Rare Malignant form causes VF and SCD

Early Repolarisation Syndrome
Genetic aspects

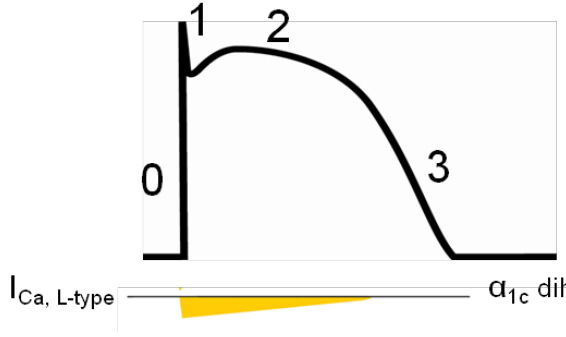
Type	Locus	Gene		Ionic current	Transmission
ERS1	12p11.23	*KCNJ8*	Kir6.1	$I_{K,ATP}$	AD
ERS2	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	AD
ERS3	10p12.33	*CACNB2b*	Cavβ2b	I_{Ca} β-subunit	AD
ERS4	7q21.11	*CACNA2D1*	Cav2δ1	I_{Ca} δ-subunit	AD
ERS5	12p12.1	*ABCC9*	ATP binding cassette	$I_{K,ATP\ modulator}$	AD
ERS6	3p21	*SCN5A*	Nav1.5	I_{Na}	AD
ERS7	3p22.2	*SCN10A*	Nav1.8	I_{Na}	AD

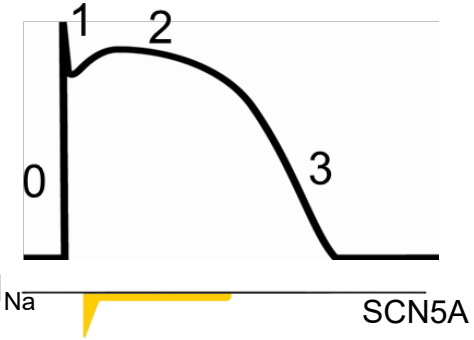
Oligogenic architecture

Gain of function
ERS1 & ERS5



Loss of function
ERS2-4 & ERS6





Early Repolarisation Syndrome

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
Early repolarization syndrome	–	–	–

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT

Catecholaminergic Polymorphic VT
At a glance

CPVT is a disease of the calcium handling in the heart

1/10000

Classic early onset (mean age 7,8yrs)

Adult onset type

High penetrance

Clinical features

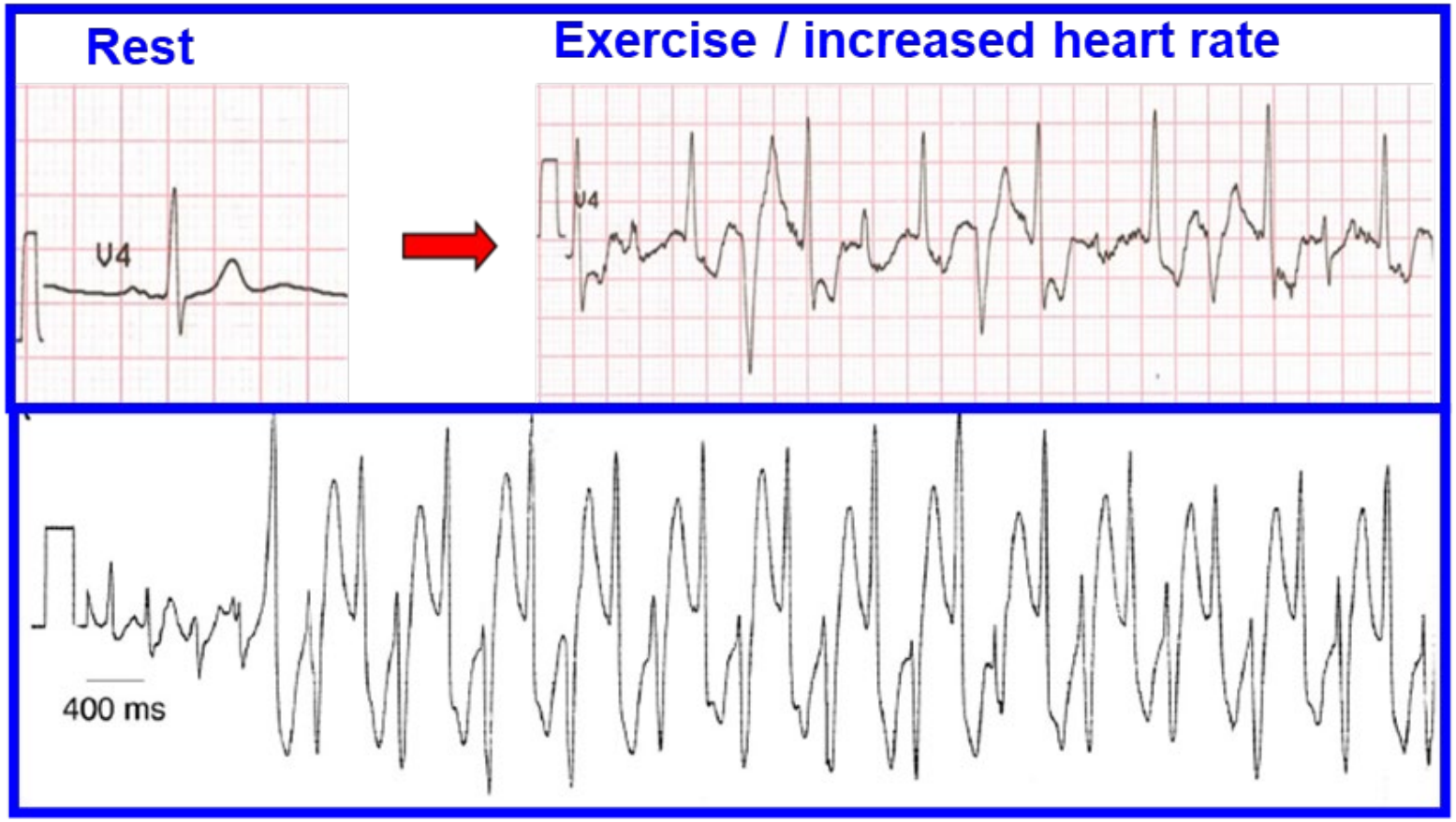
Cardiac syncope induced by stress

Near-drowning

SIDS

50% previous epilepsy diagnosis

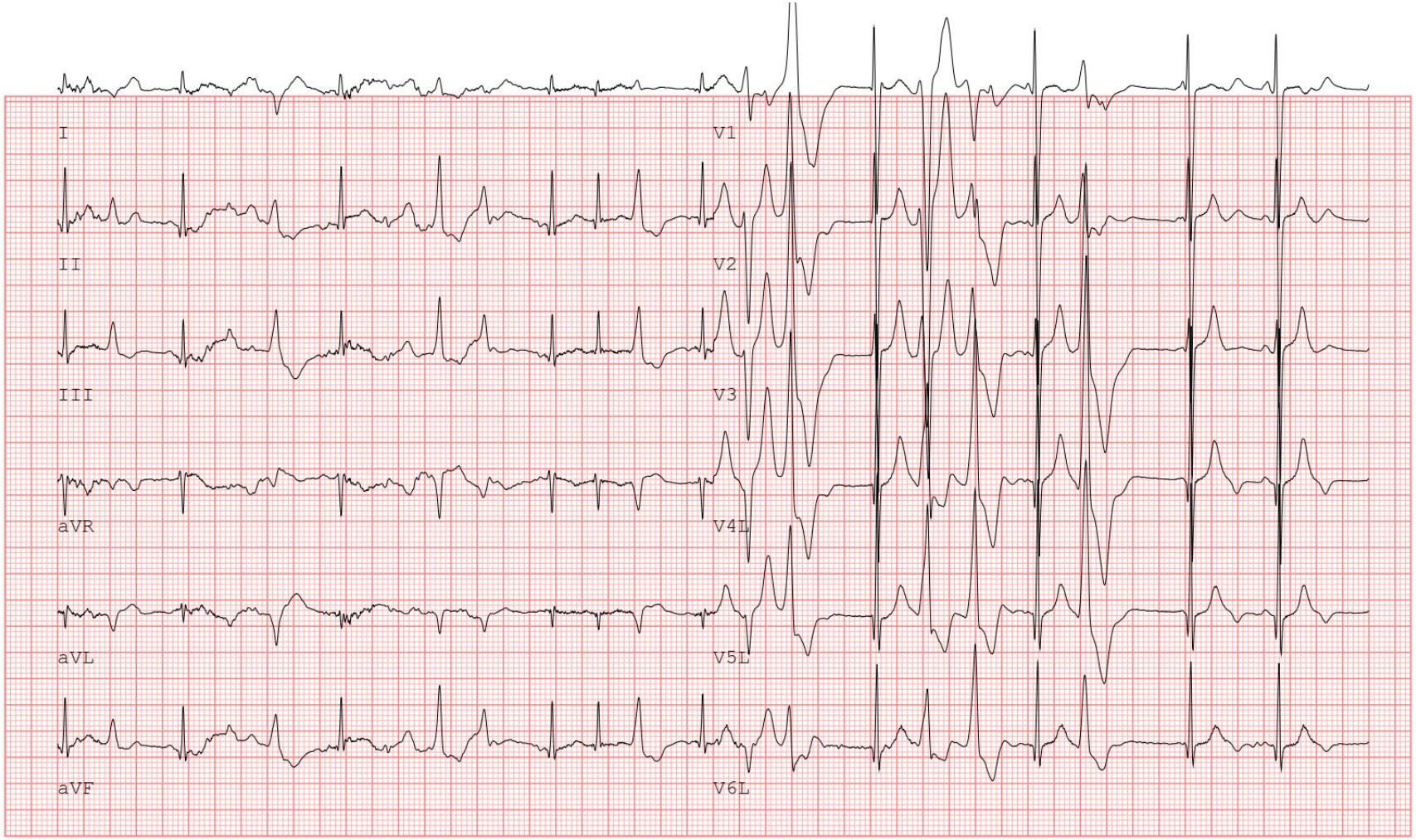
Misdiagnosis as LQTS



Catecholaminergic Polymorphic VT
At a glance

Bidirectional or Polymorphic Ventricular Tachycardia

Triggered due to elevated adrenergic tone



Catecholaminergic Polymorphic VT
Genetic aspects

70%

Type	Locus	Gene	Protein	Transmission
CPVT1	1q43	*RYR2*	RYR2	AD
CPVT2	1p13.3-p11	*CASQ2*	Calsequestrin 2	AR
CPVT3	*unknown*	*unknown*	*unknown*	
CPVT4	14q24-q31	*CALM1*	Calmodulin 1	AD
CPVT5	2q21	*CALM2*	Calmodulin 2	AD
CPVT6	19q13.32	*CALM3*	Calmodulin 3	AD
CPVT7	6q22.31	*TRDN*	Triadin	AR
CPVT8	17q23	*KCNJ2*	Kir2.1	AD
CPVT9	4q13.1	*TECRL*	Trans-2,3-Enoyl-CoA Reductase Like	

Catecholaminergic Polymorphic VT

High penetrance: 80% symptomatic <40 y.o.

Betablocker +/- flecainide: 50-74% risk reduction
+ LCSD: 87% risk reduction

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
CPVT	+++	+/-	+/-

Calcium Release Deficiency Syndrome
CRDS

Calcium Release Deficiency Syndrome

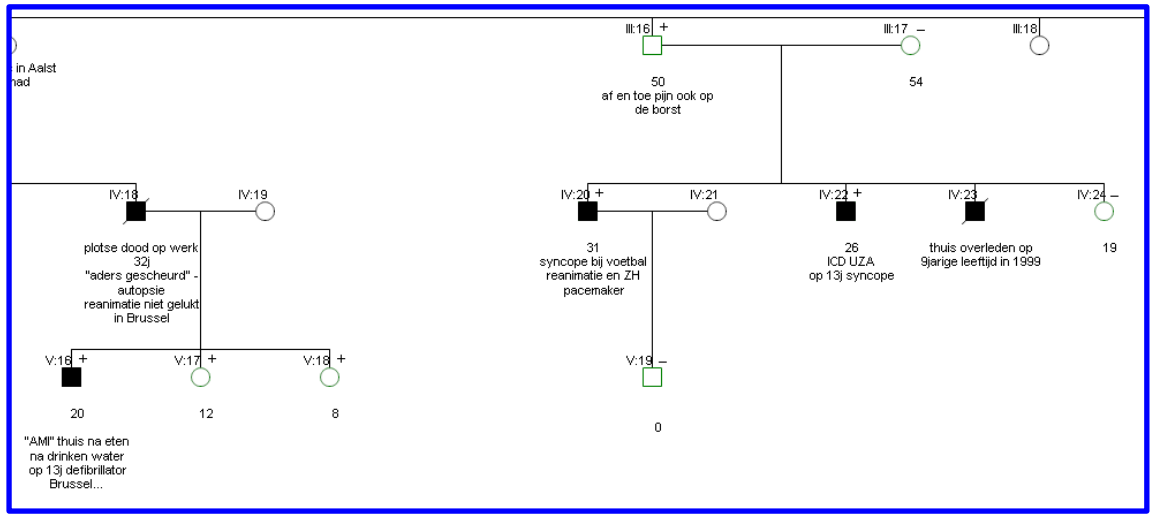
Normal ECG
Normal holter
Normal TTE

Normal exercise test
Normal EP study

Normal Ajmalin test
Normal Epinephrin test
Normal Isoprenalin response

No detectable Phenotype !

SCD during exercise
SCD during rest
High penetrance



Calcium Release Deficiency Syndrome
Genetic aspects

RYR2 c. 12334G>A or p.Asp4112Asn

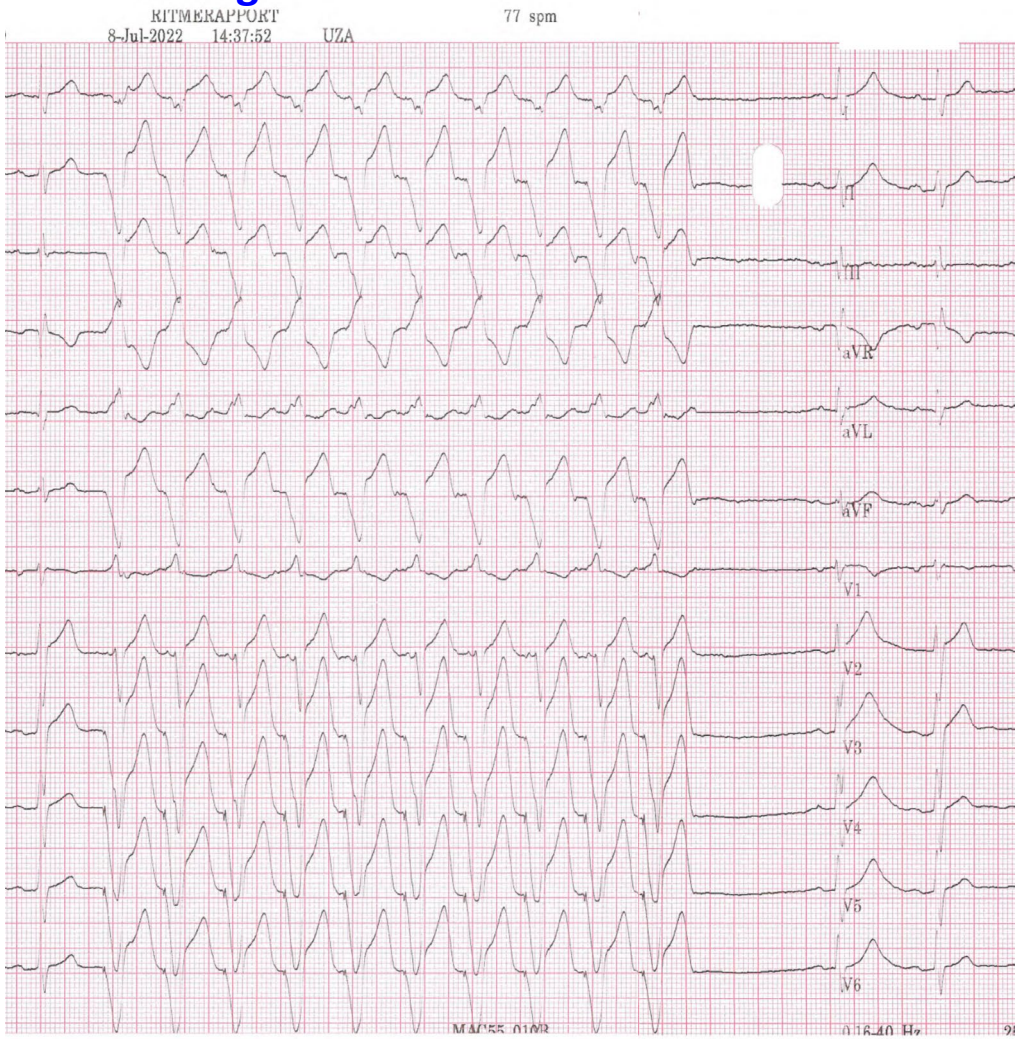
Molecular data:

1) **Highly conserved** nucleotide and highly conserved amino acid (-- chicken).
2) **In-silico predictions** (Polyphen, Mutation Taster, SIFT, Align GVGD) **all damaging**
3) **Not present** in SNP- and 1000 Genomes dbase, not present in Exome Variant Server or GNOMAD (ca. 250.000 control alleles)
4) **Within "channel region"**, known hotspot for mutations (cfr. Medeiros-Domingo et al., 2009, J. Am. Coll. Cardiol. 54:2065-2074).
5) May be **consistent with** adrenergic arrhythmogenesis **phenotype**

Functional data:

Loss of function

New diagnostic ECG criteria under review



Ni et al. JAMA. 2024 Jul 16;332(3):204-213.

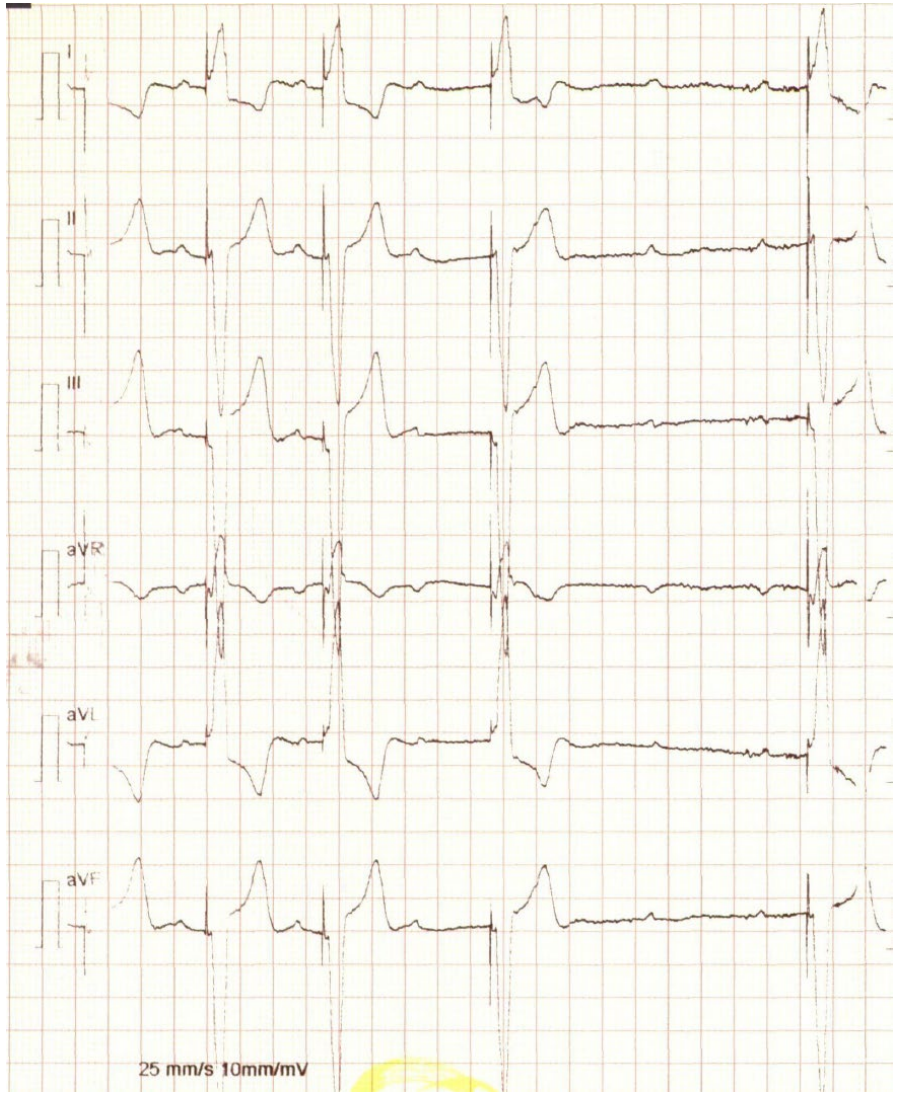
Progressive Cardiac Conduction Disorder PCCD

Progressive Cardiac Condution Disorder
PCCD

Lenegre-Lev's disease or Type IA PCCD = *SCN5A*, AD

RBBB or LAHB

3rd degree AVB

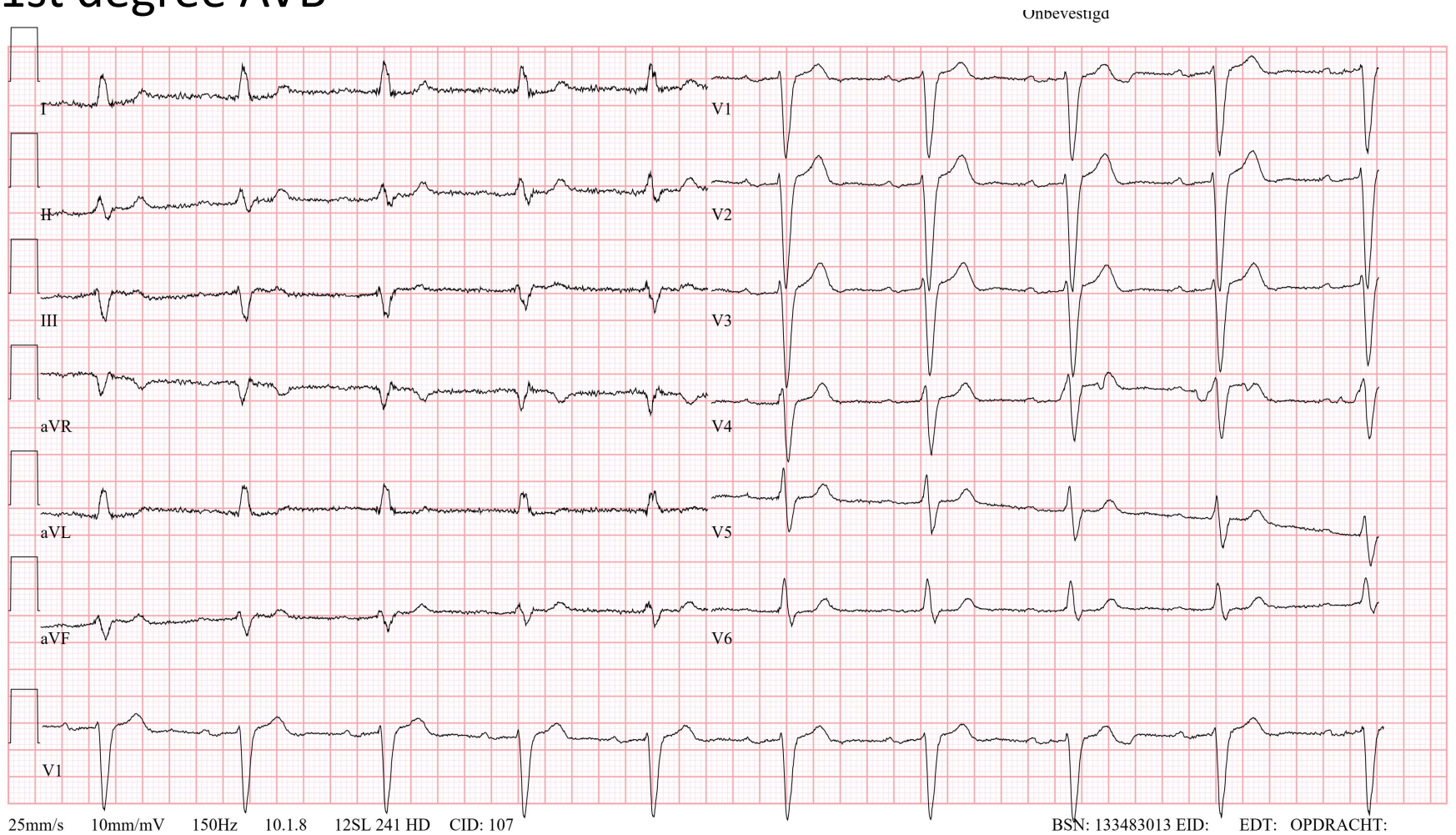


Progressive Cardiac Condution Disorder
PCCD

Lenegre-Lev's disease or Type IA PCCD = *SCN5A*, AD

LBBB

1st degree AVB

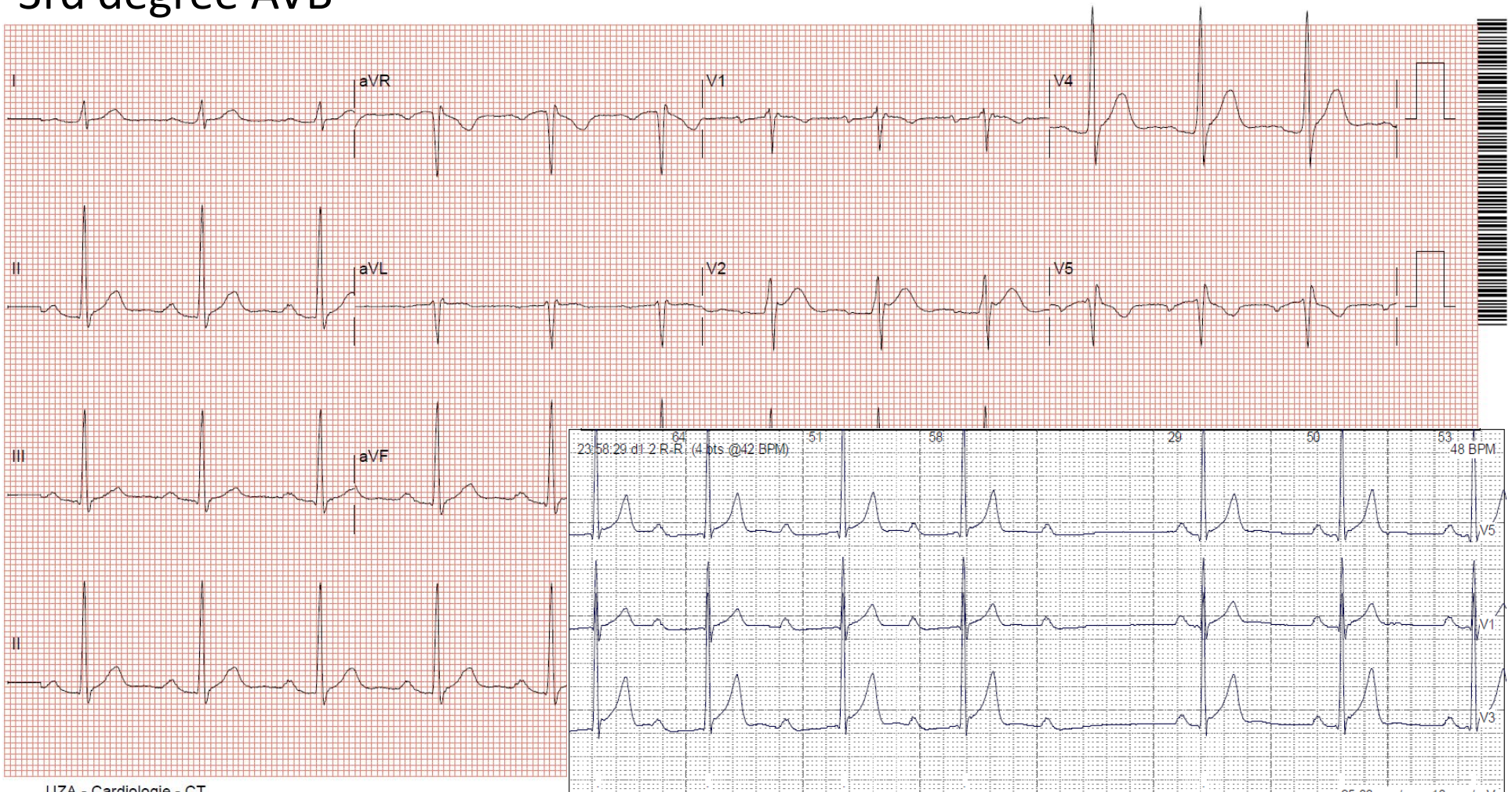


Progressive Cardiac Condution Disorder
PCCD

Type IB PCCD = *TRPM4*, AD

RBBB +/- LAHB

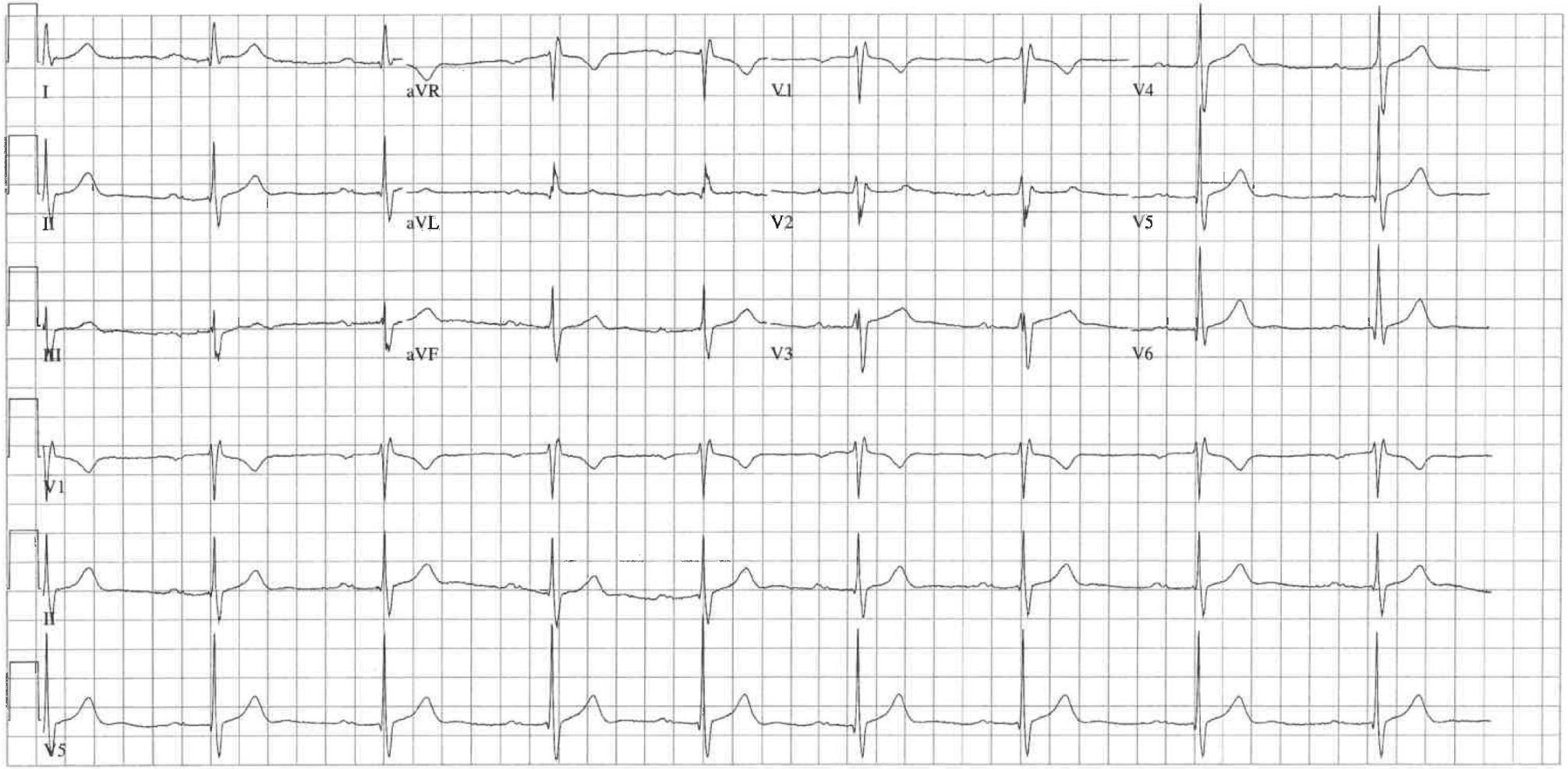
3rd degree AVB



Progressive Cardiac Condution Disorder
PCCD

Unclassified PCCD = NKX2-5, AD

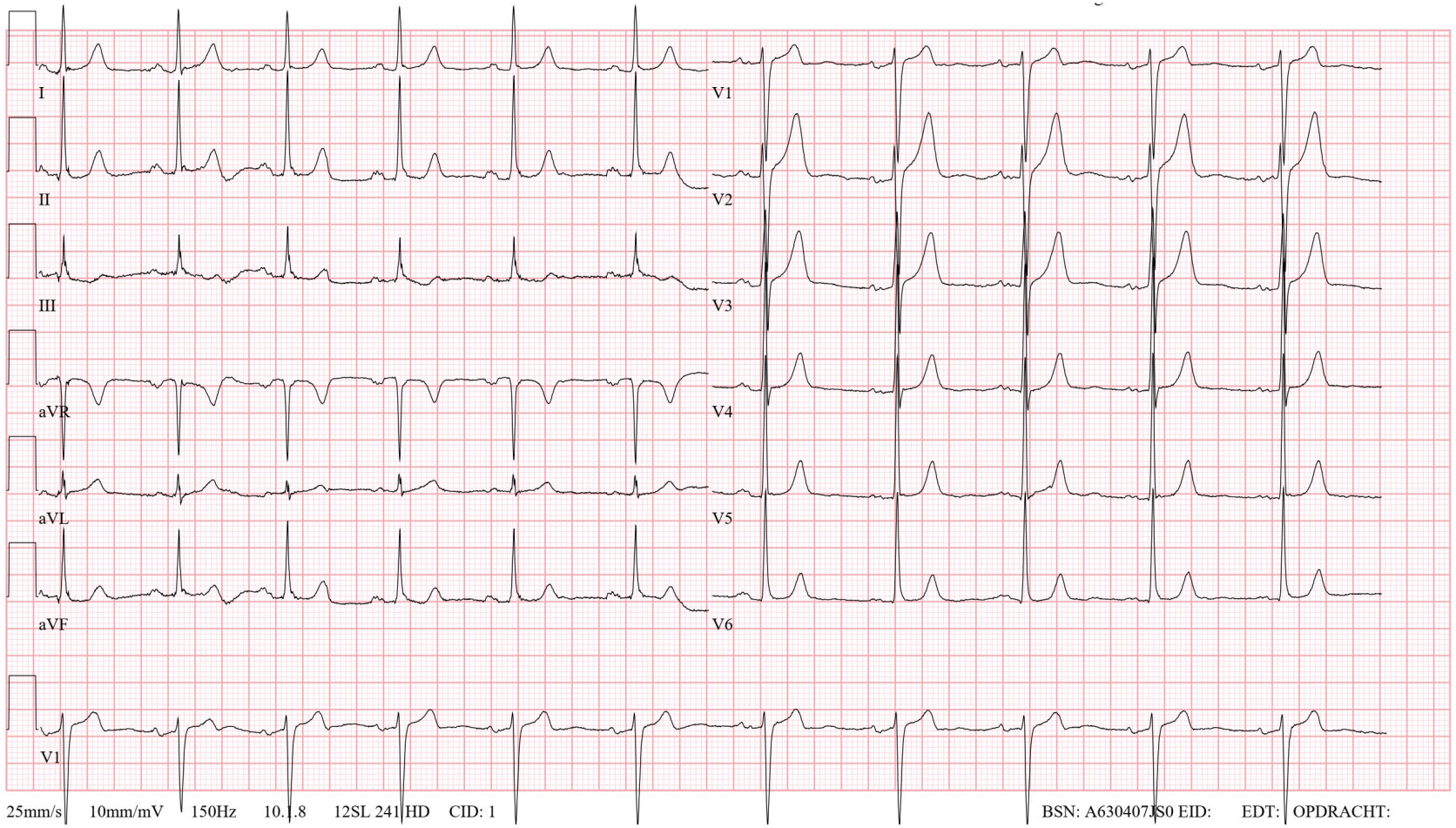
RBBB + evolving AVB

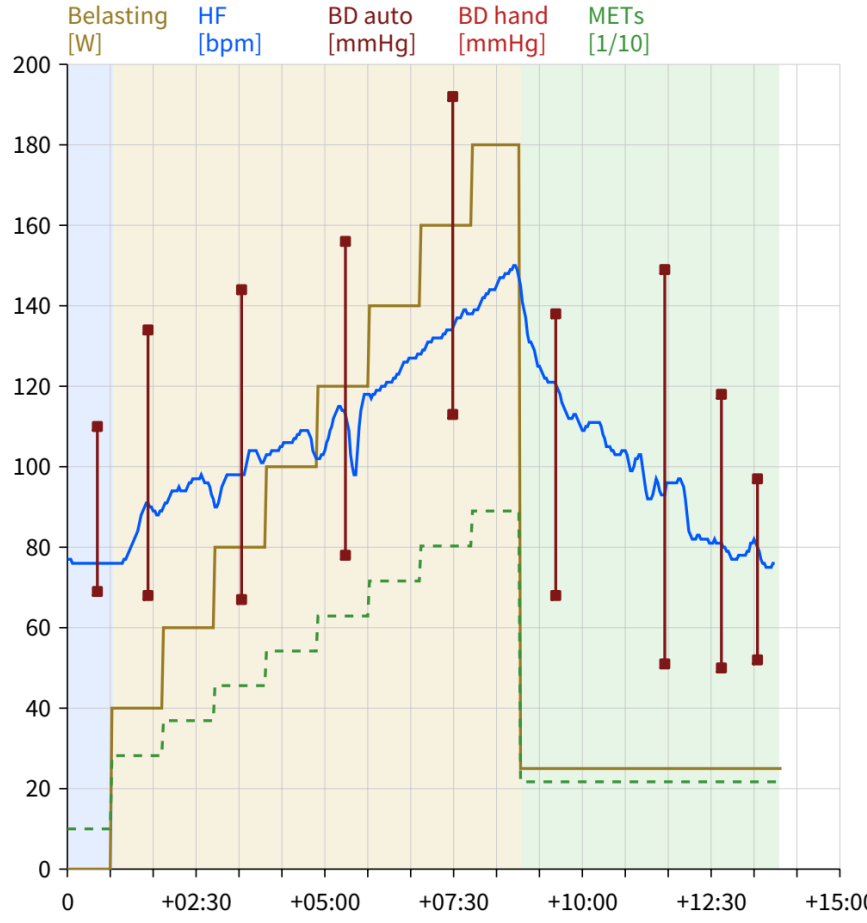


Progressive Cardiac Condution Disorder
PCCD

Unclassified PCCD = NKX2-5, AD

Non-vagal Paroxysmal AVB

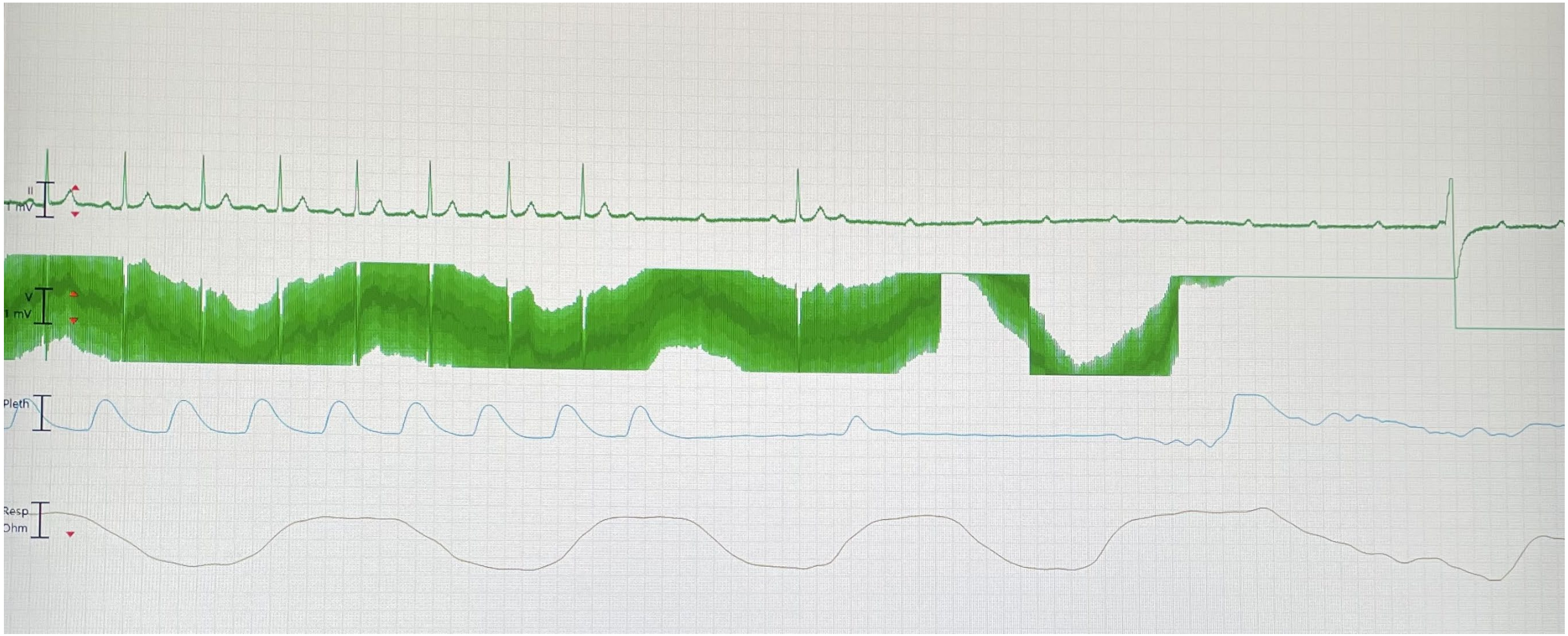




Progressive Cardiac Condution Disorder PCCD

Unclassified PCCD = NKX2-5, AD

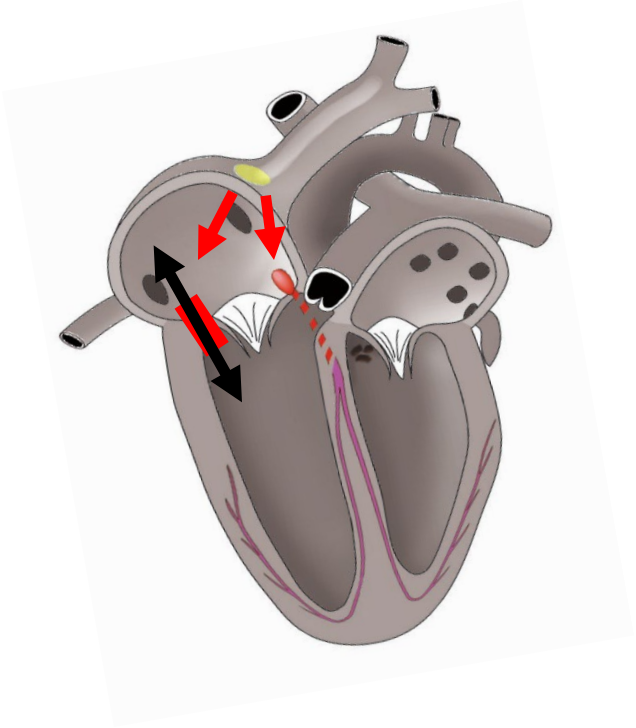
Non-vagal Paroxysmal AVB

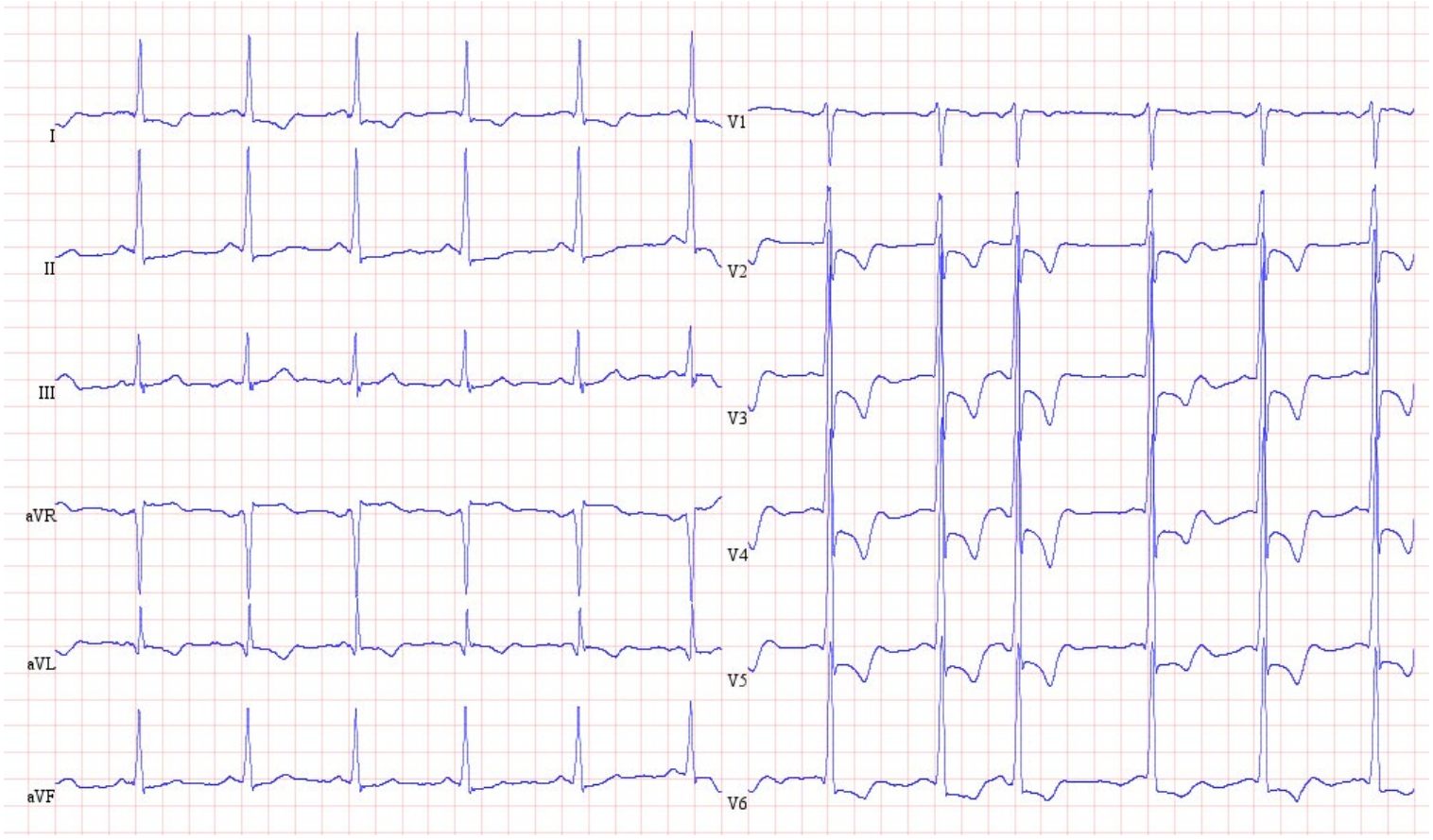


Familial Wolff-Parkinson-White
fWPW

Wolff-Parkinson-White Syndrome
fWPW

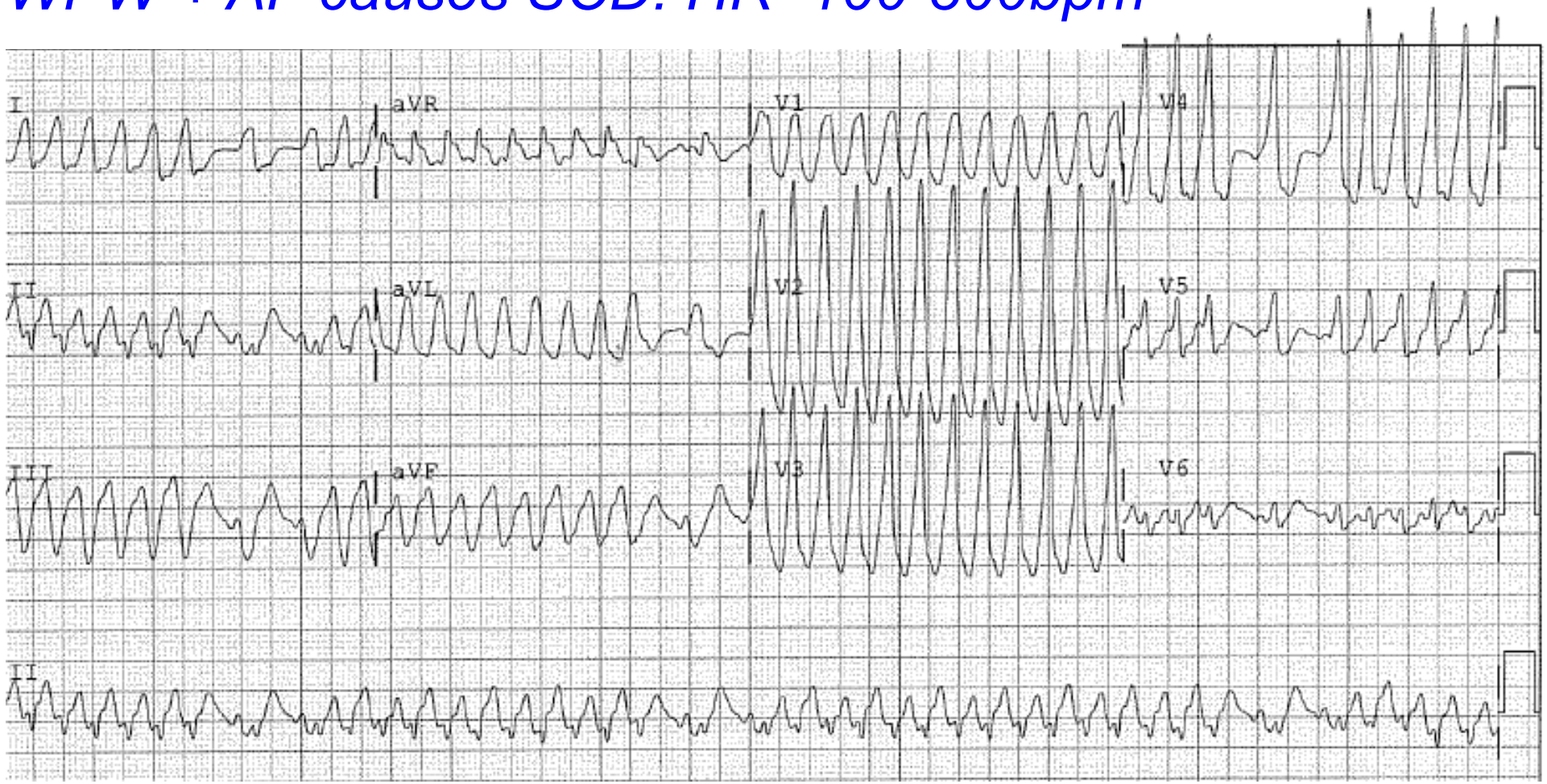
Hereditary forms exist: 1/ *PRKAG2* w. severe HCM or DCM
2/ LAMP2 Danon's disease





Wolff-Parkinson-White Syndrome
fWPW

WPW + AF causes SCD: HR~100-300bpm



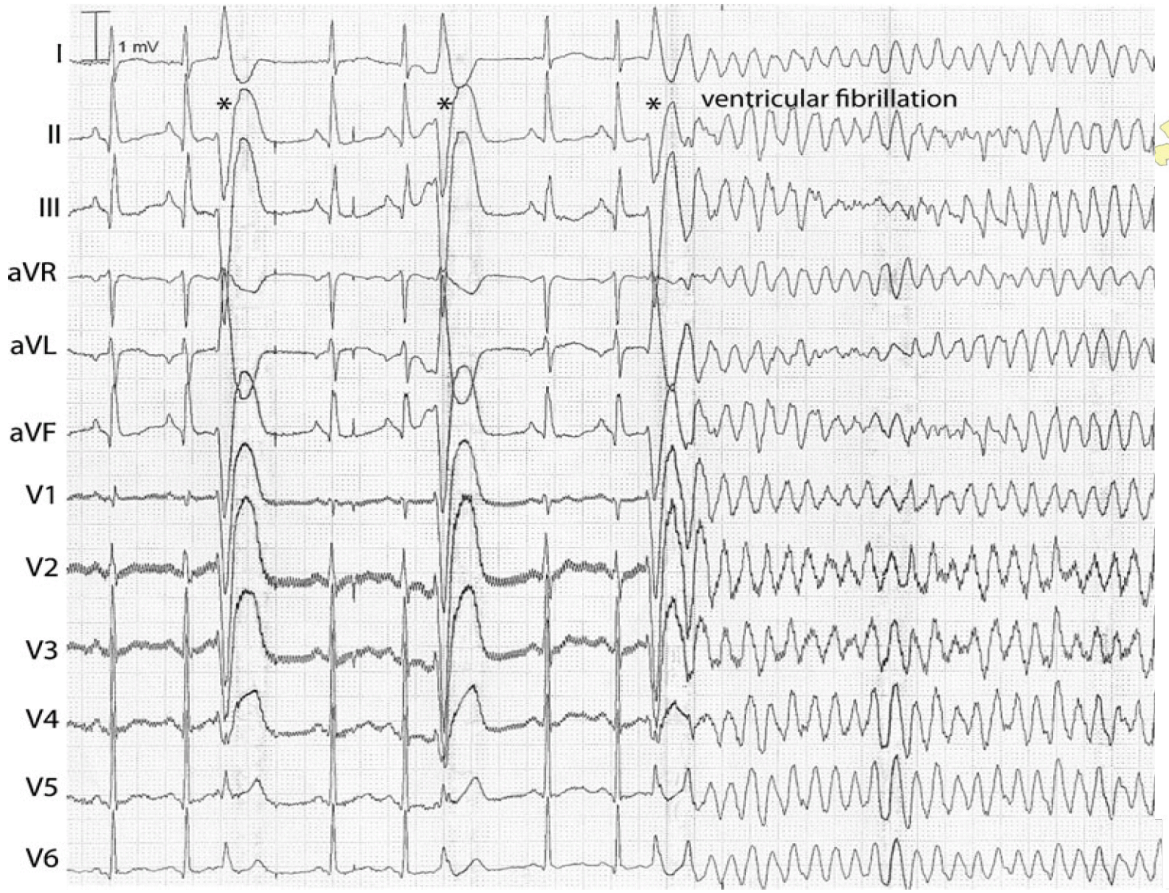
Familial Idiopathic VF
IVF

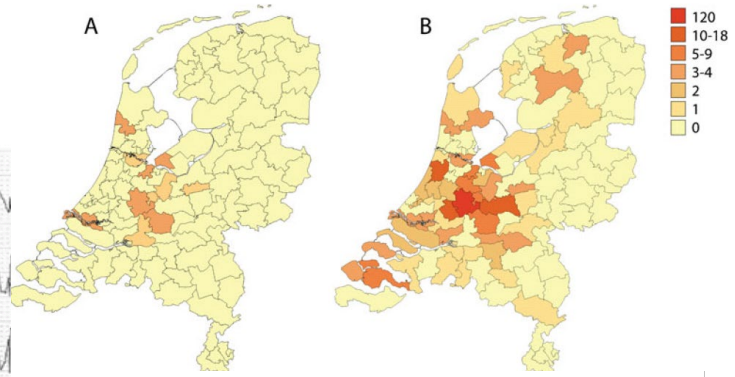
Familial Idiopathic VF

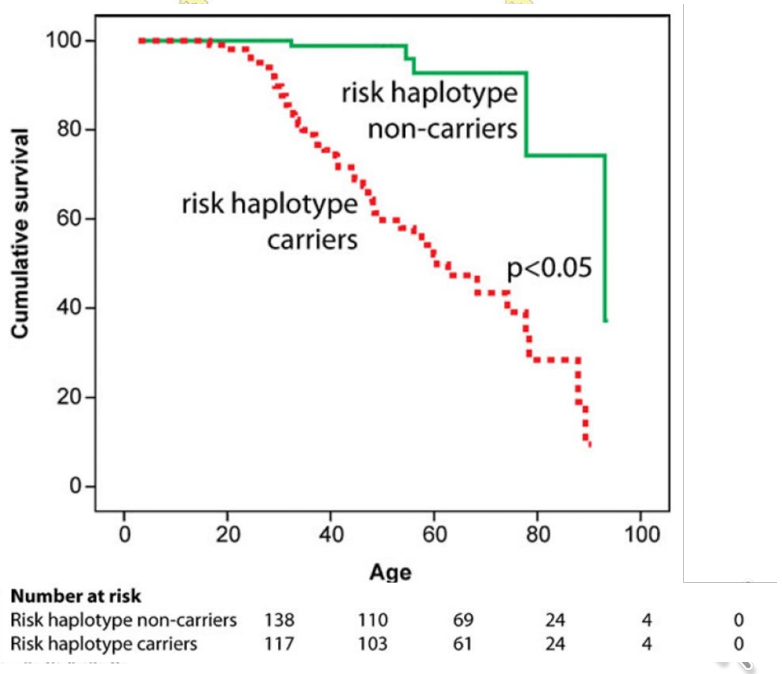
Ventricular fibrillation without any detectable cause

Short coupled PVC induced VF

Dutch *DPP6* founder haplotype







Neth Heart J (2011) 19:290–296

Multifocal Ectopic Purkinje-Related Premature Contractions

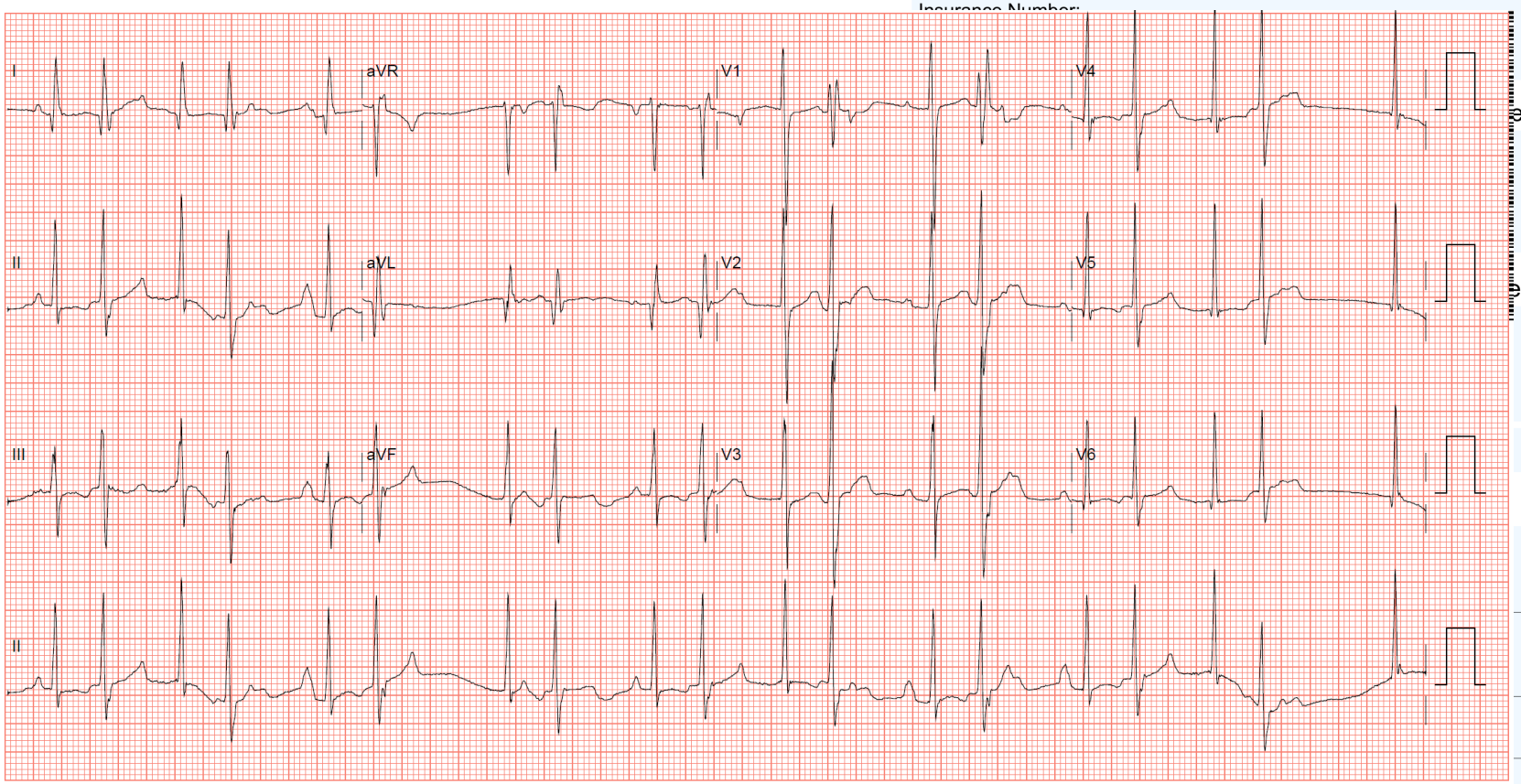
MEPPC

Multifocal Ectopic Purkinje-Related Premature Contractions

Early onset DCM
Peripartum CMP
Frequent PAC/PVC's

Order:
Patient ID2:
Date of Birth: do 10 apr 1986 (28 years)
Gender: Unknown
Insurance Number:

Recorded: do 08 jan 2015 09:01:00
Analyzed Length: 1 day 35 min 21 sec, 8,7% artefact
Recorder No.: 004296
Recorder Type: EVO
Analysis Date: vr 09 jan 2015
Analysis Channels: 1,2,3 from 3 channels
Analysis Technician: holter1



eat Counts

SVE Beats		Paced Beats	
Count	**74.398**	Count	**0**
Percent	**47 %**	Percent	**0%**
Max/Hr	**3.781** on do 18:00	Max/Hr	**0** on

pendent Events

Tachycardia	**0**
Total	
Longest	
Max Rate	

Supraventricular Arrhythmias

AF	**0 episodes**
Total Duration	
Max Rate	
SVT	**0**
Longest	
Max Rate	
SVE	**59.556**, 37,3% of total beats (372 per 1000)

UZA - Cardiologie - ECG Ambulant

F 0.15 - 150 Hz 25 mm/sec 10 mm/mV (1)

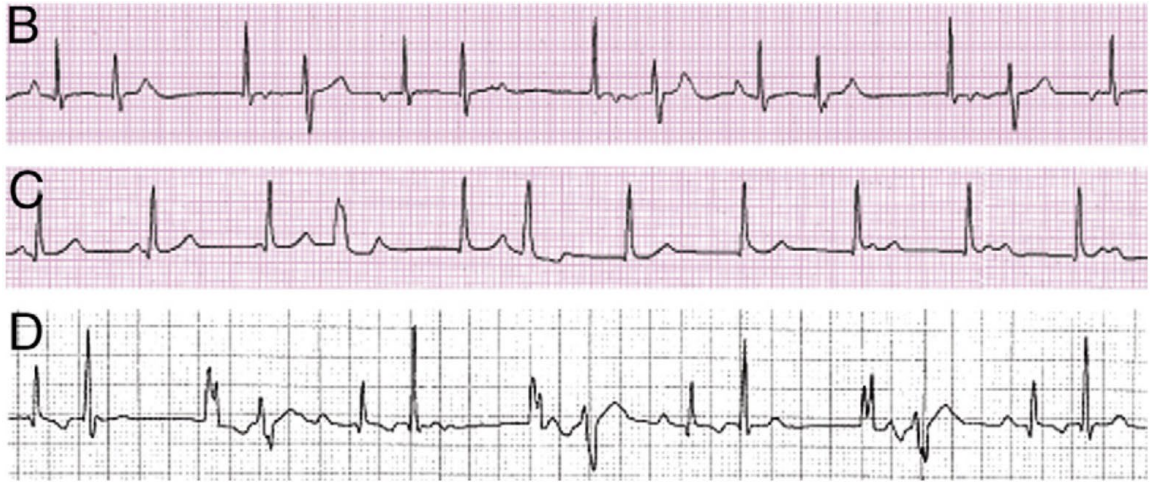
Multifocal Ectopic Purkinje-Related Premature Contractions

Heterozygous p.R222Q in *SCN5A* (UVCL5) = PATHOGENIC VARIANT

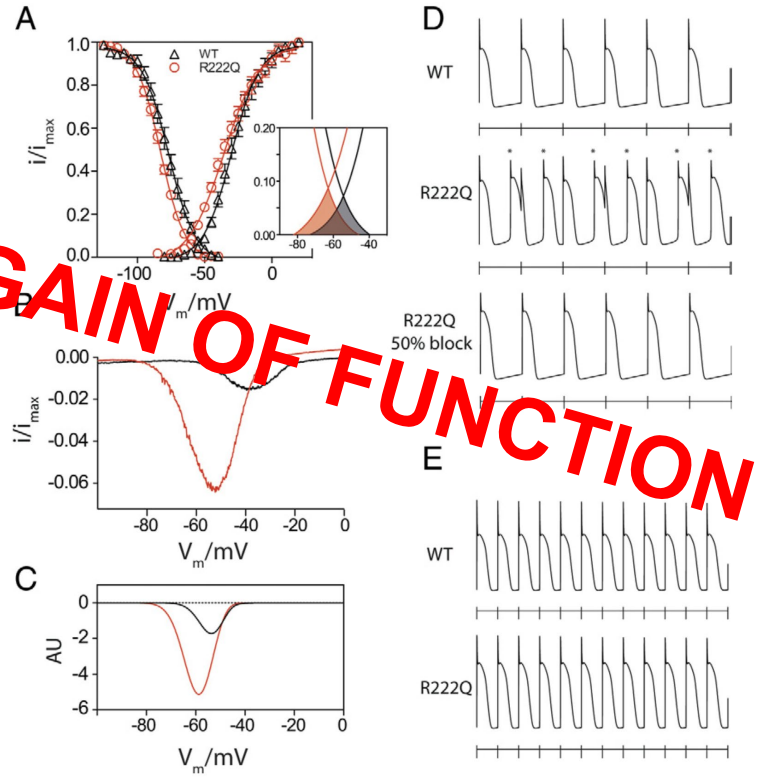
R222Q *SCN5A* Mutation Is Associated With Reversible Ventricular Ectopy and Dilated Cardiomyopathy

Stefan A. Mann, PhD,* Maria L. Castro, BMedSci(Hons),* Monique Ohanian, BMedSci(Hons),* Guanglan Guo, PhD,* Poonam Zodgekar, MSW, GradDipGenCouns,* Angela Sheu, MB, BS,* Kathryn Stockhammer, BSc, GradDipGenCouns,* Tina Thompson, BNurs,† David Playford, MB, BS, PhD,‡ Rajesh Subbiah, MB, BS, PhD,§‖ Dennis Kuchar, MD,§ Anu Aggarwal, MB, BS, PhD,† Jamie I. Vandenberg, MB, BS, PhD,*‖ Diane Fatkin, MD*§‖

Phenotype



Functional data



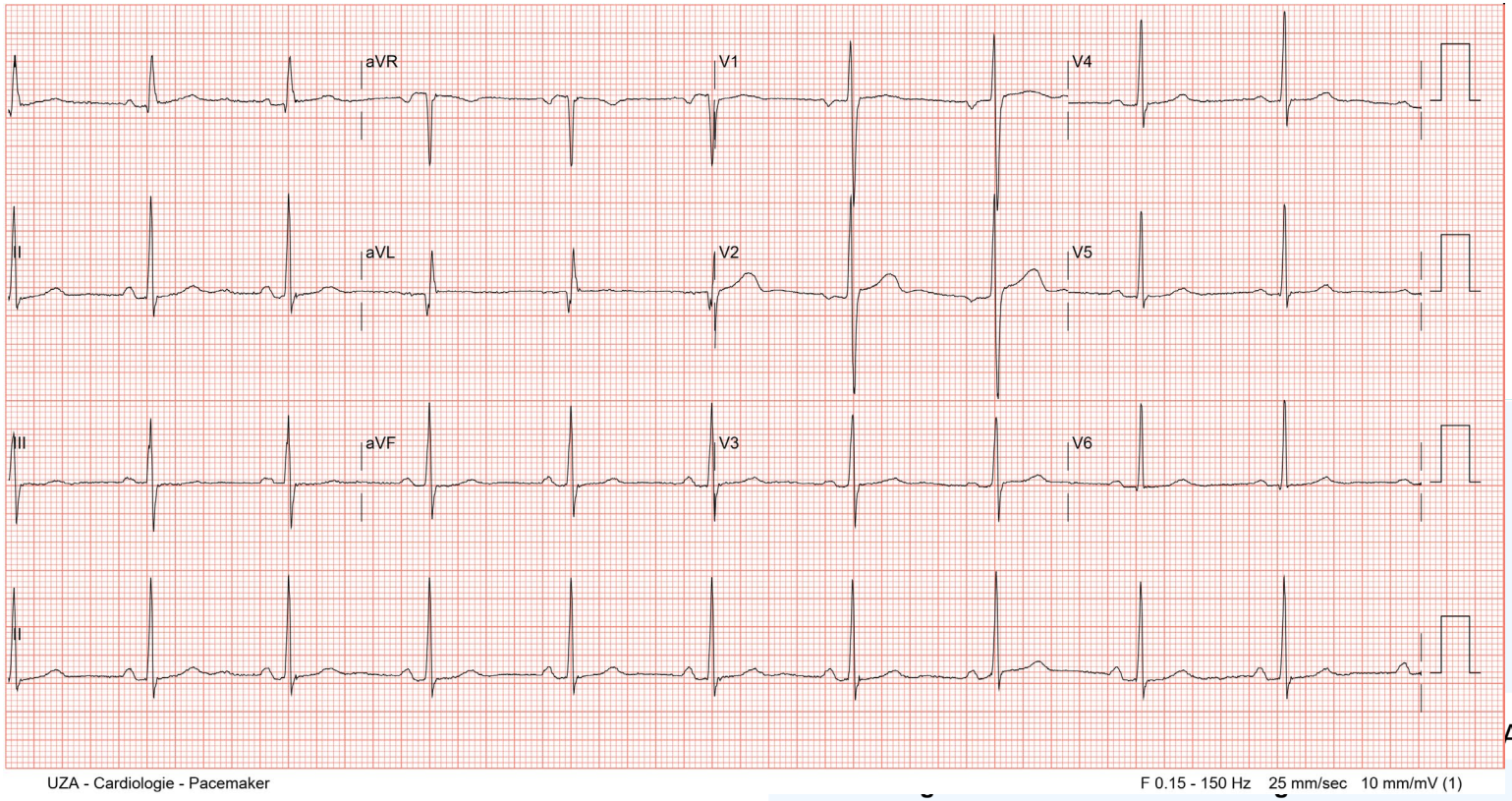
GAIN OF FUNCTION

Multifocal Ectopic Purkinje-Related Premature Contractions

Therapy:

Flecainide 150mg OD despite LVEF = molecular diagnosis tailored

ECG:



Casus: 150210514
Geregistreerd: vr 04 sep 2
Geanalyseerde lengte: 1 dag 31 m
Recordernr.:
Type recorder: Aria
Analysedatum: ma 07 sep
Analysekanalen: 1,2,3 van 3
Analysetechnicus: ,

Aantallen slagen

Aantal	**107.705**
Procent	**100 %**
Max./uur	**5.562** op za 09:00

Aantal	**128**
Procent	**<1%**
Max./uur	**91** op za 08:00

SVE-slagen

Aantal	**3**
Procent	**<1%**
Max./uur	**3** op za 08:00

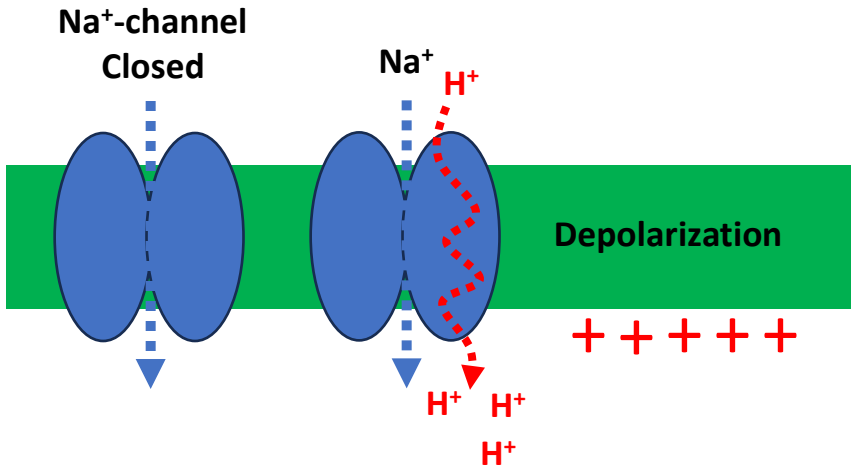
Complete restitution of LV function

Multifocal Ectopic Purkinje-Related Premature Contractions

Leaky Nav1.5 Sodium channel - p.R219H in *SCN5A* (UVCL5)

A Proton Leak Current through the Cardiac Sodium Channel Is Linked to Mixed Arrhythmia and the Dilated Cardiomyopathy Phenotype

Pascal Gosselin-Badaroudine[1], Dagmar I. Keller[2,3,4], Hai Huang[1], Valérie Pouliot[1], Aurélien Chatelier[1¤], Stefan Osswald[3], Marijke Brink[4], Mohamed Chahine[1,5*]



- H⁺/Proton leak through the channel
- Influx of + charges into cell
- Depolarization of the cell
- Above threshold potential for I_{Na+}
- Automaticity
- 'Gain of function'

Gosselin-Badaroudine et al. PLoS One. 2012;7(5):e38331.

Conclusion

Careful assessment

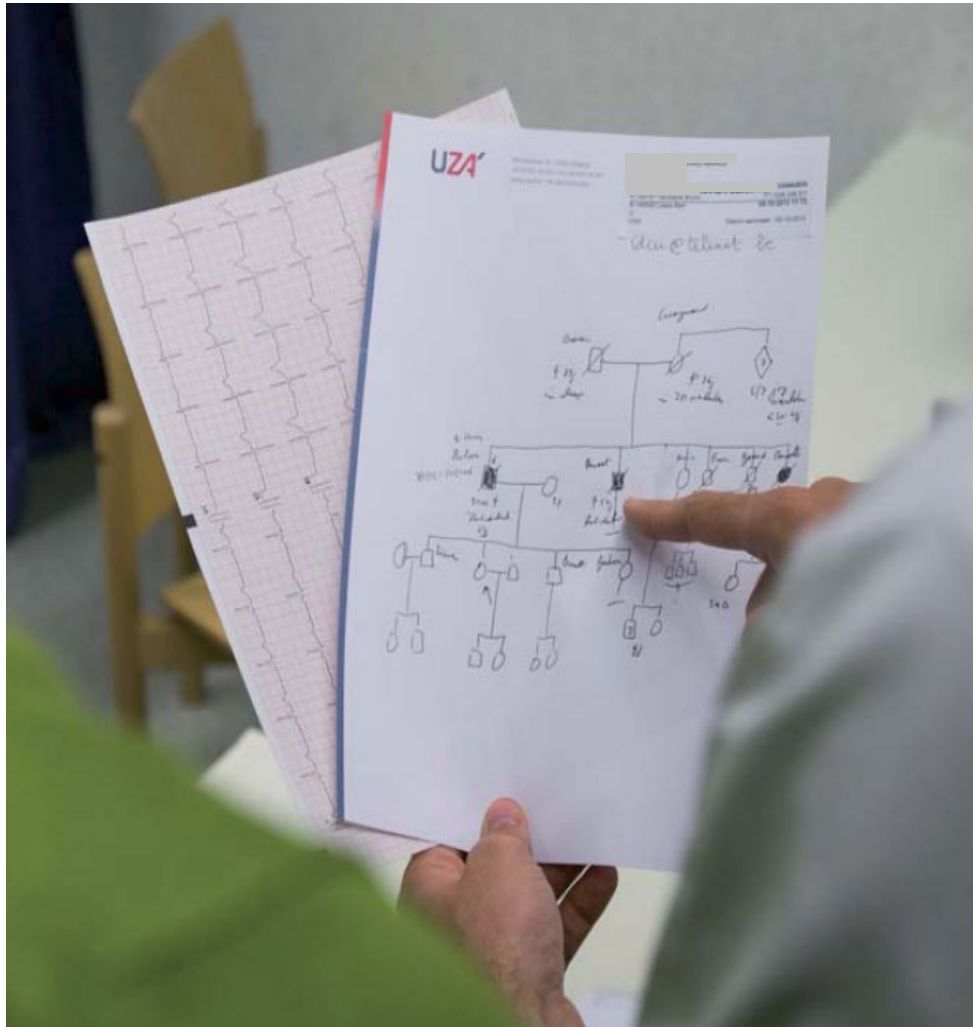
Enable tailored screening & management

Does save lives

Conclusion

Let's solve the puzzle together

Geneticists: 'Know your arrhythmias !'



Cardiologists: 'Know your genetics !'

Thanks for your attention !