Clinical and Genetic Epidemiology Winter School
06.02.2017 –17.02.2017

Personalized Medicine in Cardiology – Rhythmology as an Example

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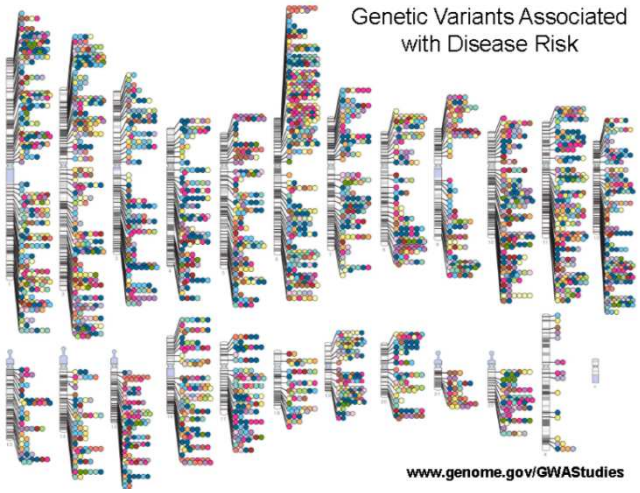
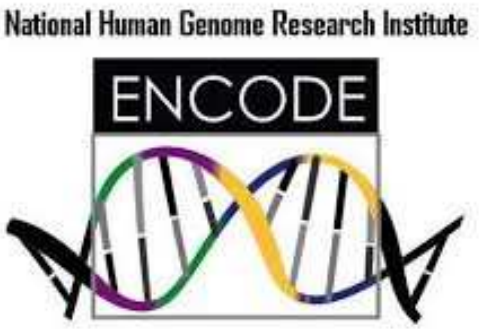
DEUTSCHES ZENTRUM FÜR HERZ-KREISLAUF-FORSCHUNG E.V.

gefördert vom Bundesministerium für Bildung und Forschung

Genome Projects





Genomic Medicine Centers Meeting VI: *Global Leaders in Genomic Medicine* (GM6), January 2014

http://www.genome.gov/27555775

Levels of personalized medicine

1. Biomarker based stratification (group building)
2. Genome based information on disease related traits (including gender medicine)
3. Assessement of individual disease risk
4. Differential therapeutic interventions
5. Unique individualized (private) therapy

essential prerequesite:

standardized detailed patient characteristics

at baseline and during follow-up and outcomes

Potential benefits of personalized medicine

1. Increased diagnostic and prognostic accuracy
2. Increased sensitivity and early (presymptomatic) diagnosis allowing for early treatment options
3. Increased prognostic accuracy (response to therapeutic interventions)
4. Optimized therapeutic strategy
5. Optimized follow-up and adjustments of therapeutic strategy

need for large numbers to demonstrate superiority of personalized medical care vs standard medical care

Cardiac Arrhythmias

substantially contribute to **drug safety** and

to **cardiovascular morbidity** and **mortality**

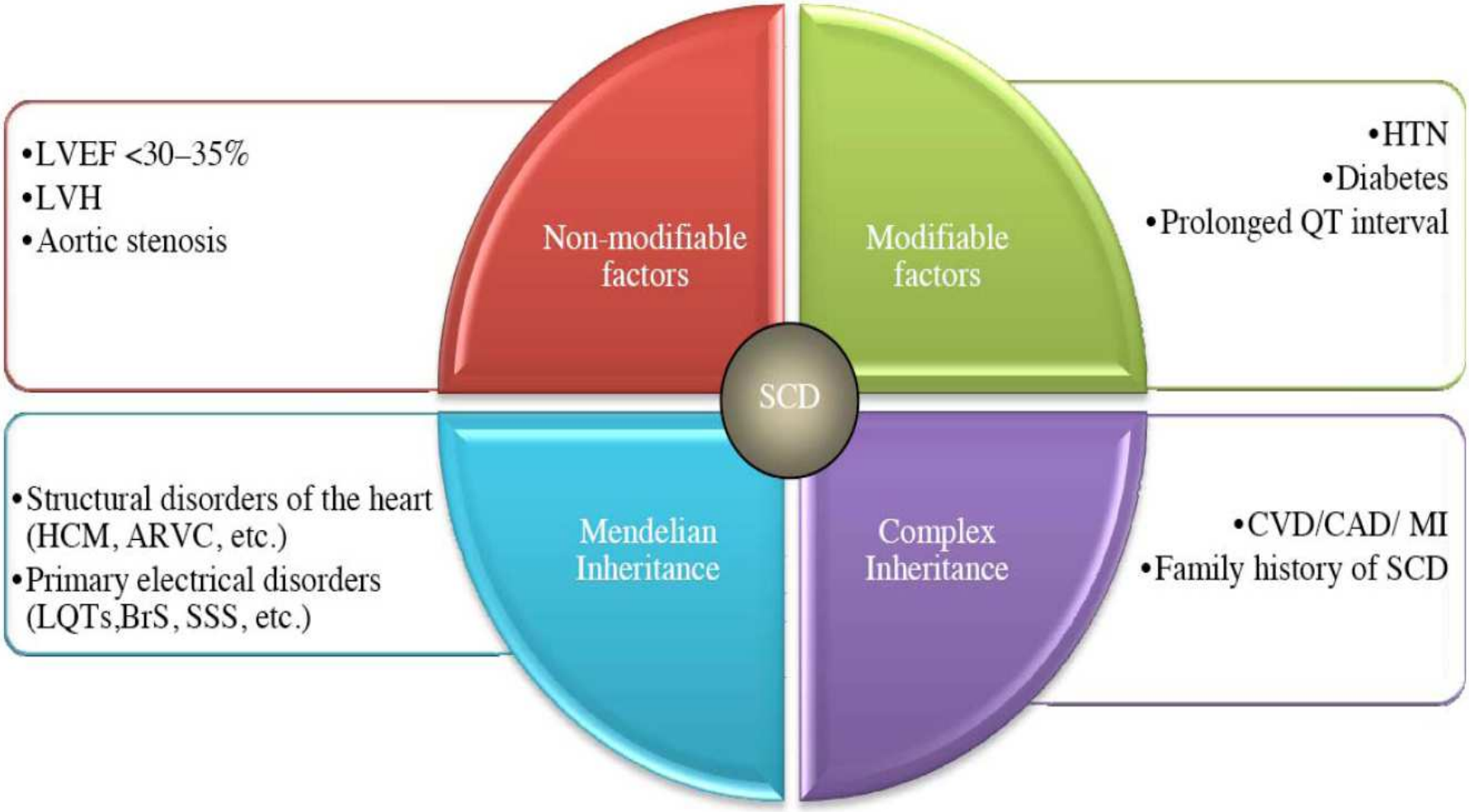
Biomarker assisted risk stratification and therapy in arrhythmias:

- Stratification ideally based on underlying pathophysiology should lead to more efficient therapy

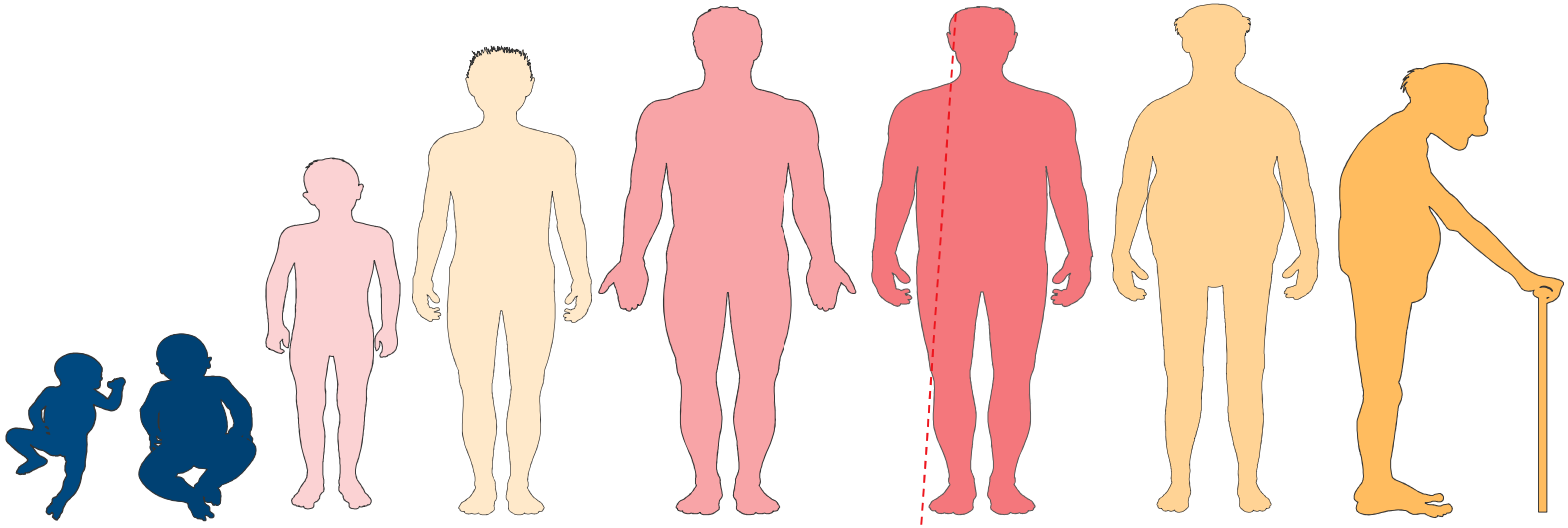
- biomarker are biological markers and signals that enable patient stratification in a qualitative and/or quantitative way (optimal sensitifity/specificity desirable)

- biomarker to optimize risk stratification should demonstrate improved risk reduction, therapy and outcome

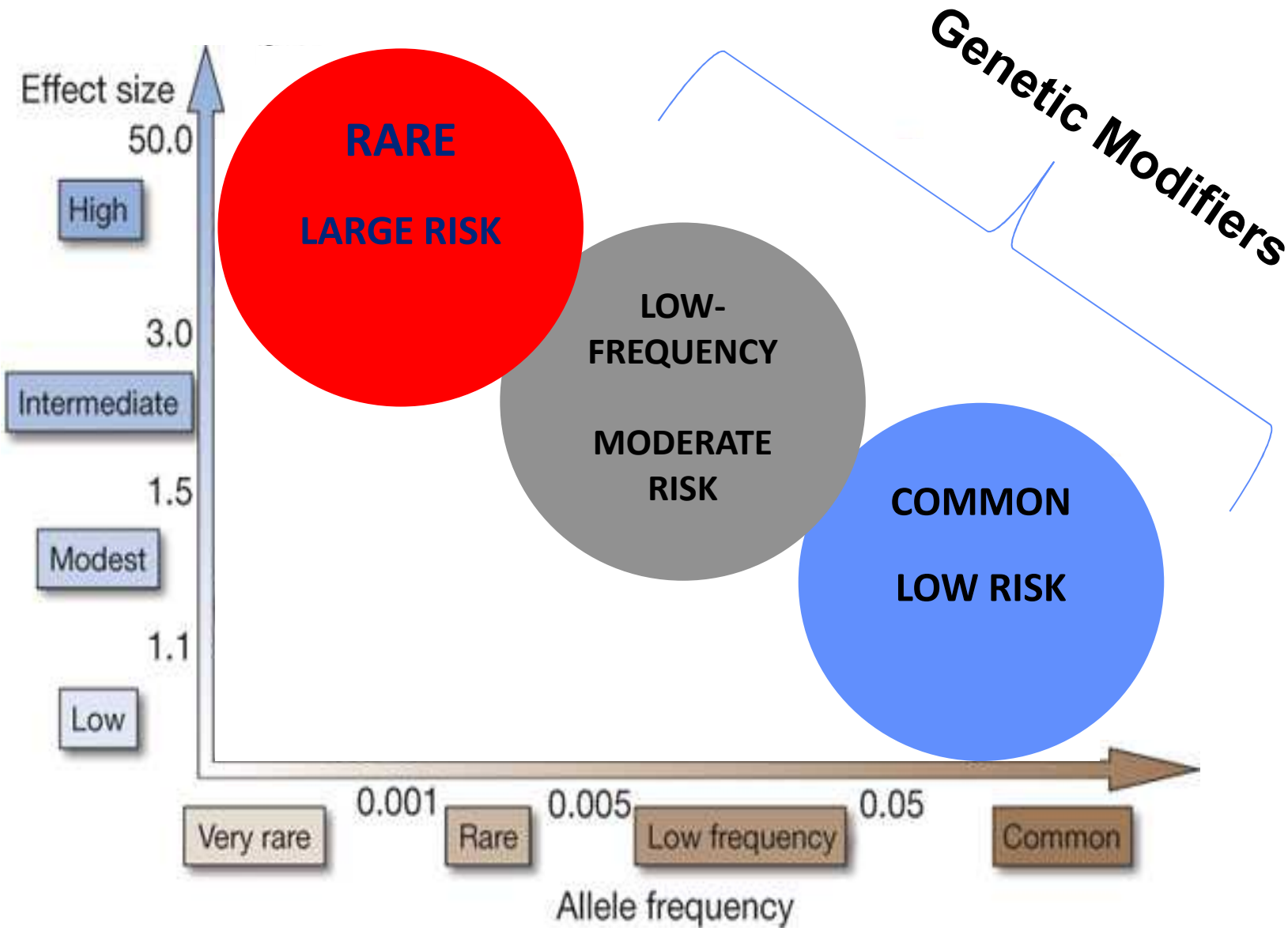
Risk stratification for sudden cardiac death



Genetic and environmental risk factors

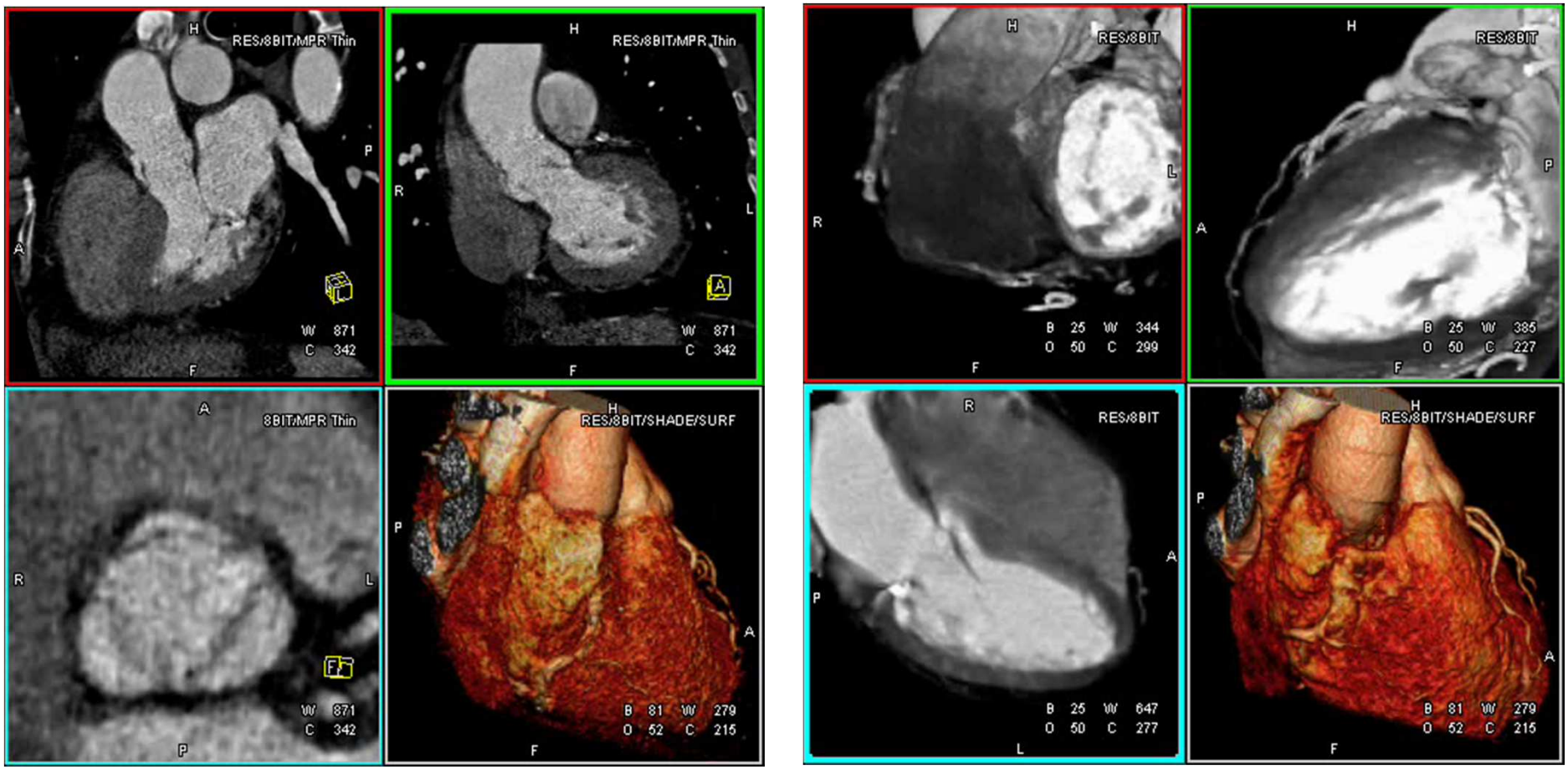


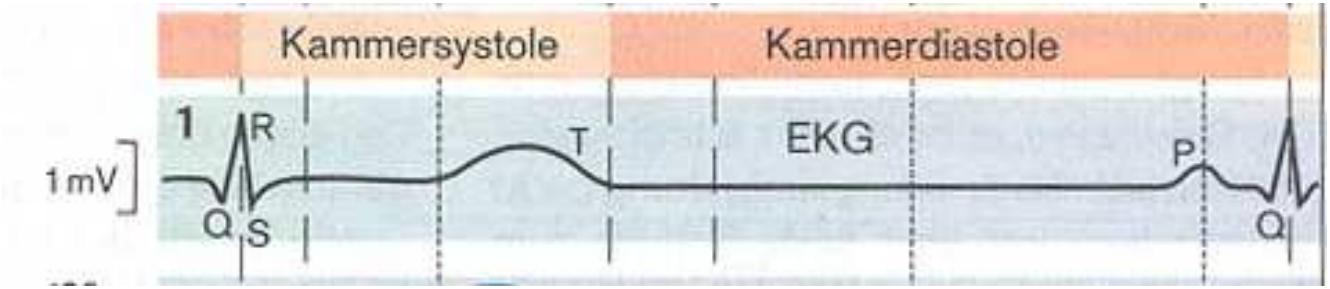
Spectrum of genetic variants that occur in the general population



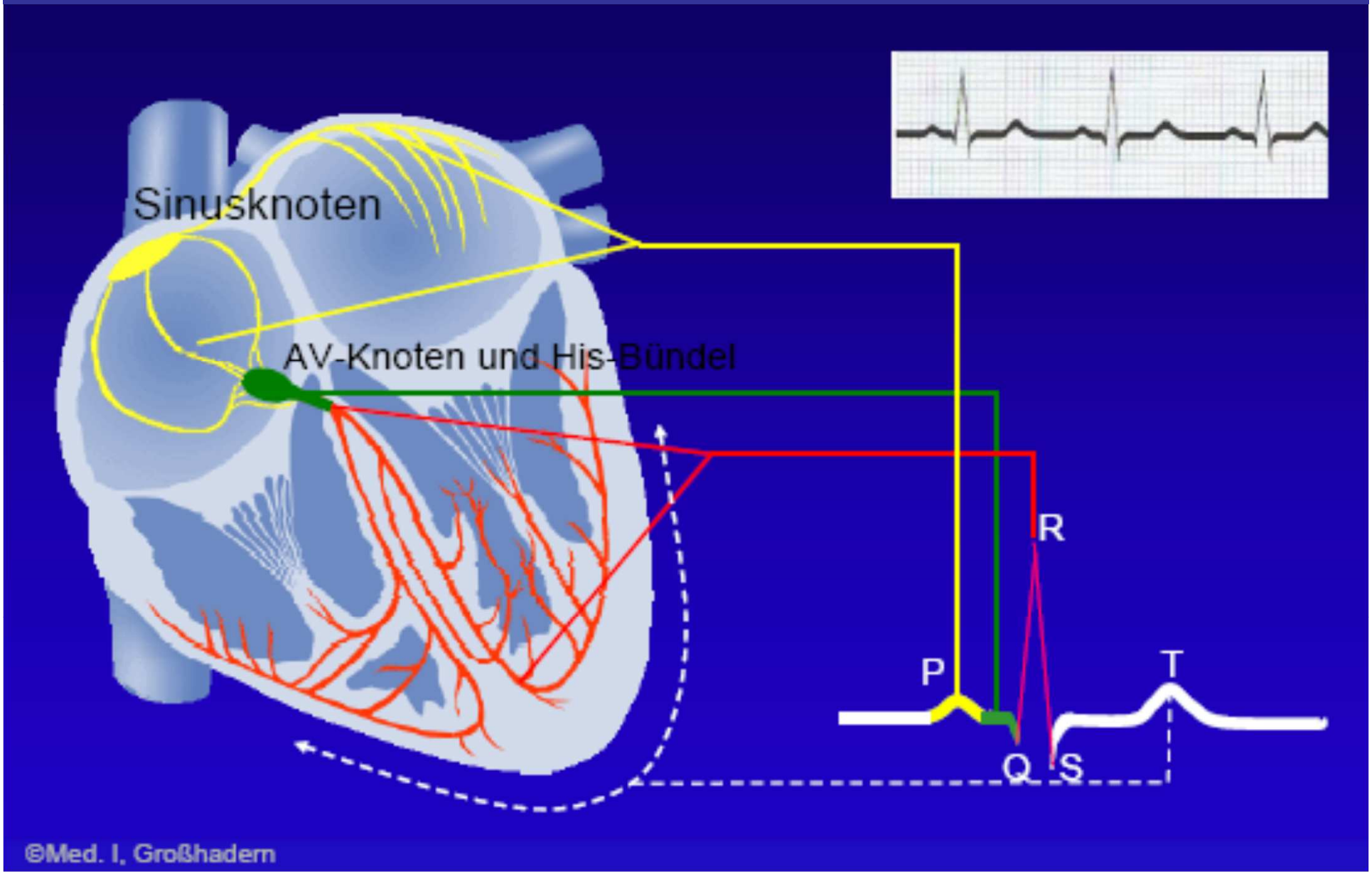
heart beat / cardiac cycle

(electromechanical coupling)





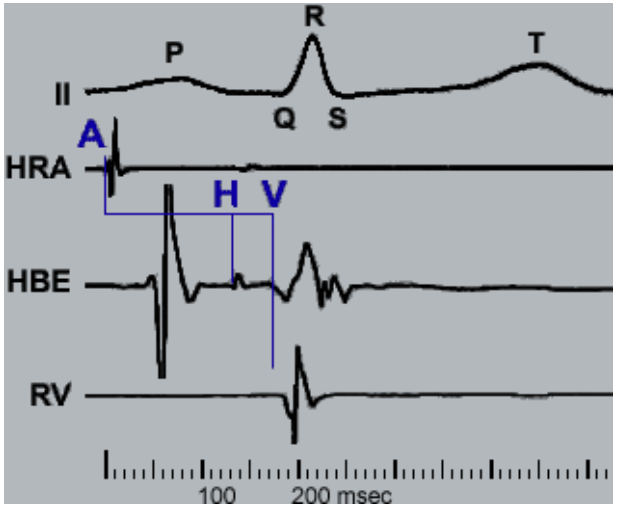
Electrical Impulse Generation and Conduction (Electrocardiogram)

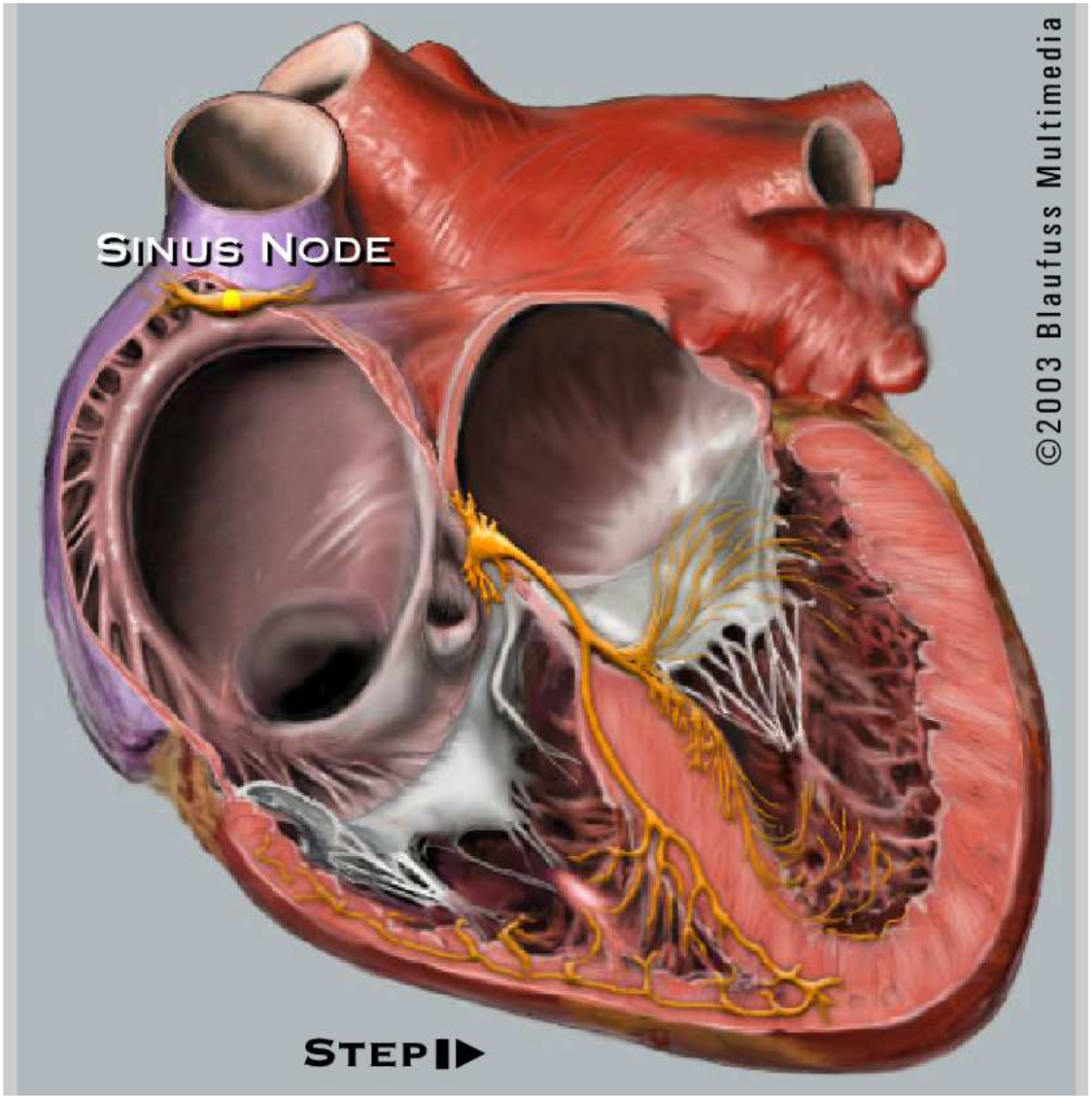


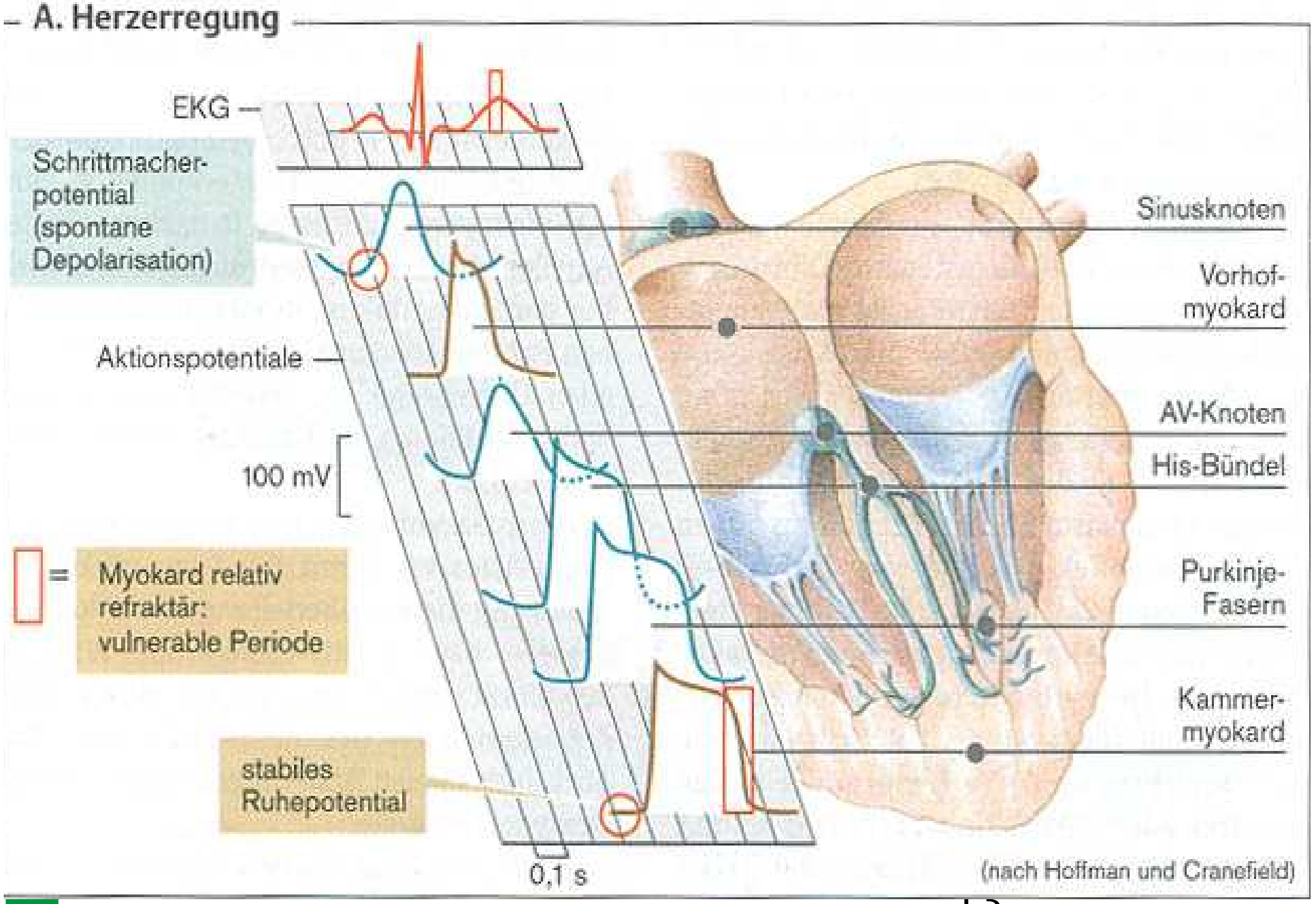
Sinusrhythm

Intrakardiale EKGs

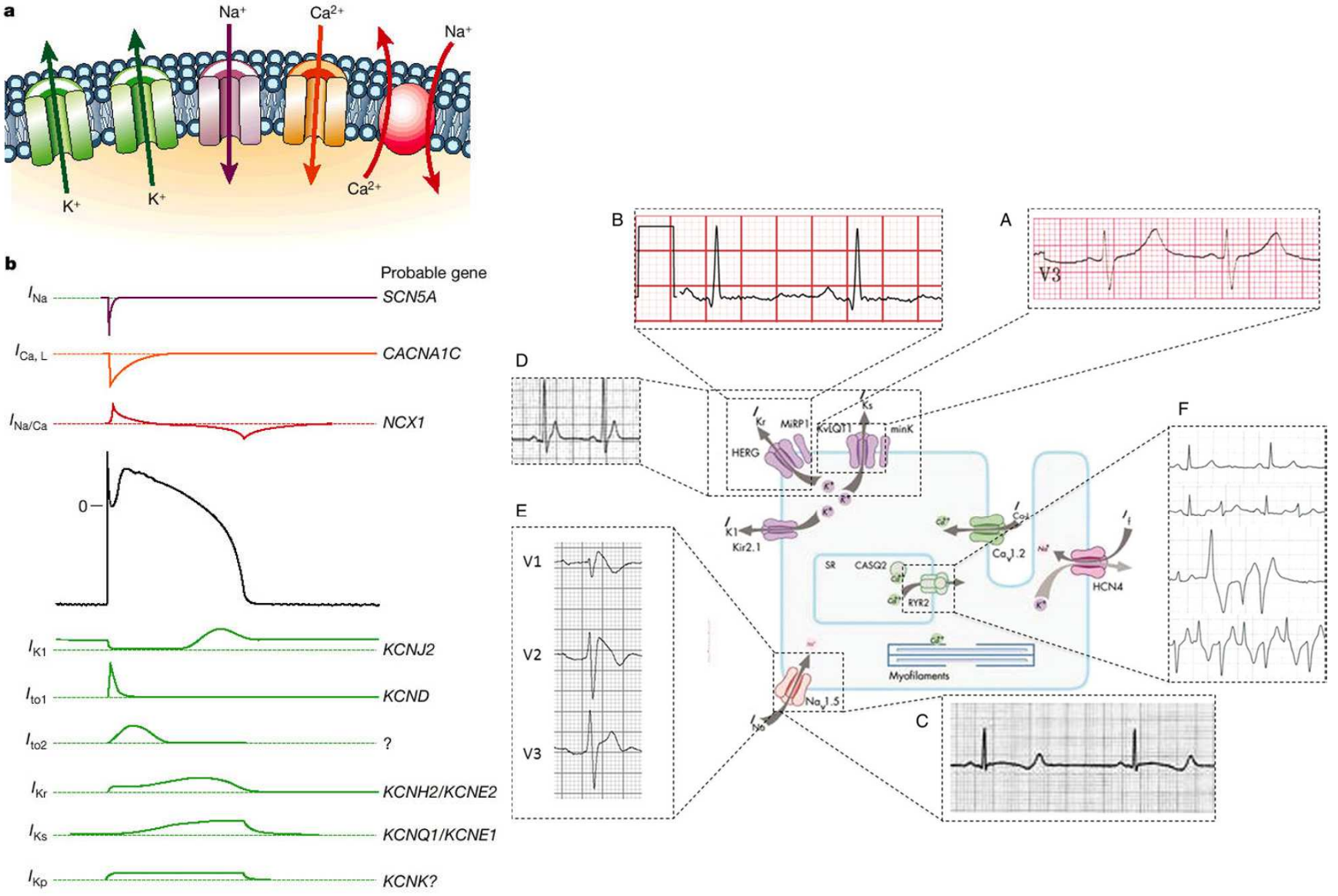
- Beginn der Vorhofdepolarisation **A**
- His Bündel Aktivierung **H**
- ventrikuläre Depolarisation **V**
- **AH + HV = PR** interval





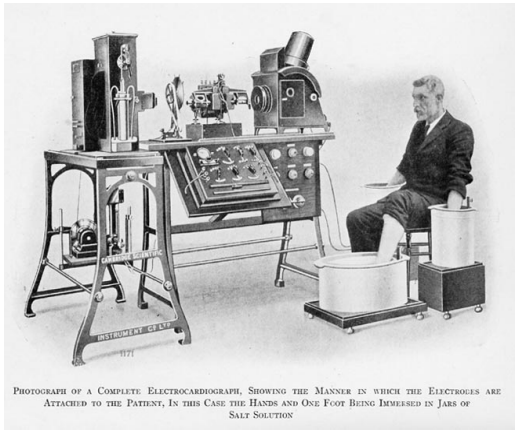

A. Herzerregung
EKG
Schrittmacher-potential (spontane Depolarisation)
Aktionspotentiale
100 mV
= Myokard relativ refraktär: vulnerable Periode
stabiles Ruhepotential
0,1 s
Sinusknoten
Vorhof-myokard
AV-Knoten
His-Bündel
Purkinje-Fasern
Kammer-myokard
(nach Hoffman und Cranefield)

Heterogeneous Genetic and ECG Features of Arrhythmias



Biomarker based personalized medicine in cardiac arrhythmia management: Examples:

- Genomics of ECG signals (focus on QT interval)
- Common genetic variants as modifiers in rare diseases (LQTS)
- Common genetic variants as modifiers in common diseases:
  - serious adverse drug reaction: drug-induced LQTS
  - Sudden Cardiac Death (SCD)



Photograph of a Complete Electrocardiograph, Showing the Manner in which the Electrodes are Attached to the Patient, In this Case the Hands and One Foot Being Immersed in Jars of Salt Solution

Willem Einthoven, ECG 1906

CLINICIAN UPDATE

Electrocardiogram

Still the Cardiologist's Best Friend

Shlomo Stern, MD

Stern S, Circulation 2006; 113:e753-e756

ECG via Smart Phone

Rhythm detection (AF) („mydiagnostick“)

ECG-signals are quantitative and qualitative markers of myocardial electrical properties

quantitative

RR-interval: sinus node function

PR-interval: atrial conduction

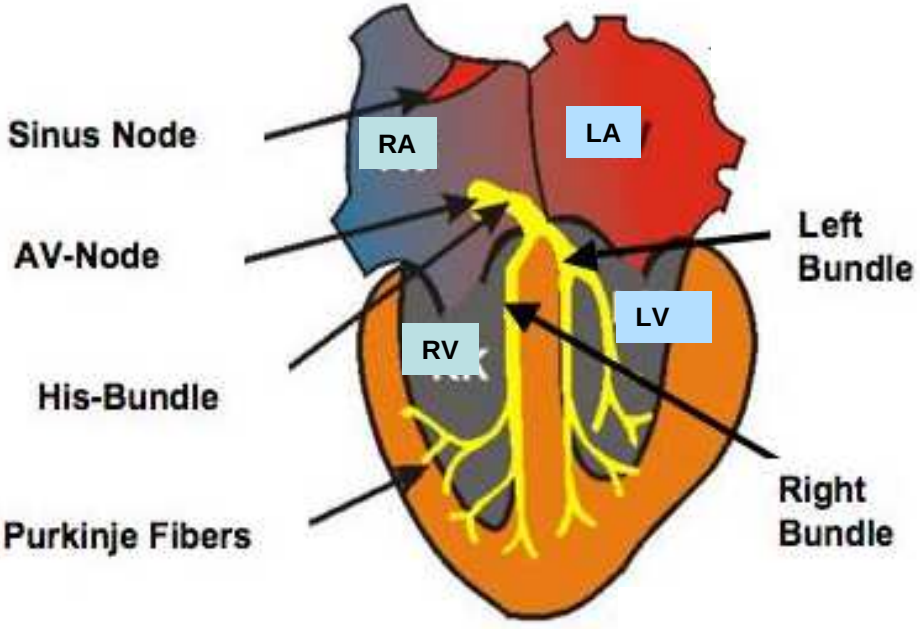
QRS-interval: ventricular conduction

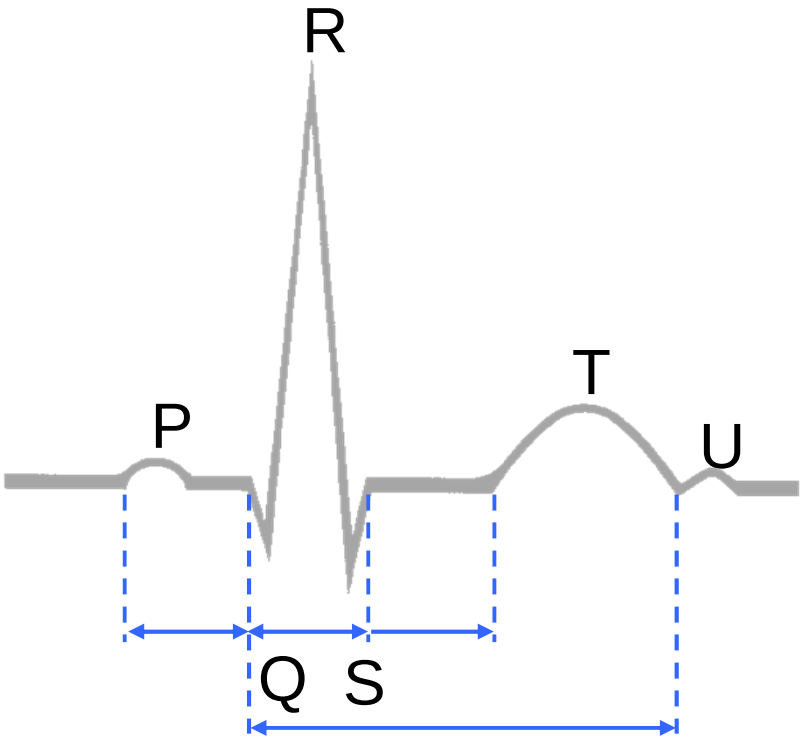
QT-interval: ventricular repolarization

qualitative

sinus rhythm + / -

early repolarization pattern

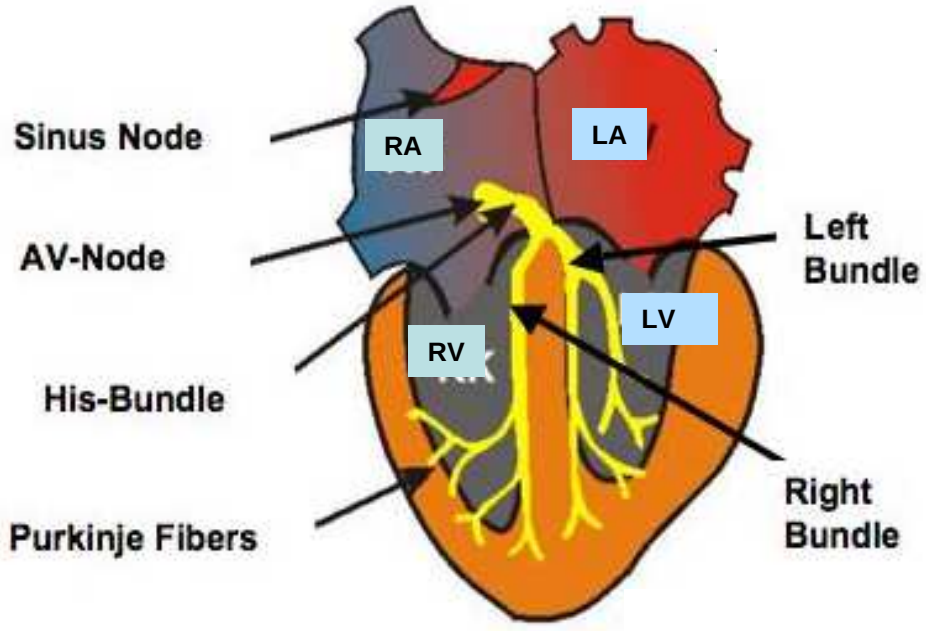


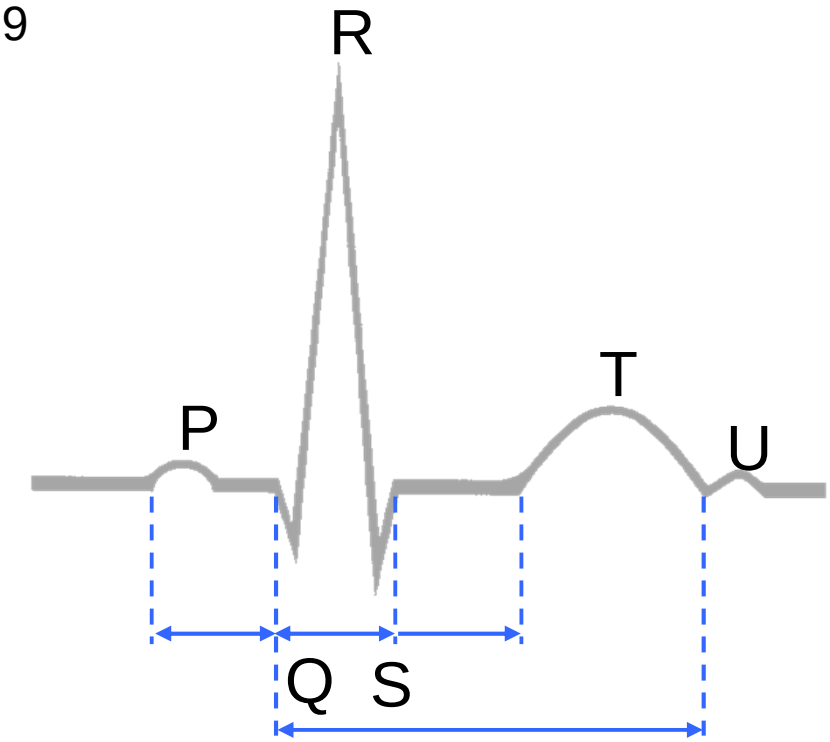


ECG-signals are heritable traits (1)

	Model 1		Model 2					Model 3			
	h^2 (SD)	P	h^2 (SD)	P	Δh^2*	$P_{\Delta h^2}$	n SNPs REFS	h^2 (SD)	P	Δh^2**	$P_{\Delta h^2}$
QRS	0.34 (0.06)	2.32×10^{-9}	0.28 (0.06)	1.30×10^{-6}	0.06	2.6×10^{-3}	21[a, b]	0.27 (0.07)	1.06×10^{-5}	0.01	0.28
QT	0.36 (0.07)	1.14×10^{-8}	0.34 (0.07)	1.00×10^{-7}	0.02	2.5×10^{-4}	36[a, c–f]	0.29 (0.07)	1.17×10^{-5}	0.05	0.15
PR	0.40 (0.06)	4.13×10^{-11}	0.39 (0.06)	1.31×10^{-10}	0.01	2.6×10^{-4}	9[a, g, h]	0.37 (0.07)	5.06×10^{-9}	0.02	1.0×10^{-3}
12LS	0.49 (0.06)	4.60×10^{-16}	0.46 (0.06)	1.44×10^{-14}	0.03	5.7×10^{-3}	23[b, i]	0.44 (0.07)	3.71×10^{-12}	0.02	0.15
CV	0.34 (0.07)	7.44×10^{-9}	0.35 (0.07)	5.20×10^{-9}	−0.002	6.3×10^{-5}	21[b]	0.35 (0.07)	1.13×10^{-8}	−0.005	0.17
SL	0.46 (0.07)	1.00×10^{-13}	0.44 (0.07)	2.74×10^{-12}	0.02	0.42	21[b]	0.43 (0.07)	6.76×10^{-11}	0.01	0.14

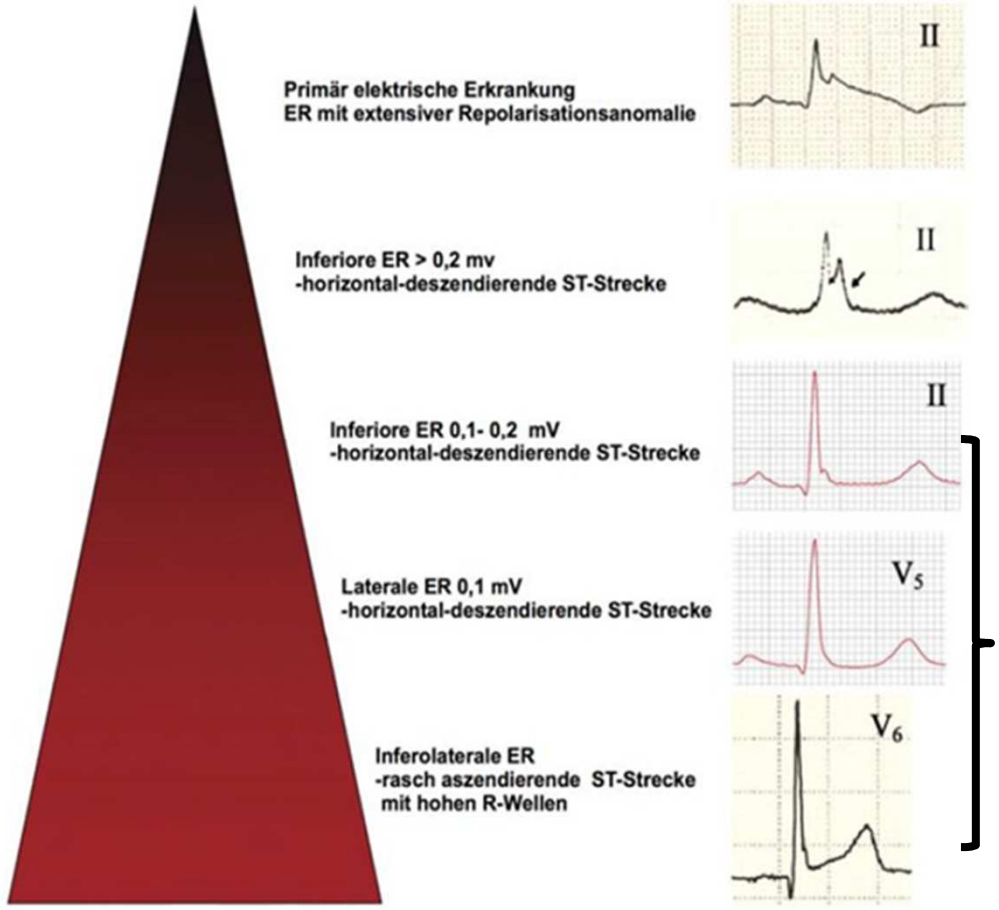
Silva CT, et al. Hum Gen (2015) 134:1211-1219





ECG-signals are heritable traits (2a)

Early Repolarization Pattern



risk for affected 1st degree family member

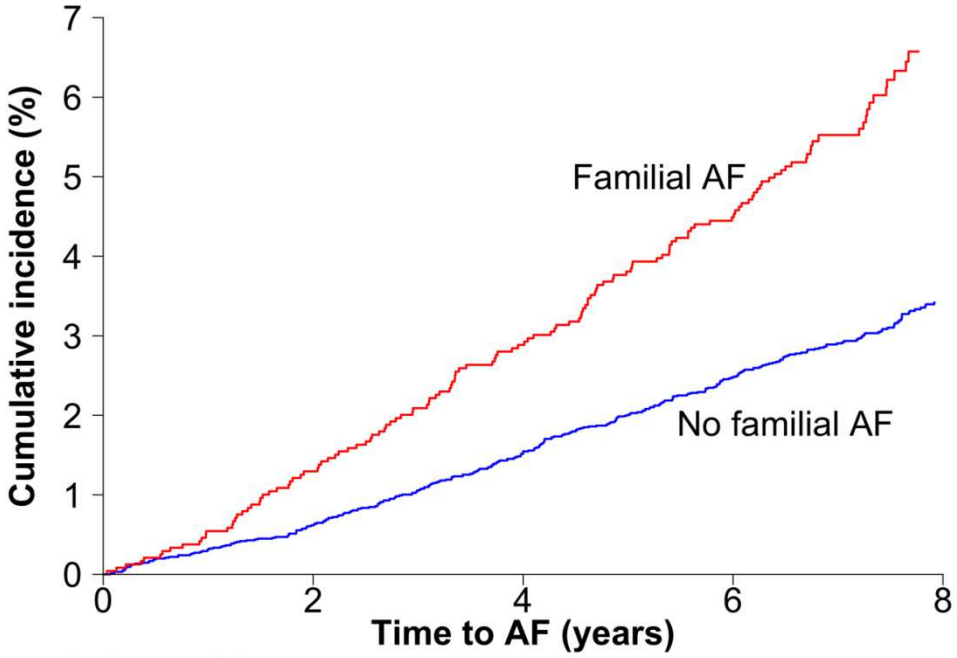
OR : 2.0-2.5

Noseworthy PA, et al.JACC 2011
Reinhard W, et al. Circ Cardiovasc Genet 2011

ECG-signals are heritable traits (2b)

AF

Framingham Heart Study



Lubitz et al JAMA 2010; 304:2263-9.

Danish twins

- Concordance rate 22 v 12%
- Heritability 62%

Iceland

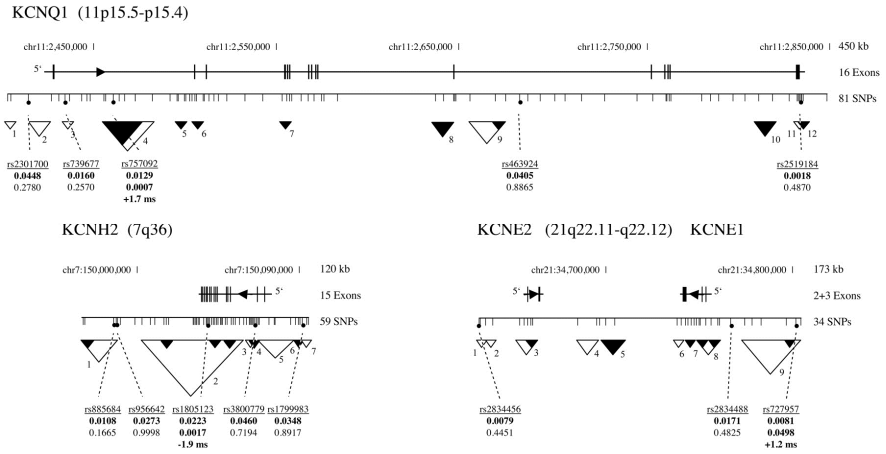
- AF in 1° relative RR 1.77

Early-onset AF

- Familial clustering
- 1° relative of those w AF have 5x greater risk

Common Variants in Myocardial Ion Channel Genes Modify the QT Interval in the General Population (screening sample: n=689, replication sample: n=3277)

Genomic structure, LD-structure, and genotyped SNPs (n=174)



Multi allelic risk score based on 5 SNPs Reaching significant replication

QT-Prolongation Score	QTc RAS±SD	From Total Sample (n=3966), n
0	412.7±13.4	79
1	415.5±16.9	462
2	416.6±16.9	1021
3	418.3±17.8	1132
4	419.3±16.9	641
5	423.2±19.4	135

multiallelic risk score: 10 ms QTc

Arne Pfeufer et al. Circulation Research. 2005;96:693-701

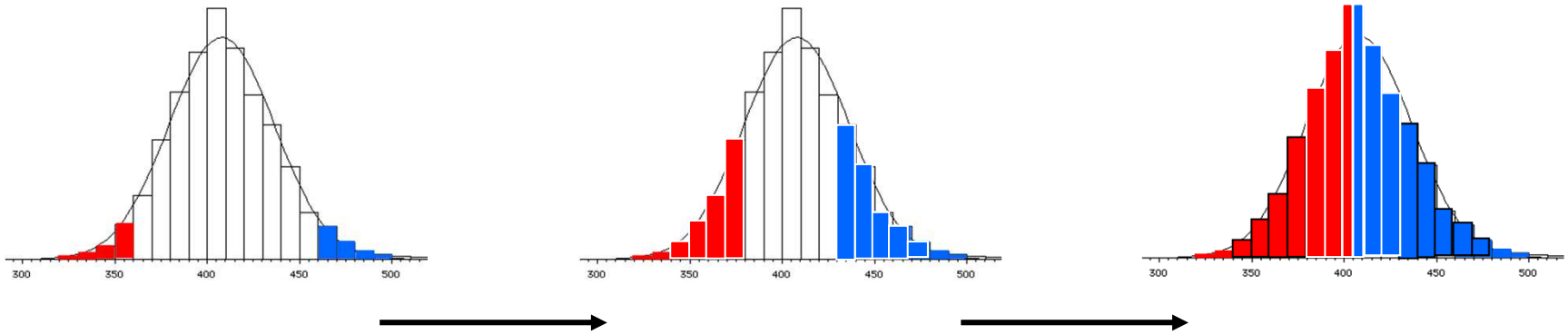
GWA of QT interval in the General Population (KORA) using 100K SNP Chip

Three stage design:

Stage 1
• n=103/103 from each extreme (top and bottom 7.5th %tile)
• strict exclusion criteria
• females only
• Genomewide genotyping

Stage 2
• n=300/300 from each extreme
• relaxed exclusion criteria (s AF,pacer, pregnancy)
• females only
• SNPs that passed stage 1

Stage 3
• n=3,966, KORA S4 survey
• relaxed exclusion criteria (s AF,pacer, pregnancy)
• both genders
• SNPs that passed stage 2



NOS1AP (Capon) modulates QT interval by 5-10 ms (1,5% var.)

Arking, Pfeufer et al., Nat. Genet 2006;38:644-651

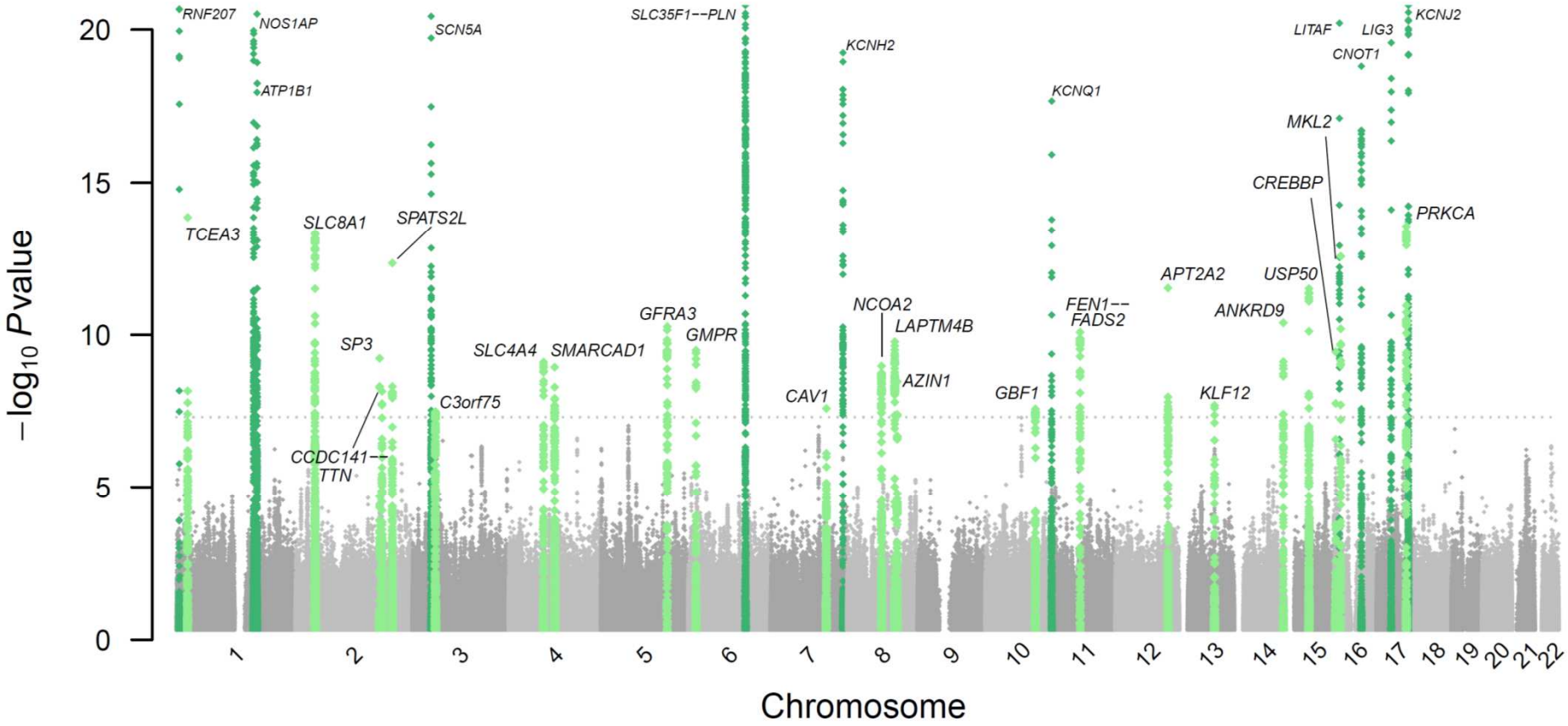
GWAS for QT-Interval

highlights role of Ca2+ signaling pathways

68 independent SNPS at 35 loci (22 new loci)

explaining 8-10% of QT-interval variance

***n* = 76,198**



Arking DE, (n=233), Newton-Cheh C, Nat Genet 2014

meta-analysis
QTGEN+QTSCD
n = 29,539

14 independent variants
10 loci
p<5E -08

SNP	Function/gene	Allele frequency	Effect Estimate (msec)	P-value
rs12143842	upstream *NOS1AP*	0.26	3.2	2E -78
rs12029454	intron *NOS1AP*	0.15	3.0	3E -45
rs16857031	intron *NOS1AP*	0.14	2.6	1E -34
rs2074238	intron *KCNQ1*	0.06	-7.9	3E -17
rs37062	intron *CNOT1*	0.24	-1.8	3E -25
rs11756438	near PLN	0.47	1.4	5E -22
rs12576239	intron *KCNQ1*	0.13	1.8	1E -15
rs846111	3' UTR *RNF207*	0.28	1.8	1E -16
rs4725982	downstream *KCNH2*	0.22	1.6	5E -16
rs8049607	upstream *LITAF*	0.49	1.2	5E -15
rs1805128	missense *KCNE1* (D85N)	0.010	8.4	2E -8
rs12053903	intron *SCN5A*	0.34	-1.2	1E -14
rs2074518	intron *LIG3*	0.46	-1.1	6E -12
rs2968864	downstream *KCNH2*	0.25	-1.4	8E -16

Newton-Cheh et al, Nature Genetics 09
Pfeufer et al Nature Genetics 09
courtesy Chris Newton-Cheh

Nitric Oxide Synthase 1 Adaptor Protein (NOS1AP)

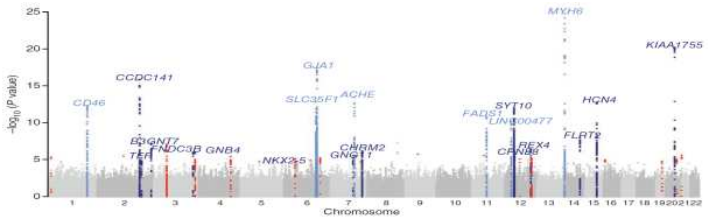
- NOS1AP when overexpressed in cardiac myocytes results in action potential shortening ($I_{Ca\text{-}L\text{-}type}\downarrow$, $I_{Kr}\uparrow$) (Chang et al. PNAS 2008;105:4477-4482)
- Common variants in NOS1AP are associated with QT interval and SCD (ARIC, CHS) OR 1.3 (95%CI 1.10-1.56, p<0.002) (Kao*, Arking*, Post*, et al. Circulation 2009;119:940-951)
- Common variants in NOS1AP are not associated with SCD (208 cases of SCD, 109

Association > Causation

- Common variants in CASQ2, GPD1L, and NOS1AP are significantly associated with risk of sudden death in patients with coronary artery disease (Westaway et al. Circ Cardiovasc Genet 2011;4(4):397-402)
- Common Variation in the *NOS1AP* Gene Is Associated With Drug-Induced QT Prolongation and Ventricular Arrhythmia (Jamshidi et al J Am Coll Cardiol 2012; 60(9):841-50

GWAS reveal genetic variants modulating ECG-signals

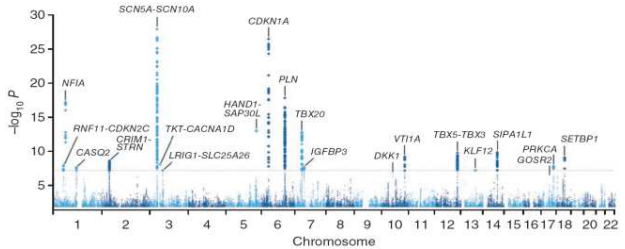
RR interval



Eijgelsheim M, et al. Hum Mol Genet. 2010

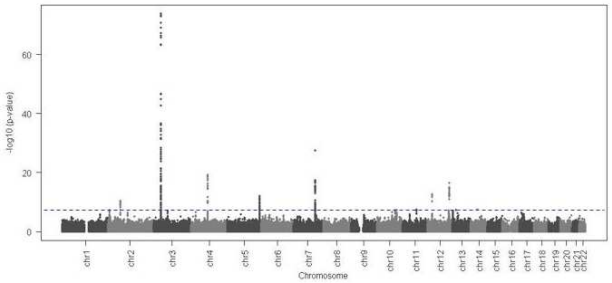
den Hoed et. al, Nature Genetics 2013

QRS interval



Satoodehnia N, et al. Nat Genet. 2010

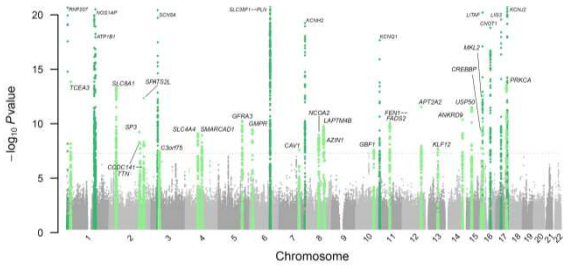
PR interval



Pfeufer et. al, Nature Genetics 2010

Holm et. al, Nature Genetics 2010

QT interval



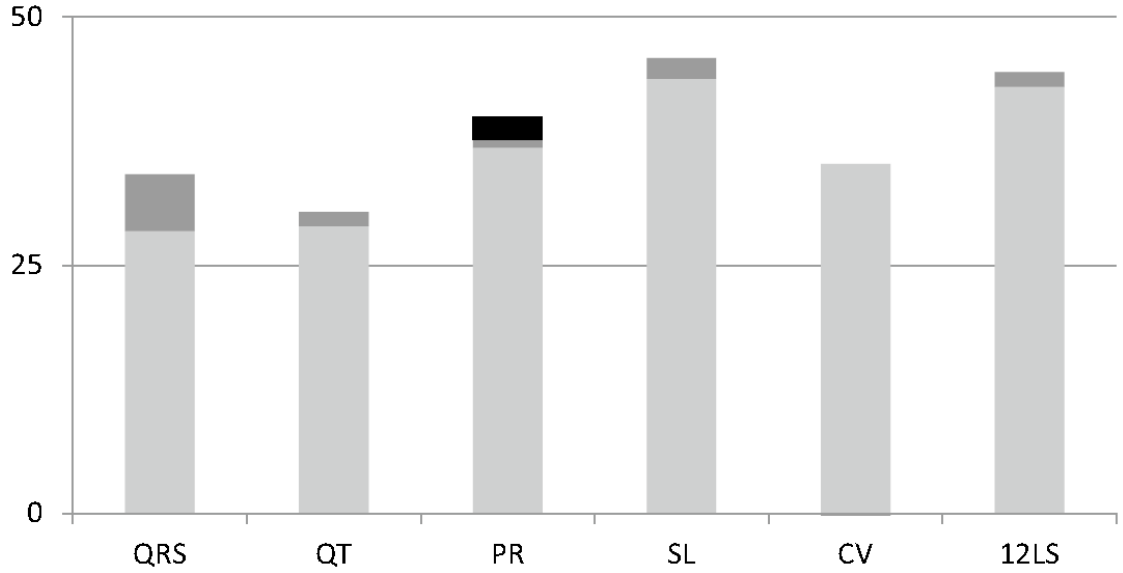
Arking D, Pfeufer A, et al. Nat Genet. 2006

Pfeufer A*, et al. Nat Genet 2009

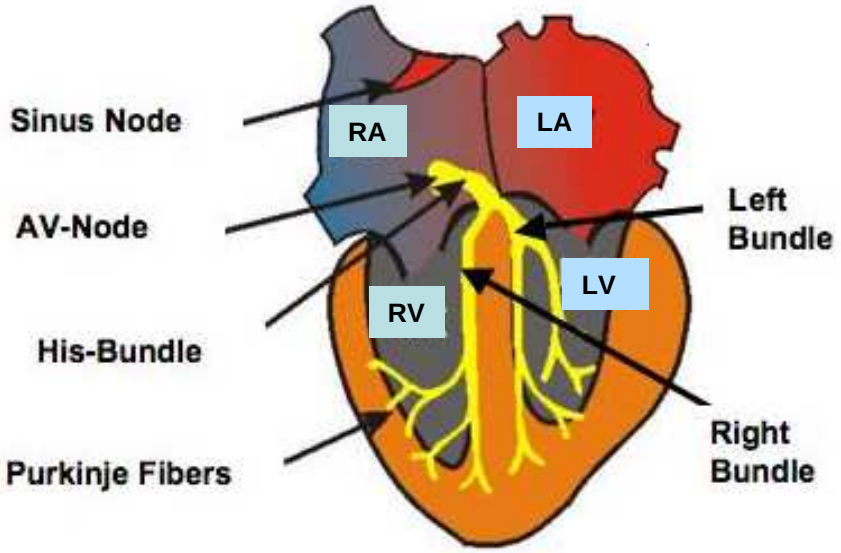
Newton-Cheh C, et al. Nat Genet 2009

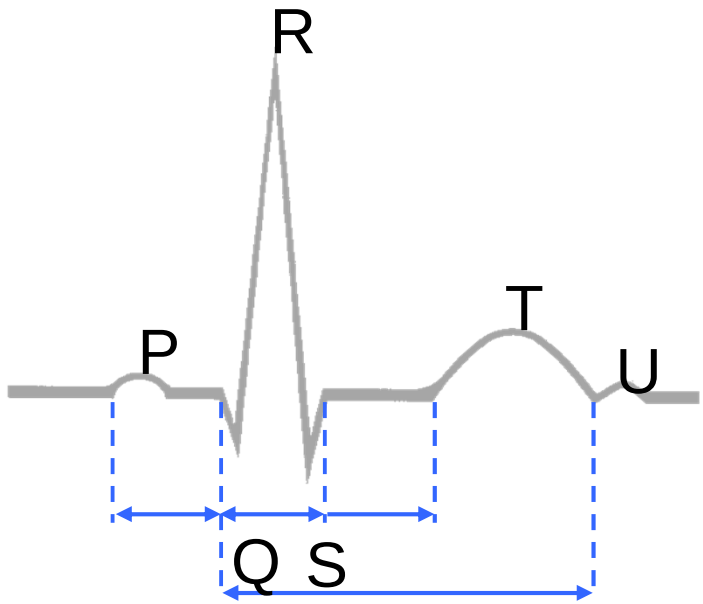
Arking DE, et al. Nat Genet 2014

ECG-signals: Missing heritability



Silva CT, et al. Hum Gen (2015) 134:1211-1219





Biomarker based personalized medicine in cardiac arrhythmia management: Examples:

- Genomics of ECG signals (focus on QT interval)
- Common genetic variants as modifiers in rare diseases (LQTS)
- Common genetic variants as modifiers in common diseases:
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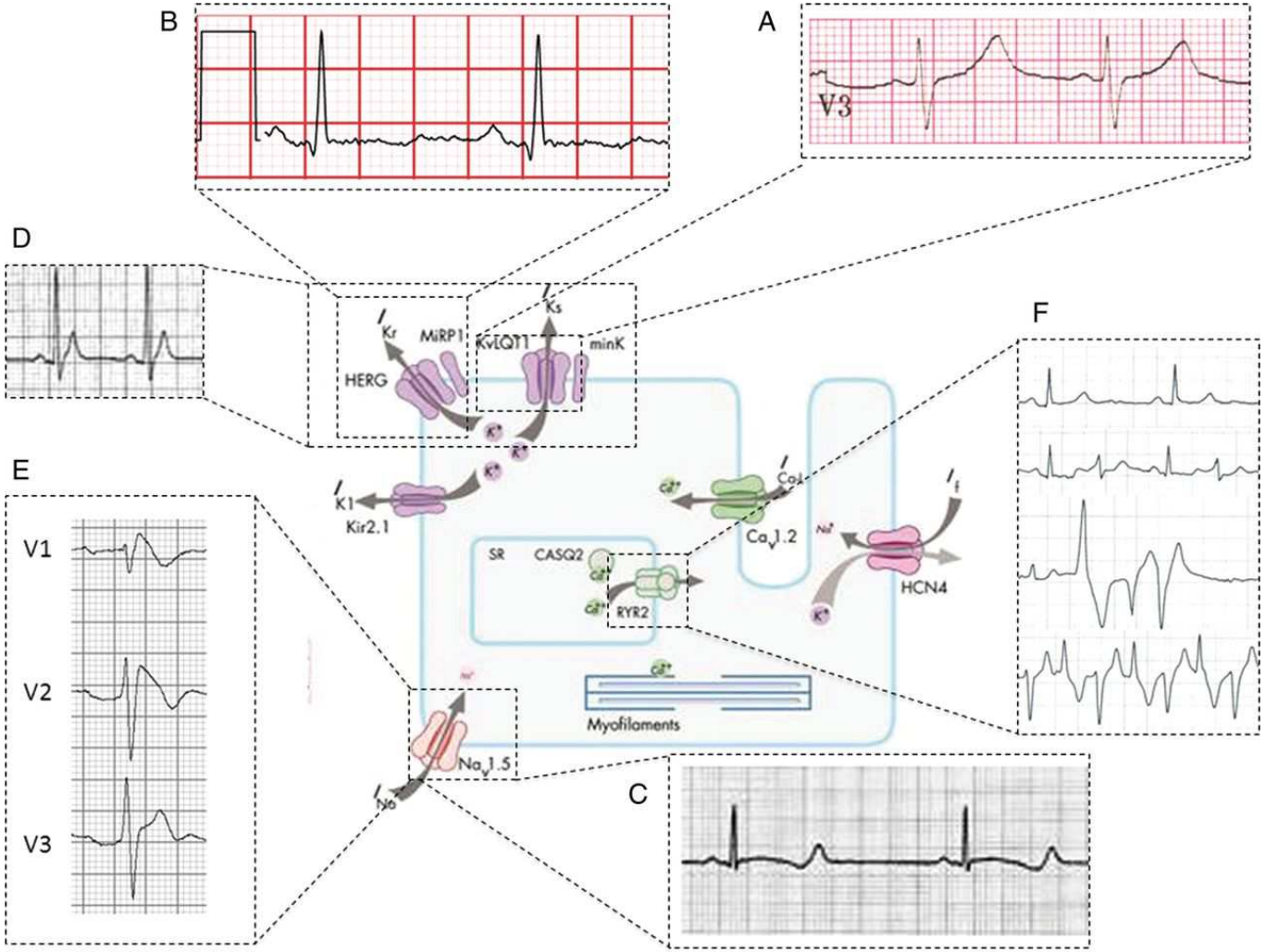
  - Sudden Cardiac Death (SCD)

Characteristic ECGs of the various cardiac channelopathies.



Krystien V.V. Lieve, and Arthur A.M. Wilde Europace 2015;17:ii1-ii6

Diagnosis and Grading the Risk of LQT

	Points
Electrocardiographic findings[a]	
A	
QTc[b]	
≥480 ms	3
460–479 ms	2
450–459 ms (in males)	1
B	
QTc[b] fourth minute of recovery from exercise stress test ≥480 ms	1
C	
Torsades de pointes[c]	2
D	
T wave alternans	1
E	
Notched T wave in three leads	1
F	
Low heart rate for age[d]	0.5
Clinical history	
A	
Syncope[c]	
With stress	2
Without stress	1
B	
Congenital deafness 0.5	0.5
Family history	
A	
Family members with definite LQTS[e]	1
B	
Unexplained SCD below age 30 among immediate family members[e]	0.5

Score: ≤1 point: low probability of LQTS; 1.5–3 points: intermediate probability of LQTS; ≥3.5 points: high probability.
[a]In the absence of medications or disorders known to affect these electrocardiographic features.
[b]QTc calculated by Bazett's formula where QTcQT/RR.
[c]Mutually exclusive.
[d]Resting heart rate below the second percentile for age.
[e]The same family member cannot be counted in A and B.

Lieve KVV and Wilde AAM ,

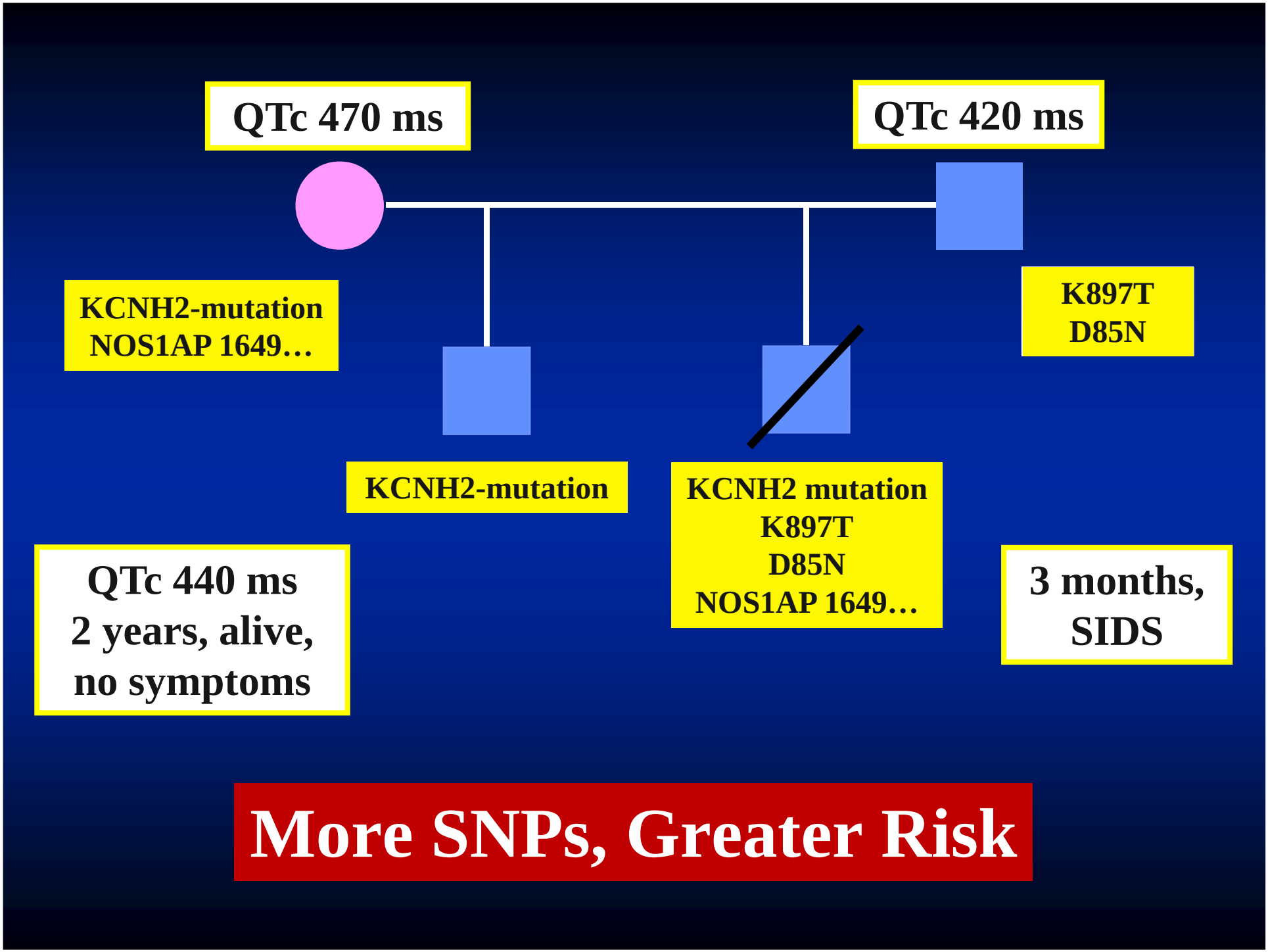
Europace 2015;17:ii1-ii6

Familial Arrhythmia Syndromes:
– Biomarker for Family Screening
- Biomarker für Risk Stratification and Therapeutic Decisions

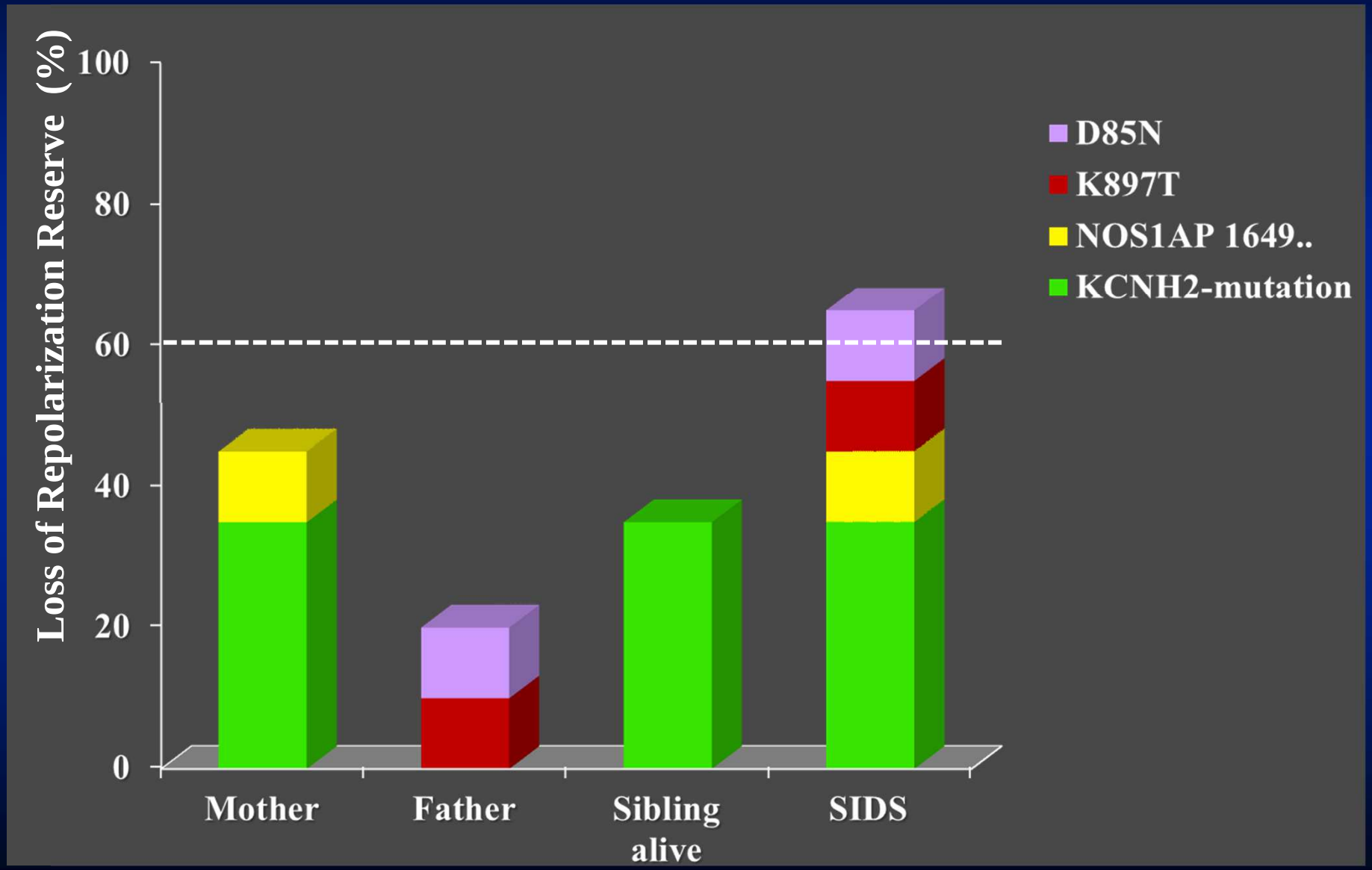
Genetically tested index patients and relatives with an inherited arrhythmia symdrome

Clinical diagnosis	Index genetically tested	Index with mutation	Relatives genetically testet	Relatives genetically affected	Relatives genetically not affected
LQTS	300	**162 (54%)**	420	**218**	202
BrS	30	**8 (27%)**	17	**10**	7
CPVT	21	**13 (62%)**	82	**19**	63
Fam. DCM	55	**18 (33%)**	39	**19**	20
ARVC	31	**19 (61%)**	68	**40**	24
HCM	101	**52 (51%)**	61	**26**	35
sum	538	**272 (51%)**	683	**332**	351

Beckmann BM and Kääb S,
LMU Spezialambulanz Familiäre Arrhythmiesyndrome 06/2015


QTc 470 ms
QTc 420 ms
KCNH2-mutation
NOS1AP 1649…
K897T
D85N
KCNH2-mutation
KCNH2 mutation
K897T
D85N
NOS1AP 1649…
QTc 440 ms
2 years, alive,
no symptoms
3 months,
SIDS
More SNPs, Greater Risk

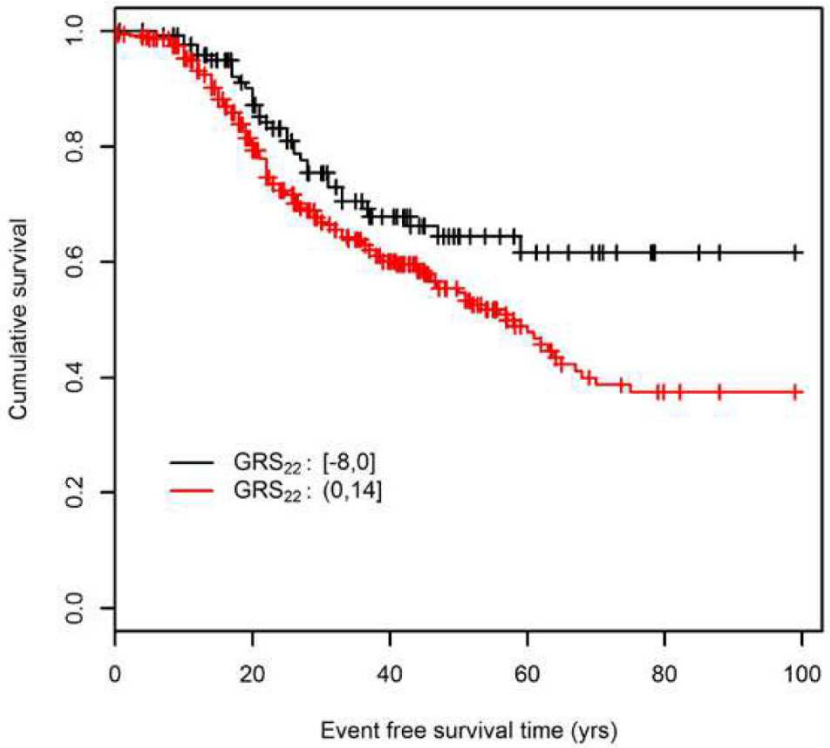
More SNPs, Greater Risk

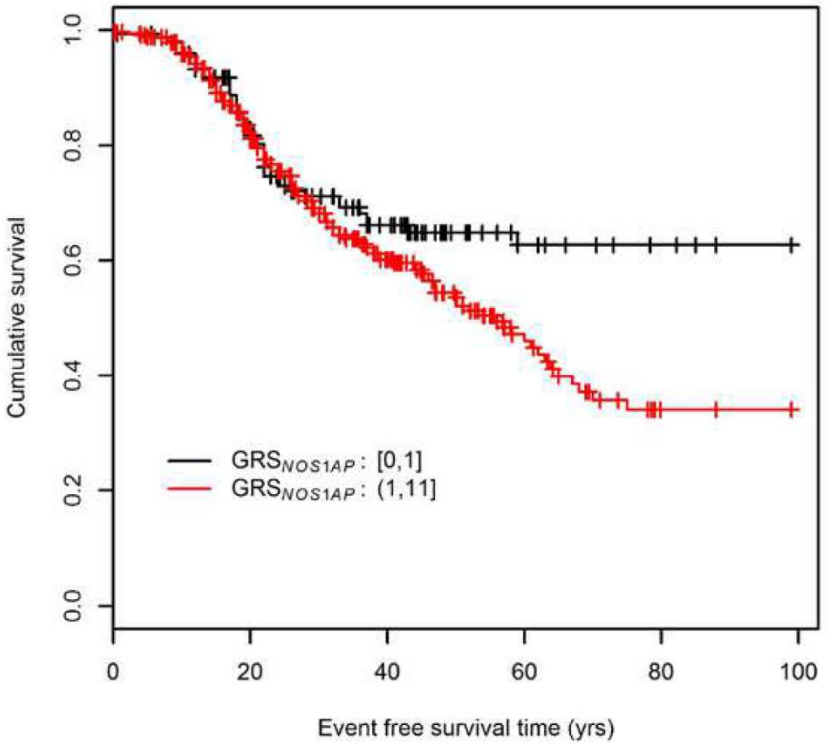


Genetic Modifiers for Disease Severity in LQT2

KCNH2 mutation carriers: n=639 (LQT2)

1201 common genetic variants in 18 candidate genes
22 common genetic variants that modulate QTc (GWAS results)





Kolder ICRM, et al. Circ Genetics 2015

Biomarker based personalized medicine in cardiac arrhythmia management: Examples:

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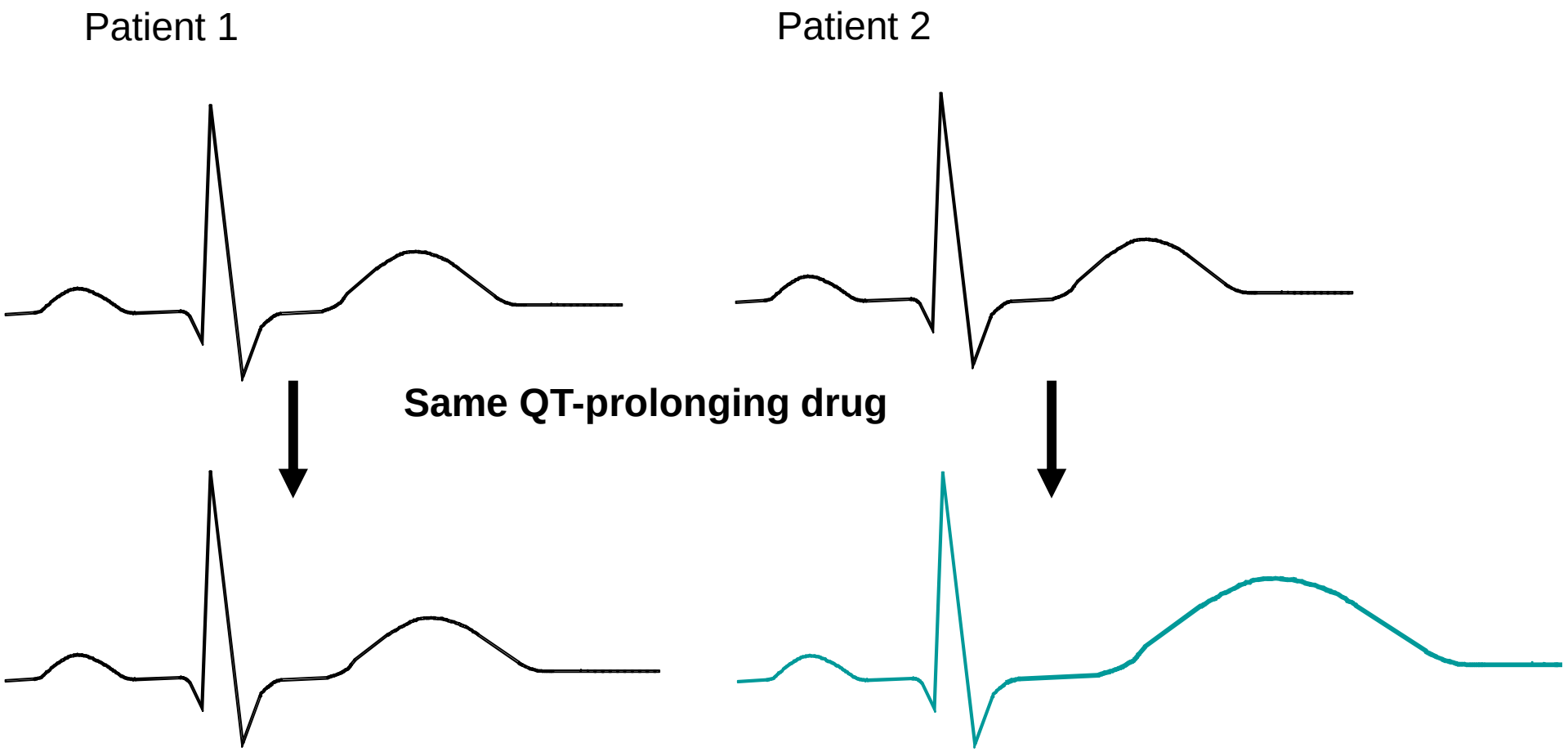
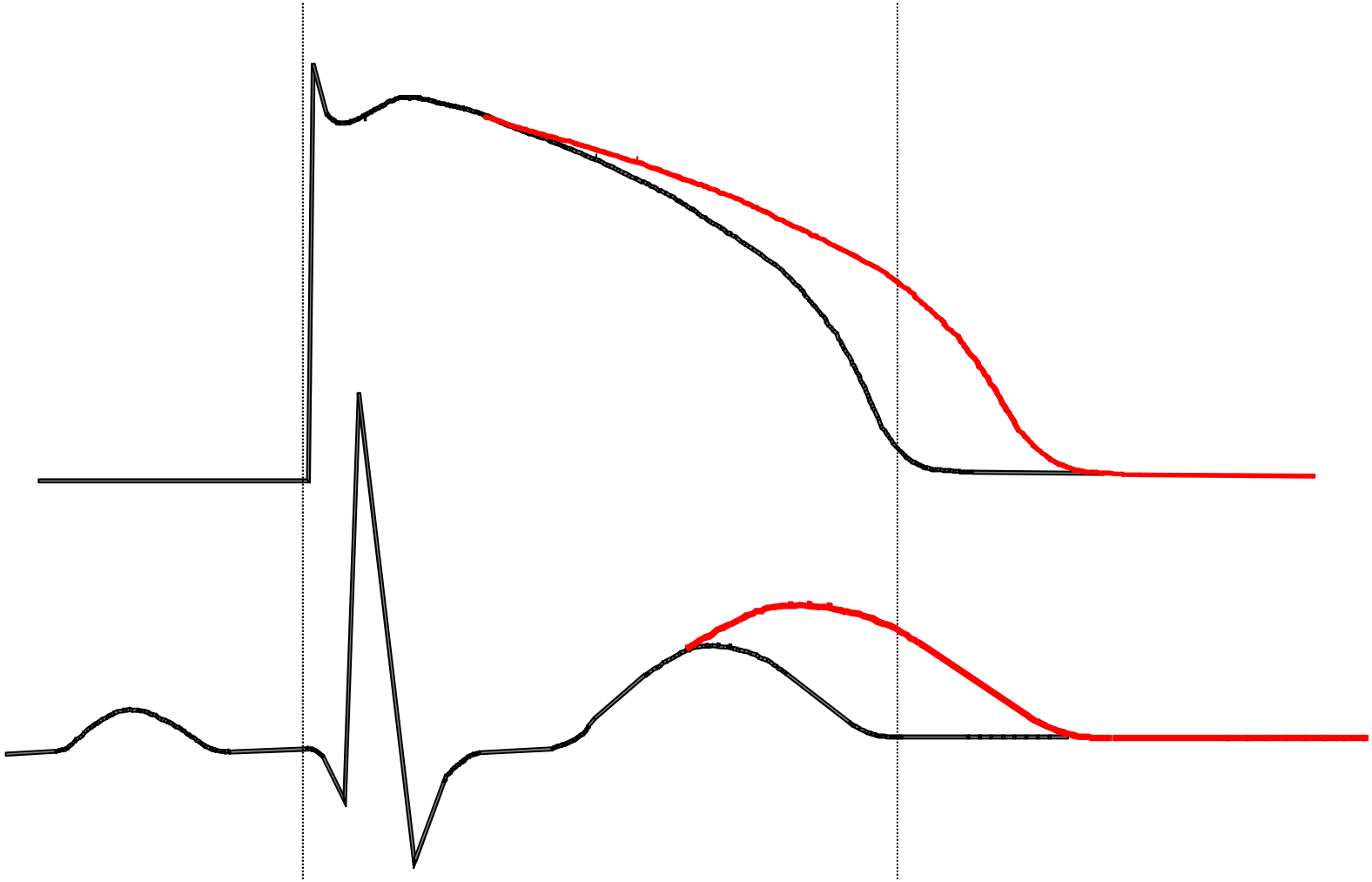
- Common genetic variants as modifiers in common diseases:
  - serious adverse drug reaction: drug-induced LQTS
  - Sudden Cardiac Death (SCD)

What turns Sinus Rhythm into Torsades?

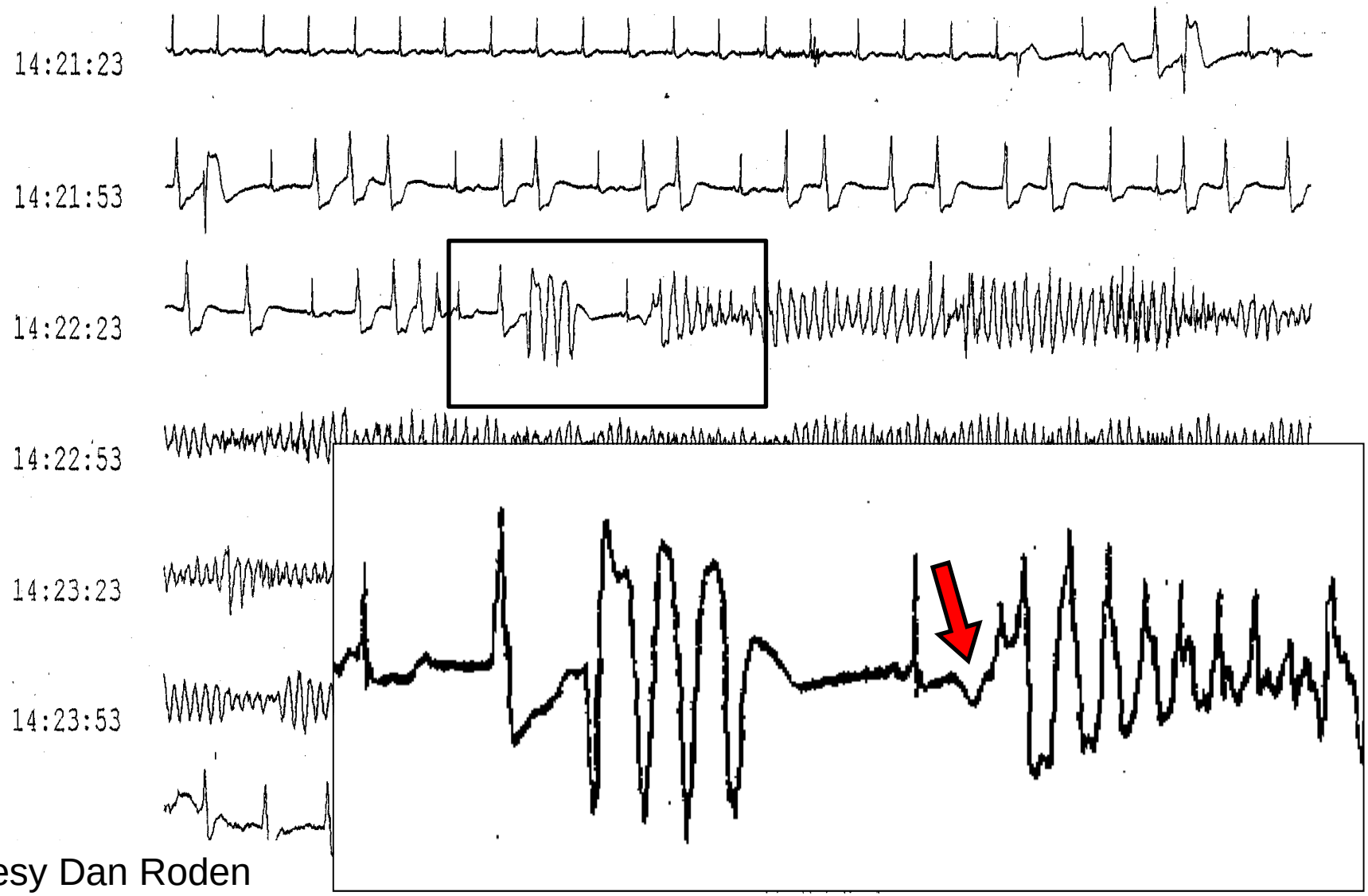
The concept of reduced repolarization reserve



The relationship between the QT interval and the cardiac action potential



72 year old on sotalol for paroxysmal AF develops hypokalemia on diuretic medication



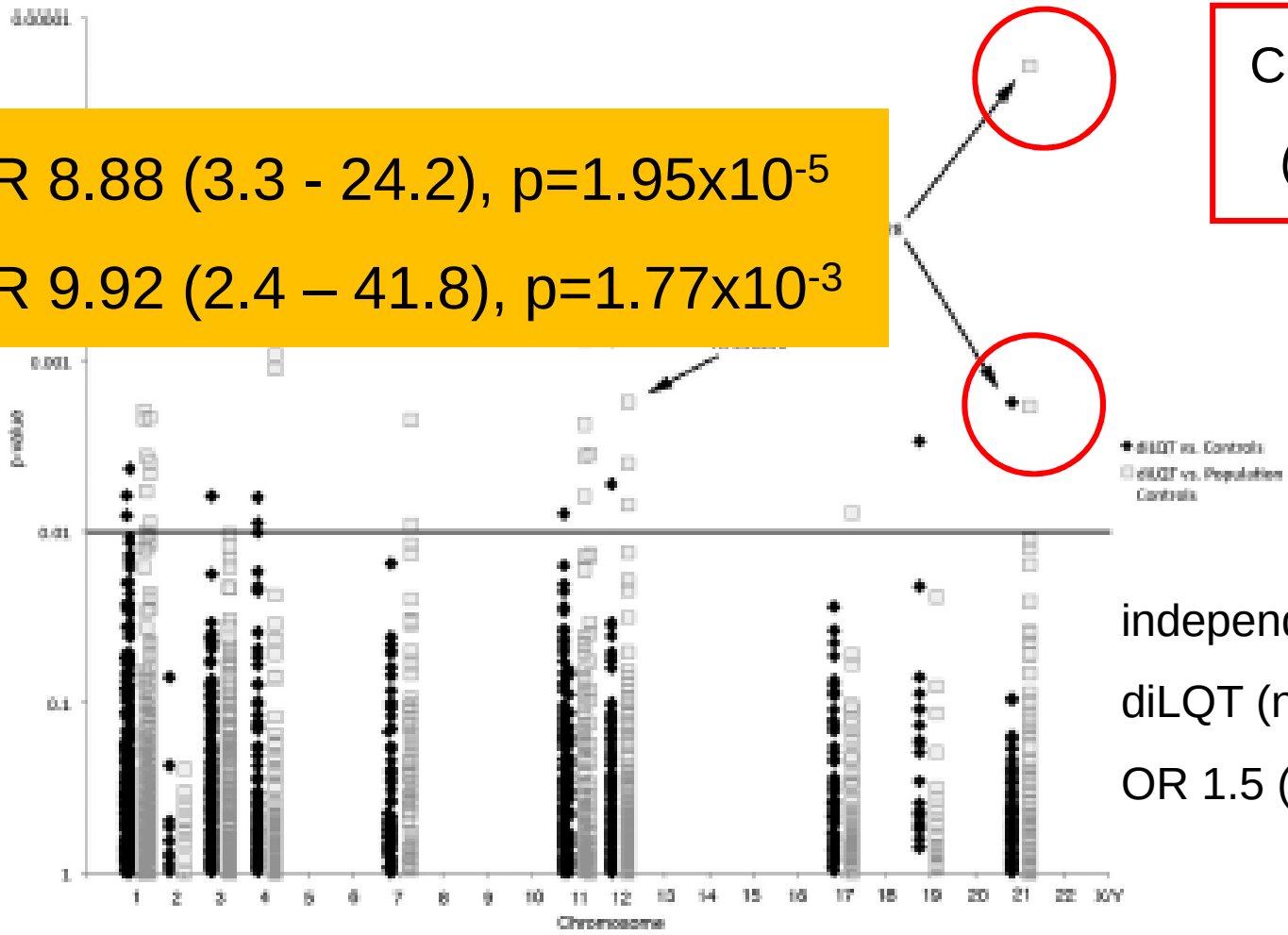
courtesy Dan Roden

Genetic Association Studies in rare diseases: face the power problem!

Drug-induced Long-QT Syndrome: Candidate gene approach (1424 SNPs in 18 genes)

drug induced LQT-Syndrome (n=176) vs population controls (n=837)

drug induced LQT-Syndrome (n=176) vs drug exposed controls (n=207)



OR 8.88 (3.3 - 24.2), $p=1.95 \times 10^{-5}$

OR 9.92 (2.4 – 41.8), $p=1.77 \times 10^{-3}$

Chr21 - rs1805128

(*KCNE1* D85N)

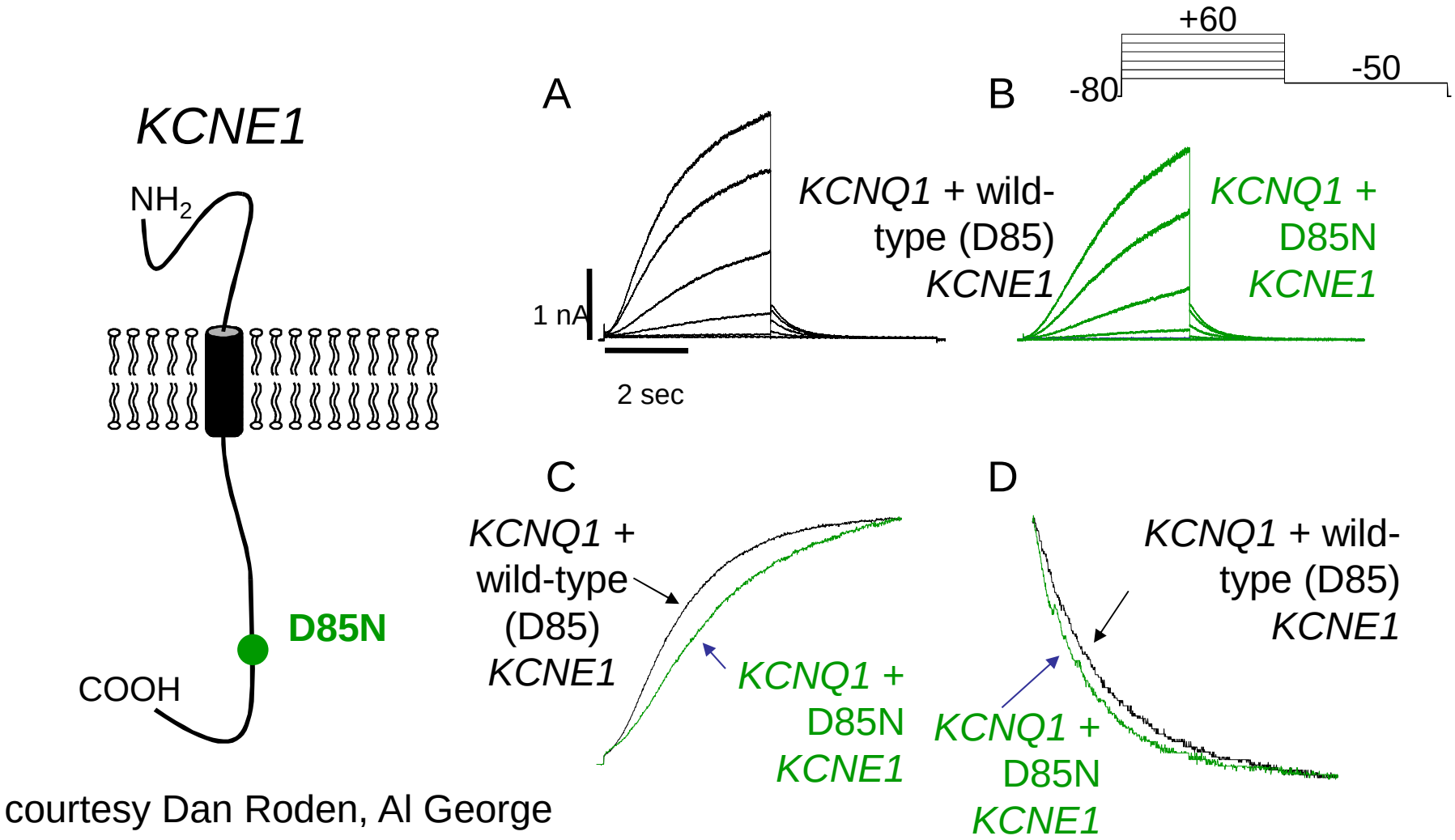
independent validation study

diLQT (n=57) controls (n=211)

OR 1.5 (0.4 – 6.6), p=0.58

Kääb S, et al., Circ Cardiovasc Genet 2012;5:91-99

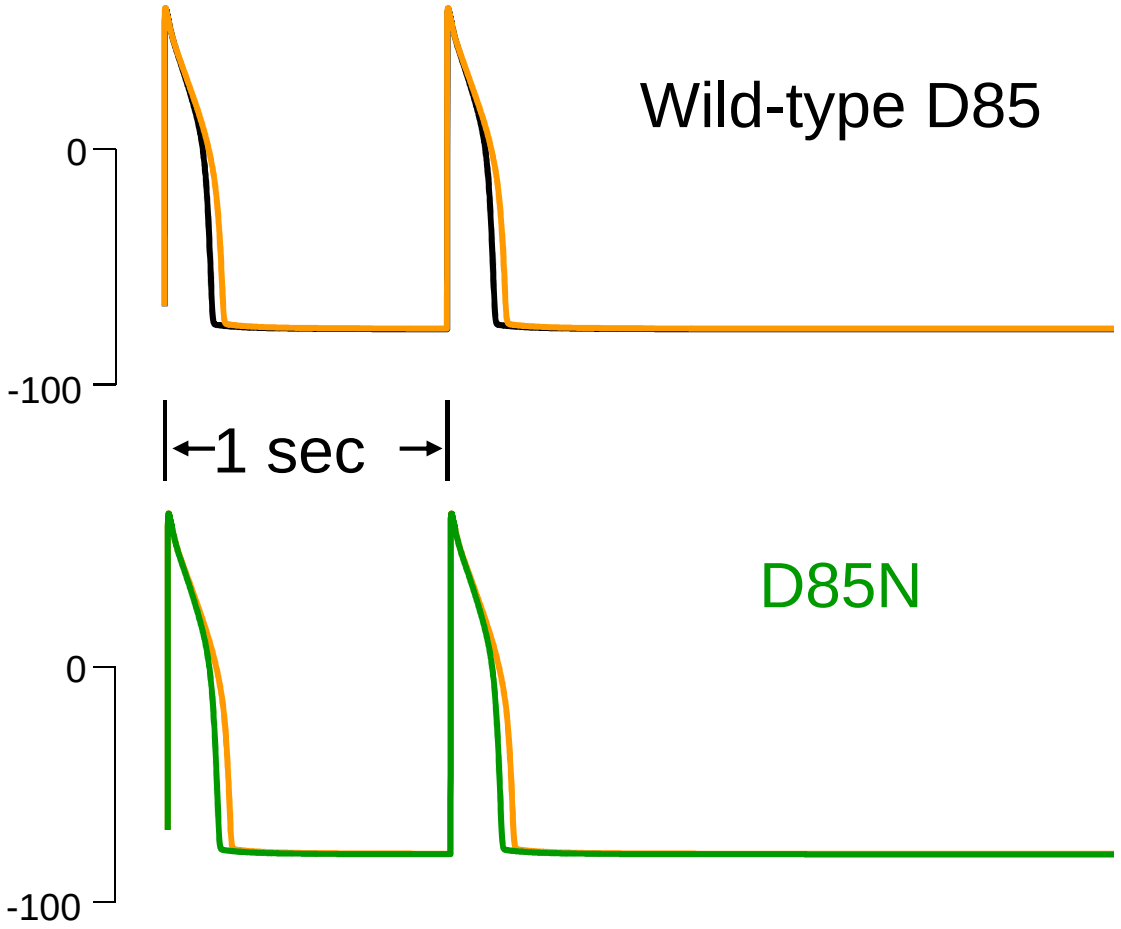
Functional Study: KCNE1-D85N (rs1805128)



courtesy Dan Roden, Al George

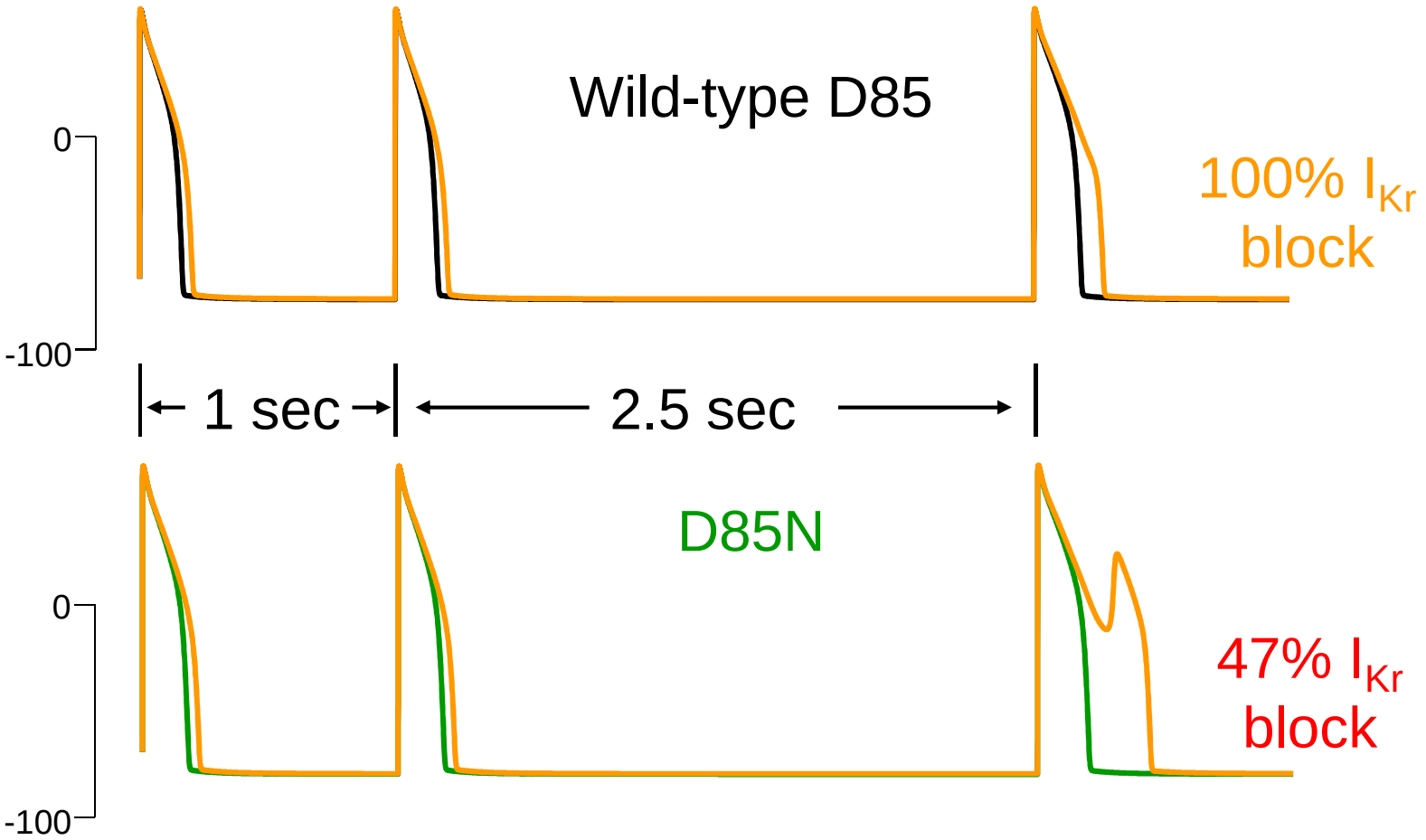
No baseline effect of D85N

Modeling shows that the changes in I_{Ks} conferred by D85N do not alter basal action potential duration even with I_{Kr} block



courtesy Dan Roden, Al George

Further repolarization stress



courtesy Dan Roden, Al George

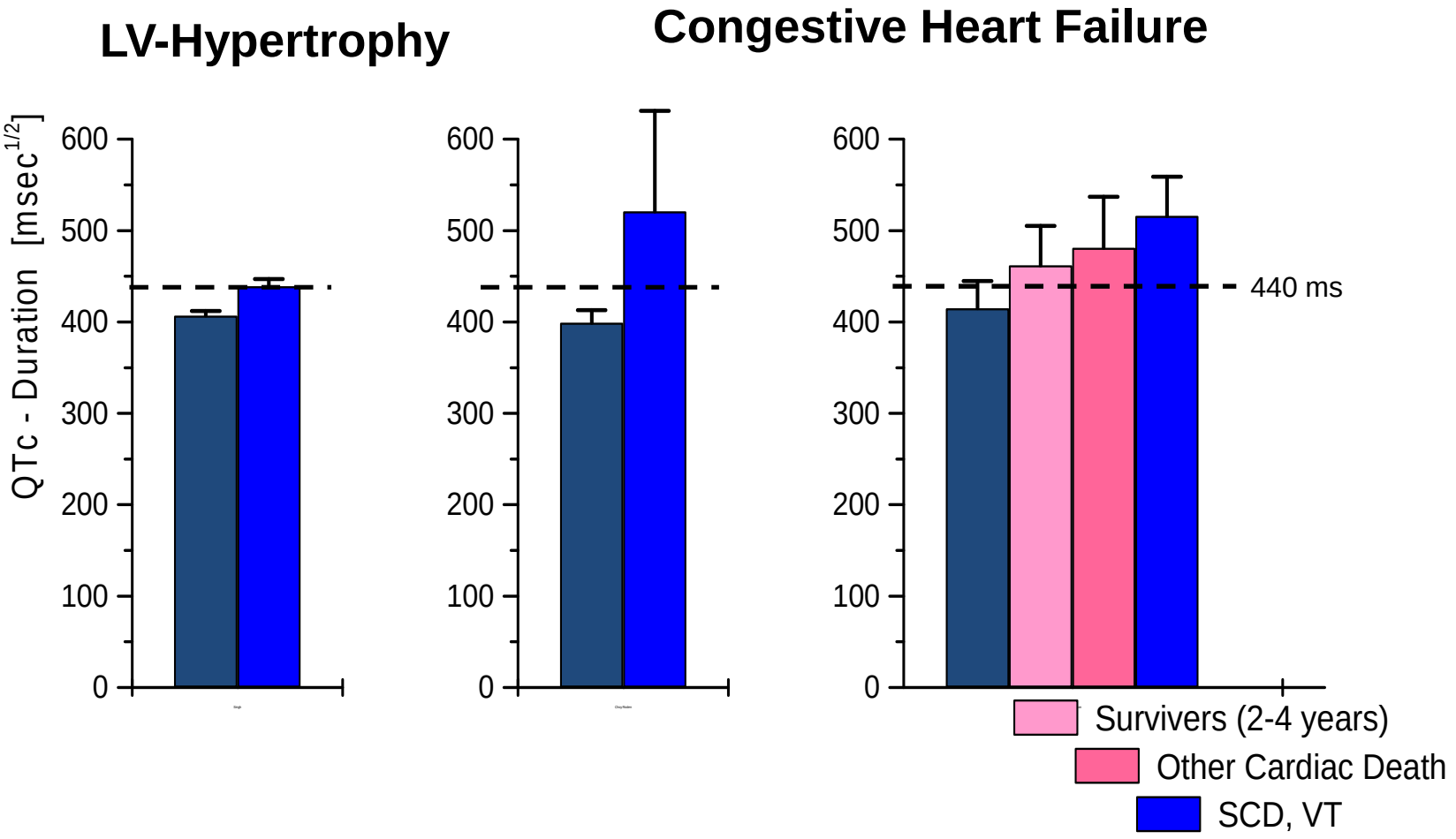
Causes of Acquired Long QT Syndrome

- Drugs
  - Drugs that frequently cause torsade de pointes
    - Disopyramide
    - Dofetilide
    - Ibutilide
    - Procainamide
    - Quinidine
    - Sotalol
  - Drugs clearly associated with torsade de pointes but with low incidence[A]
    - Amiodarone
    - Arsenic trioxide
    - Erythromycin
    - Droperidol
    - Haloperidol
    - Thioridazine
    - Methadone
- Heart block
- Hypokalemia, hypomagnesemia[B]
- Acute myocardial infarction[B]
- Subarachnoid hemorrhage and other CNS injury[B]
- Liquid protein diets and other forms of starvation[B]

for drugs with QT prolonging potential/risk
see http://www.torsades.org

Roden DM and Viswanathan PC, J Clin Invest 2005;115:2025-2032

Hypertrophy and Congestive Heart Failure in Humans: an Acquired Form of Long-QT-Syndrome

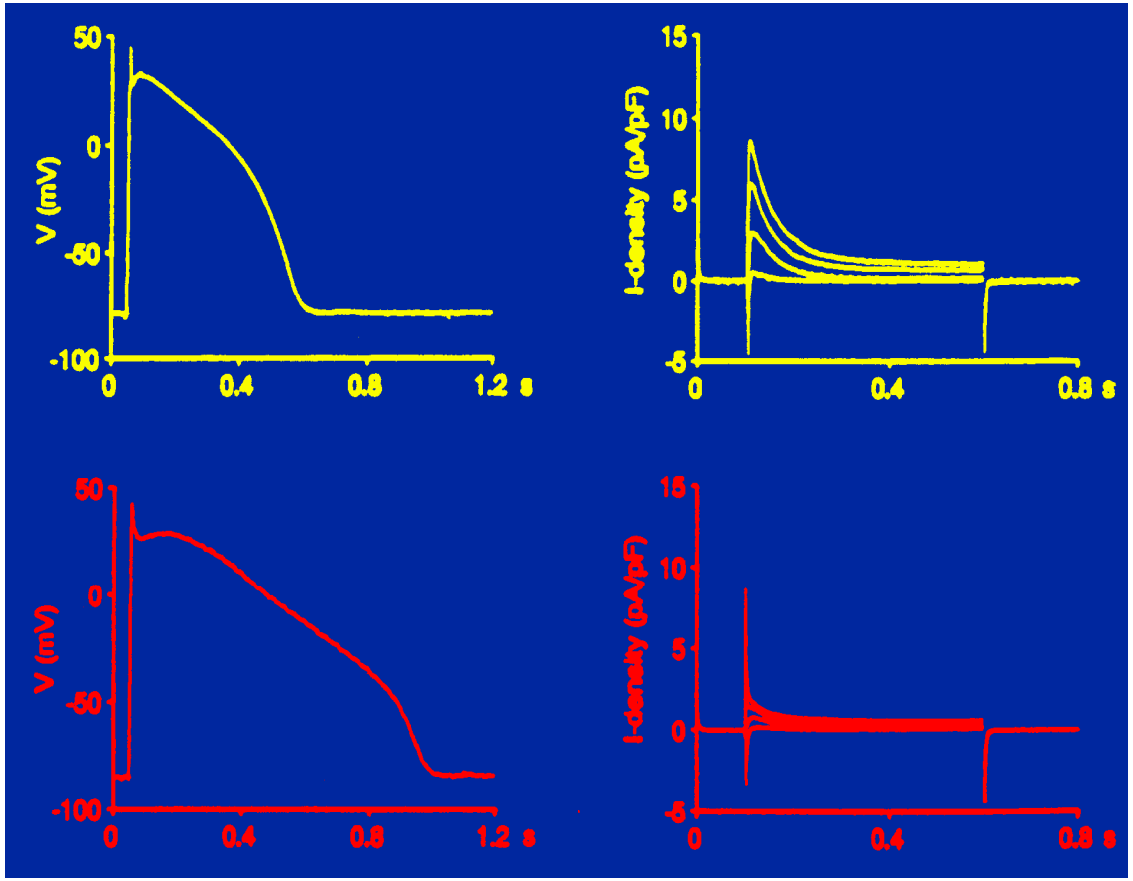


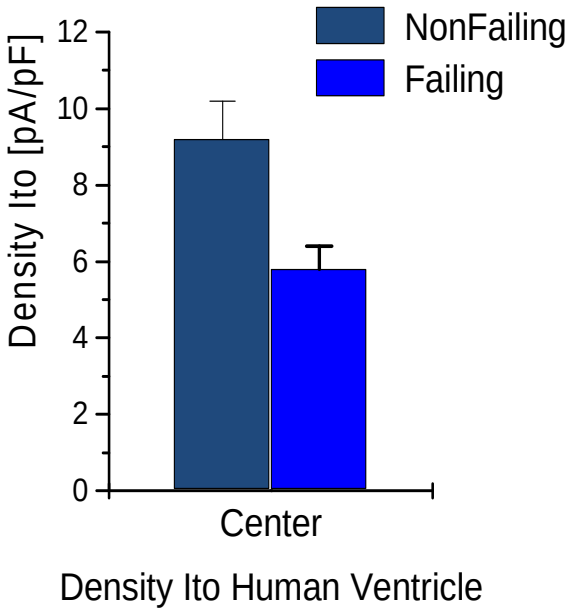
Singh JP, et al. ,
JACC 29: 778 (1997)

Choy AM et al.,
Circulation 96:2149 (1997)

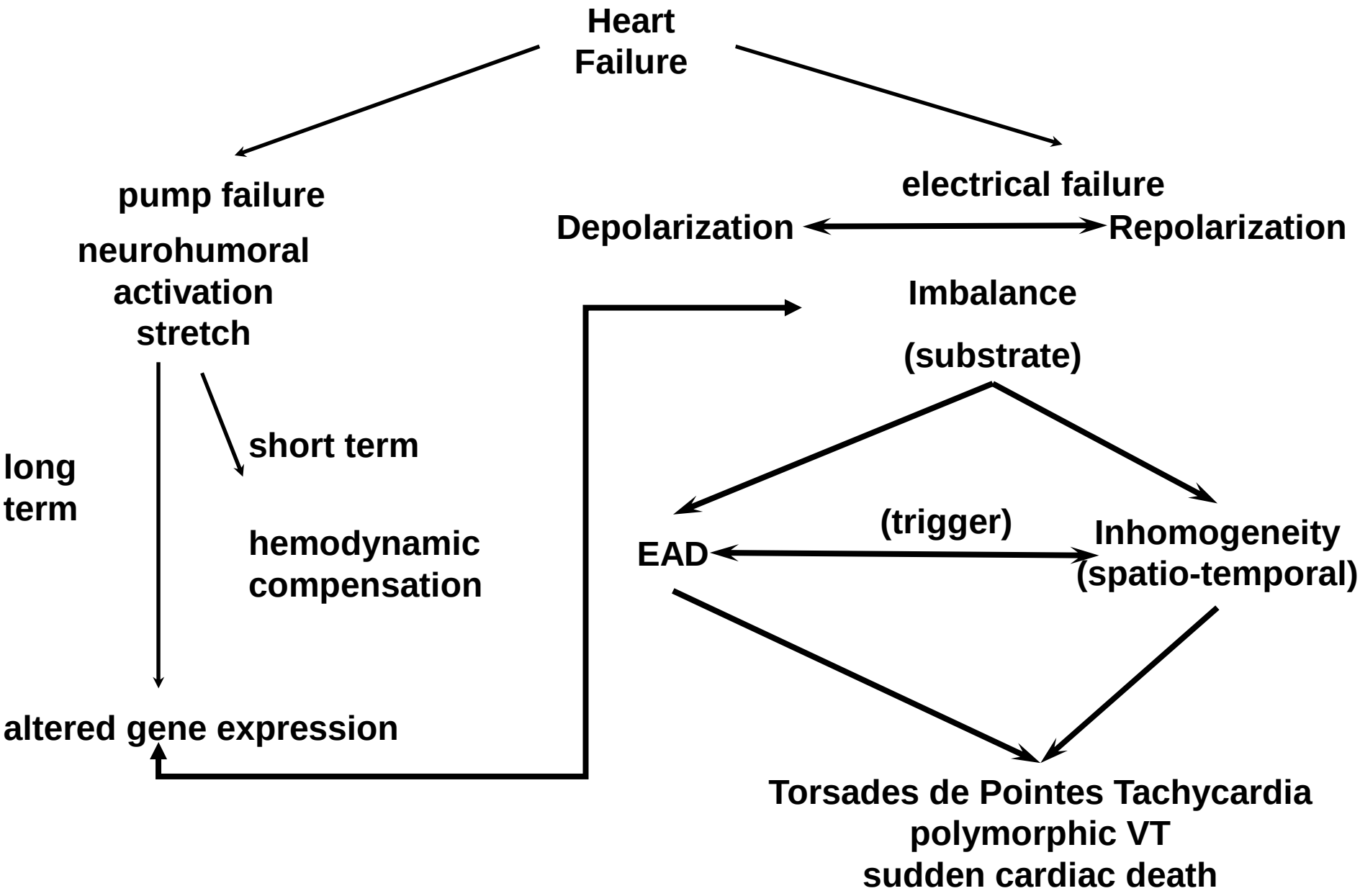
Fu G-S, et al. , Eur Heart J 18:281 (1997)

Prolongation of APD due to reduced I_{to1} in isolated human cardiomyocytes in congestive heart failure





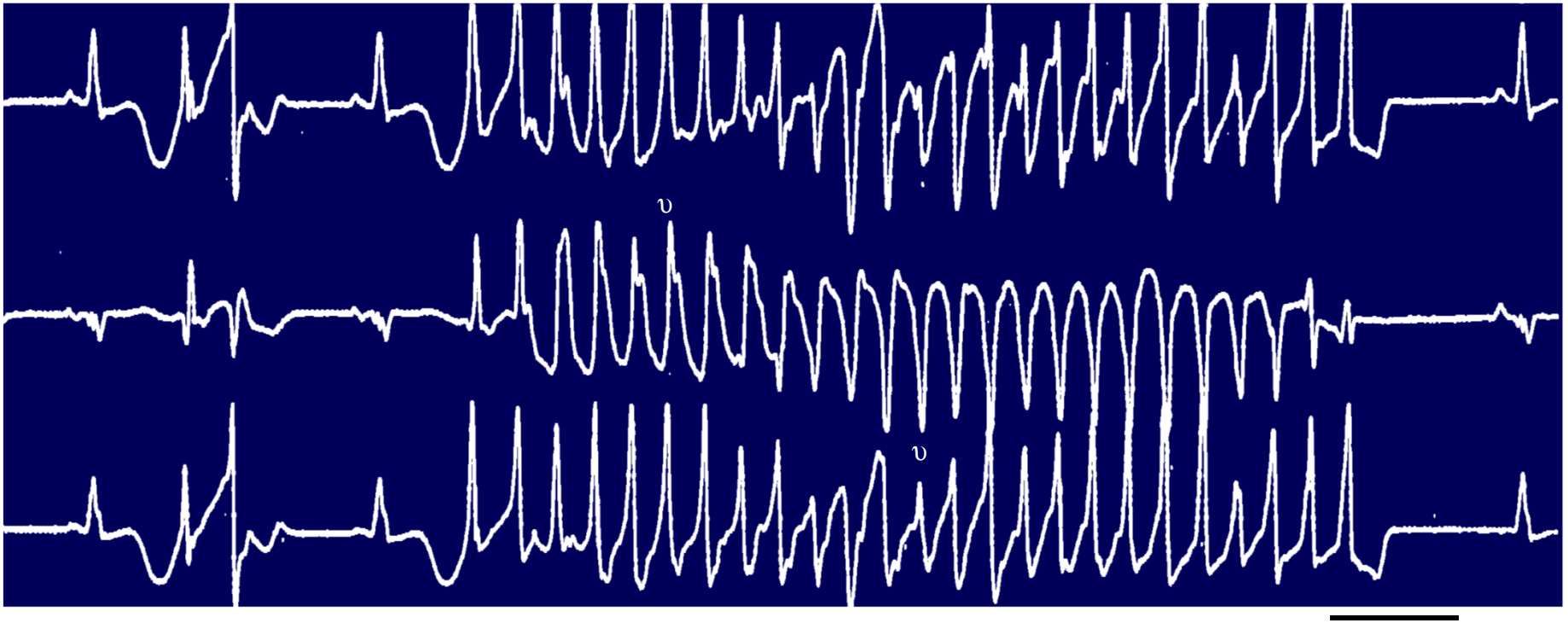
Beuckelmann DJ, Näbauer M, Erdmann E. Circ Res 73:379 (1993)



on the background of individual genetic susceptibility

What causes electrical instability?

secondary electrical cardiomyopathy

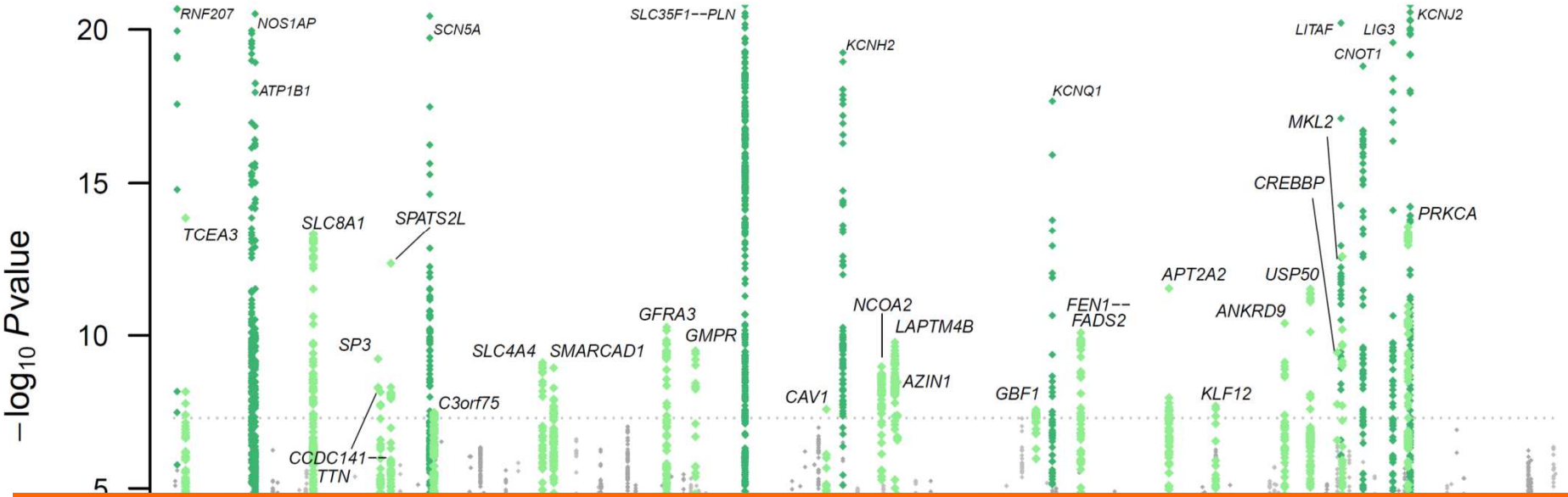


in a 65 year old female with non-familial dilative cardiomyopathy

GWAS on QT-interval highlights role of Ca2+ signaling pathways for myocardial repolarization

68 independent SNPS at 35 loci (22 new loci)

explaining 8-10% of QT-interval variance



future perspective:

Test a comprehensive set of common genetic variants in specific arrhythmia populations

Arking DE, (n=233), Newton-Cheh C, Nat Genet 2014

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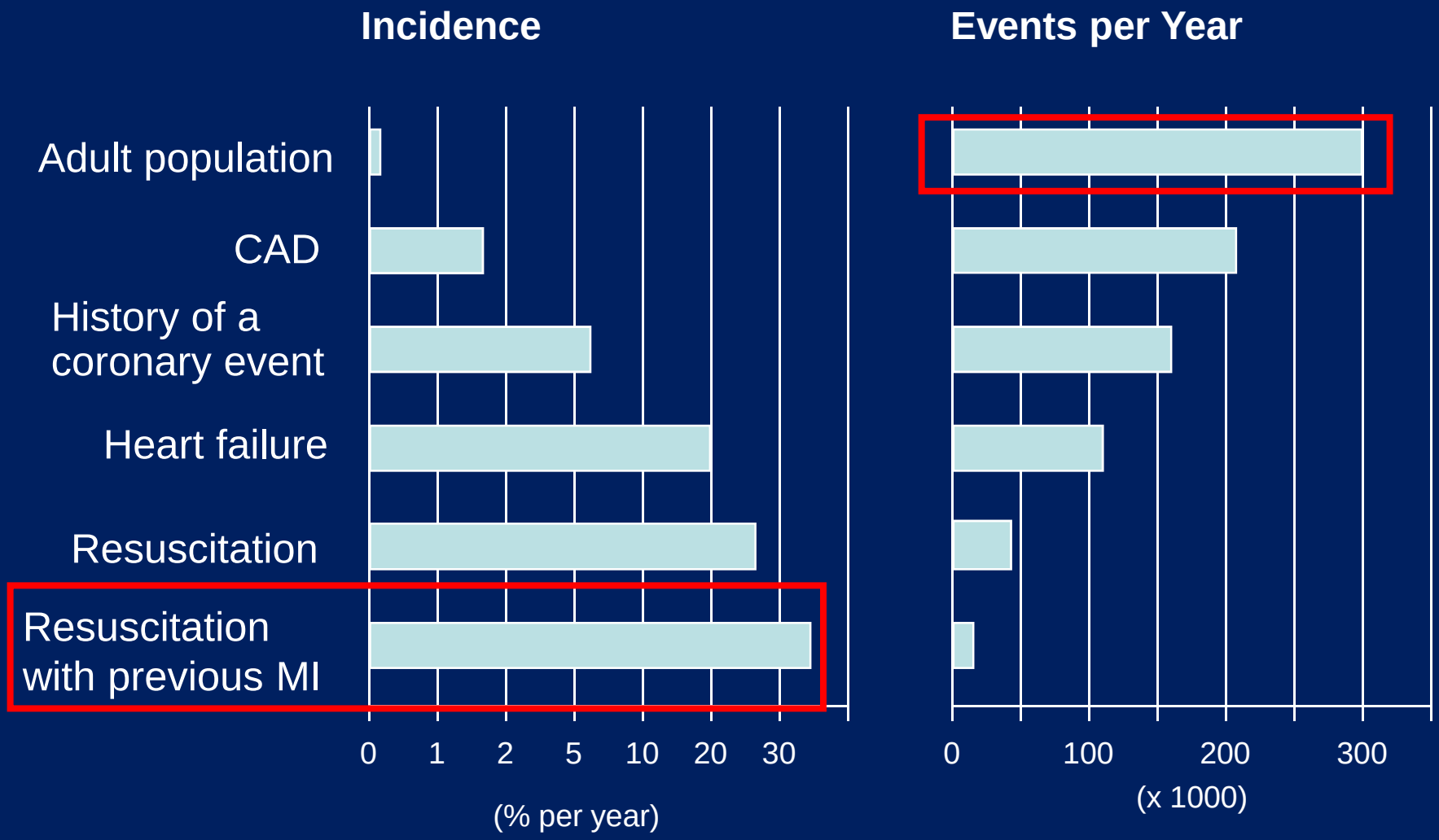
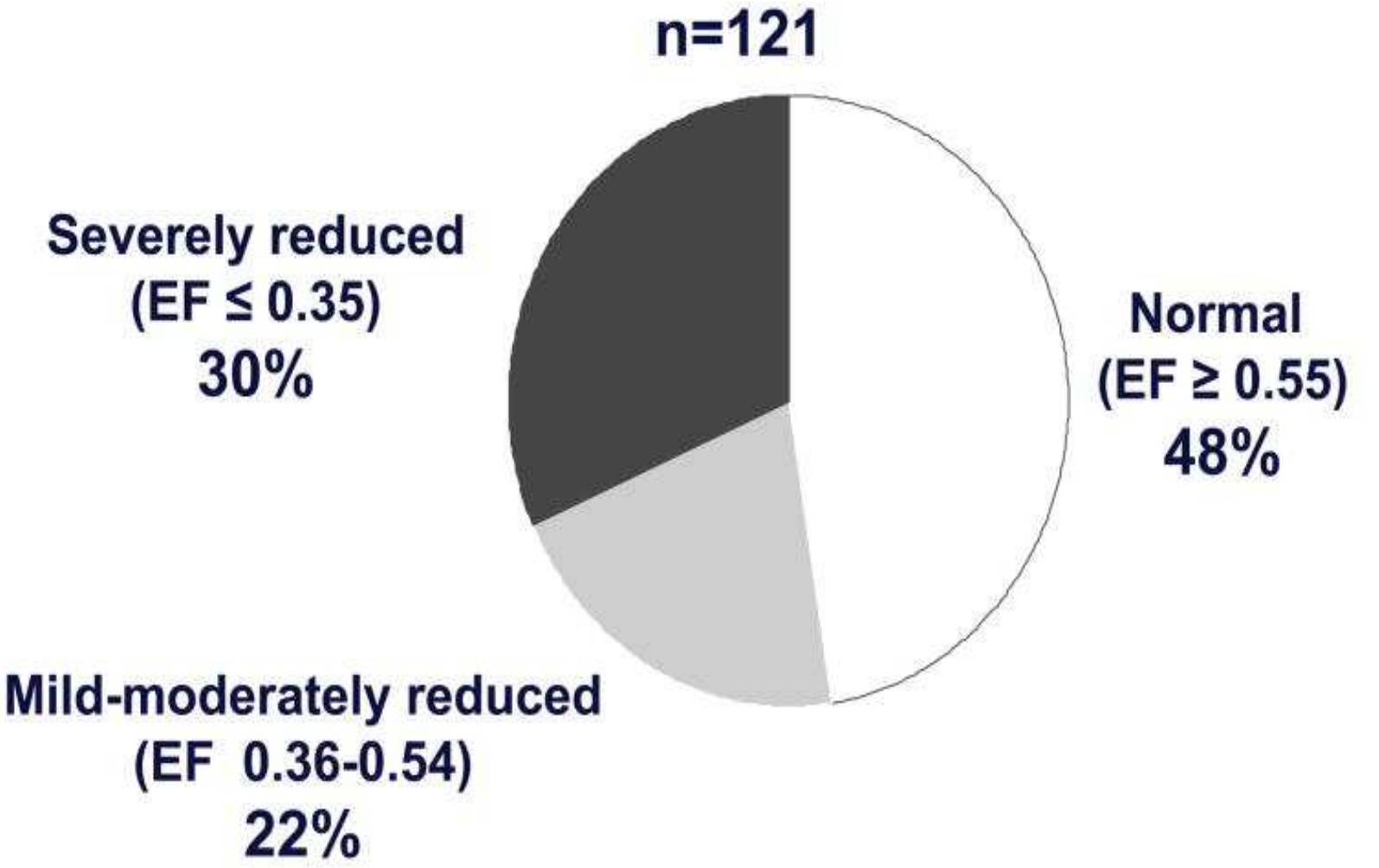


Myerburg et al., Circulation 1992

LV Dysfunction in the Community
How Much Does it Contribute to SCD?



Chugh et al., 2008

Genetic background of Channelopathies

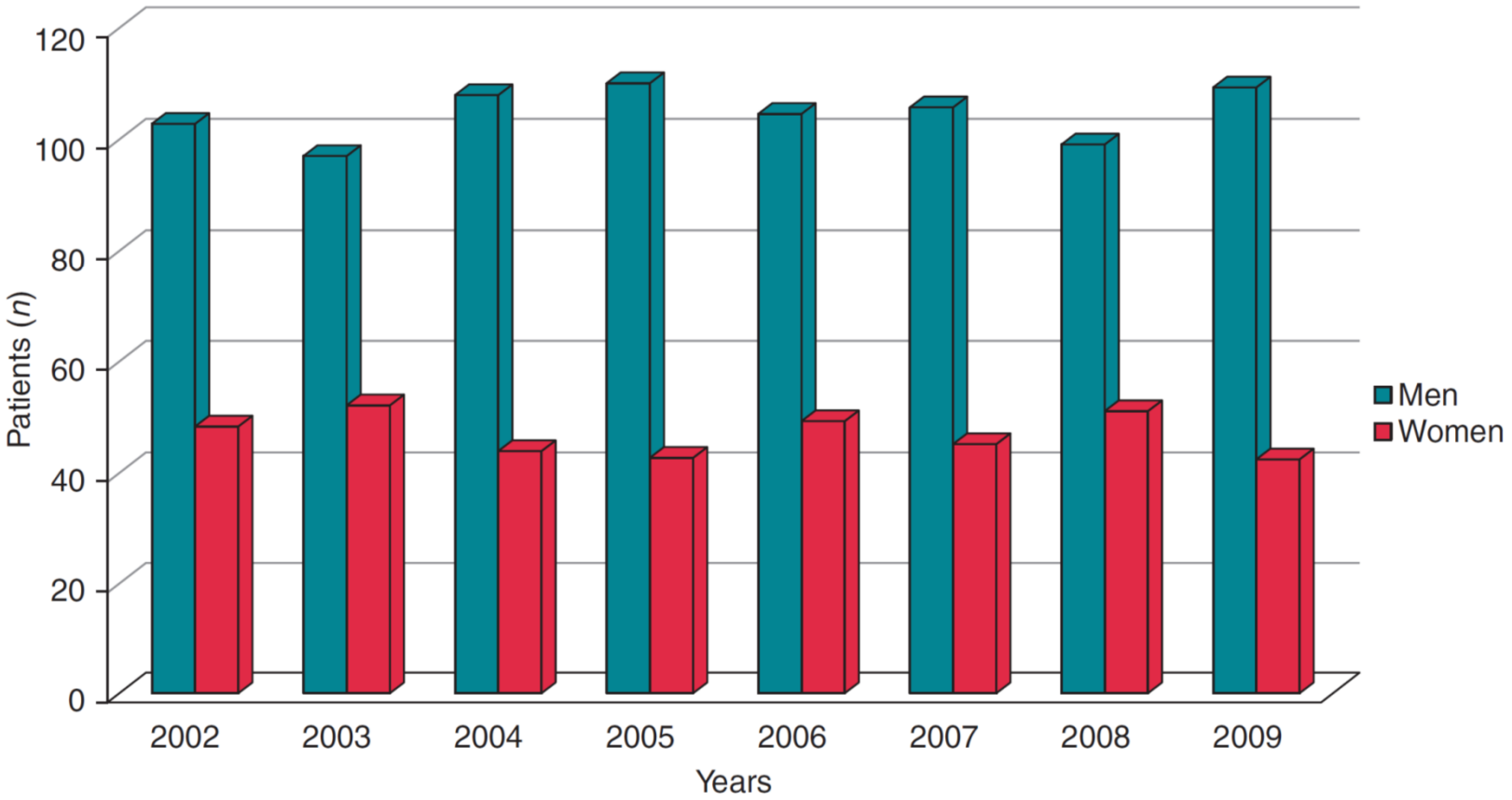
Risk Stratification for Sudden Cardiac Death

Affected Groups

	% of all SCD	Risk Stratification
no apparent heart disease	45	poor
heart disease (LVEF >40%)	40	limited
heart disease (LVEF <40%)	13	possible
primary genetic arrhythmogenic heart disease	Family screening Genetic markers with strong effects	

Wellens HJJ, Schwartz PJ, et al. EHJ 2014

Incidence of SCD in Germany



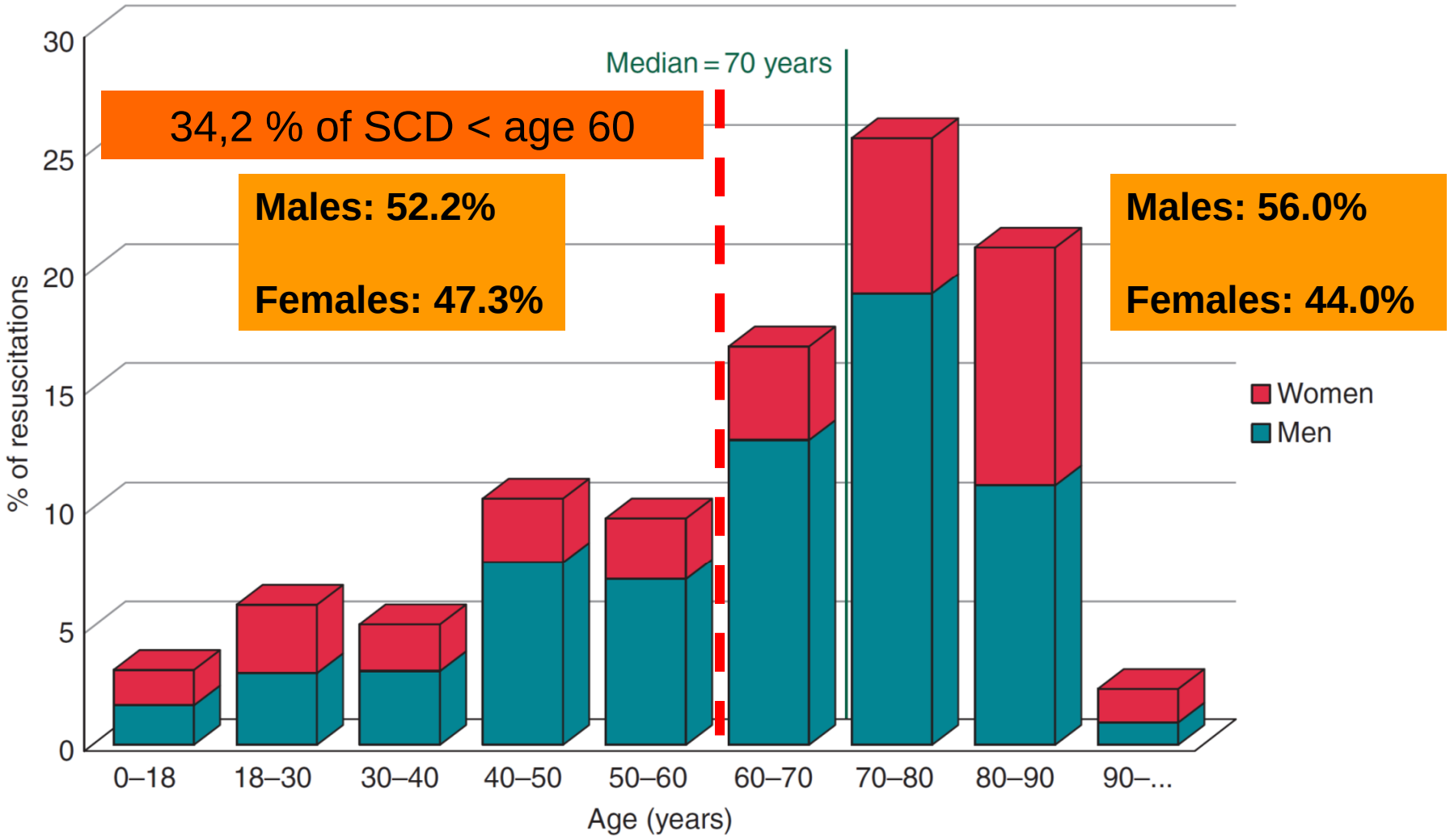
During the observation period 2002-2009 constant rate of SCD
(81 per 100.000 per year)

(county of Aurich, Population 190.000)

Martens E, et al. Europace 2014

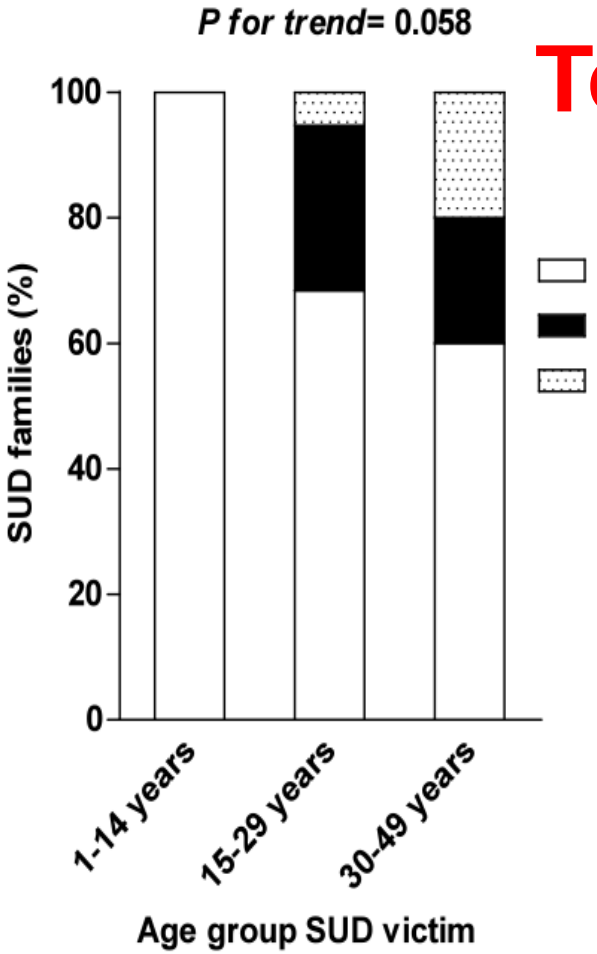
Age distribution of SCD in Germany

(2002 – 2009; n=1,212)

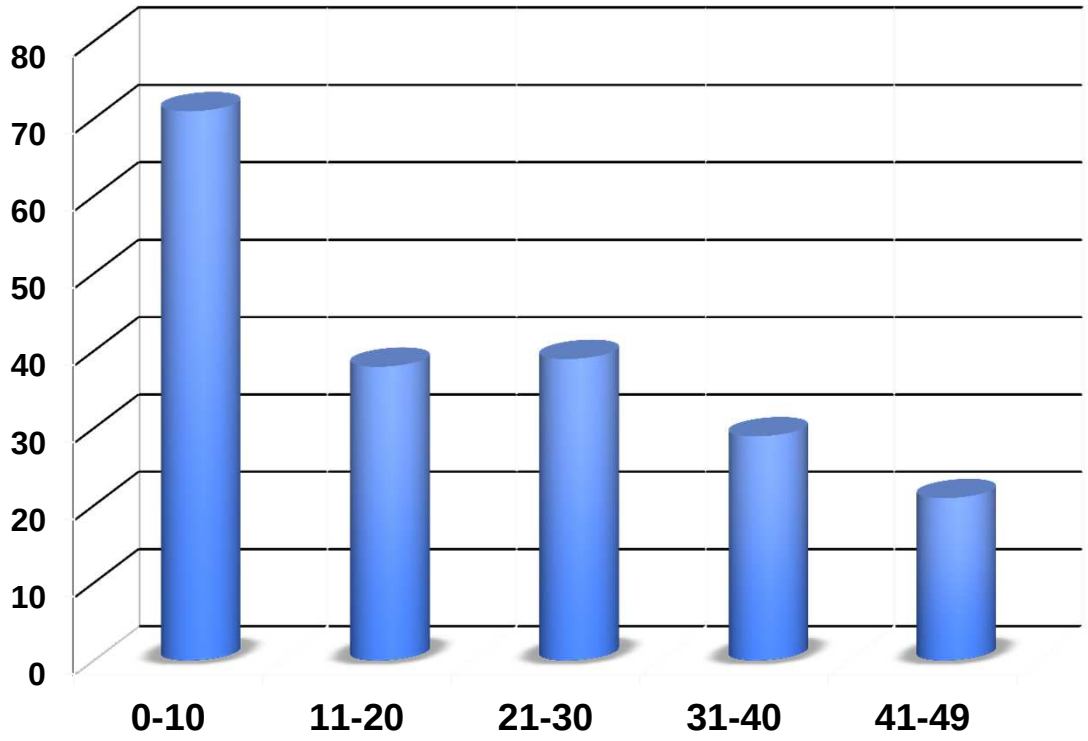


Martens E, et al. Europace 2014

Family screening after SCD (n=140)

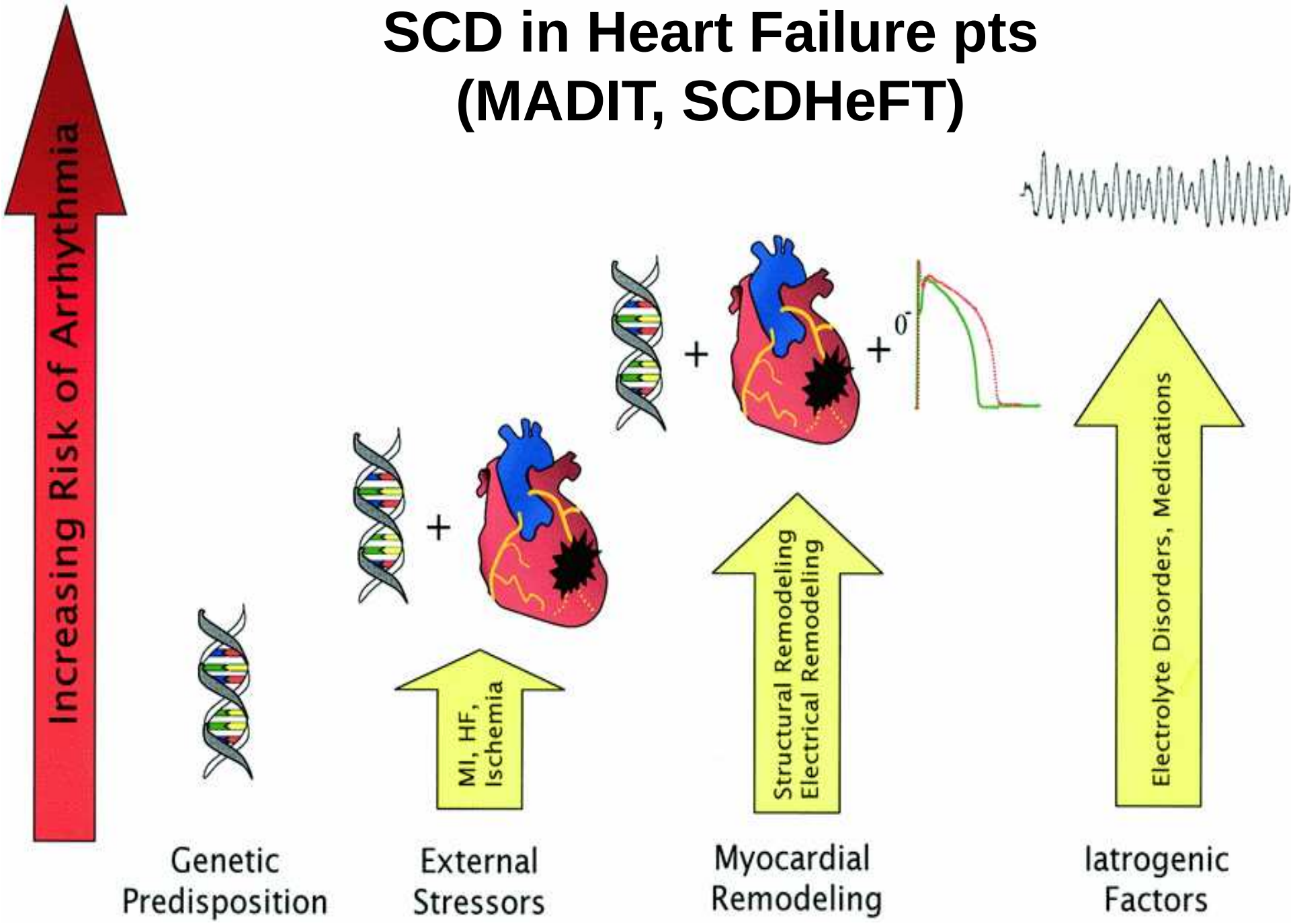


Total yield: 47 families (33%)



Van der Werf et al, Heart Rhythm 2010

SCD in Heart Failure pts (MADIT, SCDHeFT)



OPEN ACCESS Freely available online

PLoS one

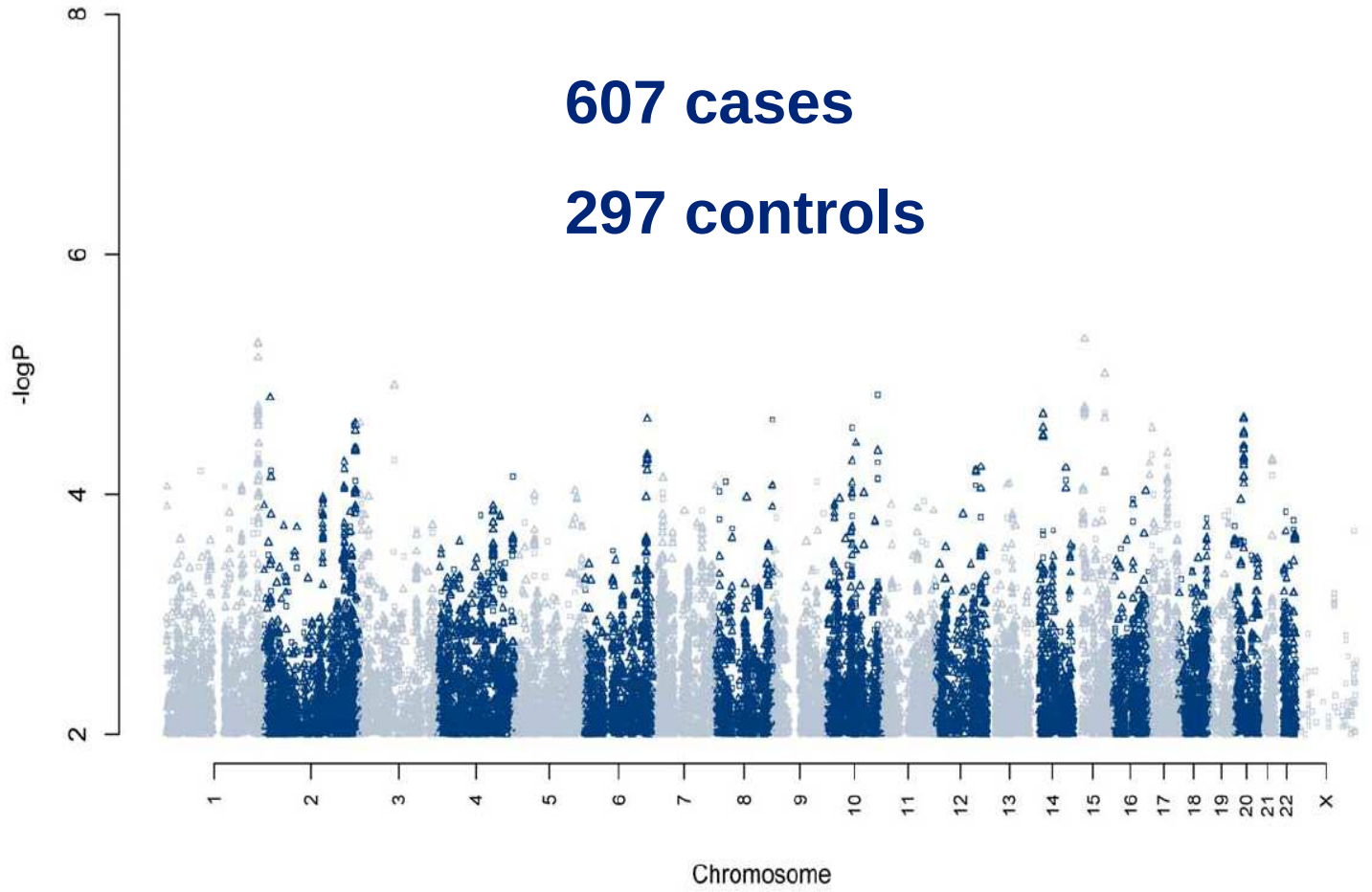
Genome-Wide Association of Implantable Cardioverter-Defibrillator Activation With Life-Threatening Ar[illegible]

Sar[illegible] Marian
Sha Orhan
Soy

GAME GWAS

607 cases

297 controls



Genetic Predisposition for Primary VF

Arrhythmia Genetics in the NEtherlands Study (NL)

Predestination (I)

Cases

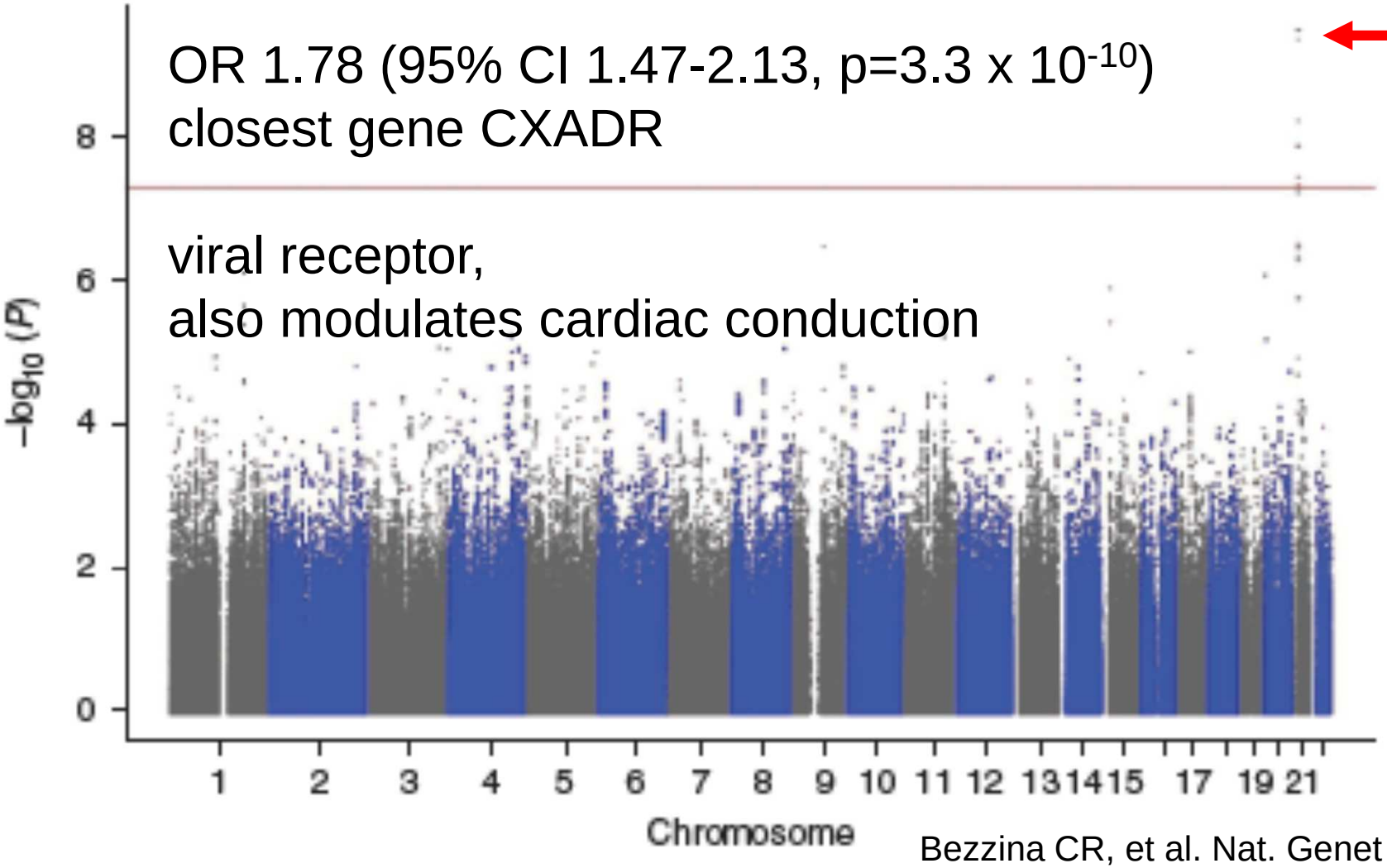
- first acute MI
- *with* VF

Controls

- first acute MI
- *no* VF

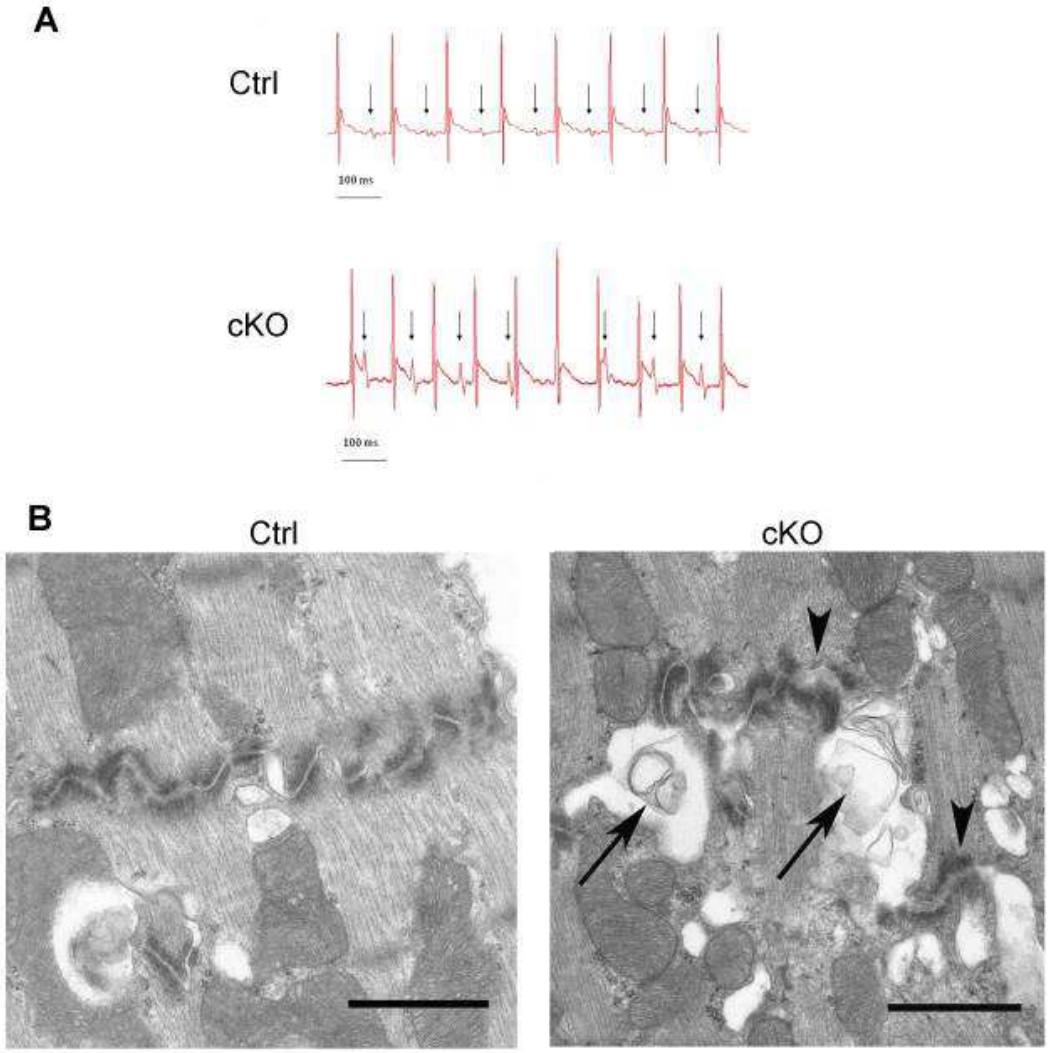
GWAS identifies a susceptibility locus at Chr 21q21 for ventricular fibrillation in acute MI

515 cases w first MI w VT/VF vs 457 controls first MI w/o VT/VF



Bezzina CR, et al. Nat. Genet 2010

Conditional knock out of CXADR produces myocardial ultra-structural changes and AV-Block



Pazirandeh A, et al., PLoS One. 2011;6(6):e20203.

Genome

99,9 % Homology

3 Billion bp

11 Mio. SNP w AF >1%

5 Mio. SNP w AF > 10%

~1 Mio tagSNP

30.000 genes

Exome

25.000 genetic variants

10.000 non-syn. variants

on average 1 non-syn. genetic variant in every third gene (exome)

Problems:

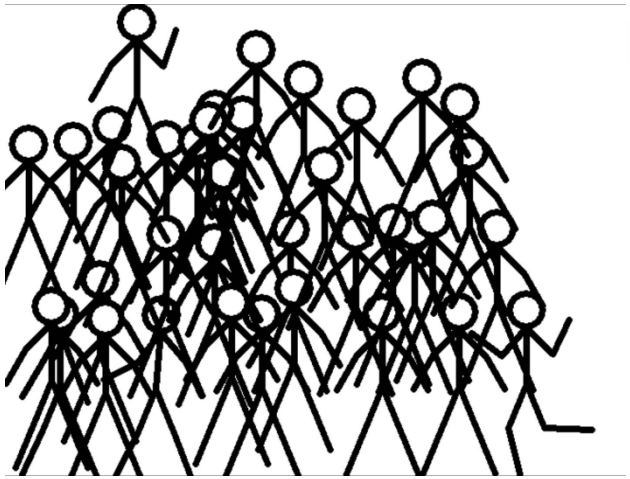
association vs. causality

limited power by:

- MAF
- effect size
- sample size

Hospital and Systemwide Genetics to Guide Treatment of Arrhythmias…

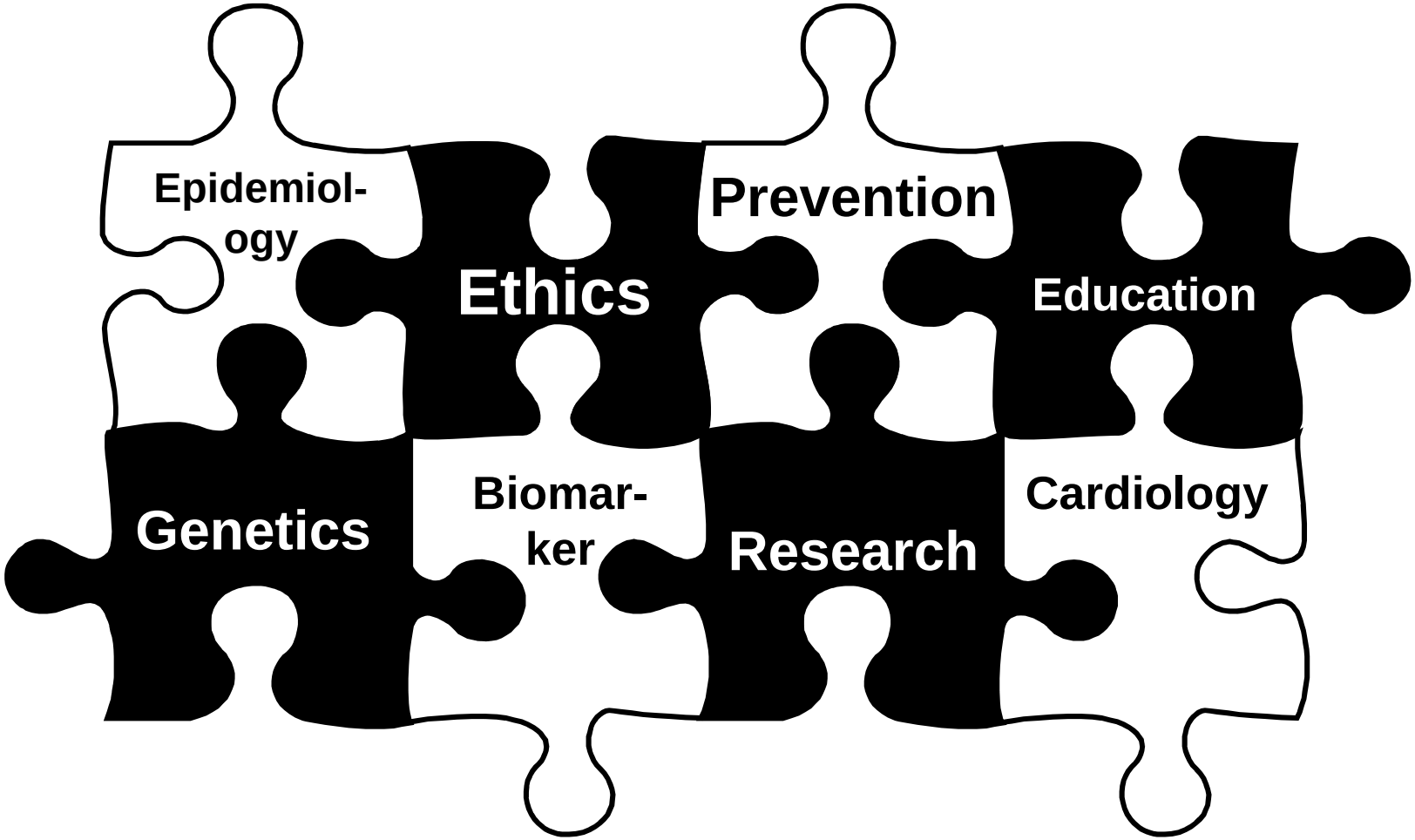
unstratified patient populations → genotyped patient populations → actionable variants to improve outcome



"Here's my sequence..."

New Yorker, 2000

…will turn discoveries into improved health


Epidemiol-
ogy
Ethics
Prevention
Education
Genetics
Biomar-
ker
Research
Cardiology

Herzlichen Dank für Ihre Aufmerksamkeit

skaab@med.lmu.de