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Genetic variants predisposing to exaggerated drug induced QT prolongation and *torsades de pointes*

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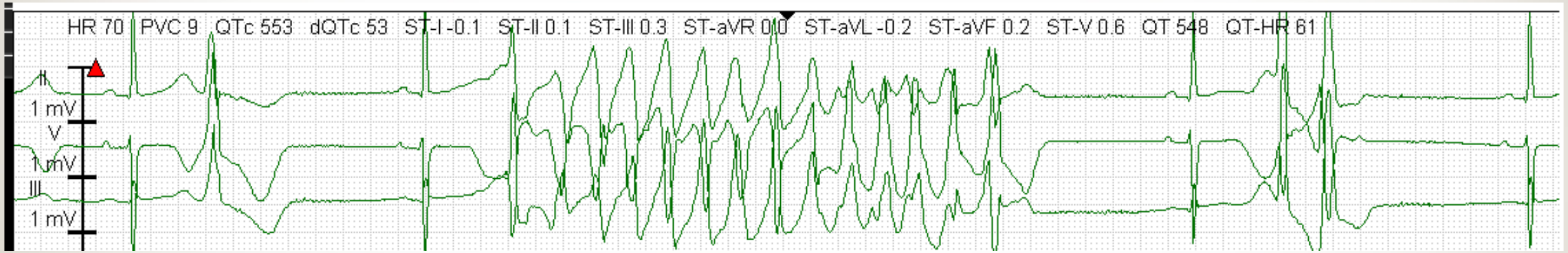
Disclosures

- Grant support: NIH, American Heart Association, Helen and Robert Kleberg Foundation
- Co-Principal Investigator, Data and Research Center, All of Us Research Program (NIH)
- Scientific Advisory Boards
  - Genomic Medicine Working Group, National Human Genome Research Institute
  - Department of Veterans Affairs Genomic Medicine Program Advisory Committee (Chair)

Summary

- The past 3 decades have seen the definition of (most of) the major molecular and genetic mechanisms controlling normal repolarization in the heart.
- Mutations (hundreds now reported) causing congenital long QT syndrome predispose to potentially fatal arrhythmias. Drugs can phenocopy this effect.
- A minority of patients with drug-induced long QT-related arrhythmias have unrecognized congenital long QT syndrome. Most don't.
- Common polymorphisms credibly associated with risk are now being defined.

“This is a really interesting arrhythmia – no one knows anything about its mechanism”

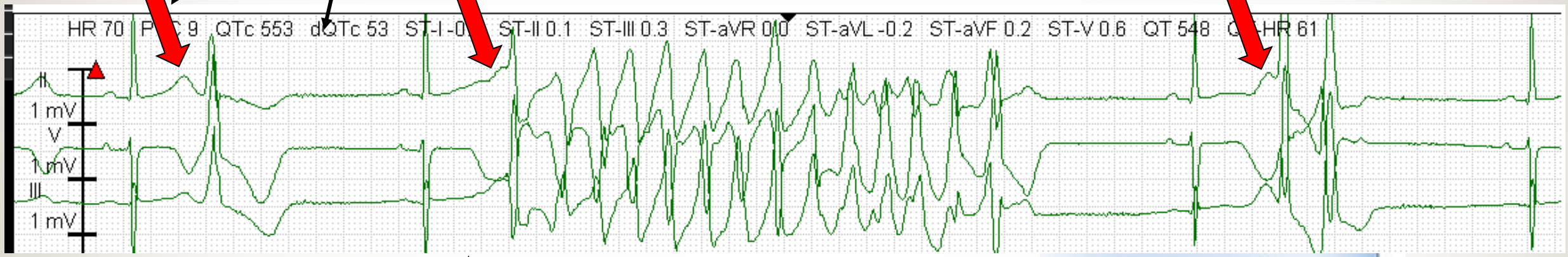


short cycle

long cycle

short cycle

polymorphic ventricular tachycardia



Sinus beat with a really long and deformed QT

Torsades de Pointes

tor sahd duh pwahnt

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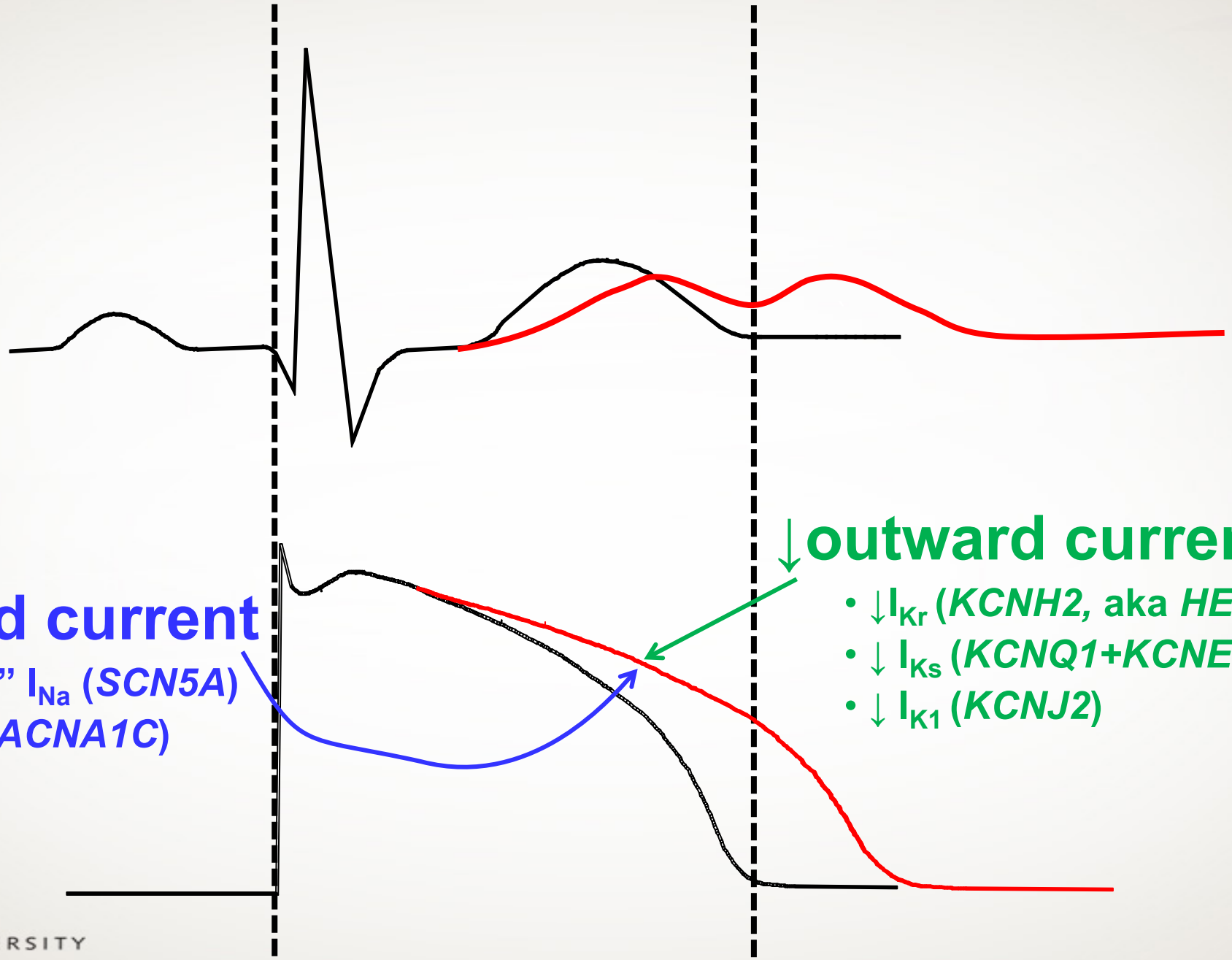
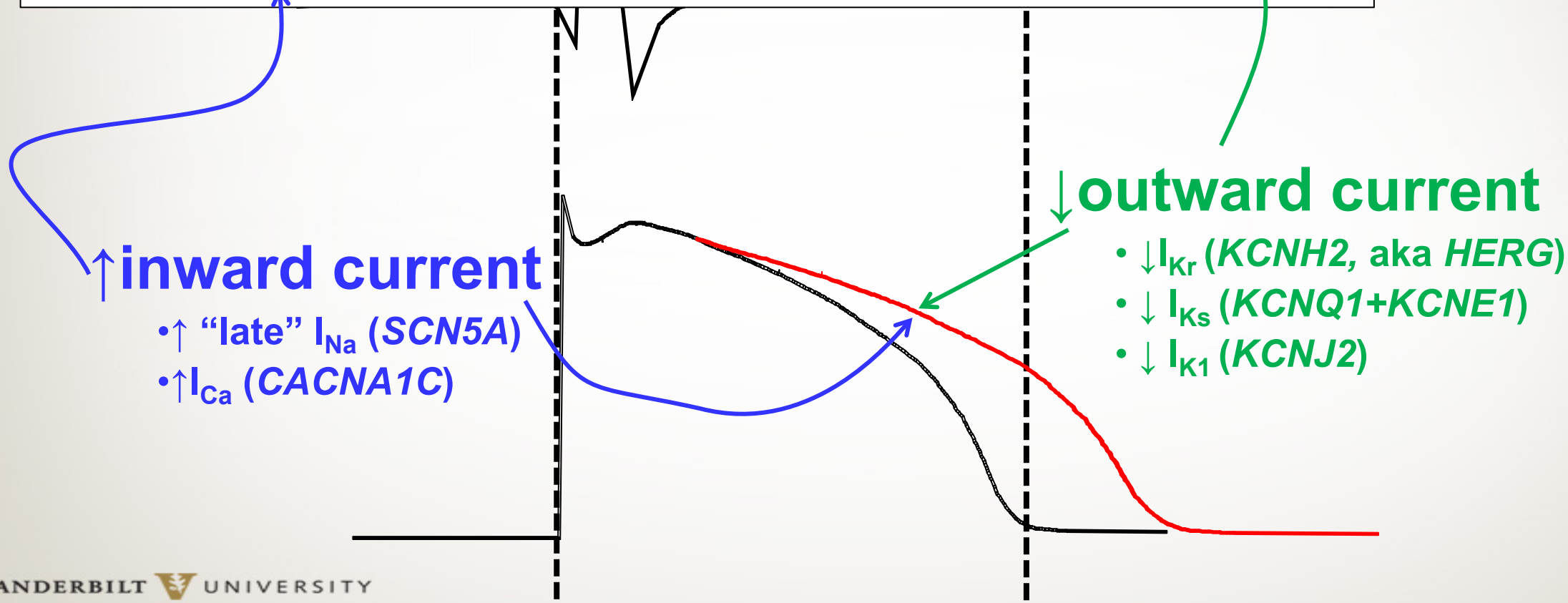
Clinical risk factors for drug-induced Torsades

- Female sex
- Hypokalemia, hypomagnesemia
- Bradycardia/pause pre-event
- Post-cardioversion for atrial fibrillation
- Unrecognized congenital long QT syndrome
- Diuretics
- Testosterone deficiency
- 4th generation Birth Control Pills
- Inflammatory states


↓outward current
• ↓I_{Kr} (*KCNH2*, aka *HERG*)
• ↓ I_{Ks} (*KCNQ1+KCNE1*)
• ↓ I_{K1} (*KCNJ2*)
↑inward current
•↑ "late" I_{Na} (*SCN5A*)
•↑I_{Ca} (*CACNA1C*)

Mutations causing the congenital Long QT syndrome lead to

- ↓I_{Ks}, I_{Kr}, I_{K1}
- ↑late I_{Na}, I_{Ca-L}



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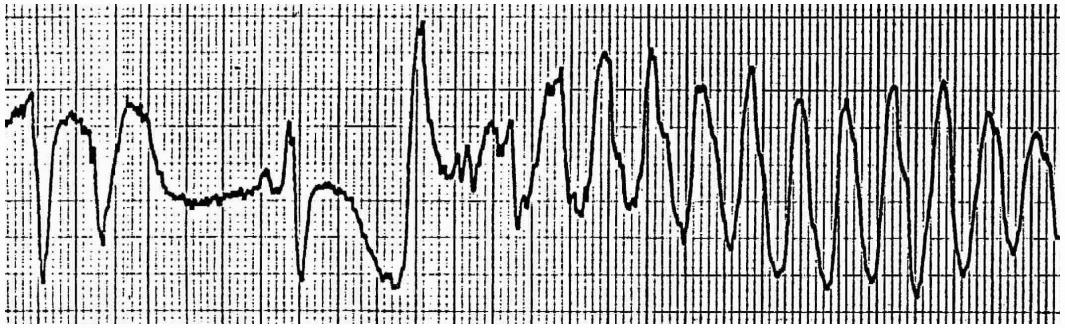
An "idiosyncratic" drug response

AR, 78 year old male

- Chronic coronary artery disease
- Normal baseline QT. Paroxysmal AF.
- 2 days after starting the very potent I_{Kr} blocker dofetilide …



No personal or family history of syncope, sudden death

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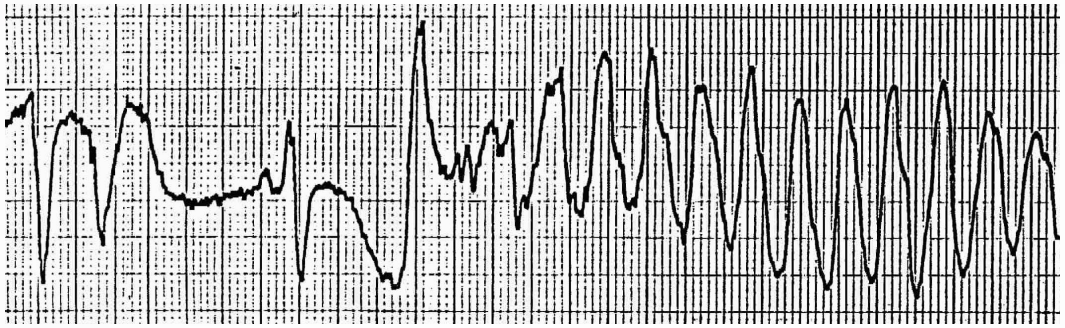
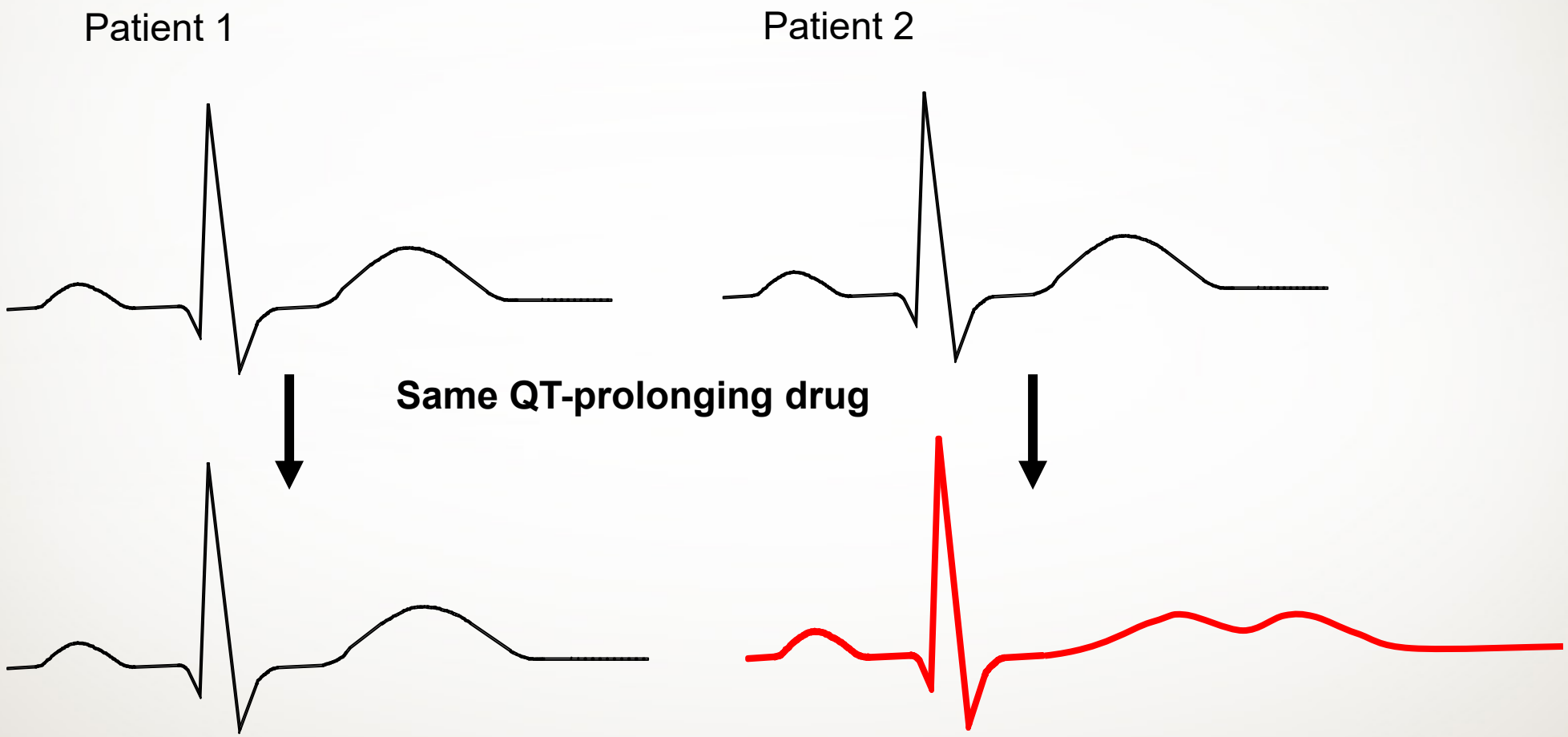


No personal or family history of syncope, sudden death

- *KCNQ1* variant leading to R583C identified
- *In vitro*: ↓I_{Ks}
- Not found in >400 ethnically-matched controls; 0-3/100,000 in gnomAD
- ∴this is likely subclinical congenital Long QT Syndrome

Why did AR only get Torsades after ~2,000,000,000 heart beats?

The concept of reduced repolarization reserve



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Torsades de Pointes Occurring in Association With Terfenadine Use

Brian P. Monahan, MD; Clifford L. Ferguson, MD; Eugene S. Killeavy, MD; Bruce K. Lloyd, MD; James Troy; Louis R. Cantilena, Jr, MD, PhD

JAMA Dec. 1990

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JAMA Dec. 1990

Glaxo Pulls Raxar, Cites Side Effects

By Stephen D. Moore
Staff Reporter of The Wall Street Journal

Glaxo Wellcome PLC withdrew an antibiotic called Raxar from more than 30 countries where it is sold, warning that the risk of rare side effects outweighs potential benefits.

Glaxo acquired rights to Raxar, known generically as grepafloxacin, three years ago from **Otsuka Pharmaceutical** Co. of Japan. But Raxar has been a commercial flop, with anemic sales of £10 million ($16.5 million) last year.

Heart-rhythm abnormalities had been observed in some patients during clinical trials and cited in the drug's prescribing instructions to physicians. Glaxo said it has monitored those heart-rhythm side effects more closely in additional clinical studies that, together with recent reports of patient deaths potentially linked with Raxar, prompted the decision to withdraw the drug.

"A recent review of data highlighted the fact that seven patients died [of heart-related events] while taking Raxar," a spokeswoman said. "We haven't yet established a causal relationship—but we can't rule it out either." Separately, three other patients taking Raxar have developed a rare condition called torsade de pointes that also involves irregular heartbeat.

An estimated 2.65 million prescriptions for Raxar have been filled since the drug was launched in August 1997.

Raxar is the second so-called quinolone antibiotic linked with side effects in recent months. Earlier this year, U.S. medical regulators advised physicians to limit use of Trovan, a quinolone from **Pfizer** Inc., after the drug was linked to severe liver side effects.

Meanwhile, drug makers **Bayer** AG and **SmithKline Beecham** PLC are counting on promising new quinolone antibiotics to provide big sales boosts, but one analyst said that the clinical data assembled for those drugs is much more impressive than Raxar's.

In New York Stock Exchange composite trading yesterday, Glaxo American depositary shares rose 25 cents to $59.8125.

Wall Street Journal
Oct. 28, 1999

Torsade
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JAMA Dec. 1990

Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2005
ICH

et Journal
999

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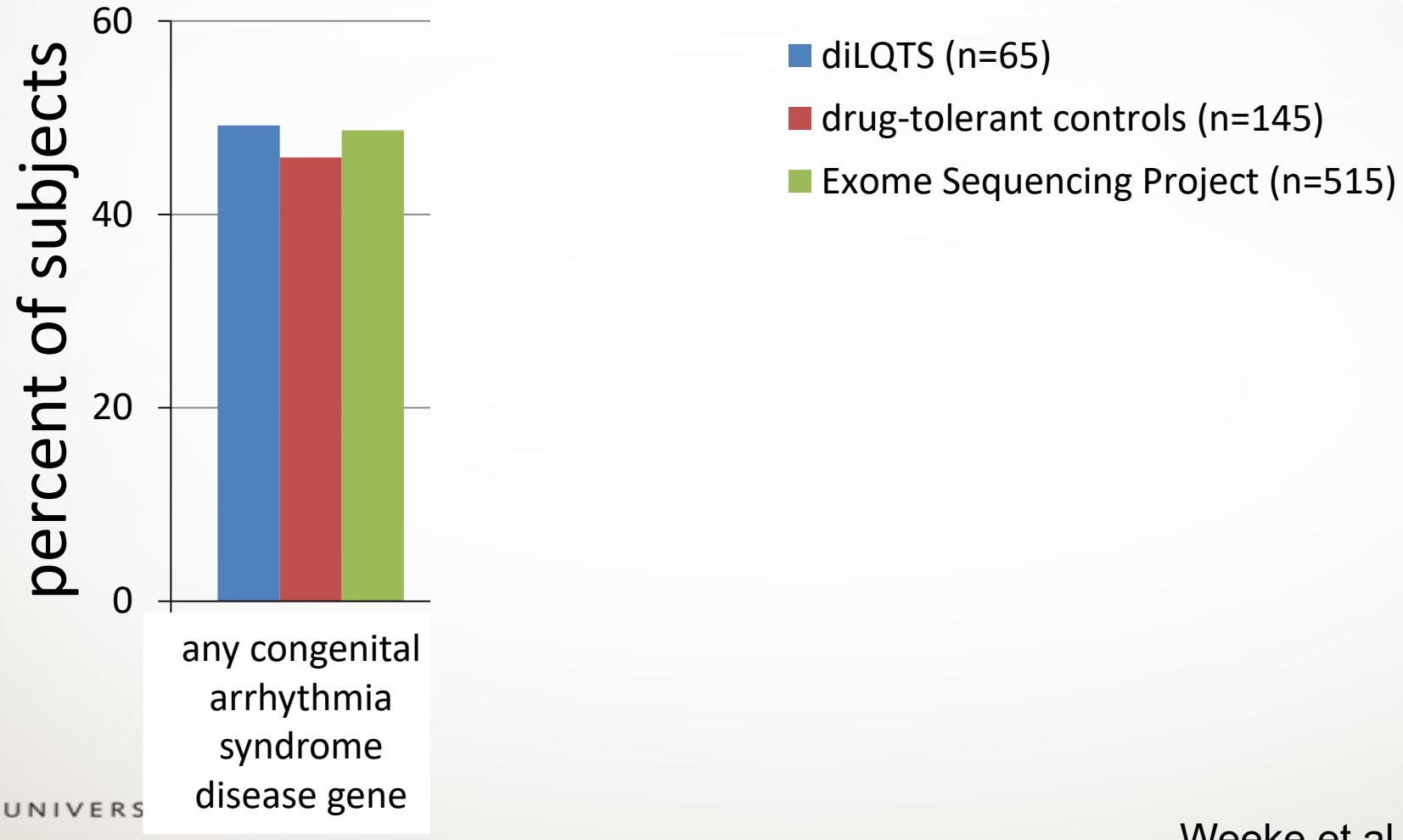
Click Here — Quick Search QTdrugs for a drug (No registration required)

Click Here — Review QTdrugs list (Free, registration required)

Attention All Commercial Users of QTdrugs Technology

Exome sequencing to answer the question "Is drug-induced long QT syndrome actually just unrecognized/non-penetrant congenital LQTS?"



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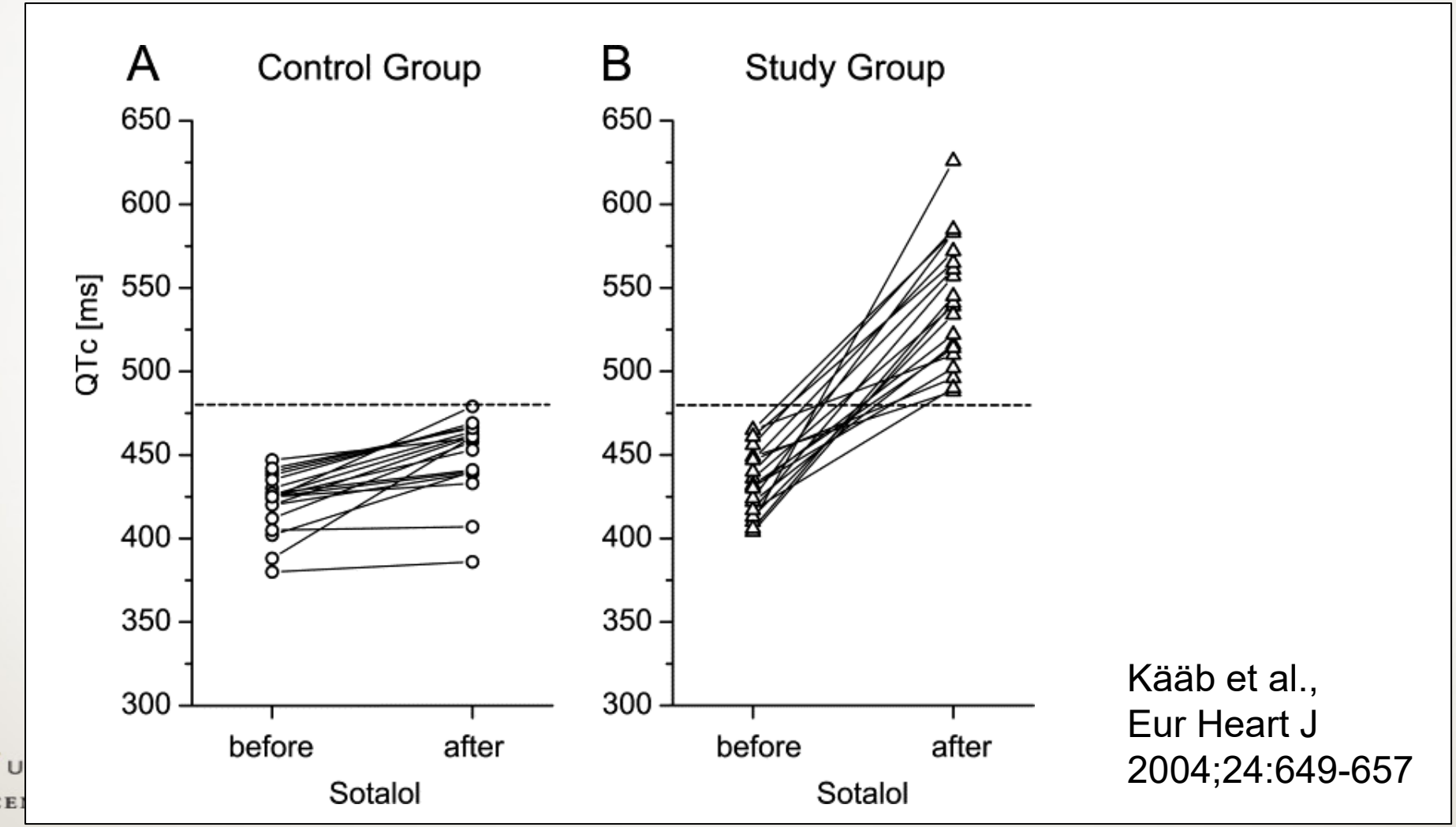
Weeke et al., 2014

Rechallenge of patients presenting with drug-induced torsades supports the idea that some patients have reduced repolarization reserve



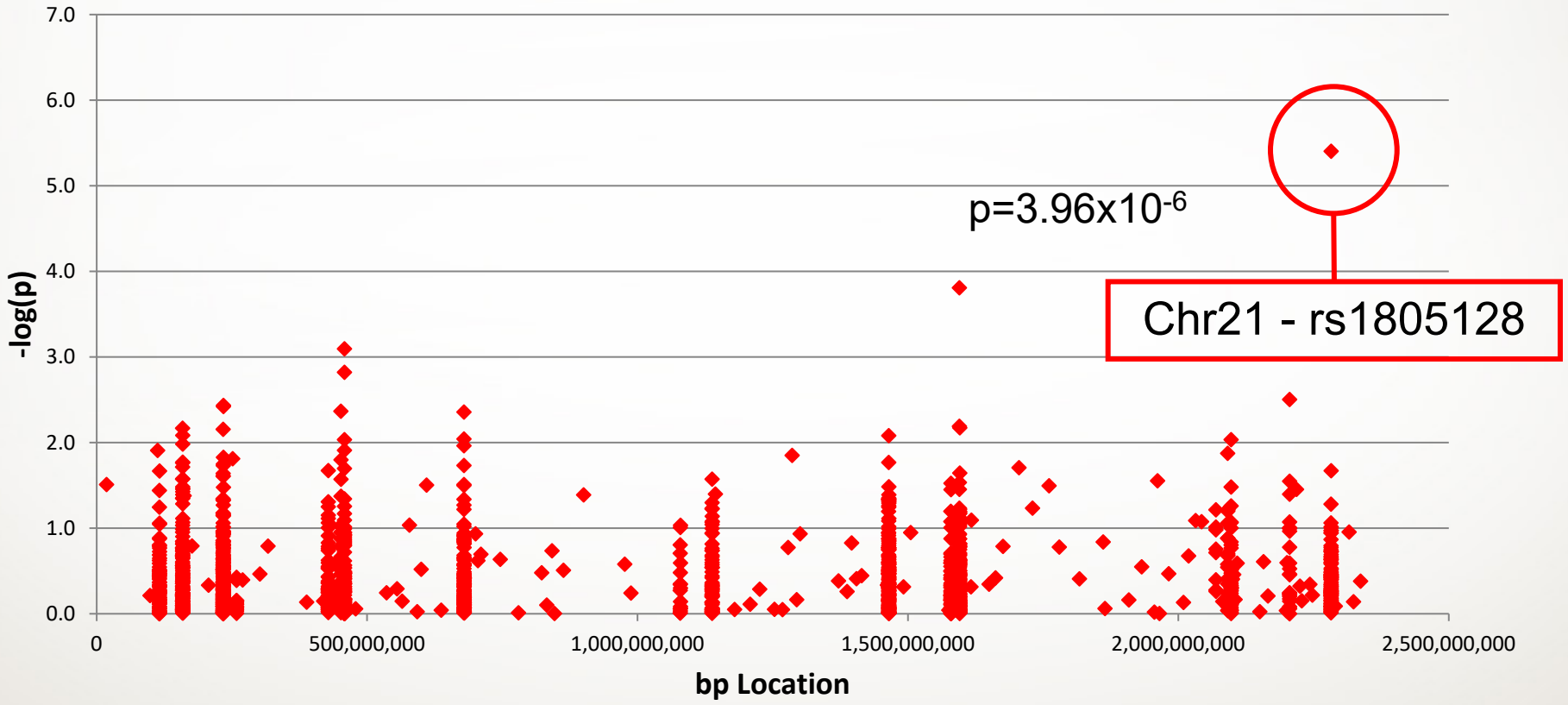
Kääb et al.,
Eur Heart J
2004;24:649-657

2005

Alliance Against SCD

176 cases versus 207 drug-exposed controls with no QTc>50 msec

~1500 Candidate SNPs/18 genes



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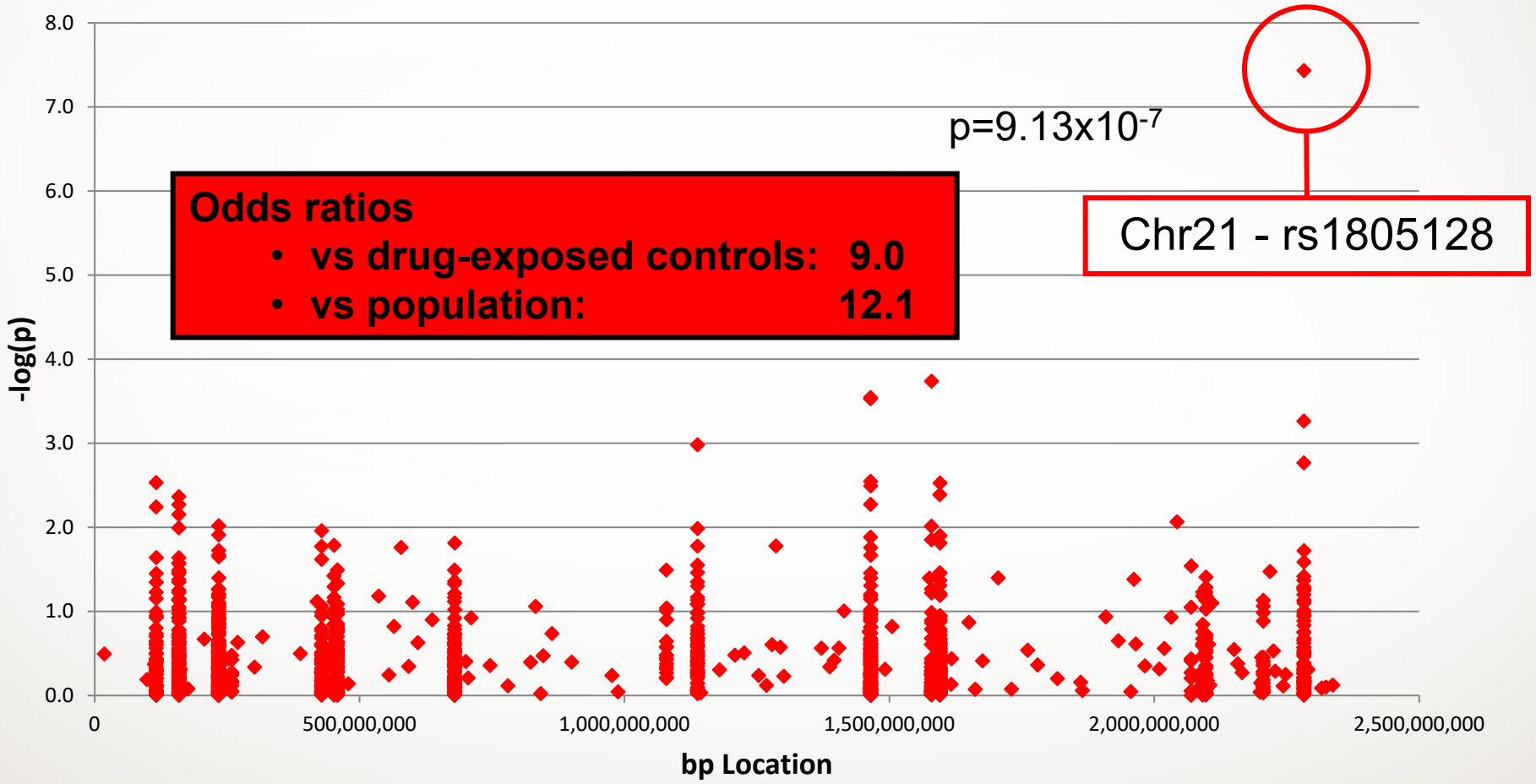
Kääb et al., 2012

176 cases versus 837 population controls

~1500 Candidate SNPs/18 genes



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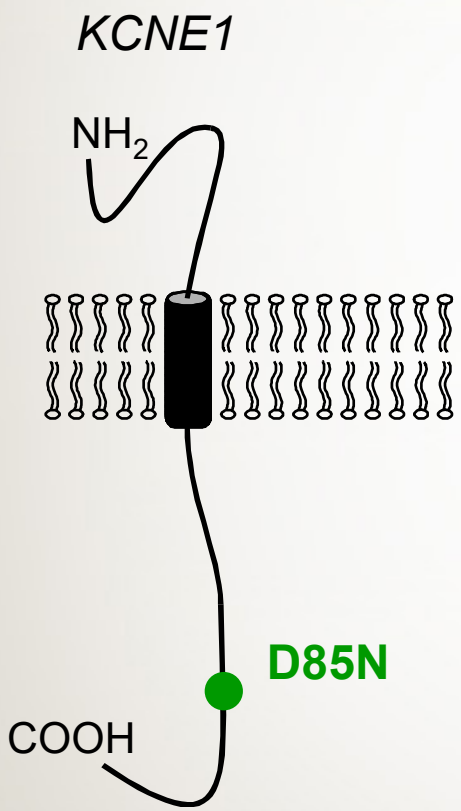
Kääb et al., 2012

Chr21 - rs1805128



- Key component of I_{Ks}
- Rare *KCNE1* mutations cause congenital long QT syndrome
- In vitro electrophysiology: D85N → mild reduction in I_{Ks}, no change in computed action potential duration, potentially arrhythmogenic at slow rates when I_{Kr} is reduced.

Population Frequencies

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Ashkenazi Jewish	263	10368	5	0.02537
European (Finnish)	424	25120	7	0.01688
European (non-Finnish)	1580	129142	9	0.01223
Other	65	7228	0	0.008993
East Asian	111	19946	0	0.005565
Latino/Admixed American	97	35438	1	0.002737
African/African-American	54	24956	0	0.002164
South Asian	43	30616	0	0.001404
XX	1174	129438	9	0.009070
XY	1463	153376	13	0.009539
Total	**2637**	**282814**	**22**	**0.009324**

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Data on other common polymorphisms

- Presented, in review.
- Coming soon.

Summary

- The past 3 decades have seen the definition of (most of) the major molecular and genetic mechanisms controlling normal repolarization in the heart.
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