

# **Pharmacogenomics of Drug-Induced Conditions**

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Director, Oates Institute for Experimental Therapeutics

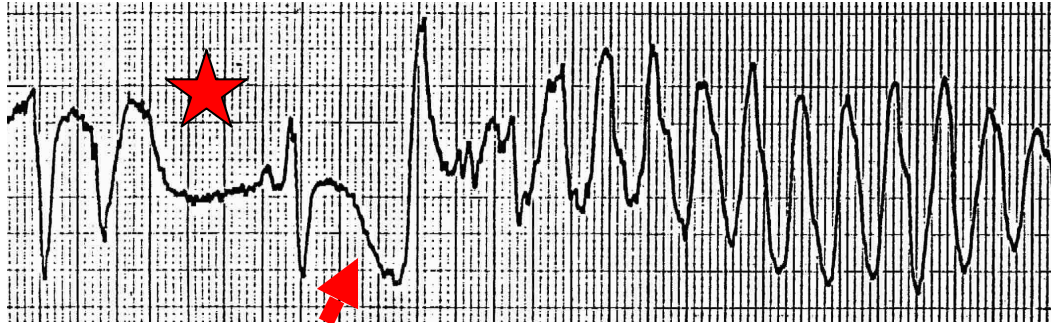
Assistant Vice-Chancellor for Personalized Medicine

Vanderbilt University School of Medicine

# An “idiosyncratic” drug response

AR, 78 year old male

- Coronary artery disease; 13 years s/p bypass surgery
- 2 days after starting dofetilide (potent  $I_{Kr}$  blocker)...



No personal or family history of syncope, sudden death

- *KCNQ1* variant leading to R583C identified
- *In vitro*:  $\downarrow I_{Ks}$
- Not found in >400 ethnically-matched controls
- $\therefore$  this is likely subclinical congenital Long QT Syndrome

# Another face of the congenital long QT syndrome

## LOCAL NEWS

# Teen collapses, dies at basketball practice

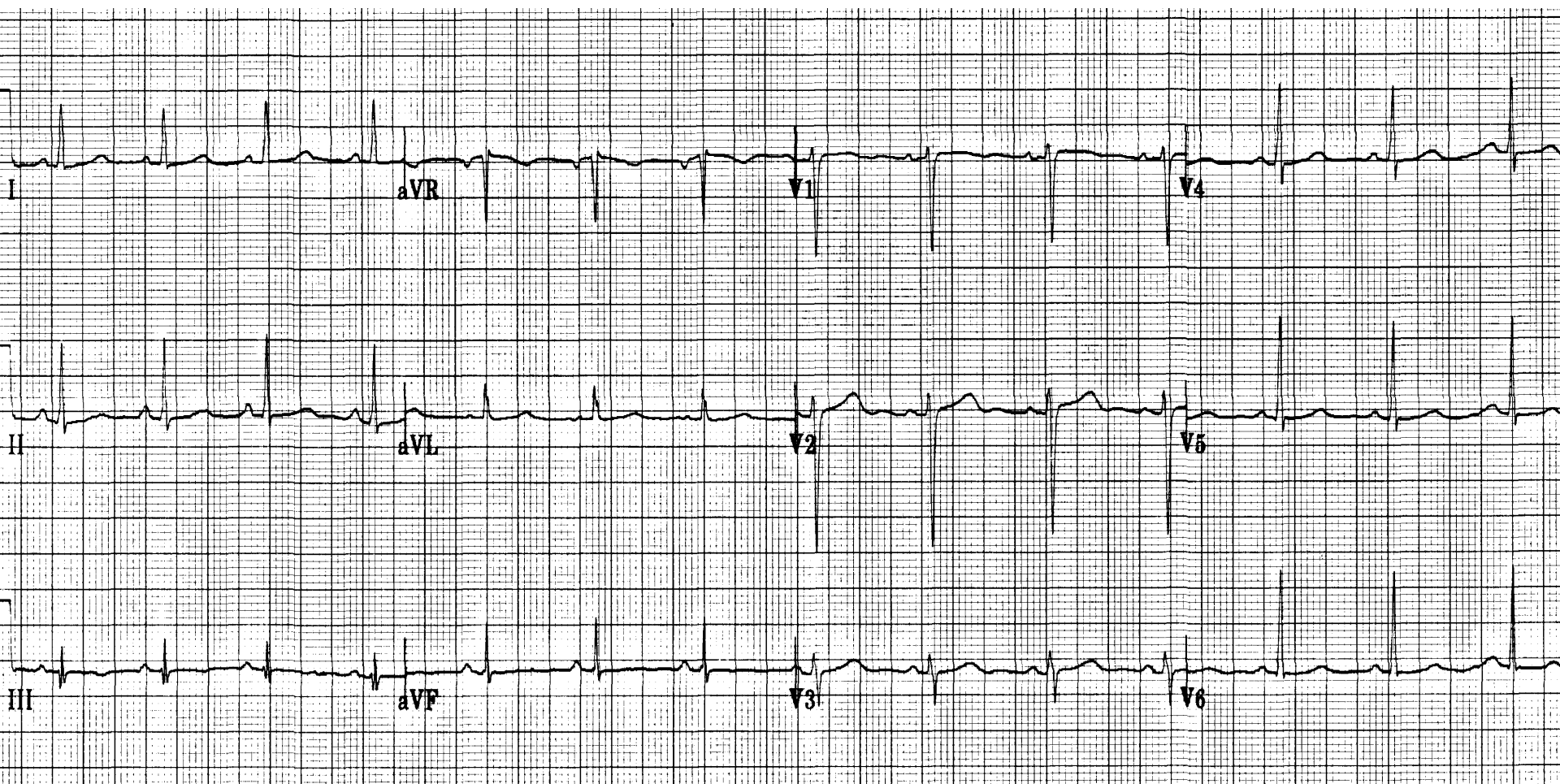
By **LEON M. TUCKER**

*Staff Writer*

**ASHLAND CITY** — Students at

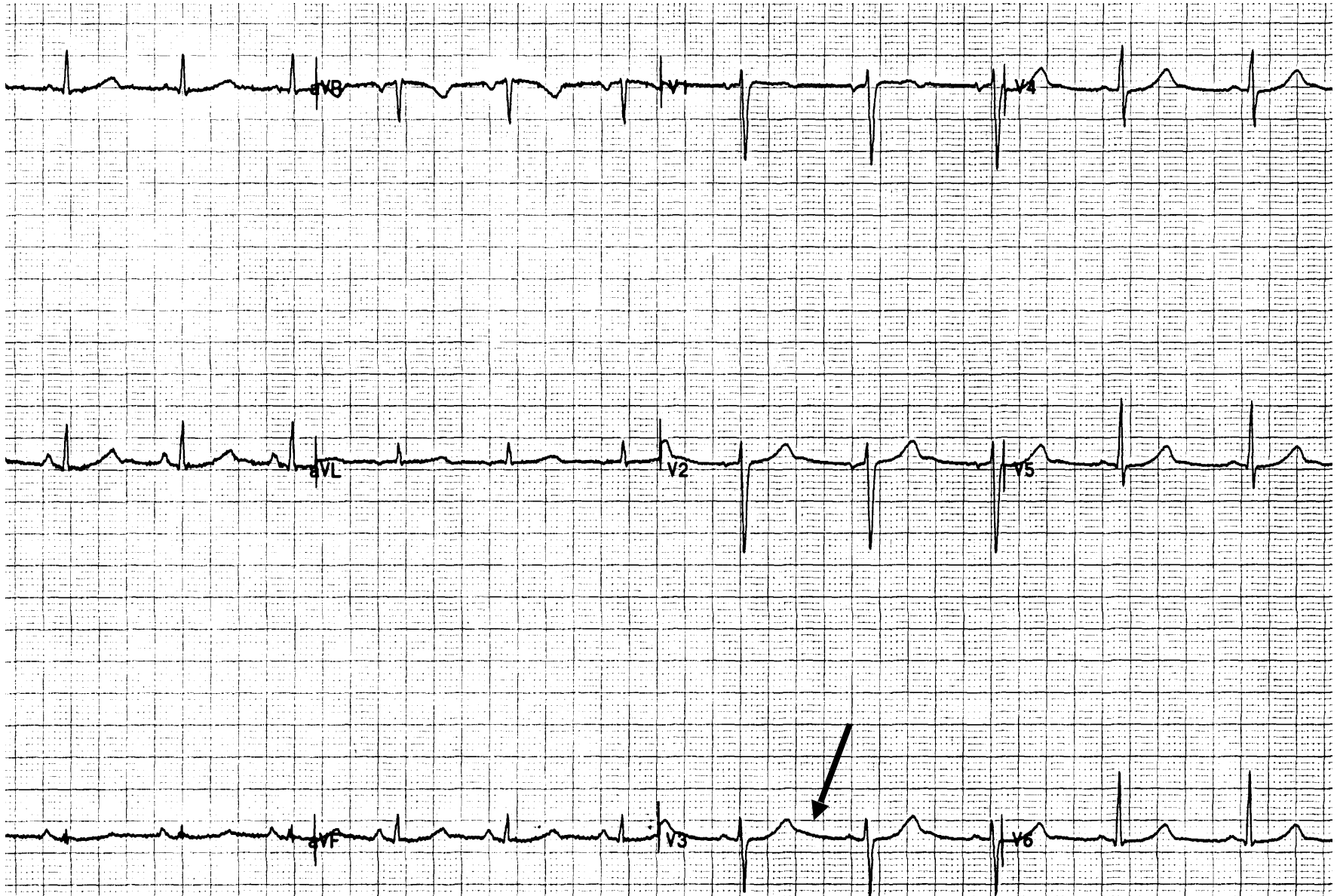
in a sports-related activity and I wonder if we are asking too much of our children." ▲

# Father's ECG

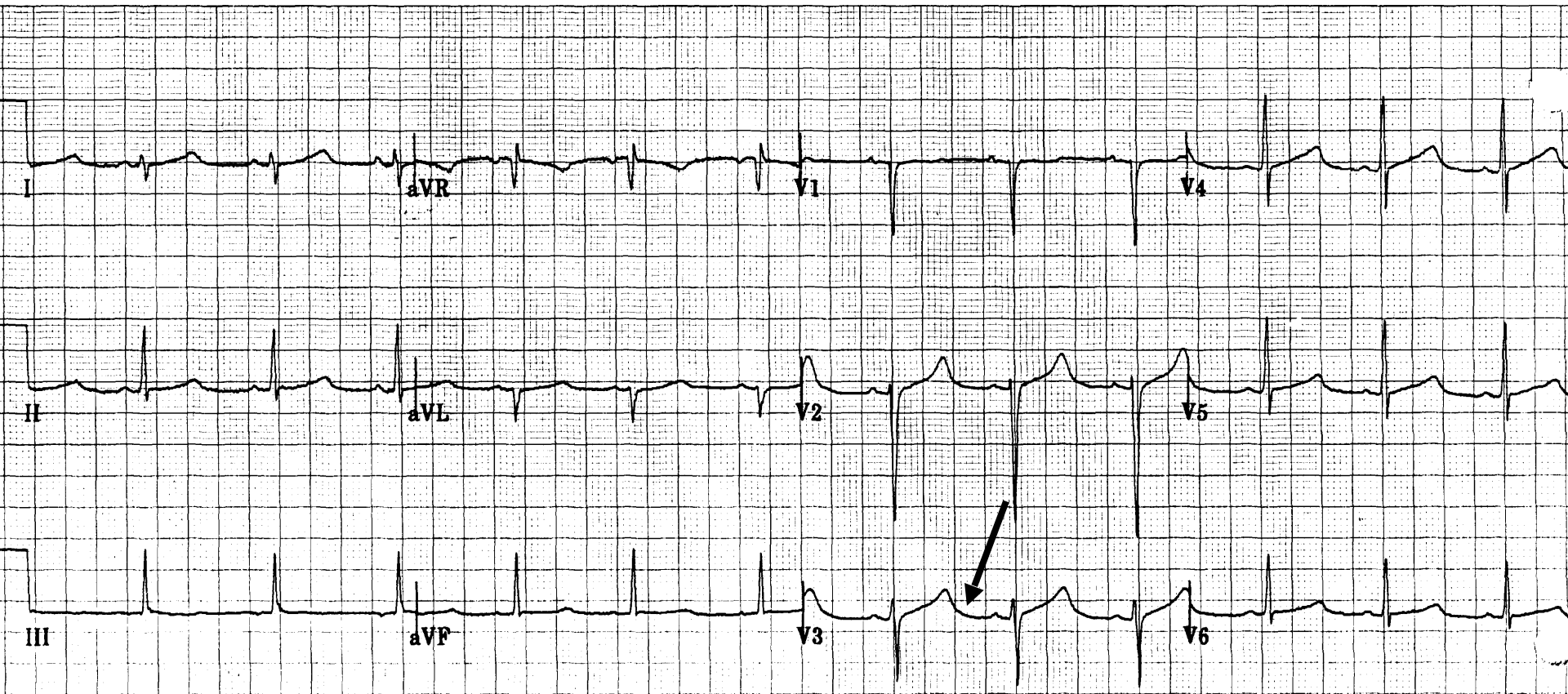




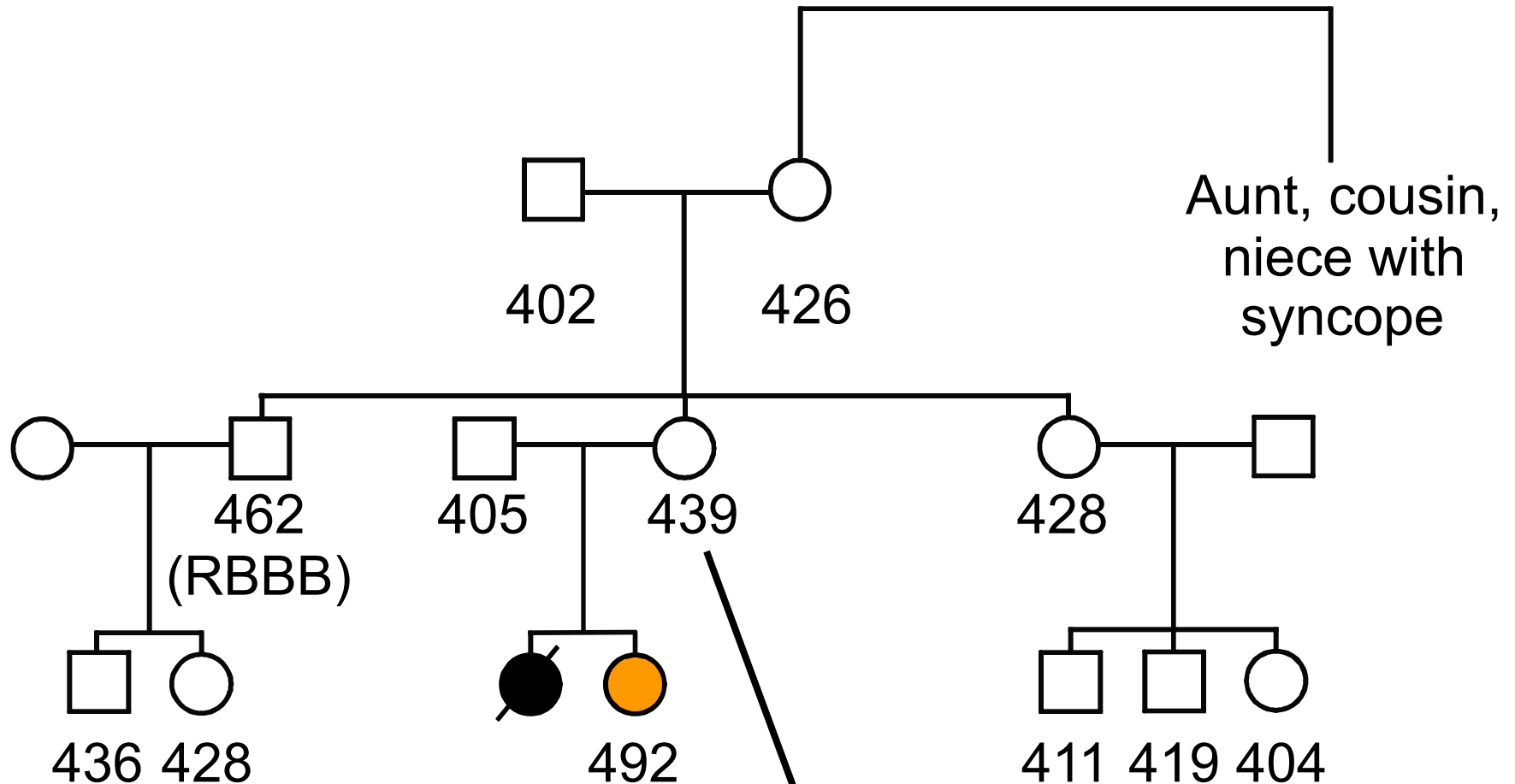
# Mother's ECG



# 9-year-old sister's ECG

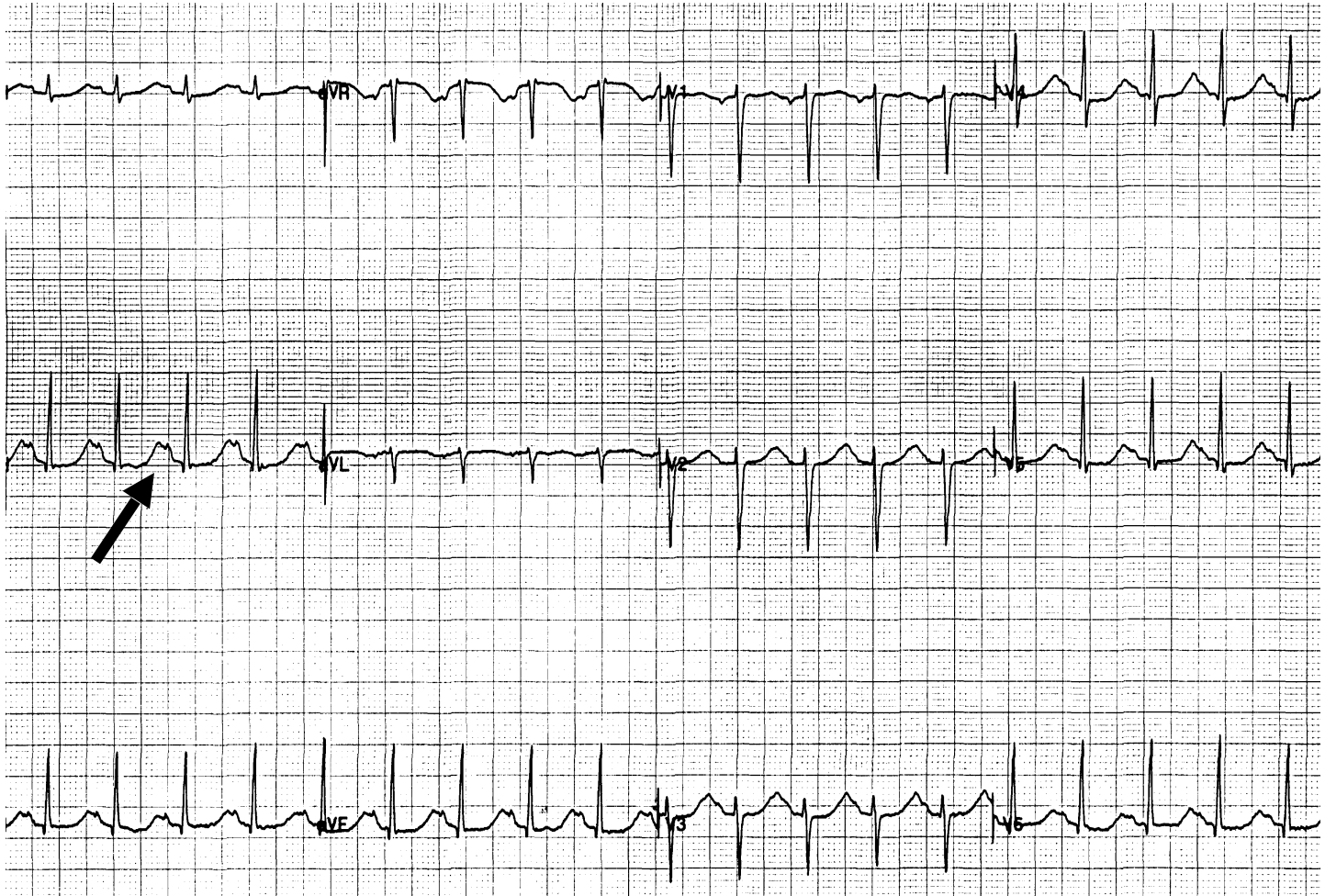


# Family tree



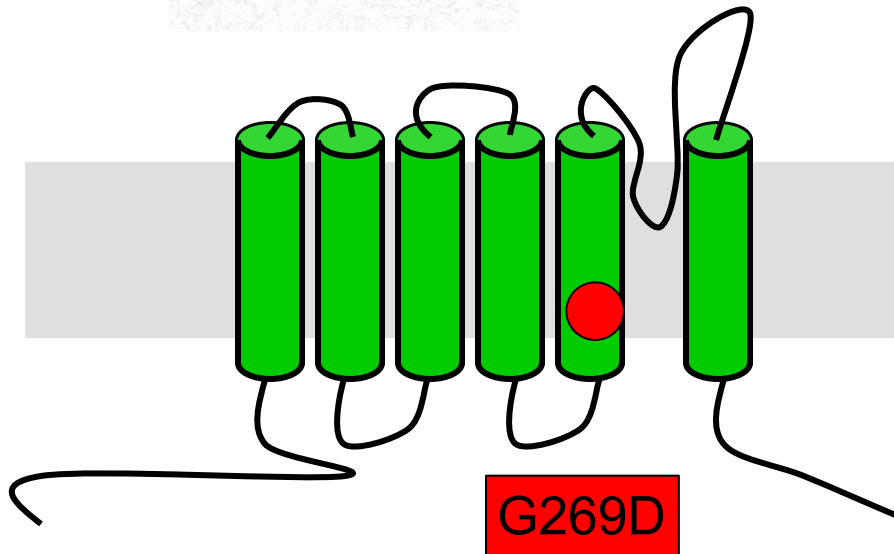
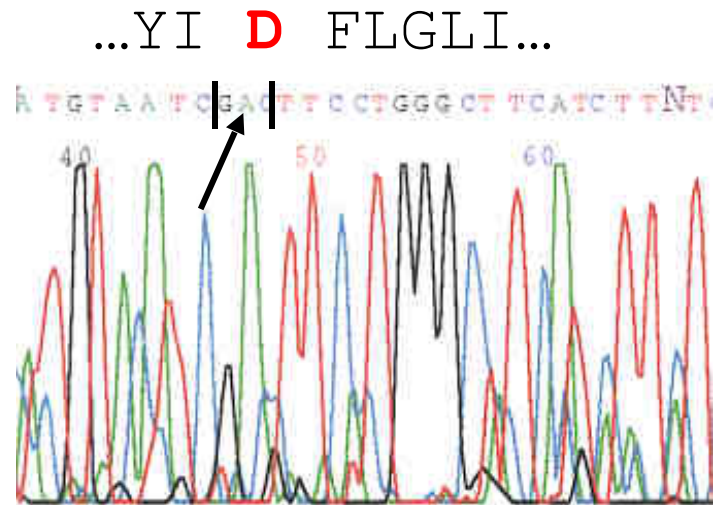
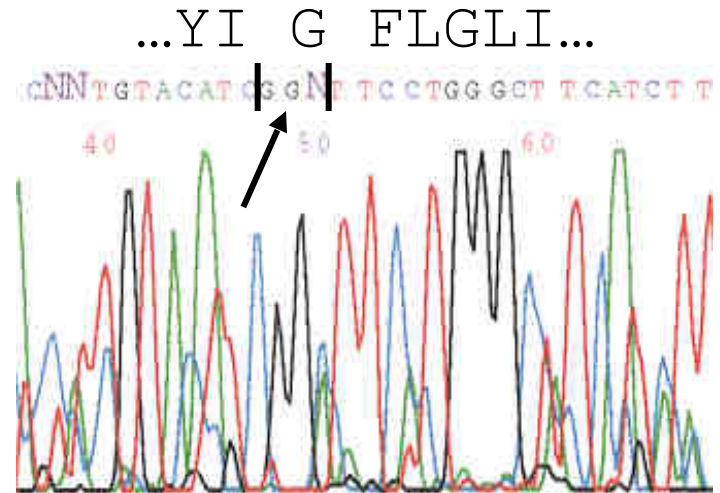
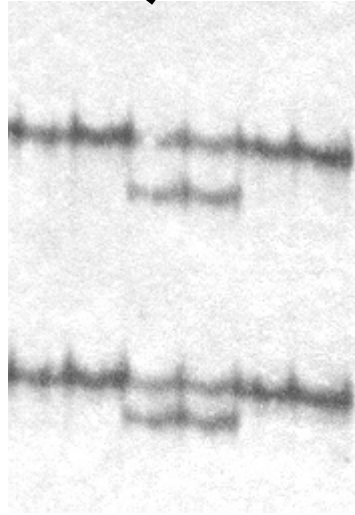
- One episode of syncope, age 20
- Multiple ER visits for acute allergic reactions → epinephrine without incident

# Mother's ECG post-exercise

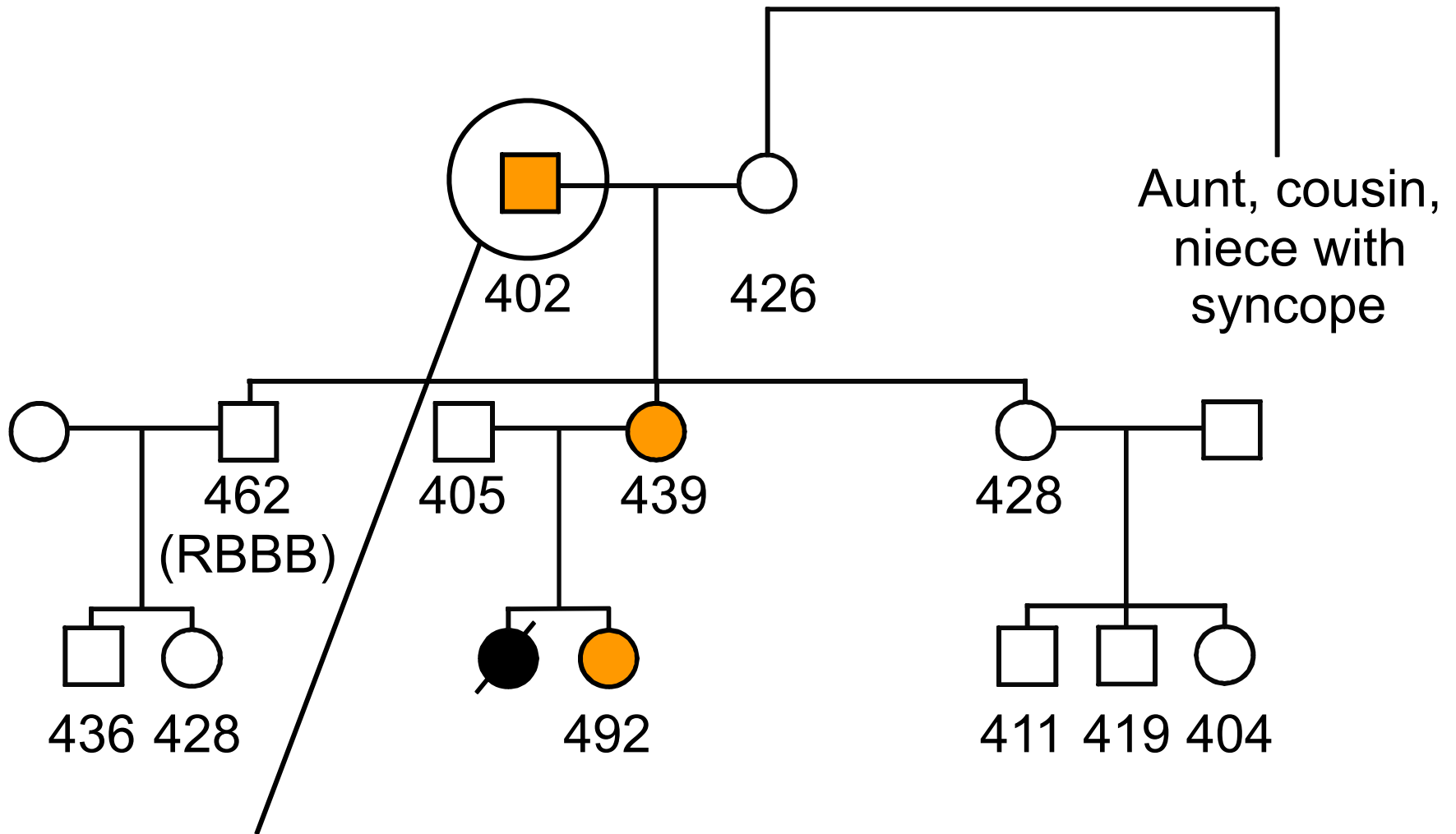


# Identifying a mutation in KCNQ1

mother  
sister



# Family tree



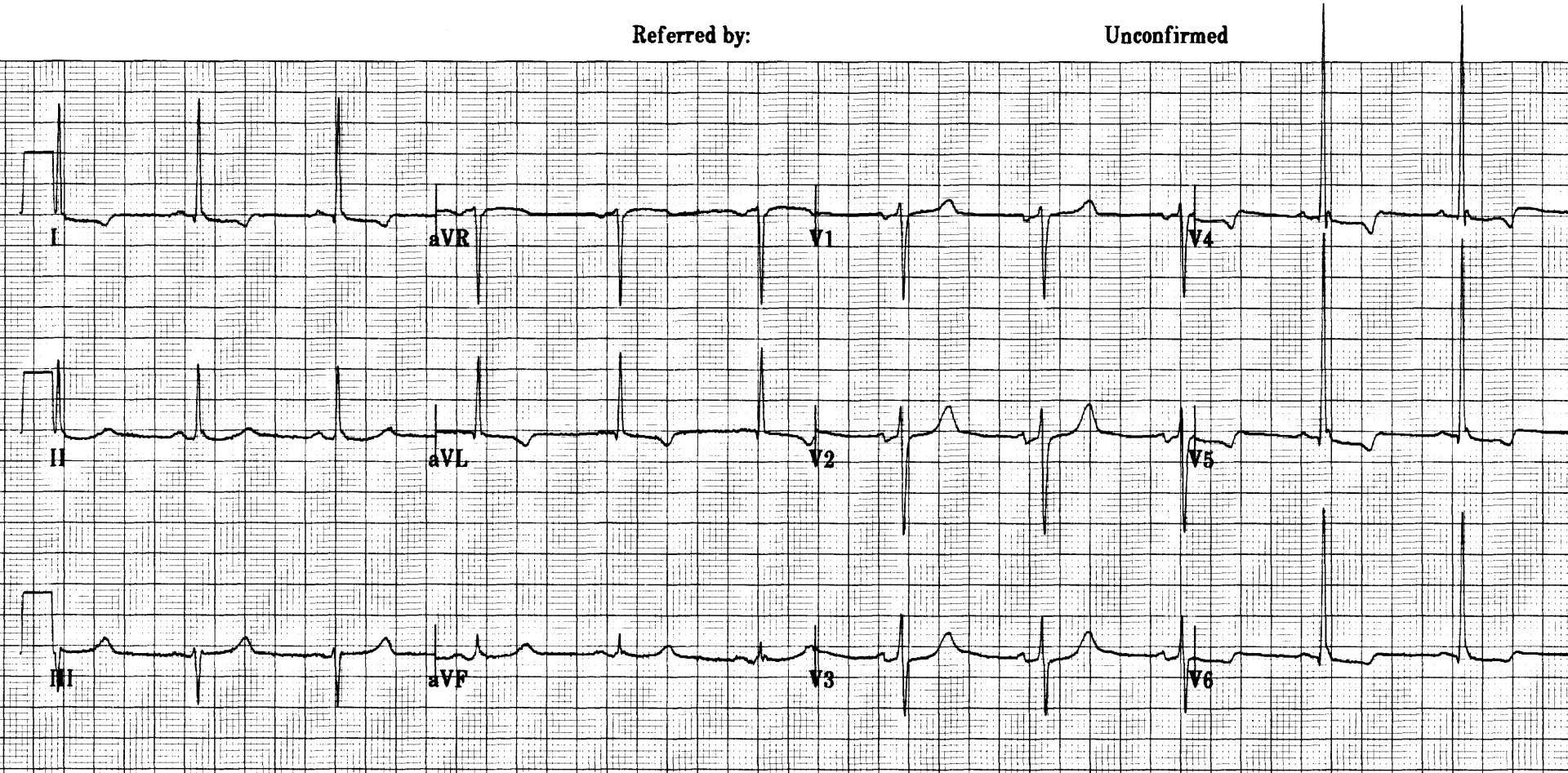
Incomplete penetrance



# Grandfather's ECG

Referred by:

Unconfirmed



# Defining the “drug-induced long QT syndrome”

- Marked QT prolongation and typical pause-dependent torsades de pointes with drug challenge, both resolving with drug withdrawal
- Variants:
  - Marked QT prolongation (e.g. >520 or 550 or 600 msec), recognized and drug withdrawn (no torsades)
  - pause-dependent polymorphic VT after administration of a suspect drug  $\pm$  modest QT prolongation often with underlying heart disease
  - No pause-dependence
- What is the culprit drug? Sometimes, initiating drug A may  $\rightarrow$  marked elevation of plasma concentrations of drug B, which is the actual culprit

# Drugs associated with Torsades de Pointes

## Torsades de Pointes common

Antiarrhythmics	disopyramide
	dofetilide
	ibutilide
	procainamide
	quinidine
	sotalol

<http://www.torsades.org>

## Other drugs clearly associated with Torsades de Pointes

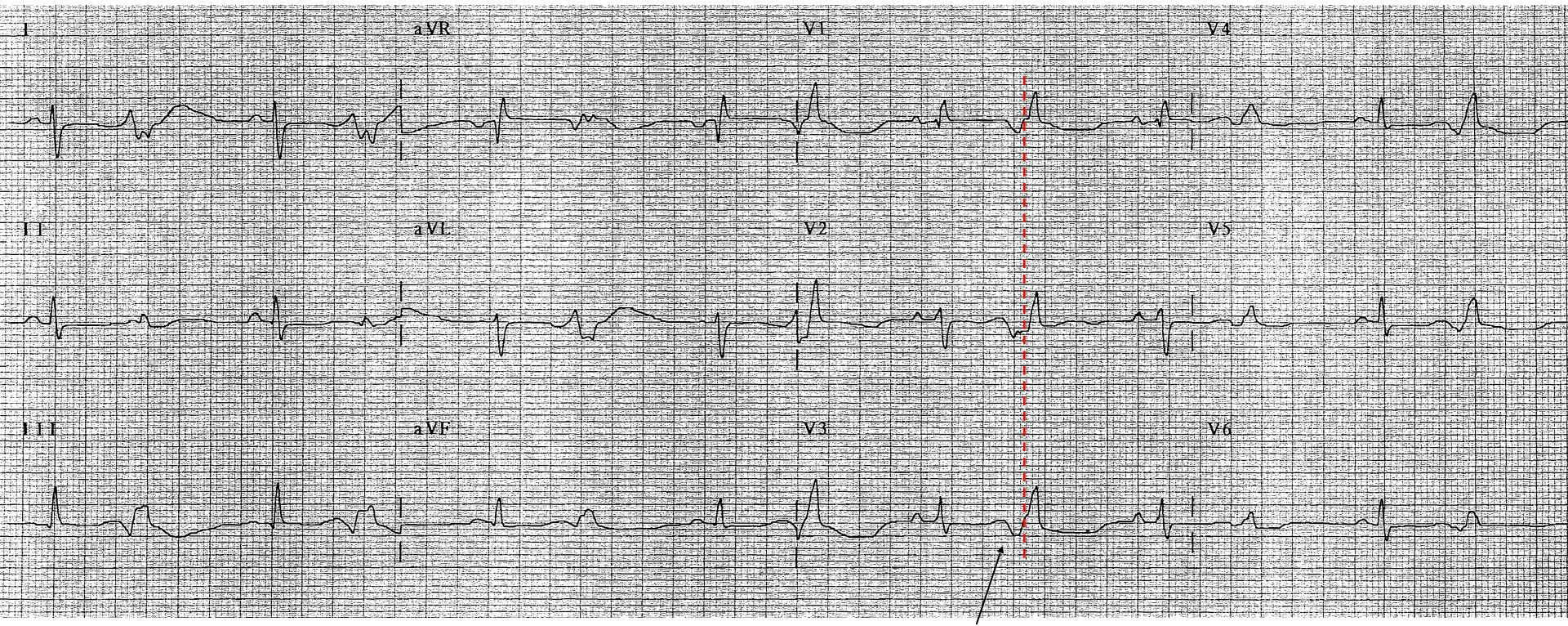
amiodarone	
arsenic trioxide	
anti-infectives:	clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
anti-emetics:	domperidone, droperidol
anti-psychotics:	chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
opioid dependence:	levomethadyl, methadone

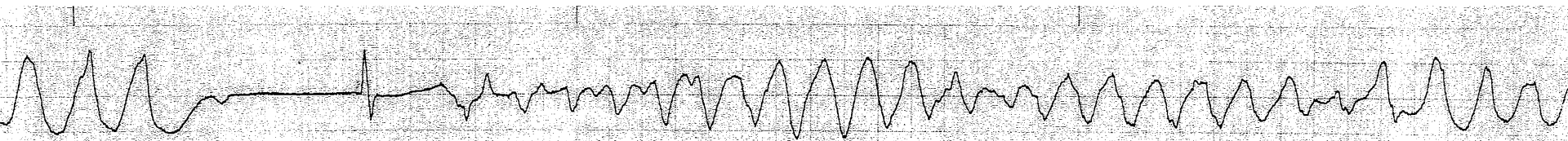
# Risk factors for diLQTS

- hypokalemia, underlying bradycardia, (hypomagnesemia)
- female gender
- recent conversion from atrial fibrillation to sinus rhythm
- CHF, ?LVH
- higher risk with higher dose/concentration (exception: quinidine)
  - Overdose
  - Impaired excretion
    - Disease of excretory organs: sotalol/dofetilide – kidneys
    - Co-administration of drugs inhibiting specific metabolic pathways
- presence of other (usually unrecognized) risk factors, often with “baseline” ↑QT:
  - congenital long QT syndrome
  - common DNA polymorphisms?
  - other QT-prolonging drugs



# 40 year old with opioid dependence on chronic methadone admitted with syncope







# **Methadone and TdP: the usual suspects**

- 17 patients (+ 1 sudden death after a recent dose increase)
- 10 female; 7 male
- High doses
- Recent dose increases
- Inhibition of drug metabolism
- $K^+ < 4.0$ : 7/17
- Not much structural heart disease

Krantz et al; Ann Int Med 2002



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## Pathologist: Meds Killed Daniel Smith

WEDNESDAY SEPTEMBER 27, 2006 05:10PM EST

THURSDAY SEPTEMBER 28, 2006 08:10AM EST UPDATED

By Nicole Weisensee Egan



Daniel and Anna Nicole Smith

PHOTO BY: INF

The death of Anna Nicole Smith's 20-year-old son Daniel was caused by a lethal combination of methadone, Zoloft and Lexapro, pathologist Dr. Cyril Wecht has revealed to PEOPLE.

Wecht said the drugs caused the cardiac dysrhythmia that led to Daniel's death. Wecht got the toxicology results from National Medical Services in Willow Grove, Pa., on Wednesday.

"In my opinion it's an accidental death," Wecht tells PEOPLE.

Wecht said that because Daniel was taking three drugs and not a large dose of a single drug, paired with the fact that he was celebrating a happy occasion with his mother, those factors point to a "tragic accidental drug death."

Asked why Daniel may have been taking methadone, which is sometimes used to help heroin addicts end their addiction, Wecht said the drug is "a legitimate

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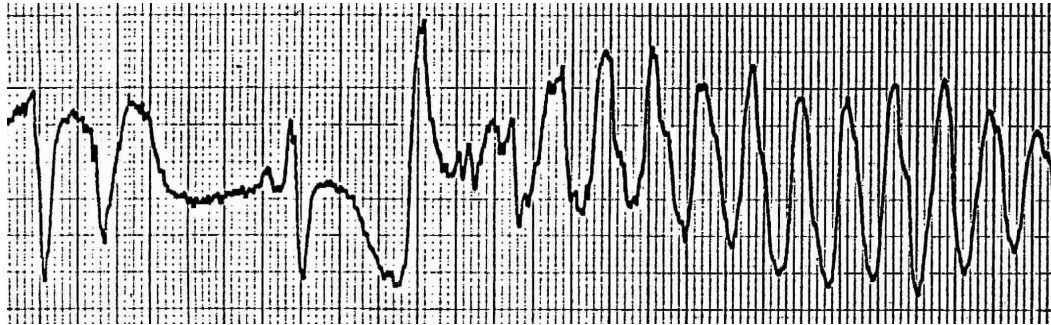


From EW.com

# An “idiosyncratic” drug response

AR, 78 year old male

- Coronary artery disease; 13 years s/p bypass surgery
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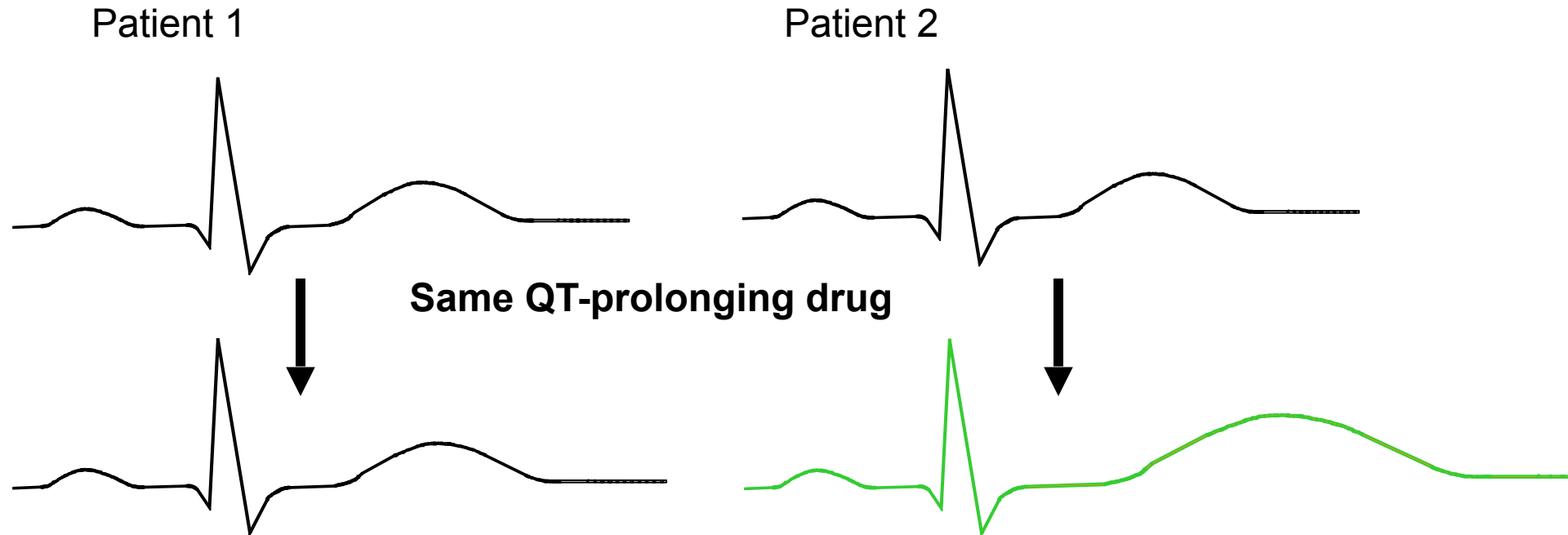
No personal or family history of syncope, sudden death

- *KCNQ1* variant leading to R583C identified
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- Not found in >400 ethnically-matched controls
- $\therefore$  this is likely subclinical congenital Long QT Syndrome

# How did AR avoid arrhythmias for 2,000,000,000 heart beats?

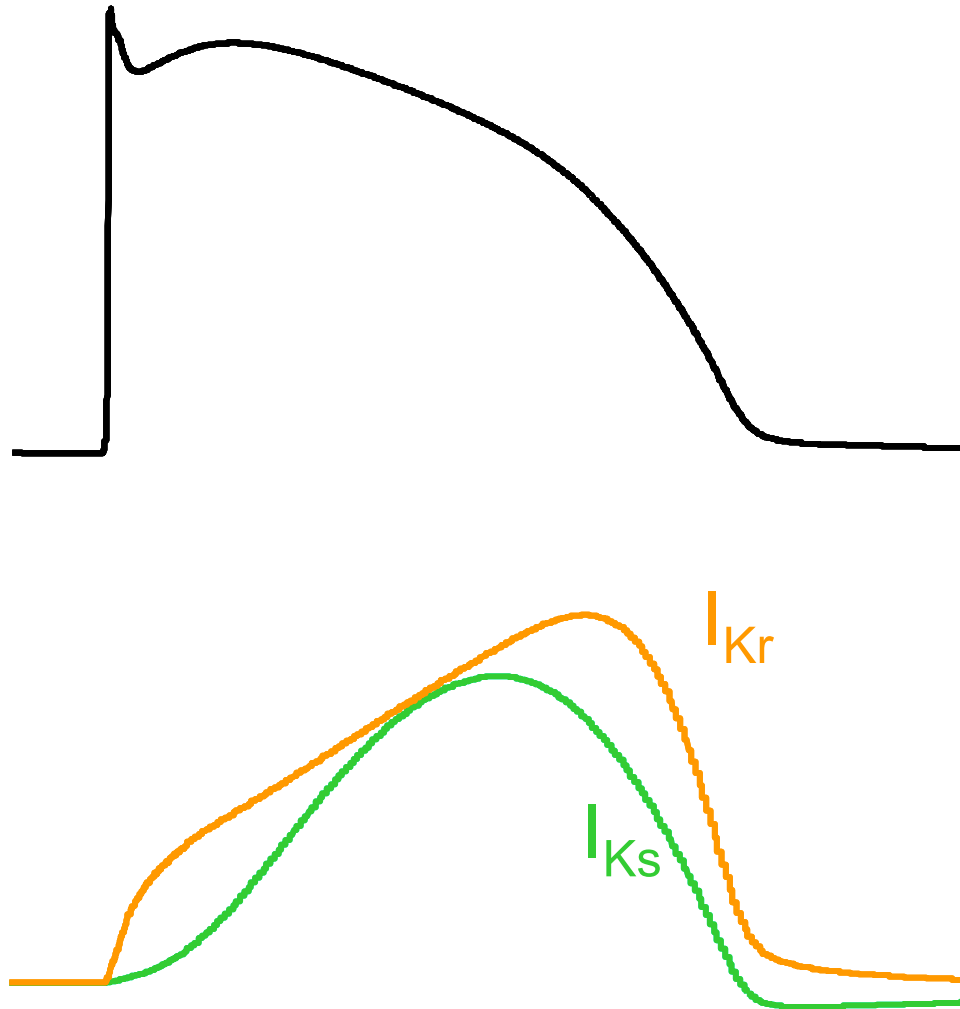
## The concept of reduced repolarization reserve

- Redundancy (“reserve”) in cardiac repolarization allowed him to maintain a normal QT until other lesions (heart disease, dofetilide) were superimposed.

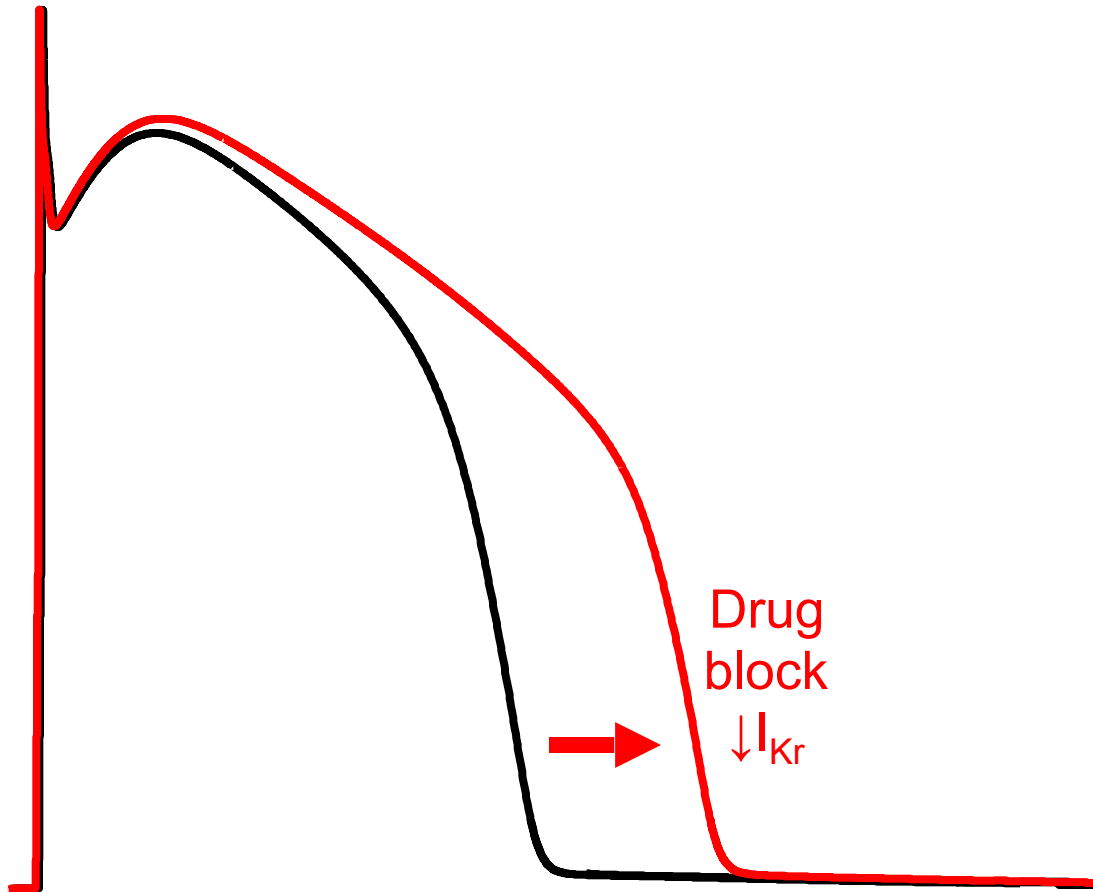


# A thought problem: how to test the hypothesis that a variant like KCNQ1/R583C actually increases arrhythmia risk?

- Association studies in large numbers of well-phenotyped subjects
- Genetically-modified mouse or other animal model
- Simulation “in silico”

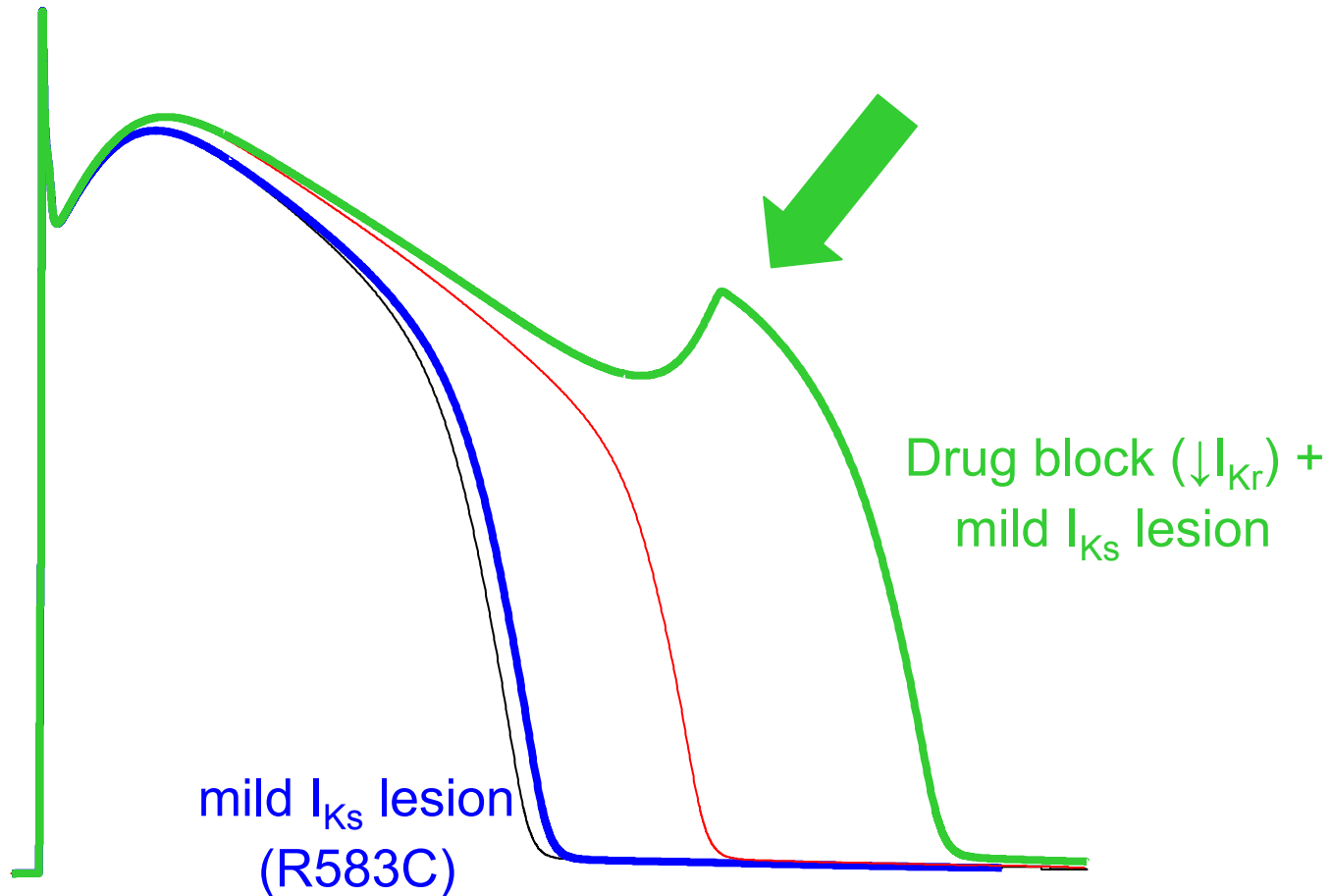


# $I_{Ks}$ lesion and repolarization reserve: a simulation example

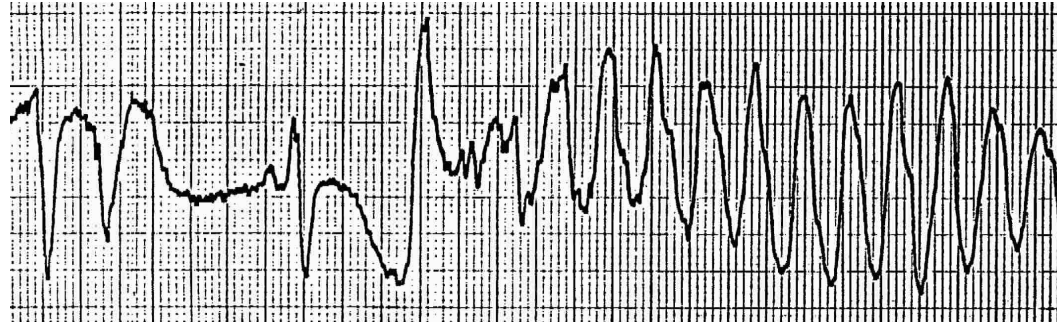




# $I_{Ks}$ lesion and repolarization reserve: a simulation example



# Drug-induced Torsades de Pointes



- ~5-10% of affected patients harbor mutations
- Mutations: Rare, usually disease-associated
- Polymorphisms:
  - Common ( $>1\%$ )
  - May or may not affect protein function
  - $>10,000,000$  Single Nucleotide Polymorphisms ("SNPs") in "the" human genome

# An example of a SNP

- *KCNA5* encodes a potassium channel protein expressed in human atrium
- In one region of the gene, the DNA sequence in 98% of patients is  
...GCGTCCACATCAACATCTC**C**GGGCTGCGCTTTGAGACGCA... but  
...GCGTCCACATCAACATCTC**T**GGGCTGCGCTTTGAGACGCA... in  
the other 2%
- In this case (but not all cases), this results in an amino acid change: ...ASTSTS**P**GCALRR... → ...ASTSTS**L**GCALRR...
- In this case (but not all cases), this amino acid change also changes the way the channel behaves *in vitro*. We would like to know if it has an effect in patients: AF susceptibility? Variable drug response in AF?

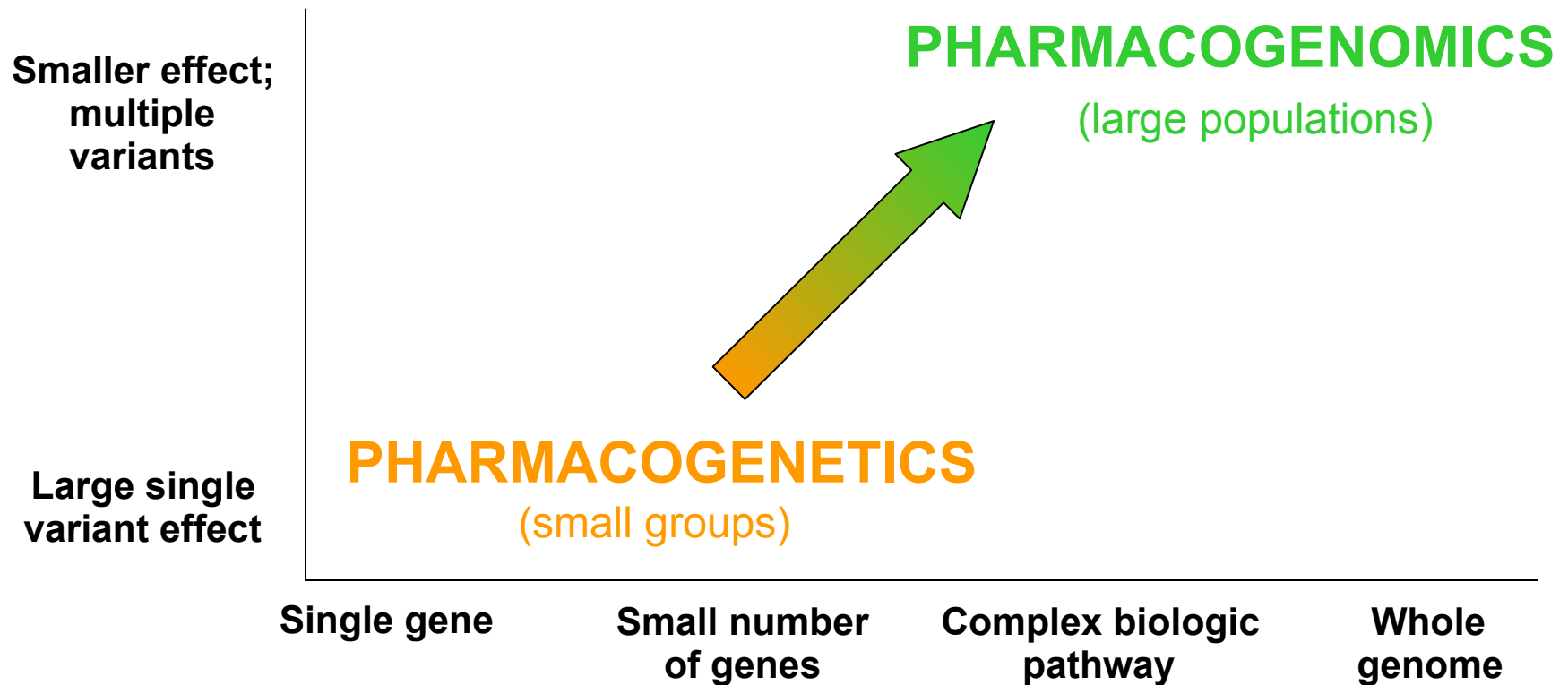
# An ethnic-specific polymorphism mediating arrhythmia susceptibility

**Table 1.** SCN5A variant frequencies in African-American arrhythmia cases and controls. Y, Y1102 allele; S, S1102 allele. Numbers in parentheses indicate the portion of each genotype as a percentage of the total cases or controls.

Genotype	Arrhythmia cases ( <i>n</i> = 23) (%)	Controls ( <i>n</i> = 100) (%)	Odds ratio (95% CI)*	<i>P</i> †
Y,Y	2(8.7)	0(0.00)		
S,Y	11(47.8)	13(13.0)		
S,S	10(43.5)	87(87.0)		
S,Y + Y,Y	13(56.5)	13(13.0)	8.7(3.2–23.9)	0.000028

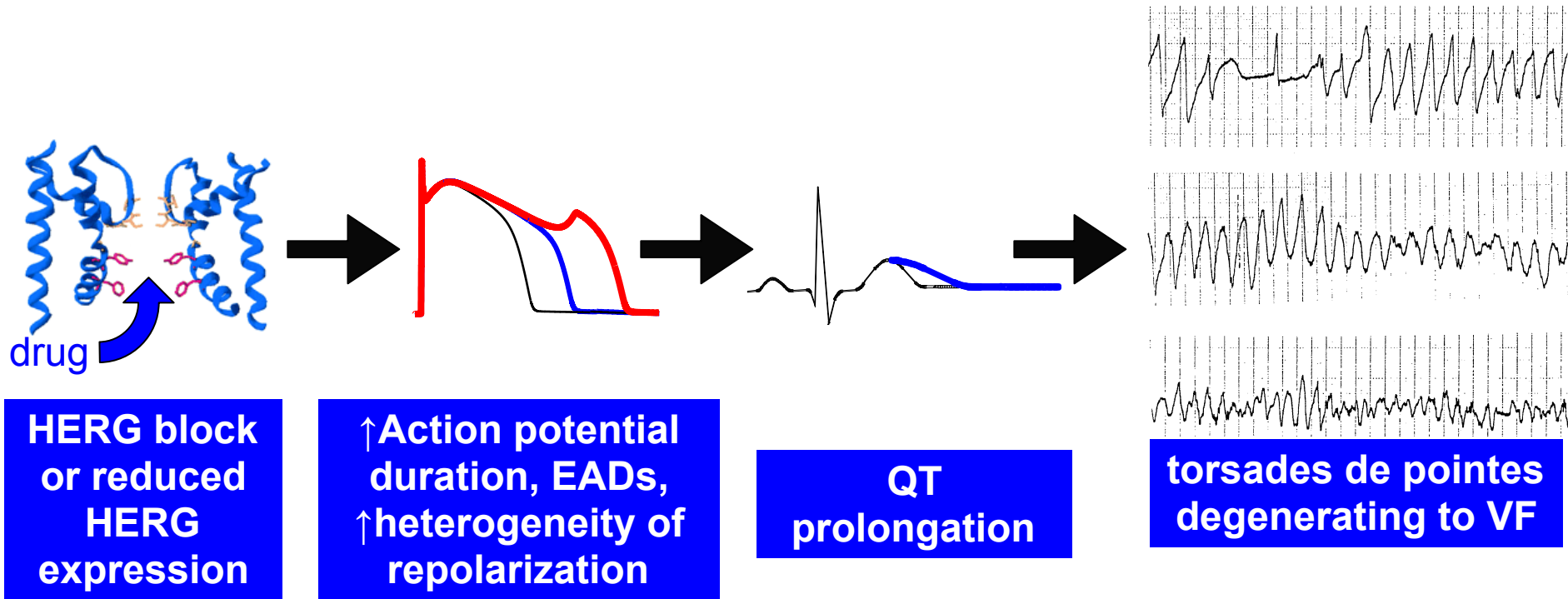
\*Odds ratio for the likelihood of arrhythmia in Y carriers (S,Y + Y,Y) versus noncarriers (S,S). †*P* value for the comparison of carriers (S,Y + Y,Y) and noncarriers (S,S) in cases and controls (Fisher's exact test).

Splawski et al., 2002



- Rare coding region variants (polymorphisms or mutations)
- Commoner coding and regulatory variants
- Detectable effects of polymorphisms in >1 gene
- Pathway analysis and whole genome approaches

# The chain between $I_{Kr}$ block and torsades de pointes contains many links



## Candidate mechanisms contributing to variability

drug  
metabolism  
or transport

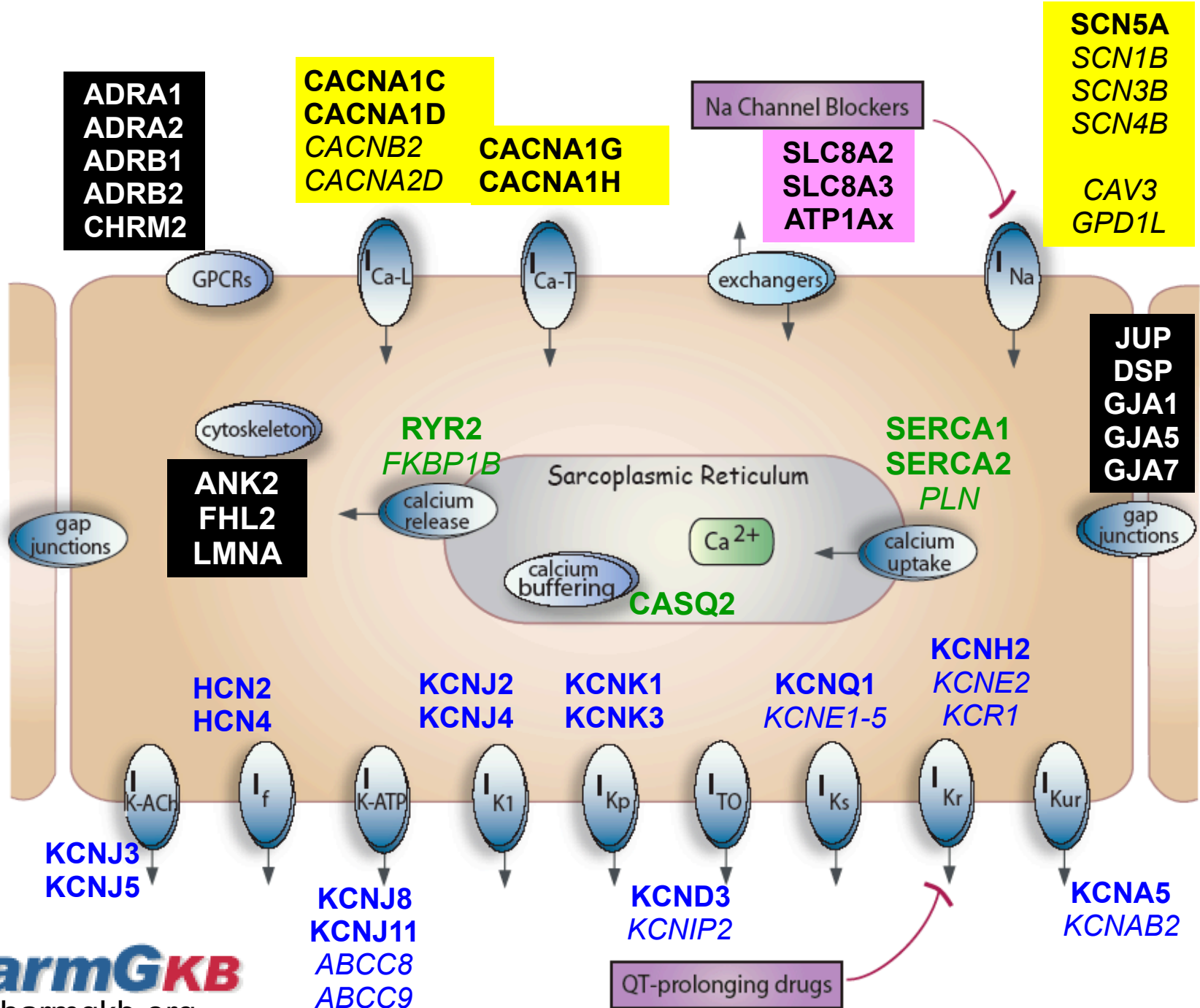
contributions of other genes in  
determining action potential and QT  
durations when HERG is blocked

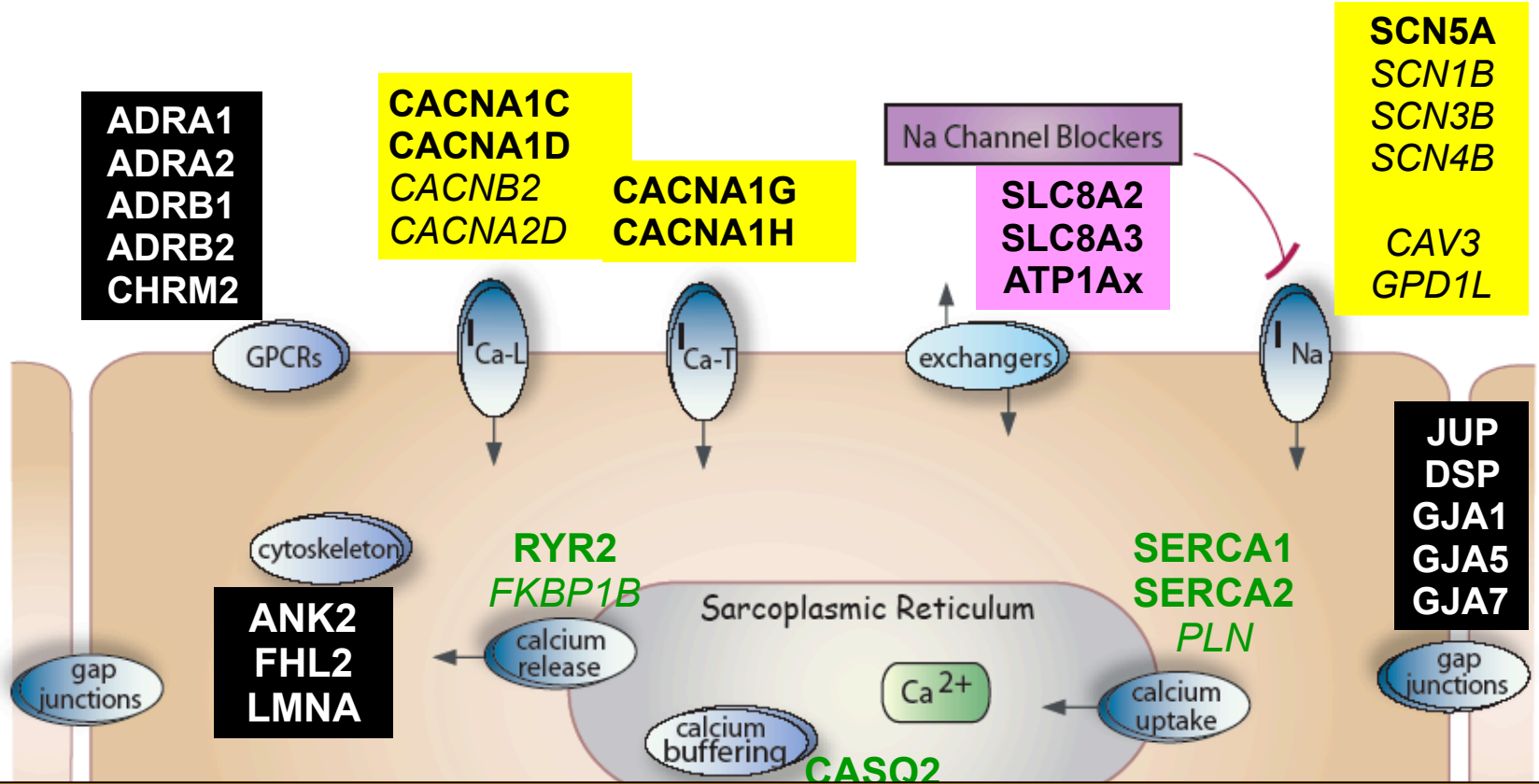
A vulnerable  
substrate?

HERG variants

Roden and Viswanathan, JCI, 2005







# The Rhythmonome

©Al George

Exogenous triggers

**KCNJ5**  
**KCNJ5**

**KCNJ8**  
**KCNJ11**  
**ABCC8**  
**ABCC9**

**KCND3**  
**KCNIP2**

**KCNA5**  
**KCNAB2**

**QT-prolonging drugs**

# 4 pharmacogenomic hypotheses

1. Common variants in the Rhythmonome modulate risk
  - Identify variants (single/dozens/1000s), then genotype patients and controls
2. Risk is conferred by many “private” variants in elements of the rhythmonome
  - New technology for cheap resequencing and information management
3. Key genes/loci modulating risk are somewhere else in the genome
  - Identify new loci (e.g. genotype  $\geq 500,000$  SNPs in cases and controls)
  - model organisms to find new genes/pathways
4. No important genomic contributor to variable drug actions

# A genomic approach to drug-induced long QT syndrome: chapter 1

- 137 patients with drug-induced torsades and 702 controls (all Caucasian)
- 145 polymorphisms assayed in 5 ion channel genes: KCNQ1 (61), KCNH2/HERG (39), SCN5A (24), KCNE1/2 cluster (21)
- Significant association with a 16.5 kb haplotype in KCNQ1, the gene encoding the pore-forming protein underlying  $I_{Ks}$  (OR 2.36;  $P=0.000089$ )

# Pharmacogenomic approaches to studying rare adverse drug events like diLQTS

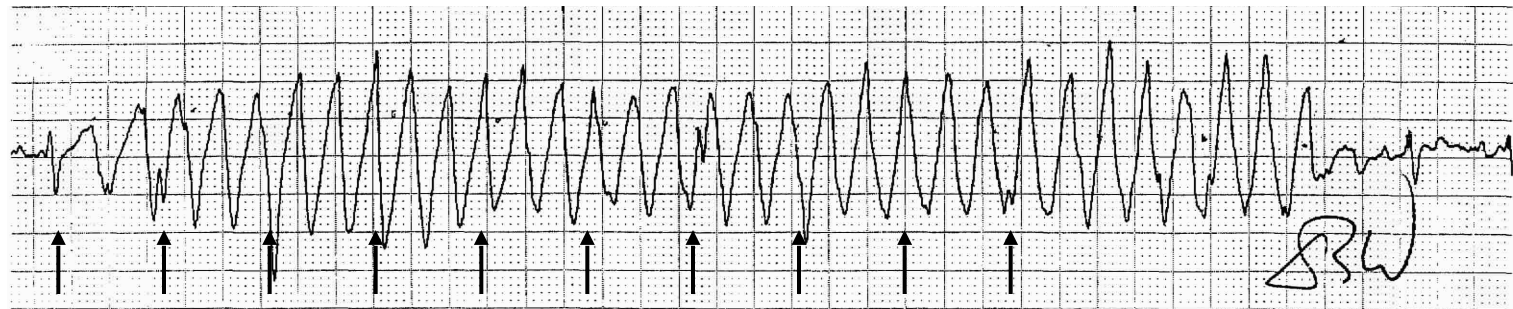
## Obstacles

- Recognizing and defining precise phenotypes
- Accumulating large datasets
- Computational challenges: Finding real biology in huge datasets
- Technological: e.g. rapid turnaround genotyping
- When is a validated association “good enough” to enter clinical practice? Outcomes? Cost-effectiveness?
- Ethical
- Economic:
  - Pharma
  - Health care systems

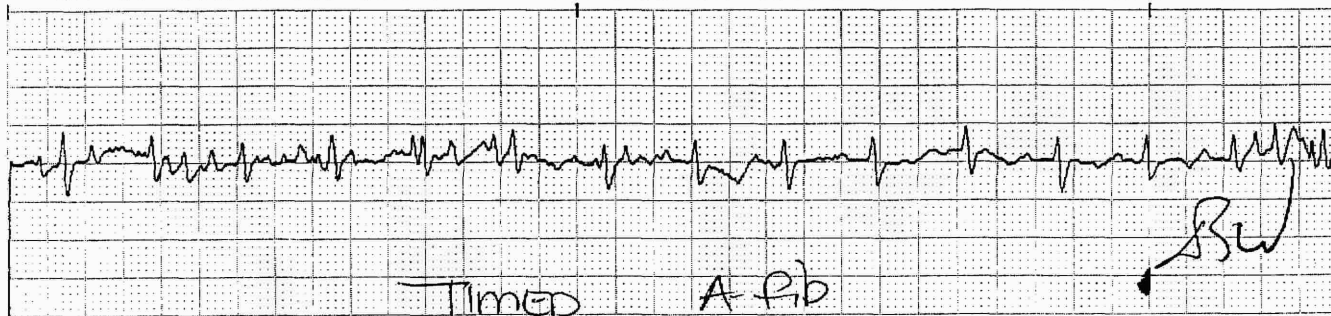
# 54 y.o. ♀ referred for evaluation of Torsades

Admitted to local hospital for asthma exacerbation; treated with loratadine and levofloxacin. No history of syncope.

Wide complex tachycardia on 1<sup>st</sup> night; may have been dizzy



CH 17 WYATT RM 254 F \* HR=118 01:29:21 PM 03/02/00 ALL GN=2 F:



# Ascertaining patients with defined outcomes like drug-induced torsades de pointes

- Accrual depends on recognition and appropriate consent mechanisms
- Methods of patient accrual:
  - Arrhythmia services (academic centers)
  - Interactions with pharmacovigilance efforts (FDA, Eudragene)
  - DNA samples linked to large electronic medical databases in health care systems or in industry



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## Vanderbilt University Medical Center Oates Institute for Experimental Therapeutics LQT MedWatch Project

Vanderbilt University Medical Center, under the direction of Dan Roden, M.D., is involved in clinical research to identify genetic markers associated with the development of drug-induced Torsades de Pointes (TdP) and Long QT (LQT).

Because of the relatively low incidence of drug-induced LQT/TdP, we are asking that colleagues with suspected cases refer history and ECG data for review as to patient eligibility. The study has been approved for remote consent by the Vanderbilt IRB.

The goal of the study is to search for new genes underlying risk for drug-induced torsades de pointes. All data from genomic analyses will be posted on public websites with no patient identifier.

Participating physicians are encouraged to report cases of drug-induced LQT/TdP to Dan Roden, M.D. [Dan.Roden@vanderbilt.edu](mailto:Dan.Roden@vanderbilt.edu) or Kris Norris RN [Kris.norris@vanderbilt.edu](mailto:Kris.norris@vanderbilt.edu).

### Inclusion criteria

One of the following must be present:

1. An uncorrected QT interval  $\geq 600$  msec while on drug that decreased to  $< 480$  msec following withdrawal of drug OR
2. An episode of TdP documented by ECG with an ECG without evidence of TdP following withdrawal of drug OR
3. TdP in addition to LQT (for subjects with bundle branch block or a pacemaker) at the time of the event.

### Exclusion criteria

1. Potassium level  $\leq 3$  mmol at onset of event ( $1 \text{ mEq/L} = 1 \text{ mmol}$ ).
2. Subarachnoid hemorrhage at onset of event.
3. Cardiac bypass  $< 24$  hours before onset of event.
4. Hospital admission diagnosis of hypothermia @ time of event.
5. Diagnosed with congenital LQT syndrome prior to onset of event.
6. Leukopenic (WBC  $< 1000$  cells/ml) at onset of event
7. History of a non-autologous bone marrow transplant at anytime in the past.

### Contact

<http://oates.mc.vanderbilt.edu/projects/alqts>

To receive a kit for enrollment and further information about the study you may contact:



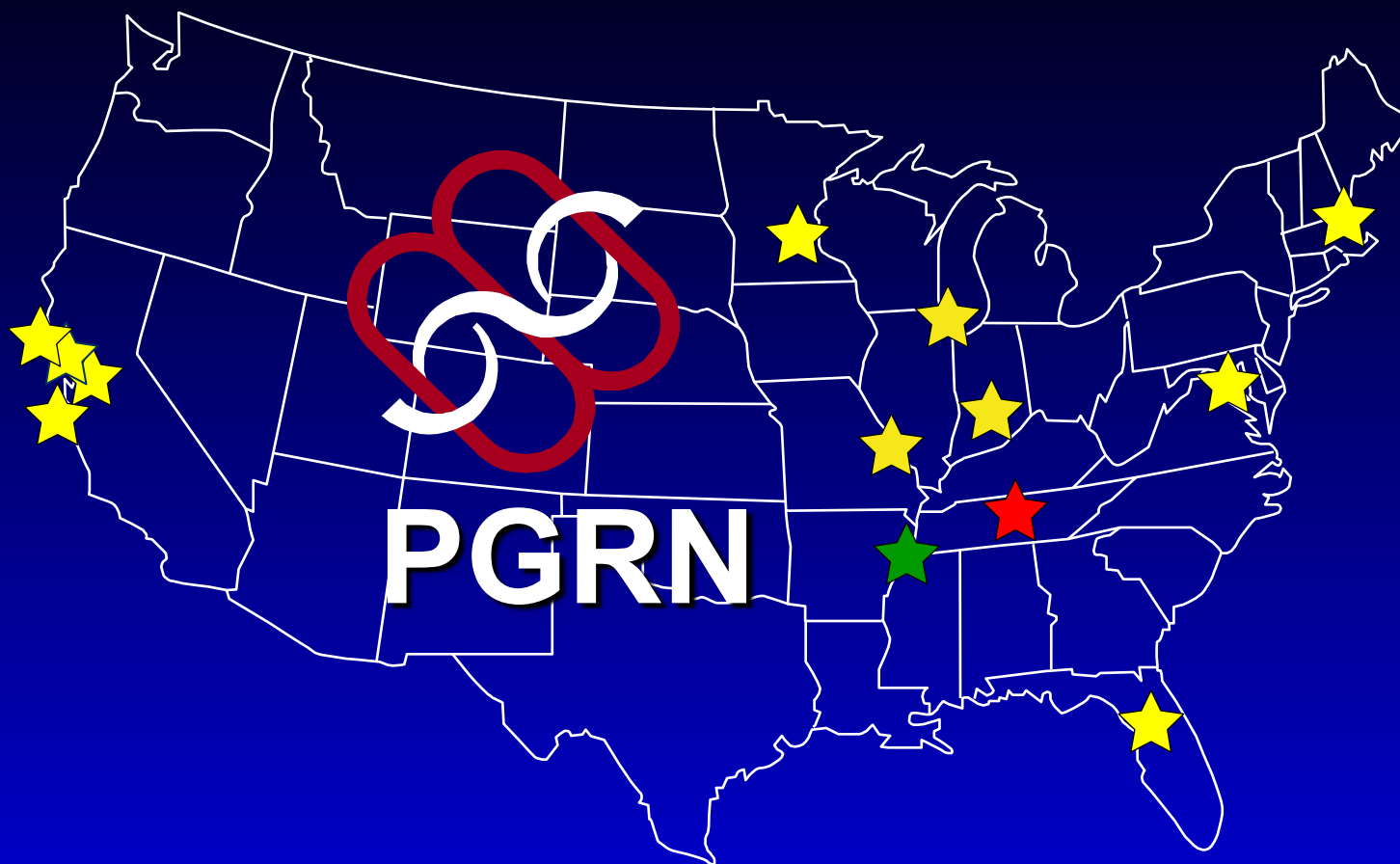
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