Pharmacogenomics of Drug-Induced Conditions

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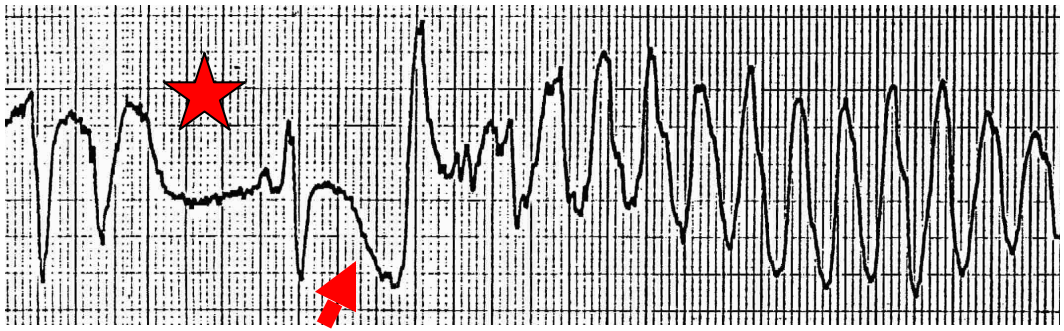
An "idiosyncratic" drug response

AR, 78 year old male

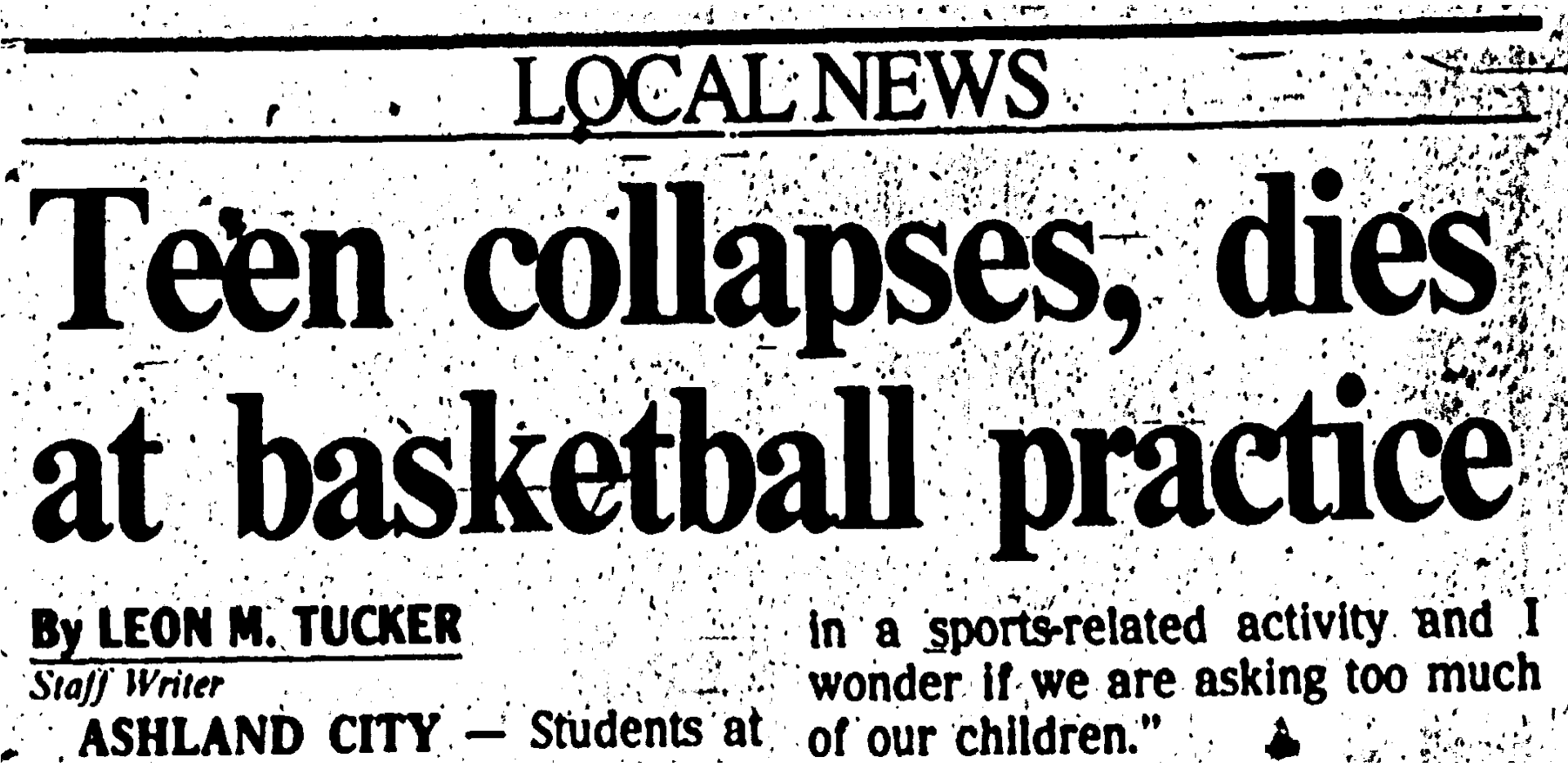
- Coronary artery disease; 13 years s/p bypass surgery
- 2 days after starting dofetilide (potent I_{Kr} blocker)…



No personal or family history of syncope, sudden death

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

Another face of the congenital long QT syndrome



LOCAL NEWS

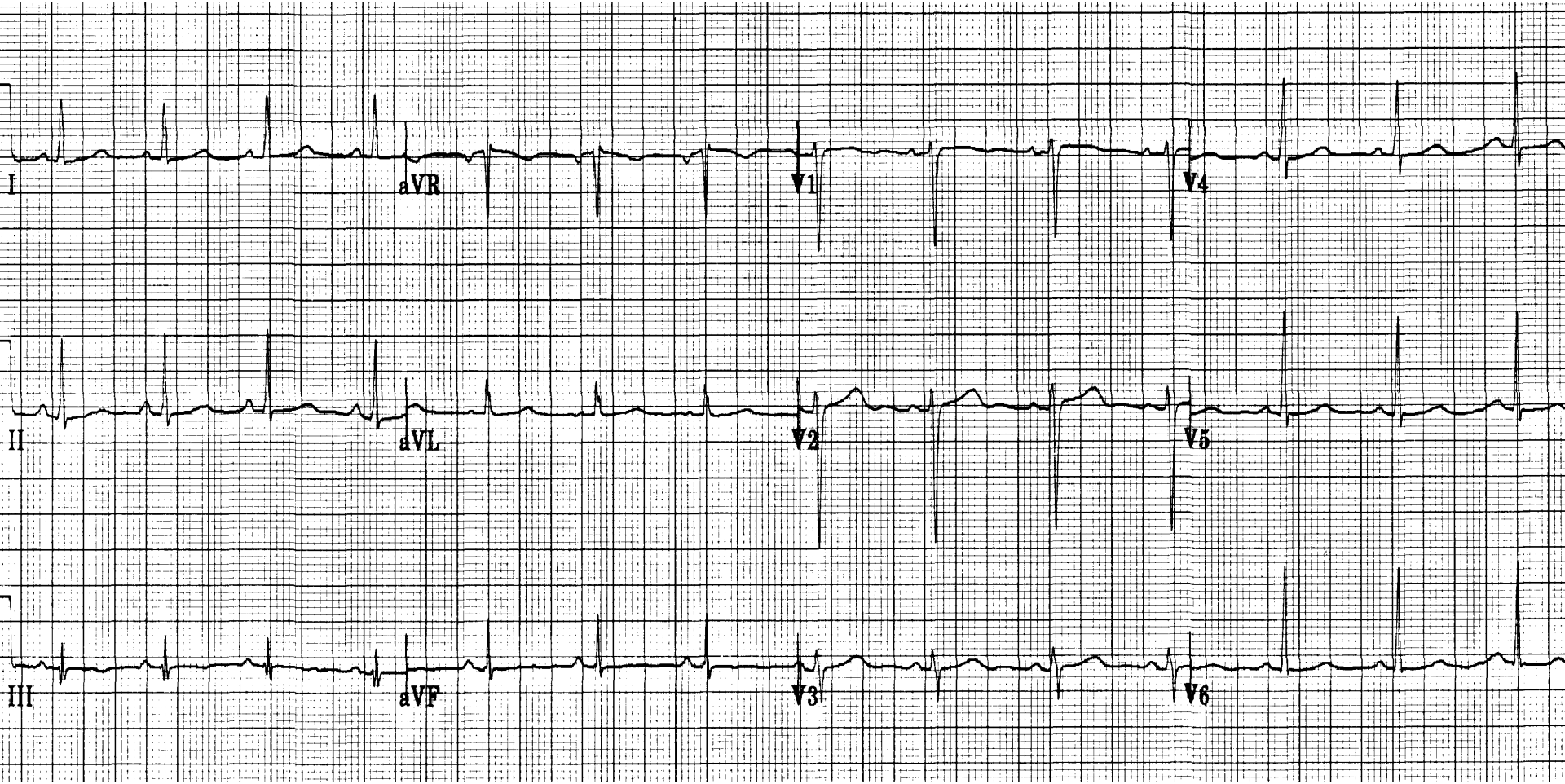
Teen collapses, dies at basketball practice

By LEON M. TUCKER
Staff Writer

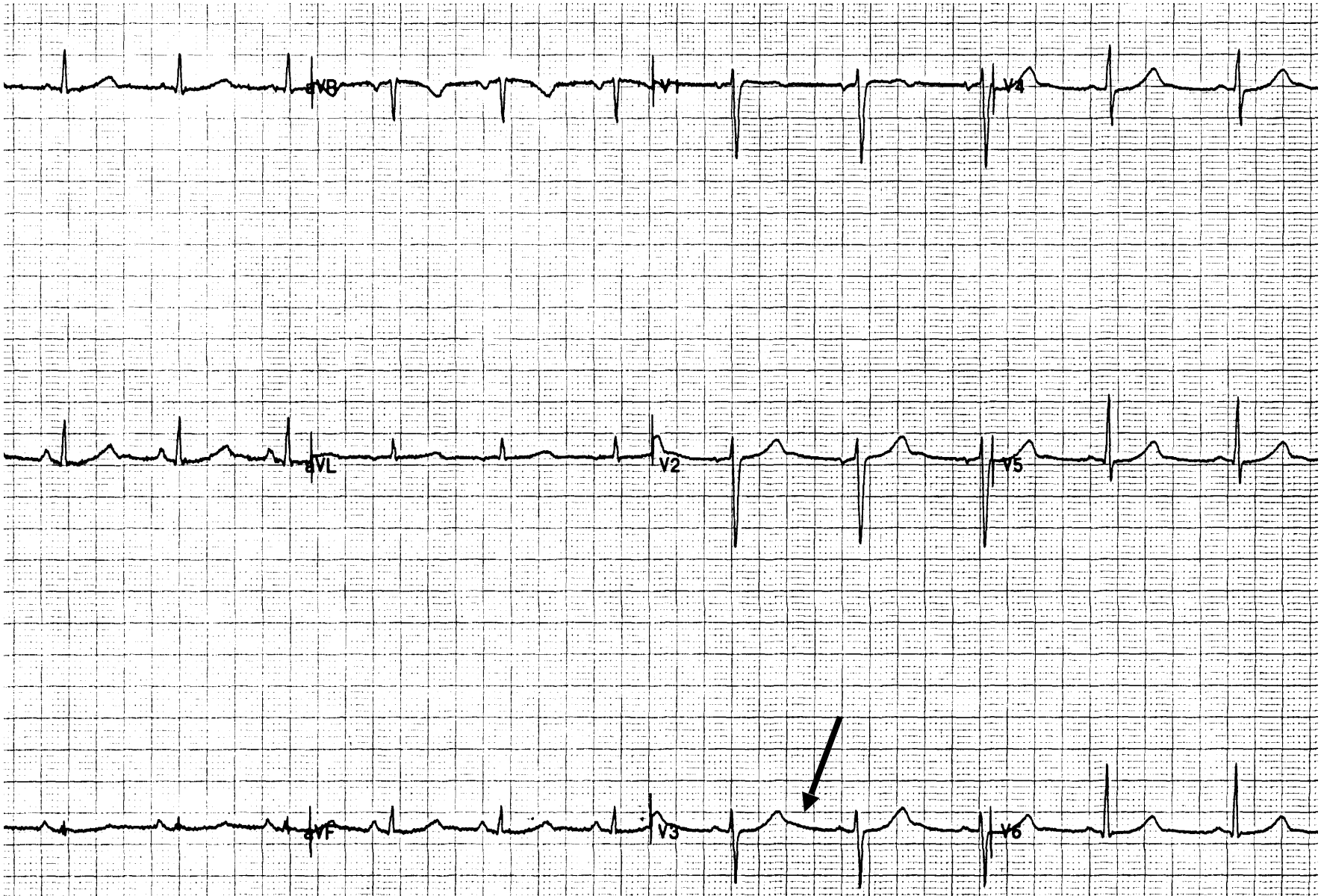
ASHLAND CITY — Students at

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

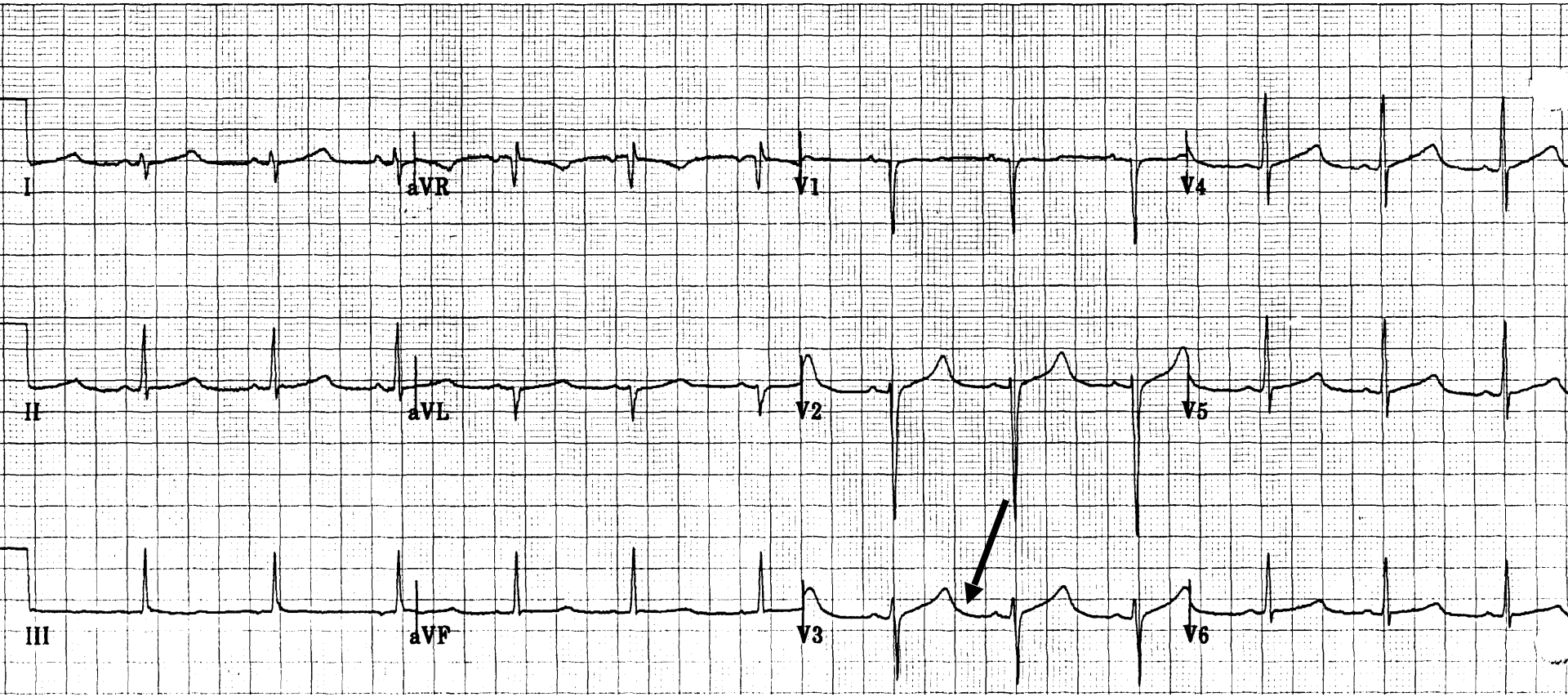
Father's ECG



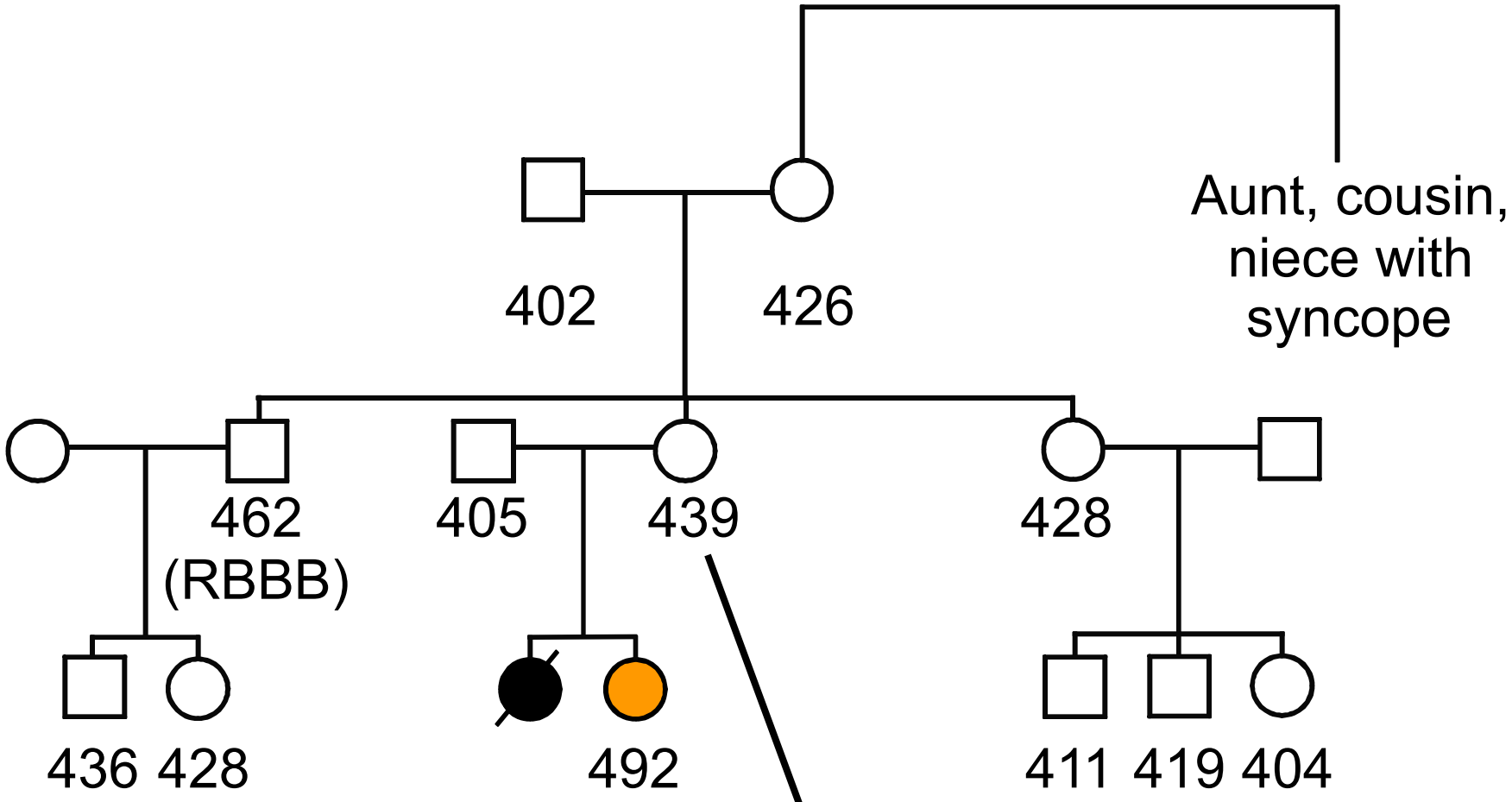
Mother's ECG



9-year-old sister's ECG

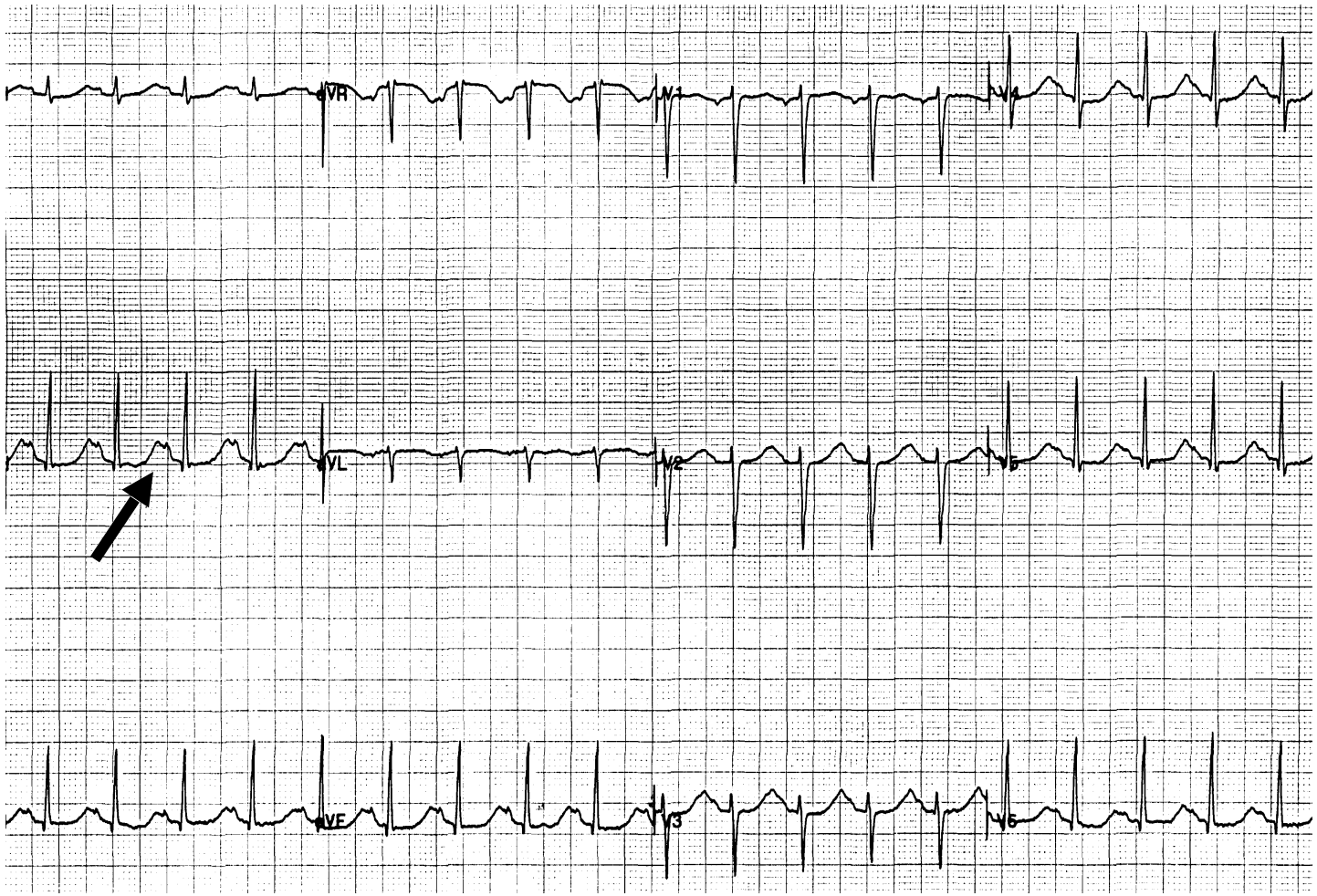


Family tree

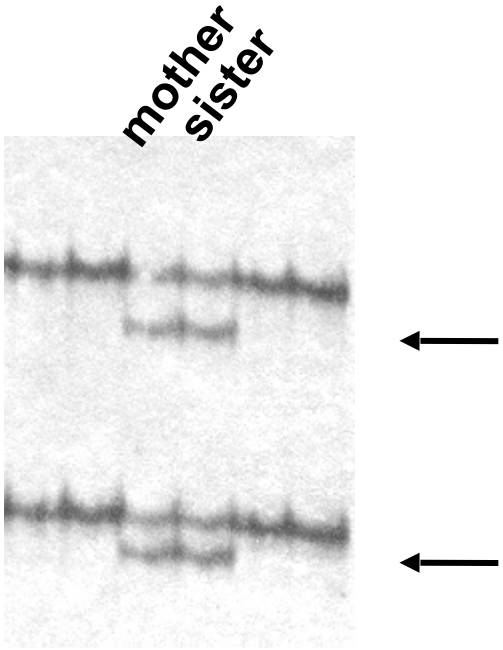


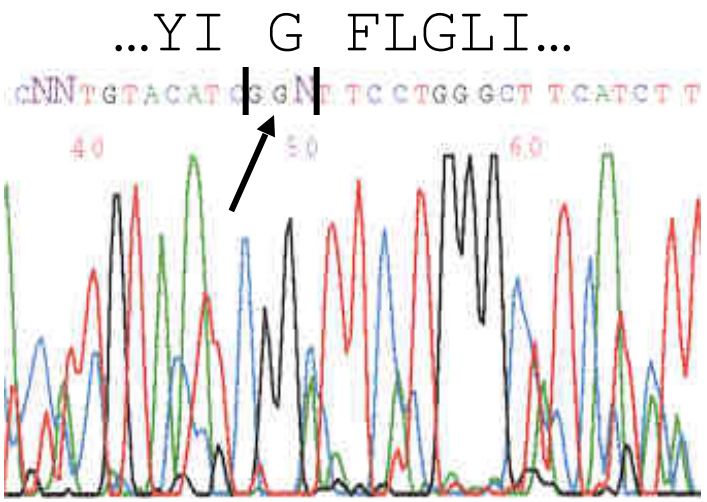
- One episode of syncope, age 20
- Multiple ER visits for acute allergic reactions → epinephrine without incident

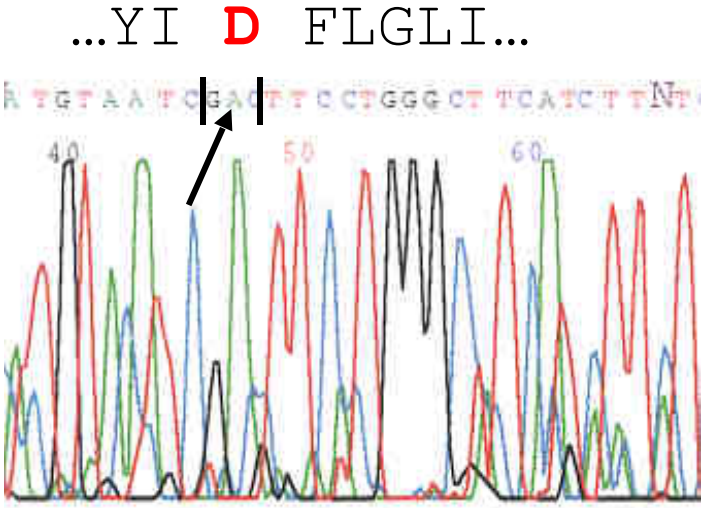
Mother's ECG post-exercise

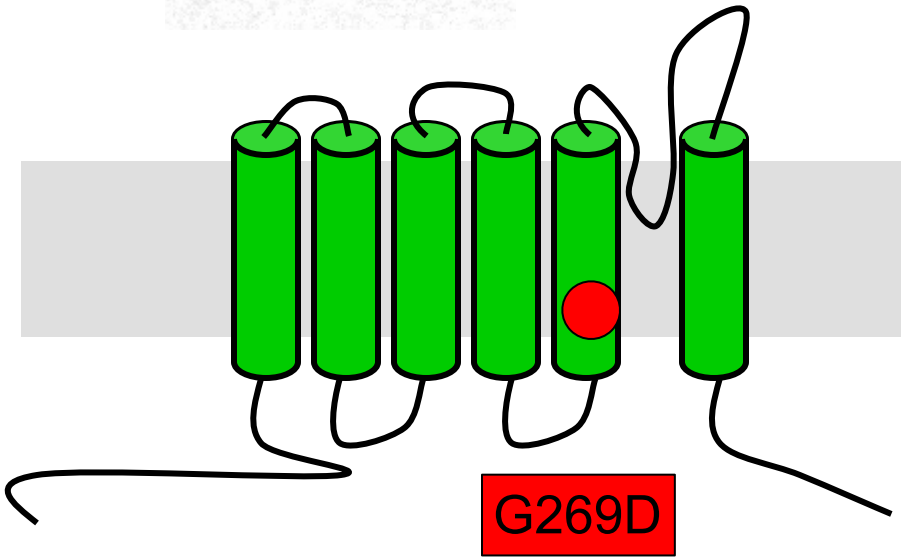


Identifying a mutation in KCNQ1









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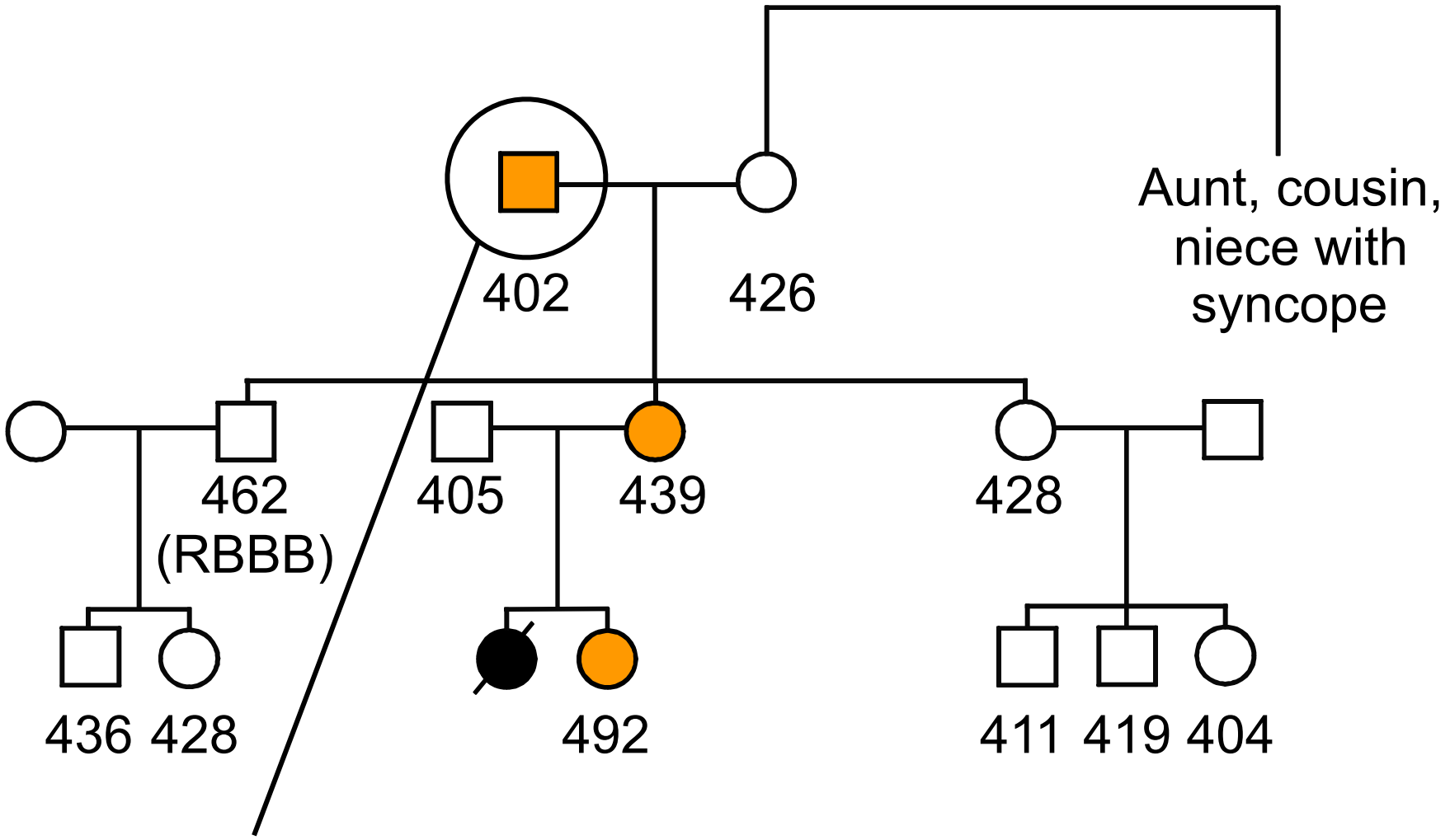
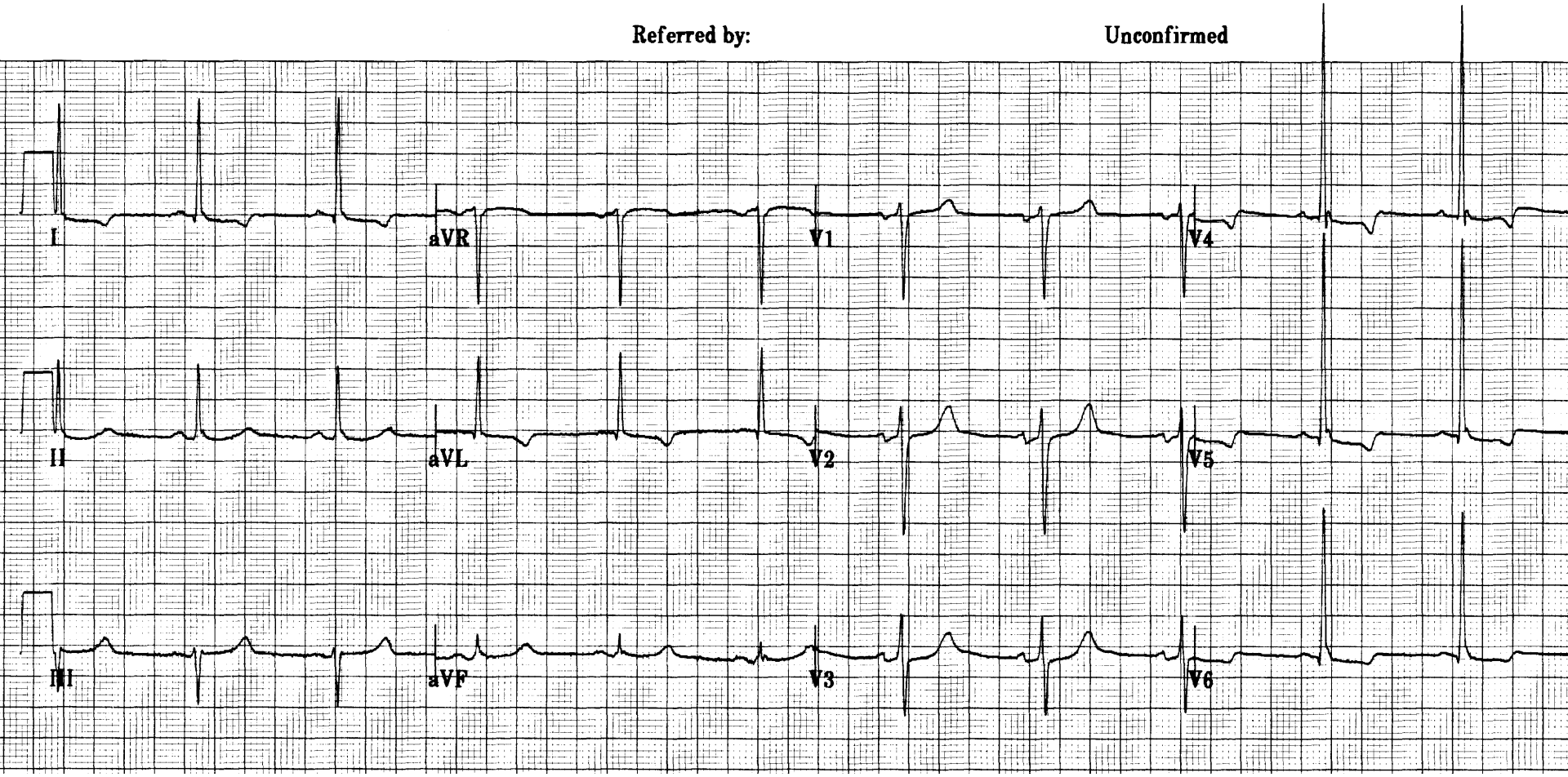

Aunt, cousin, niece with syncope
402
426
462 (RBBB)
405
439
428
436
428
492
411
419
404
Incomplete penetrance

Grandfather's ECG



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 ± modest QT prolongation often with underlying heart disease
  - No pause-dependence
- What is the culprit drug? Sometimes, initiating drug A may → 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

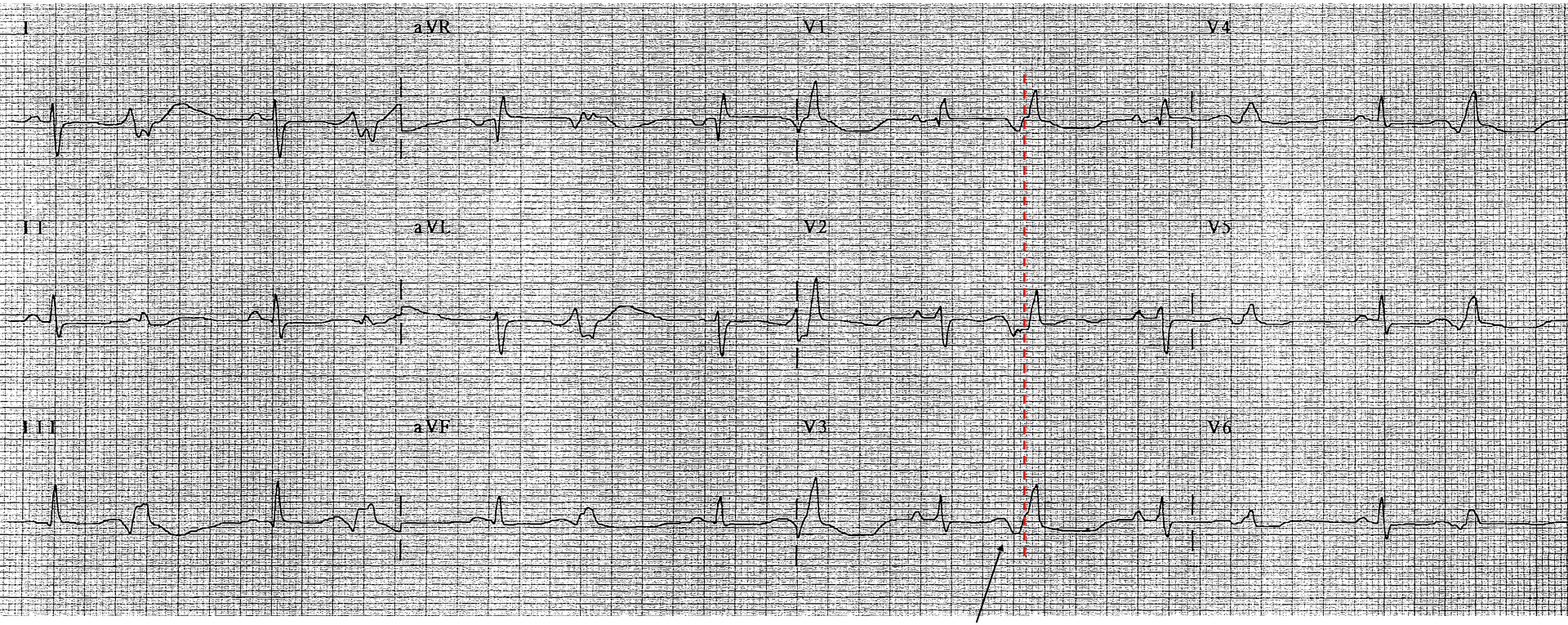
amiodarone
arsenic trioxide

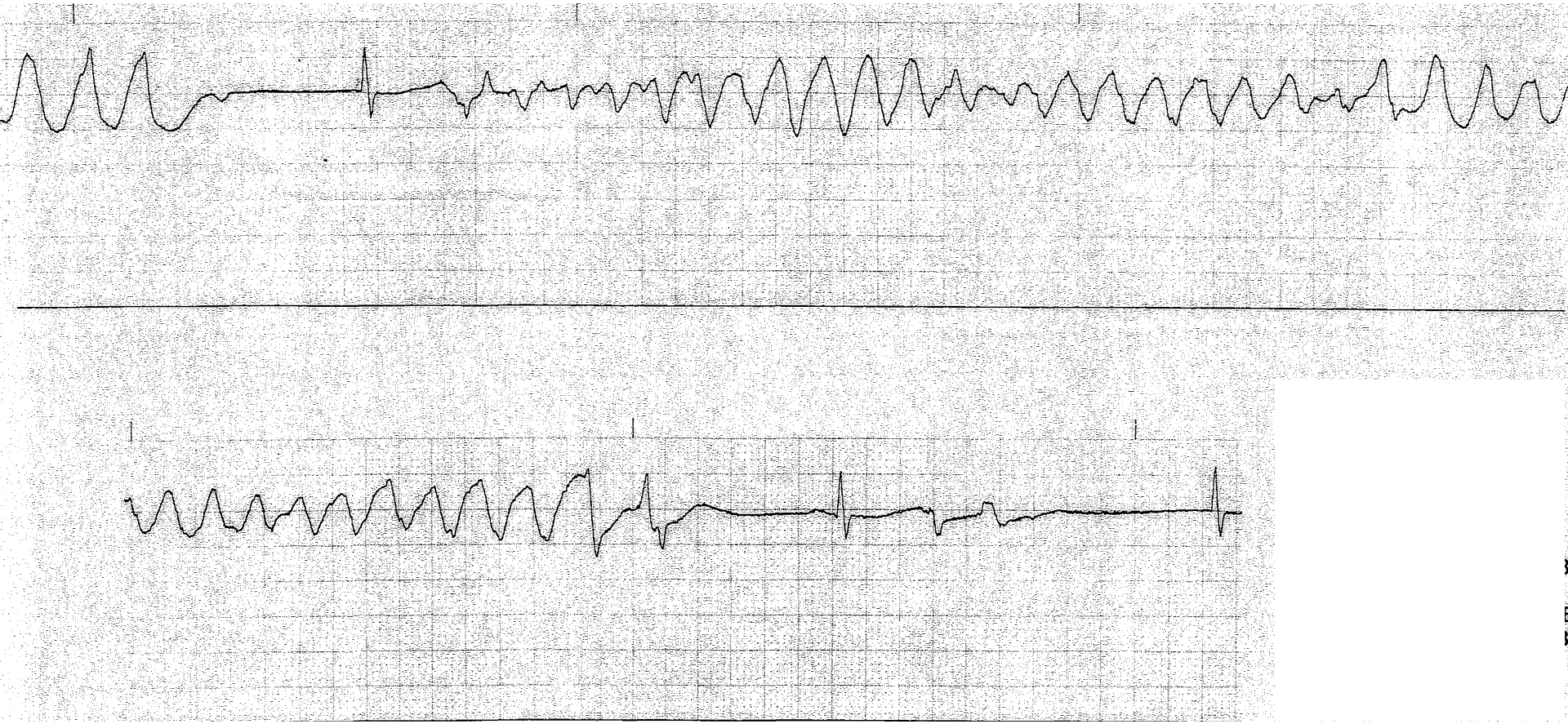
anti-infectives:	clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
anti-emetics:	domperidone, droperidol
anti-psychotics:	chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
opioid dependence:	levomethadyl, methadone

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

SEPTEMBER 28, 2006

LATEST NEWS!

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.

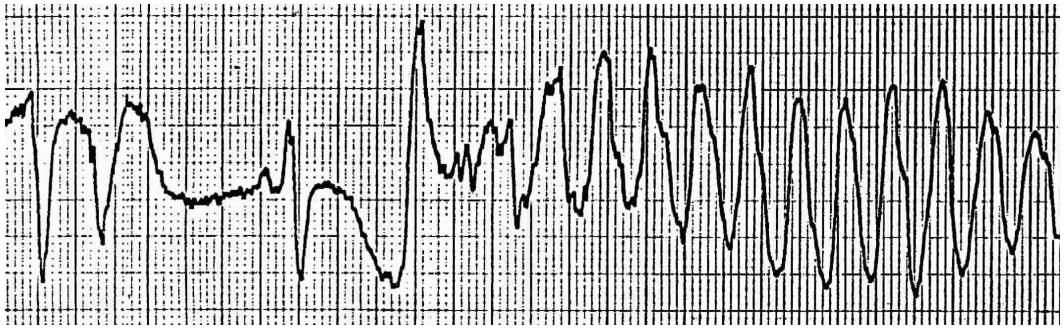
Wecht said that because Daniel was taking three drugs and not a large dose of a single drug, paired with the fact that he was celebrating a happy occasion with his mother, those factors point to a "tragic accidental drug death."

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

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)…



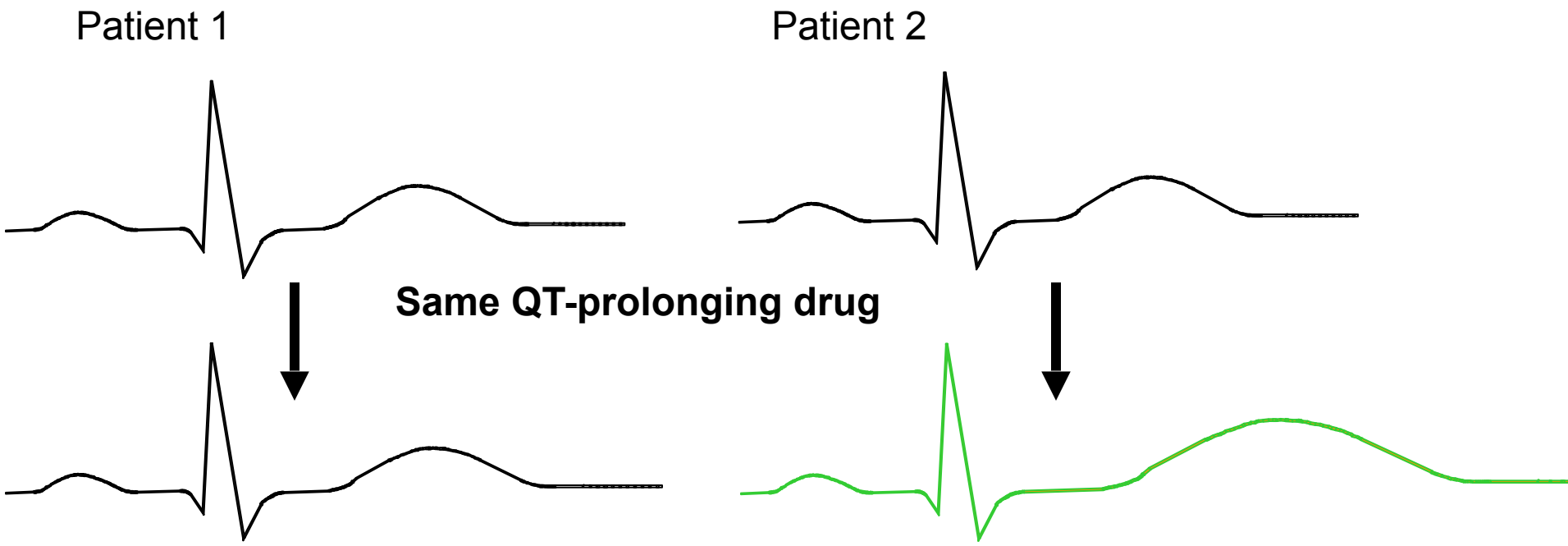
No personal or family history of syncope, sudden death

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

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

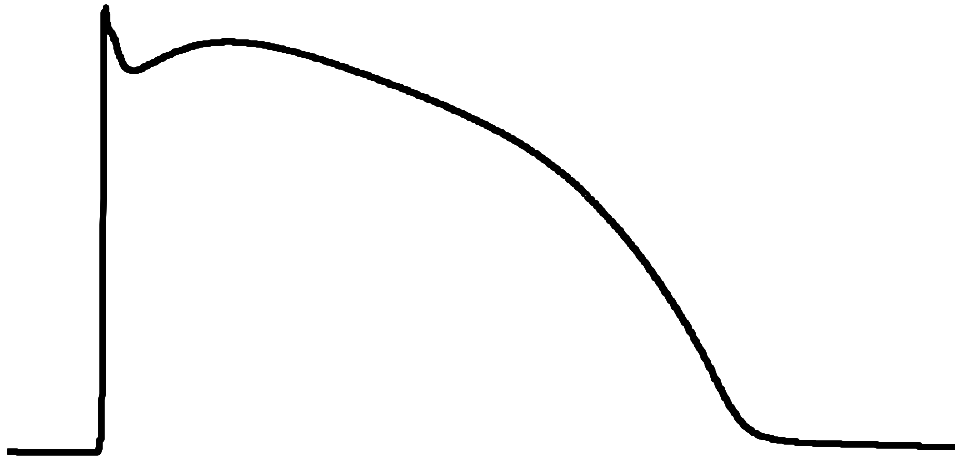
The concept of reduced repolarization reserve

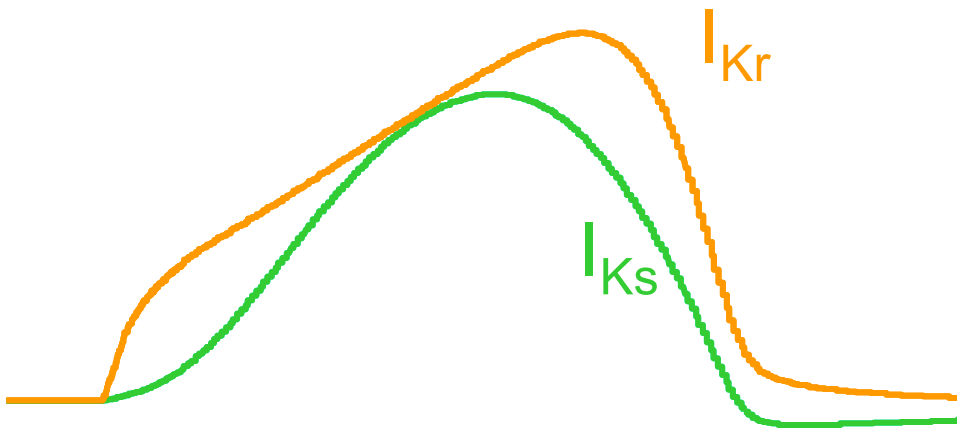
- Redundancy (“reserve”) in cardiac repolarization allowed him to maintain a normal QT until other lesions (heart disease, dofetilide) were superimposed.



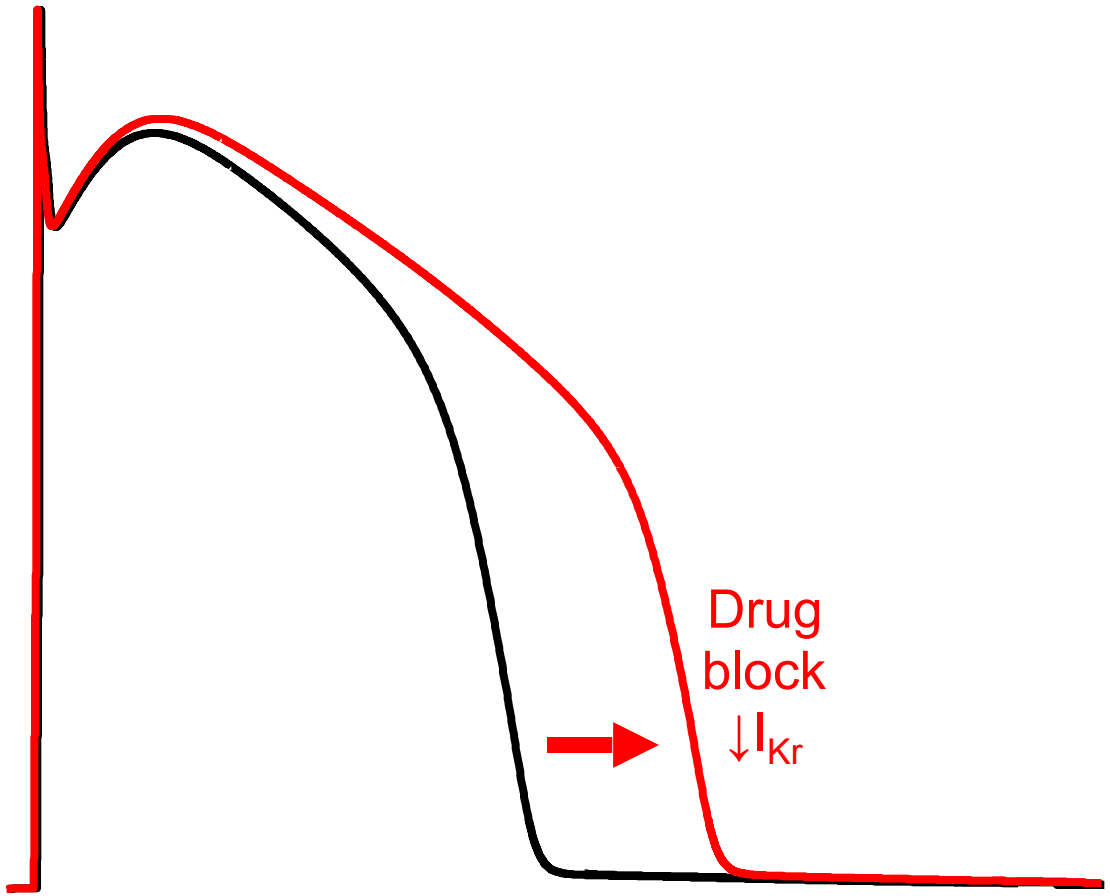
A thought problem: how to test the hypothesis that a variant like KCNQ1/R583C actually increases arrhythmia risk?

- 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



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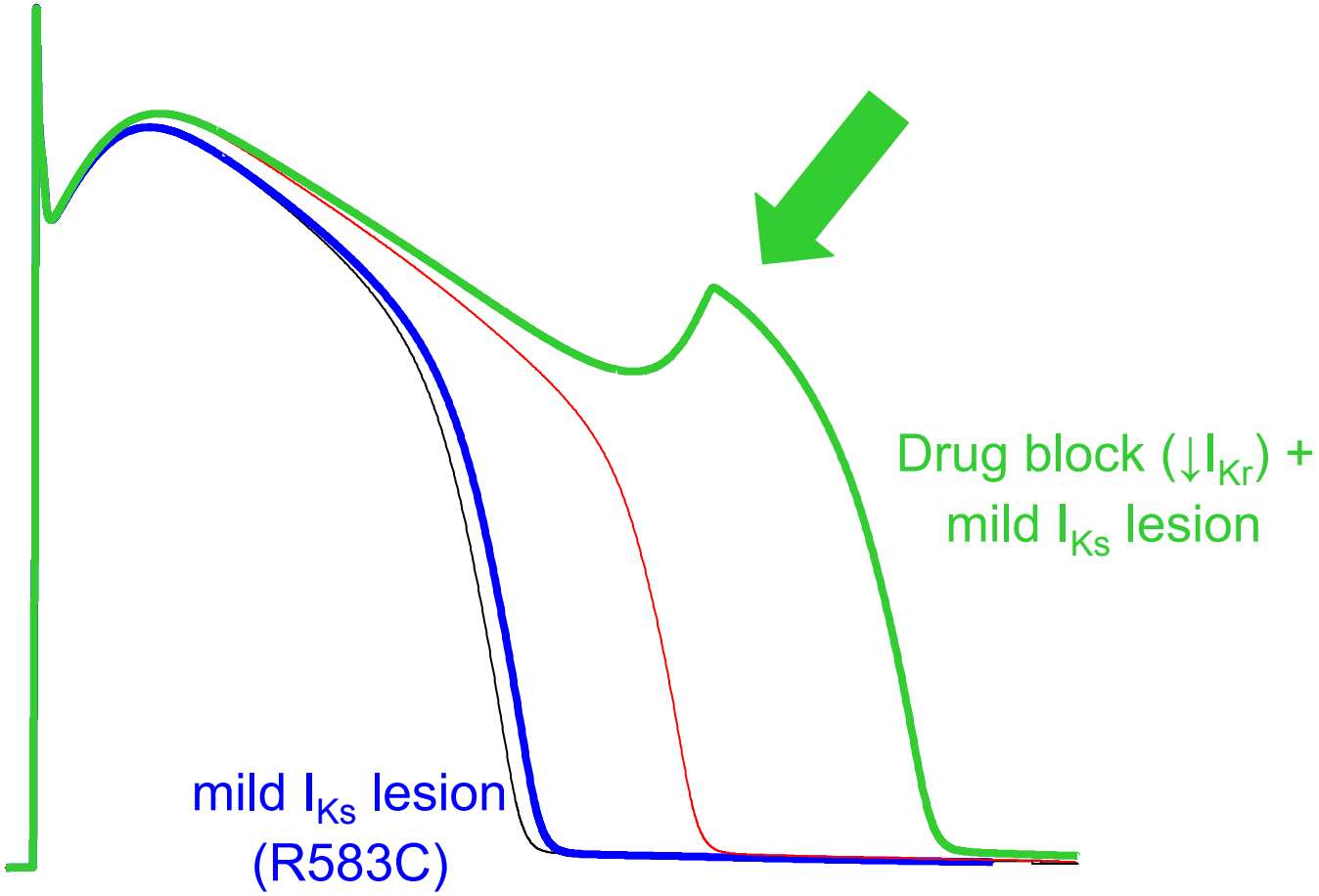
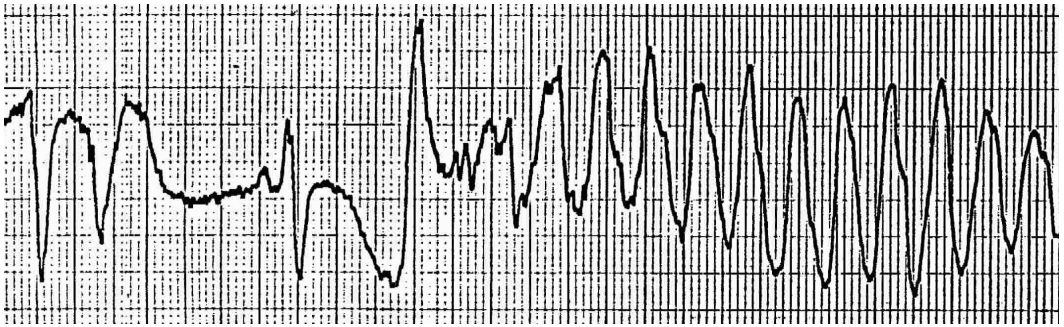


Drug-induced Torsades de Pointes



- ~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?

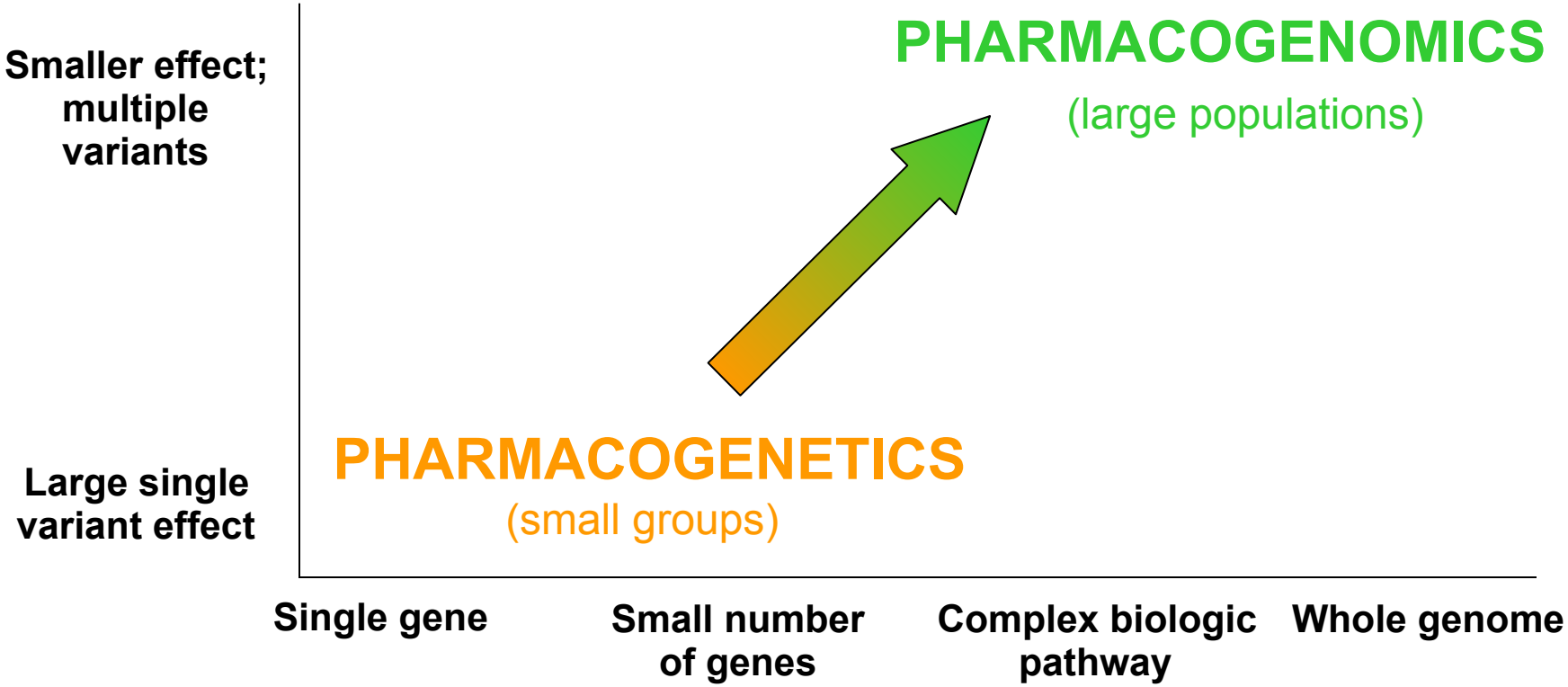
An ethnic-specific polymorphism mediating arrhythmia susceptibility

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 (n = 23) (%)	Controls (n = 100) (%)	Odds ratio (95% CI)*	P †
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

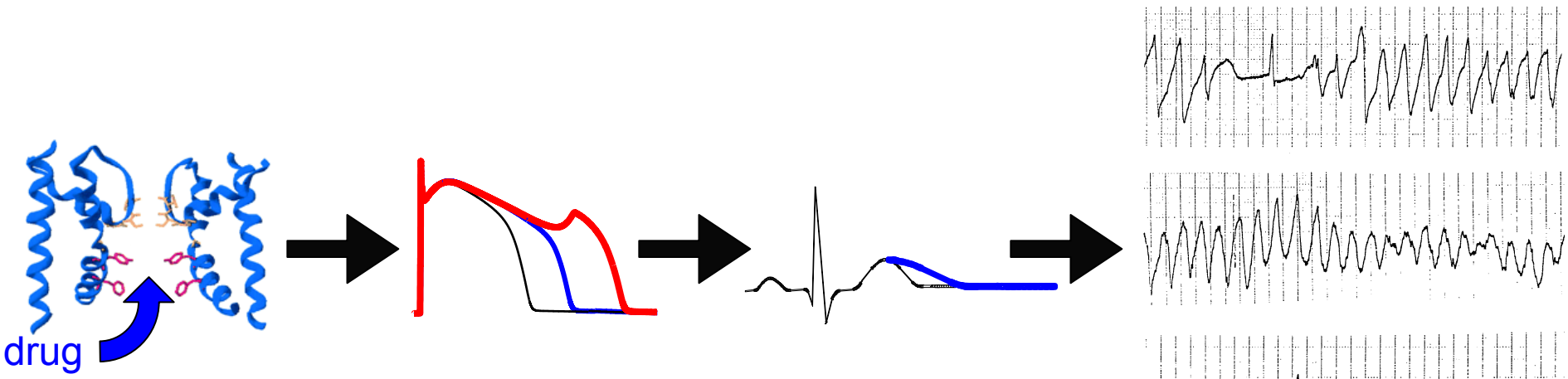
*Odds ratio for the likelihood of arrhythmia in Y carriers (S,Y + Y,Y) versus noncarriers (S,S). †P value for the comparison of carriers (S,Y + Y,Y) and noncarriers (S,S) in cases and controls (Fisher's exact test).

Splawski et al., 2002



- Rare coding region variants (polymorphisms or mutations)
- Commoner coding and regulatory variants
- Detectible 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



HERG block or reduced HERG expression

↑Action potential duration, EADs, ↑heterogeneity of repolarization

QT prolongation

torsades de pointes degenerating to VF

Candidate mechanisms contributing to variability

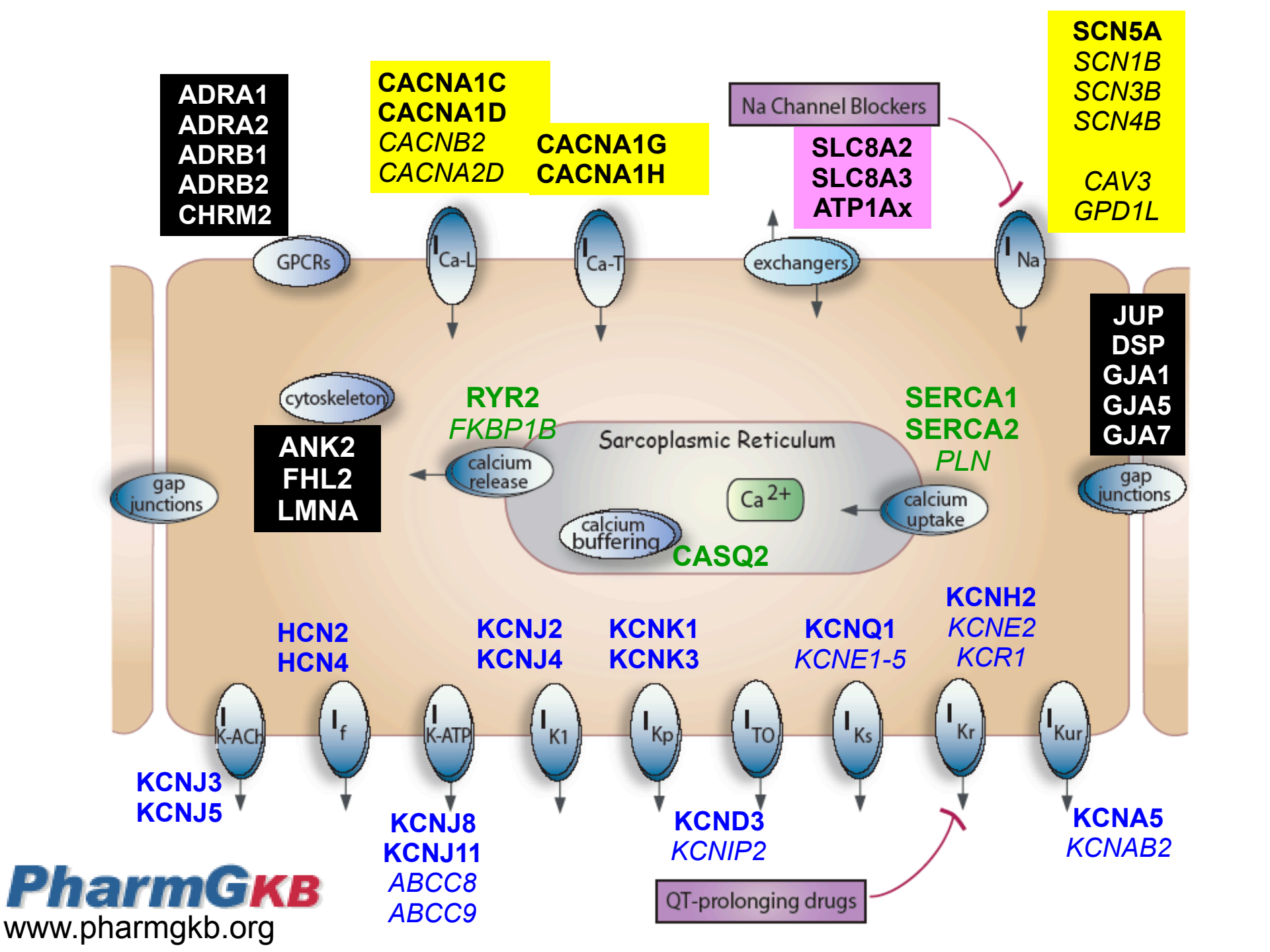
drug metabolism or transport

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

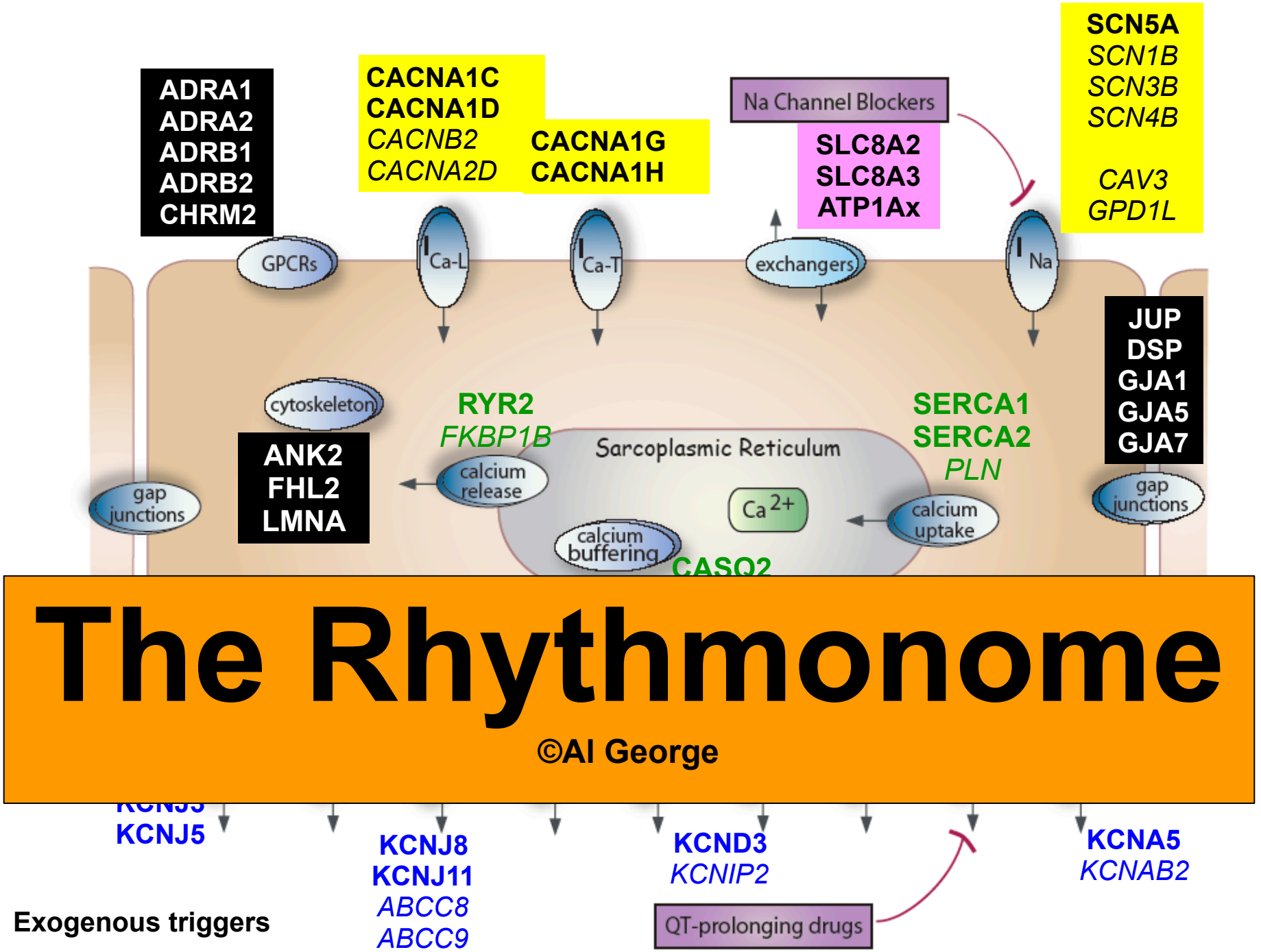
A vulnerable substrate?

HERG variants

Roden and Viswanathan, JCI, 2005



PharmGKB
www.pharmgkb.org


ADRA1
ADRA2
ADRB1
ADRB2
CHRM2
CACNA1C
CACNA1D
CACNB2
CACNA2D
CACNA1G
CACNA1H
Na Channel Blockers
SLC8A2
SLC8A3
ATP1Ax
SCN5A
SCN1B
SCN3B
SCN4B
CAV3
GPD1L
GPCRs
I Ca-L
I Ca-T
exchangers
I Na
JUP
DSP
GJA1
GJA5
GJA7
cytoskeleton
ANK2
FHL2
LMNA
RYR2
FKBP1B
Sarcoplasmic Reticulum
SERCA1
SERCA2
PLN
gap junctions
calcium release
Ca 2+
calcium uptake
calcium buffering
CASQ2
gap junctions
The Rhythmonome
©Al George
KCNJ5
KCNJ8
KCNJ11
ABCC8
ABCC9
KCND3
KCNIP2
KCNA5
KCNAB2
Exogenous triggers
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 ≥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)

Kaab, AHA 2005

Pharmacogenomic approaches to studying rare adverse drug events like diLQTS

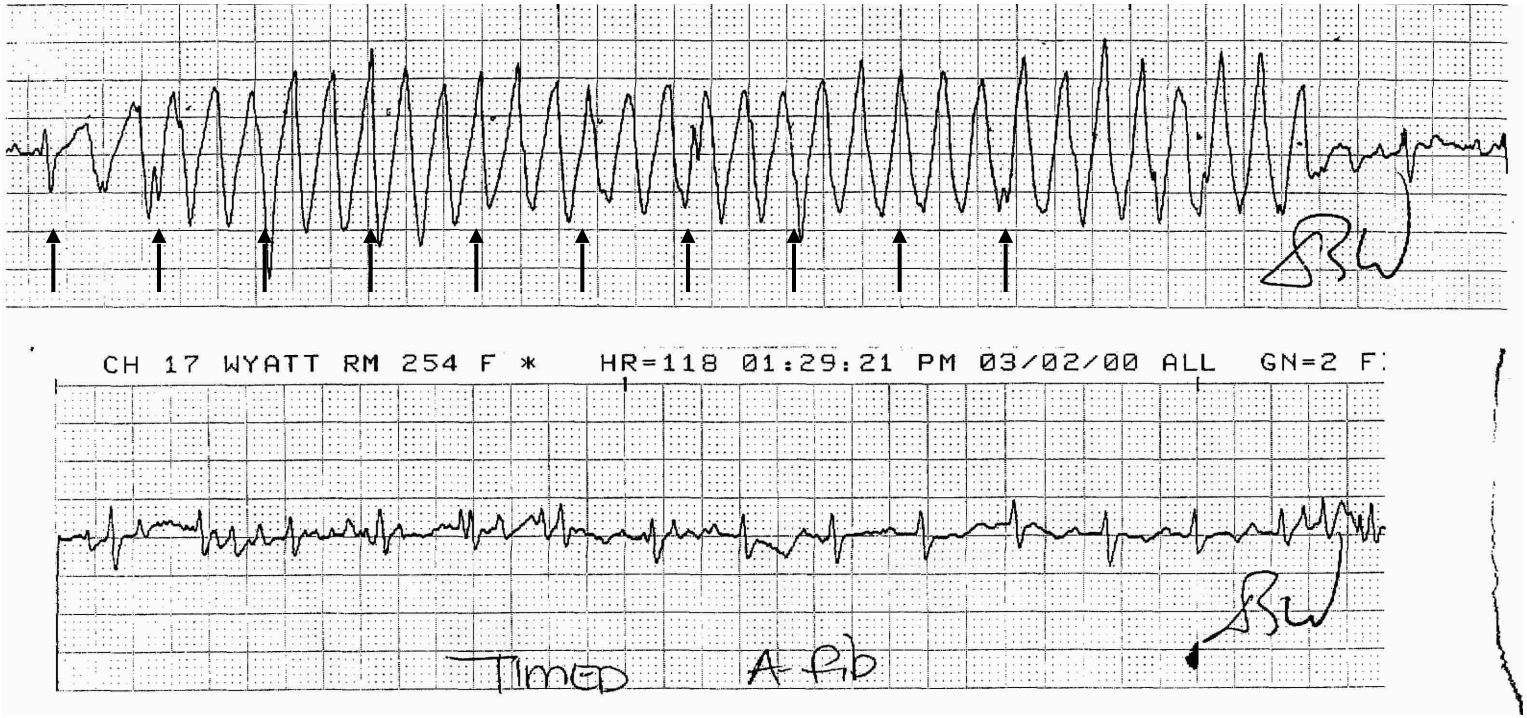
Obstacles

- 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 1st night; may have been dizzy



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

VANDERBILT UNIVERSITY

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 or Kris Norris RN Kris.norris@vanderbilt.edu.

Inclusion criteria

One of the following must be present:

1. An uncorrected QT interval >=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 <= 3mmol at onset of event (1mEq/L=1mmol).
2. Subarrachnoid 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

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

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

NIH Pharmacogenetics Research Network

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- NCI
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Primary Sites:

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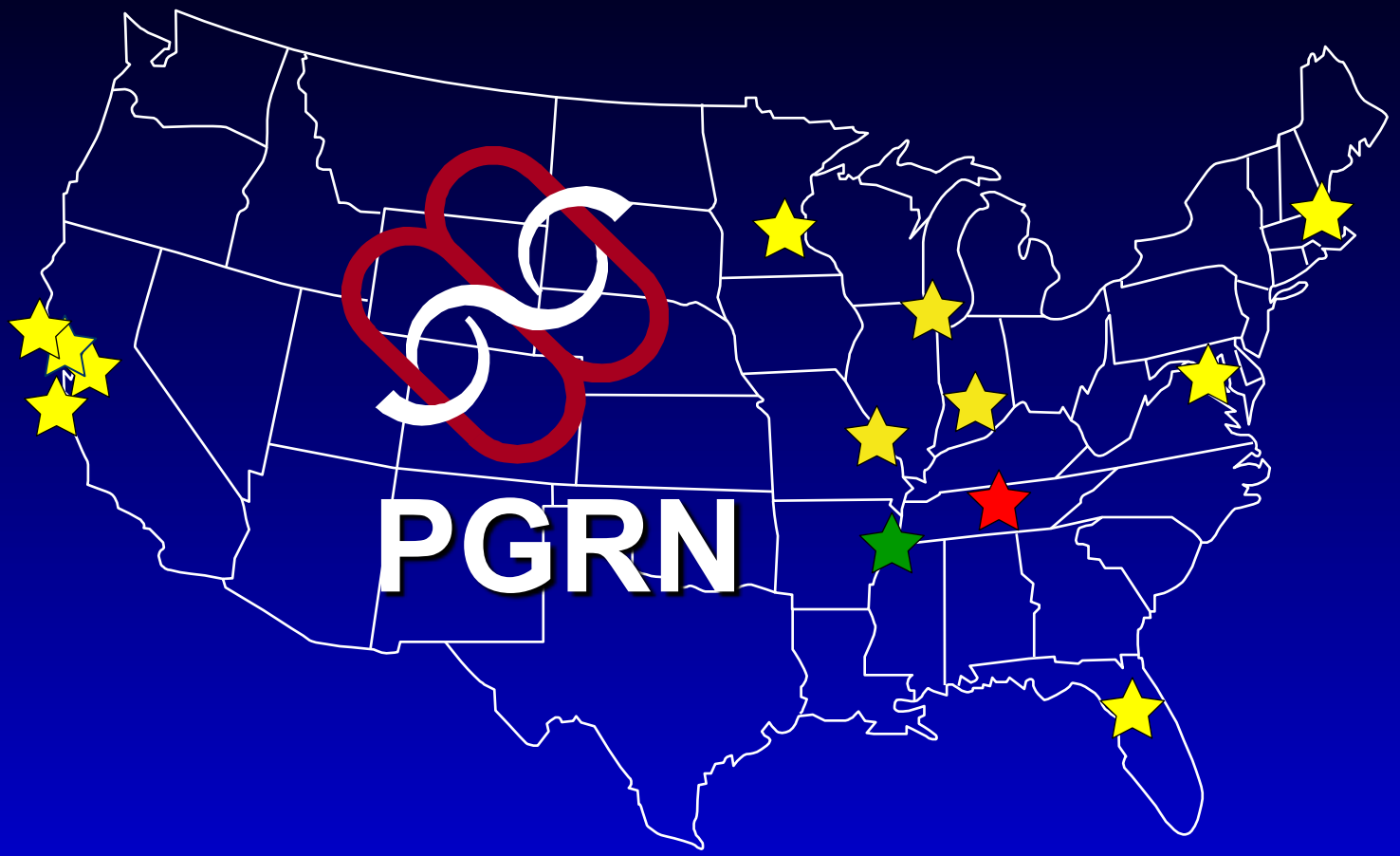
- Children's Hosp. Oakland
- Indiana Univ.
- Mayo Foundation
- Stanford Univ.
- St. Jude Children's Hosp.
- UCSF
- Univ. of Chicago
- Univ. of Florida
- Univ. of Maryland
- Vanderbilt Univ.
- Washington Univ.



www.nigms.nih.gov/pharmacogenetics

www.pharmgkb.org

PharmGKB
The Pharmacogenetics and Pharmacogenomics Knowledge Base

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NATIONAL INSTITUTES OF HEALTH

Alliance Against SCD

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