Pharmacogenetics of Drug-Induced Sudden Cardiac Arrest

Michael J. Ackerman, MD, PhD, FACC

Professor of Medicine, Pediatrics, and Pharmacology

Director, Long QT Syndrome Clinic and the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory

1st Worldwide Internet Symposium on Drug-Induced QT Prolongation
October 15th – 31st, 2007

MAYO CLINIC

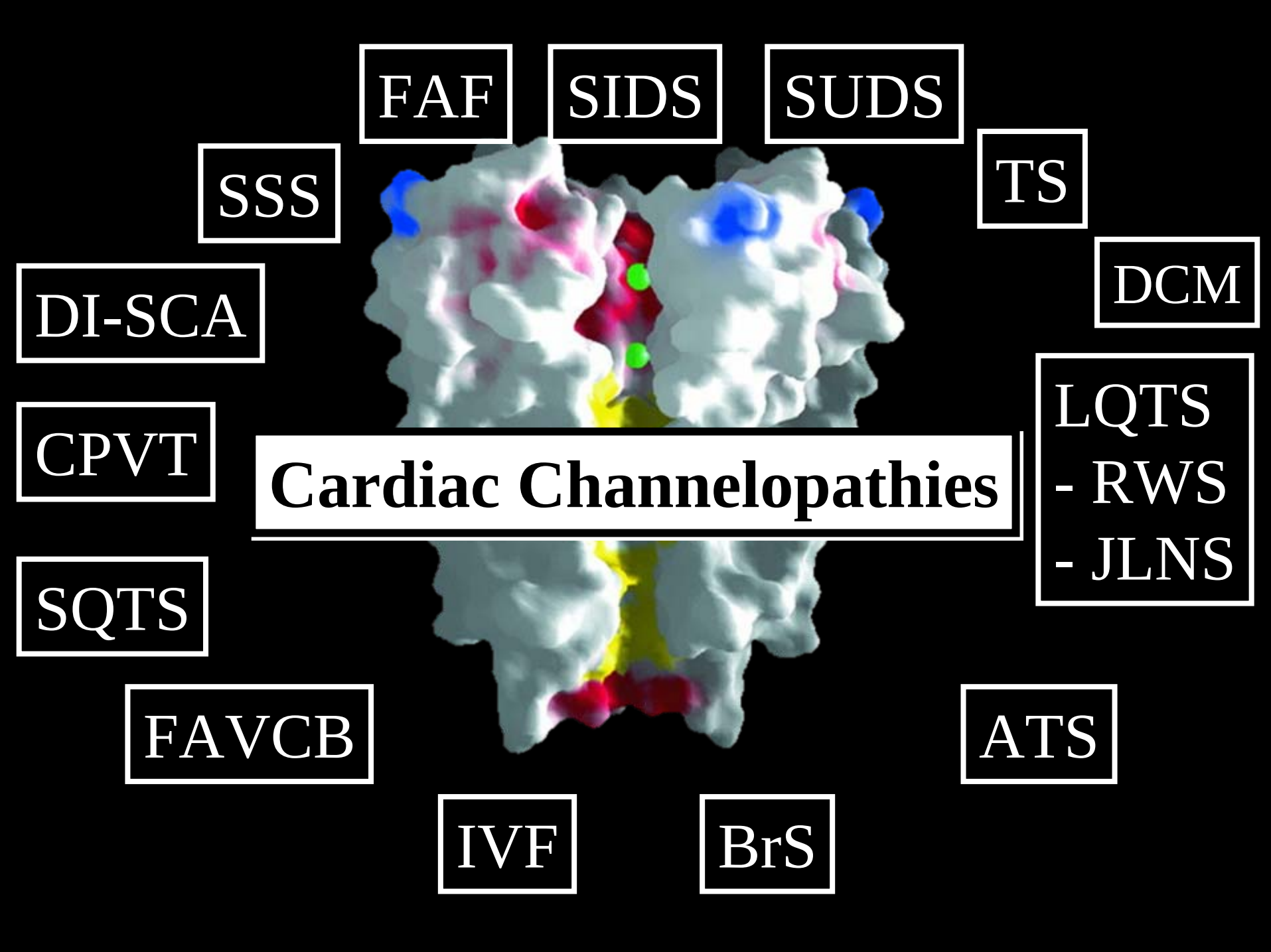
Mayo Eugenio Litta Children's Hospital

MAYO CLINIC

WINDLAND SMITH RICE
SUDDEN DEATH
GENOMICS LABORATORY

Conflicts of Interest to Disclose:

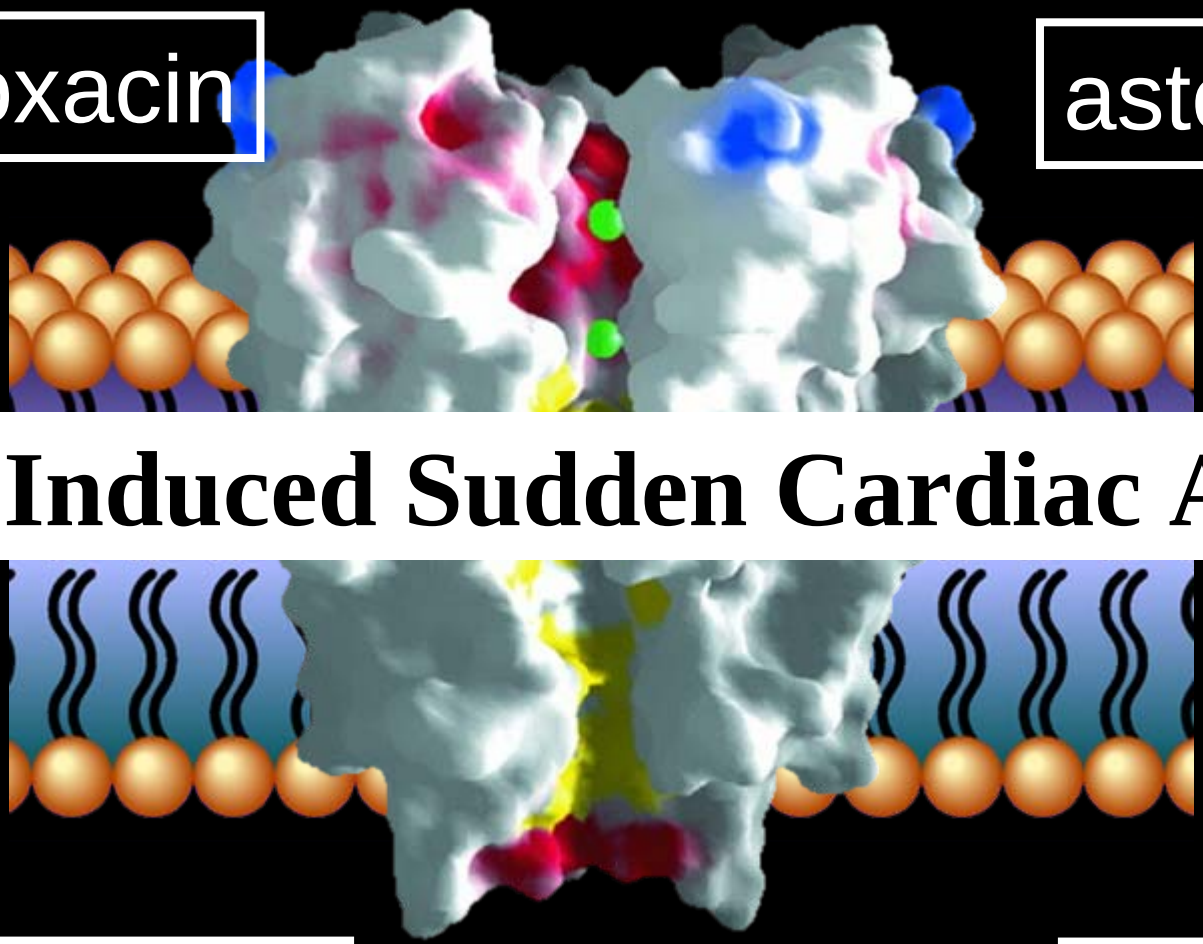
- Dr. Ackerman is a Consultant for PGxHealth, Medtronics, and Pfizer


FAF
SIDS
SUDS
SSS
TS
DCM
DI-SCA
LQTS
- RWS
- JLNS
CPVT
Cardiac Channelopathies
SQTS
FAVCB
ATS
IVF
BrS

terfenadine

sparfloxacin

astemizole



Drug-Induced Sudden Cardiac Arrest

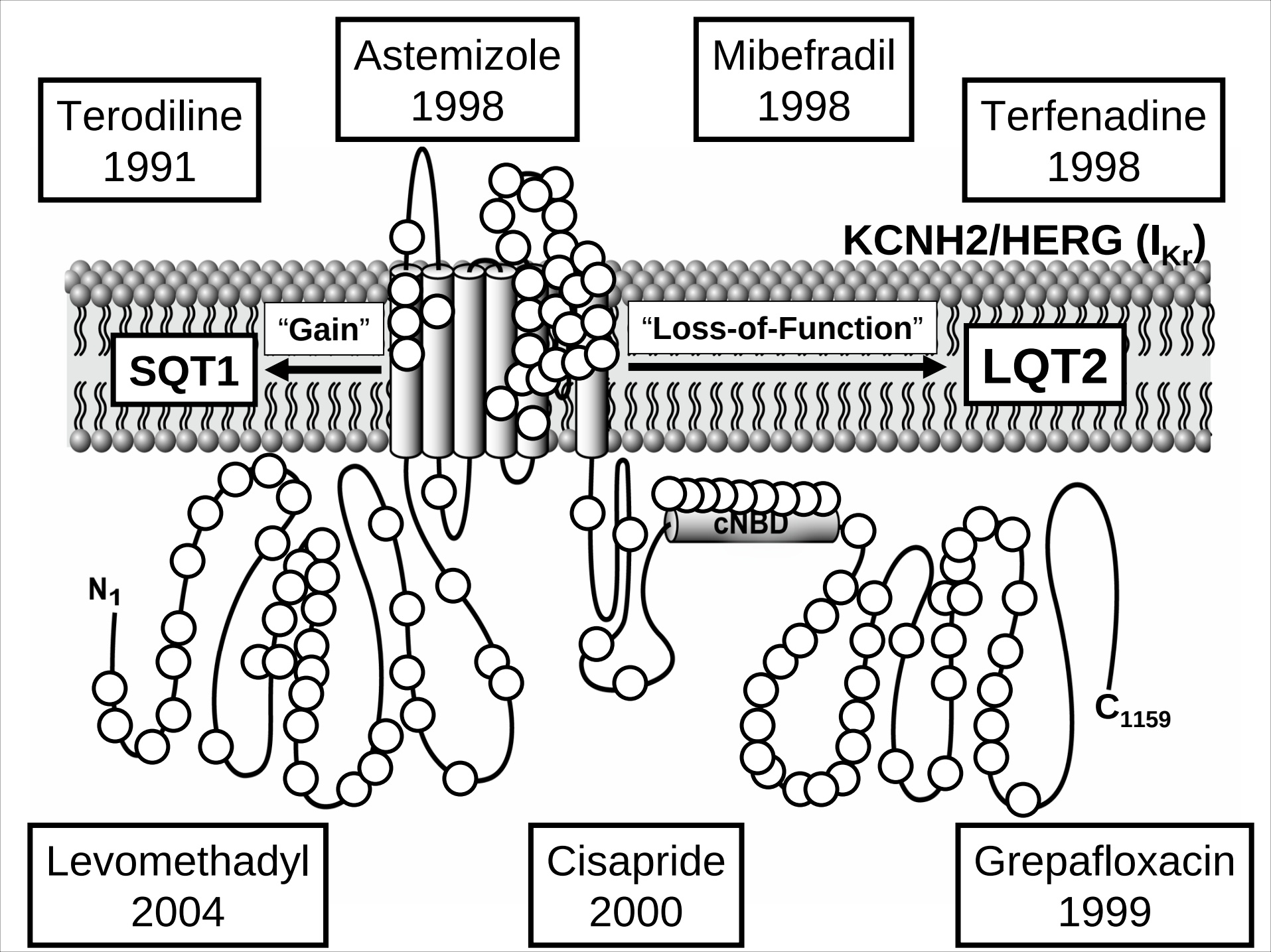
grepafloxacin

propulsid

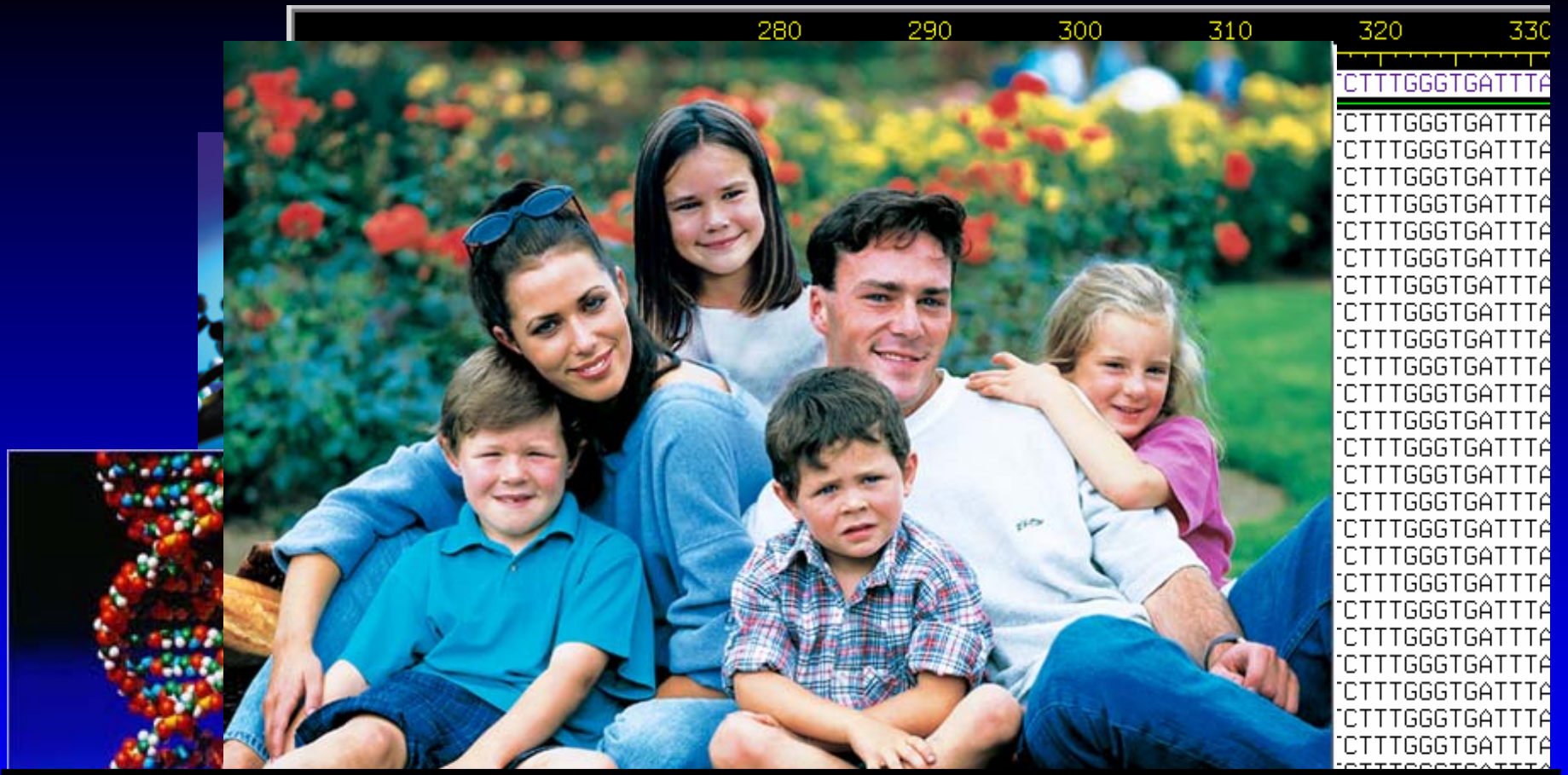
Drug-Induced Sudden Cardiac Arrest

Identification of *At-Risk Drugs*

- “Thorough QT Studies” -


Terodiline
1991
Astemizole
1998
Mibefradil
1998
Terfenadine
1998
KCNH2/HERG (I_{Kr})
"Gain"
"Loss-of-Function"
SQT1
LQT2
cNBD
N_1
C_{1159}
Levomethadyl
2004
Cisapride
2000
Grepafloxacin
1999

Drug-Induced Sudden Cardiac Arrest



Identification of At-Risk *Recipients*

- Pharmacogenetics -

Pharmacogenetics of DI-SCA

- Right Drug
- Right Dose
- Right Patient

Drugs

+

Pro-arrhythmia Genotype(s)?

=

Increased Risk of DI-TdP

A Mother's Question

Why did my 19-year-old daughter die?

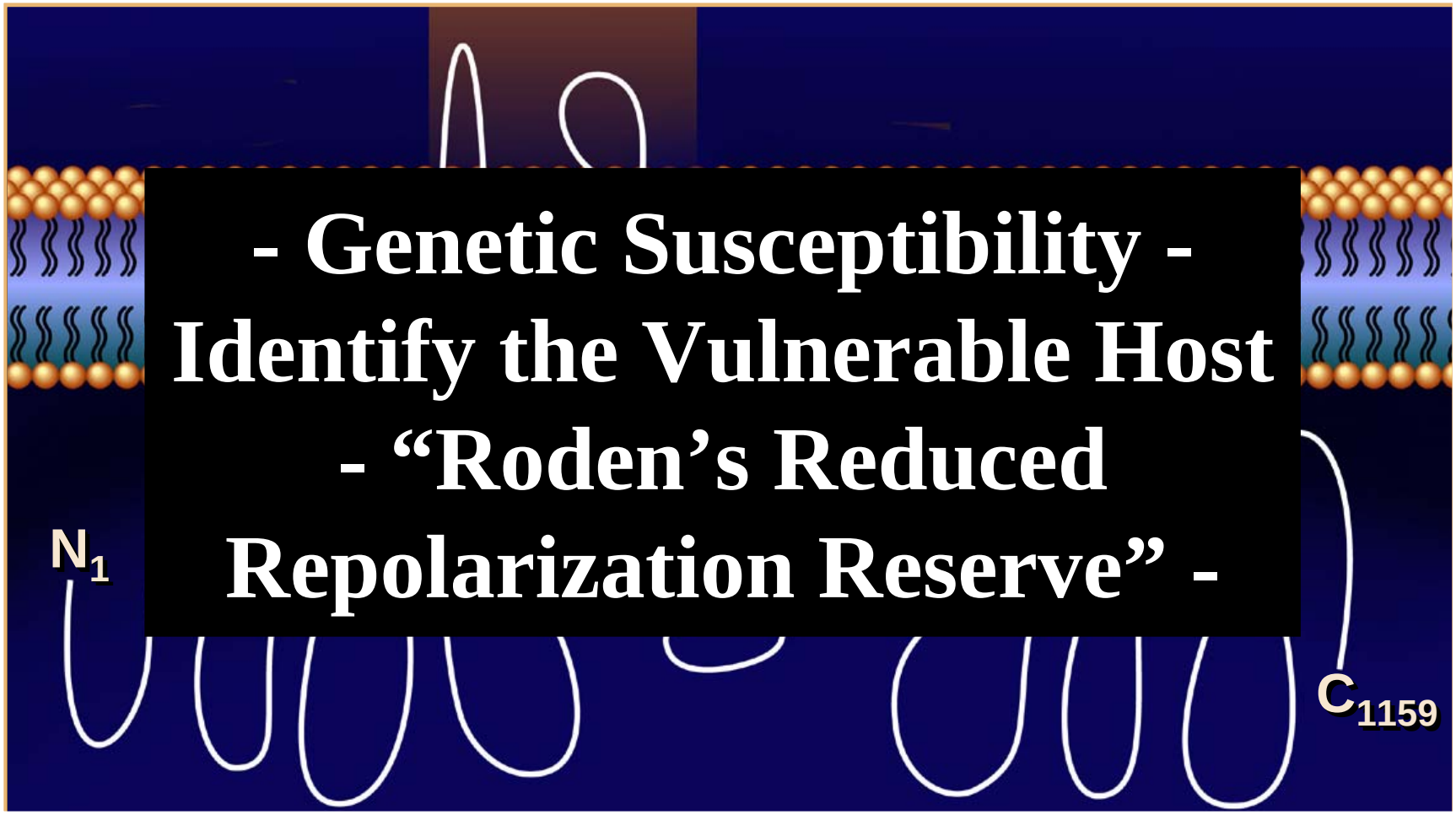
MAYO CLINIC

Pharmacogenetics of DI-SCA

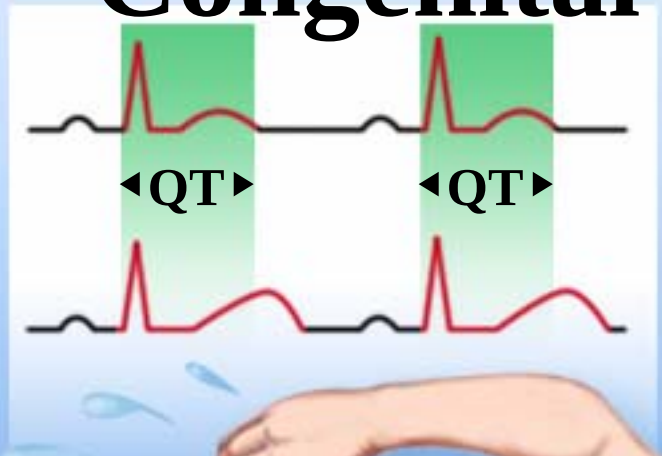
- 19-year-old white female found dead in dorm room
- Labor Day – college campus – false fire alarm
- Autopsy - therapeutic [terfenadine]
- Molecular autopsy: R176W-KCNH2
- Cause of death: Lethal arrhythmia secondary to terfenadine-induced TdP in a vulnerable host during an auditory trigger.

MAYO CLINIC

KCNH2/HERG
Ch 7q35



Congenital Long QT Syndrome

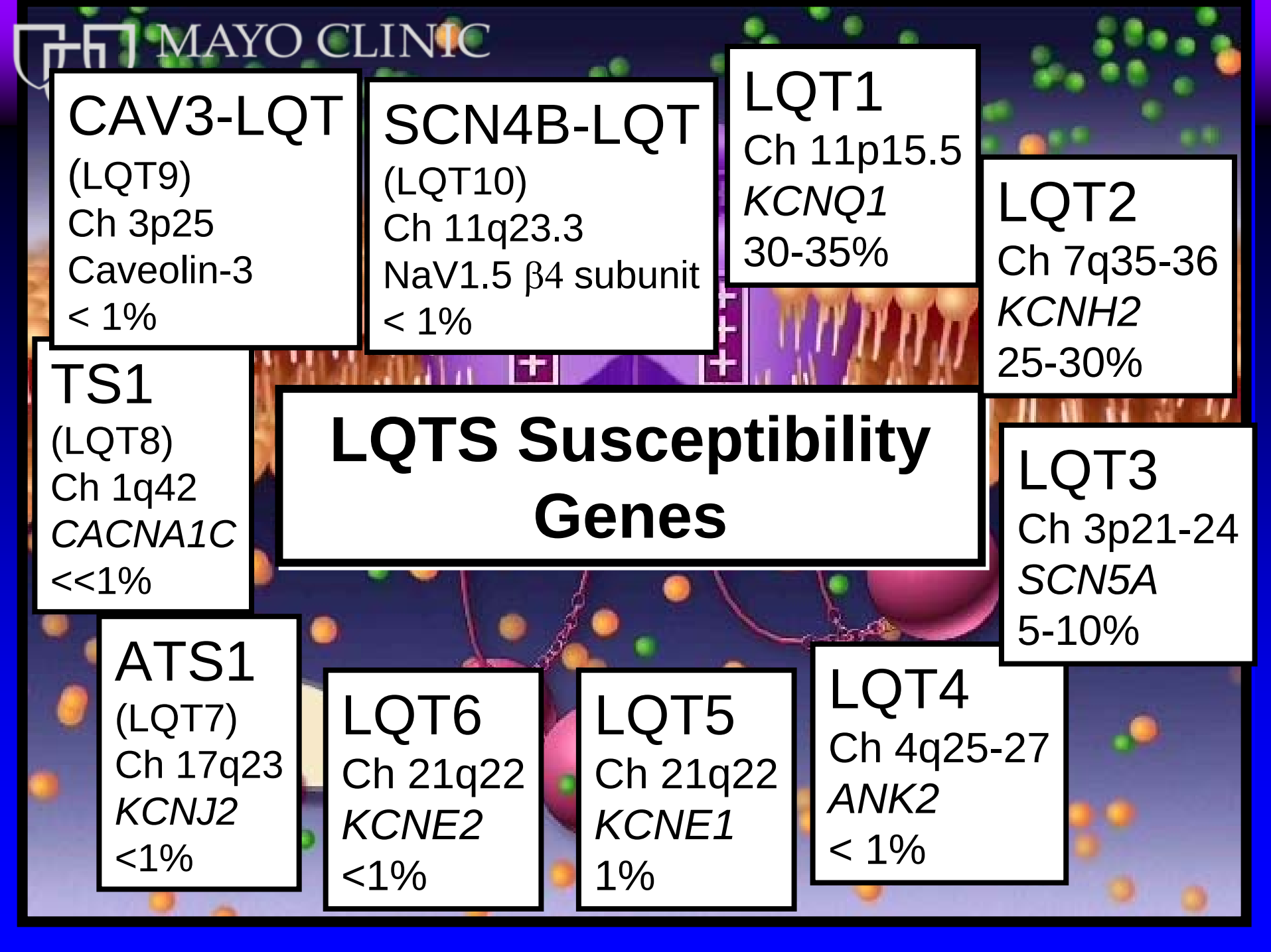


Normal QT interval

Prolonged QT

1. Syncope
2. Seizures
3. Sudden death

Torsades de pointes


MAYO CLINIC
CAV3-LQT
(LQT9)
Ch 3p25
Caveolin-3
< 1%
SCN4B-LQT
(LQT10)
Ch 11q23.3
NaV1.5 β4 subunit
< 1%
LQT1
Ch 11p15.5
KCNQ1
30-35%
LQT2
Ch 7q35-36
KCNH2
25-30%
TS1
(LQT8)
Ch 1q42
CACNA1C
<<1%
LQTS Susceptibility Genes
LQT3
Ch 3p21-24
SCN5A
5-10%
ATS1
(LQT7)
Ch 17q23
KCNJ2
<1%
LQT6
Ch 21q22
KCNE2
<1%
LQT5
Ch 21q22
KCNE1
1%
LQT4
Ch 4q25-27
ANK2
< 1%

LQTS Genetic Testing

LQT1
Ch 11p15.5
KCNQ1
30-35%

LQT2
Ch 7q35-36
KCNH2
25-30%

LQT3
Ch 3p21-24
SCN5A
5-10%

LQT6
Ch 21q22
KCNE2
<1%

LQT5
Ch 21q22
KCNE1
1%

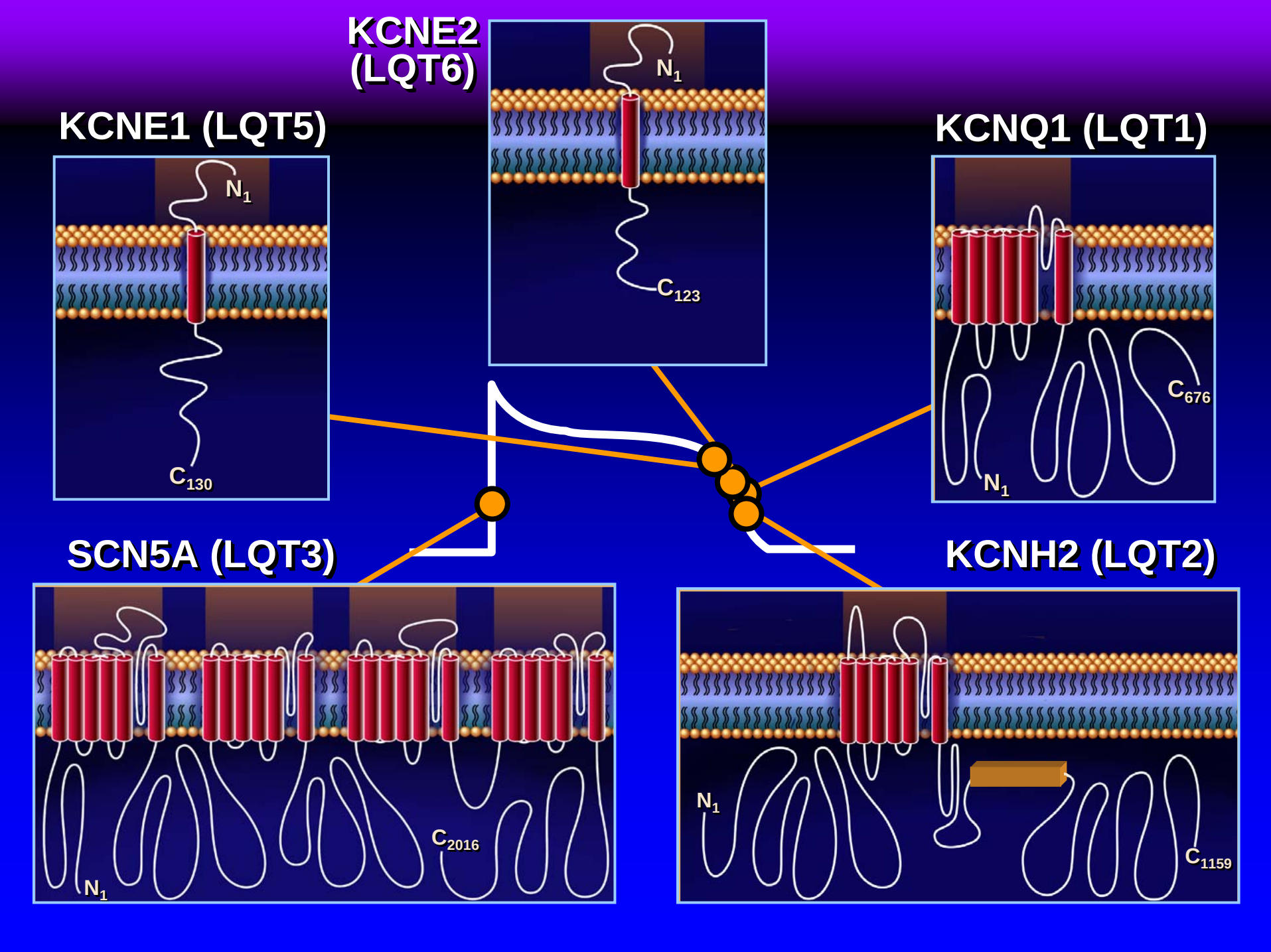
Drug-Induced Sudden Cardiac Arrest

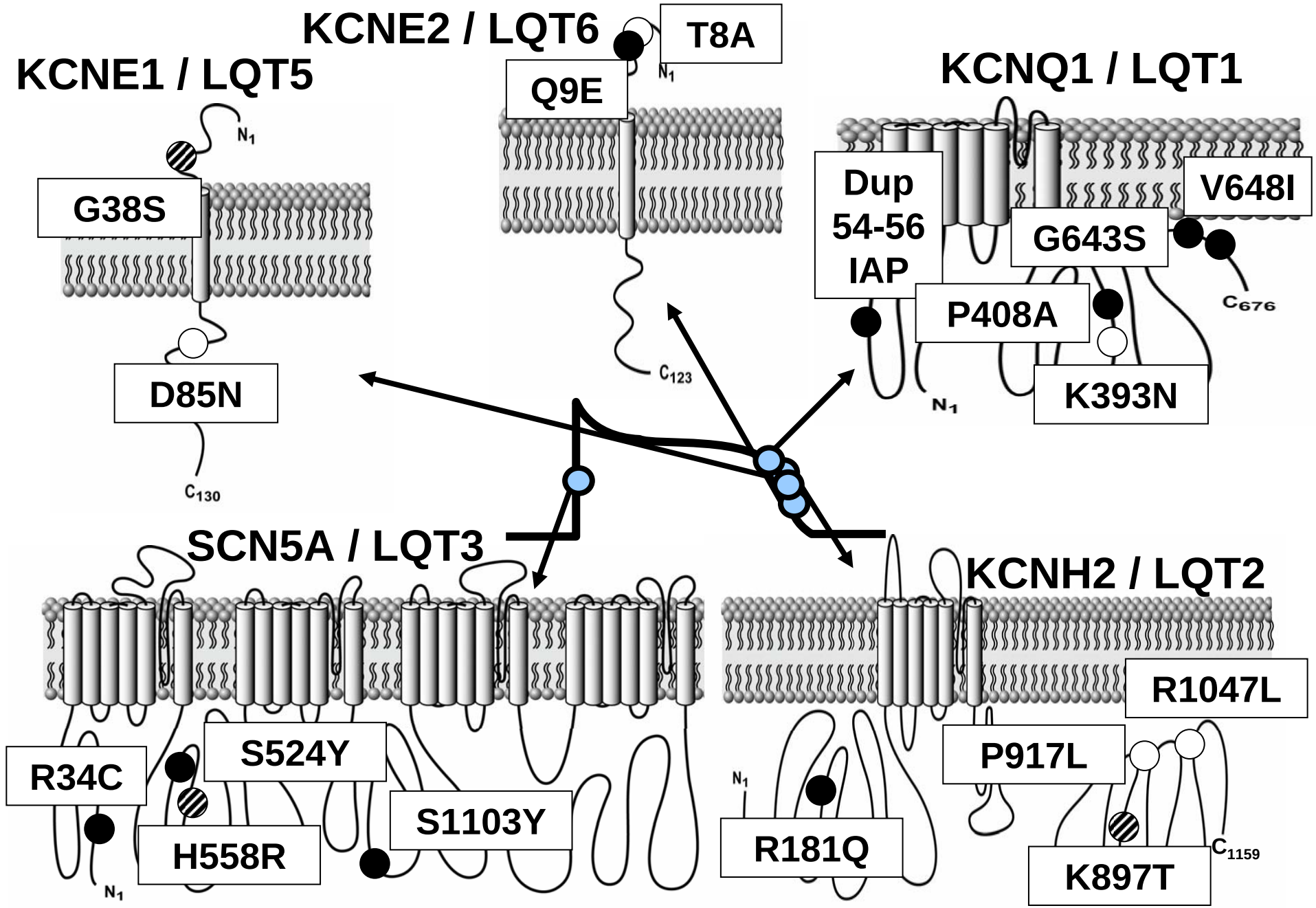
5-10%

Identification of At-Risk *Recipients*

-Pharmacogenetics –

- Yang … Roden. *Circulation* 105:1943-1948, 2002


KCNE2
(LQT6)
N1
C123
KCNE1 (LQT5)
N1
C130
KCNQ1 (LQT1)
C676
N1
SCN5A (LQT3)
C2016
N1
KCNH2 (LQT2)
N1
C1159



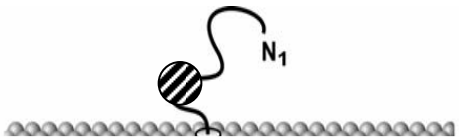
Ackerman et al. *Mayo Clin Proc.* 78:1479-1487, 2003
Ackerman et al. *Heart Rhythm.* 1:600-607, 2004

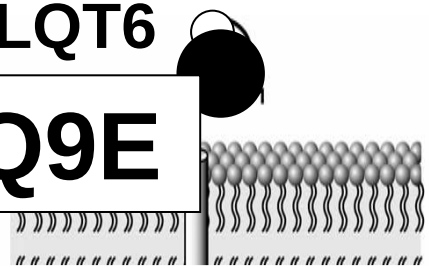
KCNE2 / LQT6

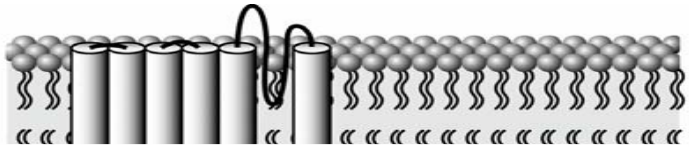
KCNE1 / LQT5

Q9E

KCNQ1 / LQT1



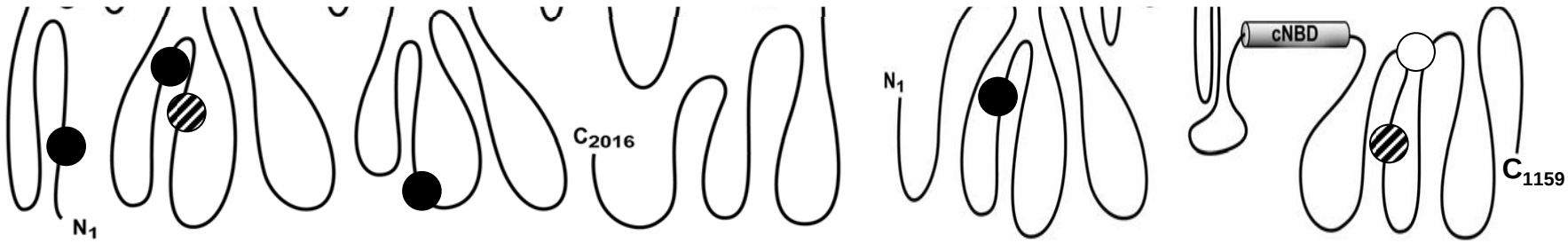




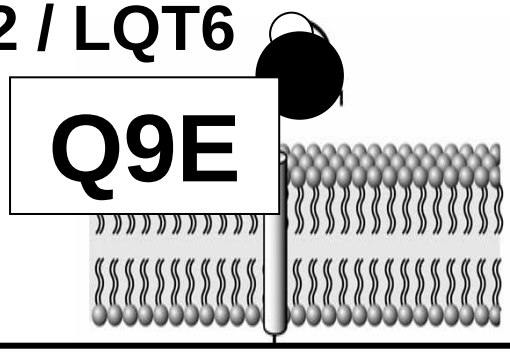
MiRP1 Forms IKr Potassium Channels with HERG and is Associated with Cardiac Arrhythmia

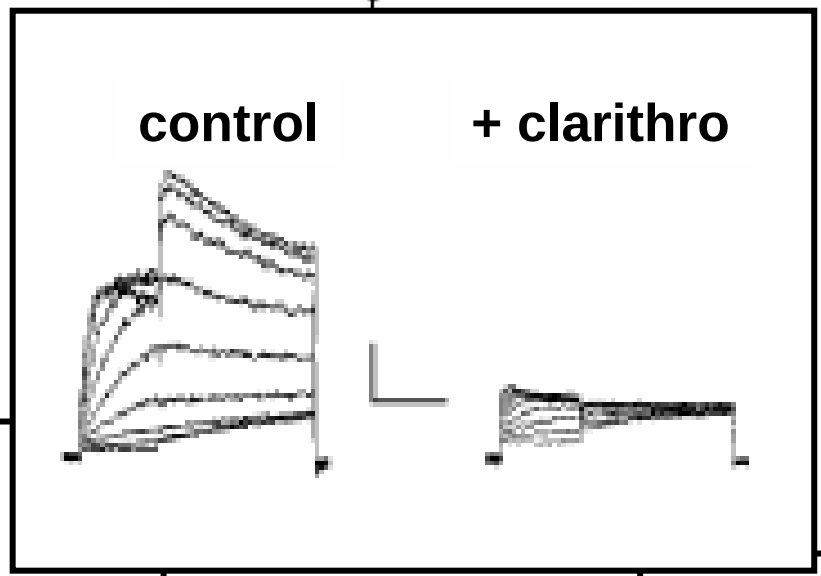
- 1 of 20 pts with DI-TdP (clarithromycin)
- 76-year-old African American female
- Absent in 1010 control individuals

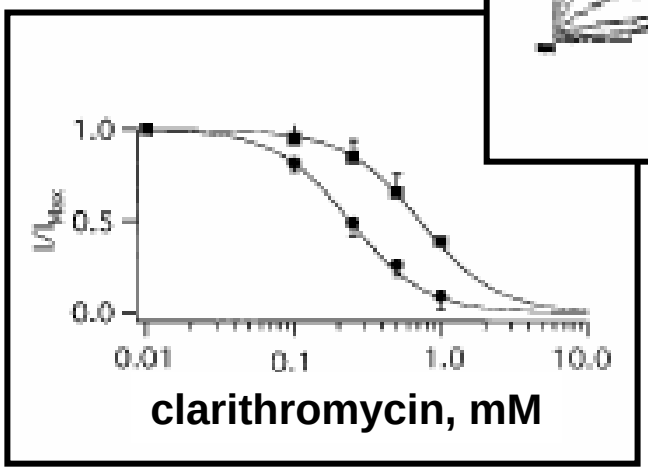
Abbott…Goldstein. *Cell* 97:175-187, 1999

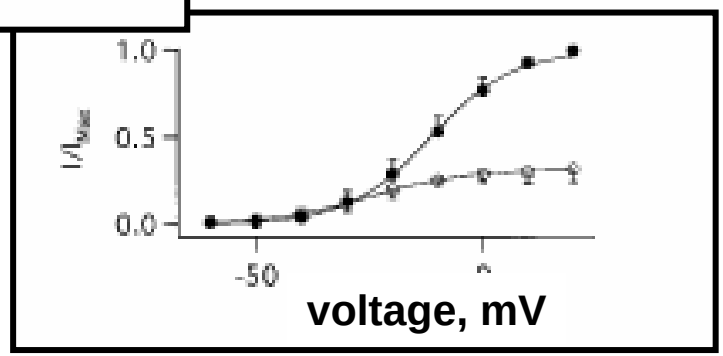


KCNE2 / LQT6

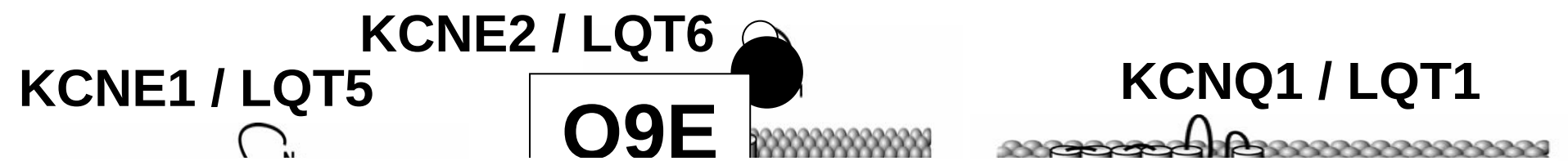








Abbott…Goldstein. *Cell* 97:175-187, 1999



MiRP1 Forms IKr Potassium Channels with HERG and is Associated with Cardiac Arrhythmia

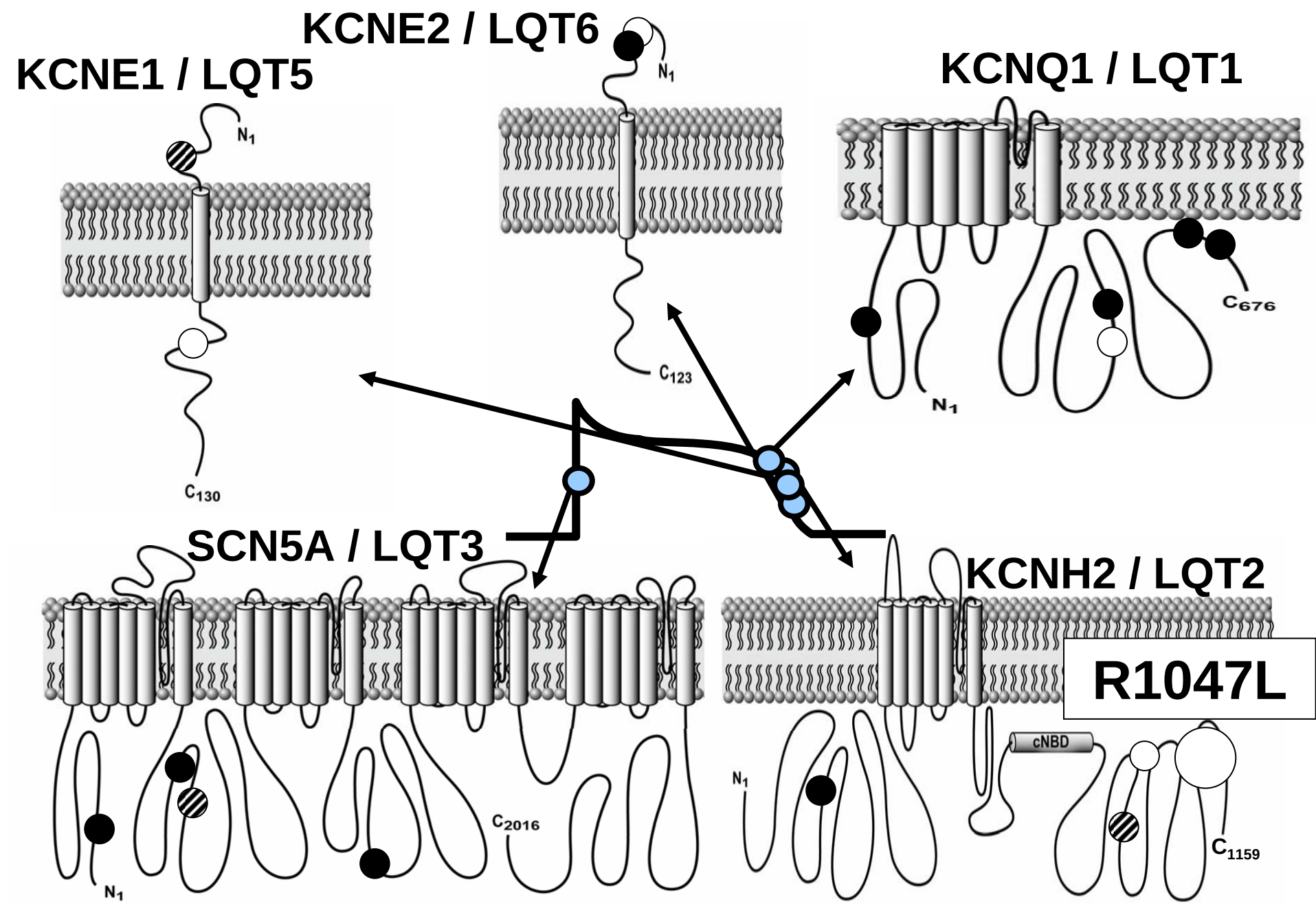
- **1 of 20 pts with DI-TdP (clarithromycin)**
- **76-year-old African American female**
- **Absent in 1010 control individuals**

Abbott…Goldstein. *Cell* 97:175-187, 1999

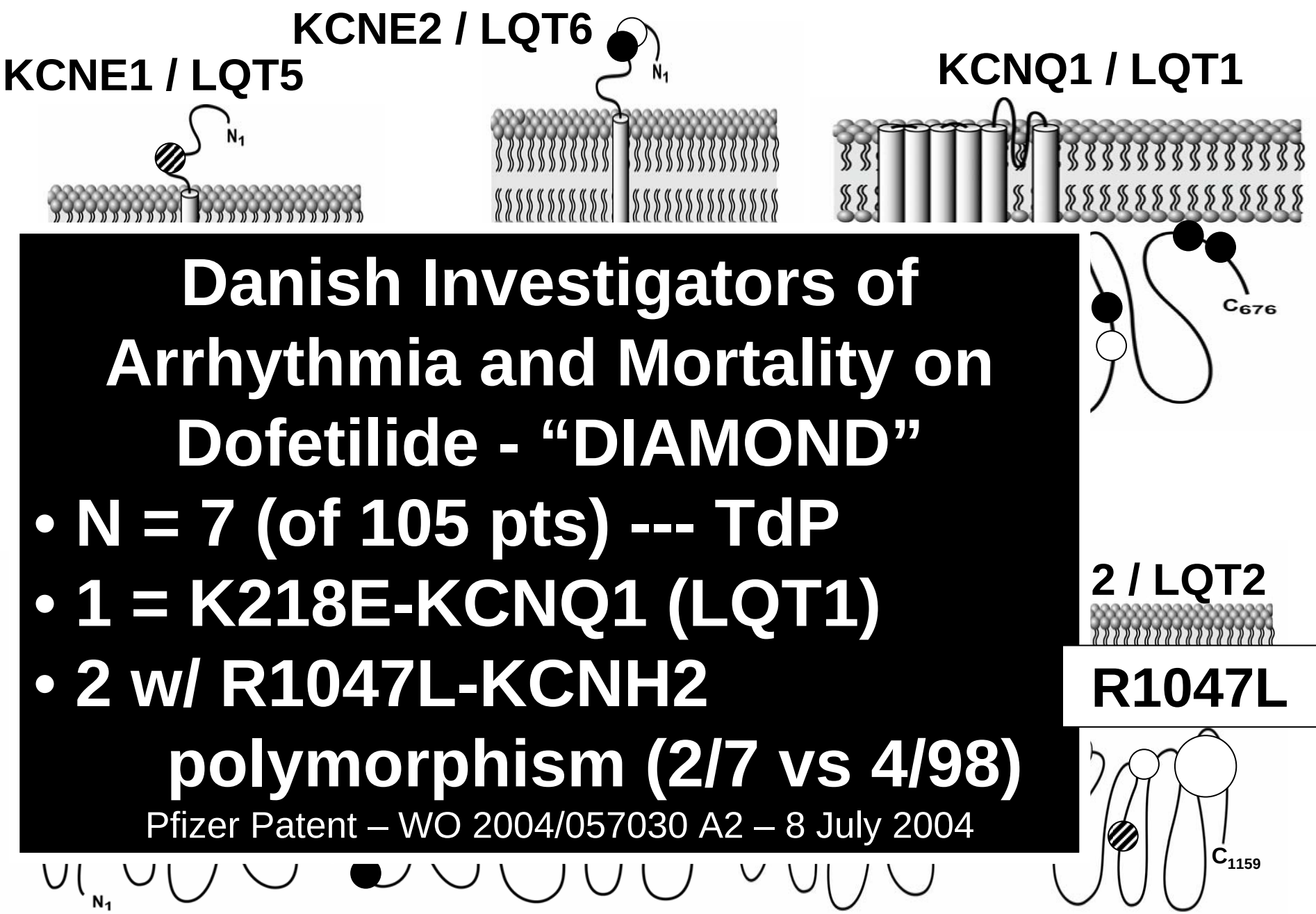
Ethnic Differences in Cardiac Potassium Channel Variants: Implications for Genetic Susceptibility to Sudden Cardiac Death and Genetic Testing for Congenital Long QT Syndrome

- 25% of blacks had uncommon polymorphisms compared to 14% whites
- **Q9E – <u>3% blacks</u>**, 0% others
- ?Pre-prescription genotyping of Q9E-MiRP1 in blacks?

Ackerman…Curran. *Mayo Clin Proc.* 78:1479-1487, 2003



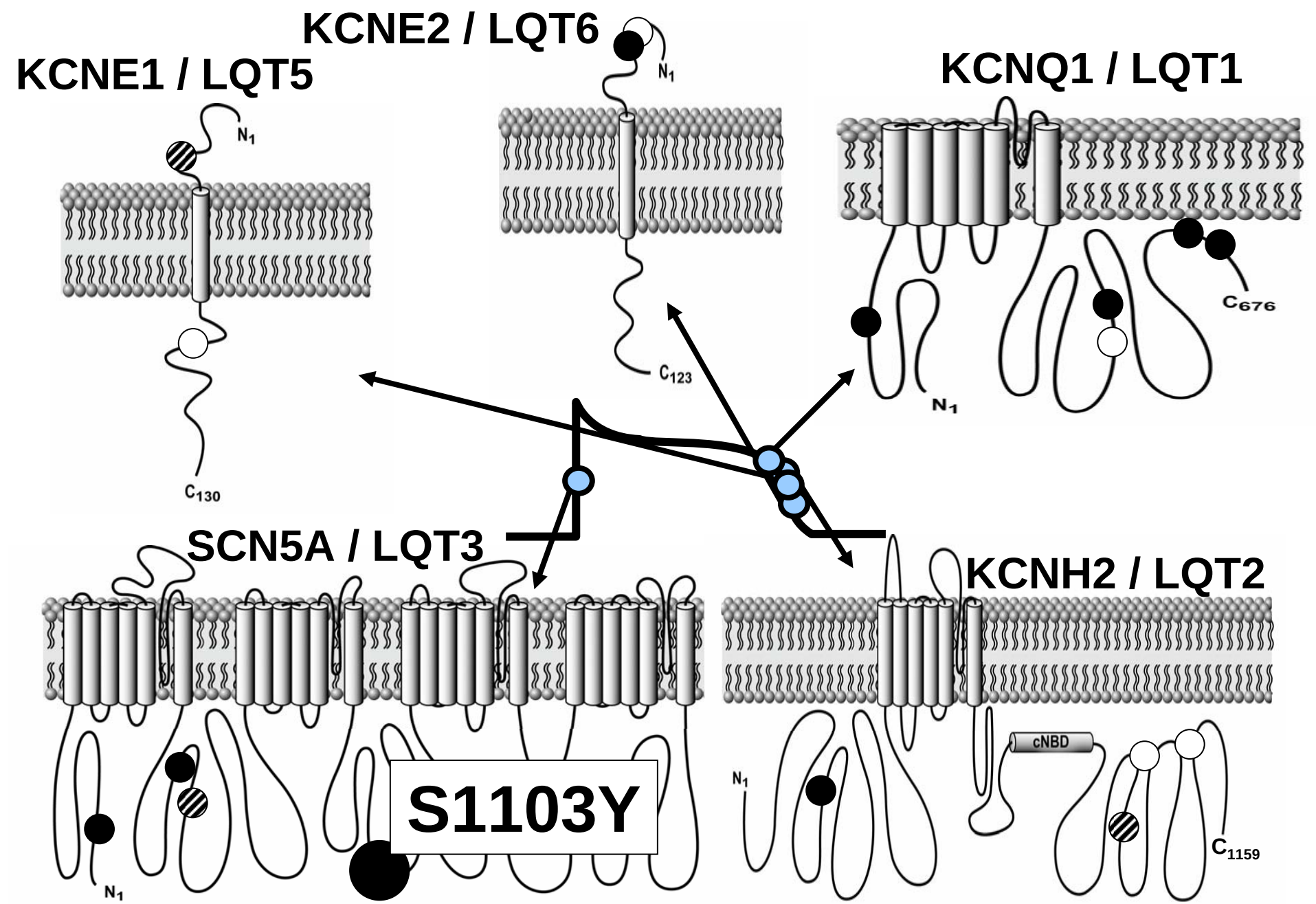
Ackerman et al. *Mayo Clin Proc.* 78:1479-1487, 2003



Danish Investigators of Arrhythmia and Mortality on Dofetilide - "DIAMOND"

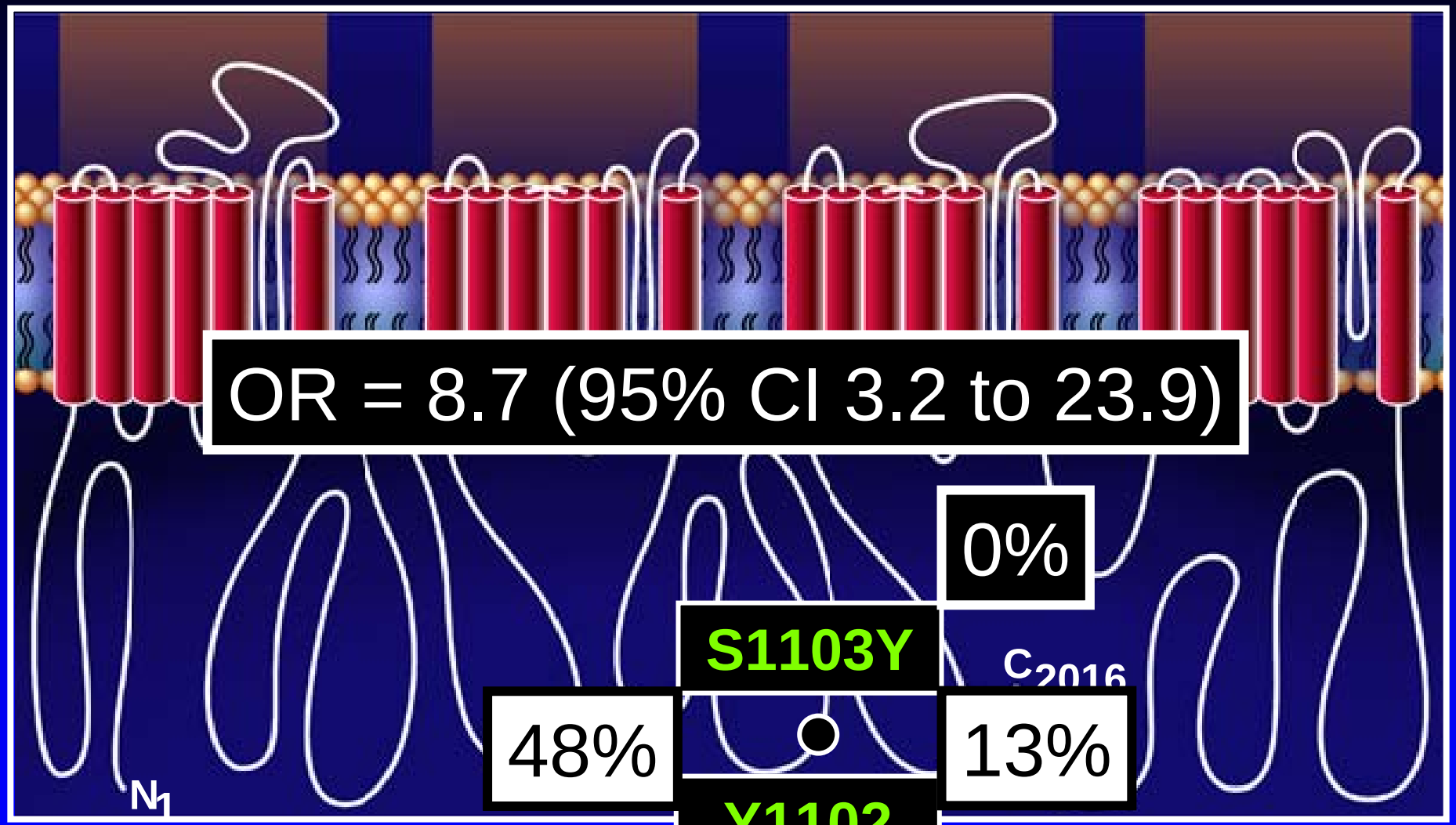
- N = 7 (of 105 pts) --- TdP
- 1 = K218E-KCNQ1 (LQT1)
- 2 w/ R1047L-KCNH2 polymorphism (2/7 vs 4/98)

Pfizer Patent – WO 2004/057030 A2 – 8 July 2004



Ackerman et al. *Heart Rhythm.* 1:600-607, 2004

S1103Y-SCN5A and Arrhythmias in Blacks

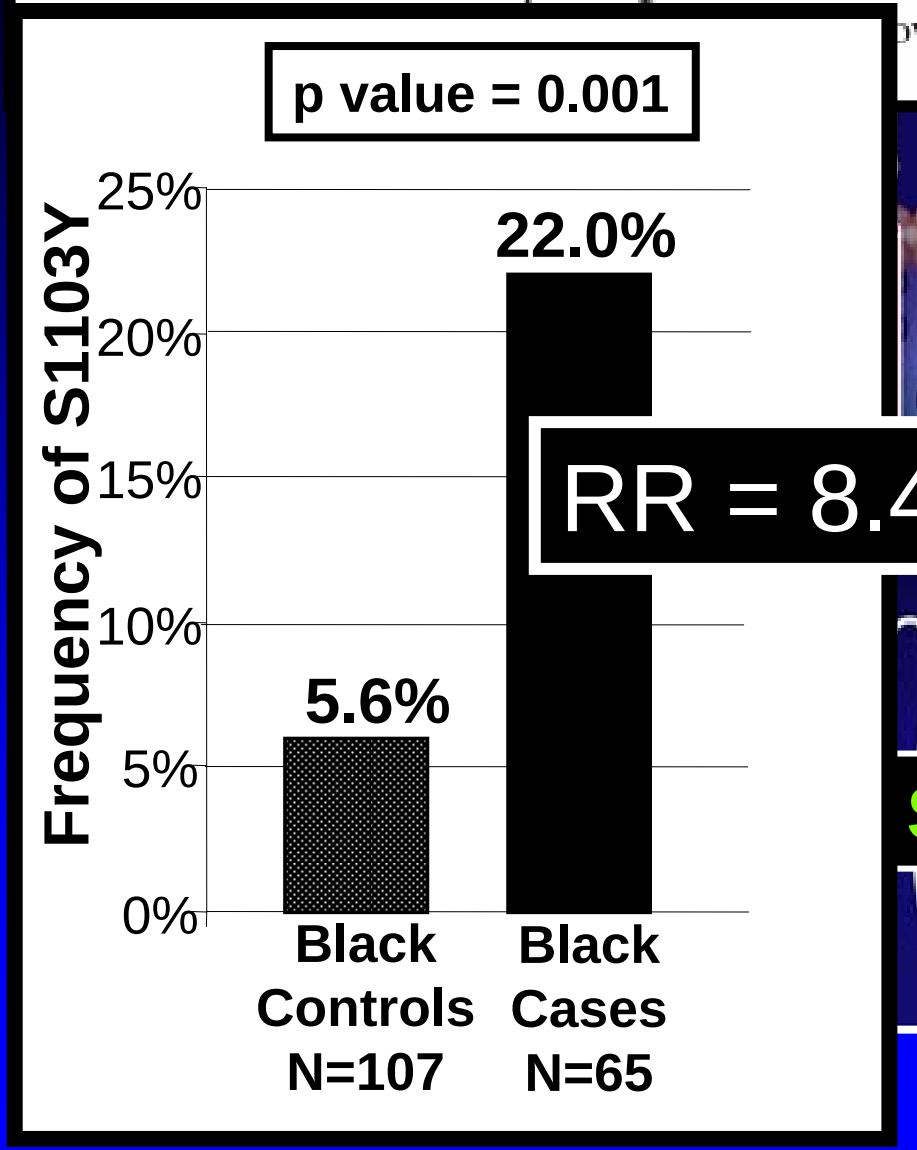


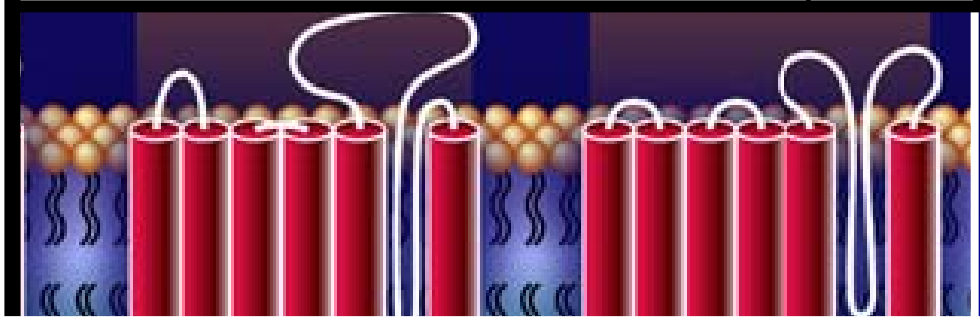
Splawski…Keating. *Science* 297:1333-1336, 2002

Role of SCN5A Y1102 Polymorphism in Sudden Cardiac Death in Blacks

Allen Burke, MD; Wendy Creighton, MD; Erik Mont, MD; Ling Li, MD; Susan Hogan, MD; owler, MD; Renu Virmani, MD

Circulation 112:798-802, 2005

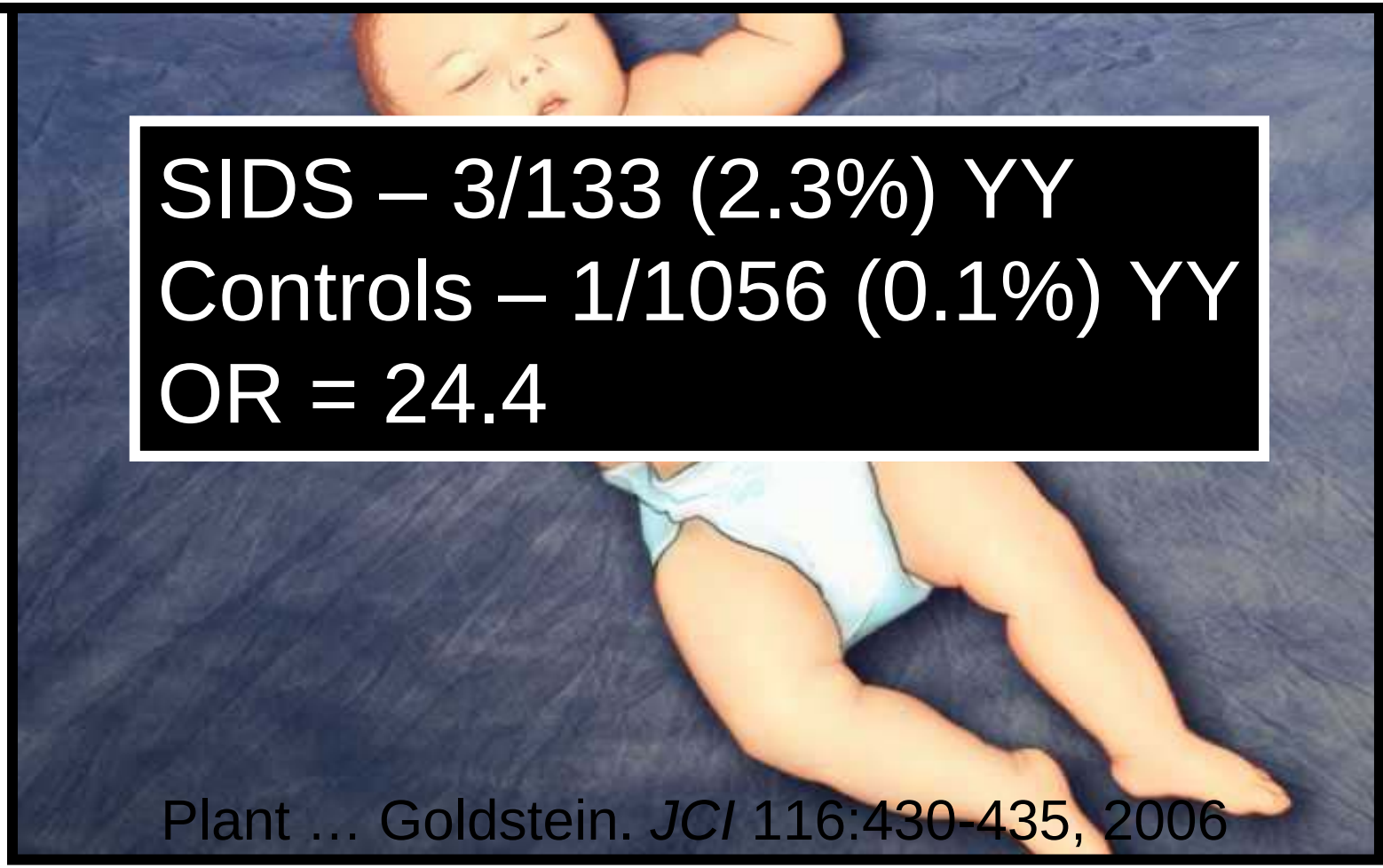




RR = 8.4 (95% CI 2.1 to 28.6)

A common cardiac sodium channel variant associated with sudden infant death in African Americans, *SCN5A* S1103Y

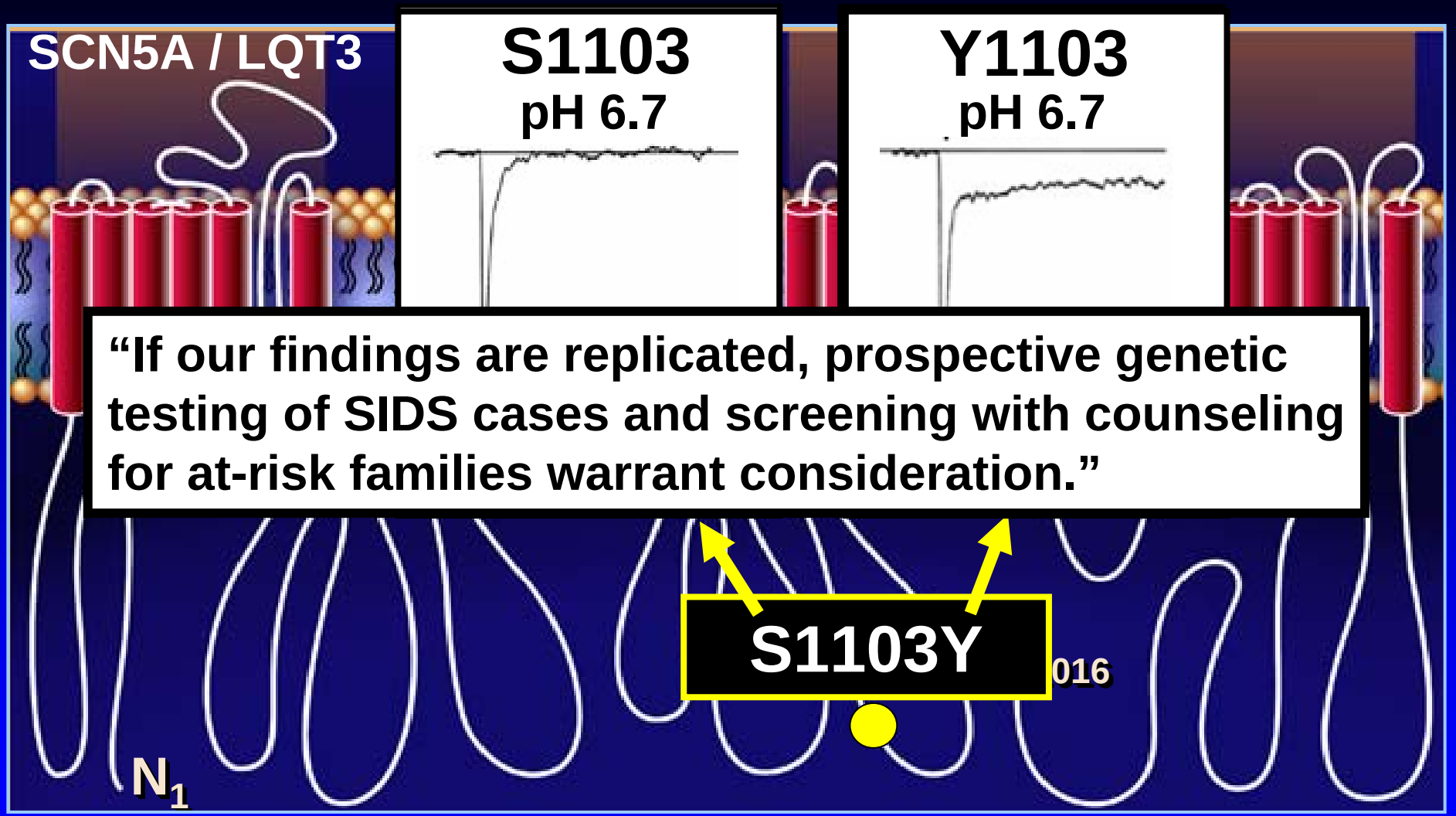
Leigh D. Plant,[1] Peter N. Bowers,[2] Qianyong Liu,[1] Thomas Morgan,[2] Tingting Zhang,[1] Matthew W. State,[2] Weidong Chen,[3] Rick A. Kittles,[4] and Steve A.N. Goldstein[1]



SIDS – 3/133 (2.3%) YY
Controls – 1/1056 (0.1%) YY
OR = 24.4

Plant … Goldstein. *JCI* 116:430-435, 2006

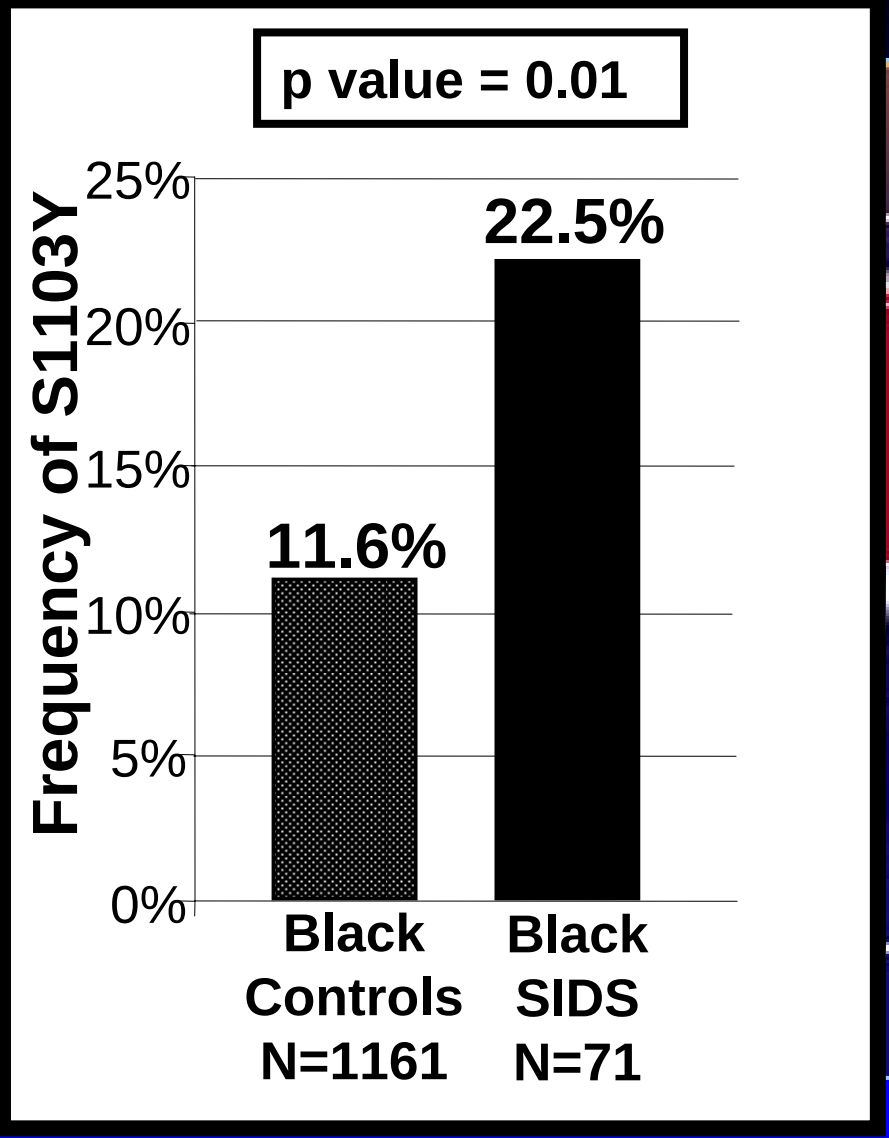
S1103Y-SCN5A and African American SIDS

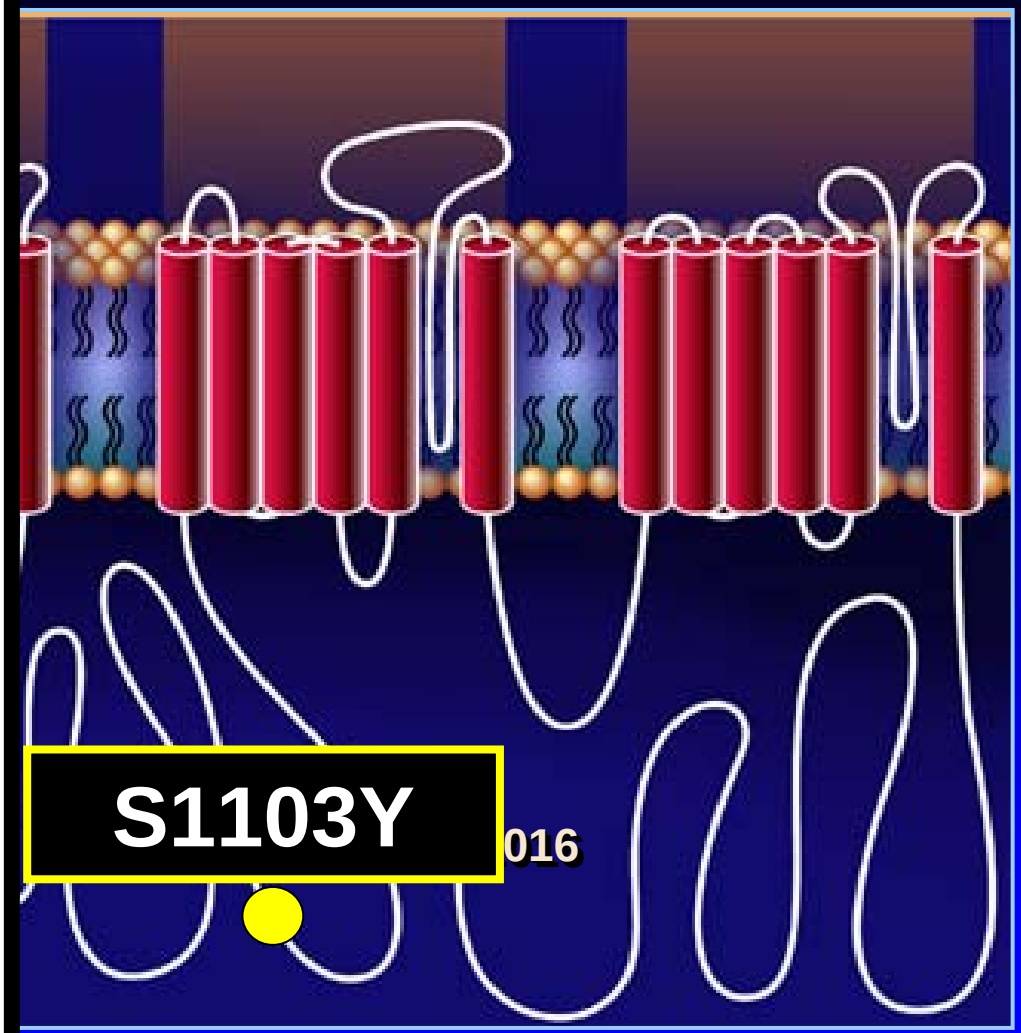


"If our findings are replicated, prospective genetic testing of SIDS cases and screening with counseling for at-risk families warrant consideration."

Plant … Goldstein. *JCI* 116:430-435, 2006

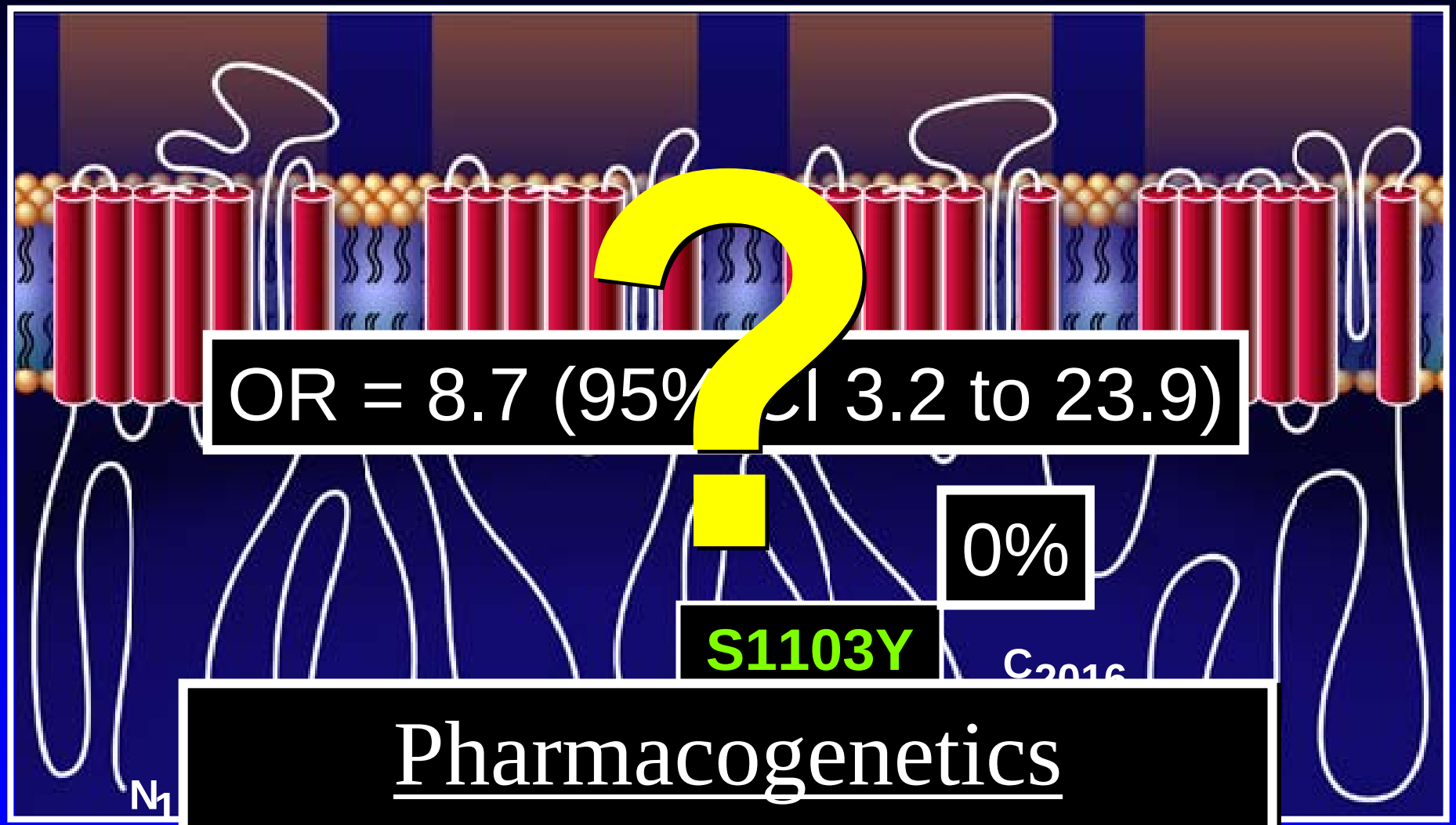
S1103Y-SCN5A and African American SIDS





Van Norstrand … Ackerman. Submitted October 2007

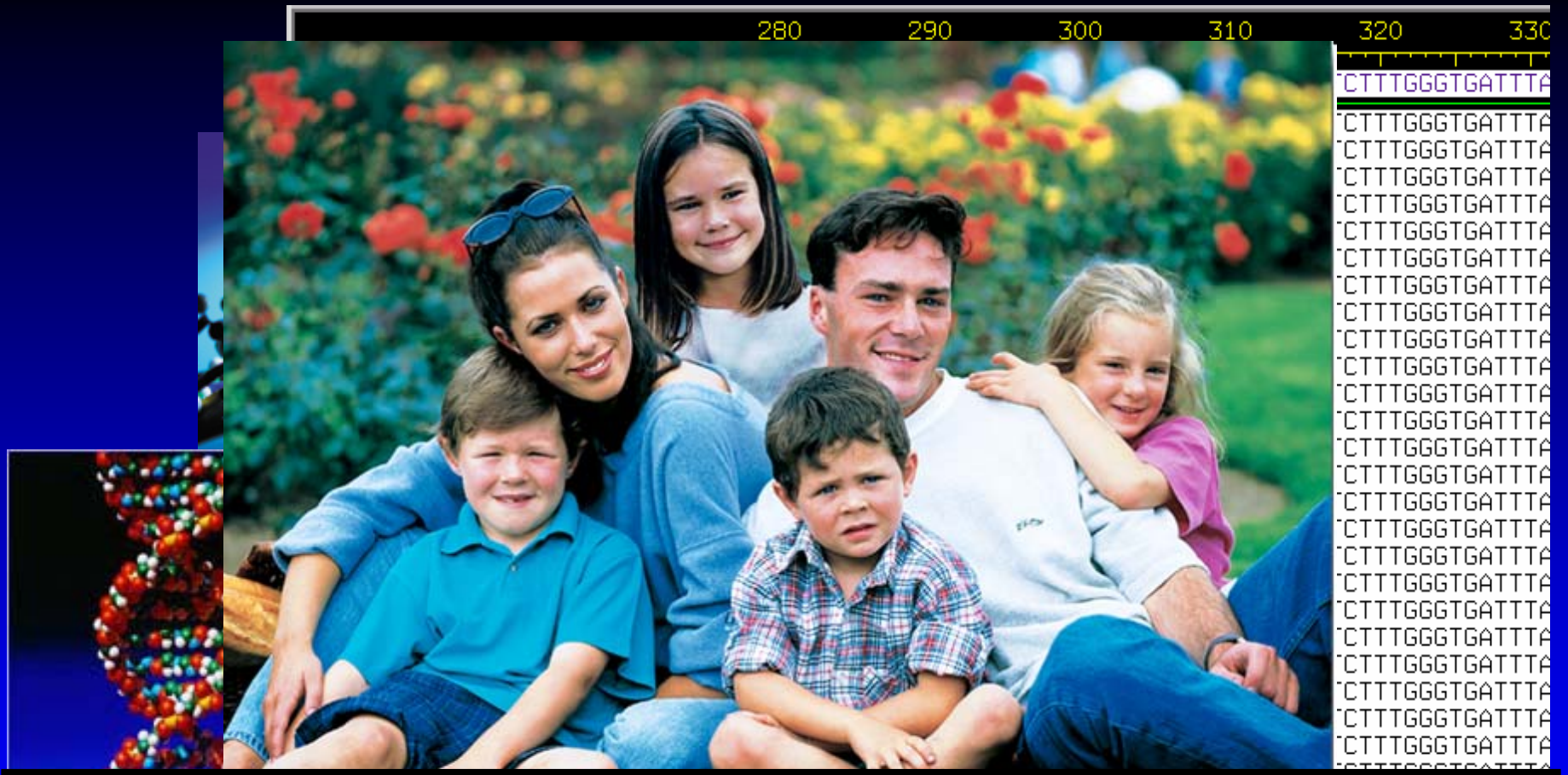
S1103Y-SCN5A and Arrhythmias in Blacks



Pharmacogenetics

Pre-prescription Genotyping

Drug-Induced Sudden Cardiac Arrest



Identification of At-Risk Recipients

- Pharmacogenetics -

Pharmacogenetics of DI-SCA

Take Home Points

1. Two strategies – At-Risk Drugs and At-Risk Recipients

2. At-Risk Drugs – Thorough QT Studies and HERG block testing

3. At-Risk Recipients – 5-10% - rare LQTS-causing mutations

4. Pre-prescription genotyping of functional channel polymorphisms that “reduce repolarization reserve” and confer susceptibility --- more investigation needed

MAYO CLINIC

WINDLAND SMITH RICE
SUDDEN DEATH
GENOMICS LABORATORY

Dr. Scholl Foundation, CJ Foundation for SIDS
Hannah Wernke Memorial Foundation
American Heart Association
National Institutes of Health

MAYO CLINIC

WINDLAND SMITH RICE
SUDDEN DEATH
GENOMICS LABORATORY

“To heal the sick and advance the science”

Dr. Charles W. Mayo