Genetics for Personalised Medicine in Arrhythmias

Peter J. Schwartz

Università di Pavia
e
Fondazione IRCCS Policlinico S. Matteo
Pavia

Where we stand

Long QT Syndrome

Where we are going

Ischemic Heart Disease

LQTS

LQT1 Mutations affecting I_{Ks}

LQT2 Mutations affecting I_{Kr}

LQT3 Mutations affecting I_{Na}

Genotype-Phenotype Correlation in the Long-QT Syndrome

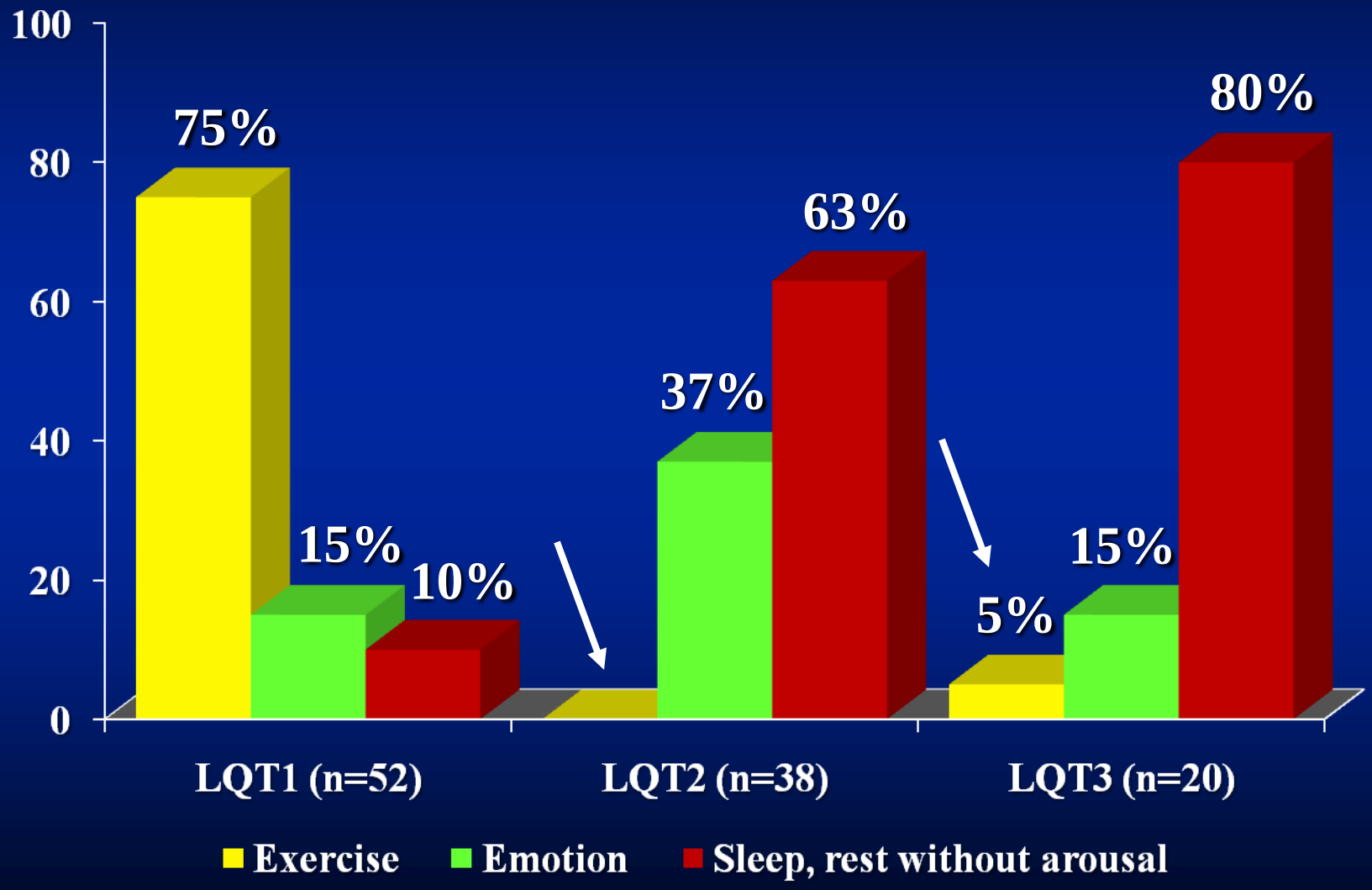
Gene-Specific Triggers for Life-Threatening Arrhythmias

Peter J. Schwartz, MD; Silvia G. Priori, MD, PhD; Carla Spazzolini, PhD; Arthur J. Moss, MD; G. Michael Vincent, MD; Carlo Napolitano, MD, PhD; Isabelle Denjoy, MD; Pascale Guicheney, MD; Günter Breithardt, MD; Mark T. Keating, MD; Jeffrey A. Towbin, MD; Alan H. Beggs, PhD; Paul Brink, MD; Arthur A.M. Wilde, MD; Lauri Toivonen, MD; Wojciech Zareba, MD, PhD; Jennifer L. Robinson, MS; Katherine W. Timothy, MS; Valerie Corfield, MD; Duangrurdee Wattanasirichaigoon, MD; Clive Corbett, MD; Wilhelm Haverkamp, MD; Eric Schulze-Bahr, MD; Michael H. Lehmann, MD; Ketty Schwartz, MD; Philippe Coumel, MD; Raffaella Bloise, MD

(*Circulation*. 2001;103:89-95.)

Based on 670 LQTS patients of known genotype and all with cardiac events

Triggers for lethal cardiac events (CA, SCD) (n=110)



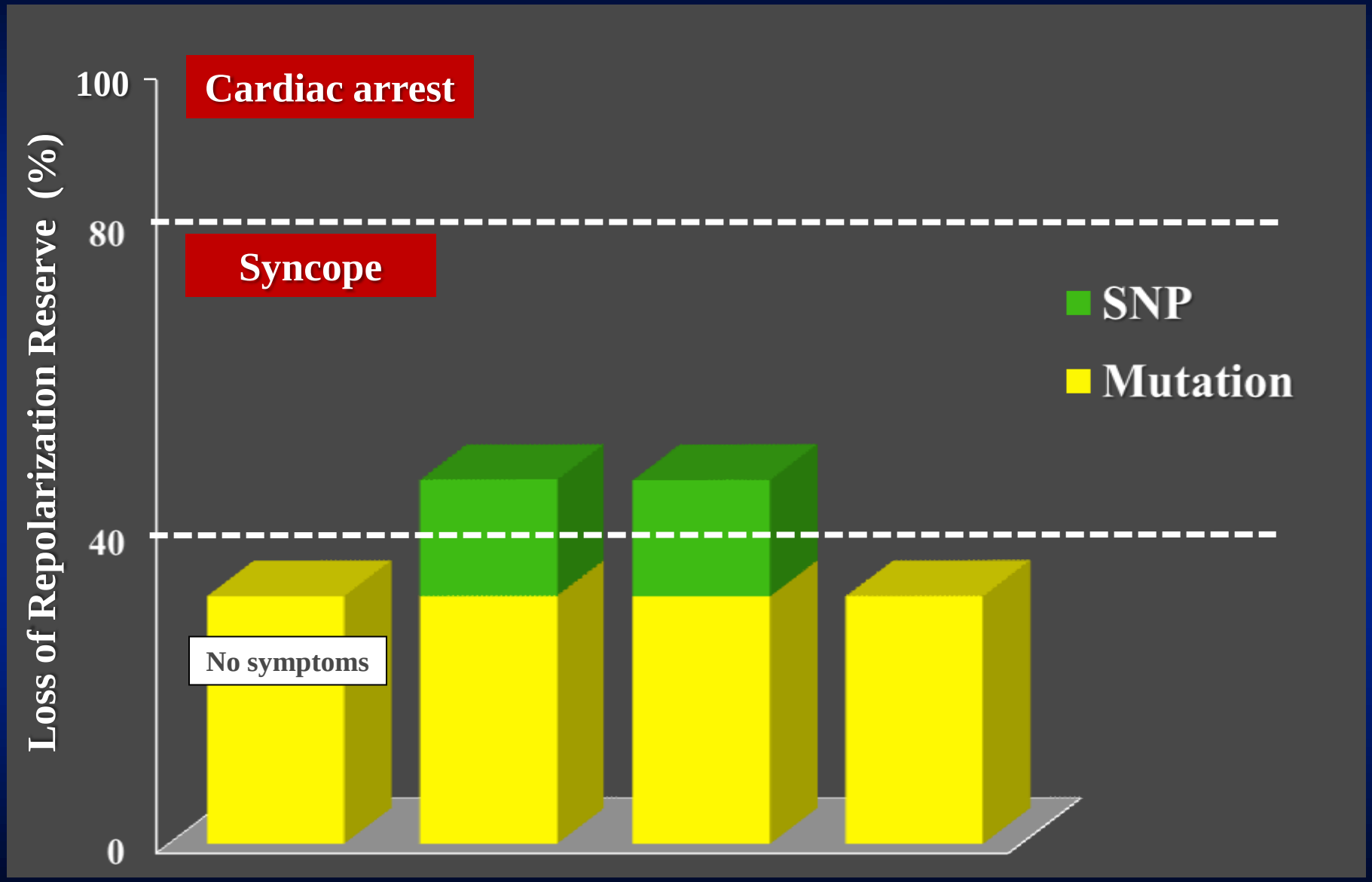
- In-vitro Fertilization
- RNA-silencing

Modifier Genes

Arrhythmic "Weight" of Modifier Genes (SNPs)

The arrhythmic contribution of a "modifier", a common polymorphism (SNP), can only be a fraction of the contribution by the disease-causing mutation.

SNPs and Cardiac Events



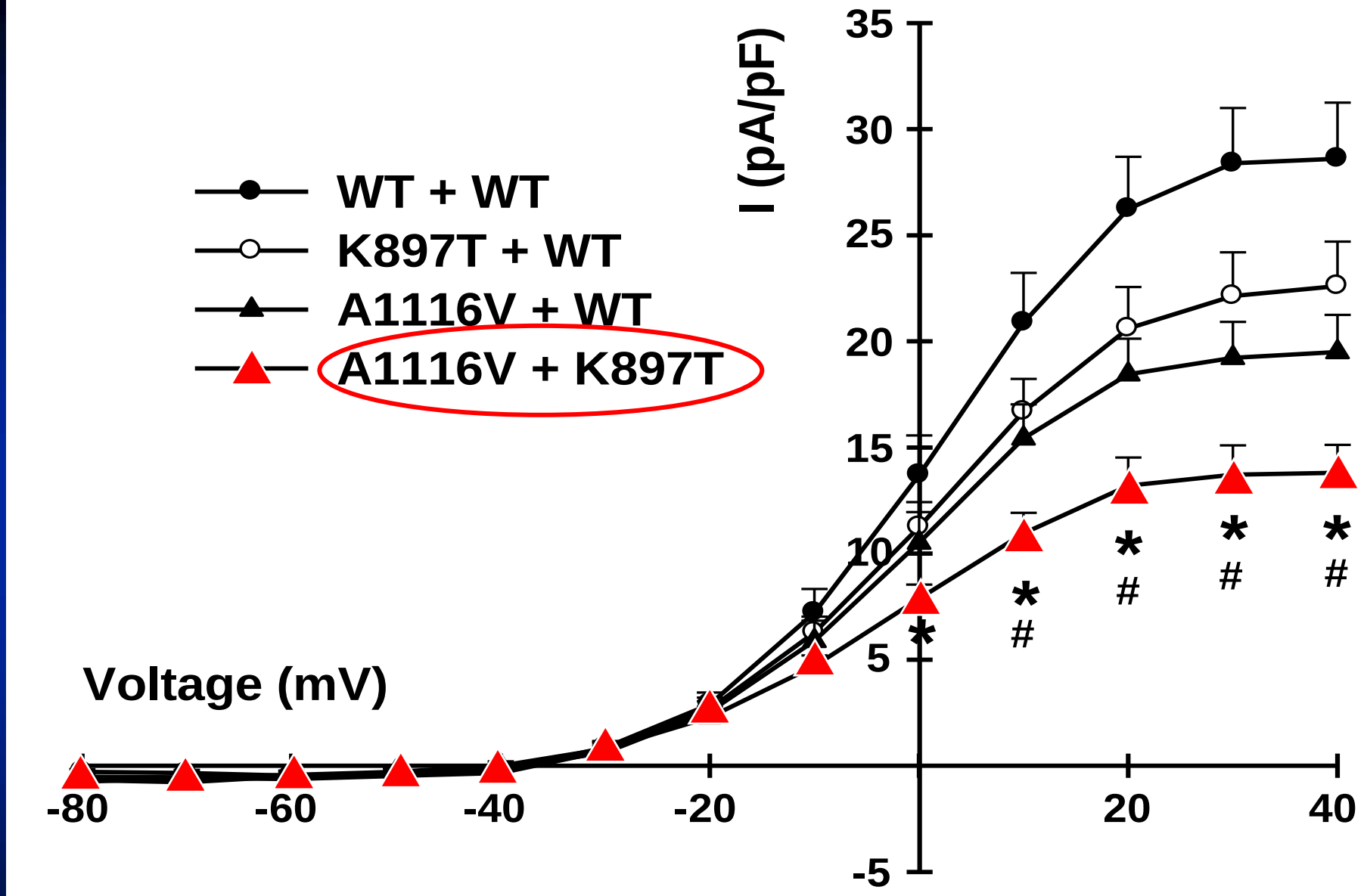
KCNH2-K897T Is a Genetic Modifier of Latent Congenital Long-QT Syndrome

Lia Crotti, MD*; Andrew L. Lundquist, PhD*; Roberto Insolia, BSc; Matteo Pedrazzini, BSc; Chiara Ferrandi, BSc; Gaetano M. De Ferrari, MD; Alessandro Vicentini, MD; Ping Yang, PhD; Dan M. Roden, MD; Alfred L. George, Jr, MD; Peter J. Schwartz, MD

(*Circulation*. 2005;112:1251-1258.)

- **Woman age 40 – VF, apparently idiopathic, normal QTc**
- **Carrier of KCNQ2-A1116V (LQT2) AND of K897T (different allele)**
- **Repeated 24-hour Holter recordings show transient QTc > 500 ms**
- **Family members carry either the mutation or the SNP**
- **Cardiac events present only in the woman with both mutation and SNP**

Crotti et al., 2005



Co-expression of A1116V with K897T reduces I_{Kr} current much more than A1116V with wild-type (WT).

CONCLUSION

A very common *KCNH2* polymorphism may modify the clinical expression of a latent LQT2 mutation.

IMPLICATION

A similar genetic mechanism may contribute to the risk for sudden death in more prevalent cardiac diseases, such as myocardial infarction or heart failure, and may facilitate drug-induced TdP.

K897T, Torsades-de-Pointes, and Acute Myocardial Infarction

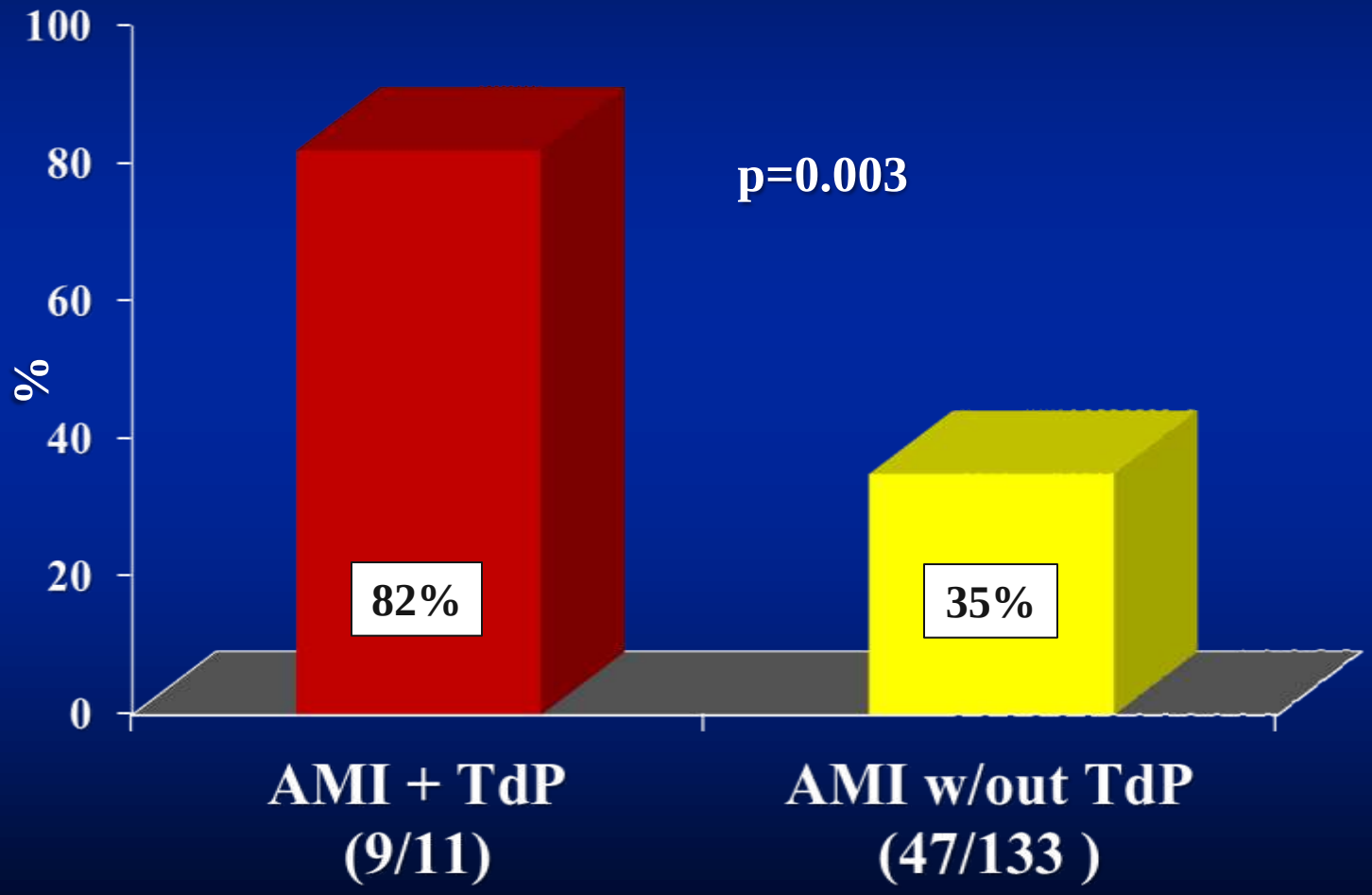
Study Population

- 13 patients with TdP during AMI
- 133 ethnically matched controls

K897T and ischemic arrhythmias

- 2/13 pts had novel LQTS mutations, previously unrecognized (1 *KCNH2* and 1 *SCN5A*)
- 9/11 pts (82%) were *KCNH2*-K897T carriers vs 35% of controls

Presence of K897T among pts with or without TdP during an acute MI



K897T and ischemic arrhythmias

Patients with AMI carrying *KCNH2*-K897T had an 8-fold greater risk of experiencing TdP compared to controls (95% C.I. 2-40).

K897T and ischemic arrhythmias

A common polymorphism, present in over 30% of the general population and previously described as an LQTS modifier, markedly increases the risk of life-threatening arrhythmias in association with an acute myocardial infarction.

How to Search for Modifier Genes?

The Importance of Founder Populations

Around 1690 A.D. a Dutchman left the Netherlands and went to South Africa and settled in Stellenbosch. He was affected by the Long QT Syndrome (LQTS), LQT1 subtype.

During the following 300 years his genes, and his mutation (A341V), travelled extensively.

In partnership with Prof. Paul Brink, at Stellenbosch University, we identified 26 families descending directly from the Dutchman with LQTS. All the affected individuals carry the A341V mutation on the KCNQ1 gene.

South African LQT1 Founder Population

***KCNQ1*-A341V**

Family members	**500**
Mutation carriers	**205**
CA / SD	**41%**
CA / SD + Syncope	**82%**

NOS1AP Is a Genetic Modifier of the Long-QT Syndrome

Lia Crotti, MD, PhD; Maria Cristina Monti, PhD; Roberto Insolia, BSc; Anna Peljto, MS;
Althea Goosen, BSc; Paul A. Brink, MD; David A. Greenberg, PhD;
Peter J. Schwartz, MD*; Alfred L. George, Jr, MD*

(*Circulation*. 2009;120:1657-1663.)

We found that subjects with the *NOS1AP* variants had an almost double risk of suffering either a cardiac arrest or sudden death:

O.R. 1.8 (95% C.I., 1.1 to 3.3)

Sudden Death in Ischemic Heart Disease

Genetics and the Pathway Toward Personalized Medicine

Family History and the Risk of Sudden Cardiac Death as a Manifestation of an Acute Coronary Event

Kari S. Kaikkonen, MD; Marja-Leena Kortelainen, MD; Eeva Linna, MD; Heikki V. Huikuri, MD

(*Circulation*. 2006;114:1462-1467.)

Family History of SCD Present in:

- 33% of SCD victims during a first coronary event n = 138
- 25% of AMI survivors n = 254

Odds Ratio 1.6 (95% C.I. 1.2 – 2.2)

Kaikkonen et al., 2006

Familial Sudden Death Is an Important Risk Factor for Primary Ventricular Fibrillation

A Case-Control Study in Acute Myocardial Infarction Patients

Lukas R.C. Dekker, MD, PhD; Connie R. Bezzina, PhD; José P.S. Henriques, MD, PhD; Michael W. Tanck, PhD; Karel T. Koch, MD, PhD; Marco W. Alings, MD, PhD; Alfred E.R. Arnold, MD, PhD; Menko-Jan de Boer, MD, PhD; Anton P.M. Gorgels, MD, PhD; H. Rolf Michels, MD, PhD; Agnes Verkerk, BSc; Freek W.A. Verheugt, MD, PhD; Felix Zijlstra, MD, PhD; Arthur A.M. Wilde, MD, PhD

(*Circulation*. 2006;114:1140-1145.)

Family History of SCD Present in:

- 43% of primary VF survivors (1st MI) n=330
- 25% of controls (1st MI w/out VF) n=372

Odds Ratio 2.72 (95% C.I. 1.8-4.0)

Dekker et al., 2006

These Data Support:

- A strong role for heritable factors in the risk for SCD during a first MI
- The presence of genetic factors that predispose to ischemia-mediated life-threatening arrhythmias

nature genetics

Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction

Connie R Bezzina[1,17], Raha Pazoki[1,2,17], Abdennasser Bardai[1,17], Roos F Marsman[1,17], Jonas S S G de Jong[3,17], Marieke T Blom[1], Brendon P Scicluna[1], J Wouter Jukema[4,5], Navin R Bindraban[3,6], Peter Lichtner[7], Arne Pfeufer[7,8], Nanette H Bishopric[9–11], Dan M Roden[12], Thomas Meitinger[7,8], Sumeet S Chugh[13], Robert J Myerburg[9], Xavier Jouven[14], Stefan Kääb[15], Lukas R C Dekker[3,16], Hanno L Tan[1,3], Michael W T Tanck[2] & Arthur A M Wilde[1,3]

Nat Genet 2010;42:688-691

AGNES
Arrhythmia Genetics in the NEtherlandS

Study Population

First MI with ventricular fibrillation	515
First MI w/out ventricular fibrillation	457

AGNES

- A genome-wide association study found a significant association with a SNP on chromosome 21.
- The closest gene to this SNP is CXADR, which encodes the coxsackie and adenovirus receptor protein already implicated in myocarditis. Thus, CXADR becomes a candidate gene.

PREDESTINATION

PRimary vEntricular fibrillation and suDden dEath during a firST myocardIal iNfArcTION: Genetic Basis

- 200 CCUs throughout Italy
- Enrolling time: 24 months
- Minimum Follow-up: 1 year

Inclusion Criteria

- First MI
- Age 18-75 years
- Cases: at least one episode of VF within 24 hours from onset of symptoms
- Controls: no VF nor sustained VT

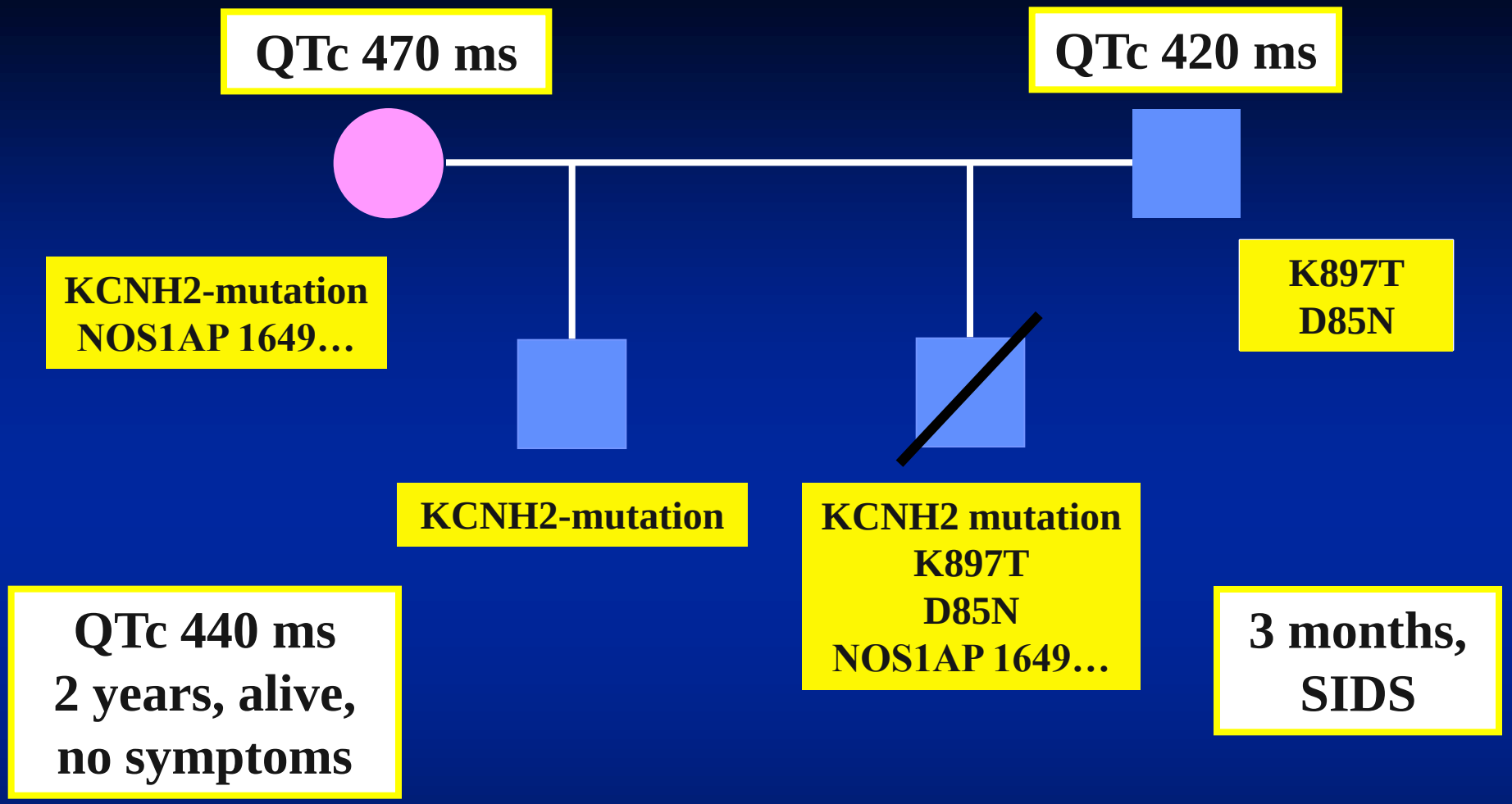
2000 cases and 2000 controls

Genetic Analysis

- Custom-made chip with 1536 SNPs of 219 genes all involved in the onset of VF
- Genome-wide association study

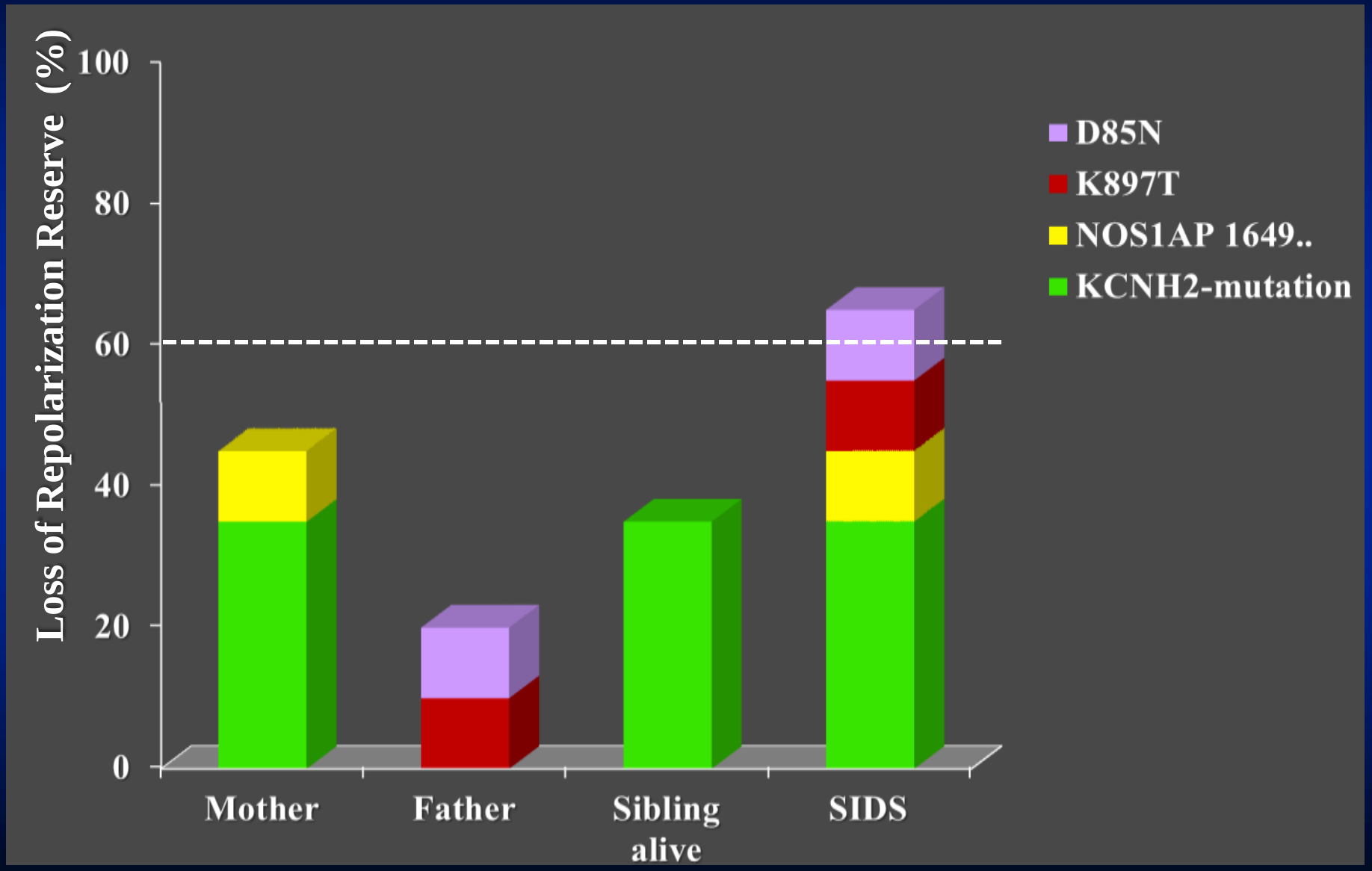
Sudden Death and the Play of Chance

The role of multiple SNPs



More SNPs, Greater Risk

More SNPs, Greater Risk



My View