Pediatric and Congenital Rhythm Congress VII

4 - 7 February 2017

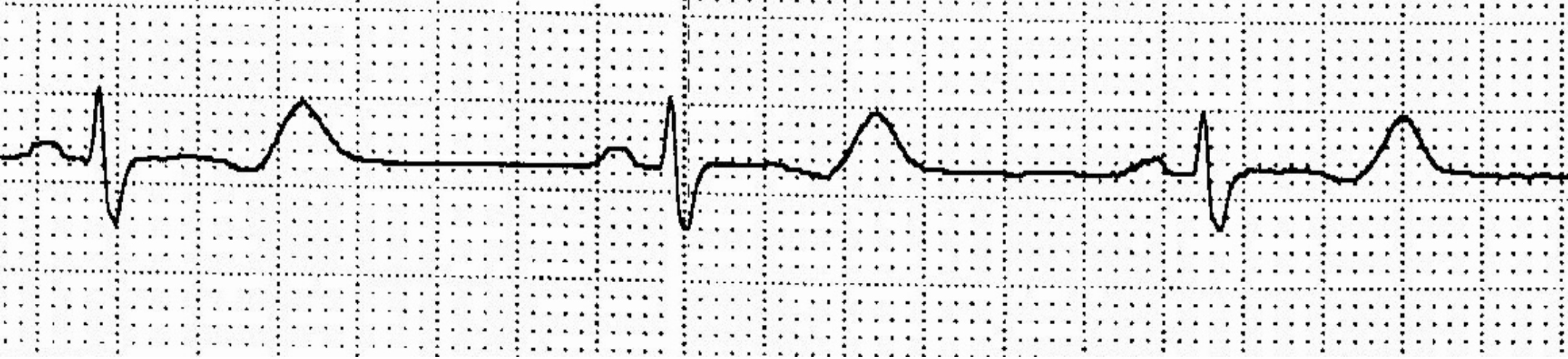
Thessaloniki/GREECE

PEDIRHYTHM VII

Risk stratification in LQTS, does genetics play a role?

Arthur AM Wilde

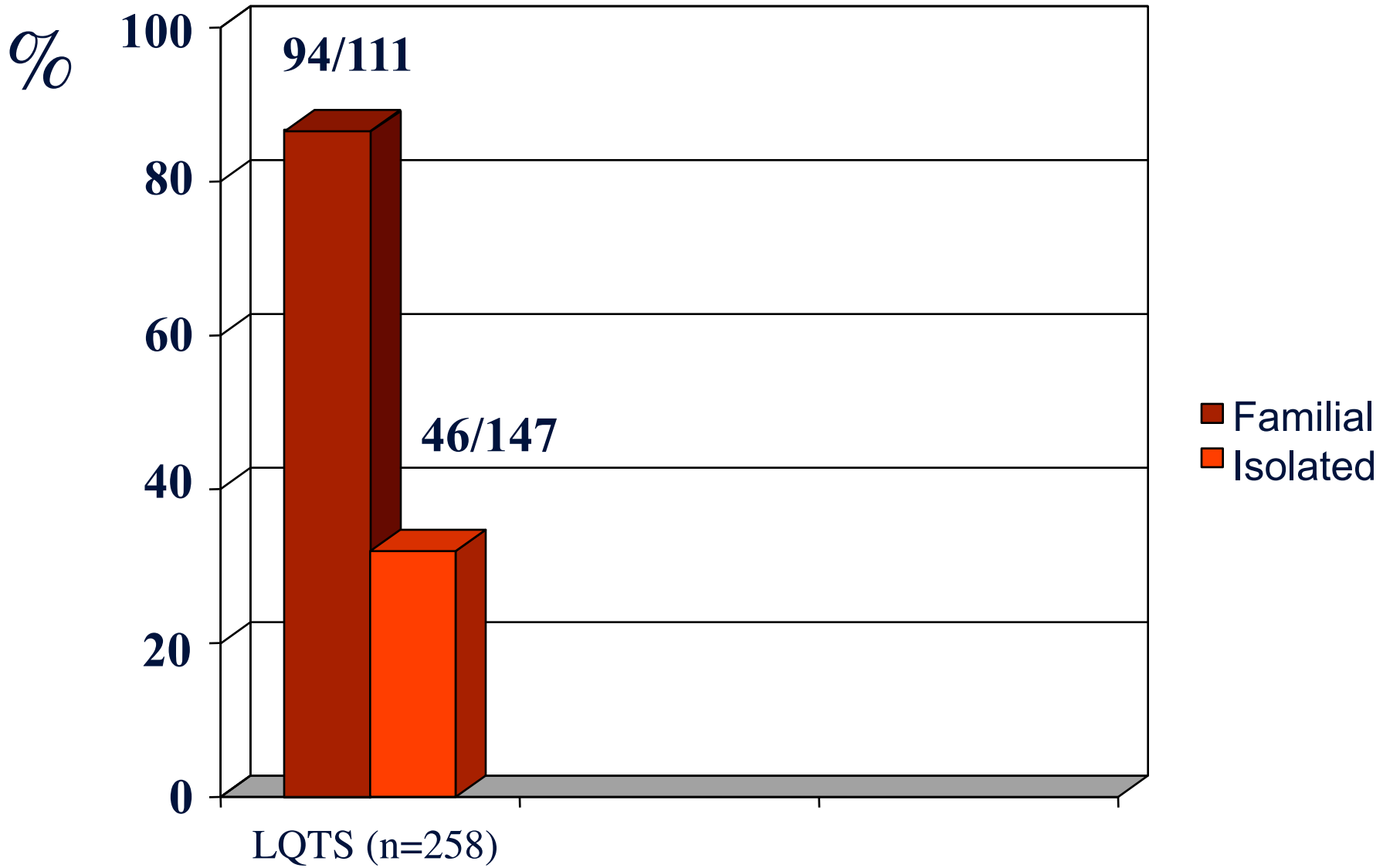
4 february 2017



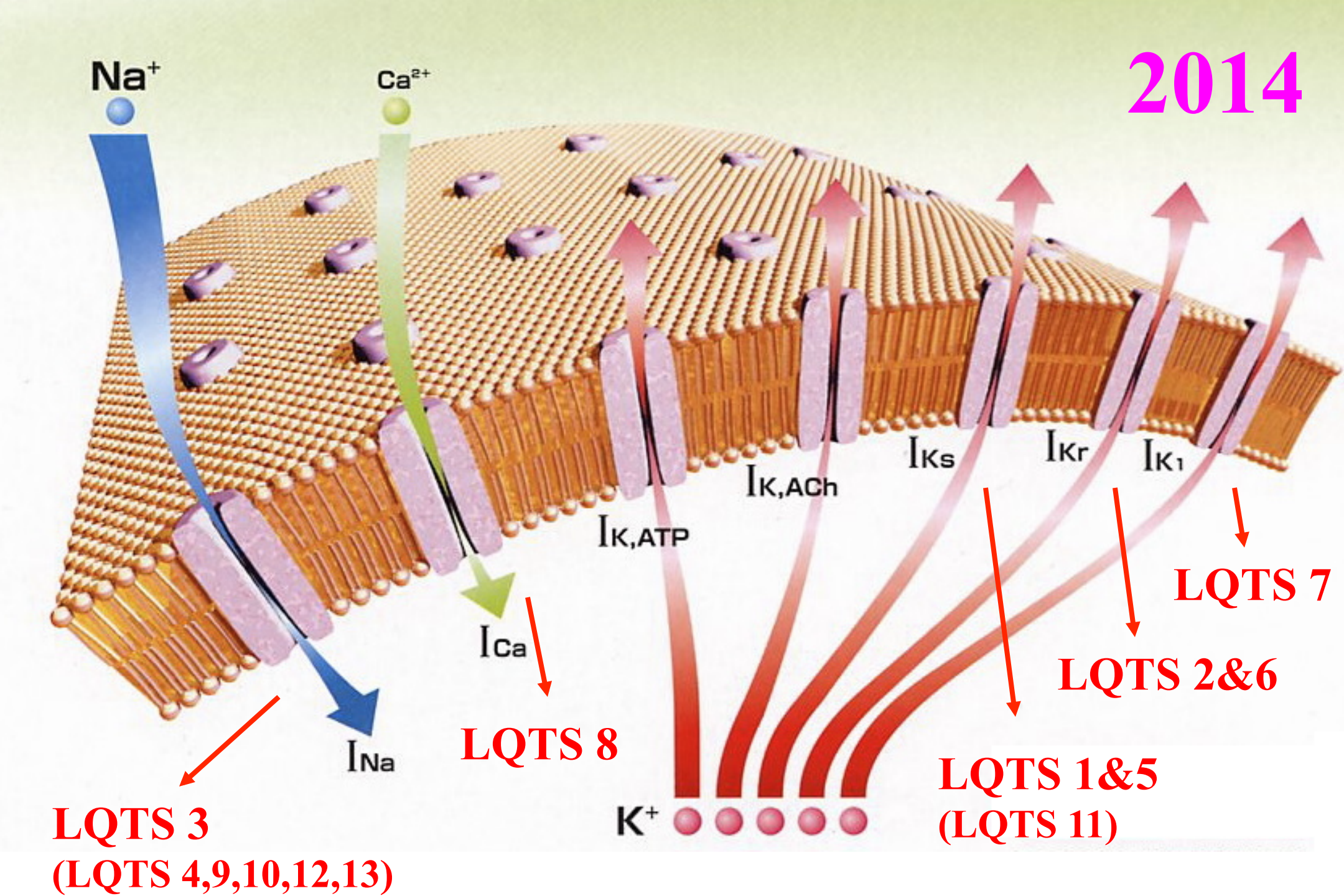
Long QT Syndrome(s)

- Autosomal dominant/autosomal rec.
- genetically heterogeneous
- 16 genes (LQTS1-16)
- ≥ 60% genotyped (≥ 90% in families)
- gene-specific features

Yield of molecular genetic screening



Hofman ea. Circulation 2013


2014
Na+
Ca2+
IK,ATP
IK,ACh
IKs
IKr
IK1
ICa
INa
K+
LQTS 8
LQTS 7
LQTS 2&6
LQTS 1&5
(LQTS 11)
LQTS 3
(LQTS 4,9,10,12,13)

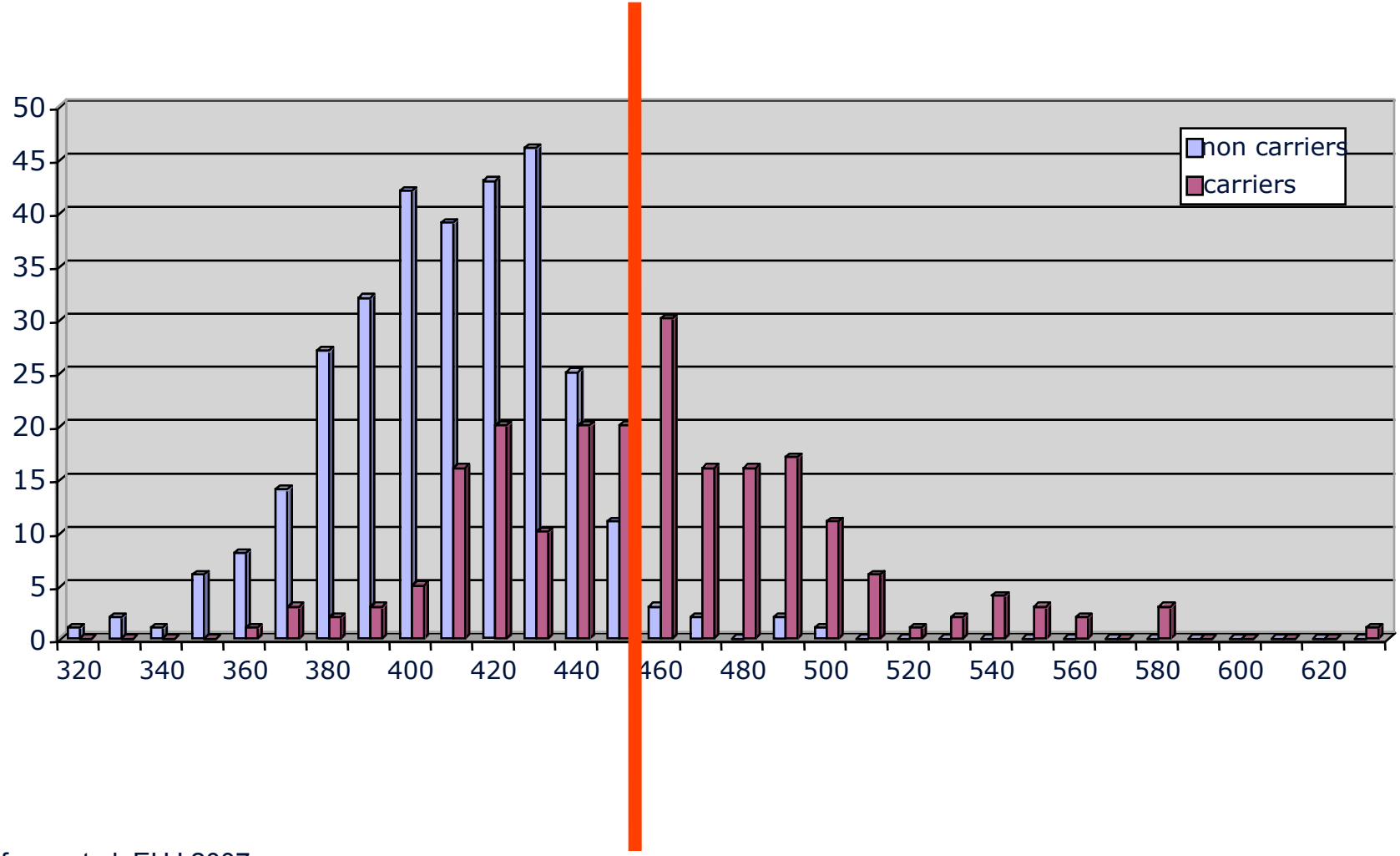
LQTS, Genetic testing

Why genetic testing?:

- ♥ Reaching a diagnosis ++
- ♥ Presymptomatic treatment ++
- ♥ Risk stratification ++
- ♥ Gene-specific treatment ++

QT_C in genotyped family members

n=517



Data after Hofman et al. EHJ 2007.

LQTS, risk stratification

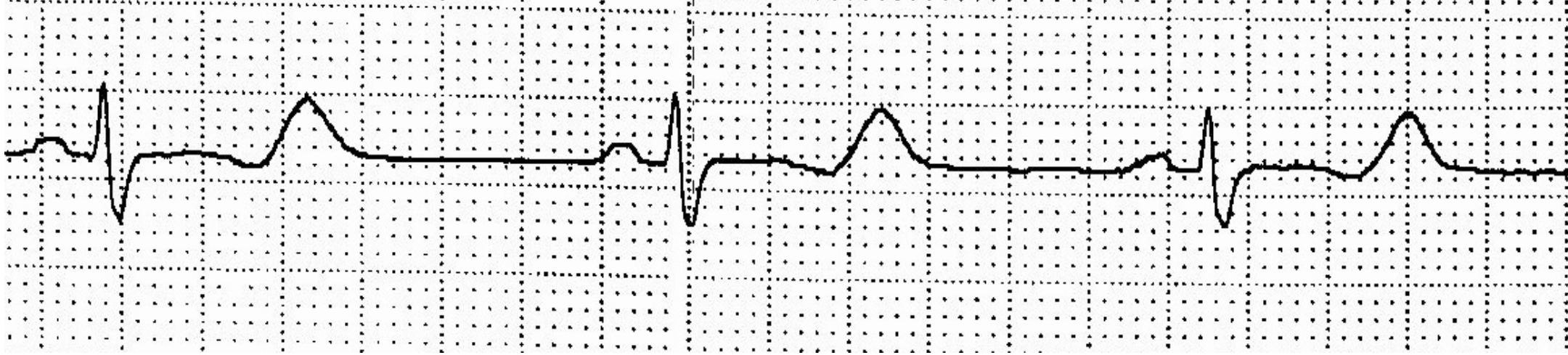
Risk depends on:

- ♥ phenotype
  - gender (<10 male)
  - QTc (≥ 500 ms)
  - specific ECG features

LQTS, risk stratification

Risk depends on:

- ♥ phenotype
  - gender (<10 male)
  - QTc (≥ 500 ms)
  - specific ECG features
- ♥ genotype



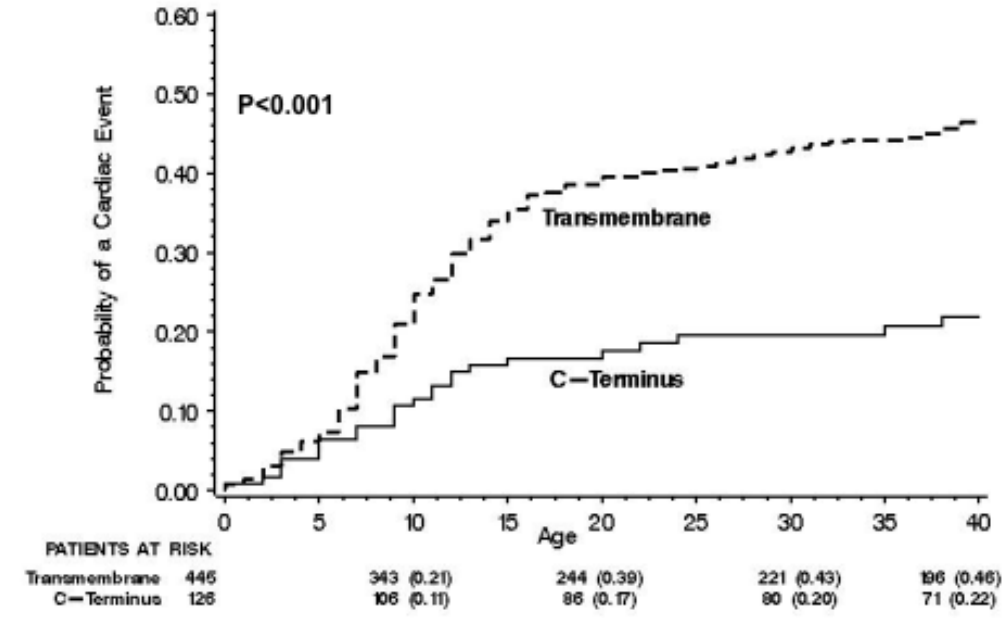
Genetic ‘real estate’:

- Transmembrane LQTS2 mutations
- Missense LQTS1 mutations
- Specific LQTS1 mutations (e.g. A341V)
- Large variation in LQT3

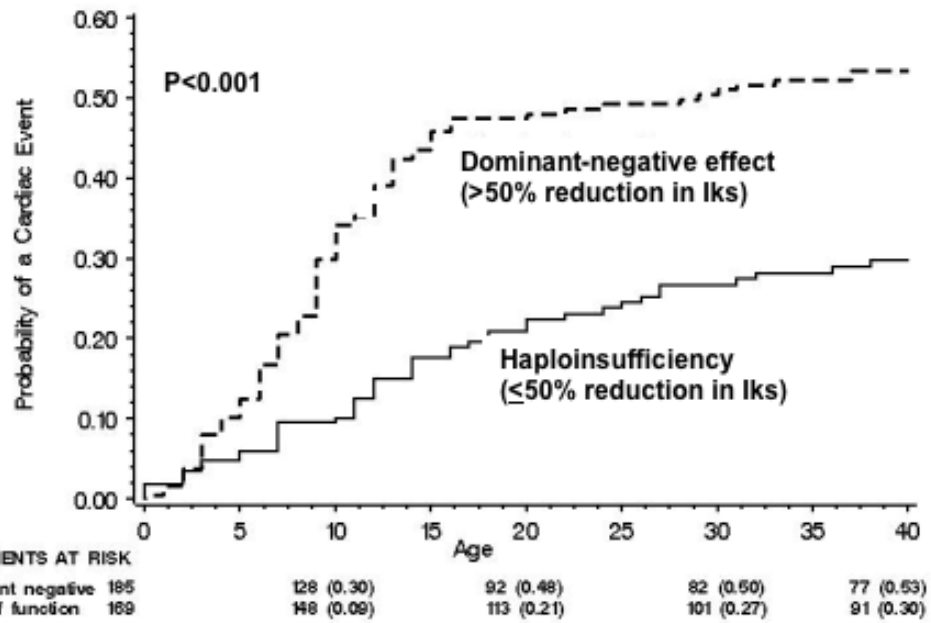
LQTS, genotype - phenotype

LQTS1

A. Location of Mutation

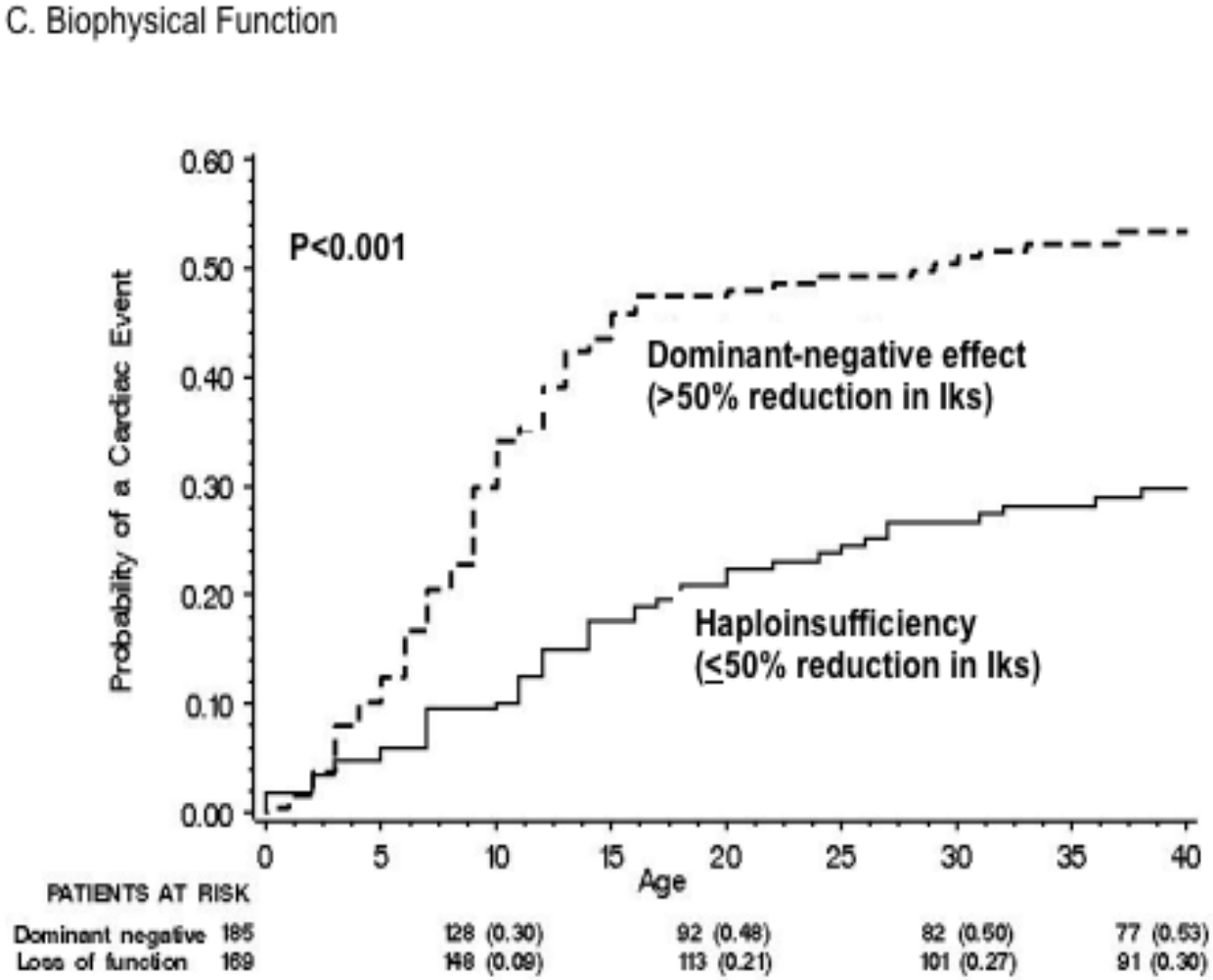


C. Biophysical Function



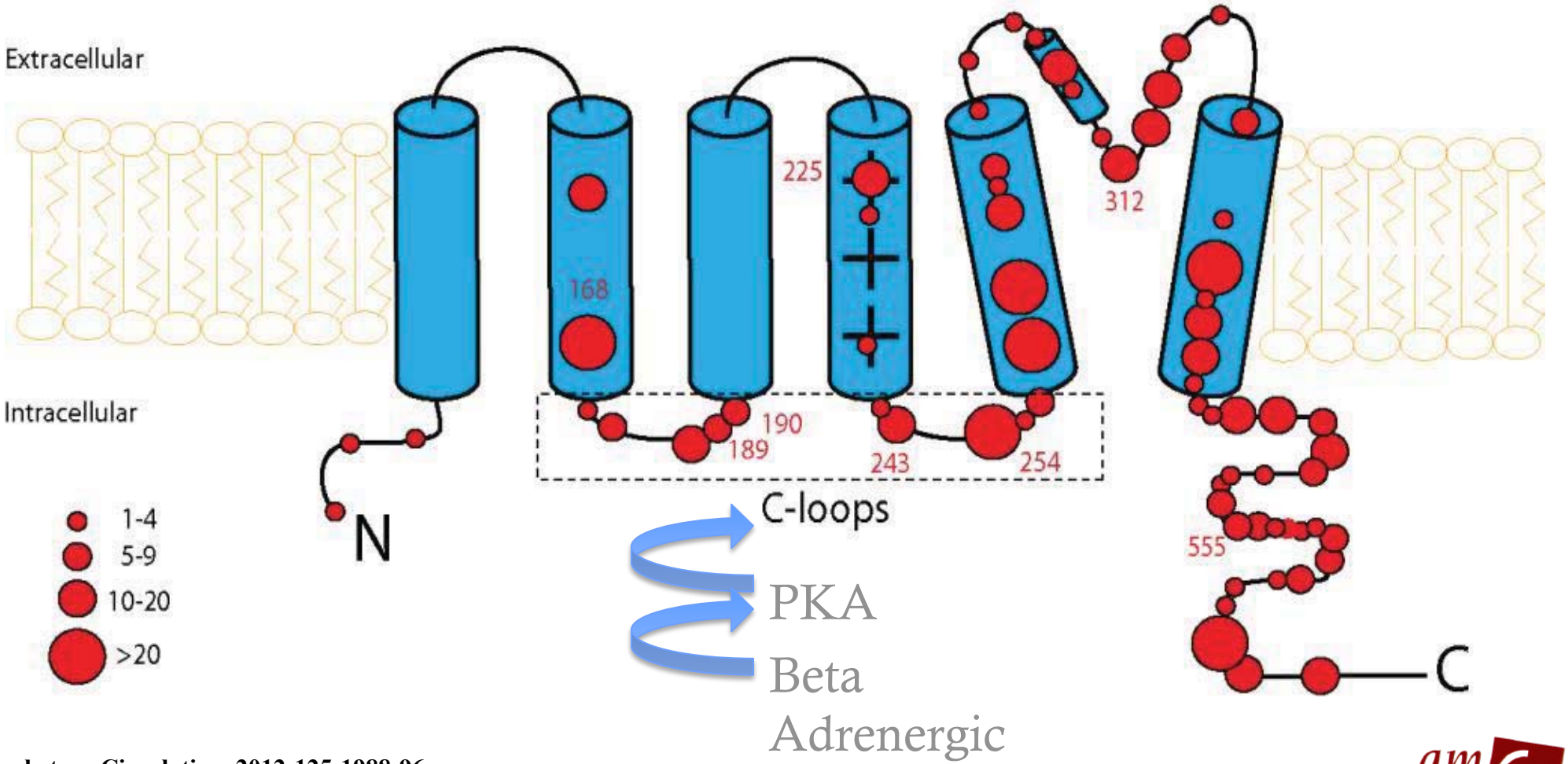
Moss, Shimizu, Wilde et al. Circulation 2007

Mutation dependent prognosis (LQTS1)



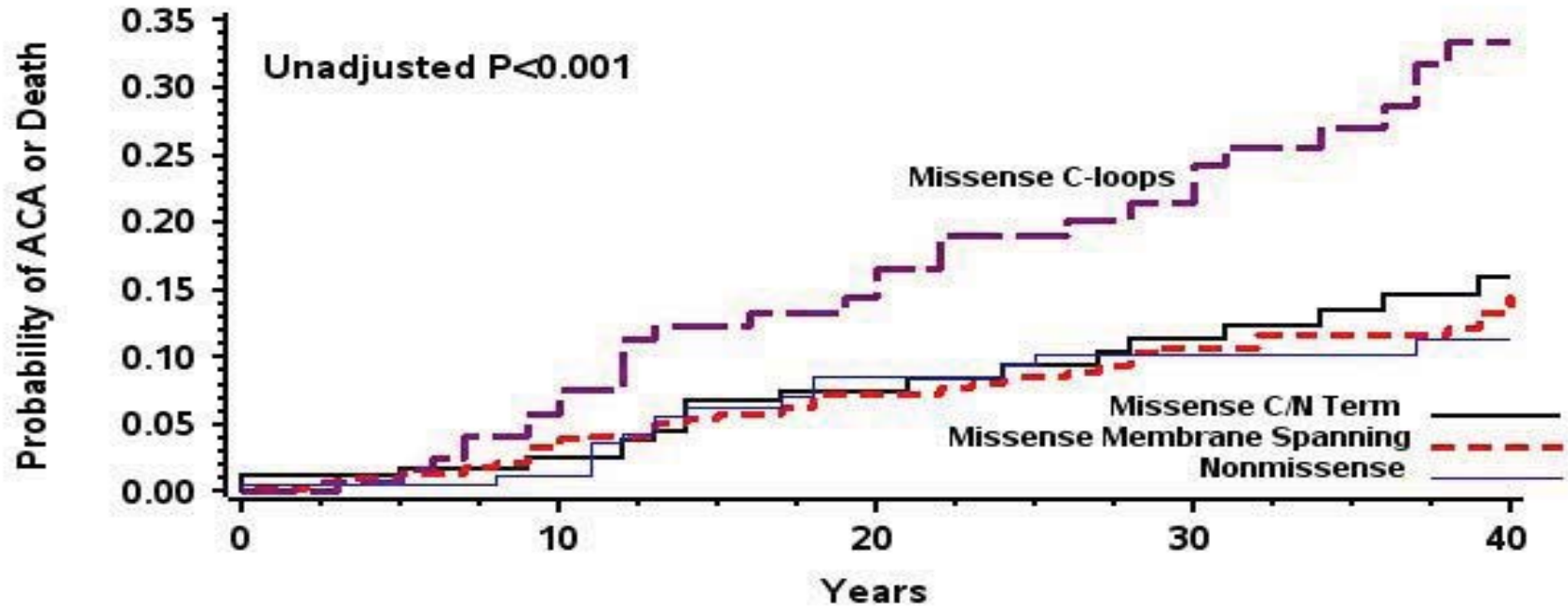
Moss, Shimizu, Wilde et al. Circulation 2007

Mutations sites in the KCNQ1 gene



Barsheshet ea, Circulation. 2012;125:1988-96.

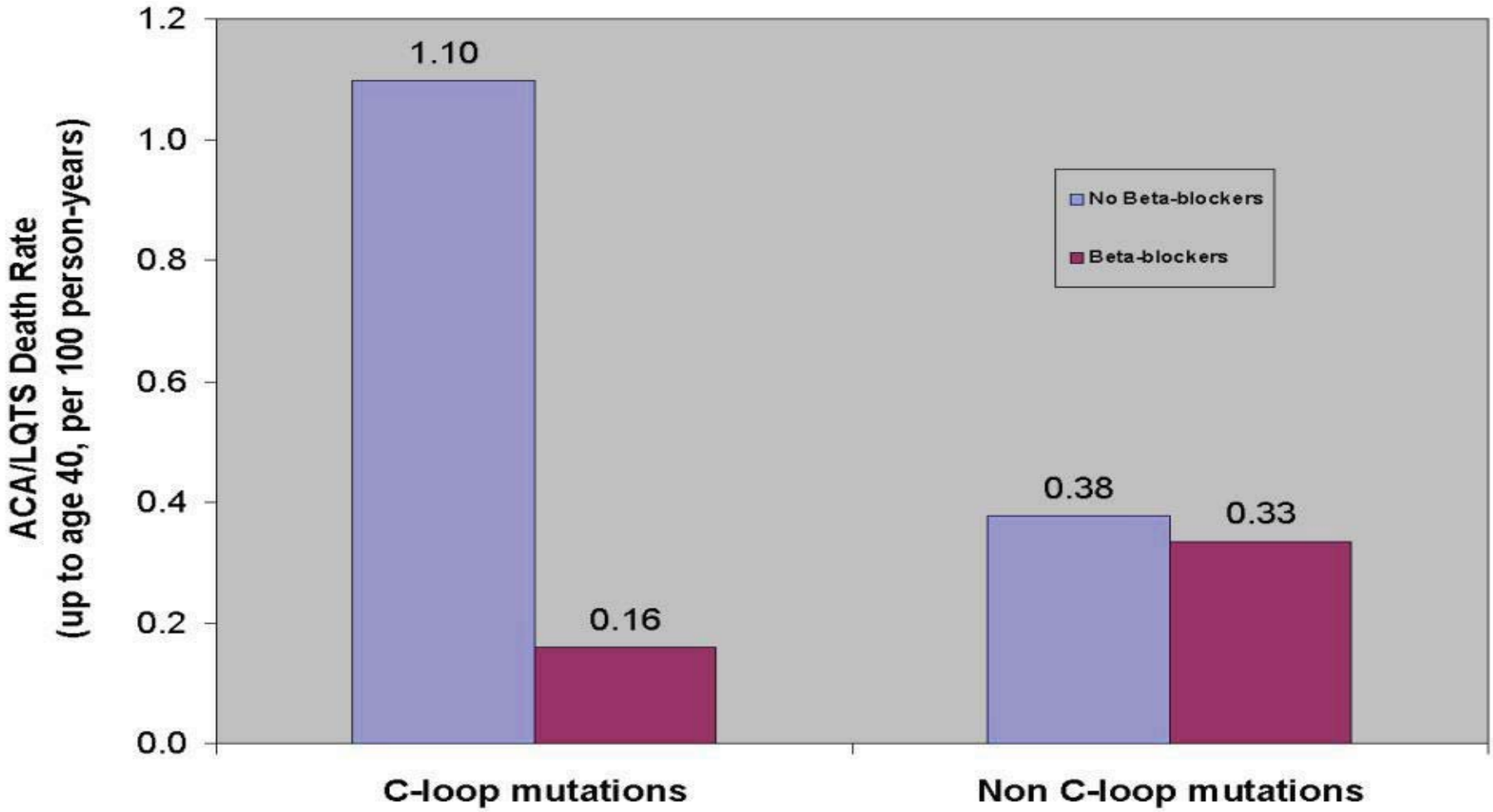
C-loop mutations associate with increased mortality



Patients at Risk					
C/N Term	172	145 (0.02)	108 (0.07)	88 (0.11)	62 (0.16)
Membr Spanning	376	328 (0.03)	242 (0.07)	192 (0.11)	154 (0.13)
C-loops	125	109 (0.06)	78 (0.14)	59 (0.22)	39 (0.33)
Nonmissense	186	157 (0.01)	119 (0.09)	95 (0.10)	69 (0.11)

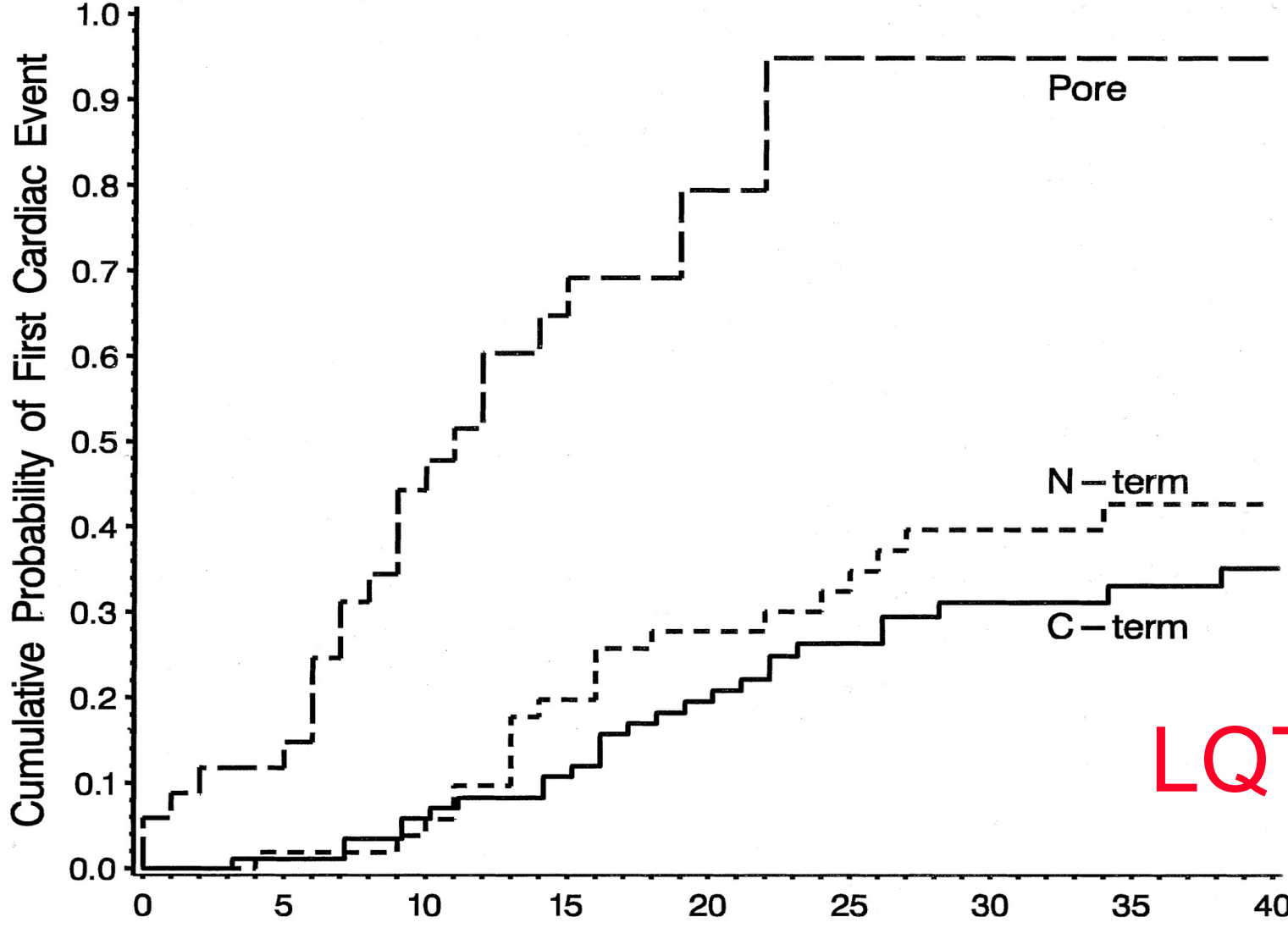
Barsheshet ea, Circulation. 2012;125:1988-96.

Increased relative benefit of beta blockers in C-loop sites



Barsheshet, Circulation. 2012 Apr 24;125(16):1988-96

Mutation dependent prognosis (LQTS2)



LQTS2

Circulation 2002;105:794-9

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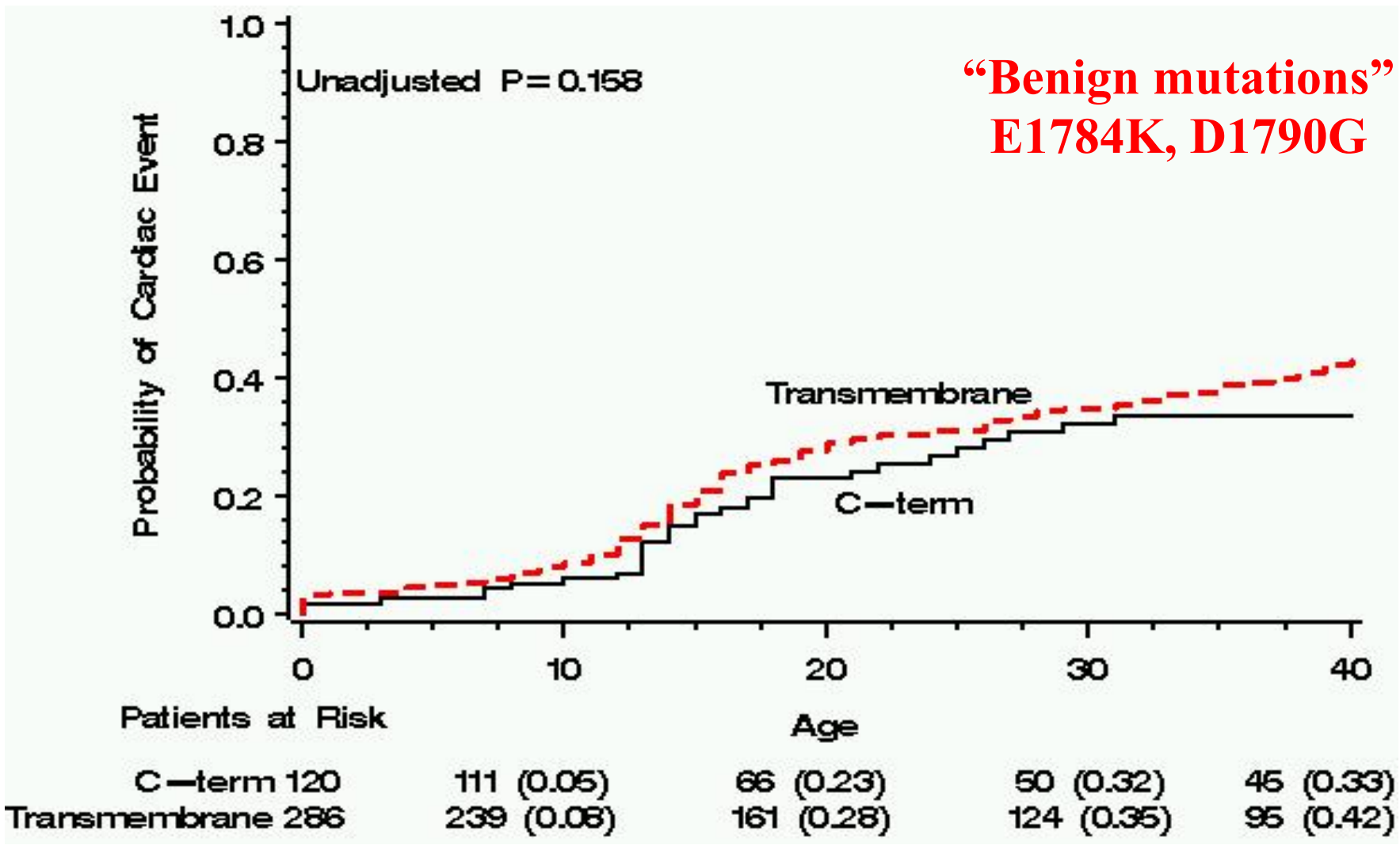
ORIGINAL RESEARCH ARTICLE

Clinical Aspects of Type 3 Long-QT Syndrome

An International Multicenter Study

Wilde et al.,
LQTS3 international registry
Circulation 2016;134:872-882

No mutation dependent prognosis (LQTS3)



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The Common Long-QT Syndrome Mutation *KCNQ1*/A341V Causes Unusually Severe Clinical Manifestations in Patients With Different Ethnic Backgrounds

Toward a Mutation-Specific Risk Stratification

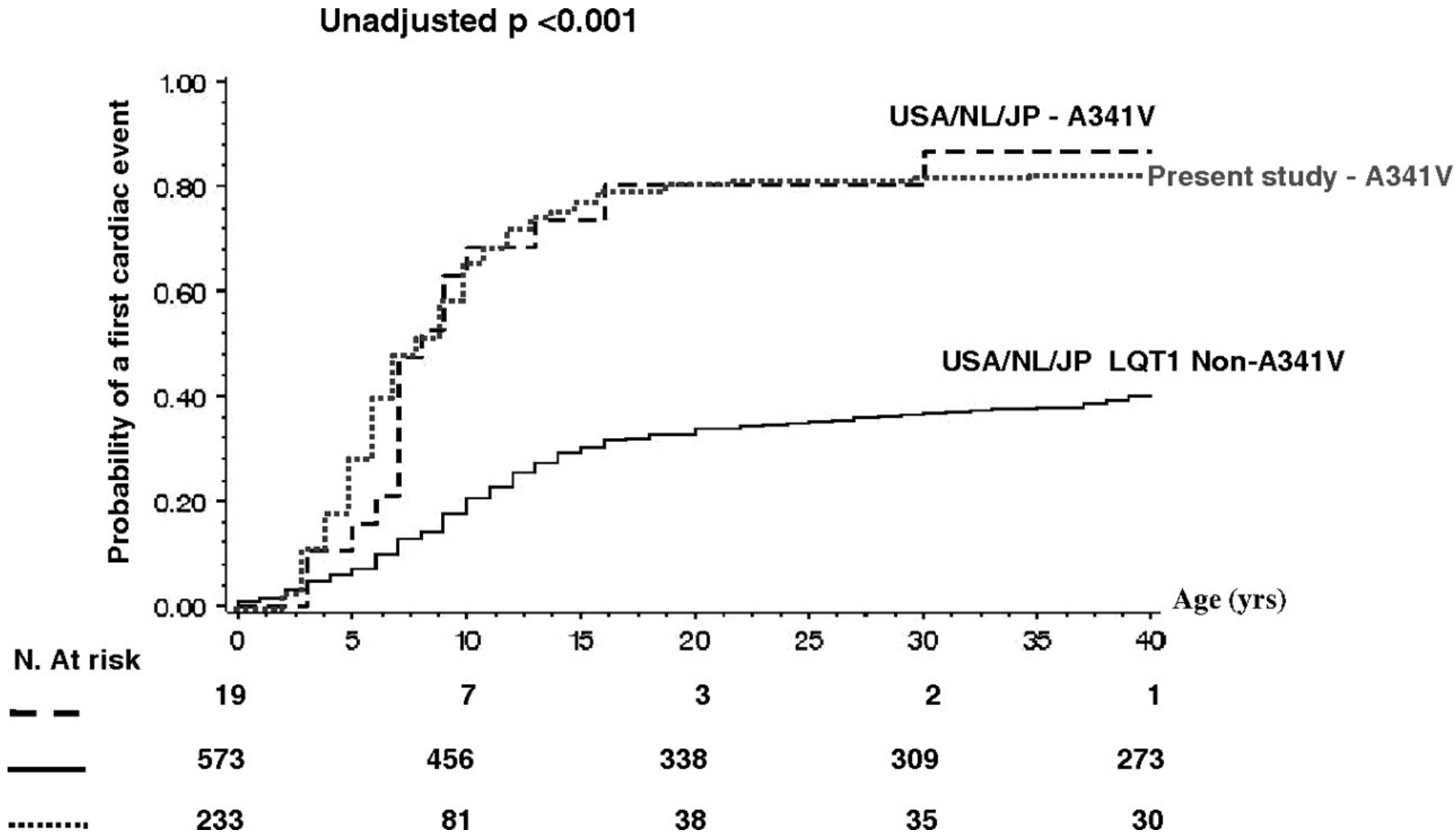
Lia Crotti, MD; Carla Spazzolini, DVM; Peter J. Schwartz, MD; Wataru Shimizu, MD; Isabelle Denjoy, MD; Eric Schulze-Bahr, MD; Elena V. Zaklyazminskaya, MD, PhD; Heikki Swan, MD; Michael J. Ackerman, MD, PhD; Arthur J. Moss, MD; Arthur A.M. Wilde, MD; Minoru Horie, MD; Paul A. Brink, MD, PhD; Roberto Insolia, PhD; Gaetano M. De Ferrari, MD; Gabriele Crimi, MD

Background—The impressive clinical heterogeneity of the long-QT syndrome (LQTS) remains partially unexplained. In a South African (SA) founder population, we identified a common LQTS type 1 (LQT1)–causing mutation (*KCNQ1*-A341V) associated with high clinical severity. We tested whether the arrhythmic risk was caused directly by A341V or by its presence in the specific ethnic setting of the SA families.

Methods and Results—Seventy-eight patients, all with a single *KCNQ1*-A341V mutation, from 21 families and 8 countries were compared with 166 SA patients with A341V and with 205 non-A341V LQT1 patients. In the 2 A341V populations (SA and non-SA), the probability of a first event through 40 years of age was similar (76% and 82%), and the QTc was 484±42 versus 485±45 ms (P=NS). Compared with the 205 non-A341V patients with the same median follow-up (30 versus 32 years), the 244 A341V patients were more likely to have cardiac events (75% versus 24%), were younger at first event (6 versus 11 years), and had a longer QTc (485±43 versus 465±38 ms) (all $P<0.001$). Arrhythmic risk remained higher ($P<0.0001$) even when the A341V patients were compared with non-A341V patients with mutations either localized to transmembrane domains or exhibiting a dominant-negative effect. A341V patients had more events despite β-blocker therapy.

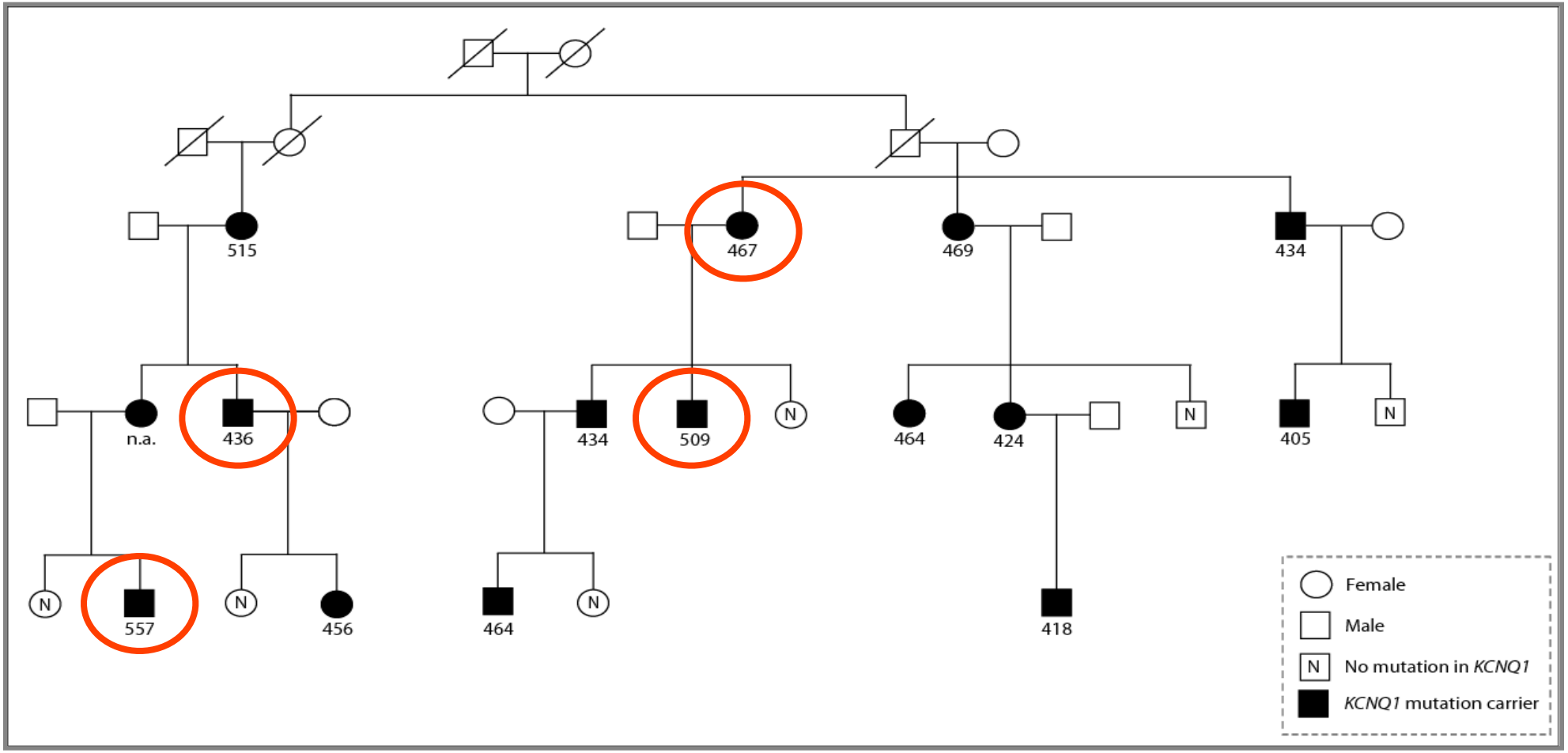
Conclusions—The hot spot *KCNQ1*-A341V predicts high clinical severity independently of the ethnic origin of the families. This higher risk of cardiac events also persists when compared with LQT1 patients with either transmembrane or dominant-negative mutations. The identification of this high-risk mutation and possibly others may improve the risk stratification and management of LQTS. (***Circulation***. **2007;116:2366-2375.**)

KCNQ1 A341V versus other KCNQ1 mutations



Long QT syndrome type 1

One identical mutation in KCNQ1



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Compound Mutations

A Common Cause of Severe Long-QT Syndrome

Peter Westenskow, BS; Igor Splawski, PhD; Katherine W. Timothy, BS;
Mark T. Keating, MD; Michael C. Sanguinetti, PhD

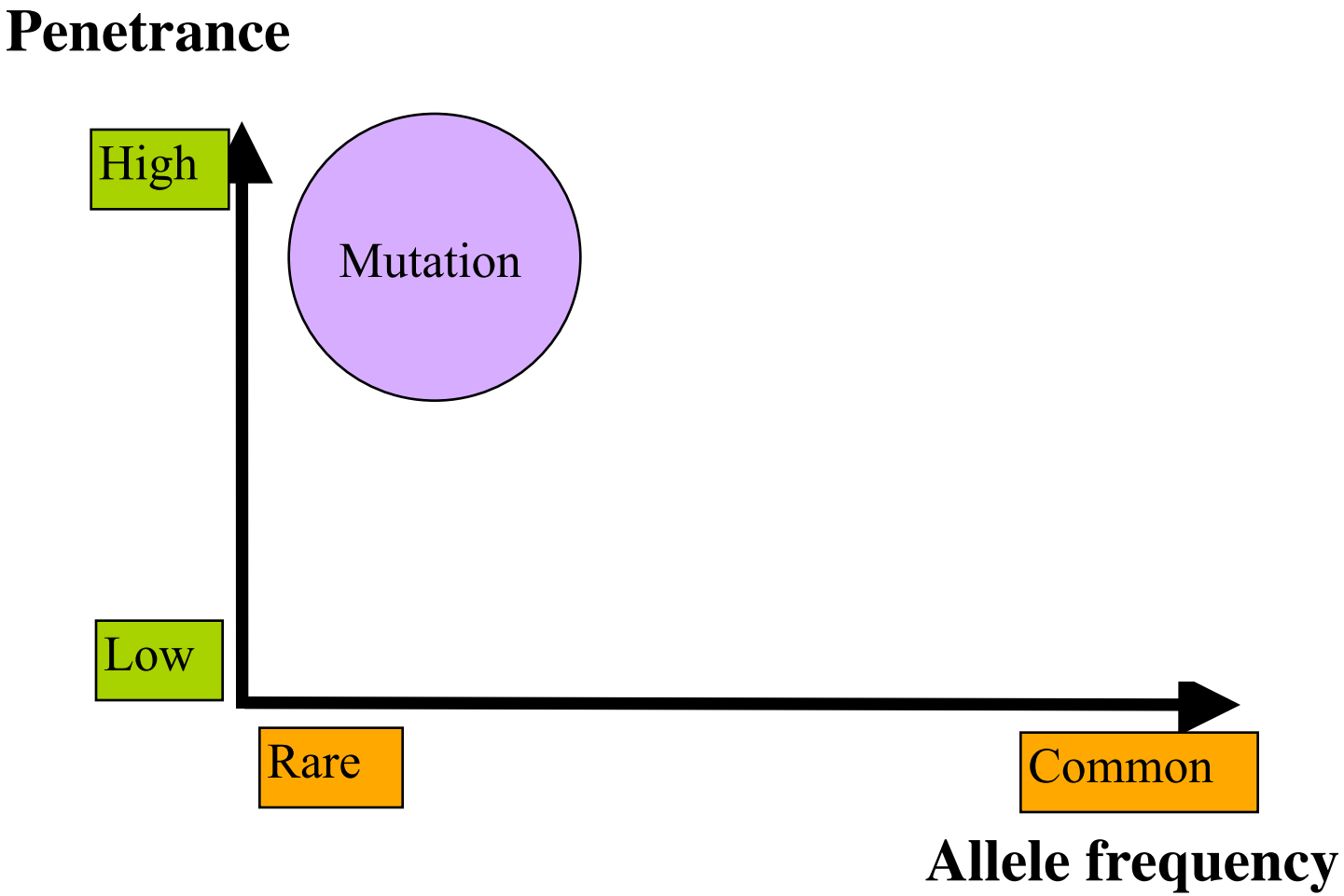
Background—Long QT syndrome (LQTS) predisposes affected individuals to sudden death from cardiac arrhythmias. Although most LQTS individuals do not have cardiac events, significant phenotypic variability exists within families. Probands can be very symptomatic. The mechanism of this phenotypic variability is not understood.

Methods and Results—Genetic analyses of KVLQT1, *HERG*, *KCNE1*, *KCNE2*, and *SCN5A* detected compound mutations in 20 of 252 LQTS probands (7.9%). Carriers of 2 mutations had longer QTc intervals (527±54 versus 489±44 ms; $P<0.001$); all had experienced cardiac events (20 of 20 [100%] versus 128 of 178 [72%]; $P<0.01$) and were 3.5-fold more likely to have cardiac arrest (9 of 16 [56%] versus 45 of 167 [27%]; $P<0.01$; OR, 3.5; 95% CI, 1.2 to 9.9) compared with probands with 1 or no identified mutation. Two-microelectrode voltage clamp of *Xenopus* oocytes was used to characterize the properties of variant slow delayed rectifier potassium (I_{Ks}) channels identified in 7 of the probands. When wild-type and variant subunits were coexpressed in appropriate ratios to mimic the genotype of the proband, the reduction in I_{Ks} density was equivalent to the additive effects of the single mutations.

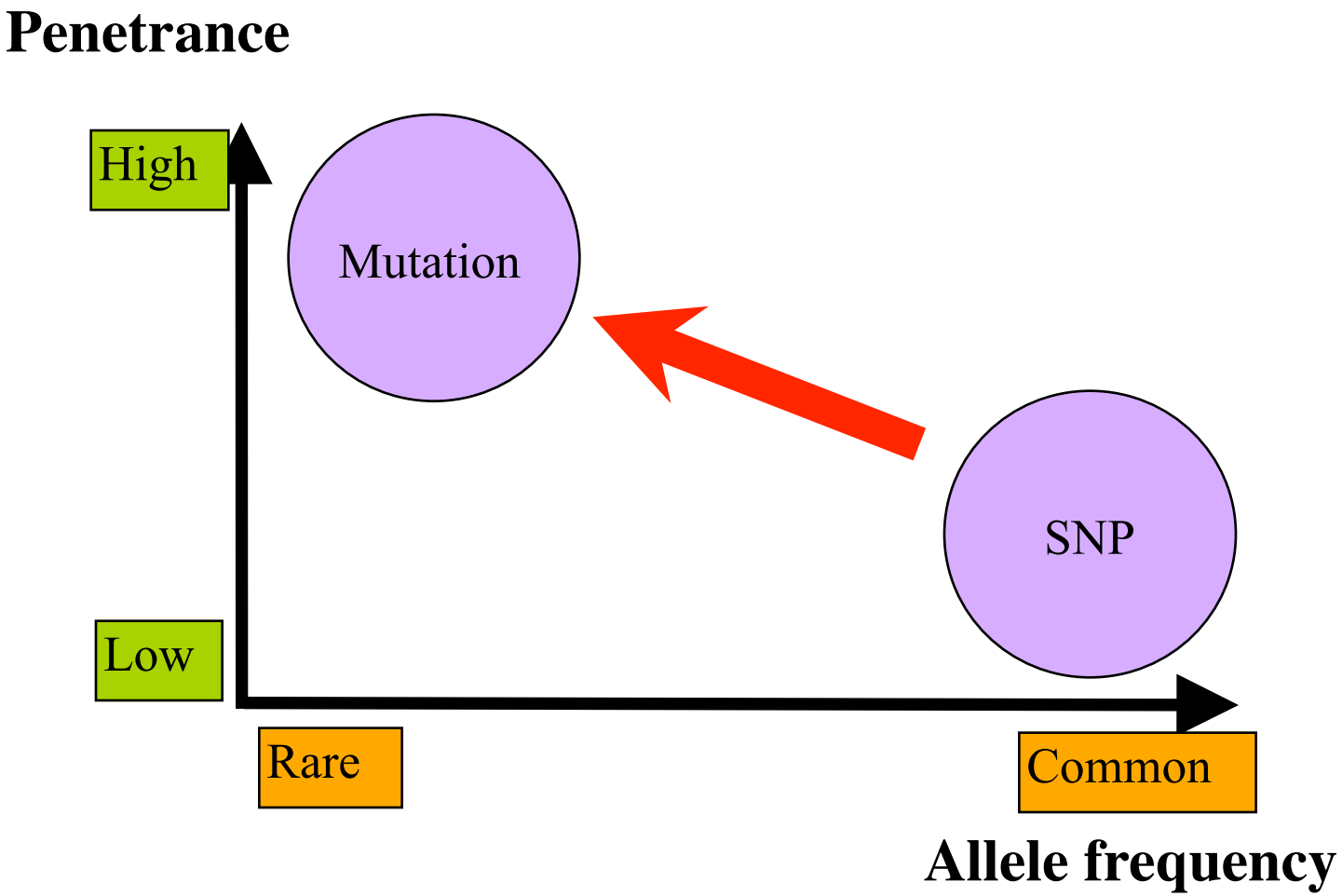
Conclusions—LQTS-associated compound mutations cause a severe phenotype and are more common than expected. Individuals with compound mutations need to be identified, and their management should be tailored to their increased risk for arrhythmias. (***Circulation*. 2004;109:1834-1841.**)

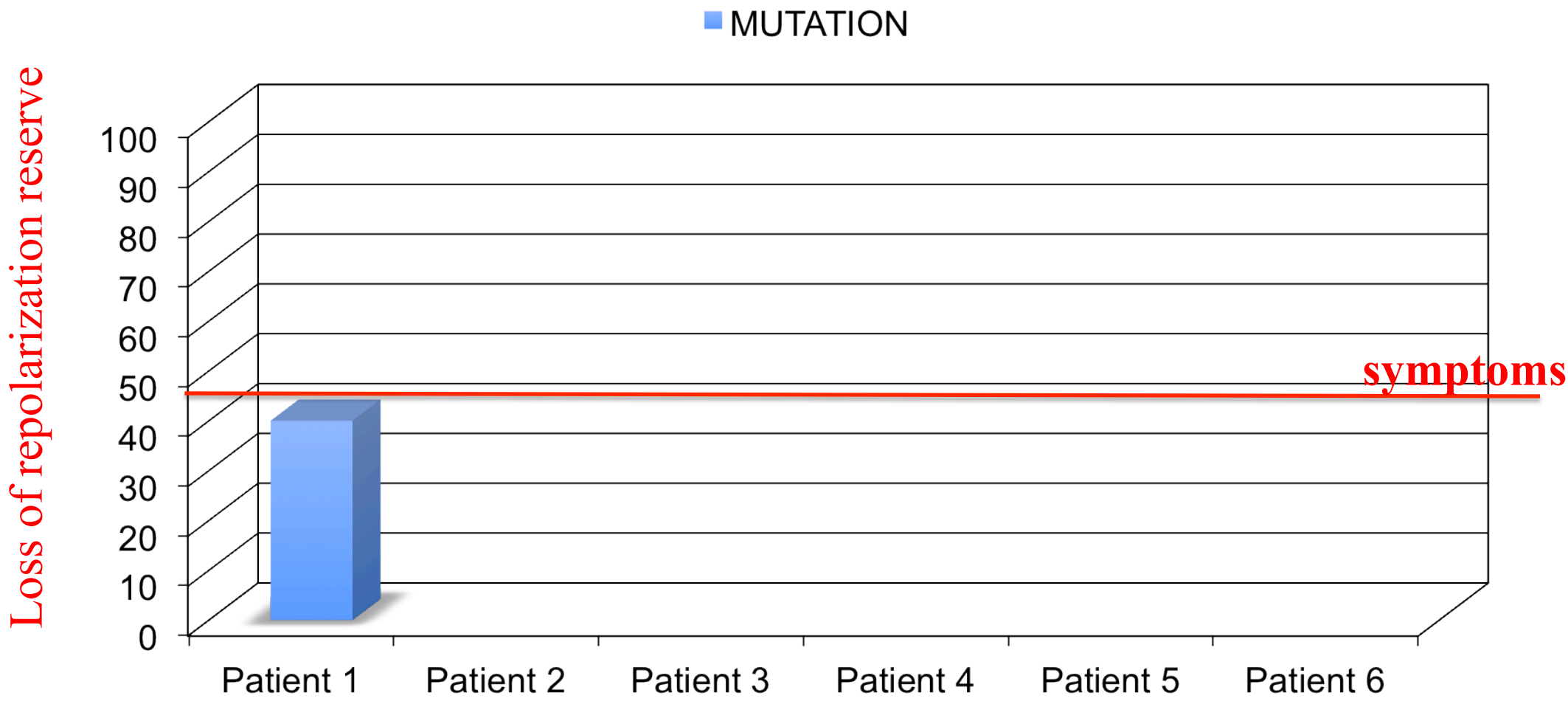
…and that includes pts with the Jervell - Lange Nielsen syndrome

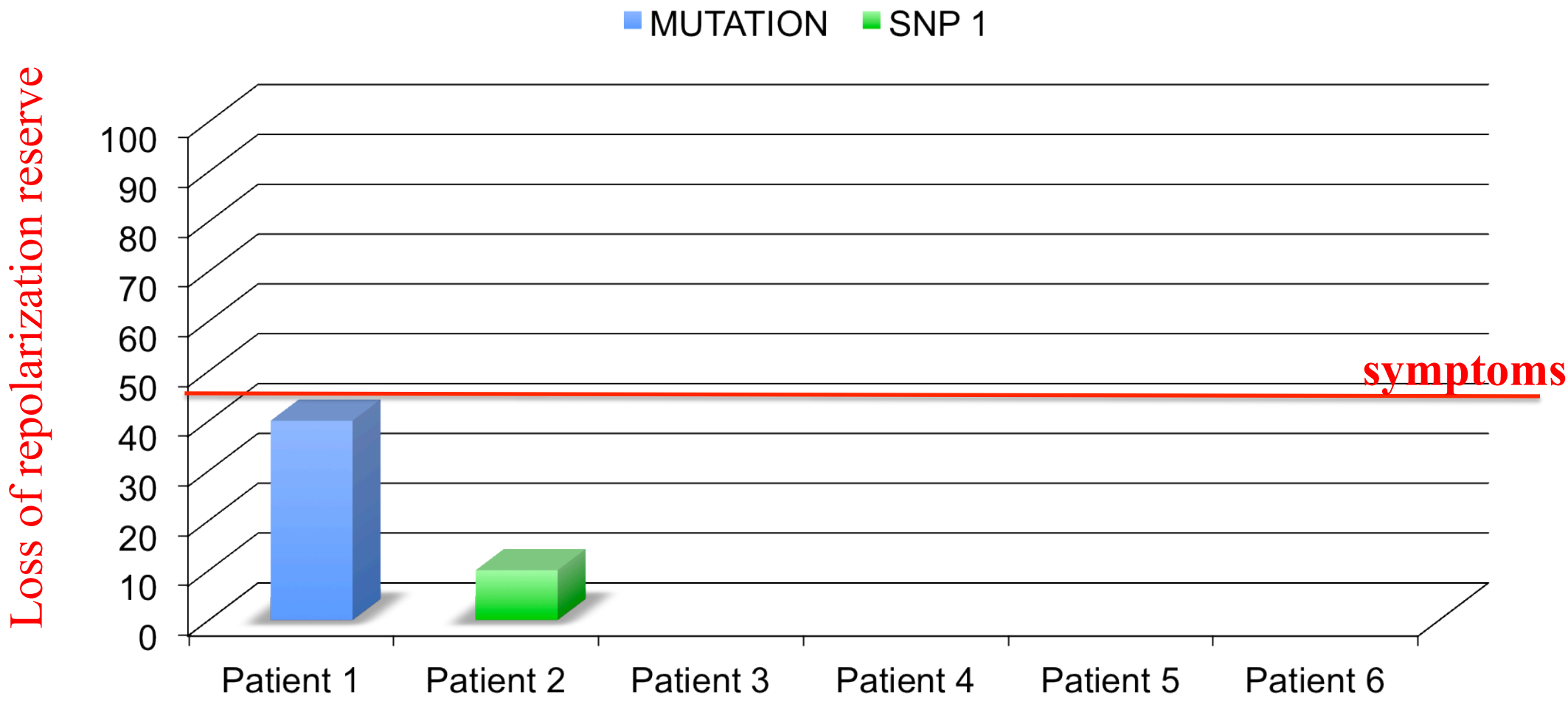
Mutations and common variants (SNP's)



Mutations and common variants (SNP's)




MUTATION
Loss of repolarization reserve
100
90
80
70
60
50
40
30
20
10
0
symptoms
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6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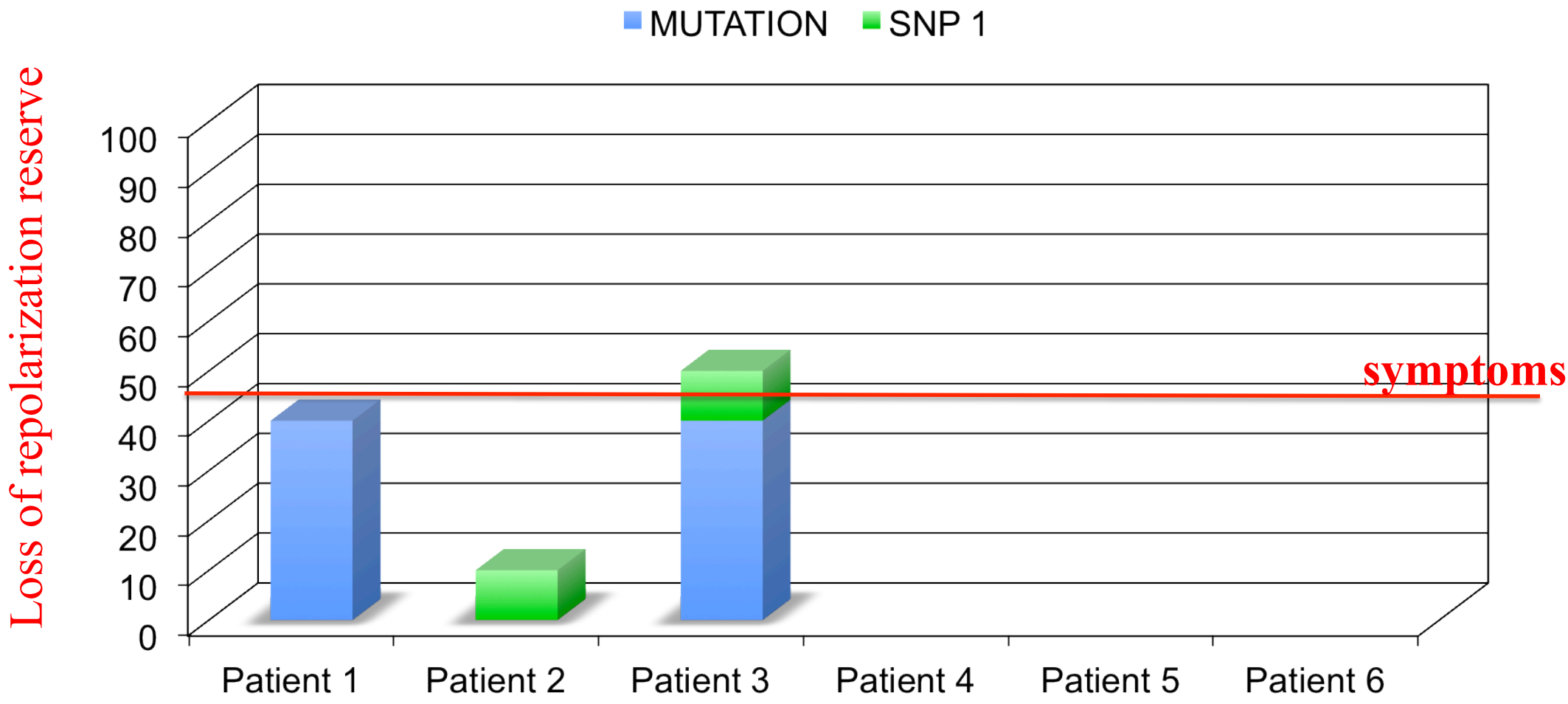
MUTATION
SNP 1
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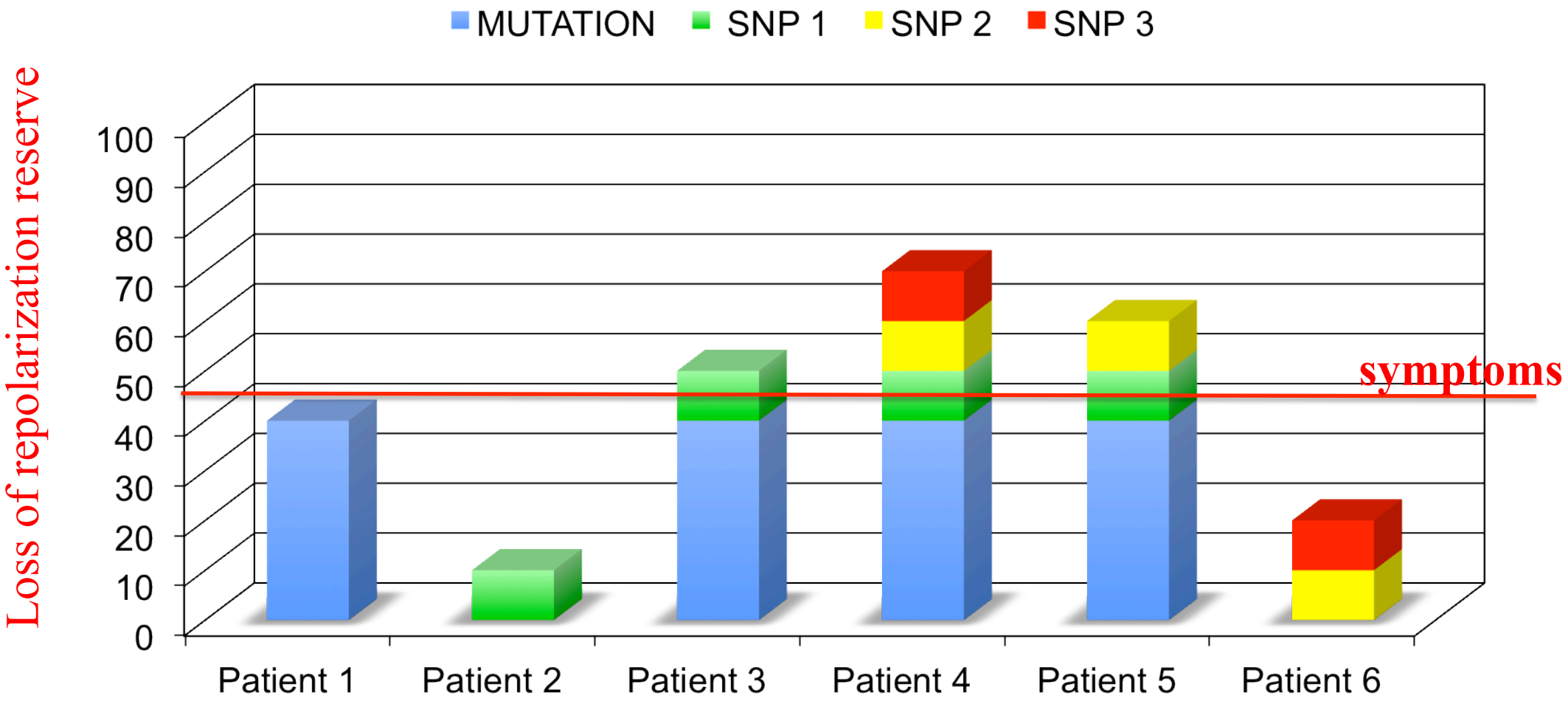
Patient 6


MUTATION
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symptoms
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Patient 3
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Patient 6

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Arrhythmia/Electrophysiology

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*

Background—In congenital long-QT syndrome (LQTS), a genetically heterogeneous disorder that predisposes to sudden cardiac death, genetic factors other than the primary mutation may modify the probability of life-threatening events. Recent evidence indicates that common variants in *NOS1AP* are associated with the QT-interval duration in the general population.

Methods and Results—We tested the hypothesis that common variants in *NOS1AP* modify the risk of clinical manifestations and the degree of QT-interval prolongation in a South African LQTS population (500 subjects, 205 mutation carriers) segregating a founder mutation in *KCNQ1* (A341V) using a family-based association analysis. *NOS1AP* variants were significantly associated with the occurrence of symptoms (rs4657139, $P=0.019$; rs16847548, $P=0.003$), with clinical severity, as manifested by a greater probability for cardiac arrest and sudden death (rs4657139, $P=0.028$; rs16847548, $P=0.014$), and with greater likelihood of having a QT interval in the top 40% of values among all mutation carriers (rs4657139, $P=0.03$; rs16847548, $P=0.03$).

Conclusions—These findings indicate that *NOS1AP*, a gene first identified as affecting the QTc interval in a general population, also influences sudden death risk in subjects with LQTS. The association of *NOS1AP* genetic variants with risk for life-threatening arrhythmias suggests that this gene is a genetic modifier of LQTS, and this knowledge may be clinically useful for risk stratification for patients with this disease, after validation in other LQTS populations. (***Circulation*. 2009;120:1657-1663.**)

European Heart Journal Advance Access published December 23, 2011

European Heart Journal
doi:10.1093/eurheartj/ehr473

FASTTRACK

CLINICAL RESEARCH

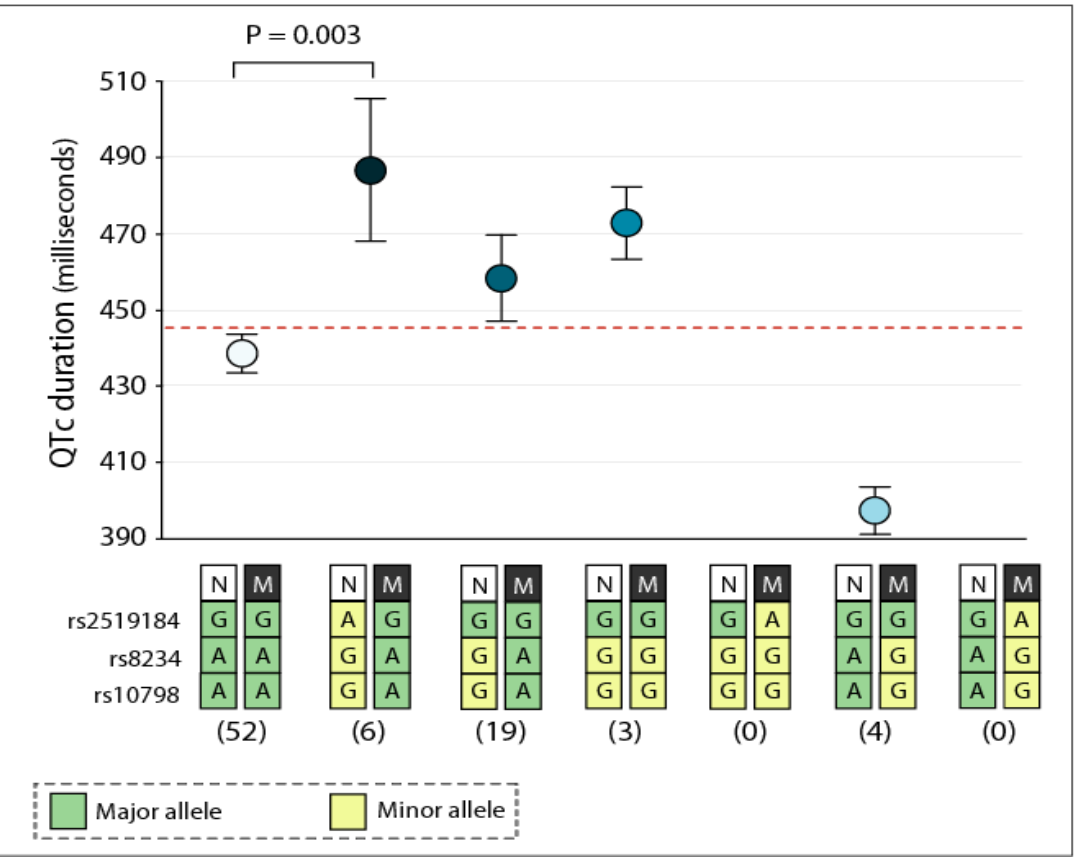
Variants in the 3′ untranslated region of the *KCNQ1*-encoded $K_v7.1$ potassium channel modify disease severity in patients with type 1 long QT syndrome in an allele-specific manner

Ahmad S. Amin[1,2†], John R. Giudicessi[3,4,5†], Anke J. Tijsen[1,2†], Anne M. Spanjaart[1,2], Yolan J. Reckman[1,2], Christine A. Klemens[1,2], Michael W. Tanck[6], Jamie D. Kapplinger[3,4,5], Nynke Hofman[7], Moritz F. Sinner[8], Martina Müller[8,9], Wino J. Wijnen[1,2], Hanno L. Tan[1,2], Connie R. Bezzina[1,2], Esther E. Creemers[1,2], Arthur A. M. Wilde[1,2*], Michael J. Ackerman[3,4,5*], and Yigal M. Pinto[1,2*]

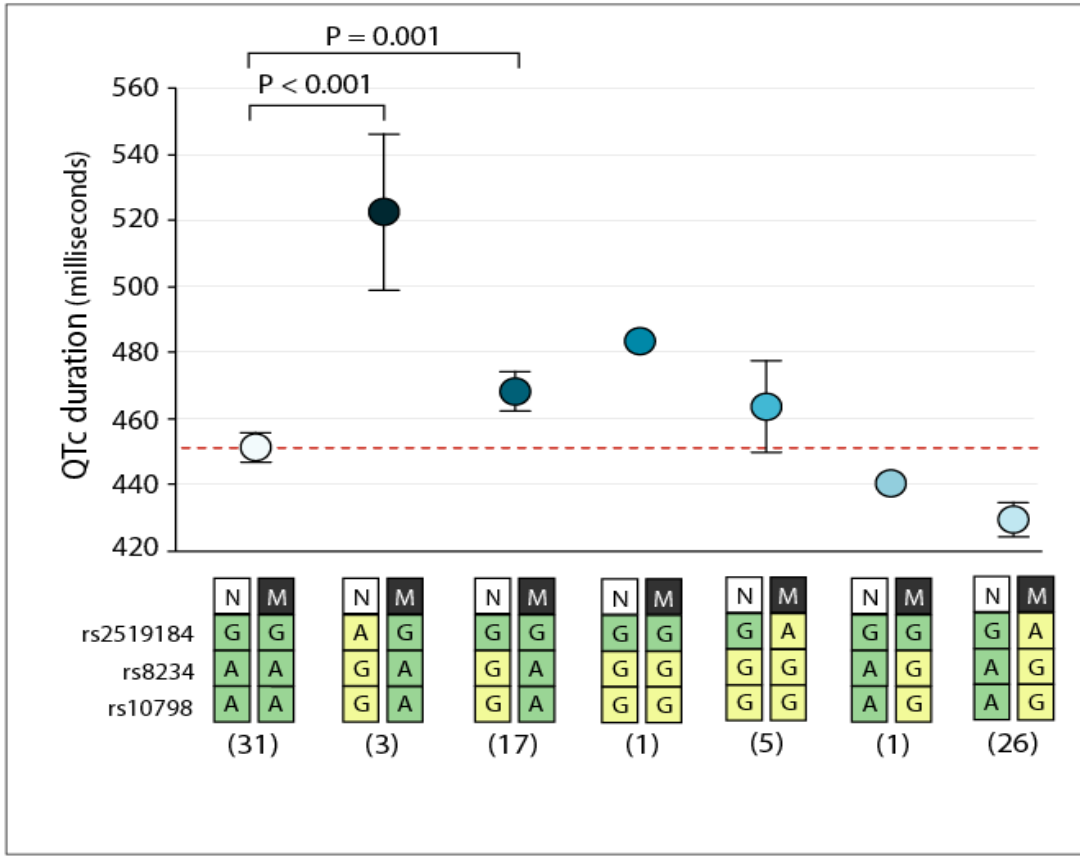
SNPs Effects of 3 SNP's in the 3'UTR area of the KCNQ1 gene on QTc

in 84 pts (discovery set) and 84 pts (replication set)

Academic Medical Center Amsterdam



Mayo Clinic Rochester, Minnesota



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Identification of a *KCNQ1* Polymorphism Acting as a Protective Modifier Against Arrhythmic Risk in Long-QT Syndrome

Sabine Duchatelet, Lia Crotti, Rachel A. Peat, Isabelle Denjoy, Hideki Itoh, Myriam Berthet, Seiko Ohno, Véronique Fressart, Maria Cristina Monti, Cristina Crocamo, Matteo Pedrazzini, Federica Dagradi, Alessandro Vicentini, Didier Klug, Paul A. Brink, Althea Goosen, Heikki Swan, Lauri Toivonen, Annukka M. Lahtinen, Kimmo Kontula, Wataru Shimizu, Minoru Horie, Alfred L. George, Jr, David-Alexandre Trégouët, Pascale Guicheney and Peter J. Schwartz

Circ Cardiovasc Genet. 2013;6:354-361; originally published online July 15, 2013;
doi: 10.1161/CIRCGENETICS.113.000023

Genetics in Long QT syndrome

In conclusion:

- ♥ has a high yield
- ♥ is important for patient identification
- ♥ is important for risk stratification
- ♥ contributes to treatment choices
- ♥ becomes more and more complex (role SNP's)


NOSTALGIA
Thank you