PEDIRHYTHM VII:

Pediatric and Congenital Rhythm Congress

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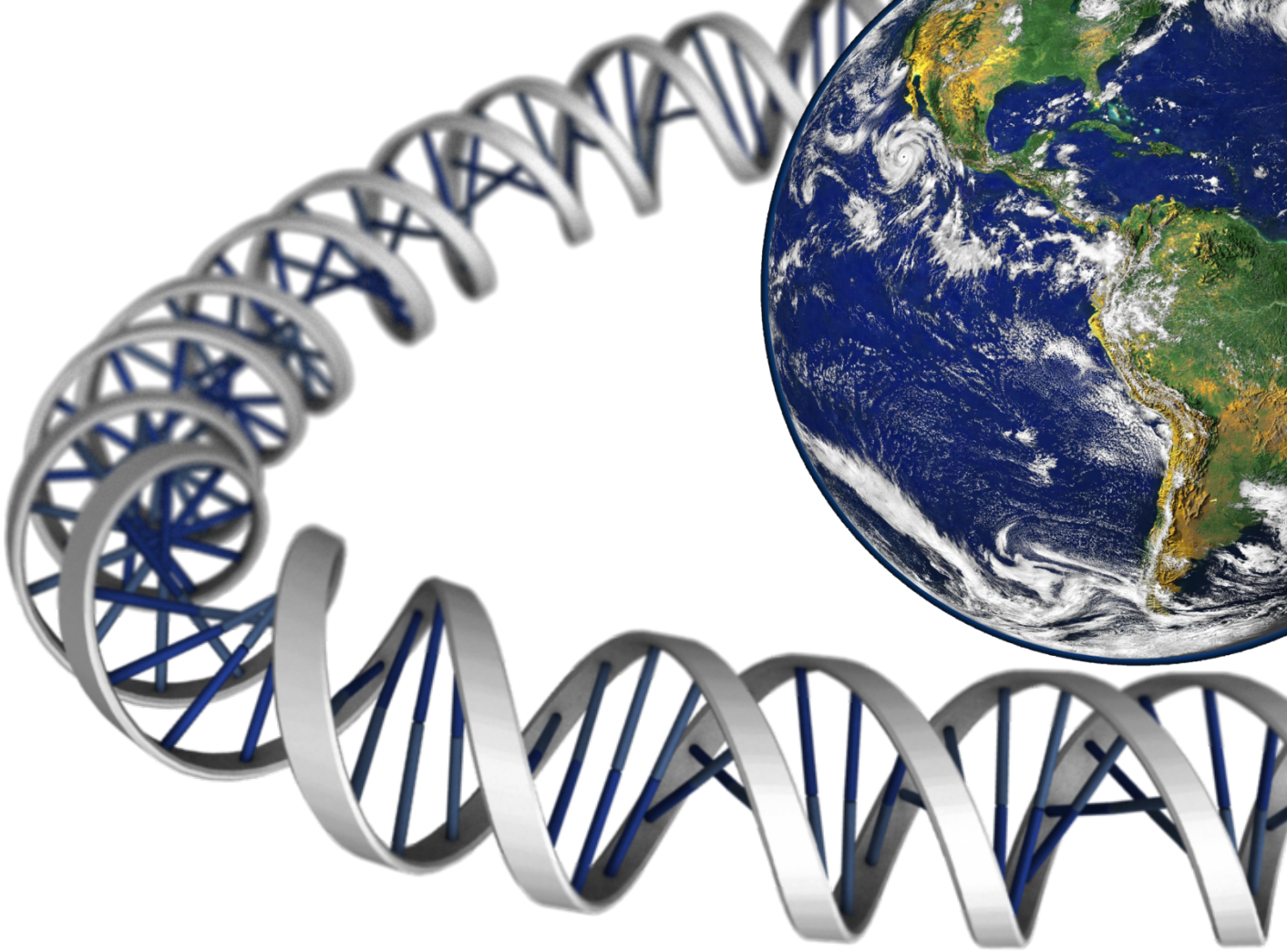


LONG QT SYNDROME

founder mutations around the world

PEDIRHYTHM VII

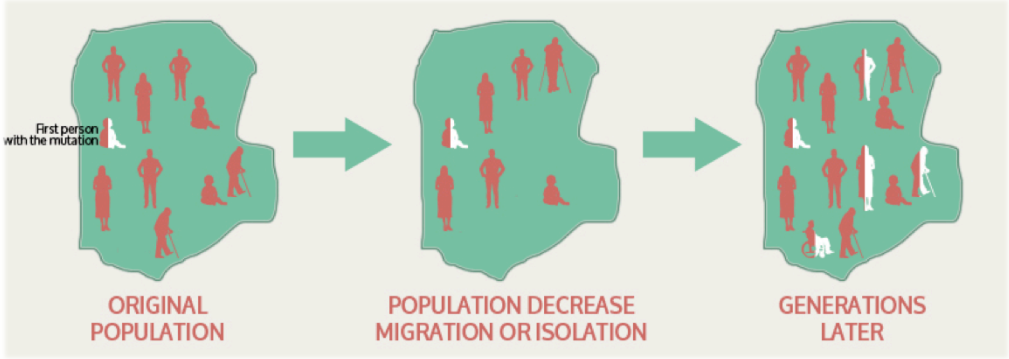
Recurrent Mutations

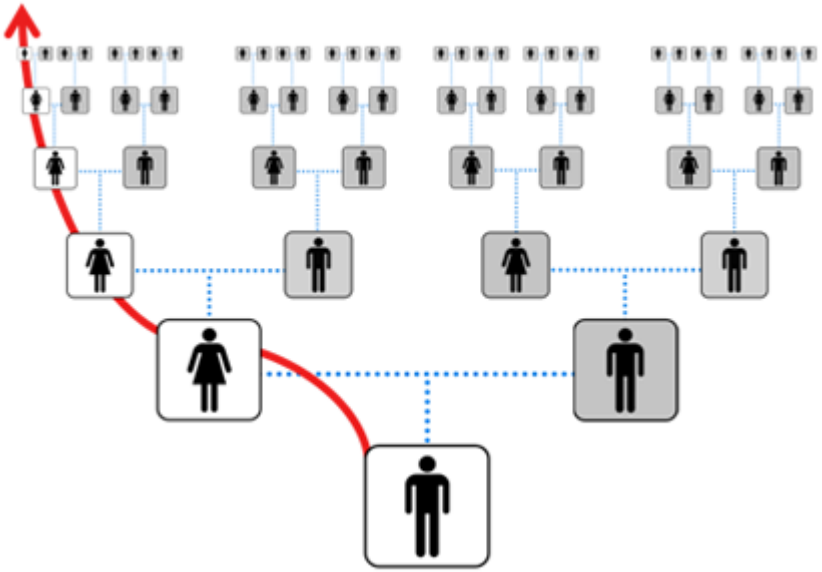
- **When the same mutation is observed over and over.**
  - It is a hot-spot mutation
    - A DNA base pair that is prone to mutation.
    - Carriers are usually not related to one another.

  OR

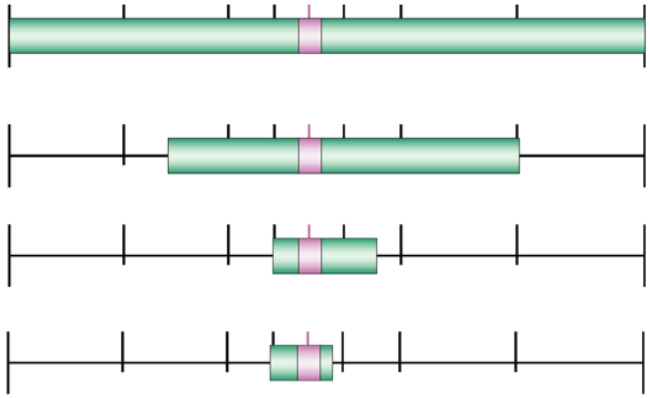
  - It is a founder mutation
    - A DNA variation that gets passed down over the generations.
    - The DNA variation can be traced back to one person (the founder).
    - The founder mutation is the genetic legacy of one long-gone ancestor.

Founder Mutation



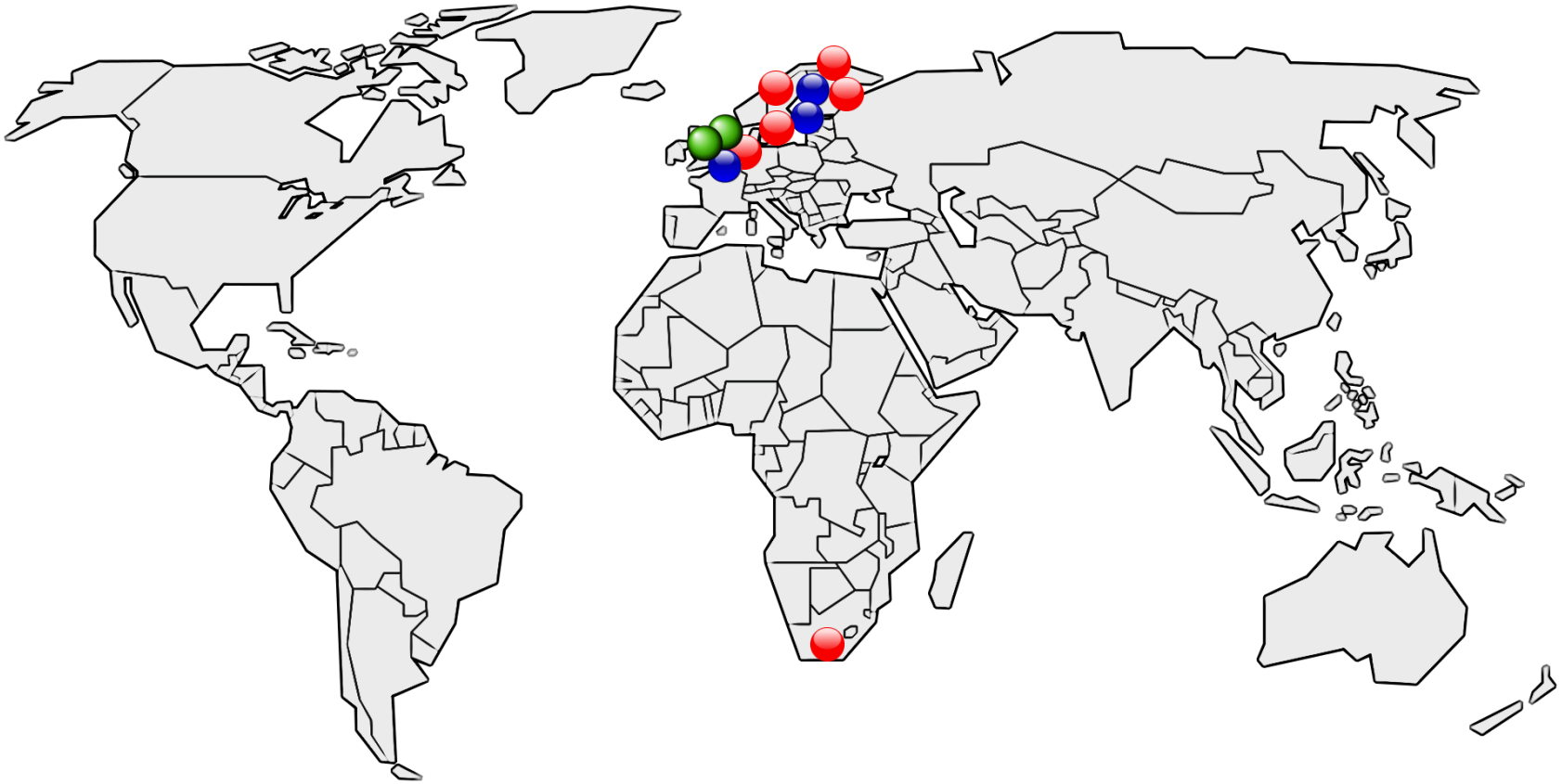


Founder Mutation

- Embedded in a DNA region (haplotype) identical to that of the founder.
- The same mutation in an identical haplotype - the same ancestor.
- Enables tracing the history of human populations and their migrations.
- Age of the 

ength of the haplotype.

Long QT Syndrome Founder Mutations



LTQS1 (*KCNQ1*)

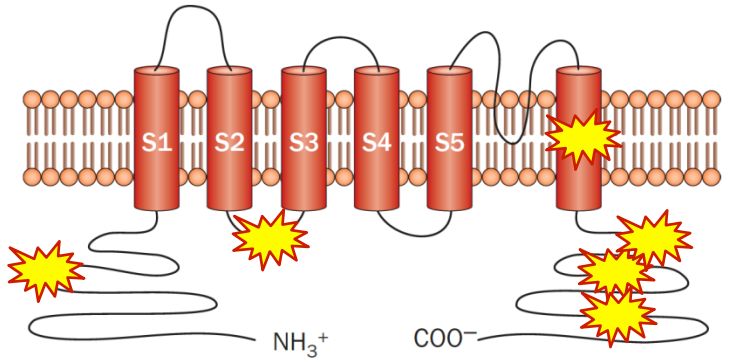
LTQS2 (*KCNH2*)

LTQS3 (*SCN5A*)

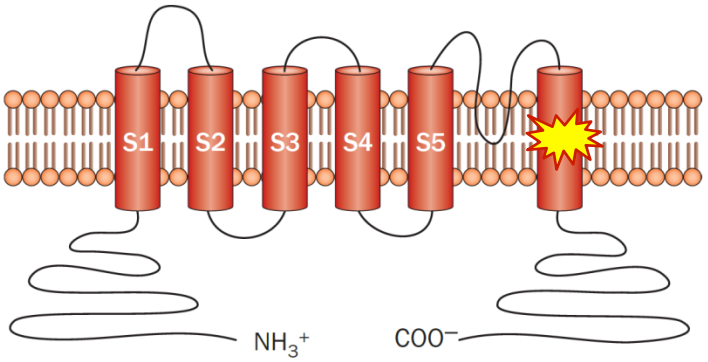
Founder mutations around the world

Long QT syndrome type 1 – *KCNQ1*

Country	Mutation
South-Africa	A341V
Finland	G589D IVS7-2A>G
Sweden	Y111C R518X
Norway	572del5
Netherlands	Y184S



A341V mutation (South-Africa)

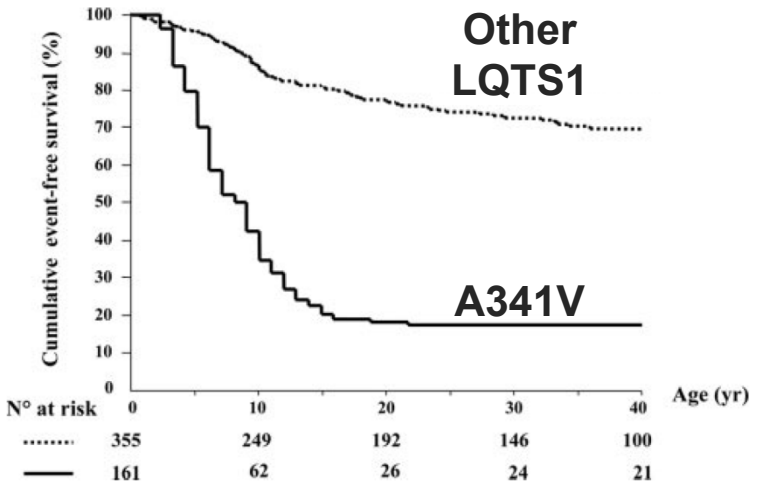


- Founded around 1700 (10 generations)
- 22 Families – Over 180 mutation carriers
- 79% Symptoms (median age 6 years)
- 14% Sudden cardiac death before age of 20 years
- Mean QTc 487 ms (406 tot 676 ms)
- QTc >500 ms associated with cardiac events
- Phenotype modified by autonomic nervous system and common genetic variants in *NOSA1P* and *AKAP9*

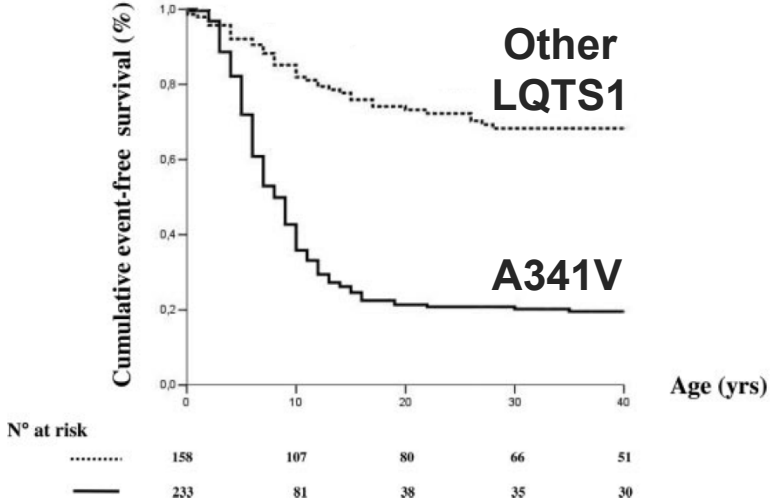
Brink, et al. *Circulation.* 2005.
Porta, et al. *J Am Coll Cardiol.* 2015.
Crotti, et al. *Circulation.* 2009.
De Villiers, et al. *Circ Cardiovasc Genet.* 2014.

A341V mutation (South-Africa)

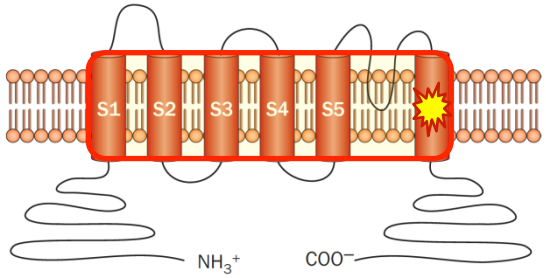
Versus other LQTS1 mutations



A341V vs. other LQTS1 mutation



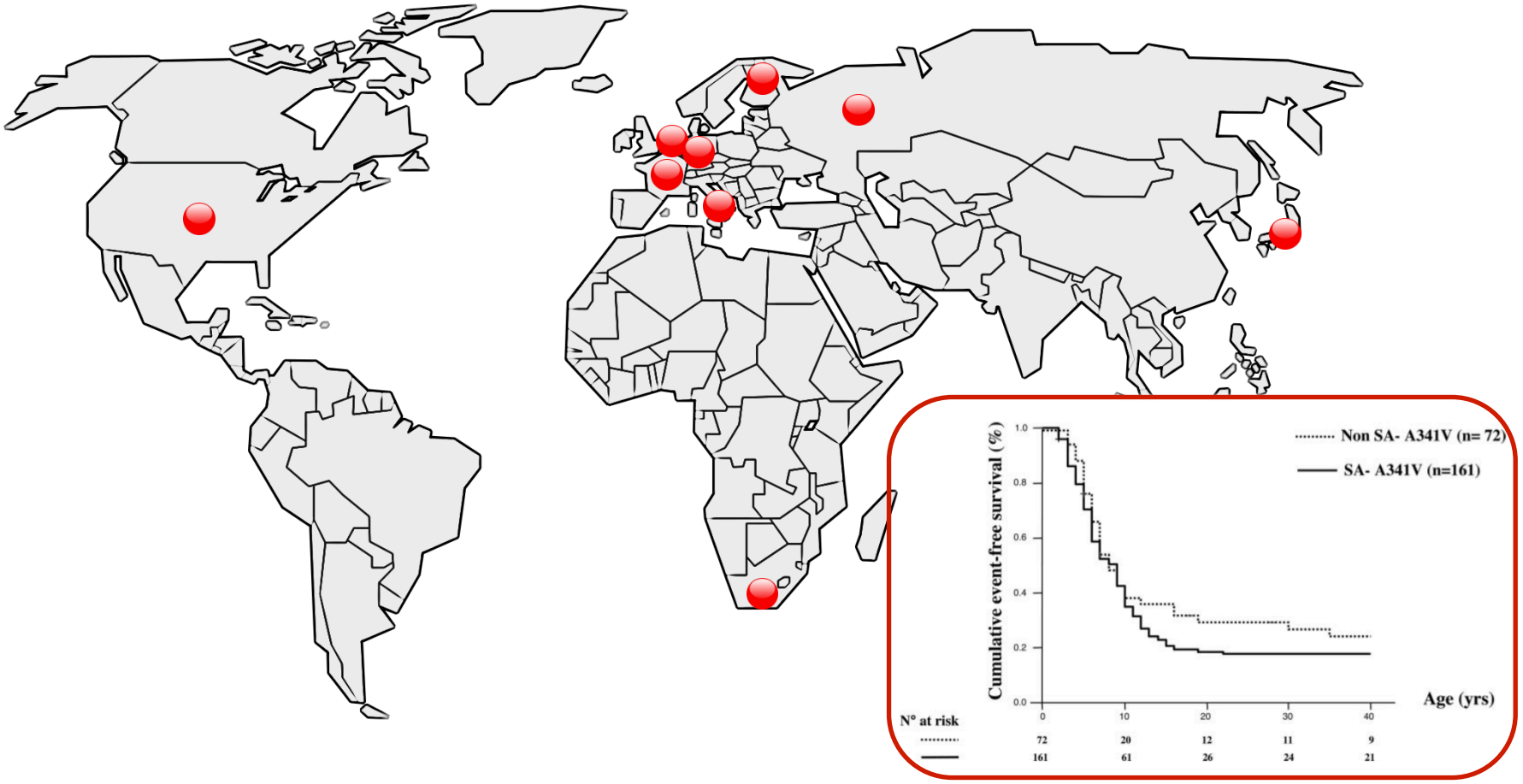
A341V vs. other LQTS1 mutations in transmembrane segments



Crotti, et al. *Circulation.* 2007.

A341V mutation (South-Africa)

And around the world

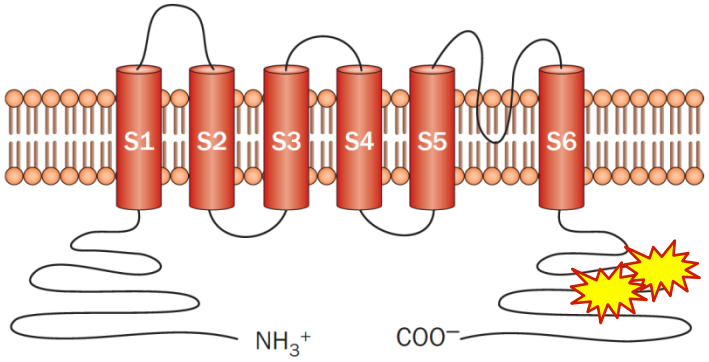


Crotti, et al. *Circulation.* 2007.

Founder mutations (Finland)

The G589D mutation

- Founded 500-750 years ago (25 generations)
- 77 Families – Over 500 mutation carriers
- 11% Symptoms
- Mean QTc 460 ms



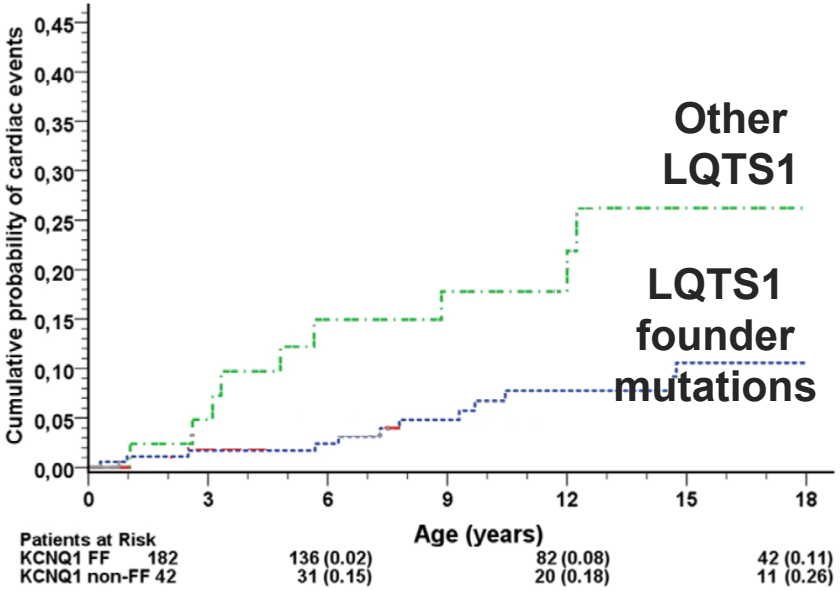
The IVS7–2A>G mutation

- 16 Families – 70 mutation carriers
- 10% Symptoms
- Mean QTc 466 ms

Crotti, et al. *Circ Cardiovasc Genet.* 2016.

Founder mutations (Finland)

- 182 Founder mutation carriers
- 42 Other *KCNQ1* mutation carriers
- Aged 0 to 18 years
- Follow-up of 12 years
- Less cardiac events in patients with
  - A founder mutation
  - QTc <470 ms
  - β-blocker therapy

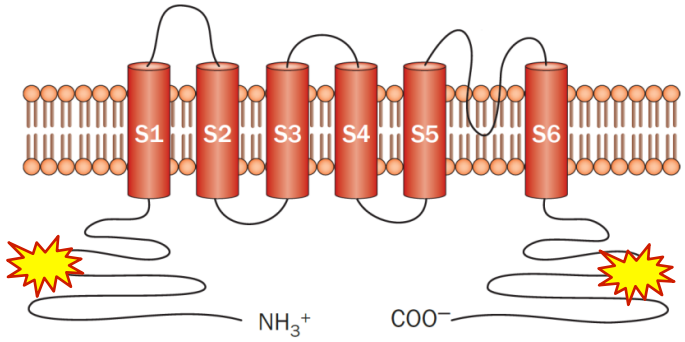


Koponen, et al. *Circ Arrhythm Electrophysiol.* 2015.

Founder mutations (Sweden)

The R518X mutation

- Found around 14th century (28 generations)
- 17 Families – 101 carriers
- 15 Homozygous (Jervell & Lange Nielsen syndrome)
  - QTc 576 ms – cardiac arrest 47%
- 86 Heterozygous
  - QTc 462 ms – cardiac arrest 1%



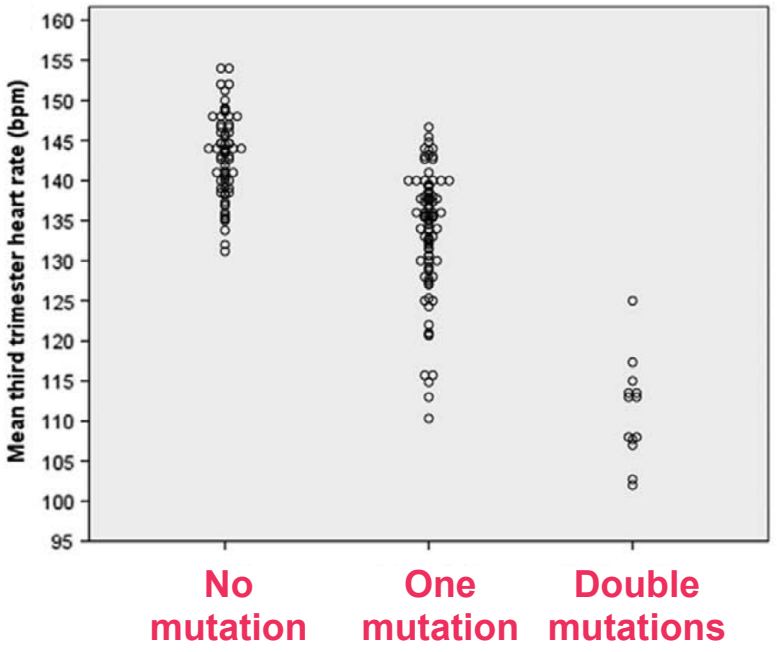
The Y111C mutation

- Founded around 1600 (22 generations)
- 37 Families – 170 carriers
- 30% Symptoms at median age of 11 years
- 1% Cardiac arrest
- QTc 481 ms

Winbo, et al. *BMC Cardiovasc Dis.* 2014.
Winbo, et al. Heart Rhythm. 2011.
Winbo, et al. Circ Cardiovasc Genet. 2009.

Founder mutations (Sweden)

- 110 fetuses with Y111C or R518X mutation
- 13 Double mutation carriers
- 74 Non-carriers
- Third trimester pre-labor fetal heart rates was correlated with mutation status and postnatal QTc and symptoms.

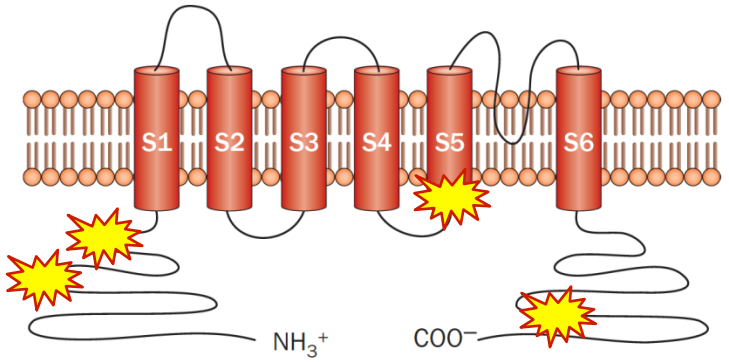


Winbo, et al. *Circ Arrhythm Electrophysiol.* 2015.

Founder mutations around the world

Long QT syndrome type 2 – *KCNH2*

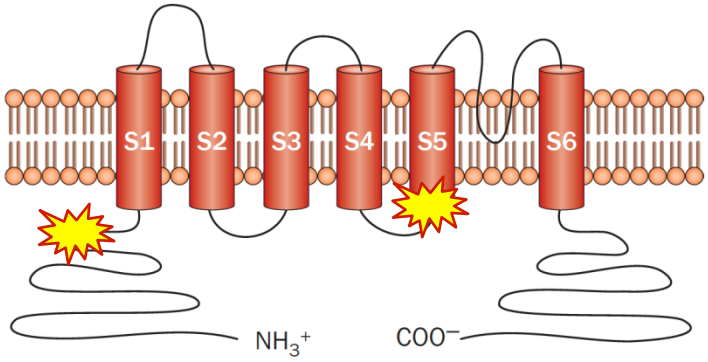
Country	Mutation
Finland	R176W L552S
Denmark	F29L
Netherlands	R582C



Founder mutations (Finland)

The R176W mutation

- 16 Families – 92 mutation carriers
- 35% Symptoms
- QTc 445 ms



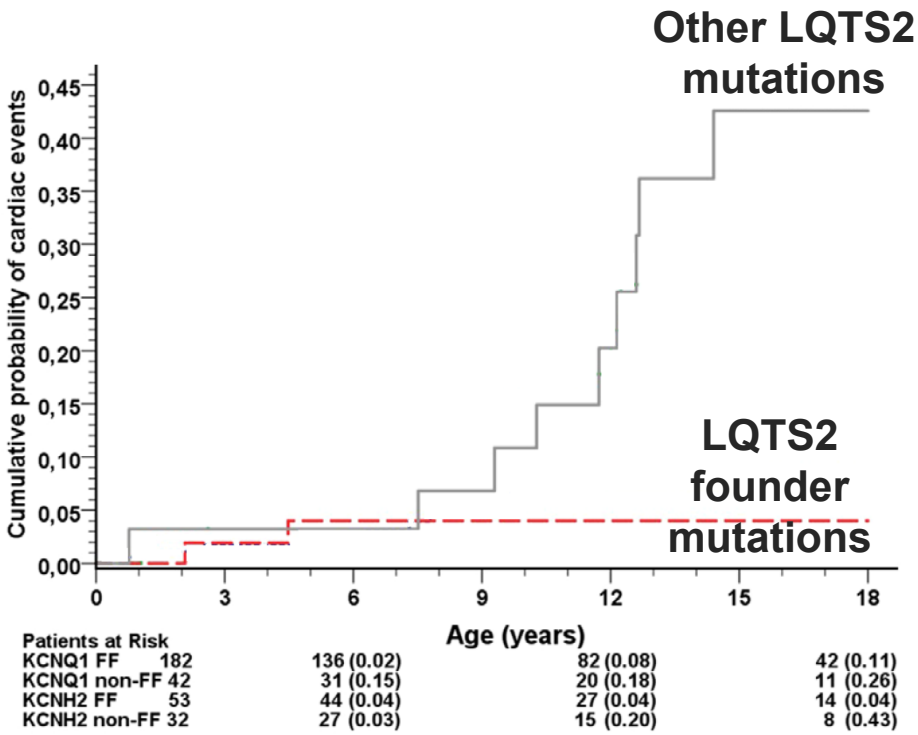
The L552S mutation

- 6 Families – 40 mutation carriers
- 2 Homoygzous children: 2:1 AV block (0 years) and TdP (2 years)
- 26% Symptoms (mean age 40 years)
- QTc 466 ms

Kanters, et al. *Scand J Clin Lab Invest. 2015.*
Piipo, et al. *J Am Coll Cardiol. 2000*

Founder mutations (Finland)

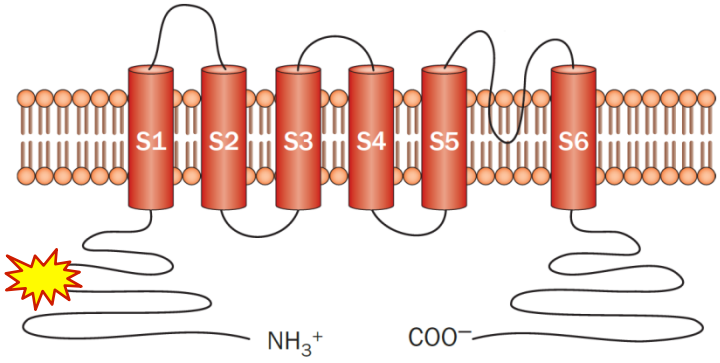
- 53 Founder mutation carriers
- 32 Other *KCNH1* mutation carriers
- Aged 0 to 18 years
- Follow-up of 12 years
- Less cardiac events in patients with
  - A founder mutation
  - By the age of 10 years: 24% vs. 0%
  - By the age of 18 years: 43% s. 4%



Koponen, et al. *Circ Arrhythm Electrophysiol.* 2015.

F29L mutation (Denmark)

- Founded around 550 years ago – 22 genera
- 5 Families – 33 mutation carriers
- 73% Symptoms (median age 16 years)
- 9% (3 of 33) Cardiac arrest
- 10 ICD's – ICD shocks in 4
- QTc 490 ms

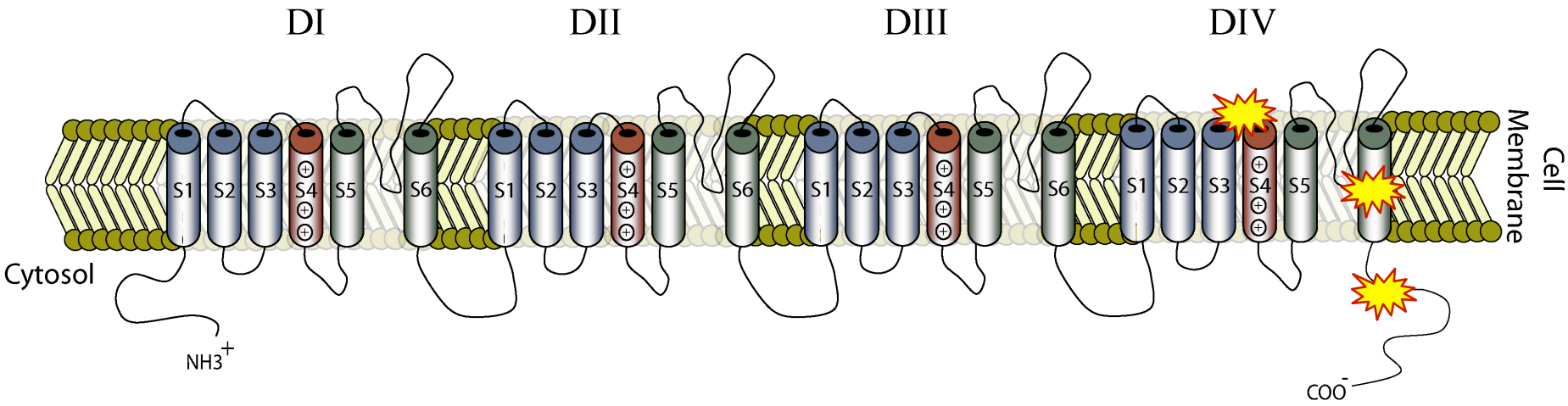


Kanters, et al. *Scand J Clin Lab Invest.* 2015.
Christiansen, et al. *BMC Medical Genetics.* 2014.

Founder mutations around the world

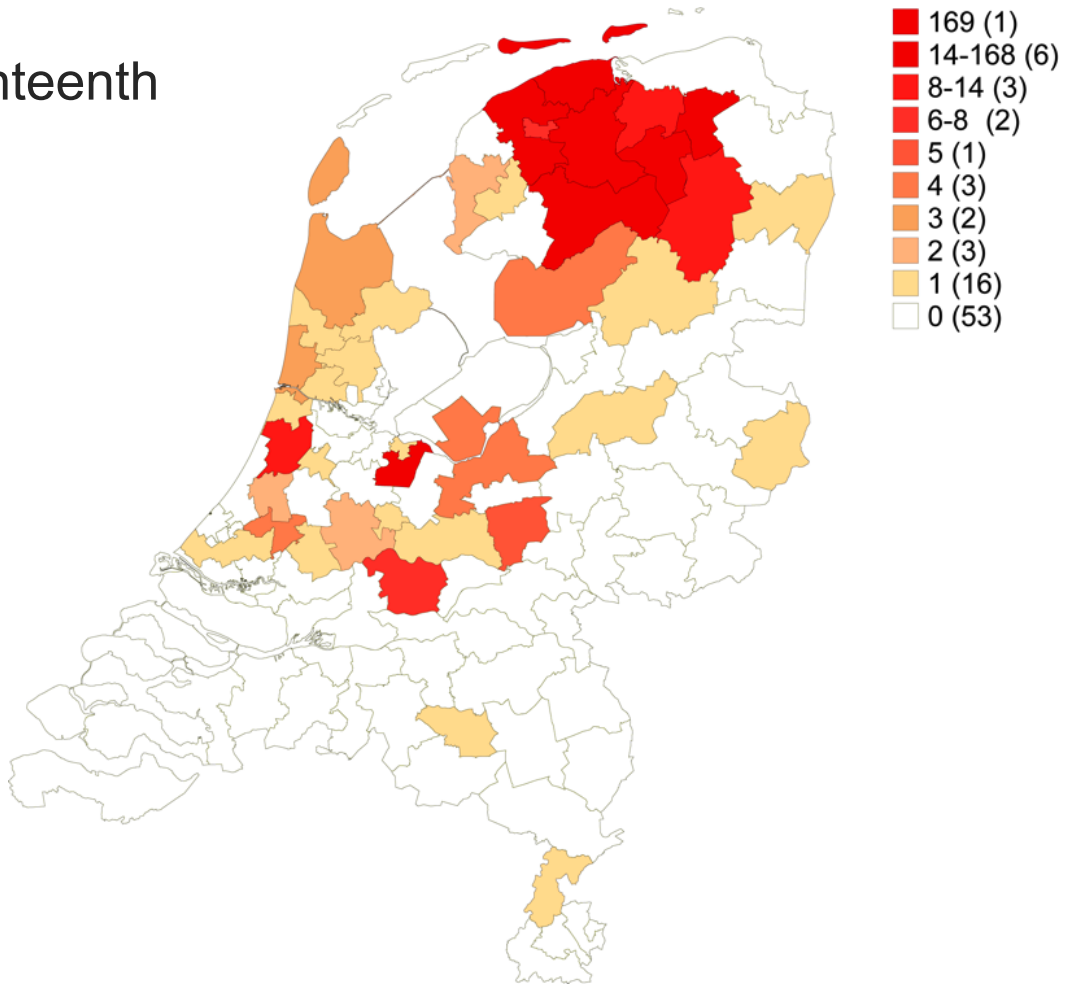
Long QT syndrome type 3 – *SCN5A*

Country	Mutation
Netherlands	p.1795insD p.1617delF I1768V



The 1795insD founder mutation

- Founded in the late eighteenth century
- Ten generations
- 378 Family members
- 149 Mutation carriers

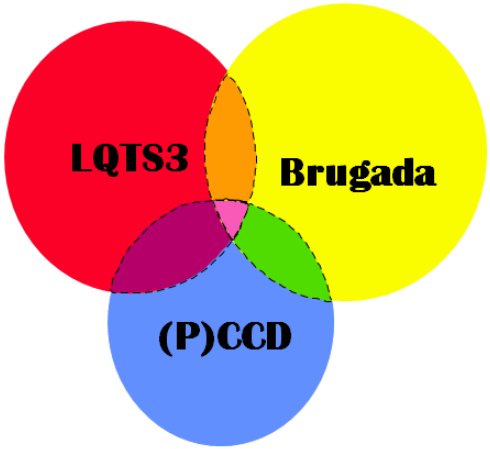


Postema, et al. *Neth Heart J.* 2009.

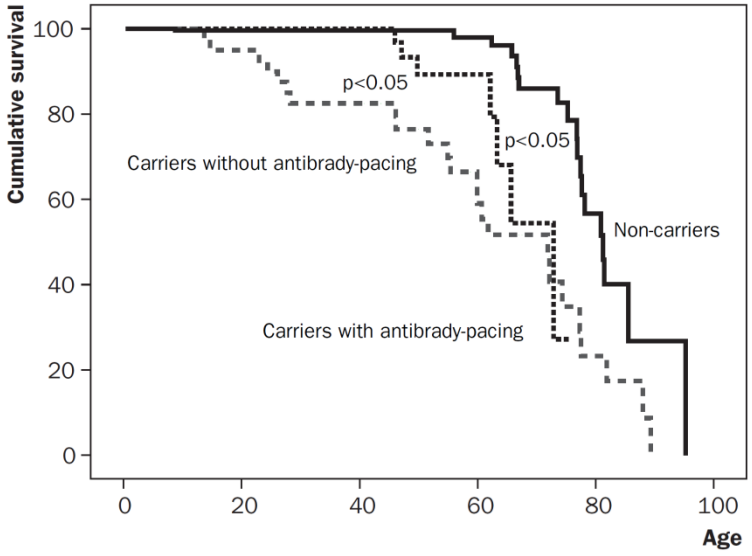
The 1795insD founder mutation

Overlap phenotype

- Bradycardia-dependent QT prolongation
- Right precordial ST elevation
- Conduction disease at all levels



- Mode of (nocturnal) death is not identified
- Pacemaker therapy proven to be beneficial.



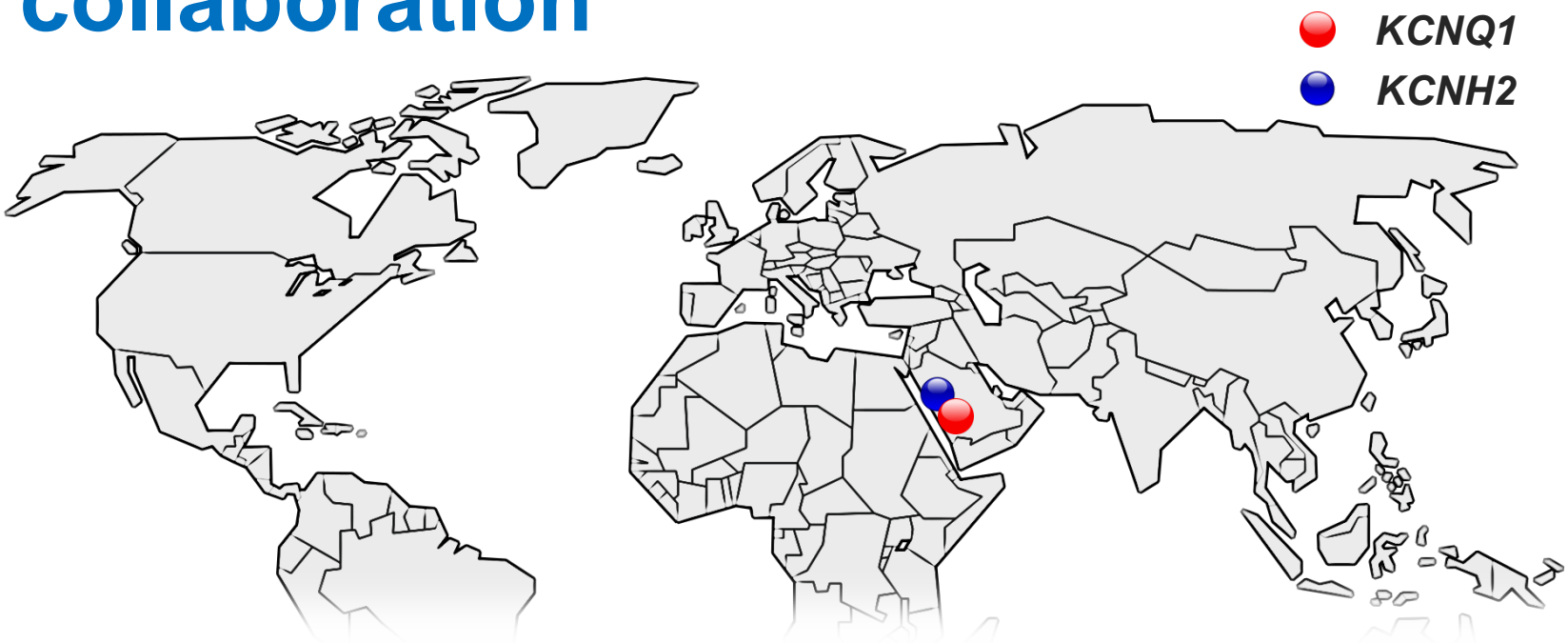
Number at risk

Non-carriers	229	201	136	52	13	0
Carriers with antibrady-pacing	99	76	41	13	0	0
Carriers without antibrady-pacing	50	38	30	16	4	0

Conclusion

- Founder mutations around the world may be more common.
- Founder mutations are often less severe mutations (but not always).
- The severity of the mutation depends on gene and its type/location.
- Finding founder mutations may prevent sudden death in family members.
- Local, national and international collaborations are needed to find them.

Example of international collaboration



Pediatr Cardiol (2009) 30:490–501
DOI 10.1007/s00246-008-9377-y

ORIGINAL ARTICLE

Clinical and Genetic Analysis of Long QT Syndrome in Children from Six Families in Saudi Arabia: Are They Different?

Zahurul A. Bhuiyan · Safar Al-Shahrani · Ayman S. Al-Khadra · Saleh Al-Ghamdi · Khalaf Al-Khalaf · Marcel M. A. M. Mannens · Arthur A. M. Wilde · Tarek S. Momenah