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BCIAP

Syncope In The Channelopathies: What Can Gene Studies Teach Us?

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CIHR IRSC
Canadian Institutes of Health Research
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HEART AND STROKE FOUNDATION

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NO CONFLICT OF INTEREST TO DECLARE

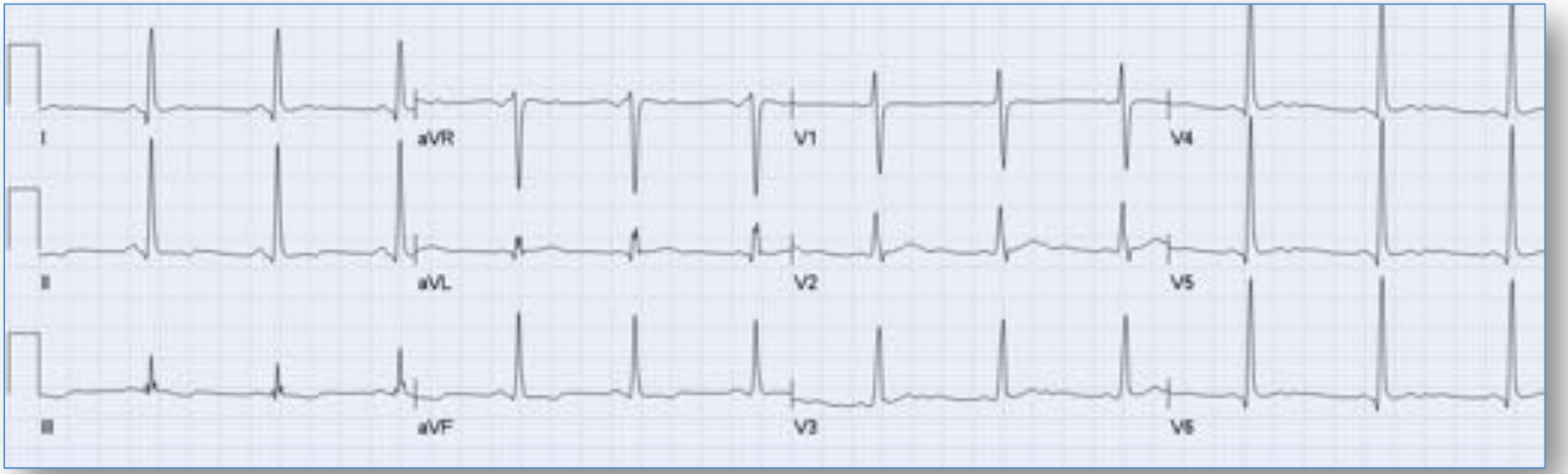
Outline

1. Case presentation
2. Recent evidence on syncope in the ion channelopathies
3. Genetics primer for use of genetic information
4. Conclusions

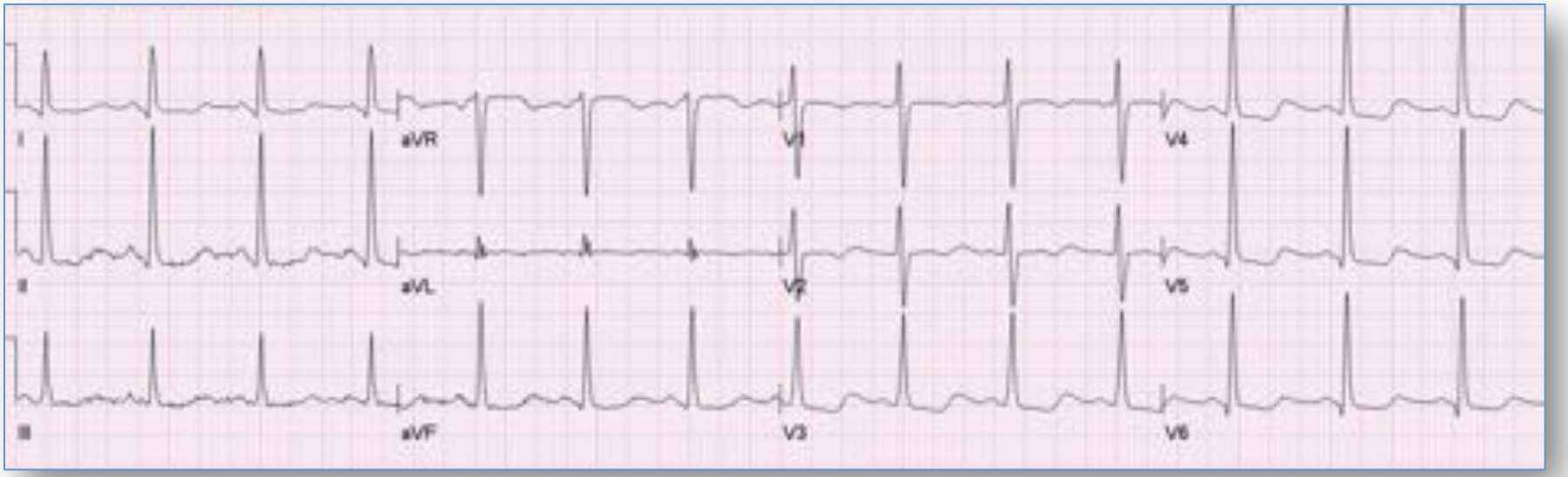
Case Presentation

- 30 year old woman
- No family history
- Syncope x 3 with GI illness
- Analgesic for pain
- Allergic reaction to codeine
  - EMS to ER
- Adrenaline in ER

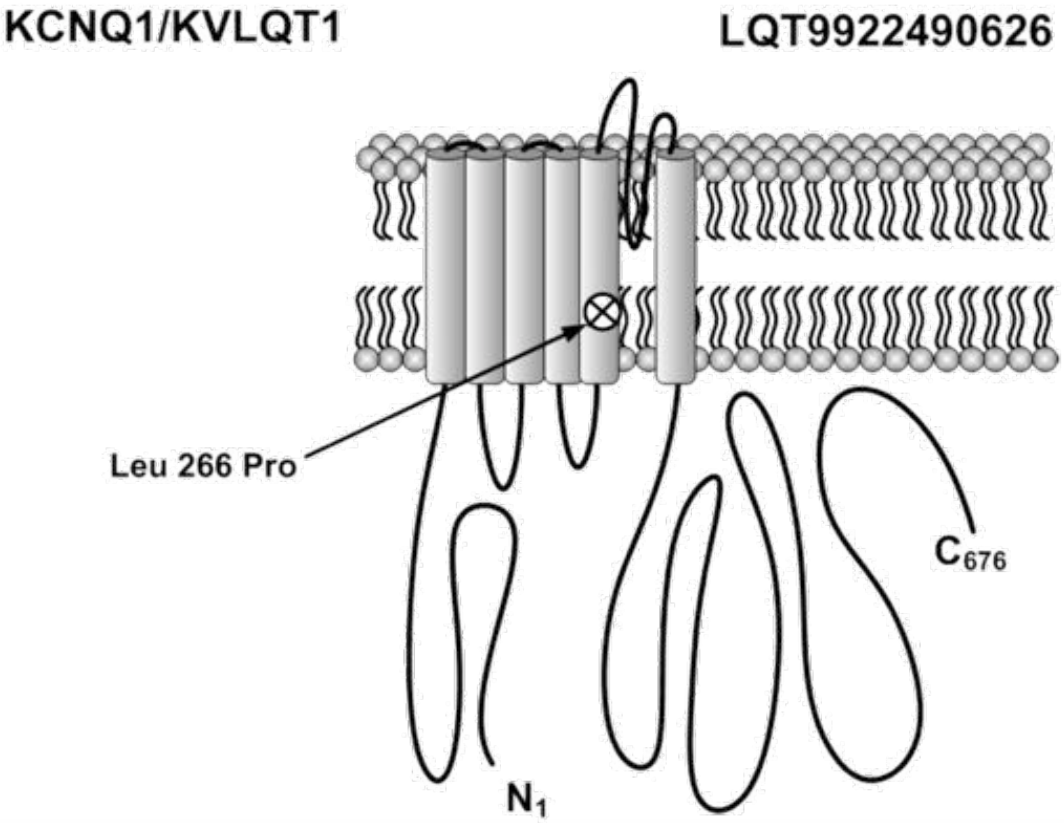
Reference ECG

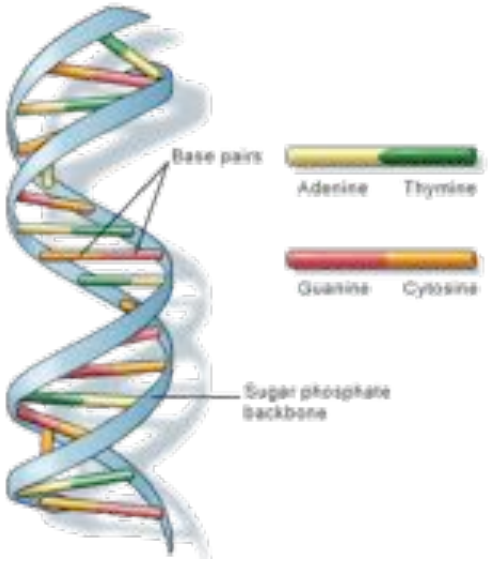


Adrenaline ECG



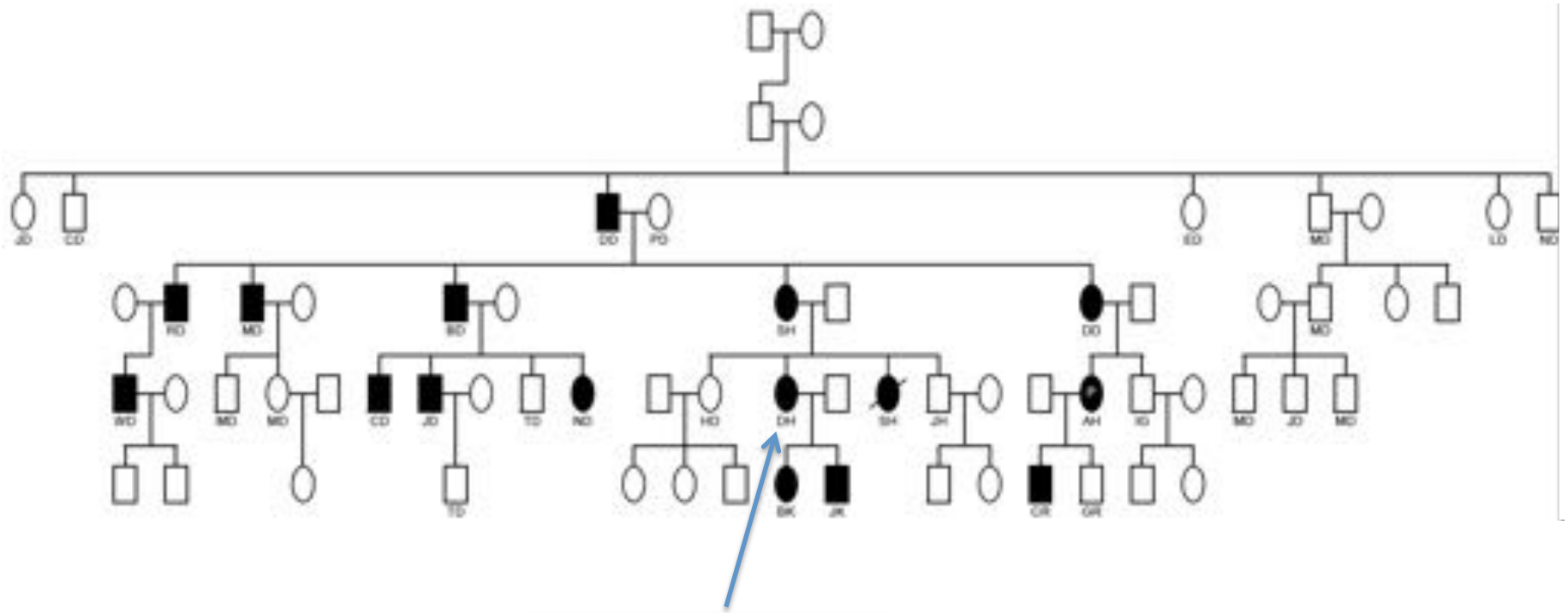
Genetic Testing





Num	Gene	Region(G)	Nucl.Change	A.A.Change	Genotype	Region(P)	Region Type(P)	Class
1	KCNQ1	exon 6	797 T>C	Leu 266 Pro	T/C	S5 domain	Transmembrane	I
2	SCN5A	exon 12	1673 A>G	His 558 Arg	A/G	DI/DII	Transmembrane spanning linker	III

Others at Risk!



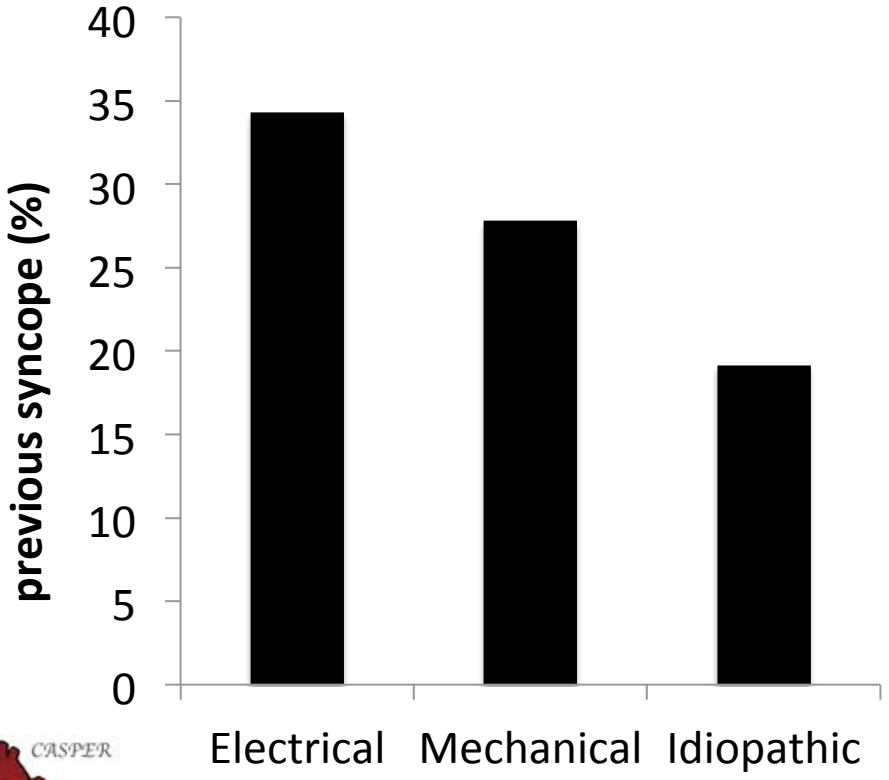
Sentinel Symptoms in Patients with Unexplained Cardiac Arrest: From the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER)

- 100 Unexplained cardiac arrest patients and 63 family members
- Pre enrolment symptoms ascertained
- Prior syncope in 26% of cardiac arrest patients - Calgary syncope score
- 24 of 25 cardiac arrest patients who completed the syncope questionnaires had a syncope versus seizure score **<** 1 favoring syncope.

Krahn et al, JCE 23: 60-66, 2012

Sentinel Symptoms in Patients with Unexplained Cardiac Arrest: From the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER)

- The area under the receiver operator curve (ROC) for the syncope mechanism score was 0.79 for identifying patients with subsequent cardiac arrest (95% CI, 0.6328–0.9395, P = 0.004).
- A score of ≤ –2 had a sensitivity of 68% and specificity of 85%.



Krahn et al, JCE 23: 60-66, 2012

Syncope in Brugada syndrome: Prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes

Louise R.A. Olde Nordkamp, MD,* Arja S. Vink, MD,* Arthur A.M. Wilde, MD, PhD,* Freek J. de Lange, MD, PhD,* Jonas S.S.G. de Jong, MD,* Wouter Wieling, MD, PhD,† Nynke van Dijk, MD, PhD,‡ Hanno L. Tan, MD, PhD*

The event interview was conducted by one investigator (A.V.) and consisted of a standardized systematic history taking of the event similar to the ESC guidelines on syncope

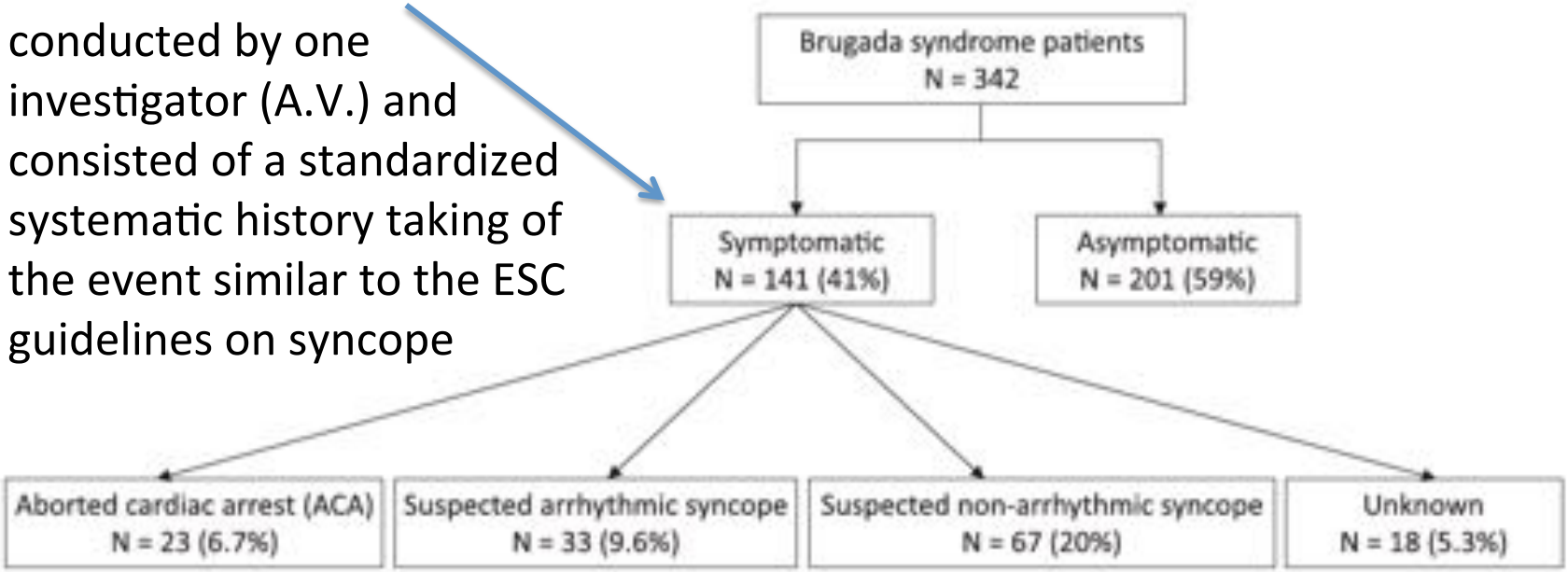


Figure 1 Flow chart.

Heart Rhythm 2015;12:367–375

Aborted Cardiac Arrest vs. Non-Arrhythmic Syncope

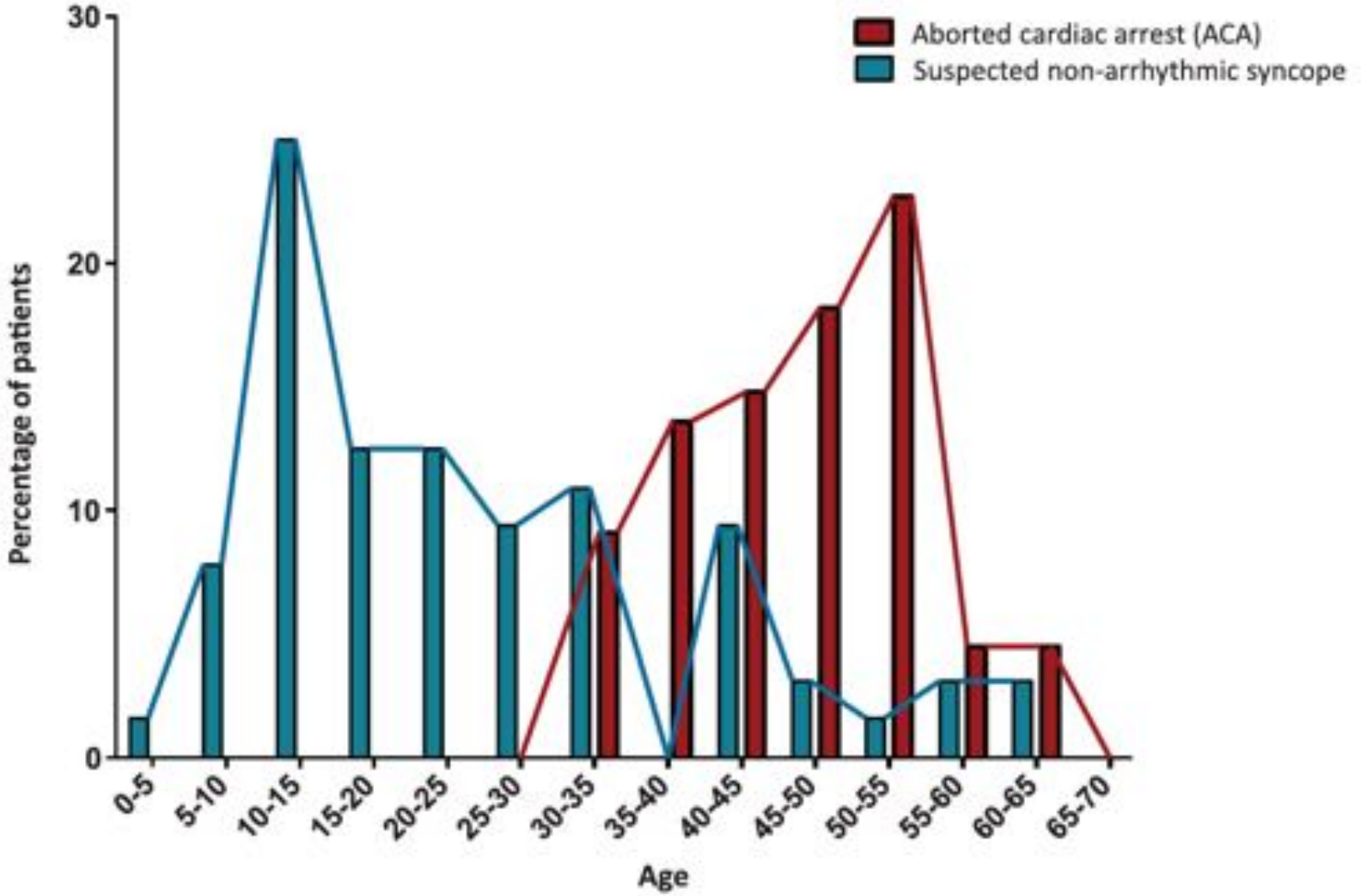


Figure 2 Age distribution at first event.

Heart Rhythm2015;12:367–375

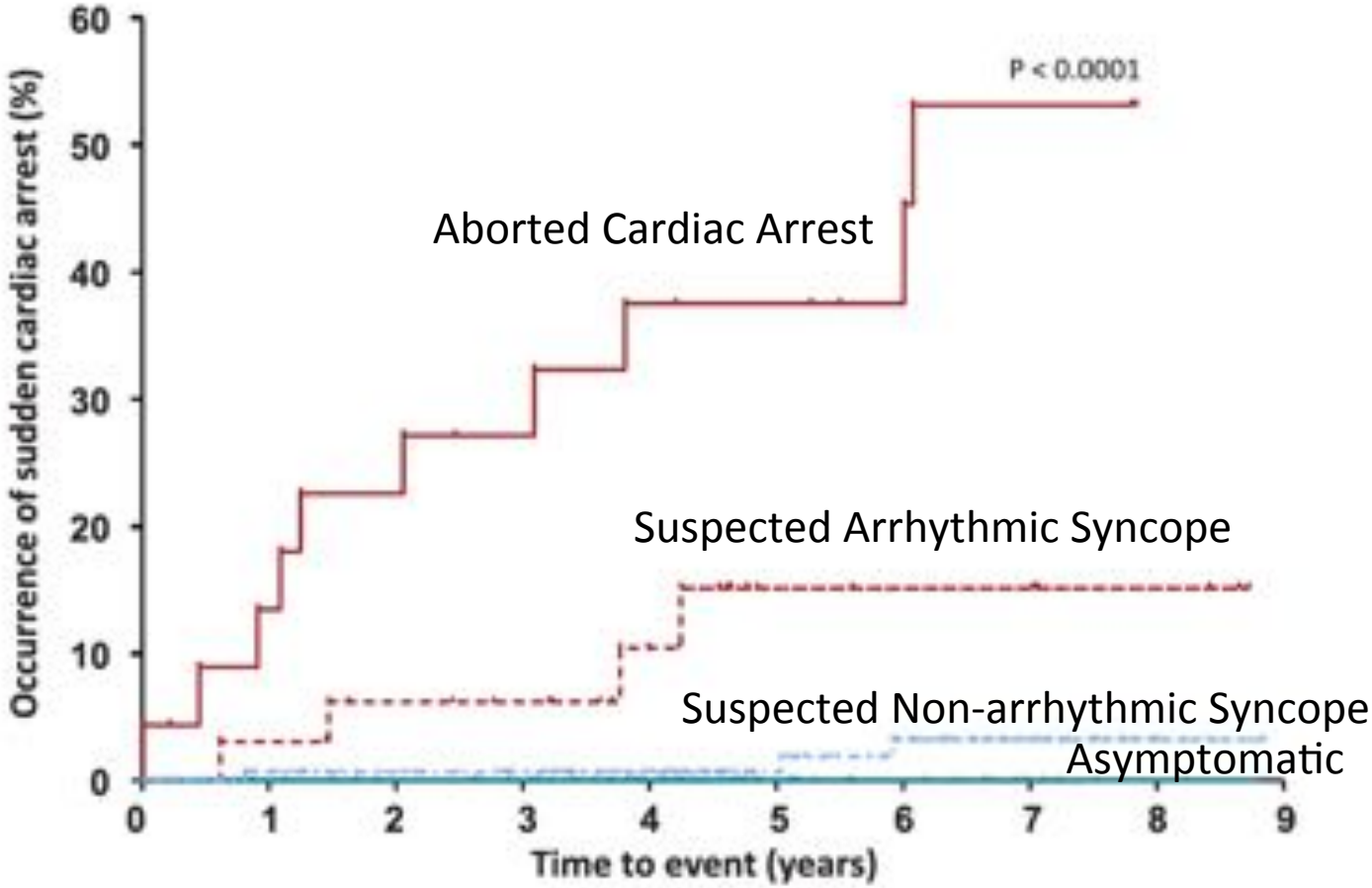
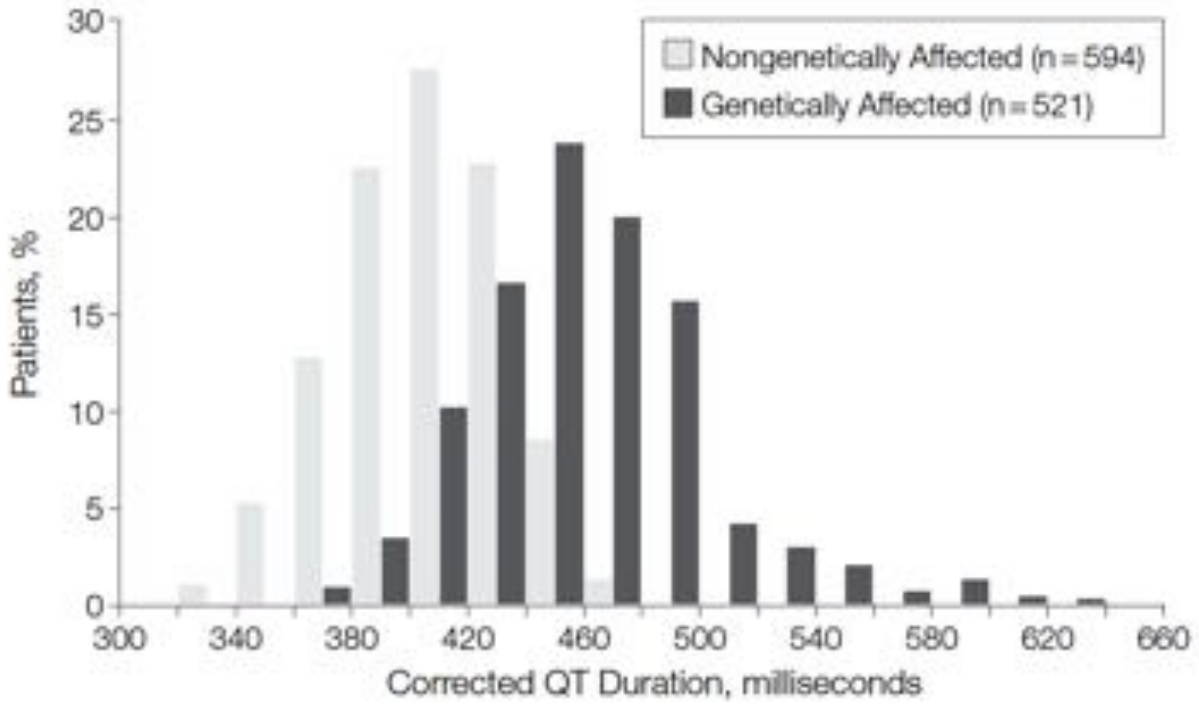


Figure 3 Occurrence of aborted cardiac arrest during follow-up by baseline category.

QT Overlap LQTS and Normal

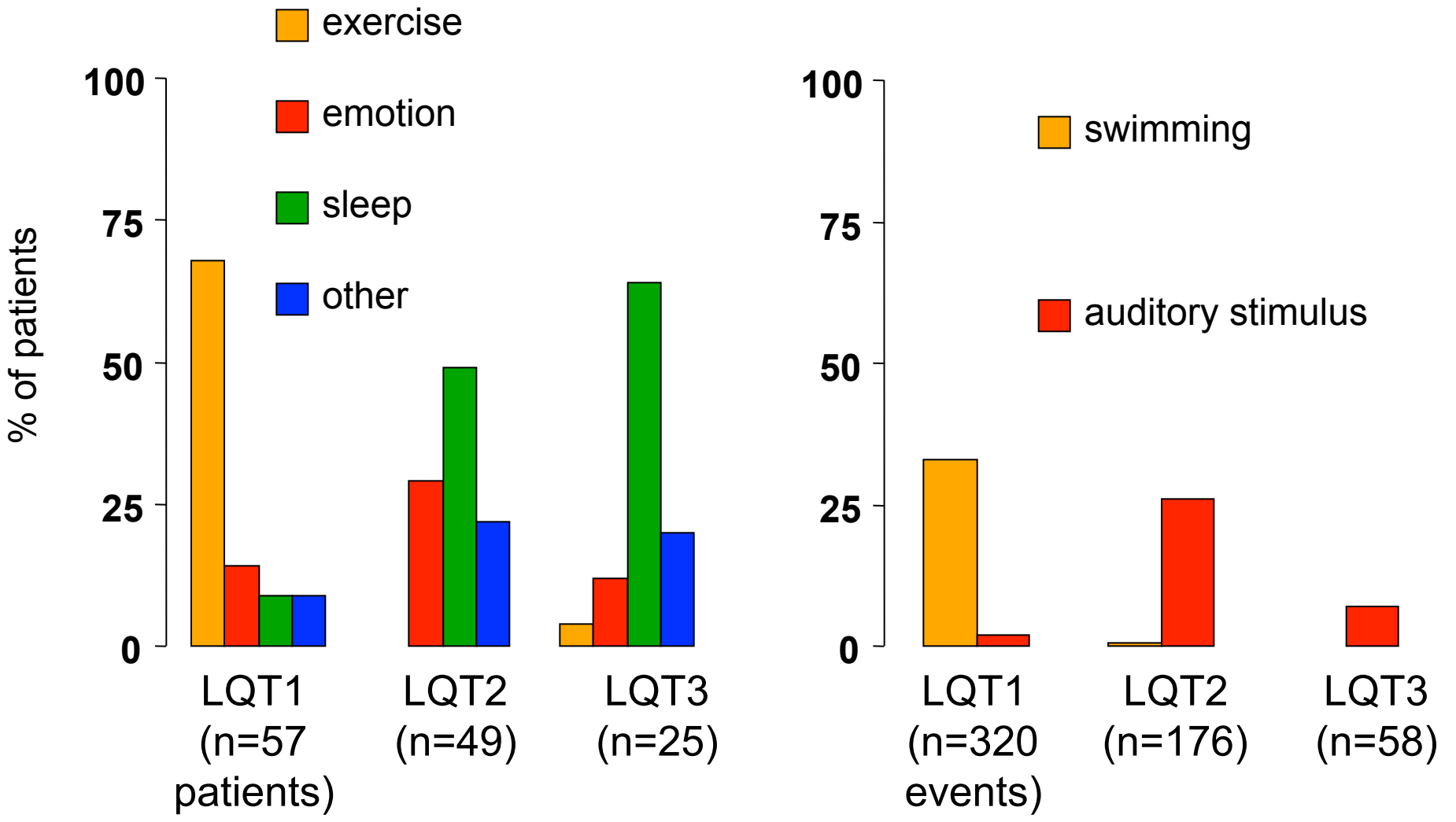
Figure 1. Corrected QT Distribution in Families With Long QT Syndrome



The percentage of individuals for each 20-millisecond cluster of corrected QT duration in the 2 groups of genetically affected (n=817) and nongenetically affected individuals (n=521). Numbers on the x-axis represent the cluster upper limit.

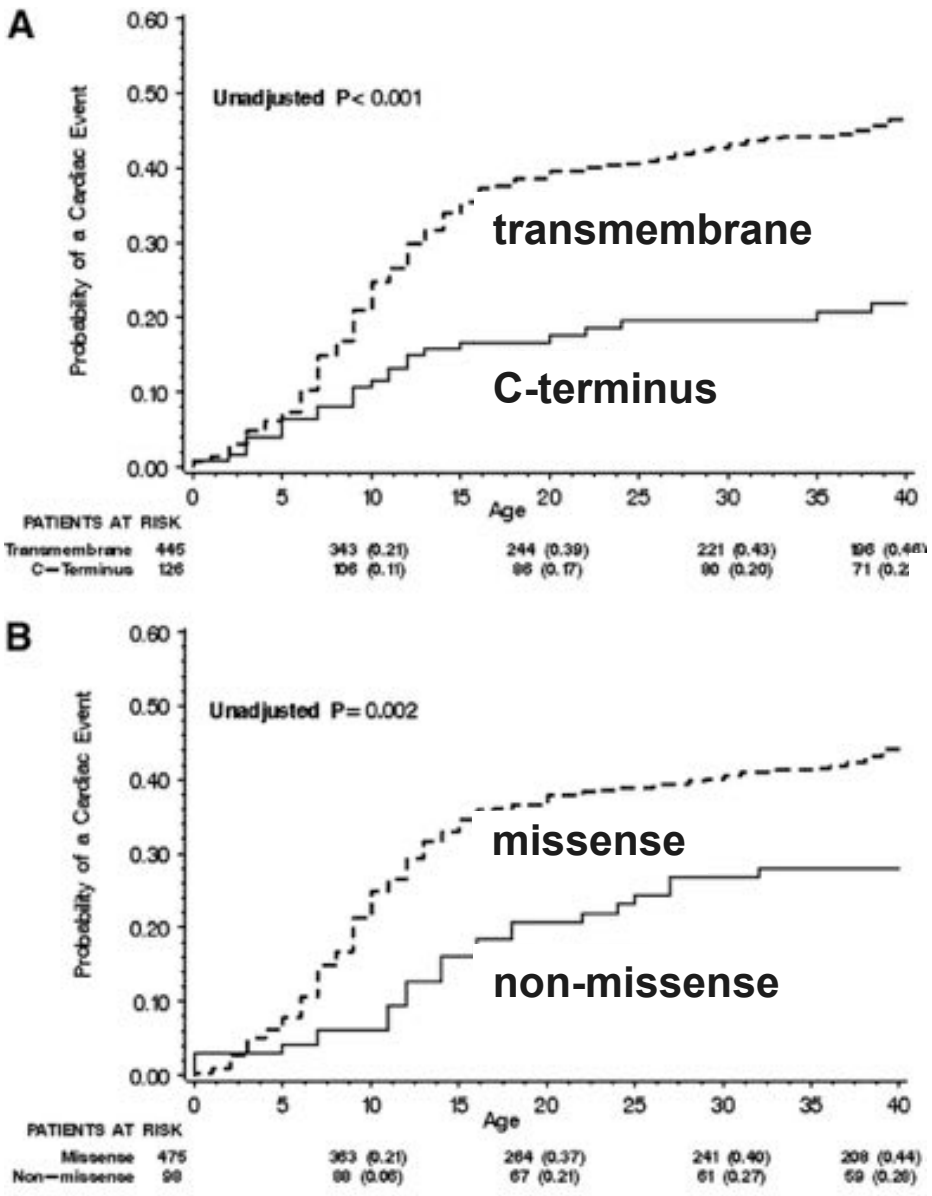
Napolitano JAMA 2005

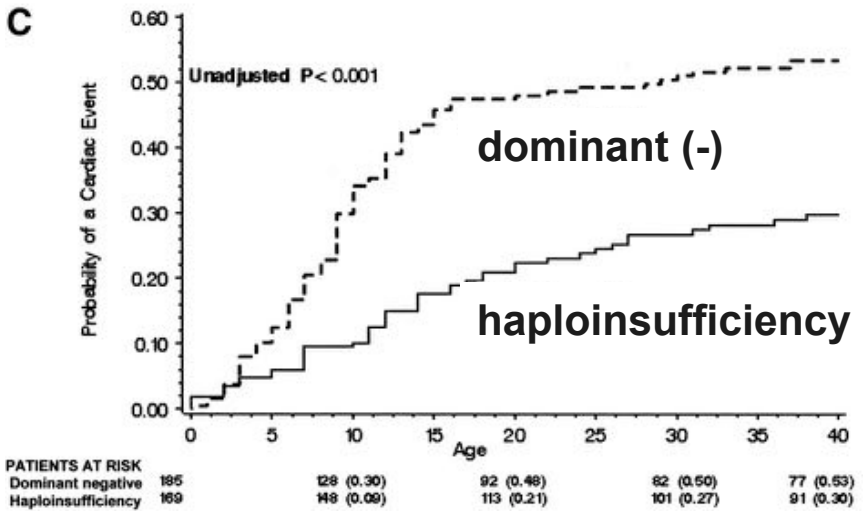
LQT - Triggers by genotype



Schwartz et al., 2001

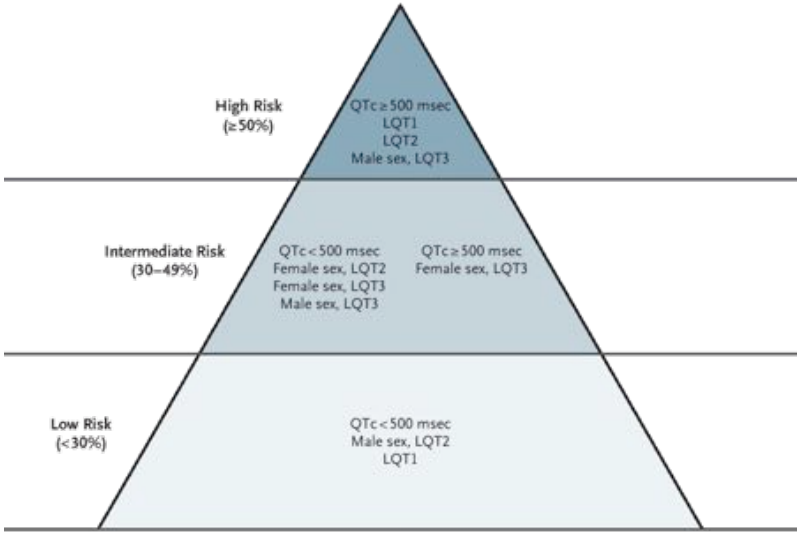
Prognosis by protein domain affected *KCNQ1*



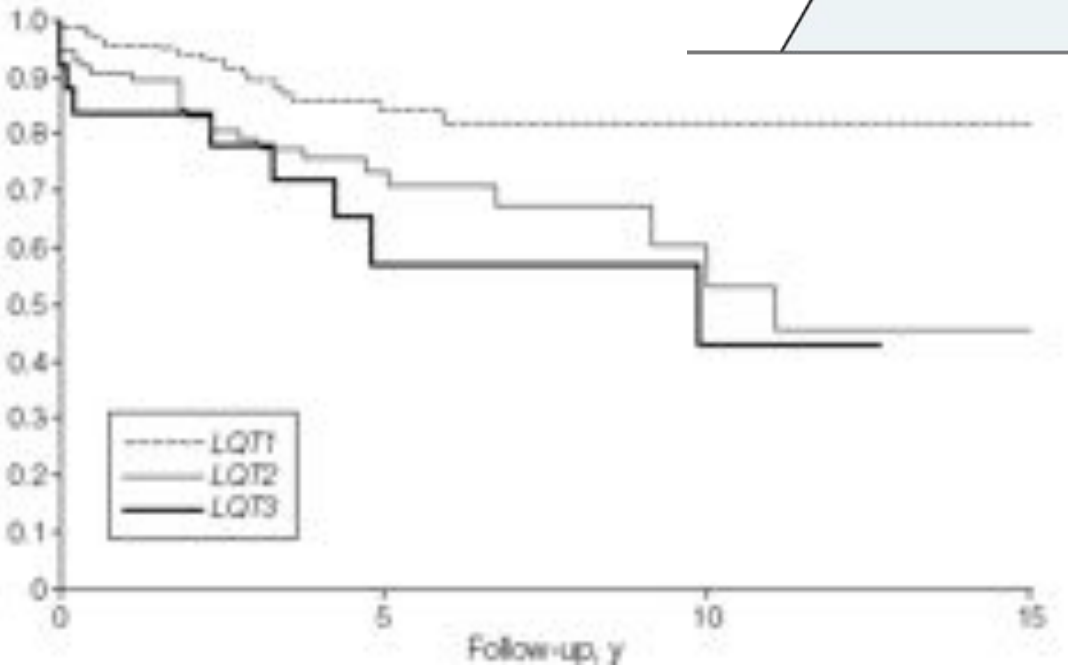


Moss et al., Circ 2007

- Genotype affects
  - Risk
  - Response to β-blockers
  - So does haplotype, location, etc



Event-free survival among patients on beta-blockers



Priori; 2004

Predictors of failure of beta-blockade:

1st event at age <7 years; QT>500 msec on therapy; LQT2 *or* LQT3

Role of Genetic Testing

- 3 situations that warrant testing
  - Clear diagnosis in the index case (proband) with positive genetic test aids in prognosis and Rx
  - Proband results facilitates family screening
  - Borderline case may help as a tie breaker
- Not a useful screen in every patient with minimal evidence of disease
- Counseling before testing and complex interpretation afterwards
- Yield 20-75% in IAC related conditions

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Genetic Testing Utility

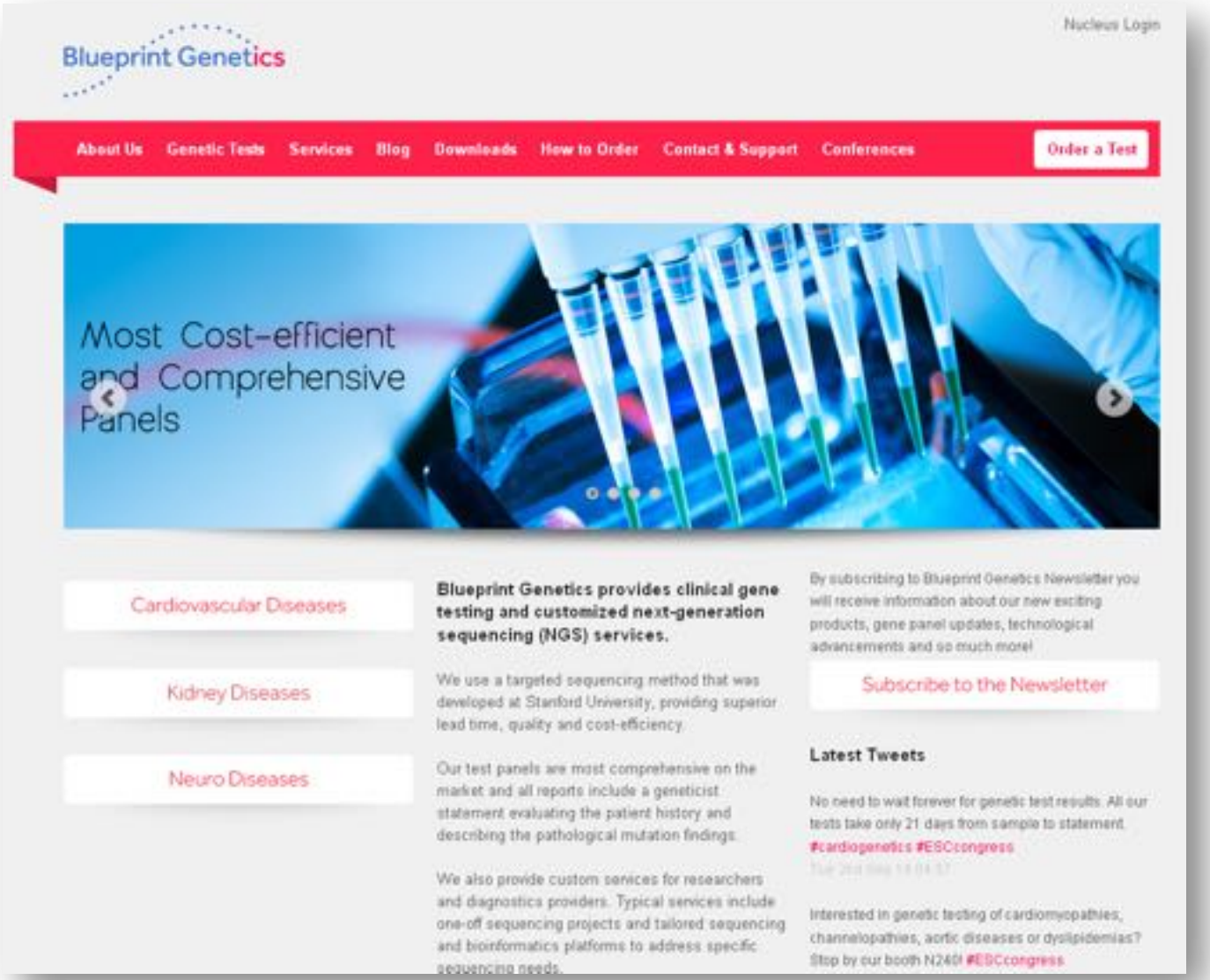
Yield:

- 75% in LQT
- 40-50% in ARVC and CPVT
- 20% in Brugada

- Prognostic utility in Long QT only

Genetic Testing - Logistics

- Counsel and consent
- Blood test in most: sputum may work
- Sent to labs in the US and Europe
- Cost 1000-2000 Euros for index case (proband). 100-200 Euros for family members.
- Total time as little as 3-4 weeks



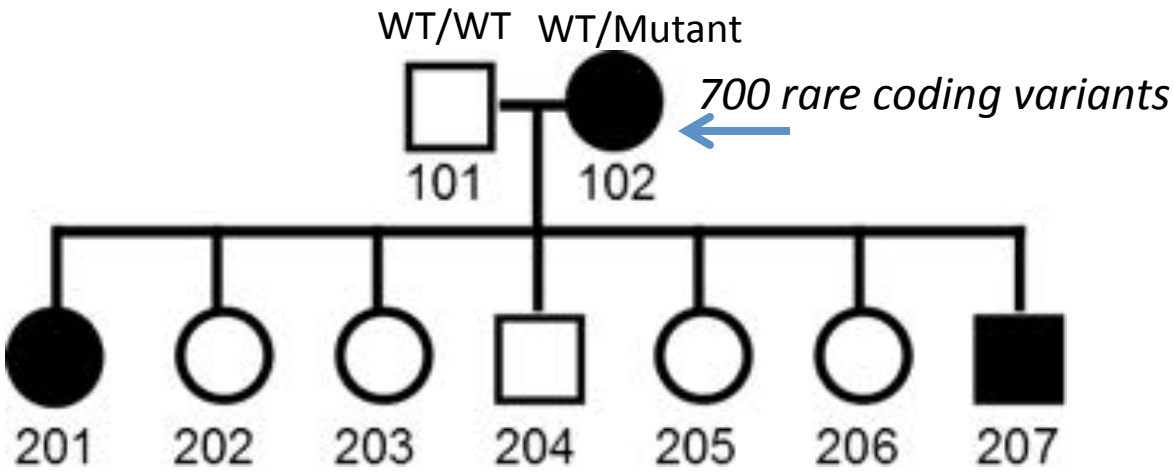
Finnish company, CLIA certification pending, rapid, cost effective, responsive team

Testing Costs

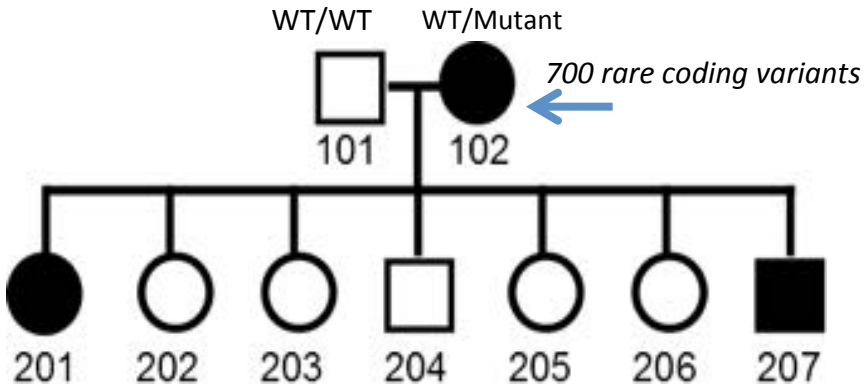
Test code	Test name	Turnaround Time (days)	Price (€)
	Index patient testing		
	TESTS FOR CARDIOVASCULAR DISORDERS		
01051	Pan Cardiomyopathy Panel – 103 genes	21	€1,500
01061	Core Cardiomyopathy Panel – 72 genes	21	€1,400
01121	Heart Panel – 133 genes	21	€1,900
01081	Noonan Syndrome Panel – 12 genes	21	€1,200
01021	Arrhythmia Panel – 47 genes	21	€1,600
01031	Brugada Syndrome Panel – 18 genes	21	€1,100
01041	Catecholaminergic Polymorphic VT Panel – 6 genes	21	€1,200
01071	Long QT Syndrome Panel – 16 genes	21	€1,000
01101	Short QT Syndrome Panel – 6 genes	21	€1,000

Which "Rare" Variant is Causal? Mendelian/Family Genetics

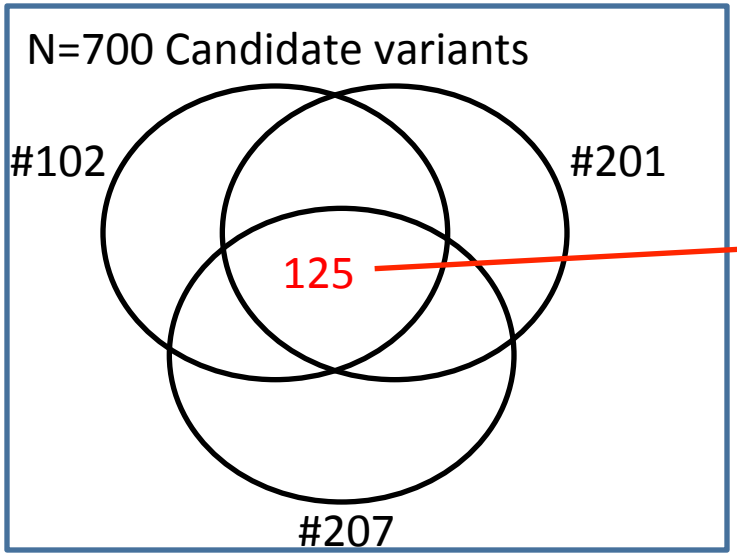
With ~700 rare or novel exome (coding) variants per patient, where do you begin to look for causal variants?



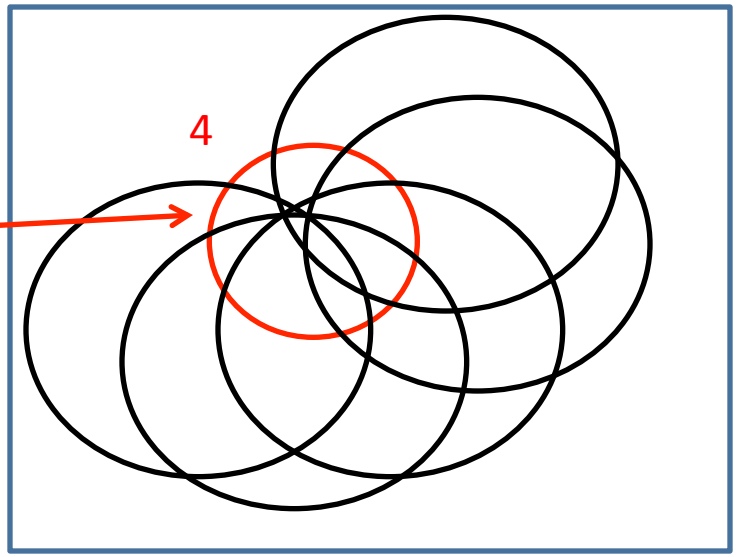
Which "Rare" Coding Variant is Causal?



Rare mutations shared by all affected:



Rare mutations shared by all affected – not present in any unaffected family members:



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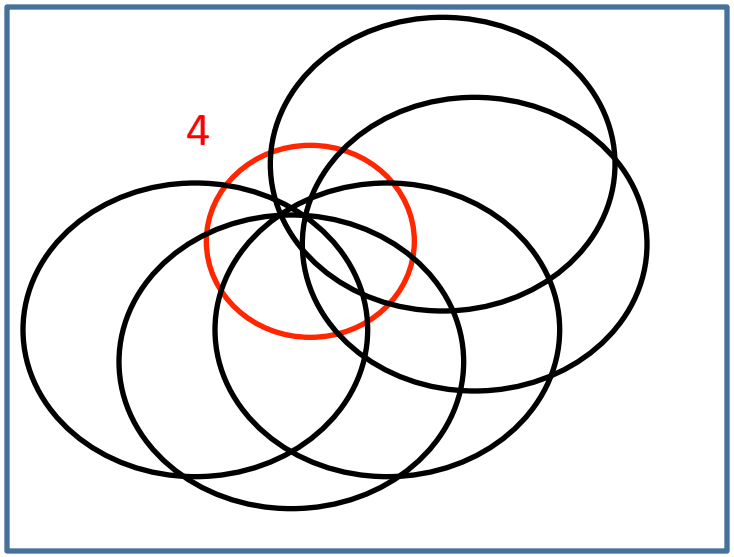

FUNCTIONAL	GENETIC
Predicted damaging?	Conservation
In vitro mutant expression	Segregation
In vivo KO or KI	Case-control
	Expression

Conclusions

- Clinical presentation of syncope with IACs is often atypical and has a unique trigger
- Genetic testing is available, capable and getting cheaper and bigger/better
- More is not necessarily better, so you need genetic expertise or access to expertise
- The fundamental principles of “family” medicine should prevail
- The major clinical wins are in protecting family members and improving proband care

Important Websites

- www.qtdrugs.org
- www.brugadadrugs.org
-
- akrahn@mail.ubc.ca

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