

Genetics of LQTS and other causes of sudden death

Brief overview and update
LQTS, CPVT, ARVC

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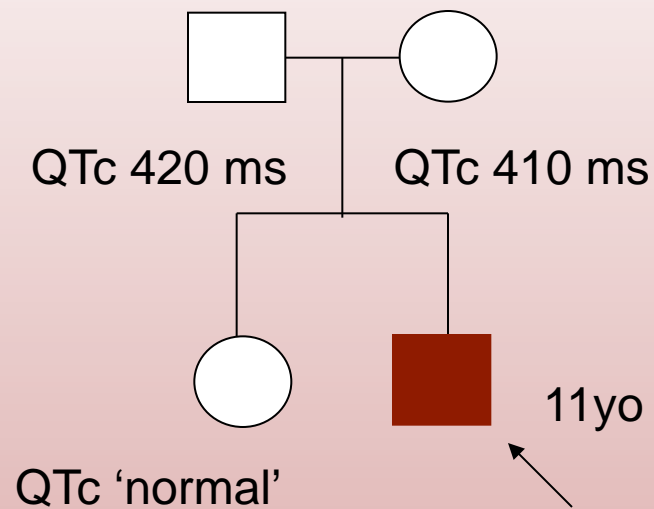
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	LQTS	ARVC	CPVT
Defect	Ion channels	Desmosomal proteins	Ca channel, Ca handling
Autopsy	Normal	Diagnostic	Normal
Triggers	Exercise (LQT1,2) Stress, noise (LQT2) Sleep/rest (LQT3,2)	Exercise>rest	During or right after exercise Stress
At-risk group	Sex & age, QT length, genotype	Athletes 20-45yo	Males>females Children>adults
Clinical testing	ECG, exercise testing	ECG, SAECG, MRI, biopsy, EP study, holter...	Exercise testing
Genetic testing	~75%	~30-50%	~50-70%

A family in search of answers



11yo - syncope while running

- QTc 525 ms

- put on beta-blockers

13yo - recurrent syncope, on
beta-blockers

- ICD implanted

15yo - sequencing of 5 LQTS genes

- no mutation found

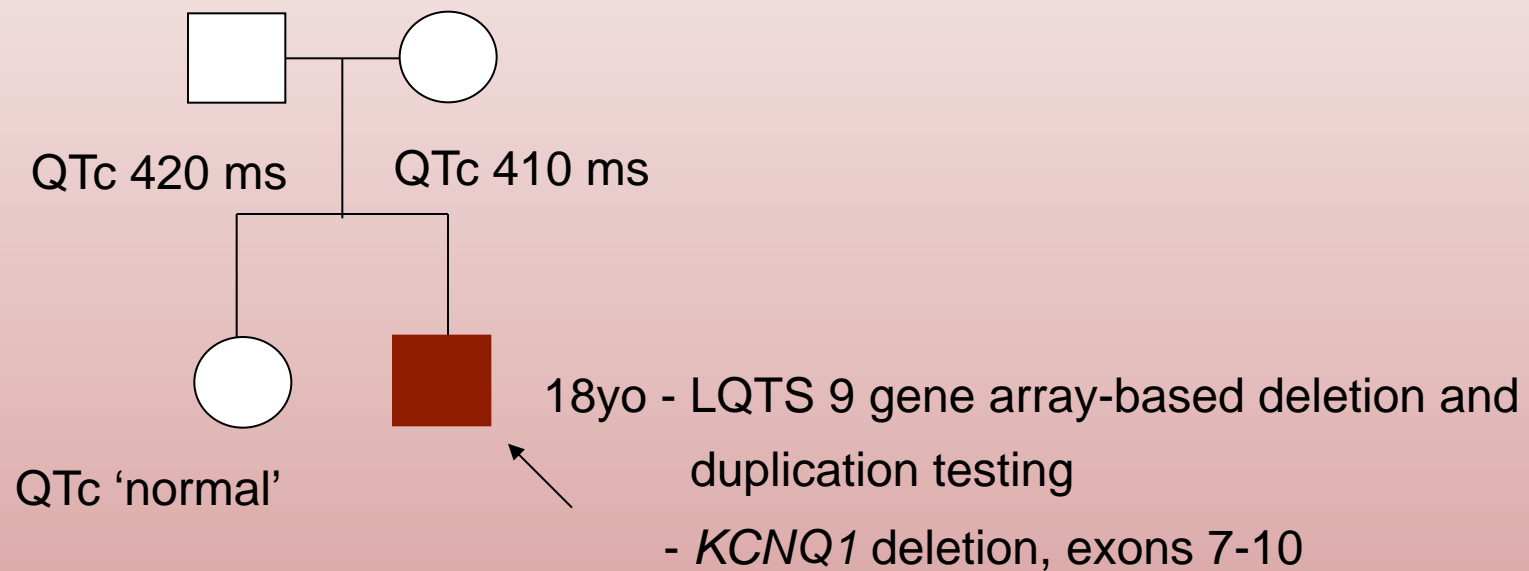
- (70% yield)

Identification of large gene deletions and duplications in *KCNQ1* and *KCNH2* in patients with long QT syndrome

Carey-Anne Eddy, BSc (Hons), MSc (Med),*[‡] Judith M. MacCormick, MBChB,*[†]
Seo-Kyung Chung, BSc (Hons),*[¶] Jackie R. Crawford, NZCS,* Donald R. Love, PhD, FRCPath,*[§]
Mark I. Rees, BSc (Hons), PhD,*^{¶¶} Jonathan R. Skinner, MB ChB, FRACP, FRCPCH, MD,*[†]
Andrew N. Shelling, BPhEd, BSc (Hons), PhD*[‡] (Heart Rhythm 2008;5:1275–1281)

- n=26 LQTS patients, normal sequencing
- MLPA, RT-PCR - select exons - *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*
- 11.5% (3/26) had deletions or duplications
 - *KCNQ1* deletion of exons 6-14; 11yo male, QTc 580 ms
 - *KCNH2* deletion of exons 6-14; 22yo female, QTc 560 ms, family history of SCD in sister
 - *KCNH2* duplication of exons 9-14; 12yo male, QTc 550 ms, family history of SCD in mother
- Adds 2-3% to overall yield of LQTS testing

A family in search of answers



A New Diagnostic Test for Arrhythmogenic Right Ventricular Cardiomyopathy

Angeliki Asimaki, Ph.D., Harikrishna Tandri, M.D., Hayden Huang, Ph.D., Marc K. Halushka, M.D., Ph.D., Shiva Gautam, Ph.D., Cristina Basso, M.D., Ph.D., Gaetano Thiene, M.D., Adalena Tsatsopoulou, M.D., Nikos Protonotarios, M.D., William J. McKenna, M.D., D.Sc., Hugh Calkins, M.D., and Jeffrey E. Saffitz, M.D., Ph.D.

- Immunohistochemistry - desmosomal proteins
- Plakoglobin signal:
 - reduced in 11/11 ARVC myocardial samples
 - Maintained in 25/25 control myocardial samples (10 normal, 5 HCM, 5 DCM, 5 ischemic CM)
- Blinded analysis:
 - Sensitivity: 91%
 - Specificity: 82%
 - PPV: 83%
 - NPV: 90%

N Engl J Med 2009;360:1075-84.

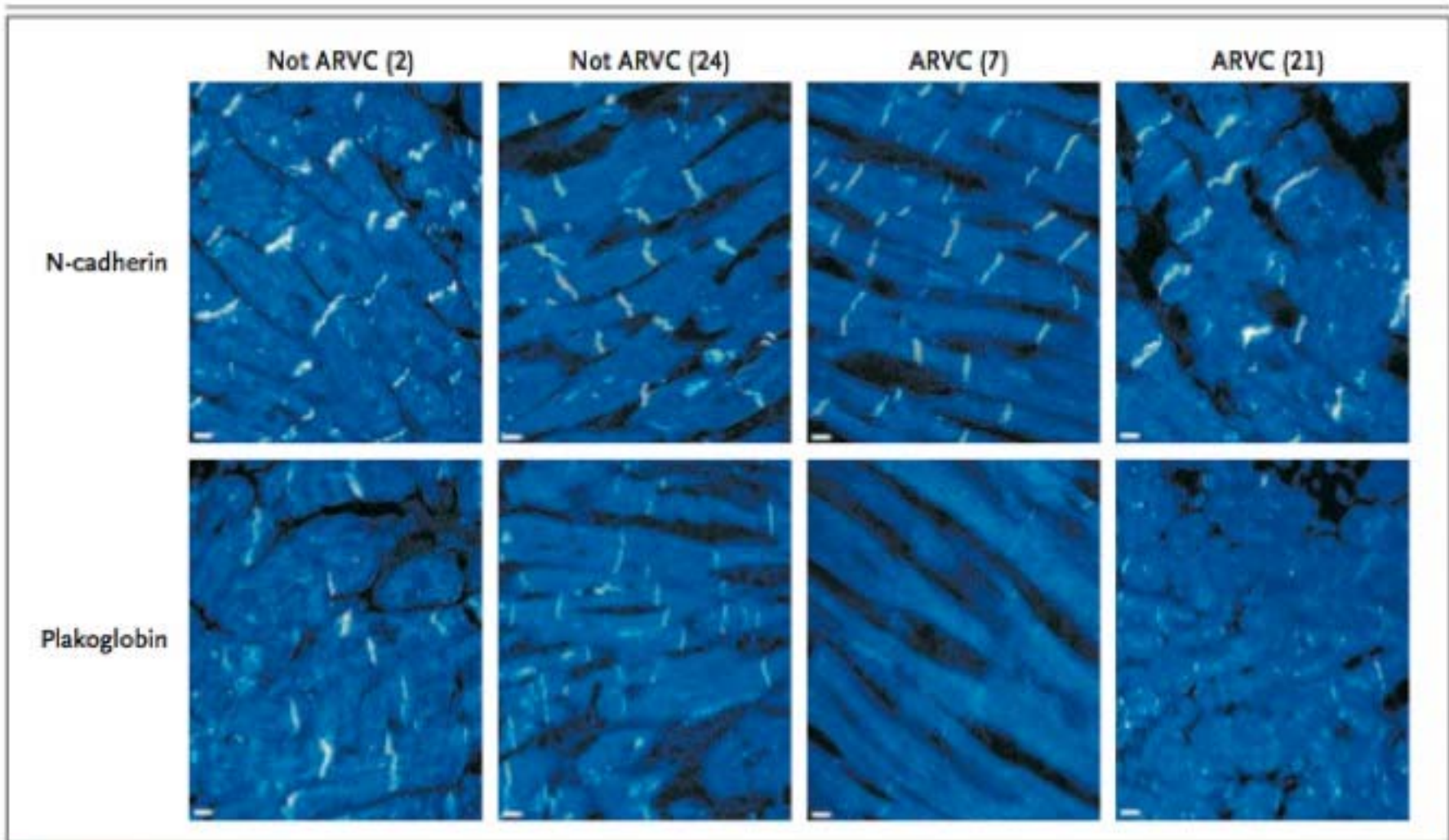


Figure 3. Immunofluorescence Images of Endomyocardial-Biopsy Samples from Two Subjects with ARVC and Two Subjects without ARVC.

N Engl J Med 2009;360:1075-84.

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

Meiso Hayashi, MD; Isabelle Denjoy, MD; Fabrice Extramiana, MD, PhD; Alice Maltret, MD; Nathalie Roux Buisson, MD; Jean-Marc Lupoglazoff, MD, PhD; Didier Klug, MD; Miyuki Hayashi, MD; Seiji Takatsuki, MD; Elisabeth Villain, MD; Joël Kamblock, MD; Anne Messali, MD; Pascale Guicheney, PhD; Joël Lunardi, MD, PhD; Antoine Leenhardt, MD

(Circulation. 2009;119:2426-2434.)

n=50 probands, 51 affected relatives

Follow-up = 7.9y

Associated with increased risk of cardiac events:

- Absence of beta-blockers
- History aborted cardiac arrest
- Younger age at diagnosis

Not associated risk of cardiac events:

- Syncopal history
- Proband vs. relative, symptomatic vs. asymptomatic, exercise test

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Relatives:

- Sensitivity of exercise stress test in asymptomatic relatives: 58%
- Asymptomatic mutation carriers with normal exercise stress tests - 2/17 had cardiac events
- No difference in event rate - probands vs. relatives
- Authors recommend *all* mutation carriers be prescribed beta-blockers

Genetic testing yield:

- *RYR2* 70% (57/105 exons)
- *CASQ2* 7% (11/11 exons)

Questions?