Genetics in Cardiology

Prof Chris Semsarian MBBS PhD MPH

University of Sydney, Australia

@CSHeartResearch

THE UNIVERSITY OF SYDNEY

RPA

Centenary Institute life saving research
Cancer. Inflammation. Cardiovascular.

Korean Heart Rhythm Society
COI Disclosure

Prof Chris Semsarian:

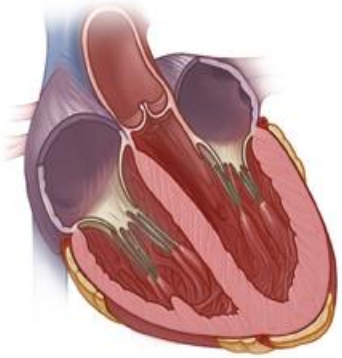
The authors have **no** financial conflicts of interest to disclose concerning the presentation

KHRS 2019

Inherited Cardiovascular Disease

Cardiomyopathy
HCM, DCM, RCM, ARVC, LVNC

Arrhythmia
e.g. LQTS, CPVT, Brugada, SQT



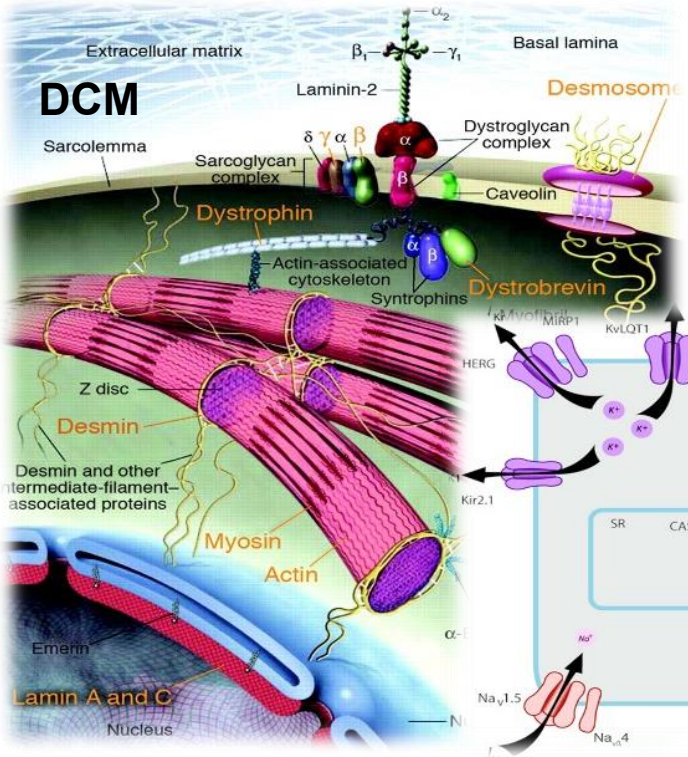
Vascular
e.g. Marfan, Ehler-Danlos IV

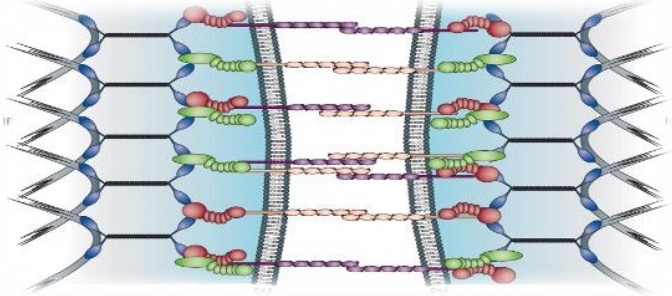
Metabolic
e.g. FH, homocystinuria

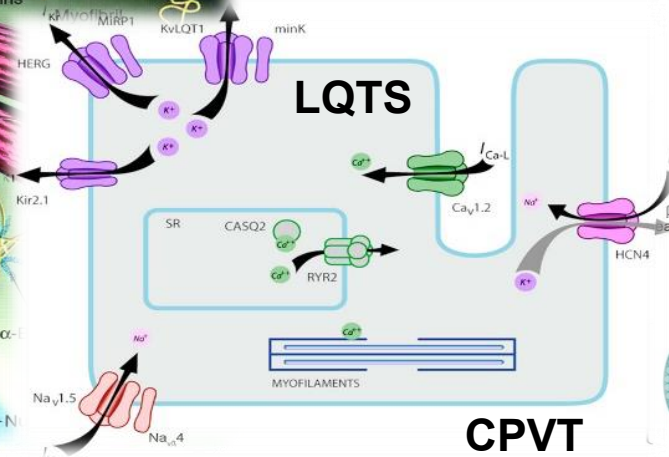
Congenital
e.g. ASD, TOF, myxomas

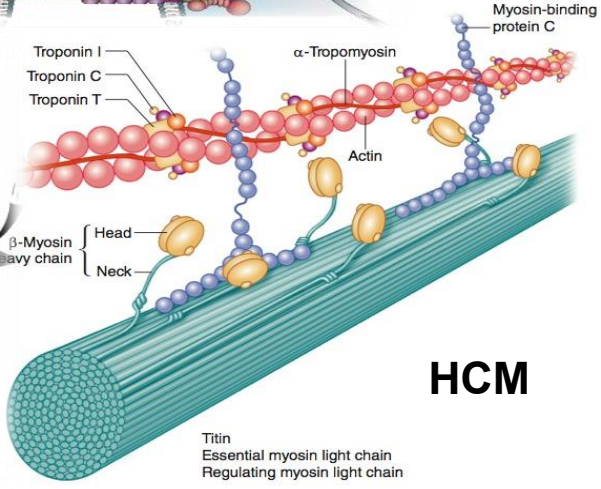
Genetics in Cardiology in 2023

Precise Genetic Diagnosis of Cardiac Disease

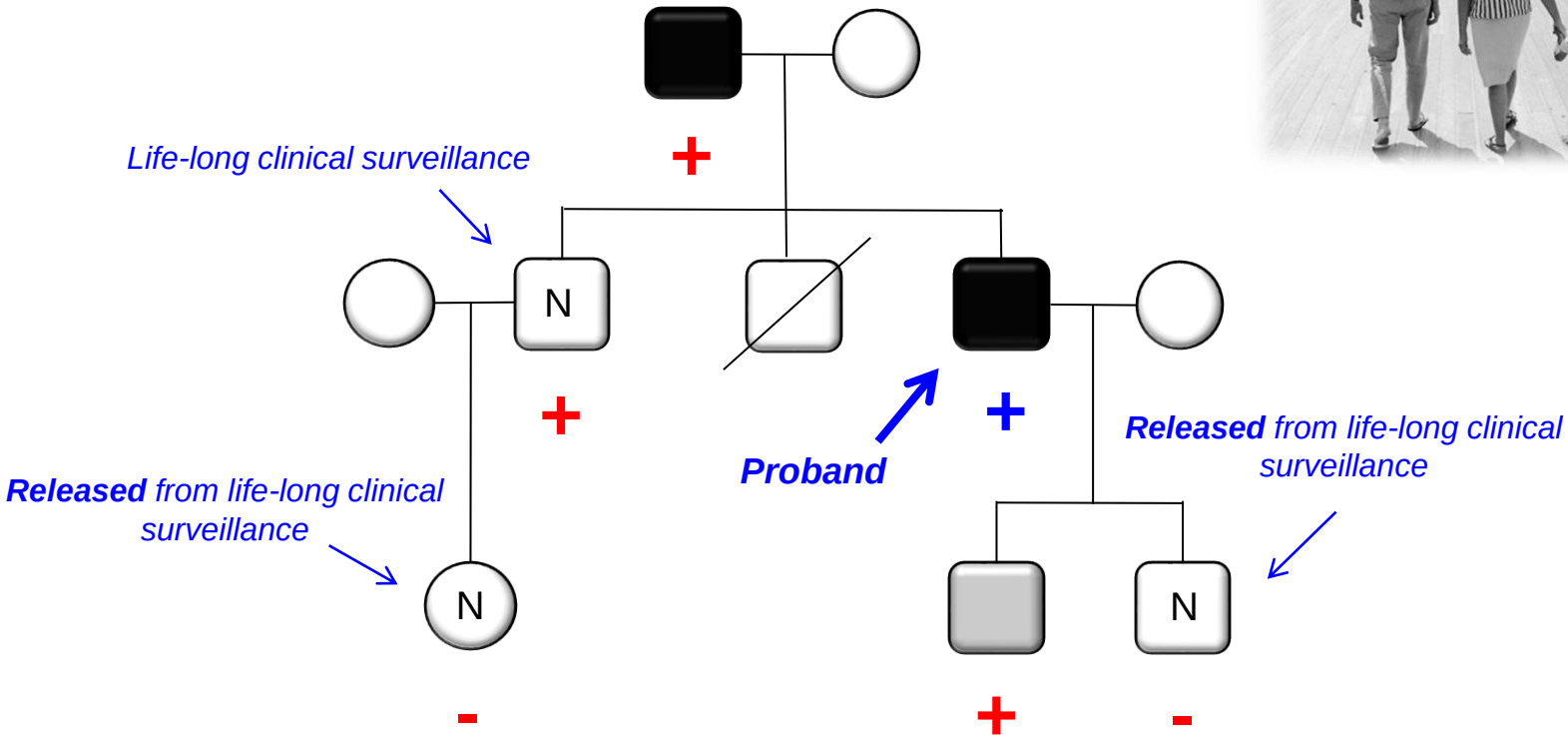




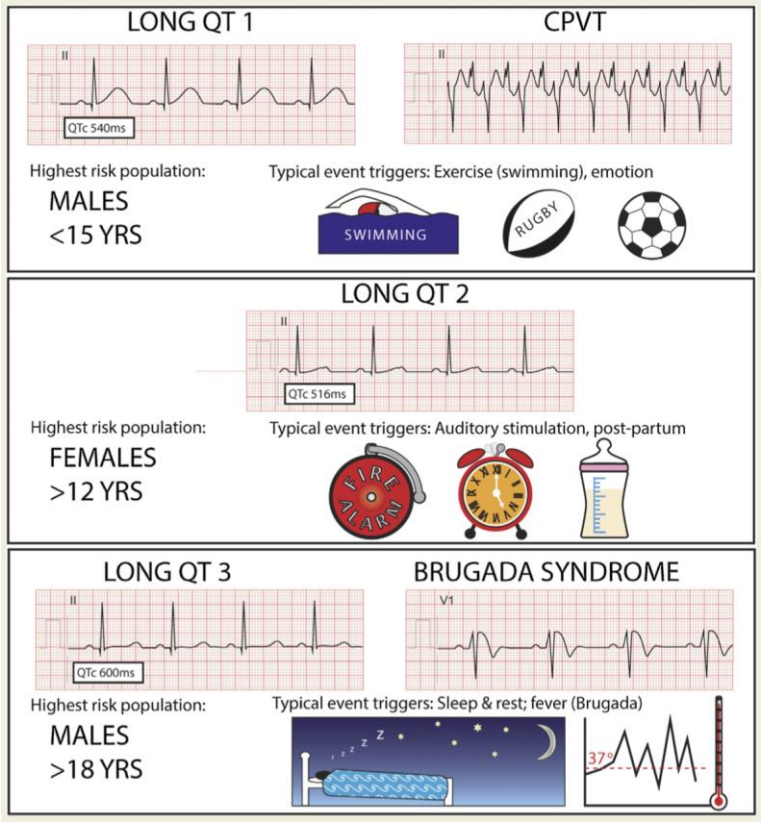




Predictive Genetic Testing in Families



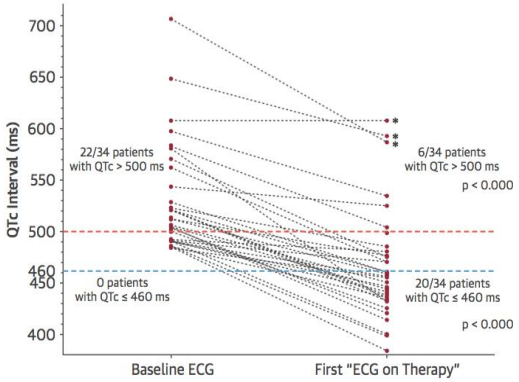
Genotype Guiding Therapy in Long QT Syndrome

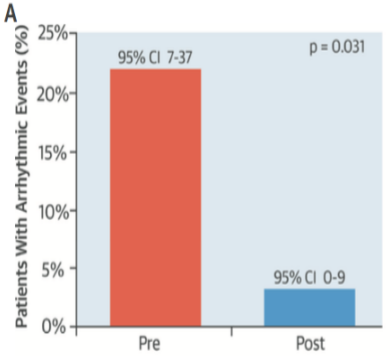


JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER
VOL. 67, NO. 9, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.12.033

Gene-Specific Therapy With Mexiletine Reduces Arrhythmic Events in Patients With Long QT Syndrome Type 3

Andrea Mazzanti, MD,[a] Riccardo Maragna, BS,[a] Alessandro Faragli, MD,[a] Nicola Monteforte, MD,[a] Raffaella Bloise, MD,[a] Mirella Memmi, PhD,[a] Valeria Novelli, PhD,[a] Paola Baiardi, PhD,[a] Vincenzo Bagnardi, PhD,[b] Susan P. Etheridge, MD,[c] Carlo Napolitano, MD, PhD,[a] Silvia G. Priori, MD, PhD[a,d]





Heart Lung Circ,2019

KHRS 2023

Genotype Guiding Therapy in Long QT Syndrome

Circulation: Genomic and Precision Medicine

ORIGINAL ARTICLE

Suppression and Replacement Gene Therapy for *KCNH2*-Mediated Arrhythmias

Sahej Bains, BS; Wei Zhou, MD; Steven M. Dotzler, BA; Katherine Martinez; CS John Kim, PhD; David J. Tester, BS; Dan Ye, MD; Michael J. Ackerman, MD, PhD

BACKGROUND: *KCNH2*-mediated arrhythmia syndromes are caused by loss-of-function (type 2 long QT syndrome [LQT2]) or gain-of-function (type 1 short QT syndrome [SQT1]) pathogenic variants in the *KCNH2*-encoded $K_v11.1$ potassium channel, which is essential for the cardiac action potential.

METHODS: A dual-component "suppression-and-replacement" (SupRep) *KCNH2* gene therapy was created by cloning into a single construct a custom-designed *KCNH2* short hairpin RNA with ~80% knockdown (suppression) and a "short hairpin RNA-immune" *KCNH2* cDNA (replacement). Induced pluripotent stem cell-derived cardiomyocytes and their CRISPR-Cas9 variant-corrected isogenic control (IC) induced pluripotent stem cell-derived cardiomyocytes were made for 2 LQT2- (G604S, N633S) and 1 SQT1- (N588K) causative variants. All variant lines were treated with KCNH2-SupRep or non-targeting control short hairpin RNA (shCT). The action potential duration (APD) at 90% repolarization (APD_{90}) was measured using FluoVolt voltage dye.

RESULTS: KCNH2-SupRep achieved variant-independent rescue of both pathologic phenotypes. For LQT2-causative variants, treatment with KCNH2-SupRep resulted in shortening of the pathologically prolonged APD_{90} to near curative (IC-like) APD_{90} levels (G604S IC, 471±25 ms; N633S IC, 405±55 ms) compared with treatment with shCT (G604S: SupRep-treated, 452±76 ms versus shCT-treated, 550±41 ms; $P<0.0001$; N633S: SupRep-treated, 399±105 ms versus shCT-treated, 577±39 ms, $P<0.0001$). Conversely, for the SQT1-causative variant, N588K, treatment with KCNH2-SupRep resulted in therapeutic prolongation of the pathologically shortened APD_{90} (IC: 429±16 ms; SupRep-treated: 396±61 ms; shCT-treated: 274±12 ms).

CONCLUSIONS: We provide the first proof-of-principle gene therapy for correction of both LQT2 and SQT1. KCNH2-SupRep gene therapy successfully normalized the pathologic APD_{90}, thereby eliminating the pathognomonic feature of both LQT2 and SQT1.

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 1832–1836
doi:10.1093/eurheartj/ehz023

EHJ BRIEF COMMUNICATION
Arrhythmia/electrophysiology

From patient-specific induced pluripotent stem cells to clinical translation in long QT syndrome Type 2

Peter J. Schwartz[1,2]*, Massimiliano Gnecchi[3,4]*, Federica Dagradi[1], Silvia Castelletti[1], Gianfranco Parati[5,6], Carla Spazzolini[1], Luca Sala[2], and Lia Crotti[1,2,5,6]*

[1]Istituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmias of Genetic Origin, Via Pier Lombardo 22, 20135 Milan, Italy; [2]Istituto Auxologico Italiano, IRCCS, Laboratory of Cardiovascular Genetics, Via Zucchi 18, 20095 Cusano Milanino Italy; [3]Coronary Care Unit, Laboratory of Experimental Cardiology for Cell and Molecular Therapy, IRCCS Policlinico San Matteo Foundation, Viale Golgi 19, 27100 Pavia, Italy; [4]Department of Molecular Medicine, Unit of Cardiology, University of Pavia, Viale Golgi 19, 27100 Pavia, Italy; [5]Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Piazzale Brescia 20, 20149 Milan, Italy; and [6]Department of Medicine and Surgery, University of Milano-Bicocca, Via Cadore 48, 20900 Monza, Italy

Received 5 December 2018; revised 19 December 2018; editorial decision 15 January 2019; accepted 15 January 2019; online publish-ahead-of-print 6 February 2019

Aims Having shown that Lumacaftor rescued the hERG trafficking defect in the induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) of two LQT2 patients, we tested whether the commercial association Lumacaftor + Ivacaftor (LUM + IVA) could shorten the QTc in the same two patients.

Methods and results After hospital admission and 1 day of baseline recordings, half dose LUM + IVA was administered on Day 1, followed by full dose (LUM 800 mg + IVA 500 mg) for 7 days. A continuous 12-lead Holter ECG allowed a large number of blind QTc measurements. Lumacaftor + Ivacaftor shortened QTc significantly in both patients: in V6 from 551 ± 22 ms to 523 ± 35 ms in Patient 1 (Pt1) and from 472 ± 21 ms to 449 ± 20 ms in Patient 2 (Pt2); in DII from 562 ± 25 ms to 549 ± 35 ms in Pt1 and from 485 ± 32 ms to 452 ± 18 ms in Pt2. In both patients, the percentage of QTc values in the lower tertile increased strikingly: in V6 from 33% to 68% and from 33% to 76%; in DII from 33% to 50% and from 33% to 87%. In the wash-out period a rebound in QTc was observed. On treatment, both patients developed diarrhoea, Pt1 more than Pt2.

Conclusion This represents the first attempt to validate in patients the *in vitro* results of a drug repurposing strategy for cardiovascular disorders. Lumacaftor + Ivacaftor shortened significantly the QTc in the two LQT2 patients with a trafficking defect, largely confirming the findings in their iPSC-CMs but with smaller quantitative changes. The findings are encouraging but immediate translation into clinical practice, without validation in more patients, would be premature.

KHRS 2023

Sudden Cardiac Death in the Young

Died in front of his dad

Up-and-coming soccer star collapses on field

By EDITH BEVIN

Hamide. Picture: ACTION SNAPS

HE was tipped to be Australia's next international soccer star — but Ohmeer Hamide's family were yesterday struggling to understand why the 17-year-old collapsed and died during a game.

Fans, including Ohmeer's father, watched in horror as the talented Sydney United left-winger dropped to the ground at Edensor Park about 10 minutes into Saturday's game against Dulwich Hill.

Five ambulance crews were unable to revive the soccer player and he was pronounced dead from a suspected heart attack at Fairfield Hospital.

Ohmeer had shown no signs of serious illness or any hint of a heart condition.

His father Kahled Hamide yesterday told of his horror at watching his "best friend" dying in front of him.

"I saw him when he collapsed," Mr Hamide, who had encouraged his son to take up the game nine years ago, said.

"He took the ball and he ran and then we saw him collapse.

"The referee stopped the game and I ran on to the field — he couldn't breathe.

"We called the ambulance straight away. Five ambulances came but . . .

"Nobody believes what's happened. Still now I can't believe that he's dead."

Sydney United youth league co-ordinator Tibo Bacic said Ohmeer was due to travel to England and Ireland next month to be coached by some of the best trainers from top sides Liverpool, Chelsea, Charlton and Everton.

Bacic said Ohmeer's skill would also have made it very likely that he would have attracted the attention of UK talent scouts.

Ohmeer was picked up by Sydney United scouts three years ago while playing for a smaller club.

"It is a big loss to football in Australia to have such a talented young player taken away," Bacic said. "He had the drive and the potential to represent Australia. We were actually taking a couple of squads over to Ireland and England in September/October and he was going with them.

The Hamides' grief was intensified yesterday when they were told Ohmeer's body would not be released by Westmead Morgue in time to perform funeral rites that the Muslim faith dictates must be held within 24 hours of death.

Olympic swimming hopeful died from undiagnosed heart defect, inquest told

A teenage Olympic swimming hopeful died after suffering from a serious undiagnosed heart defect, an inquest has heard.

Chloe had competed in Olympic trials against Rebecca Adlington Photo: PA

Search for answers after Xav dies at 20

Xavier O'Grady, with his dad Patrick and his eldest sister Gabriella, 24 hours before he died.

ADELLA BEANI

THIS is the last photo taken of Xavier O'Grady – just 24 hours before the fit and healthy young man died at the half-marathon finish line.

The 20-year-old from Sydney had travelled to Melbourne in October with his family to compete in the race with his dad when he collapsed.

Within hours, Xavier – who was just two months shy of turning 21 – had died.

His distraught parents Patrick and Alison, along with their daughters Gabriella and Annaliese, are still struggling to make sense of the tragedy, five months on.

"The actual day was obviously very traumatic. I finished before Xavier and we saw him enter the Melbourne Cricket Ground and run down the home stretch and cross the line but we didn't see him after that," Mr O'Grady said.

"Eventually, when he didn't appear, I made my way to the medical tent where I was informed that there was a heart issue but they wouldn't let us see him at that point."

Xavier is one of the four young Australians aged between 15 and 35 who die each week from sudden cardiac death.

Royal Prince Alfred Hospital cardiologist Chris Semsarian, who has spent more than 20 years researching the phenomenon of fit young people, particularly men, dying suddenly, said often there are no warning signs. "In over 50 per cent of young sudden deaths, there is no warning sign. The first presentation of the condition is sudden death," Prof Semsarian said.

"The rest can have symptoms and the main one we investigate further is if a young person has a blackout fairly commonly.

"If I see blood and I faint, that's normal. If I'm standing in 40C temperatures for hours and hours outside that's normal.

"If I faint while driving, crossing the road or even when exercising or playing sports, that's abnormal. Other possible symptoms include minor chest pains and a family history with heart disease."

Prof Semsarian said there were a number of preventive strategies for young people at high risk of heart problems.

"Preventive strategies include things like modifying exercise like avoiding really high-level elite sports and also using drugs like beta-blockers to slow down the heart," he said.

"We can even put in devices in the chest called defibrillators which can sit under the chest wall and will monitor the heart rhythm and if it goes into a rhythm that could lead to sudden death, it detects it and delivers the shock."

The O'Gradys have set a campaign called Heartbeat for Xav to help Prof Semsarian and his team research the condition further.

They have already raised nearly $500,000.

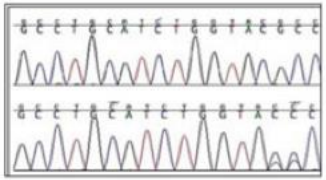
The family are encouraging people to participate in the Gold Coast marathon weekend on July 1-2 in honour of their son.

To find out more, visit centenary.org.au/heartbeat-for-xav

The Molecular Autopsy in Sudden Death

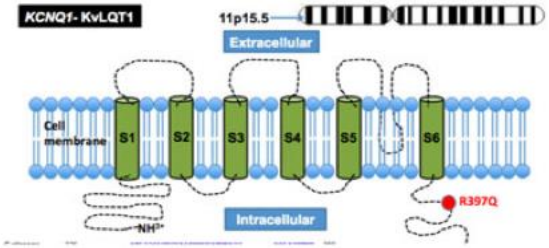
Postmortem blood

DNA extraction



Genetic analysis

- Sanger sequencing
- Cardiac gene panels
- Whole exome / genomes



Pathogenic (disease-causing) mutation

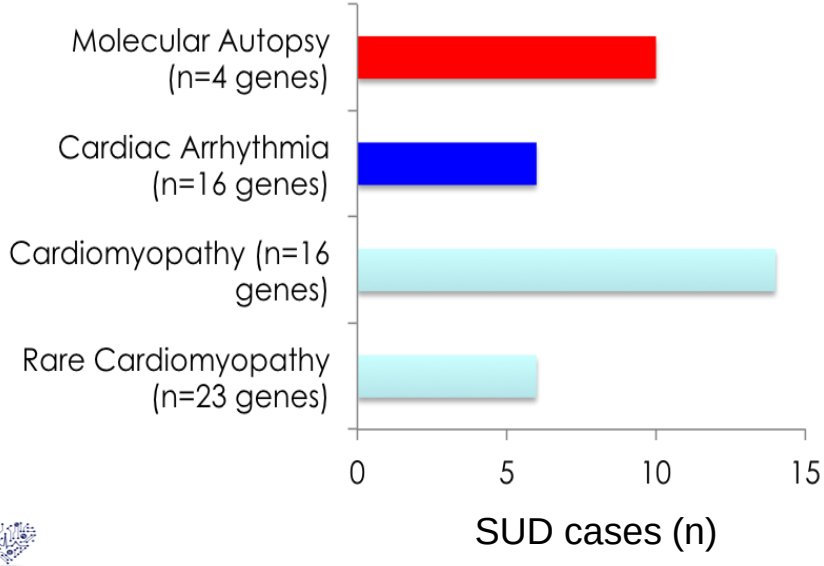
Genetic screening:

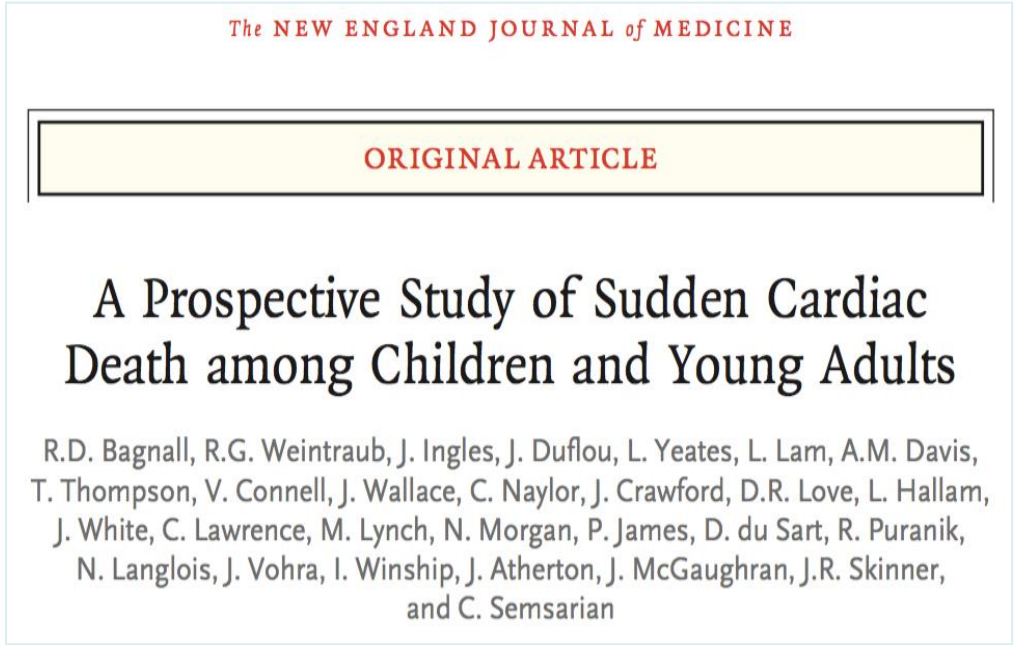
- Cardiac gene panels
- Exomes
- Genomes

Semsarian, et al. Eur Heart J, 2015

Genetic Causes of Sudden Cardiac Death

- 15-20% genetic cause established
- Consistent with USA, Europe, Asia
- Mainly LQTS, CPVT, BrS etc




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Prospective Study of Sudden Cardiac Death among Children and Young Adults

R.D. Bagnall, R.G. Weintraub, J. Ingles, J. Duflou, L. Yeates, L. Lam, A.M. Davis, T. Thompson, V. Connell, J. Wallace, C. Naylor, J. Crawford, D.R. Love, L. Hallam, J. White, C. Lawrence, M. Lynch, N. Morgan, P. James, D. du Sart, R. Puranik, N. Langlois, J. Vohra, I. Winship, J. Atherton, J. McGaughran, J.R. Skinner, and C. Semsarian

Bagnall et al, N Engl J Med, 2016

‘Concealed Cardiomyopathies’ in Sudden Death

ORIGINAL INVESTIGATIONS

Concealed Cardiomyopathy in Autopsy-Inconclusive Cases of Sudden Cardiac Death and Implications for Families

Julia C. Isbister, MBBS,[a,b,c] Natalie Nowak, BAnVetBioSc,[a,c] Laura Yeates, BSc, GradDipGenCouns,[a,b,c,d,e] Emma S. Singer, BMedSc,[a,b] Raymond W. Sy, MBBS, PhD,[b,c] Jodie Ingles, PhD, MPH,[b,c,d,e] Hariharan Raju, MBChB, PhD,[b,f] Richard D. Bagnall, PhD,[a,b] Christopher Semsarian, MBBS, PhD, MPH[a,b,c]

ABSTRACT

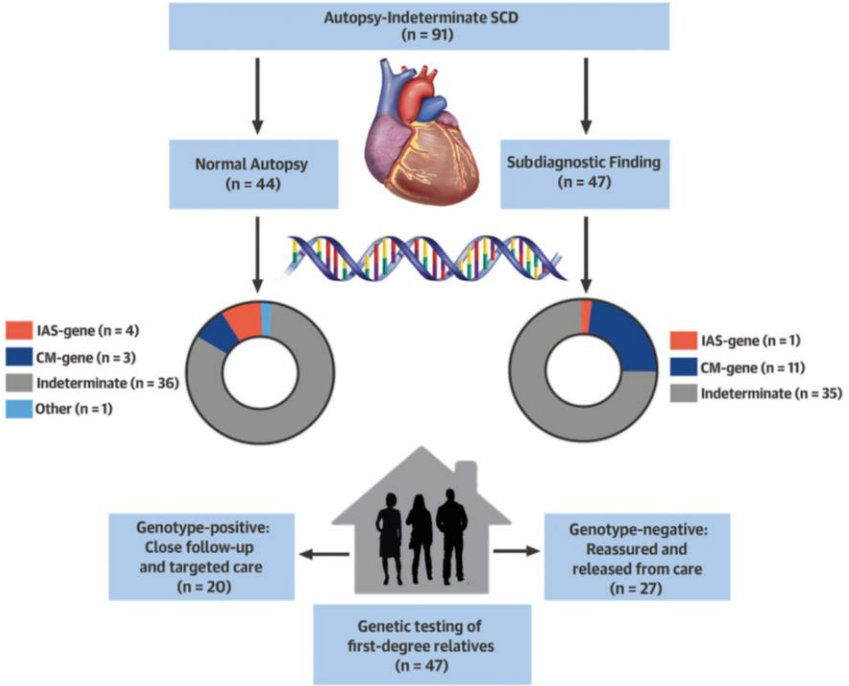
BACKGROUND Genetic testing following sudden cardiac death (SCD) is currently guided by autopsy findings, despite the inherent challenges of autopsy examination and mounting evidence that malignant arrhythmia may occur before structural changes in inherited cardiomyopathy, so-called “concealed cardiomyopathy” (CCM).

OBJECTIVES The authors sought to identify the spectrum of genes implicated in autopsy-inconclusive SCD and describe the impact of identifying CCM on the ongoing care of SCD families.

METHODS Using a standardized framework for adjudication, autopsy-inconclusive SCD cases were identified as having a structurally normal heart or subdiagnostic findings of uncertain significance on autopsy. Genetic variants were classified for pathogenicity using the American College of Medical Genetics and Genomics guidelines. Family follow-up was performed where possible.

RESULTS Twenty disease-causing variants were identified among 91 autopsy-inconclusive SCD cases (mean age 25.4 ± 10.7 years) with a similar rate regardless of the presence or absence of subdiagnostic findings (25.5% vs 18.2%;

CENTRAL ILLUSTRATION Identification of Concealed Cardiomyopathy Following Autopsy-Inconclusive SCD Guides Management of Families



Isbister JC, et al. J Am Coll Cardiol. 2022;80(22):2057-2068.

‘Concealed Cardiomyopathies’ in SCA Survivors

Hidden cause of cardiac arrests uncovered in perfectly healthy hearts

By Kate Aubusson
October 19, 2020 – 12.00am

Save Share A A A

6 View all comments

Hidden in the genes of one in four young people who survive an inexplicable sudden cardiac arrest may be the trigger for their mysterious brush with death.

Almost a quarter (22 per cent) of 36 cardiac arrest survivors had genetic mutations that explained why their seemingly healthy heart had malfunctioned, a new study by researchers at the University of Sydney's Centenary Institute and Royal Prince Alfred Hospital found.

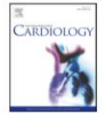
James Medway is a champion rower who had a near sudden death cardiac arrest at the age of 27 in 2019. LOUISE

DSP c.7641C>G
(p.Tyr2547Stop)

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



“Concealed cardiomyopathy” as a cause of previously unexplained sudden cardiac arrest

Julia C. Isbister [a,b,c,1], Natalie Nowak [a,1], Alexandra Butters [a,b,1], Laura Yeates [a,b,c,1], Belinda Gray [b,c,1], Raymond W. Sy [b,c,1], Jodie Ingles [a,b,c,1], Richard D. Bagnall [b,c,1], Christopher Semsarian [a,b,c,*,1]

[a] Agnes Ginges Centre for Molecular Cardiology Centenary Institute, The University of Sydney, Sydney, Australia
[b] Faculty of Medicine and Heath, The University of Sydney, Sydney, Australia
[c] Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia

ARTICLE INFO

Article history:
Received 5 September 2020
Accepted 9 September 2020
Available online xxxx

Keywords:
Sudden cardiac arrest
Clinically-idiopathic
Genetic testing

ABSTRACT

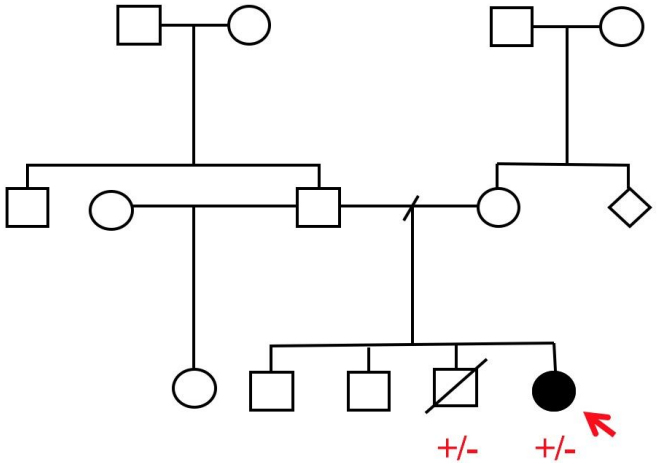
Background: Genetic heart disease is a common cause of sudden cardiac arrest (SCA) in the young and those without an ischaemic precipitant. Identifying a cause of SCA in these patients allows for targeted care and family screening. Current guidelines recommend limited, phenotype-guided genetic testing in SCA survivors where a specific genetic condition is suspected and genetic testing is not recommended in clinically-idiopathic SCA survivors.
Objective: To investigate the diagnostic utility of broad, multi-phenotype genetic testing in clinically-idiopathic SCA survivors.
Methods: Clinically-idiopathic SCA survivors underwent analysis of genes known to be associated with either car-

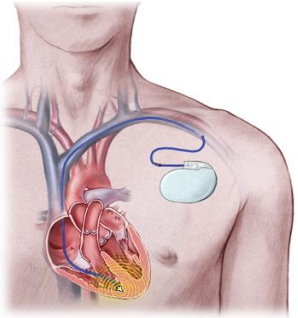
19% of clinically idiopathic SCA survivors had disease-causing variant in cardiomyopathy genes (*ACTN2*, *DES*, *DSP*, *MYBPC3*, *MYH7*, *PKP2*)

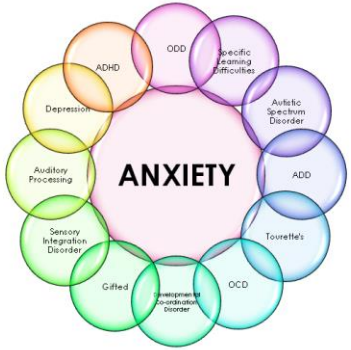
Isbister et al. Int J Cardiol, 2021

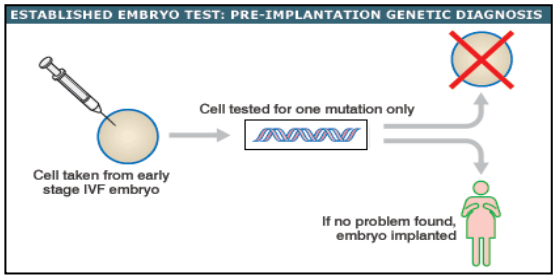
Impact of Genetic Testing in Sudden Cardiac Death

- Establishing a cause of death
- A level of closure for the family
- Screening the family & SCD prevention
- Reproductive decisions in future



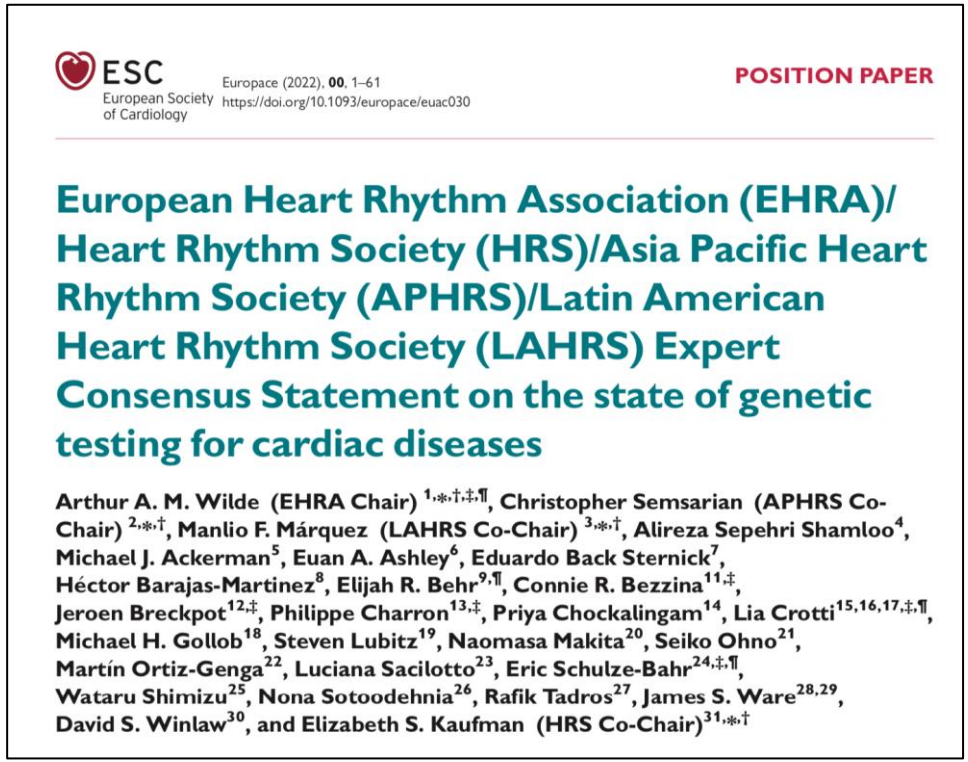






KHRS 2023

Cardiac Genetic Testing Guidelines



ESC European Society of Cardiology

Europace (2022), **00**, 1–61
https://doi.org/10.1093/europace/euac030

POSITION PAPER

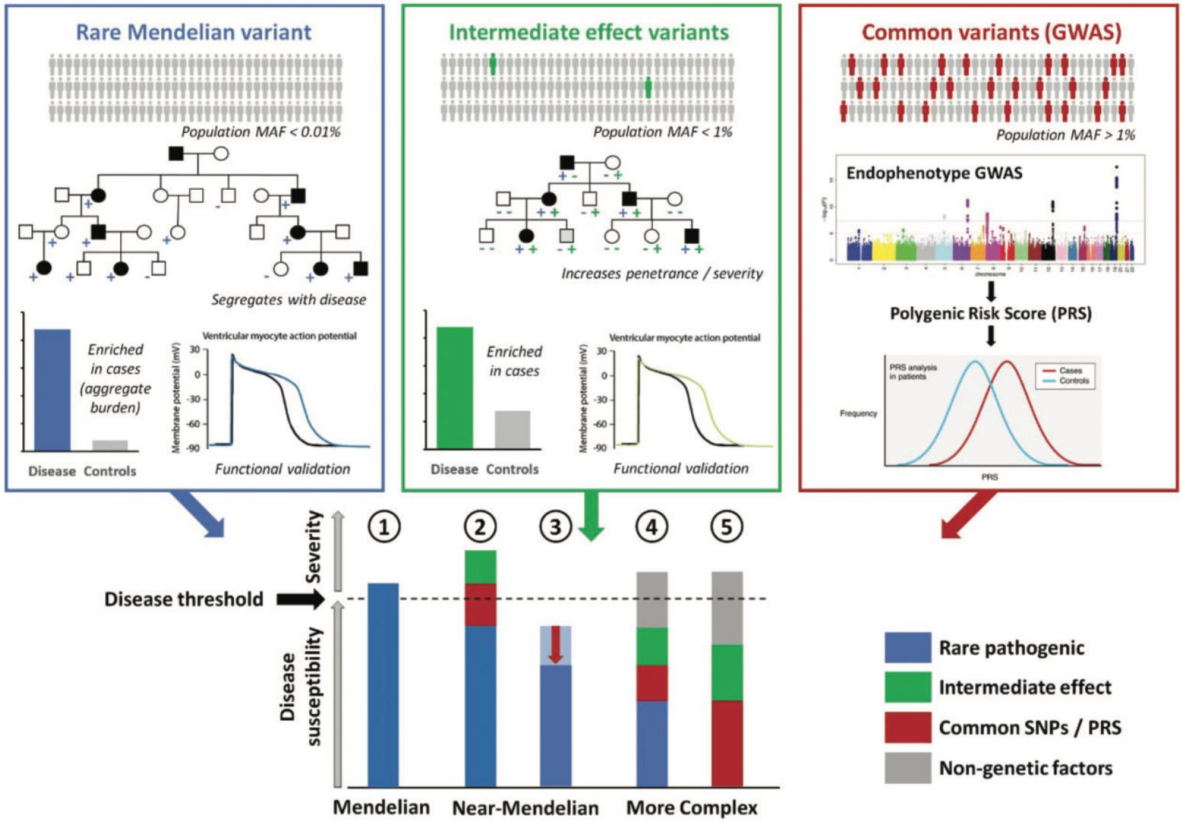
European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

Arthur A. M. Wilde (EHRA Chair)[1,*,†,‡,¶], Christopher Semsarian (APHRS Co-Chair)[2,*,†], Manlio F. Márquez (LAHRS Co-Chair)[3,*,†], Alireza Sepehri Shamloo[4], Michael J. Ackerman[5], Euan A. Ashley[6], Eduardo Back Sternick[7], Héctor Barajas-Martinez[8], Elijah R. Behr[9,¶], Connie R. Bezzina[11,‡], Jeroen Breckpot[12,‡], Philippe Charron[13,‡], Priya Chockalingam[14], Lia Crotti[15,16,17,‡,¶], Michael H. Gollob[18], Steven Lubitz[19], Naomasa Makita[20], Seiko Ohno[21], Martín Ortiz-Genga[22], Luciana Sacilotto[23], Eric Schulze-Bahr[24,‡,¶], Wataru Shimizu[25], Nona Sotoodehnia[26], Rafik Tadros[27], James S. Ware[28,29], David S. Winlaw[30], and Elizabeth S. Kaufman (HRS Co-Chair)[31,*,†]

Wilde, Semsarian et al, Europace, Heart Rhythm, 2022

Disease	Diagnostic	Prognostic	Therapeutic
Arrhythmia syndromes			
Long QT syndrome	+++	+++	+++
CPVT	+++	+	+
Brugada syndrome	+	+	+
Progressive cardiac conduction disease	+	+	+
Short QT syndrome	+	+	+
Sinus node disease	–	+	–
Atrial fibrillation	–	+	–
Early repolarization syndrome	–	–	–
Cardiomyopathies			
Hypertrophic cardiomyopathy	+++	++	++
Dilated cardiomyopathy	++	+++	++
Arrhythmogenic cardiomyopathy	+++	++	++
Left ventricular non-compaction	+	+	–
Restrictive cardiomyopathy	+	+	+
Congenital heart disease			
Syndromic CHD	+++	+	–
Non-syndromic CHD	+	–	–
Familial CHD	++	–	–

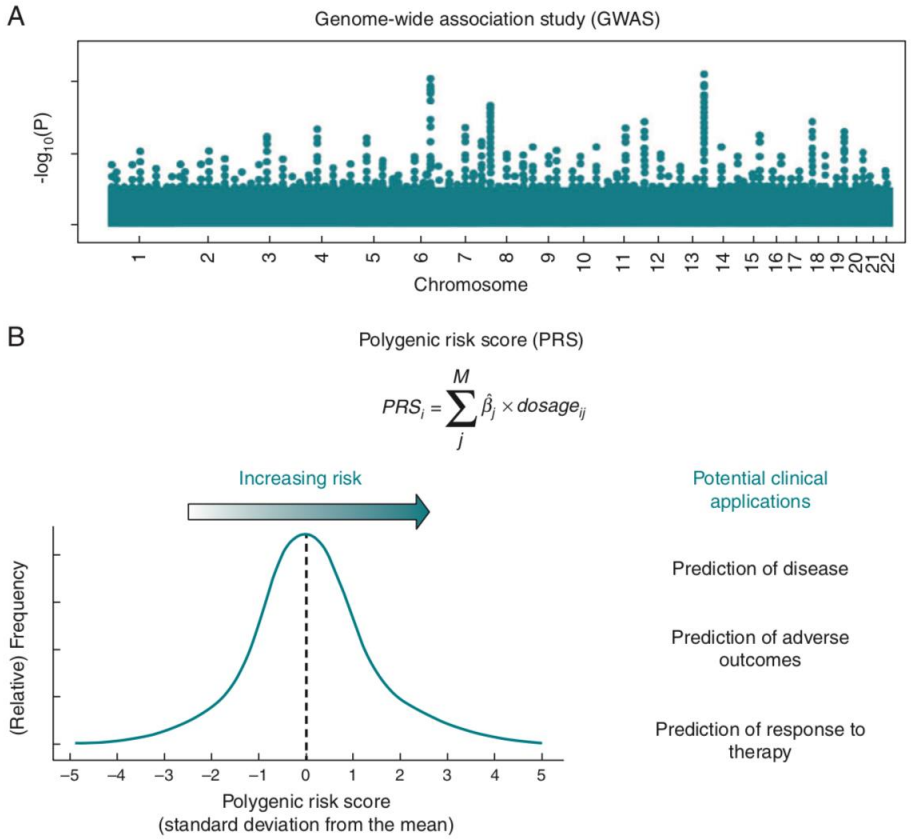
Modes of Inheritance and Genetic Mechanisms



KHRS 2023

Wilde, Semsarian et al, Europace, Heart Rhythm, 2022

Emergence of Polygenic Risk Scores



- CAD
- LQTS
- HCM
- Others

KHRS 2023

Wilde, Semsarian et al, Europace, Heart Rhythm, 2022

(Hopefully) Useful Flow Diagrams for Genetic Testing

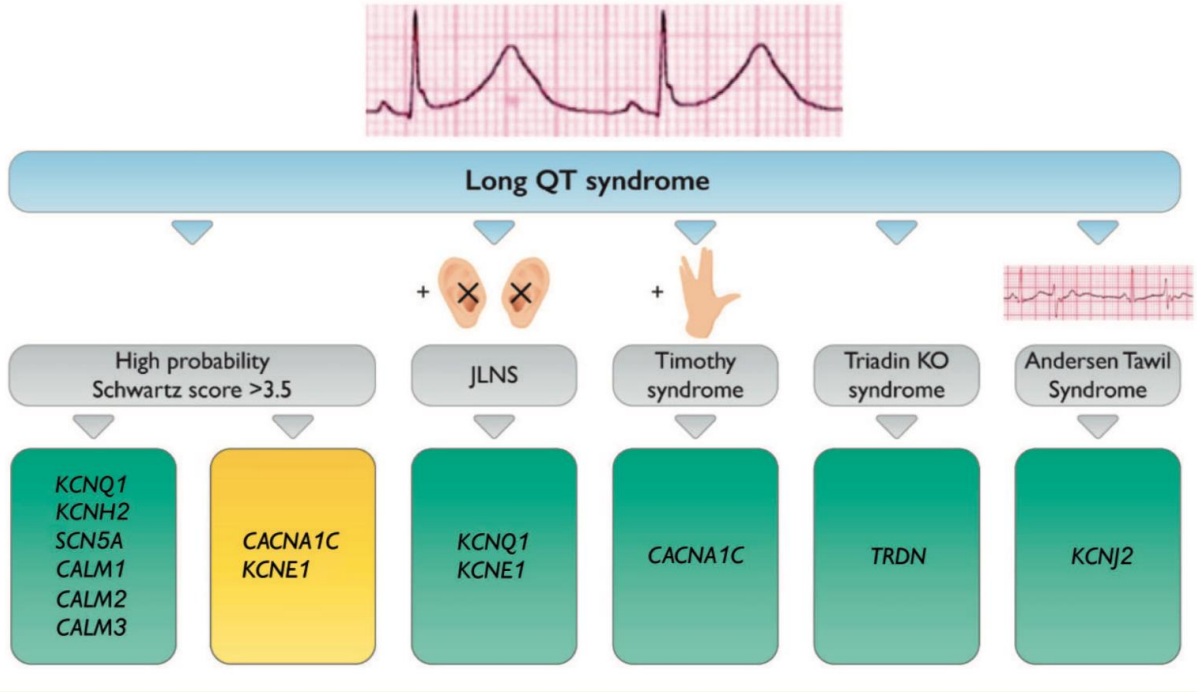


Figure 3 Clinical algorithm for genetic testing and family screening in long-QT syndrome.

KHRS 2023

Wilde, Semsarian et al, Europace, Heart Rhythm, 2022

Useful Flow Diagrams for Genetic Testing

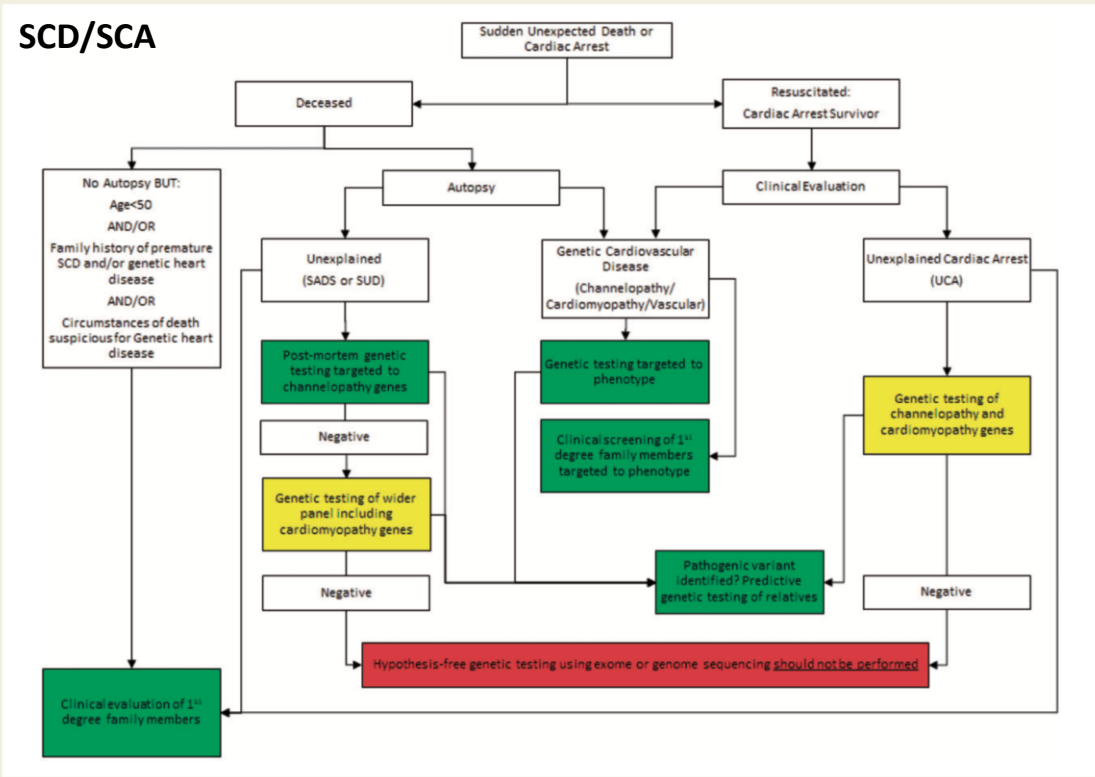


Figure 6 Flowchart of the work up of a sudden cardiac death or non-fatal cardiac arrest.

KHRS 2023

Wilde, Semsarian et al, Europace, Heart Rhythm, 2022

Take Home Messages

Cardiac genetic testing is leading to more precise **diagnosis, therapy and prognosis** in patients and families

The molecular autopsy can define the cause of sudden death in the young

Defining a precise genetic cause can facilitate **family screening** and inform **reproductive decisions**

Exciting times ahead in terms of **polygenic mechanisms** and risk scores, **new gene discoveries**, and development of **gene-based therapies**

Acknowledgements

Agnes Ginges Centre for Molecular Cardiology
University of Sydney, RPAH, Centenary Institute

Collaborators

National

International

Funding Bodies

NSW GOVERNMENT Health

Heart Foundation

Australian Genomics Health Alliance

NHMRC

THE UNIVERSITY OF SYDNEY

RPA

Centenary Institute research for life

follow us on twitter

@CSHeartResearch

Medical Research Future Fund

HeartKids

KHRS 2023

Thank you

@CSHeartResearch

chrissemsarian.com