Genetic Testing in Sudden Cardiac Death

Current and Future

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No Disclosures
Sudden Cardiac Death in the Young

Died in front of his dad

By EDITH KEVIN

EA was tipped to be Australia's next international soccer star — until Khaled Hamadi's family were yesterday told of his horror at watching his "best friend" dying in front of him.

"I saw him when he collapsed," Mr Hamadi, 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." "I stood and the game was on the field — he couldn't breathe. We called the ambulance straight away. Five ambulances came but... Nobody believed what's happened," he said.

Nobody believed that he's dead." Sydney United youth coach and former national team manager Barry O'Brien was due to travel to Melbourne and spend seven months training at the club's newest director of youth development. He was actually taking a couple of squads over to Ireland and England in September-October and was going with them. The Hamadi family was in crisis yesterday when they were told O'Brien's last words had been released by Westmead Hospital, where he was treated. They were shocked to hear that the Mihicz family, who had been held in a coma since birth, had died.

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.

Supporting Vinni's Sport in Talent 100

Traffic

Olah had competed in Olympic trials against Rebecca Adlington. Photo: PA

Sudden Cardiac Death in the Young

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Causes of Sudden Cardiac Death in Young

**Structural**
- Cardiomyopathies
- Myocarditis
- Coronary artery disease
- ARVC
- Aortic dissection
- Coronary anomalies

**Arrhythmogenic**
- Long QT syndrome
- Brugada syndrome
- CPVT
- “Idiopathic VF”
- Early Repolarisation
- Others, e.g. SQT, SIDS

**ABNORMAL POSTMORTEM**

**NEGATIVE POSTMORTEM**
What is the Role of Genetics in Sudden Death?

- DCM
- HCM
- ARVC
- LQTS
- CPVT
Postmortem Evaluation in SCD and Tissue for DNA

Needs to be comprehensive:

- Pre-morbid details
- Any clinical history
- Liaison with family (early)
- Comprehensive forensic examination
- Suitable tissue sample for DNA analysis, e.g. blood

Key points of best-practice guidelines on postmortem investigation of sudden death of a young person*

- A full postmortem examination should be completed in all cases of sudden unexpected death in young people (0–40 years).
- The investigation, ideally led by a pathologist, involves a team approach, including as a minimum:
  - A person designated to liaise with the family;
  - Specialist cardiology involvement with the family when non-cardiac causes are excluded; and
  - Laboratories with molecular genetics, toxicology and metabolic expertise.
- A detailed antecedent clinical history must be obtained.
- A detailed and relevant family history must be obtained.
- Liaison with the family should be established early and be ongoing until a cause of death is ascertained.
- Skilled macroscopic and microscopic examination of the organs is required, particularly of the heart (especially right ventricular muscle), and the brain. This may require some specimens to be examined by other specialists.
- Adequate histological material must be obtained for review or, if necessary, referral.

* Tissue or blood suitable for DNA extraction must be obtained (paraffin-embedded tissue blocks are not suitable).
SCD in the Young
SCD in the Young: Australia & NZ

- All SCD aged 1-35 yrs
- All Australia and NZ
- 2010-2012 prospective and population-based
- Comprehensive autopsy
- \( n = 490 \) SCD cases

Overall Incidence = 1.3 per 100,000
“Molecular Autopsy” in Sudden Death Cases

4-gene screen in SUD:
- KCNQ1 (LQT1)
- KCNH2 (LQT2)
- SCN5A (LQT3, BrS)
- RYR2 (CPVT)

Genetic Analysis in Sudden Cardiac Death

**Molecular Autopsy (4 genes)**

**Exome/Genome Sequencing (~22,000 genes)**

**Cardiac Gene Panels (50-100 genes)**
Genetic Analysis Summary in Unexplained SCD Cases

- N=113 unexplained cases
- Minimum 59 cardiac genes
- Mainly inherited arrhythmia and cardiomyopathy genes
- 27% (31/113) clinically relevant cardiac gene variant identified
- Consistent with USA, Europe, Asia
A Prospective Study of Sudden Cardiac Death among Children and Young Adults


**Genetics of Unexplained SCD cases**

- MYH7: Arg663His
- PKP2: Glu85Metfs*26
- MYBPC3: Leu994Phe
- MYBPC3: Arg335Cys
- ACTC1: Ala321Thr

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Value of Genetic Testing in Sudden Death

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

Sudden Death Cases (Postmortem in 0-40 yo)

Cardiac Causes (includes “arrhythmia”)

“Normal” Postmortem (SUD ~ 40%)

Definite Cause (50-55%)

Inherited Cause or SUD or Non-specific

Non-specific Findings (e.g. “fibrosis” ~ 5-10%)

Non-Cardiac Causes (e.g. pulm embolus)

Comprehensive Postmortem

Molecular Autopsy Genetic Analysis

Clinical +/- Genetic Screening (initially all 1st-degree relatives)

Genetics in SCD: The Future
Defining the Cause of SCD: the “Molecular Autopsy”

- Sudden unexplained death
- **Sudden explained cardiac death**, e.g. HCM, ARVC
- **Sudden unexpected death in epilepsy** (Bagnall et al. Ann Neurol, 2016)


Is Blood the Only DNA Source in SCD Cases?

- Whole exome sequencing of DNA from paraffin-embedded tissue (Bagnall et al. Genet Med, 2017)

1. Postmortem investigation
2. Blood or tissue collection
3. DNA extraction
4. Massively parallel sequencing
5. Genetic analysis
6. Family screening

Exome sequencing–based molecular autopsy of formalin-fixed paraffin-embedded tissue after sudden death

Richard D. Bagnall, PhD, Jodie Ingle, MPH, PhD, Laura Yeates, BSc, Samuel F. Berkovic, MD, and Christopher Semsarian, MBBS, PhD.
Can Whole Genome Sequencing Increase Diagnosis Rate?

- WGS on 58 HCM families some with SCD
- Deep intronic variants and alternate splicing, mitochondrial mutations
- WGS adds up to 20% pick up over panels and exomes

Bagnall et al, J Am Coll Cardiol, 2018
Polygenic Mechanisms in SCD

Oligogenic or Polygenic Mechanisms

Polygenic Risk Scores, e.g. CAD, LQTS
Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults

Implications for Primary Prevention

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ABSTRACT

BACKGROUND Coronary artery disease (CAD) has substantial heritability and a polygenic architecture. However, the potential of genomic risk scores to help predict CAD outcomes has not been evaluated comprehensively, because available studies have involved limited genomic scope and limited sample sizes.

OBJECTIVES This study sought to construct a genomic risk score for CAD and to estimate its potential as a screening tool for primary prevention.

METHODS Using a meta-analytic approach to combine large-scale, genome-wide, and targeted genetic association data, we developed a new genomic risk score for CAD (metaGRS) consisting of 1.7 million genetic variants. We externally tested metaGRS, both by itself and in combination with available data on conventional risk factors, in 22,242 CAD cases and 460,387 noncases from the UK Biobank.

RESULTS The hazard ratio (HR) for CAD was 1.71 (95% confidence interval [CI]: 1.68 to 1.73) per SD increase in metaGRS, an association larger than any other externally tested genetic risk score previously published. The metaGRS stratified individuals into significantly different life course trajectories of CAD risk, with those in the top 20% of metaGRS distribution having an HR of 4.17 (95% CI: 3.97 to 4.38) compared with those in the bottom 20%. The corresponding HR was 2.83 (95% CI: 2.61 to 3.07) among individuals on lipid-lowering or antihypertensive medications. The metaGRS had a higher C-index (C = 0.623, 95% CI: 0.605 to 0.631) for incident CAD than any of 6 conventional factors (smoking, diabetes, hypertension, body mass index, self-reported high cholesterol, and family history). For men in the top 20% of metaGRS with >2 conventional factors, 10% cumulative risk of CAD was reached by 48 years of age.

CONCLUSIONS The genomic score developed and evaluated here substantially advances the concept of using genomic information to stratify individuals with different trajectories of CAD risk and highlights the potential for genomic screening in early life to complement conventional risk prediction. (J Am Coll Cardiol. 2018;72:1883-93)

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Take Home Messages

Sudden cardiac death in the young is an important complication of a number of genetic heart diseases.

Many issues are to be considered relating to the victim (cause of death) and the surviving family including clinical screening, genetic testing (molecular autopsy), prevention.

Specialized clinics are required which utilize a multidisciplinary approach to care.

Ultimate goal is to prevent sudden cardiac death in the young.
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Heart Kids
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