Genetic and Genomic perspectives of the Sudden Cardiac Death

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Disclaimer & Acknowledgements

NHS Wales
GIG Cymru
All Wales Medical Genetics Service

Cardiff University
Prifysgol Caerdydd

British Heart Foundation
Fight for Every Heartbeat
bhf.org.uk

University of South Wales
Prifysgol De Cymru

Association for Inherited Cardiac Conditions
Spectrum of genetic disorders

- **CHROMOSOMAL**
  - Aneuploidy
  - Micro Del/Dup

- **MENDELIAN SINGLE GENE**
  - Modifier genes
  - Epigenetics

- **POLYGENIC/MULTIFACTORIAL**
  - Low risk alleles
  - SNPS/CNVs

- **MITOCHONDRIAL**
INHERITED CARDIOVASCULAR DISEASES
MONOGENIC
CARDIOMYOPATHIES
AORTOPATHIES
CHANNELOPATHIES
INHERITED CARDIOVASCULAR DISEASES

- Chromosomal- aneuploidy (Down/Turner)
- Chromosomal- microdeletion/ microduplication
- Multiple Malformation Syndromes with CHD
- Isolated CHD (rare Monogenic- Familial Bicuspid
- Inherited metabolic disorders (Monogenic)
- Mitochondrial genetic syndromes
- Oligogenic/Multigenic Cardiac phenotypes
- Complex Cardiovascular diseases- CAD/ Hypertension
## Incidence of Sudden Unexplained/Cardiac Death: Danish study (2000-2006)

doi:10.1093/eurheartj/eht509

<table>
<thead>
<tr>
<th>Incidence rates (per 100 000 person-years)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden unexpected death</td>
<td>1.5</td>
</tr>
<tr>
<td>Sudden cardiac death (SCD)</td>
<td>1.1</td>
</tr>
<tr>
<td>SCD, autopsied cases only</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Sudden Cardiac Death (1-35 yrs)
NEJM June 2016 374:25

A  All Sudden Cardiac Deaths and Unexplained Sudden Cardiac Deaths

B  Sudden Cardiac Death According to Age Group

C  Causes of Sudden Cardiac Death
Sudden Cardiac Death (0–40 years)

- Cause identified (~70%)
  - Coronary Artery Disease (25%)
    - HCM (10–15%)
  - Myocarditis (5–10%)
    - ARVC (1–10%)
  - Structural Heart Disease
    - Others

- No cause identified i.e. SADS (~30%)
  - Arrhythmogenic Disease
    - LQTS (15–20%)
    - CPVT (10–15%)
  - Others

From: Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives
Eur Heart J | Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Sudden Cardiac Death (N=490)</th>
<th>Explained Sudden Cardiac Death (N=292)</th>
<th>Unexplained Sudden Cardiac Death (N=198)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>24±10</td>
<td>27±8</td>
<td>20±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>137 (28)</td>
<td>72 (25)</td>
<td>65 (33)</td>
<td>0.048</td>
</tr>
<tr>
<td>Activity at death — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>56/365 (15)</td>
<td>34/199 (17)</td>
<td>22/166 (13)</td>
<td>0.31</td>
</tr>
<tr>
<td>Sleep</td>
<td>139/365 (38)</td>
<td>59/199 (30)</td>
<td>80/166 (48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Attempted resuscitation — no./total no. (%)</td>
<td>297/360 (82)</td>
<td>168/197 (85)</td>
<td>129/163 (79)</td>
<td>0.13</td>
</tr>
<tr>
<td>Death during nighttime — no./total no. (%)</td>
<td>204/349 (58)</td>
<td>103/199 (52)</td>
<td>101/150 (67)</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Age, gender and triggers specific correlations of conditions causing SCD and SADS (Sheppard et al, St. George’s Hospital)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVC</td>
<td></td>
<td>Exercise, Athletic activity</td>
</tr>
<tr>
<td>HCM</td>
<td>Late adolescence-early adulthood</td>
<td>Exercise</td>
</tr>
<tr>
<td>LQTS1</td>
<td>Male children female adults</td>
<td>Younger age, Exercise, Swimming, pharmacological</td>
</tr>
<tr>
<td>LQTS2</td>
<td>Post-partum in females</td>
<td>Auditory stimuli, stress, pharmacological</td>
</tr>
<tr>
<td>LQTS3</td>
<td></td>
<td>Sleep, pharmacological</td>
</tr>
<tr>
<td>BrS</td>
<td>Male gender</td>
<td>Young-middle age adults, Fever, sleep, post-prandial, pharmacological</td>
</tr>
<tr>
<td>SQTS</td>
<td>Late adolescence-early adulthood</td>
<td></td>
</tr>
<tr>
<td>Coronary Spasm</td>
<td></td>
<td>Rest, morning</td>
</tr>
<tr>
<td>CPVT</td>
<td>Male</td>
<td>Childhood - early adolescence, Exercise, Stress</td>
</tr>
<tr>
<td>WPW syndrome</td>
<td></td>
<td>Exercise, Athletic activity</td>
</tr>
</tbody>
</table>
Main studies assessing genetic testing in the assessment of SADS

FFPE: Formalin-fixed paraffin embedded tissue, LQTS panel: *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2* genes, WES: Whole exome sequencing, NGS: Next generation sequencing, # population based studies, $ Exertion related deaths without mutations in LQT1-3 or RYR2, *Non-diagnostic structural disease in autopsy

<table>
<thead>
<tr>
<th>Genes tested</th>
<th>Source of DNA</th>
<th>Number of cases</th>
<th>Age of population studied (y)</th>
<th>Overall CPVT1 Yield (%)</th>
<th>CPVT1 LQT1-3 Yield (%)</th>
<th>Minor arrhythmia genes yield (%)</th>
<th>Cardiomyopathy genes yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ilo et al. 2004)</td>
<td>LQTS panel</td>
<td>FFPE</td>
<td>10</td>
<td>13-29</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>et al. 2004)</td>
<td>LQTS panel</td>
<td>FFPE</td>
<td>12</td>
<td>22-51</td>
<td>17</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>ton et al. 2013</td>
<td>RYR2 (22 exons)</td>
<td>Frozen tissues</td>
<td>14</td>
<td>1-43</td>
<td>21</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>ilo et al. 2008)</td>
<td><em>KCNQ1, SCN5A</em></td>
<td>FFPE</td>
<td>59</td>
<td>1-35</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>et al. 2006)</td>
<td>RYR2 (24 exons)</td>
<td>Autopsy blood samples</td>
<td>18</td>
<td>2-42</td>
<td>11</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>ng et al. 2010)</td>
<td>LQTS panel</td>
<td>Guthrie cards</td>
<td>19</td>
<td>1-34</td>
<td>21</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>ir et al. 2011)&quot;</td>
<td>LQTS panel</td>
<td>Autopsy frozen blood or tissue</td>
<td>33</td>
<td>1-40</td>
<td>15</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>et al. 2012)</td>
<td>LQTS panel, <em>KCNJ2, ANK1 CACNA1C:TS1, RYR2</em> (18 exons)</td>
<td>Autopsy frozen blood or tissue</td>
<td>173</td>
<td>1-69</td>
<td>26</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>il et al. 2012)*</td>
<td><em>KCNQ1 KCNH2 SCN5A</em></td>
<td>Dried blood spot samples or autopsy blood</td>
<td>44</td>
<td>1-35</td>
<td>11</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>il et al. n.d.)</td>
<td>RYR2 (29 exons)</td>
<td>Autopsy frozen blood</td>
<td>36</td>
<td>0-40</td>
<td>11</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>
## Sudden Unexplained/Cardiac Death

### Etiology: Cardiac 70%; Non-Cardiac 30%

doi:10.1093/eurheartj/eht509

<table>
<thead>
<tr>
<th>Cause of death, autopsied sudden unexpected death cases (n = 88)</th>
<th>n</th>
<th>Potentially inherited cardiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained deaths</td>
<td>25</td>
<td>x</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>ARVC</td>
<td>4</td>
<td>x</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>3</td>
<td>x</td>
</tr>
<tr>
<td>Thoracic aortic dissection</td>
<td>3</td>
<td>x</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pulmonary cardiac disease</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Malformation of coronary artery</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>2</td>
<td>x</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2</td>
<td>x</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>1</td>
<td>x</td>
</tr>
<tr>
<td>Conduction defect</td>
<td>1</td>
<td>x</td>
</tr>
<tr>
<td>iLVH</td>
<td>1</td>
<td>x</td>
</tr>
<tr>
<td>Rejection of transplanted heart</td>
<td>1</td>
<td>x</td>
</tr>
<tr>
<td>LQTS</td>
<td>1</td>
<td>x</td>
</tr>
<tr>
<td><strong>Total cardiac disease</strong></td>
<td>62 (70%)</td>
<td>43 (49%)</td>
</tr>
</tbody>
</table>
Myocarditis in Sudden Cardiac Death

Kostić-Banović et al. (2005) SUDDEN CARDIAC DEATH IN CHILDREN Medicine and Biology Vol.12, No 2, pp. 85 - 88

- Viral myocarditis
- Rheumatic myocarditis
- Hypersensitivity reactions/inflammation
- Fiedler’s myocarditis - Giant cell myocarditis
Genetic Studies in SCD

- Infrequent/ uncommon part of SCD Autopsy
- Conventional DNA analysis using single gene analysis approach, e.g KCNQ1/MyBPC3/MUH7
- Few reports on set of 4 genes using PCR gel analysis
- From 2010 onwards few convincing reports on SCD post mortem analysis (Molecular autopsy)

- NEXT GENERATION SEQUENCING TESTING
Collection of newer technologies that use a combination of new strategies related to how genetic samples are prepared, advanced methods of DNA sequencing and imaging, and novel approaches to genomic alignment and assembly.
Next Generation Genome Sequencing
Multi-Gene Panels
Whole Exome Sequencing
Whole Genome Sequencing

SUDDEN UNEXPLAINED (CARDIAC) DEATH

SUDDEN ARRHYTHMIC DEATH SYNDROME (SADS)
Postmortem blood

DNA extraction

Pathogenic (disease-causing) mutation

Genetic analysis
- Sanger sequencing
- Cardiac gene panels
- Whole exome / genomes
<table>
<thead>
<tr>
<th>INHERITED CARDIO-VASCULAR DISEASES PANEL</th>
<th>195 genes</th>
<th>CARDIOMYOPATHIES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left ventricular non-compaction cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arrhythmogenic cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardio-facio-cutaneous syndrome (Noonan, Leopard, Costello, etc.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long QT syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short QT syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Catecholaminergic polymorphic VT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brugada syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J wave syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac conduction disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrial fibrillation (research only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital heart diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skeletal myopathy</td>
</tr>
</tbody>
</table>

| AORTA PANEL | 30 genes | Marfan syndrome, Loeys-Dietz syndrome, TAAD, Ehlers-Danlos syndrome, etc... |

| SUDDEN DEATH PANEL | 195 genes |
|---------------------|-----------|---------------------------------|
|                     |           | SUDDEN DEATH PANEL |
|                     |           | Marfan syndrome, Loeys-Dietz syndrome, TAAD, Ehlers-Danlos syndrome, etc... |
## PATHOGENICITY

<table>
<thead>
<tr>
<th>BASIC INFORMATION</th>
<th>CLINICAL INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of mutation</td>
<td>Present/absent in healthy individuals</td>
</tr>
<tr>
<td>Change amino acids?</td>
<td>Cosegregation within the family</td>
</tr>
<tr>
<td>Conservation</td>
<td>(Consider different inheritance patterns)</td>
</tr>
<tr>
<td>Other bioinformatic studies</td>
<td>Previous descriptions (other families)</td>
</tr>
<tr>
<td>Functional studies</td>
<td></td>
</tr>
<tr>
<td>Animal models</td>
<td></td>
</tr>
</tbody>
</table>
Polymorphisms not associated with disease

Polymorphisms possibly associated with disease

Mutations not disease causing

Mutations probably/possibly disease causing

Disease causing mutations

FREQUENCY IN THE POPULATION

POLYMORPHISMS

MUTATIONS

NON-PATHOGENIC

PATHOGENIC
CENTRAL ILLUSTRATION: Sudden Arrhythmic Death Syndrome: Genetic Testing and Clinical Screening

A. Yield of Genetic Testing in 302 SADS Cases

- VUS 42%
- Pathogenic 6.5%
- Likely Pathogenic 6.5%
- No rare variant 44%

B. Overview of Likely Pathogenic Variants

- KCNQ1 (n = 4)
- KCNH2 (n = 7)
- TTN (n = 3)
- PLN (n = 1)
- PKP2 (n = 1)
- MYH7 (n = 1)
- CACNAT1 (n = 1)
- SCN5A (n = 4)
- SCN1B (n = 1)

C. Yield of Clinical Screening in 82 Families

- CPVT 5%
- LQTS 4%
- BrS 17%
- None 74%

D. Overlapping Diagnosis in 7 of 82 Evaluated Families

- Molecular Diagnosis in SADS Case (n = 18)
  - 11 (13%)
  - 7 (8.5%)

- Clinical Diagnosis in Family (n = 21)
  - 14 (17%)

- Overlapping Diagnosis: 11 (13%)

E. Combined Diagnostic Yield in a Subset of 82 Families: 39%

- CPVT 10%
- Cardiomyopathy 4%
- LQTS 7%
- BrS 18%
- None 61%

Utility of Post-Mortem Genetic Testing in Cases of Sudden Arrhythmic Death Syndrome [Lahrouchi et al. JACC 69:17 2017]

• Probably the largest UK study (St.George’s)
• Clinical and genetic evaluation in 302 SCD cases
• Genetic testing using next generation sequencing methods led to 13% detection of actionable pathogenic variants in both inherited primary electrical and cardiomyopathy genes
• The main etiologies established were catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (17 [6%] and 11 [4%], respectively).
• Gene-based rare variants association analysis showed enrichment of rare predicted deleterious variants in RYR2 (p 1/4 5 10-5).
• Combining molecular autopsy with clinical evaluation in surviving families increased diagnostic yield from 26% to 39%.
ACMG Classification of Variants
[Richards et al. GeneMed 2015; 17:405-424]

• I Pathogenic
• II Likely pathogenic
• III Variants of unknown significance (VUS)
• IV Likely Benign
• V Benign
Classification of Variants - ACMG Criteria
288 variants in 170 cases

[Lahrouchi et al. JACC 2017 69:17]

![Bar chart showing the distribution of variants by gene category.]

- **Primary electrical disease**
  - Pathogenic (P): 19
  - Likely Pathogenic (LP): 15
  - Variant of Unknown Significance (VUS): 82

- **Cardiomyopathy**
  - Pathogenic (P): 1
  - Likely Pathogenic (LP): 5
  - Variant of Unknown Significance (VUS): 166

Ratio of VUS to P and LP variants:
- Primary electrical disease: 2.4:1
- Cardiomyopathy: 28:1
Inherited Cardiomyopathy: Clinical presentation

- Sudden Death
  - Young adults
  - Athletes
  - Arrhythmia
  - Trigger
- Diastolic dysfunction
- AF (stroke)
- MR
- LVOT obstruction
- Dilated CM
- Angina
- Microvascular disease
- Venturi effect
- Syncope
- No Symptoms
- Variable symptoms
- Variable gene penetrance & expression
- Arrhythmia
- Baro-reflexes
- LVOT obstruction
- No Symptoms
Inherited Cardiomyopathies

Hypertrophic [HCM]
Dilated [DCM]
Restrictive [RCM]
Arrhythmogenic right ventricular cardiomyopathy [ARVC]
Ventricular non-compaction [VNC]
Other complex forms Unknown
Molecular defects in human cardiomyopathies

- **Sarcomere**
  - Myosin heavy chain
  - Myosin essential light chain
  - Myosin regulatory light chain
  - Cardiac actin
  - Troponin-T
  - Troponin-I
  - A-Tropomyosin
  - Myosin binding protein-C
  - Titin/titin-related protein
  - Titin
  - Telethonin (T-cap)
  - Z-disk-associated proteins
  - MLP

- **Sarcolemma cytoskeleton**
  - Dystrophin
  - β-Sarcoglycan
  - δ-Sarcoglycan
  - A-Dystrobrevin
  - Metavinculin

- **Intermediate filaments**
  - Desmin
  - Lamin A/C

HCM  DCM  RCM  HCM  HCM
Hypertrophic Cardiomyopathy

1:500

Sudden death
Difficult prognosis
Family screening
Heterogeneity
RAS-MAPK: Noonan/Costello/CFC
1-2%
MYBPC3 + MYH7 Mutations

- MYBPC3
  - Borderline LVH
  - SD 17 years

- MYH7
  - RCM, AF
  - IVS: 20mm
  - SD 10 years

- RCM awaiting for HTx

- Heart weight: 750 gr
  - IVS: 40mm
  - PW: 34mm
  - RV: 17mm

- 3-year-old
  - Asymmetric LVH
  - MYH7
HCM+WPW

PRKAG2 ex7 Arg302Gln

Cardiomyopathy
PM
SD 40 yrs
SD 45 yrs
Sincopa
Pediatric age

WPW
HCM
SD 41 yrs

Danon Disease

LAMP2 ex7 Val310Ile

HCM with late dilating evolution

HCM
Myopathy
Mental retardation

Short PR
HCM

ECG signal
Beta-MHC + MtDNA

Mother and son

Loss of COX

ABNORMAL MT

CTRL

MtDNA mutation: modifier
Case History

- 5 generation family
- Hypertrophic cardiomyopathy in 5 affected members over 4 generations
- Unexplained/ Cardiac related cause death - 3 members
- Unusual clinical picture
- Recurrent ventricular tachycardia
- Emergency procedures - pacemaker; ablation
- 5 gene HCM panel negative
- Multi-gene NGS panel - *PRKAG2* positive
Clinical Case History-Contd.

- Hypertrophic cardiomyopathy
- Recurrent ventricular tachycardia
- Abnormal ECG- short PR interval
- Negative 5 gene HCM panel result
- NGS HCM panel testing
- PRKAG2 gene mutation- pathogenic
- ? Wolff-Parkinson-White evolving to HCM
NGS FAMILIAL CARDIOMYOPATHY PANEL (HCM AND PRIMARY DCM)

- 90 GENE PANEL: ABCC9, ACTC1, ACTN2, ADRB1, ADRB2, ADRB3, AGL, ANK2, ANKRD1, BAG3, BRAF, CALR3, CAV3, CBL, CRYAB, CSRP3, CTF1, DES, DMD, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FHL1, FHL2, FNTN, FLNC, FXN, GAA, GLA, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAPK2, MYOT, MYOZ2, MYPN, NEBL, NEXN, NRAS, PDLIM3, PKP2, PKP4, PLEC, PLN, PNN, PRKAG2, PSEN1, PSEN2, PTPN11, RAF1, RBM20, RPSA, RYR2, SCN5A, SDHA, SGCD, SHOC2, SLC5A4, SOS1, SPRED1, SYNE1, SYNE2, TAZ, TCAP, TGFB3, TMEM53, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL

- 56 HCM GENE PANEL
Dilated Cardiomyopathy

1/5000-10000, idiopathic
30% “genetic”
AD
XL (dystrophin)
AR (Metabolic)
MtDNA
Penetrance age related
From DCM to...

Clinically oriented genetic investigation

“DCM”

Dystrofinopathies
Laminopathies
Desminopathies
Mitocondriopathies
Epicardinopathies
Actinopathies
Zaspopathies
Tafazzinopathies
Desmosonopathies
Two different types of DCM carry different risk

- Cardiolaminopathies (n=60)
  - 15 sudden cardiac deaths (SCD)
  - 12 appropriate ICD interventions
  - 15 events for HF (HTx and death)

- Cardiodystrophphinopathies (n=32)
  - No sudden death
  - No syncope
  - 6 with ICD: no intervention
  - Unique severe problem: death for HF: 17 events
    - 8 HTx
    - 9 deaths in waiting list for HTx

SCD RISK IN TITIN ASSOCIATED DCM?
Left Ventricular Non-Compaction

- Developmental
- Heterogeneous
- May be part of congenital heart disease
- May be part of chromosomal disorder
- May complicate familial DCM
- Characteristic pathology
- Several genes/proteins
- Sarcomere genes most common
- Clinical variation
- Sudden death risk?
Ventricular Non-compaction

Hypertrophic Cardiomyopathy

Dilated Cardiomyopathy

A

C
ARVC - clinical features

Variability of age of onset, penetrance and clinical features

High sudden cardiac death risk

Ventricular/supraventricular arrhythmia
ARVC- Genetics

>8 disease loci

6 known genes

- ryanodine receptor 2
- plakoglobin (Naxos)
- plakophilin
- desmoplakin

? Diverse pathophysiology- not well understood
Disease-Causing Mutations in Desmososomal Proteins

- **Naxos** (Plakoglobin)
- **Carvajal** (Desmoplakin)
- **ARVC8** (Desmoplakin)
- **Plakophillin-2**

Color Legend:
- Desmoplakin
- Desmoglein
- Desmocollin
- Plakophilin
- Plakoglobin

Intermediate filament
Inherited Arrhythmias

• Long QT syndrome (12 types); Brugada syndrome (~6 ECG types), Short QT; Early repolarisation and rare types

• Ion channelopathies
• Repolarisation molecular defects
• Mainly potassium channel genes
• Sodium channel and other modifier genes
• Conventional genetic testing- 5 common genes: \textit{KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2}
Inherited Arrhythmia Syndromes

Simulation from: Zeng et al., 1995 Circ. Res 77:140
Inherited Long QT syndrome

Romano-Ward syndrome

1/10,000 → 3-4000 deaths of children and young adults per year in USA

Autosomal dominant (mostly)

or autosomal recessive (with deafness)

Many different “channelopathies” cause prolonged ventricular repolarisation
ECG changes in Brugada syndrome

Short PR
RBBB
ST elevation
V1-V3
Brugada syndrome

- Not uncommon? Prevalence unknown
- Common among Oriental peoples
- May only present with unexplained death
- Nocturnal in Far East
- Genetic and clinical heterogeneity
- Autosomal dominant inheritance
- Oligogenic/Multigenic?
- Mainly a sodium ion channelopathy (SCN5A)
- Typical and atypical ECG changes
- Unmasking by azmeline/flecainide challenge
- No drug treatment- ICD only choice!
NGS: INHERITED ARRHYTHMIAS

- **LQTS: 13 GENE PANEL** - AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA

- **LQTS: 5 GENES DELETIONS/DUPLICATIONS (MLPA)** - KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2

- **LQTS SYNDROMES** - 3 GENE PANEL: KCNJ2 (ANDERSON-TAWILL), CACN1C (TIMOTHY), KCNQ1 (JERVELL & Lange-NIELSON)

- **BRUGADA: 13 GENE PANEL** - CACN1C, CACNB2, GPD1L, HCN4, KCND3, KCNE1L, KCNE3, KCNJ8, RANGRF, SCN1B, SCN2B, SCN3B, SCN5A

- **BRUGADA CLASSIC**: SCN5A (MLPA & SANGER SEQUENCING)
CLINICAL CASE HISTORY

• Large family with multiple LQTS cases
• Sudden cardiac death - 6 years old
• New miss fatal cardiac event
• Recurrent ventricular tachycardia
• Unusual facial/mandibular development
• Short stature - proportionate
• Recurrent non-specific episodic muscular weakness
• Negative on conventional 5 gene panel
• NGS- KCNJ2 gene mutation
• Final diagnosis- ANDERSON-TAWILL SYNDROME
SADS/SCD: Current Practice

- Detailed clinical information including family history
- Coroner’s autopsy assisted by experts
- Conventional and expert cardiac histopathology in all cases (whole heart)
- DNA stored in all cases (Blood/Spleen)
- Molecular autopsy using NGS multi-gene panel comprising of all major structural/ arrhythmia gene mutations
- Validation in both parents or clinically affected family member
- Functional/ Computational variant analysis for pathogenicity
- Cascade clinical and genetic evaluation of first degree relatives supported with adequate and appropriate genetic counselling.
<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Encoded protein</th>
<th>Disease</th>
<th>% of disease</th>
<th>% of SADS</th>
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<tbody>
<tr>
<td>SADSa</td>
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<tr>
<td>KCNQ1</td>
<td>IKs K+ channel α-subunit</td>
<td>LQTS1 35–40</td>
<td>10–15</td>
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<tr>
<td>KCNH2</td>
<td>IKr K+ channel α-subunit</td>
<td>LQTS2 30–35</td>
<td>1–5</td>
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<tr>
<td>SCN5A</td>
<td>INa Na+ channel α-subunit</td>
<td>LQTS3 5–10</td>
<td>&lt;1</td>
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<tr>
<td>BrS</td>
<td></td>
<td></td>
<td>15–25</td>
<td>&lt;1</td>
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<tr>
<td>RYR2</td>
<td>Ryanodine receptor</td>
<td>CPVT1 60–65</td>
<td>10–15</td>
<td></td>
</tr>
</tbody>
</table>

LQTS, long-QT syndrome; BrS, Brugada syndrome; CPVT1, catecholaminergic polymorphic ventricular tachycardia type 1; SADS, sudden arrhythmic death syndrome (normal postmortem)

aPick-up rate for molecular autopsy.
Postmortem criteria for ‘negative autopsy’

• Structurally normal heart
• No abnormal histopathological findings in the heart
• No other cause of death identified at postmortem, e.g. pulmonary embolus
• Normal toxicology screen
• No pre-death clinical features to suggest other cause of sudden death, e.g. epilepsy
Genetic Counselling
• Material appropriate for DNA analysis should be obtained from the deceased person at the time of autopsy; targeted genetic testing be carried out guided by SCD victim and/or clinical assessment of the surviving family members

• Comprehensive and expert clinical assessment of surviving relatives with targeted genetic analysis in those with clinical abnormalities

• Genetic testing should not be carried out in borderline/suspected ICC cases outside the setting of expert clinical and detailed assessment
KEY TAKE HOME MESSAGE:

• A cardiac autopsy should be performed in every victim of unexpected sudden death. Blood and/or suitable tissues should be stored during the autopsy for subsequent genetic analysis when a cause of death is not identified or suspected to be heritable.

• Expert cardiac pathology is indispensable in the assessment of SADS and can differentiate pathological from normal findings.

• Autopsy findings of uncertain significance such as idiopathic fibrosis or idiopathic left ventricular hypertrophy should be interpreted accurately and treated as SADS.

• Systematic and comprehensive cardiological evaluation for surviving first-degree relatives is imperative in determining the cause of death, in guiding the genetic investigation in the family and in providing co-segregation information for appropriate genotype-phenotype correlations.

• Molecular autopsy is a complementary diagnostic tool providing useful genetic information regarding the pathogenesis of SADS. Cautious interpretation of
MULTI-DISCIPLINARY SUDDEN CARDIAC DEATH TEAM
Coroner’s Pathologist

Coroner/Coroner’s Officer

RELATIVE/PATIENT

BHF Genetics Information Service gives details of nearest ICC clinic + letter to take to GP advising referral + details of bereavement support & SCD charities

GP

Charities (CRY, SADS etc), bereavement service

Inherited Cardiac Conditions Centre
Cardiologists
Geneticist
Chemical Pathologist
Paediatrician

UK/Overseas Cardiologist/Geneticist

Local Cardiologist

Genetics Lab Service
Thank you