SADS and the Role of Molecular Autopsy

Elijah R. Behr MD FRCP
Unexpected sudden death

Sudden death
Normal autopsy

Syncope
Daughter 1: Long QT Syndrome
Daughter 1: Ajmaline test Brugada Syndrome
Son: Long QT Syndrome and RV delay
Long QT syndrome and sinus node disease

Variable T wave morphology

Chronotropic incompetence
Sister 1: Brugada ECG phenotypes
Father: AV Conduction Delay, RV Delay and Sinus node disease
LQTS BrS SSS CCD overlap: SCN5A E1784K

Phenotype negative

BrS

LQTS SND Concealed BrS and LQTS

SND +/- CCD

5

9

10

34

35

41

69

70
Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Silvia G. Priori, (HRS Chairperson)¹, Arthur A. Wilde, (EHRA Chairperson)², Minoru Horie, (APHRS Chairperson)³, Yongkeun Cho, (APHRS Chairperson)⁴, Elijah R. Behr⁵, Charles Berul⁶, Nico Blom⁷*, Josep Brugada⁸, Chern-En Chiang⁹, Heikki Huikuri¹⁰, Prince Kannankeril¹¹‡, Andrew Krahn¹², Antoine Leenhardt¹³, Arthur Moss¹⁴, Peter J. Schwartz¹⁵, Wataru Shimizu¹⁶, Gordon Tomaselli¹⁷‡, Cynthia Tracy%¹⁸
Sudden Cardiac Death

50-100,000 p.a. in the UK

- Ischaemic: 81%
- Other: 15%
- Unexplained (SADS): 4%
Epidemiology of Young SCD: 1-35 yrs old

European annual incidence
- 2.8 per 100,000 (Denmark)
- 2.9 per 100,000 (Ireland)
- 1.8 per 100,000 (England/Wales)
- 1.0 per 100,000 (Veneto, Italy)

Sports / Training (screened populations)
- 2.1 per 100,000 (Veneto, Italy)
- 13.0 per 100,000 (US military)
Causes of Young Sudden Death

Expert Consensus Recommendations on Diagnosis

1. **It is recommended** that an unexplained sudden death occurring in an individual older than 1 year of age is known as “sudden unexplained death syndrome” (SUDS).

2. **It is recommended** that a SUDS death with negative pathological and toxicological assessment is termed “sudden arrhythmic death syndrome” (SADS).
The ‘normal heart’ is common in most series of young SCD

- Winkel et. al. 2011: 43%
- Morentin et. al. 2003: 19%
- Doolan et. al. 2004: 31%
- Puranik et. al. 2005: 29%
- Margey et. al. 2011: 26%
- Corrado et. al. 2001: 17%
- de Noronha et. al.: 23%
SADS: Circumstances of Death
(n=780, 60% Male, 90% No PMH/ prior symptoms)
Approaches

Unexplained Sudden Death

Molecular autopsy

Familial evaluation

Diagnose cause of death

Identify others at risk
SUDS

No Autopsy Undertaken
Suspicion of genetic disease (premature sudden death, family history of sudden death)

Pathology (Class I)
- Coroner’s or medical examiner’s autopsy undertaken
- Retention of tissue suitable for DNA extraction
- Expert cardiac pathology

Identifiable cause
If disease is likely to be inherited (e.g. HCM, ARVC) then instigate appropriate evaluation in inherited cardiac disease clinic

Arrhythmia focused molecular autopsy (Class IIa)

SADS (Class I)
- Normal autopsy
- Negative toxicology
- Normal expert pathologist’s assessment ‡

Retrospective work-up of personal/family history and circumstances of the sudden death (Class I)
CRY Centre for Cardiac Pathology
200 consecutive SCD cases
158 (79%) with provisional diagnosis
94/158 (59%) matched expert opinion
Over-diagnose cardiomyopathy (ARVC)
Underdiagnose normal heart

De Noronha et al, Europace 2013
## Mismatch

<table>
<thead>
<tr>
<th>Expert opinion</th>
<th>ARVC</th>
<th>HCM</th>
<th>LVH</th>
<th>DCM</th>
<th>CM NOS</th>
<th>Other CM</th>
<th>Inflammation</th>
<th>Valvular disease</th>
<th>Normal heart</th>
<th>Other</th>
<th>Total</th>
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<td>CM NOS</td>
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<tr>
<td>Other CM</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>0</td>
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<td>15</td>
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<td>Inflammation</td>
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<td>0</td>
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<td>4</td>
<td>0</td>
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<td>0</td>
<td>5</td>
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<tr>
<td>Valvular disease</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
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<td>Normal</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2</td>
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<td>80</td>
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<td>Other pathology</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21</strong></td>
<td><strong>17</strong></td>
<td><strong>15</strong></td>
<td><strong>6</strong></td>
<td><strong>5</strong></td>
<td><strong>10</strong></td>
<td><strong>9</strong></td>
<td><strong>5</strong></td>
<td><strong>57</strong></td>
<td><strong>13</strong></td>
<td><strong>158</strong></td>
</tr>
</tbody>
</table>

De Noronha et al, Europace 2013
SCD victims whose families were referred for cardiac evaluation
n=340

Post-mortem review
Negative toxicology

Definite Cardiac Pathology

Ambiguous/Non-specific Autopsy
n=41 (12%)

Normal Autopsy (SADS)

Positive Family Screening
n=21

Cardiomyopathy
n=2

Ion-channelopathy
n=19 (46%)

Brugada syndrome
n=14

Long QT syndrome
N=4

CPVT
n=1
Ambiguous results still ion channel disease

Papadakis et al, CircEP 2013
Familial Evaluation
(Class I)
First degree relatives
Obligate carriers
Symptomatic relatives
Familial Evaluation
(Class I)
First degree relatives
Obligate carriers
Symptomatic relatives

Initial Evaluation
(Class I)
Personal and family history
Physical examination
Resting ECG with high RV leads
Exercise ECG
Echocardiogram

Additional tests to be considered:
(Class IIa)
24 hour ECG, Signal Averaged ECG
Long QT syndrome

RR = 1120ms

QT = 620ms

QTc = 585ms
The Brugada Syndrome
Catecholaminergic Polymorphic VT (CPVT)
Role for the Exercise ECG

2006-2010: 308 blood relatives of 148 SADS victims
Completed at least 3 minutes of Bruce
30 (9.8%) abnormal
15 (4.9 %) supported diagnosis of ICC
Familial Evaluation

First degree relatives
Obligate carriers
Symptomatic relatives

Initial Evaluation

Personal and family history
Physical examination
Resting ECG
Exercise ECG
Echocardiogram

Additional tests to be considered:
24 hour ECG, Signal Averaged ECG

Normal Heart

Normal ECG consider:

Epinephrine test (Class IIb)

Ajmaline test (Class IIa)
Class Ic Challenge:

Baseline 2 mins 3 mins
Specificity in SADS?
Epinephrine challenge?

Epinephrine testing in LQT1

Epinephrine 0.1 µg/kg/min
Group I = QTc ≥ 460ms (carriers)
Group II = QTc < 460ms (carriers)
Group III = non carrier family members
Group IV = controls

<table>
<thead>
<tr>
<th></th>
<th>Sens.</th>
<th>Spec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>59%</td>
<td>100%</td>
</tr>
<tr>
<td>Epi</td>
<td>91%</td>
<td>100%</td>
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</table>

Shimizu et al JACC 2003
Epinephrine Challenge?

Specificity in SADS?

Epinephrine challenge more useful in CPVT diagnosis than ExECG
Familial Evaluation

First degree relatives
   Obligate carriers
   Symptomatic relatives

Initial Evaluation

Personal and family history
   Physical examination
      Resting ECG
      Exercise ECG
      Echocardiogram

Additional tests to be considered:
   24 hour ECG, Signal Averaged ECG

Normal Heart

Normal ECG
  consider:
    Epinephrine test
    Ajmaline test

ECG suspicious RV repolarization
  consider:
Additional tests to be considered:
24 hour ECG, Signal Averaged ECG

Familial Evaluation
First degree relatives
Obligate carriers
Symptomatic relatives

Initial Evaluation
Personal and family history
Physical examination
Resting ECG
Exercise ECG
Echocardiogram

Normal Heart
Epinephrine test
Ajmaline test

Normal ECG
consider:

ECG suspicious RV repolarization
consider:

CMR Imaging (Class IIa)
Familial Evaluation

First degree relatives  
Obligate carriers  
Symptomatic relatives

Initial Evaluation

Personal and family history  
Physical examination  
Resting ECG  
Exercise ECG  
Echocardiogram

Additional tests to be considered:

24 hour ECG, Signal Averaged ECG

Normal Heart

Normal ECG  
consider:

Epinephrine test

Ajmaline test

Abnormal or Equivocal Cardiac Morphology

ECG suspicious RV repolarization consider:

CMR Imaging (Class IIa)
Follow-Up (Class I)
• If asymptomatic and fully grown adult discharge from care
• If symptoms develop or new information becomes available in family then review
• If child, then follow-up in case of age related expression of disease

Manage according to diagnosis
• Refer to guidelines
• Offer family cascade clinical and/or genetic testing

Diagnosis Made?
Yes
No
SADS: Diagnostic Yield of Clinical Evaluation

Overall: 3.1% mean (range: 0.0-11.6)
Overall: 10.3% mean (range: 0.0-38.6)
Overall: 11.3% mean (range: 4.4-28.1)
Overall: 7.1% mean (range: 0.0-15.8)

Overall diagnostic yield: 29.0% mean (range: 13.2-52.6)
SADS: Diagnostic Yield of Gene Testing Targeted to Phenotype

Mean 32%
Mean 42%
Mean 41%
Mean 84%

Miles and Behr, Translational Research 2015
How can a comprehensive ‘molecular autopsy’ help?

Is there a ‘diagnostic’ mutation?
YES

Is it present in the parents?
NO – sporadic/reassure
focus on offspring
YES – evaluate/follow-up carriers
Family 3

- SADS 3yo
  + de novo RYR2: p.M4002V

Family 6

- Not screened
  + BrS
  + SADS 39yo

Family 5

- mosaic
  - CPVT
  - UA
  + UA
  - SADS post exercise
    + Hx of syncope
    6yo
  + RYR2: p.P4596S carrier

Family 6

- + SCN5A: p.R121W carrier
<table>
<thead>
<tr>
<th>Class</th>
<th>Evaluation of Family Member Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Class I</td>
<td>• Genetic screening of the first degree relatives of a SUDS victim <em>is recommended</em> whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDS victim.</td>
</tr>
</tbody>
</table>
Historical Pitfalls

Pathogenicity = Absence in small controls

But LQTS has 1:2000 prevalence
And CPVT 1:10,000

And multitude of variants cause each condition
# Yield and Signal to Noise Ratio

<table>
<thead>
<tr>
<th>Disease</th>
<th>Main genes</th>
<th>Yield</th>
<th>% of Controls with a Rare VUS</th>
<th>Signal-to-Noise (S:N) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS</td>
<td>KCNQ1, KCNH2, SCN5A</td>
<td>75%</td>
<td>4%</td>
<td>19 to 1</td>
</tr>
<tr>
<td>CPVT</td>
<td>RyR2</td>
<td>60%</td>
<td>3%</td>
<td>20 to 1</td>
</tr>
<tr>
<td>BrS</td>
<td>SCN5A</td>
<td>20%</td>
<td>2%</td>
<td>10 to 1</td>
</tr>
</tbody>
</table>

Adapted from Ackerman et al, HR and Europace 2011
Sudden death and cardiac arrest without phenotype: the utility of genetic testing

Yanushi D. Wijeyeratne, BMedSci, BMBS, MRCP\textsuperscript{a,b}, and Elijah R. Behr, MD, FRCP\textsuperscript{a,b,*}

\textsuperscript{a}Department of Cardiology, Prince of Wales Hospital, Sydney, Australia. \textsuperscript{b}The University of Sydney, Sydney, Australia. \textsuperscript{*}Department of Medicine, University of Sydney, Sydney, Australia.
SCD in the Young – Australia & NZ

All SCD aged 1-35 yrs

All Australia and NZ

2010-2012 prospective and population-based

N= 490 SCD cases

![Bar chart showing the distribution of SCD cases by cause. The chart indicates that 40% of cases were unexplained.](chart.png)
Genetic Analysis in Unexplained SCD Cases

N=113 unexplained cases
Minimum 59 cardiac genes
Mainly arrhythmia and cardiomyopathy genes
Genetics of unexplained SCD cases

MAF<0.1% filter

*In silico* tools

27% (n=31) ‘clinically relevant’ cardiac gene mutation identified

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**Molecular Autopsy**

(n=4 genes)

**Cardiac Arrhythmia**

(n=16 genes)

**Cardiomyopathy**

(n=16 genes)

**Rare Cardiomyopathy**

(n=23 genes)

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SUD cases (n)
International Molecular Autopsy and Family Study
Study design and inclusion criteria

• International SADS cohort (UK, NZ, DK, NL)
• NGS panel consisting of 77 genes linked to cardiomyopathy and primary electrical disease
## Results

Who are these sudden cardiac death cases?

<table>
<thead>
<tr>
<th>Variable</th>
<th>SADS (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>25 ± 13 years</td>
</tr>
<tr>
<td>Male gender, number (%)</td>
<td>197 (65%)</td>
</tr>
<tr>
<td>Circumstance of death</td>
<td></td>
</tr>
<tr>
<td>- Sleep and rest, number (%)</td>
<td>188 (72%)</td>
</tr>
<tr>
<td>- Exercise and Emotion, number (%)</td>
<td>30 (11%)</td>
</tr>
<tr>
<td>Syncope prior to death</td>
<td>50 (19%)</td>
</tr>
<tr>
<td>Family history of SCD, number (%)</td>
<td>19 (7%)</td>
</tr>
</tbody>
</table>
Distribution of age and gender

<table>
<thead>
<tr>
<th>Age at Death (Years)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-18</td>
<td>8%</td>
<td>22%</td>
</tr>
<tr>
<td>19-35</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>36-65</td>
<td>8%</td>
<td>13%</td>
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</table>
Results
Outcome of genetic and clinical testing
Unrelated to age
Exclusions:
  
  Synonymous variants not located at splice sites
  Non-truncating variants in TTN
  >1 in 10,000 MAF in ExAC

ACMG classification
<table>
<thead>
<tr>
<th>Data Type</th>
<th>Benign</th>
<th>Supporting</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Strong</th>
<th>Very strong</th>
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<tbody>
<tr>
<td>Population data</td>
<td>MAF is too high for disorder BA1/BS1 OR observation in controls inconsistent with disease penetrance BS2</td>
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<td></td>
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</tr>
<tr>
<td>Computational and predictive data</td>
<td>Multiple lines of computational evidence suggest no impact on gene/gene product BP4</td>
<td>Multiple lines of computational evidence support a deleterious effect on the gene/gene product PP3</td>
<td>Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5</td>
<td>Same amino acid change as an established pathogenic variant PS1</td>
<td>Predicted null variant in a gene where LOF is a known mechanism of disease PVS1</td>
<td></td>
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<tr>
<td>Functional data</td>
<td>Well-established functional studies show no deleterious effect BS3</td>
<td>Missense in gene with low rate of benign missense variants and path. missenses common PP2</td>
<td>Mutational hot spot or well-studied functional domain without benign variation PM1</td>
<td>Well-established functional studies show a deleterious effect PS3</td>
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<tr>
<td>Segregation data</td>
<td>Nonsegregation with disease BS4</td>
<td>Cosegregation with disease in multiple affected family members PP1</td>
<td>Increased segregation data</td>
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<td>De novo data</td>
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<tr>
<td>Allelic data</td>
<td>Observed in (\text{trans}) with a dominant variant BP2</td>
<td>Observed in (\text{cis}) with a pathogenic variant BP2</td>
<td>For recessive disorders, detected in (\text{trans}) with a pathogenic variant PM3</td>
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<tr>
<td>Other database</td>
<td>Reputable source w/out shared data = benign BP6</td>
<td>Reputable source = pathogenic PP5</td>
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<tr>
<td>Other data</td>
<td>Found in case with an alternate cause BP5</td>
<td>Patient's phenotype or FH highly specific for gene PP4</td>
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</tbody>
</table>
Results
Outcome of genetic and clinical testing
Unrelated to age
Exclusions:

- Synonymous variants not located at splice sites
- Non-truncating variants in TTN
- >1 in 10,000 MAF in ExAC

ACMG classification

Overall genetic yield of post-mortem genetic testing is 13%
ACMG Classification of 288 variants in 170 cases

Ratio of VUS to P and LP variants:
- 2.4:1
- 28:1

Gene category:
- Primary electrical disease: 19 (Pathogenic), 15 (Likely Pathogenic), 82 (Variant of Unknown Significance)
- Cardiomyopathy: 1 (Pathogenic), 5 (Likely Pathogenic), 166 (Variant of Unknown Significance)
Why do we find variants in cardiomyopathy associated genes in these autopsy negative SCD cases?

1. Subclinical cardiomyopathic changes that could have been missed at autopsy
2. Non-diagnostic minor pathological changes
3. The cardiomyopathy genes are large (373 Kb versus 166 Kb)
4. Some cardiomyopathy variants can be arrhythmic before onset of cardiomyopathy
5. Not causal but innocent bystanders
Results
Molecular diagnosis with ACMG guidelines

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
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<tbody>
<tr>
<td>CPVT</td>
<td>17</td>
</tr>
<tr>
<td>LQTS</td>
<td>12</td>
</tr>
<tr>
<td>BrS</td>
<td>5</td>
</tr>
<tr>
<td>CMP</td>
<td>6</td>
</tr>
</tbody>
</table>

- KCNH2: 7
- KCNQ1: 4
- CACNA1C: 1
- RYR2: 17
- TTN: 3
- SCN5A: 4
- SCN1B: 1
- MYH7: 1
- PKP2: 1
- PLN: 1
# Burden Analysis:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein altering MAF1in10000 and CADD &gt;25</th>
<th>Synonymous MAF 1in1000</th>
<th>Synonymous MAF 1in10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYR2</td>
<td>5.00E-05</td>
<td>0.890331</td>
<td>0.0620057</td>
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<tr>
<td>KCNH2</td>
<td>0.0079</td>
<td>0.502687</td>
<td>0.0591</td>
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<td>HCN4</td>
<td>0.023</td>
<td>0.0153</td>
<td>0.196942</td>
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<td>LDB3</td>
<td>0.0614931</td>
<td>0.496728</td>
<td>0.620295</td>
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<td>MYPN</td>
<td>0.0924561</td>
<td>0.0339</td>
<td>0.047775</td>
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<tr>
<td>KCNQ1</td>
<td>0.0952276</td>
<td>0.436984</td>
<td>0.625825</td>
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<tr>
<td>TMEM43</td>
<td>0.120778</td>
<td>0.789</td>
<td>0.420351</td>
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<td>TTN</td>
<td>0.157059</td>
<td>0.346995</td>
<td>0.397691</td>
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<td>KCNJ5</td>
<td>0.164204</td>
<td>0.05735</td>
<td>0.0589345</td>
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</table>
## Results

### Genotype-phenotype correlation: RYR2 variants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non RYR2 (n=285)</th>
<th>RYR2 (n=17)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>25 ± 13</td>
<td>15 ± 9</td>
<td>0.002</td>
</tr>
<tr>
<td>Male gender, number (%)</td>
<td>183 (64%)</td>
<td>14 (82%)</td>
<td>0.1918</td>
</tr>
<tr>
<td>Circumstance of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sleep/Rest, number (%)</td>
<td>183 (75%)</td>
<td>5 (29%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>- Exercise/Emotion, number (%)</td>
<td>21 (9%)</td>
<td>9 (53%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of SCD, number (%)</td>
<td>16 (6%)</td>
<td>3 (20%)</td>
<td>0.0791</td>
</tr>
</tbody>
</table>

**RYR2-SADS patients are younger and die more often during exercise/extreme emotion**

Five patients where misdiagnosed with epilepsy
Yield of Clinical Evaluation in 82 Families

- None: 74%
- BrS: 17%
- CPVT: 5%
- LQTS: 4%
**Results**

Combined yield of genetic and clinical testing (39%)

In 82 families both genetic testing in SADS case and evaluation of relative had been performed.

- **Molecular diagnosis in SADS case (n=18):**
  - 11 cases (13%)

- **Clinical diagnosis in family (n=24):**
  - 17 cases (21%)
  - 7 cases (8.5%)

- LQTS in 2; BrS in 1; and CPVT in 4.
Conclusions

Optimal evaluation of SADS death

Ensure expert pathology
Whole heart and DNA retention
Ambiguous pathology = SADS until proven otherwise
Conclusions

Optimal evaluation of family

First degree relatives
Syncopal patients
Obligate carriers
High RV leads for class 1 blocker tests
CMR
? Epinephrine ?
Conclusions

Role of Molecular autopsy

Next Gen - cost-efficient high throughput
Likely cause of death identified in 13%
Limitations of VUS and noise
ACMG criteria
Cardiomyopathy
Combined with clinical evaluation of relatives increases yield to 39%
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