Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families

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Aims

At least 4% of sudden deaths are unexplained at autopsy [sudden arrhythmic death syndrome (SADS)] and a quarter may be due to inherited cardiac disease. We hypothesized that comprehensive clinical investigation of SADS families would identify more susceptible individuals and causes of death.

Methods and results

Fifty seven consecutively referred families with SADS death underwent evaluation including resting 12 lead, 24 h and exercise ECG and 2D echocardiography. Other investigations included signal averaged ECG, ajmaline testing, cardiac magnetic resonance imaging, and mutation analysis. First-degree relatives [184/262 (70%)] underwent evaluation, 13 (7%) reporting unexplained syncope. Seventeen (30%) families had a history of additional unexplained premature sudden death(s). Thirty families (53%) were diagnosed with inheritable heart disease: 13 definite long QT syndrome (LQTS), three possible/probable LQTS, five Brugada syndrome, five arrhythmogenic right ventricular cardiomyopathy (ARVC), and four other cardiomyopathies. One SCN5A and four KCNH2 mutations (38%) were identified in 13 definite LQTS families, one SCN5A mutation (20%) in five Brugada syndrome families and one (25%) PKP2 (plakophillin2) mutation in four ARVC families.

Conclusion

Over half of SADS deaths were likely to be due to inherited heart disease; accurate identification is vital for appropriate prophylaxis amongst relatives who should undergo comprehensive cardiological evaluation, guided and confirmed by mutation analysis.

Keywords

SADS • Sudden death • Clinical genetics • Long QT syndrome • Brugada syndrome • Cardiomyopathy

Introduction

Previous prospective study of sudden and unexpected deaths in apparently healthy adults in England had identified that in 4.1% of cases, a full coroner’s post-mortem, a toxicological screen, and an expert cardiac autopsy failed to reveal any underlying cause of death.1 A second English prospective population-based survey of victims of unexplained sudden death aged 4–64 years with normal cardiac pathology [the sudden arrhythmic death syndrome (SADS) study] suggested that up to ~500 such deaths occur per annum,2 equivalent to 2500 deaths per annum in USA. As part of the study, we evaluated first-degree blood relatives from 32 families of victims of SADS death.3 A research protocol with a limited clinical evaluation (history, resting and 24 h electrocardiogram (ECG) 2D echocardiography and exercise ECG at the physician’s discretion) diagnosed inherited cardiac disease in 7/32 families (22%), four with long QT syndrome (LQTS). Tan et al.4 published results of the comprehensive evaluation of 43 families with a high frequency of unexplained sudden deaths. Seventeen (40%) were identified with inherited cardiac disease including catecholaminergic polymorphic ventricular tachycardia (CPVT), LQTS, Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC).

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We have undertaken a new study of a second group of unselected families consecutively referred to our institution, in which a SADS death had occurred. We hypothesized that a more comprehensive clinical and genetic evaluation of SADS victims and their families would identify a greater proportion of the probable causes of such deaths and aimed to determine the proportion of relatives at risk of sudden death.

**Methods**

Sixty-five consecutive families with a possible SADS death, newly referred to St George’s Hospital, London, were considered for the study (Figure 1). Fifty-seven families were included in the study group having met the inclusion criteria for a SADS death: a sudden unexpected death; age 4–64 years; last seen alive and well within 12 h of being found dead; no prior recorded cardiac disease; a normal full coroner’s post-mortem; negative toxicology results; and a normal expert cardiac pathologist’s examination of the heart, tissue samples or slides, if available. Autopsy reports were assessed for non-cardiac causes of sudden death and structural heart disease as part of this process. For example, hypertrophic cardiomyopathy (HCM), an important cause of sudden death in the young, can usually be detected at post-mortem and these families were either not referred as having a SADS death or not included.\(^1\) The cohort therefore consisted of families with at least one unexplained sudden death where non-cardiac causes, such as pulmonary embolus, cerebral haemorrhage, and drugs, and structural cardiac causes, such as cardiomyopathy, valvular disease, and myocarditis, had been excluded.

**Familial evaluation**

A proband’s prior history was determined by review of coroner’s reports, primary care physicians’ records and interview with relatives. The assessment of families then focused upon the initial systematic evaluation of as many first-degree blood relatives as possible: historical review, physical examination, echocardiography and resting, 24 h and exercise ECG. Evaluation was limited to echocardiography and ECG in children was unable to comply with other tests. Blood relatives who were not first-degree (non-first-degree relatives) were evaluated for one or more of the following reasons: (i) familial anxiety prompted a premature referral; (ii) the presence of worrying symptoms; (iii) as part of clinical evaluation/cascade genetic testing after the diagnosis of inherited heart disease in a first-degree relative. Standard criteria for the diagnosis of LQTS (the Schwartz score)\(^5\) were utilized. In addition, during exercise and 24 h ECG recordings, periods of sufficient quality and heart rate stability were examined, commonly during the recovery phase, for accurate measurement of the maximal QTc interval.\(^6,7\) In conjunction with genetic testing results (discussed later), an overall assessment of the likelihood of an individual carrying LQTS (high, intermediate, and low probability) and a family harbouring LQTS (definite or possible/probable) was then made. Standard criteria for the type 1 Brugada ECG pattern and diagnosis of the Brugada syndrome were employed.\(^8\) Additional investigations were performed depending on the results of initial evaluation as summarized in Figure 2. If ECG recordings and echocardiography were normal or type 2 and/or 3 Brugada ECG patterns were present then ajmaline testing\(^8\) was undertaken. If there were echocardiographic abnormalities [including equivocal right ventricular (RV) findings] and/or ECG features suggestive of cardiomyopathy, then cardiac magnetic resonance (CMR) imaging and signal averaged ECG (SAECG) were undertaken. Standard criteria for the diagnosis of ARVC in families with a
history of sudden death were utilized.\textsuperscript{9,10} Any further investigations were undertaken as indicated by overall clinical findings. If a relative could not be evaluated at St George’s, then data were collected with the assistance of their relatives, relevant physician, and a telephone interview. Investigation results were classified by two of the authors (E.R.B. and W.J.M.) as normal, equivocal or abnormal. In the event of a disagreement a senior colleague (E.R.) was consulted and a consensus agreed. When inherited cardiac disease was diagnosed, the relevant physicians were informed, appropriate management instigated, and follow-up and extended familial evaluation arranged.

**Genetic testing**

After appropriate counselling, mutation analysis was offered to families using DNA extracted from proband tissues and/or affected relatives’ blood samples. The strategy employed is indicated in Figure 2 and proceeded alongside clinical evaluation of relatives. Therefore, when proband DNA was available, it was analysed for most genes recognized to cause inherited arrhythmia syndromes – the molecular autopsy (discussed later). Unfortunately, the quality and quantity of this DNA and subsequent mutation analysis was often limited by the nature of retained tissue paraffin blocks. DNA was not available in 33 probands. In 25 families, including 14 where proband DNA eventually became available, mutation analysis was undertaken in a relative with phenotypic abnormalities suggestive of inherited arrhythmia syndromes or ARVC. This was targeted according to phenotypic features and circumstances of death in the proband. If an unequivocal mutation (known or highly probable) was identified in a proband or relative then the family was offered cascade screening. If an equivocal (unknown or possible) mutation was identified co-segregation analysis was performed to determine causality and hence the value of further predictive testing in other family members.

**Figure 2** Recommended diagnostic algorithm for families with a sudden arrhythmic death syndrome (SADS) death.
Polymerase chain reaction (PCR) was utilized with primers derived from the published exons and their flanking intronic sequences to amplify the coding regions of genes responsible for cardiac ion channel subunits and their associated proteins implicated in the inherited arrhythmia syndromes (LQTS, short QT syndrome, Brugada syndrome, Andersen’s syndrome and CPVT): all exons of KCNQ1, KCNE1, KCNH2, KCNE2, SCN5A, ANK2, KCNJ2, CAV3, CASQ2, and selected exons (7–9, 13–16, 43–50, 82–84, and 87–105) of hRyR2.\textsuperscript{20,21} If ARVC was diagnosed or suspected in relatives then analysis for mutations in the plakophilin2 (PKP2) and desmoplakin genes was undertaken.\textsuperscript{22,23} All PCR products were subjected to single stranded conformational polymorphism (SSCP) screening with polyacrylamide gel electrophoresis to identify non-conforming bands in comparison with an ethnically matched 400-allele control panel. PCR products showing an aberrant SSCP pattern were sequenced bi-directionally to identify any base changes relative to the published genomic DNA sequences, known mutations, and polymorphisms.

**Statistics**

Data collection and observational analysis employed Microsoft Access 2000 © (version 9), SPSS© (version 12) were utilized for statistical analysis. Pearson’s χ² or Fisher’s exact tests were used to compare proportions. The Binomial test for equal proportions was used to compare dichotomous variables (gender). Student’s t-test was used to compare continuous variables. P-values < 0.05 were considered statistically significant.

**Results**

Figure 1 describes the numbers of families, probands, and relatives who were included, underwent evaluation, and then successful genetic testing.

**Proband and family characteristics**

Most SADS probands were male and/or died at rest or in sleep although statistical significance was not achieved (Table 1). Close to half had previously reported cardiac symptoms (syncope 19%), mainly to their relatives. None had undergone appropriate cardiac assessment as a result of these symptoms. Table 2 illustrates the characteristics of their families and relatives.

**Results of evaluation**

In 30/57 (53%) families, definite and possible/probable inherited heart disease was identified (Figure 3). In one of these families clinical evaluation did not contribute to a diagnosis but mutation analysis of the proband’s DNA identified a likely LQTS disease causing mutation (KCNH2-A80V). A quarter of evaluated first-degree relatives and two-fifths of non-first-degree relatives were diagnosed as affected with likely inherited heart disease (Table 3 and Figure 1).

**Predictors of a diagnosis in an individual and in a family**

Affected first degree relatives were similar to unaffected first degree relatives except that they were more likely to report a cardiac symptom especially syncope (Table 4). There were practically no differences between diagnosed and undiagnosed SADS probands and their families (including family size and proportion evaluated). The only significant difference was a higher frequency of syncope amongst first-degree relatives in a family with a diagnosis (Table 4).

**Investigations and their utility**

Each of the initial investigations undertaken in all first degree relatives contributed either separately or in combination to a diagnosis of inherited heart disease in an individual: 16% of all ECGs, 11% of all exercise ECGs, 9% of all 24 h ECG, and 2% of all echocardiograms. Additional investigations also contributed to a diagnosis of inherited heart disease in an individual: 3/91 of all SAECGs (3%), 6/50 of all ajmaline tests (12%), and 4/25 of all CMR scans (16%). Examples of ECGs are supplied in Supplementary data, online.

**Mutation analysis**

DNA was extracted from tissue or post-mortem blood samples from 24 SADS probands and underwent ‘molecular autopsy’. This included eight probands whose families later demonstrated structural heart disease. Disease causing mutations that co-segregated with phenotype in a pedigree were detected in 2/6 (33%) probands with a subsequent familial diagnosis of definite or possible/probable LQTS (KCNH2: Q376sp and E544fsX49) and 1/4 (25%) with a familial diagnosis of ARVC (PKP2-S140F). Of 11 relatives who underwent cascade testing, seven carried mutations: four with KCNH2-E544fsX49, one with KCNH2-Q376sp, and two with PKP2-S140F. Two novel mutations SCNSA-P1187L and SCNSA-G1935S were detected in one proband and one, KCNH2-A80V, was detected in another. These could not be assessed further because all relatives evaluated were either unaffected non-carriers or apparently unaffected relatives refused gene testing. In the one family in whom a relative was later diagnosed with HCM, proband DNA was available and underwent testing for inherited arrhythmia syndrome and HCM genes without a mutation being detected. Thirty-three relatives from 15 families whose probands'
DNA were unavailable for analysis also underwent testing. Five relatives with LQTS carried mutations (four with KCNH2-S55L and one with SCNSA-T370M) and nine with Brugada syndrome (SCNSA-E1784K). In one ARVC family no proband DNA was available for mutation analysis and relatives refused testing.

Table 5 summarizes the 11 potential ion channel gene mutations that were detected but not found in controls. SCNSA-E1784K, KCNH2-S55L, and SCNSA-Q376sp had been previously described. The novel mutations, SCNSA-A1680T, hRyR2-V2435I, and SCNSA-L461V failed to segregate with the disease phenotype and were therefore thought to be rare polymorphisms. No KCNJ2, ANK2, CAV3 or CASQ2 mutations were detected. Overall, the systematic genetic study of 31 probands and their families without any evidence of structural heart disease at autopsy or familial evaluation revealed eight ion channel mutations (26%).

Diagnosing long QT syndrome

Definite LQTS was diagnosed in 12/57 (21%) families with 25 affected individuals (17 first degree relatives) and possible/probable LQTS was diagnosed in 3/57 (5%) families with five affected individuals (three first degree relatives). One proband was considered a definite LQTS carrier based on genetic testing results (discussed earlier). The clinical features of probands and families are elaborated in Supplementary material online, Table S1. One proband, in whom antemortem data were available, and seven relatives, scored 4 or more on the Schwartz score (high probability LQTS), utilizing the resting ECG, of which four carried a mutation. Twenty-two relatives scored 4 or more on the Schwartz score (intermediate or low probability of LQTS) on the presenting ECG but further ECGs and careful assessment of the QTc during 24 h and exercise ECGs as well as

**Table 2 Characteristics of families and relatives**

<table>
<thead>
<tr>
<th></th>
<th>First-degree relatives</th>
<th>Non-first-degree relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>262</td>
<td>–</td>
</tr>
<tr>
<td>Total evaluated</td>
<td>184</td>
<td>38</td>
</tr>
<tr>
<td>Male:female (%)</td>
<td>77 (42%):107 (58%)*</td>
<td>22 (58%):16 (42%)</td>
</tr>
<tr>
<td>Total no. of relatives/family: mean (range)</td>
<td>4.60 (2–13)</td>
<td>–</td>
</tr>
<tr>
<td>Evaluated no. of relatives/family: mean</td>
<td>3.22</td>
<td>–</td>
</tr>
<tr>
<td>Mean proportion (range) of each family’s relatives evaluated</td>
<td>68.3% (10–100%)</td>
<td>–</td>
</tr>
<tr>
<td>Mean age (range, median)</td>
<td>32.3 (1–72, 32)</td>
<td>19 (2–80)</td>
</tr>
</tbody>
</table>

Relationship to proband:
- Parents: 69
- Siblings: 85
- Offspring: 30

Evaluated relatives ≥ 1 cardiac symptom:
- Total: 44 (24%)
- Syncpe: 13 (7%)

No. of families with history of unexpected premature sudden death:
- Any relative(s): 17 (30%)
- First-degree relative(s): 6 (11%)
- Non-first-degree relative(s): 14 (25%)

No. of unexpected premature sudden deaths (excluding proband):
- First-degree relative(s): 7
- Non-first-degree relative(s): 28

*P = 0.033.
*aAge < 45 years.

![Figure 3](https://academic.oup.com/eurheartj/article-abstract/29/13/1670/436846)

Figure 3 Pie chart describing the diagnoses made in sudden arrhythmic death syndrome (SADS) families.
Diagnosing Brugada syndrome
Sixteen relatives (11 first-degree) were diagnosed with Brugada syndrome. Eleven fulfilled clinical diagnostic criteria, five of whom carried the SCN5A-E1784K mutation. Four carried the SCN5A-E1784K mutation without fulfilling criteria, three of whom did not undergo ajmaline testing due to their young age. One was an obligate carrier.

Diagnosing structural heart disease
Of the nine families diagnosed with inherited structural heart disease only one proband’s heart (ARVC family) did not undergo an expert cardiac pathologist’s assessment. The whole hearts of the majority of these probands [HCM (1), DCM (1), ARVC (2), and left ventricular non-compaction (2) families] underwent expert assessment. There was, however, no evidence of structural heart disease in any proband.

Nine first-degree relatives were diagnosed with ARVC, often requiring a full range of investigations. One relative’s echocardiogram revealed left ventricular dilatation and she was subsequently found to carry the known PKP2-S140F mutation. Her father and dead brother’s DNA also carried the same mutation and her father’s CMR scan demonstrated a non-diagnostic regional wall motion abnormality in the RV free wall.

Left ventricular non-compaction was diagnosed in three relatives, all demonstrating typical echocardiographic morphological features. Two had equivocal ECGs with minor T-wave abnormalities. Dilated and hypertrophic cardiomyopathies were diagnosed in three first degree relatives due to the detection of significant echocardiographic abnormalities in all three and abnormal resting ECGs in two.28,29

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**Table 3** Numbers of relatives affected by inherited heart disease with associated percentages

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>First-degree relatives</th>
<th>Non-first-degree relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS – high probability</td>
<td>13 (28%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>LQTS – intermediate probability</td>
<td>7 (15%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>11 (24%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>ARVC</td>
<td>9 (20%)</td>
<td>–</td>
</tr>
<tr>
<td>Left ventricular non-compaction</td>
<td>3 (7%)</td>
<td>–</td>
</tr>
<tr>
<td>DCM</td>
<td>2 (4%)</td>
<td>–</td>
</tr>
<tr>
<td>HCM</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>46 (100%)</td>
<td>15 (100%)</td>
</tr>
</tbody>
</table>

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**Table 4** Predictors of a diagnosis of inherited heart disease in evaluated first-degree relatives and families: first degree relatives are considered initially as individuals and then as part of families

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Diagnosis present</th>
<th>Diagnosis absent</th>
<th>Statistical significance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. relatives</td>
<td>46 (25%)</td>
<td>138 (75%)</td>
<td>–</td>
</tr>
<tr>
<td>Age (years) mean</td>
<td>31.0</td>
<td>36.8</td>
<td>ns</td>
</tr>
<tr>
<td>Male</td>
<td>39%</td>
<td>41%</td>
<td>ns</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>46%</td>
<td>18%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Presyncope</td>
<td>7%</td>
<td>1%</td>
<td>P = 0.035</td>
</tr>
<tr>
<td>Syncope</td>
<td>20%</td>
<td>4%</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Families

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Diagnosis present</th>
<th>Diagnosis absent</th>
<th>Statistical significance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of families</td>
<td>30 (53%)</td>
<td>27 (47%)</td>
<td>–</td>
</tr>
<tr>
<td>Total no. of evaluated relatives</td>
<td>102 (55%)</td>
<td>82 (45%)</td>
<td>–</td>
</tr>
<tr>
<td>Mean (range) number of first degree relatives/family</td>
<td>4.8 (2–8)</td>
<td>4.4 (2–10)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean proportion of each family evaluated</td>
<td>65%</td>
<td>72%</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years) mean</td>
<td>32.1</td>
<td>32.5</td>
<td>ns</td>
</tr>
<tr>
<td>Male</td>
<td>41%</td>
<td>43%</td>
<td>ns</td>
</tr>
<tr>
<td>First-degree relatives reporting symptoms</td>
<td>28 (27%)</td>
<td>16 (20%)</td>
<td>ns</td>
</tr>
<tr>
<td>First-degree relatives reporting syncope</td>
<td>11 (11%)</td>
<td>2 (2%)</td>
<td>P = 0.028</td>
</tr>
<tr>
<td>FH previous premature unexplained SD(s)</td>
<td>11/30 (37%)</td>
<td>6/27 (22%)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean no. previous premature unexplained SD(s)/family</td>
<td>0.83</td>
<td>0.37</td>
<td>ns</td>
</tr>
</tbody>
</table>

FH, family history; SD, sudden death.

*a* <45 years old.
Immediate management
Thirty-one out of 61 affected relatives received therapeutic interventions including betablockers in 30, the majority of whom carried LQTS, and ICDs in seven, three with Brugada syndrome (one asymptomatic) and four with LQTS (three symptomatic and one with other high risk features). All received appropriate life style and drug avoidance advice.

Discussion
Over half of SADS families who underwent cardiac evaluation had features of inherited cardiac disease, approximately one quarter of first-degree relatives being identified as likely to be affected. The conditions detected, and therefore likely to be culpable for the probands’ deaths, were LQTS, Brugada syndrome, and subtle structural disease, particularly ARVC. Approximately 7% of relatives had suffered syncopal episodes, a similar prevalence to phenotypically normal relatives in the international LQTS registry. One quarter of families had a history of additional premature sudden deaths. The cohort therefore appears to be at high risk of cardiac events and therapeutic intervention was possible with measures proven to protect individuals carrying genetic cardiac disease from sudden death. 

Table 5 Results of mutation analysis in sudden arrhythmic death syndrome (SADS) families

<table>
<thead>
<tr>
<th>Cardiac diagnosis</th>
<th>Number of families with a mutation detected (%)</th>
<th>Mutations detected (unequivocal unless otherwise stated)</th>
<th>Probable novel rare polymorphisms detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite LQTS</td>
<td>5/13 (38%)</td>
<td>KCNH2: Q376sp&lt;sup&gt;26&lt;/sup&gt;, E544fs49K, A80V, S55L&lt;sup&gt;25&lt;/sup&gt;</td>
<td>SCN5A: T370M</td>
</tr>
<tr>
<td>Possible/probable LQTS</td>
<td>0/3</td>
<td>SCN5A: E1784K&lt;sup&gt;24&lt;/sup&gt;</td>
<td>SCN5A: L461V&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>1/5 (20%)</td>
<td>SCN5A: L461V&lt;sup&gt;6&lt;/sup&gt;</td>
<td>hRyR2: V2435F&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>ARVC</td>
<td>1/4 (25%)</td>
<td>PKP2: S140F&lt;sup&gt;23&lt;/sup&gt;</td>
<td>SCN5A: A1680T</td>
</tr>
<tr>
<td>Other structural disease</td>
<td>0/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1/10 (10%)</td>
<td>SCN5A: P1187L&lt;sup&gt;a&lt;/sup&gt;, G1935S&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 continued...

<table>
<thead>
<tr>
<th>Cardiac diagnosis</th>
<th>Number of families with a mutation detected (%)</th>
<th>Mutations detected (unequivocal unless otherwise stated)</th>
<th>Probable novel rare polymorphisms detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1/10 (10%)</td>
<td>SCN5A: P1187L&lt;sup&gt;a&lt;/sup&gt;, G1935S&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Two equivocal mutations in the same proband.
<sup>b</sup>Two rare polymorphisms in the same relative.

The autopsy: how was structural disease missed?
Inherited structural heart disease was detected in relatives yet was not identified at post-mortem despite additional assessment by a specialist cardiac pathologist in the majority of cases. There are three possible reasons for this: (i) Structural genetic myocardial conditions, even when expressed insufficiently at a microscopic level to meet diagnostic criteria, may cause sudden death. (ii) Even thorough expert histopathological evaluation of a macroscopically normal heart may fail to identify areas of myocardium where sufficient abnormality is present to meet diagnostic criteria and cause sudden death. (iii) Insufficient tissue may be available to evaluate the heart thoroughly and satisfactorily, in particular the RV.

Comparison with other studies
This study was undertaken in a tertiary centre. There was therefore a possibility of referral bias, which may have resulted in families with less obvious inherited heart disease being studied. This may have in turn resulted in an underestimate of the frequency of such disease.

We therefore compared the results of this study with our previously reported experience in the SADS study, a national population-based prospective survey that recruited via coroners rather than physicians. SADS study probands were older (30 vs. 26 years) and, in addition to a full coroner’s autopsy, all underwent expert cardiac pathological evaluation compared with 75% in the current cohort. This reflected that the current study’s sample was generated from real-world referrals where an expert cardiac pathologist’s evaluation may not always be feasible. There were no other significant differences in the characteristics of probands (including the male
predominance), their relatives and their family histories. This suggested that the current cohort is similar to the SADS study’s unselected sample.\(^3\)

In comparison with the restricted research protocol of the initial SADS study\(^2\) a comprehensive range of investigations (Figure 2) improved the diagnostic yield of both non-structural and structural inherited heart disease amongst first degree relatives (25 vs. 5.5%) and hence SADS families (54 vs. 22%). All investigative tools contributed to individuals’ and hence families’ ultimate diagnoses. Ajmaline provocation was vital to the diagnosis of Brugada syndrome.\(^8\) A diagnosis of ARVC, however, required detection of a few subtle manifestations, no single test carrying sufficient sensitivity to be the sole diagnostic tool. This may explain why the limited protocol of the SADS study had failed to diagnose ARVC and Brugada syndrome in relatives.

Tan et al.\(^4\) utilized a similar comprehensive investigative strategy in families with frequent sudden unexplained deaths and achieved similar diagnostic yields. The overall malignant nature of the histories of those families who were diagnosed with inherited cardiac diseases was consistent, however, with genetic disease even before familial evaluation was undertaken. Indeed the presence of two or more premature sudden unexplained deaths in a family was a predictor of a diagnosis. Our current study had a lower frequency of additional sudden unexplained deaths and such a family history was not of predictive value. This, however, may have been a limitation of the study’s sample size. The only significant predictor of a successful diagnosis was the reporting by first-degree relatives of syncope.

Tan’s group also differed in that approximately half of index cases had not undergone any pathological examination and the circumstances of death were strongly associated with exertion rather than rest or sleep. This is reflected by 5/43 families being diagnosed with CPVT and carrying mutations in hRyR2 (19;20) and 2/4 LQTS families carrying KCNQ1 mutations.\(^32\) All demonstrated characteristic ventricular arrhythmia and/or sudden death on exercise. Interestingly Tester et al.\(^21,34\) have described seven carriers of hRyR2 mutations and five carriers of KCNQ1 mutations in 49 medical examiner cases of sudden unexpected death with normal autopsies and a mixture of exertional, sleep-associated, and unknown circumstances of death.

In the current cohort, no mutations were detected in KCNQ1 or CASQ2 and only one potential variant of hRyR2 was identified although it failed to co-segregate with phenotype. Tan’s series appears to be a selected high-risk group without thorough pathological assessment. The SADS population described here and elsewhere\(^3\) may therefore reflect the spectrum of young ‘normal heart’ sudden death more accurately. In Tester’s series a significant proportion of LQT1 and hRyR2 mutations were novel and may have represented uncommon non-pathogenic variants. There remains, however, a difference in genetic composition when compared with the current cohort. This may be explained either by chance or by a difference in methodology when receiving selected autopsy referrals from medical examiners compared with the referral of families as described here.

Nonetheless, a common message does arise from the current study and the three other comparators\(^3,4,21,34\) that an expert pathological and molecular autopsy in SADS cases is important and that their families warrant evaluation.\(^35\)

**Mutation analysis**

The presence of potential mutations in SCN5A and KCNH2 amongst SADS families was expected as the characteristic circumstances of death in LQT2, LQT3\(^36\) and Brugada syndrome\(^8\) include death during sleep, at rest or after sudden arousal from sleep, a feature of the majority of SADS victims. KCNH2 and SCN5A mutations have also been detected in other series of sudden unexpected deaths\(^34,37\) including infants.\(^38\) LQT3 and Brugada syndrome also present more commonly and with greater severity amongst males, another SADS proband characteristic.\(^8,39\) SCN5A-E1704K had been reported previously as causing LQT3,\(^24\) although our family’s features were consistent with an overlap of Brugada and LQTS.

The majority of diagnosed cases were not confirmed by genetic testing. Current knowledge means that ~60–70% of patients with LQTS and a minority of those with Brugada syndrome and ARVC can be genotyped.\(^8,21,23,25,26\) The 38% yield in definite LQTS families may be due to the spectrum of LQTS being studied or may be a chance finding. The proportion of families without evidence of structural disease and carrying an LQTS/Brugada syndrome mutation [8/31 (26%)] compares favourably with the proportions reported in two other autopsy series of unexplained sudden deaths described by Chugh et al.\(^27\) [2/12 (17%)] and Tester and Ackerman\(^34\) [10/49 (20%)].

Only one (10%) proband from families without a diagnosis, who underwent testing, was identified as carrying mutations (SCN5A-P1187L, SCN5A-G1933S). The yield of testing in this group may have been limited by the difficulty of extracting sufficient quality DNA from paraffin fixed blocks, the commonest form of retained tissue sample.

**The family: risk of sudden death and undiagnosed disease**

The detection of inherited heart disease in a family appeared to differentiate the family members’ level of risk when compared with undiagnosed families due to a higher frequency of syncope amongst relatives. Another marker of inherited heart disease is the presence of a family history of additional sudden premature death(s), but diagnosed families were not significantly different from the undiagnosed. This suggested that those carriers with sufficient expression of inherited disease to merit a diagnosis also tended to be symptomatic. Less penetrant disease that failed to cause symptoms but still caused sudden deaths may therefore be present in some of the 47% of undiagnosed families whose members remain potentially at risk. Consequently an improvement of diagnostic yield is important.

**Improving the yield**

A greater use of expert cardiac pathologists and retention of the whole heart for their histological review as well as frozen spleen or blood for mutation analysis are vital for improved diagnostics. There was no bias in favour of larger or more thoroughly evaluated families receiving a diagnosis in this study. Nonetheless, encouraging a full evaluation of all first degree relatives (particularly males who attended less frequently than females) or potential obligate carriers may maximize the chances of identifying incompletely penetrant disease. Improvement of the investigative
armamentarium should also be considered. More comprehensive ajmaline testing may increase diagnoses of Brugada syndrome although its sensitivity is not 100%. More comprehensive testing of the RyR2 gene may diagnose non-penetrant CPVT.

**Practical clinical guidelines**

Figure 4 provides recommendations for clinicians faced with a family with a young sudden death and places the SADS investigative algorithm (Figure 2) in context. Genetic testing in arrhythmia syndromes or cardiomyopathy should be comprehensive for the major genes involved as compound heterozygosity is prevalent and causes more severe disease.

**Summary**

These data underscore that SADS deaths are caused by inherited heart disease and more comprehensive clinical and genetic evaluation of families identifies more relatives at risk of sudden death.

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**Figure 4** Suggested practical guidelines for clinicians faced with a family with an unexpected and/or unexplained young sudden death. Asterisk: may not be feasible and requires family's consent.
The potential number of deaths involved is significant and there are risk stratification algorithms and effective treatments available for these inherited cardiac conditions. This highlights the importance of the prompt recognition of symptomatic young people for these inherited cardiac conditions. This highlights the importance of the prompt recognition of symptomatic young people for these inherited cardiac conditions.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References


