**TITLE PAGE**

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**Full title:** Investigation of the Family of Sudden Cardiac Death Victims

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**HIGHLIGHTS**

* A significant proportion of sudden cardiac deaths in the young are caused by an underlying inherited cardiac condition, either structural or purely arrhythmogenic.
* Sudden cardiac death at a young age mandates cardiological investigation in the surviving family.
* First-degree relatives, obligate carriers, and symptomatic relatives are more likely to be affected and they thus should be prioritized for evaluation
* Clinical evaluation of family members is staged, less invasive investigations being offered first and more invasive tests being subsequently considered if a diagnosis is not made.
* Clinical evaluation has a substantial diagnostic yield in blood related family members.
* In SCD cases where a mutation is revealed by molecular autopsy, initial familial genetic testing should focus on the parents to determine whether the gene mutation is inherited, or arose *de novo* in the deceased. If inherited, targeted cascade genetic screening is offered to asymptomatic relatives in conjunction with clinical evaluation and alongside comprehensive pre- and post-test genetic counseling.
* If a diagnosis is made in the family then genetic testing can be offered targeted to the phenotype.
* Specialized multidisciplinary cardiac genetic teams have a pivotal role in management of the family of sudden cardiac death victims.

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**NON-STRUCTURED ABSTRACT**

228 words (<300 words)

Sudden cardiac death in the young is a devastating event and a significant proportion of cases are caused by an underlying inherited cardiac condition. This justifies investigation of surviving blood relatives in order to identify a definite diagnosis and to prevent further deaths. First-degree relatives, obligate carriers, and symptomatic relatives are family members who are more likely to be affected and/or at risk and should be prioritized for evaluation. Cardiological clinical evaluation of family members is staged, less invasive investigations being first offered and more invasive tests being subsequently considered if a diagnosis is not made. If a phenotype is identified, then targeted genetic testing can be undertaken. Results of post-mortem genetic testing (the molecular autopsy) in the decedent may confirm familial results or guide cascade testing in order to identify presymptomatic individuals. When a genetic diagnosis is made in the sudden death case, initial familial genetic testing should focus on the parents to determine whether the mutation is inherited, or arose *de novo* in the deceased. Management of the surviving family and genetic counselling should be offered in the setting of a specialized, multidisciplinary cardiac genetic team to offer the most accurate care and support to family members. Further research into understanding the genetic basis of sudden cardiac death and new diagnostic modalities will contribute to improve management and prevention of sudden cardiac death in the young.

**KEYWORDS**

Sudden cardiac death; post-mortem; molecular autopsy; gene; family; screening.

**INTRODUCTION**

Sudden cardiac death (SCD) in the young carries devastating consequences for both the surviving family and the community. Unexplained sudden death (Sudden unexplained death syndrome, SUDS) refers to a sudden cardiac death that occurs in an apparently healthy and often young individual within an hour of the onset of symptoms and for no apparent reason.(1,2) It is a diagnosis of exclusion that covers a number of possible etiologies. If the death remains unexplained despite thorough death scene investigation and comprehensive post-mortem examination, including histopathology and toxicology, the term sudden arrhythmic death syndrome or SADS is preferred.(3,4) The term sudden infant death syndrome or SIDS is used in cases under 1 year of age,(5) although this diagnosis implies a more stringent circumstantial and forensic investigation.(6) There is also much less data around the role for clinical cardiological evaluation in SIDS.

Not only is the proportion of SADS apparently higher in the young, but victims are also more commonly young men who die suddenly in their sleep or at rest.(4) Indeed, an undiagnosed inherited cardiac condition is likely to explain a substantial subset of SADS in adult victims (7) as well as in infants and children.(8) Once a diagnosis of SADS has been made, further management tries to establish the exact cause of death in the deceased and involves investigation of surviving family members. The aim is to avoid additional deaths among relatives in case of an underlying inherited cardiac disorder.

Investigation of the surviving family is particularly relevant in cases of: (a) SUDS or SADS; (b) family history of premature sudden death; (c) or post-mortem examination suggesting an inherited structural cardiac disease such as a hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy (9).

This review article aims to provide a comprehensive up-to-date approach for evaluation and management of family members of young SUDS or SADS victims.

**BACKGROUND**

**Epidemiology of unexplained sudden cardiac death.** Incidence and prevalence of SADS vary according to studies. In the United Kingdom, the incidence of SADS among the general population aged 4 to 64 years has been estimated to be up to 1.34/100,000 per annum (4) with 4.1% of sudden cardiac death in the age group 16 to 64 years being unexplained (10), whereas a 0.76/100,000 year incidence of SADS, accounting for 27% of the SCD in subjects aged 14 to 35 years old has been reported in an Irish study (11). This is consistent with an Australian study performed in the 5 to 35-year-old age group (12).

The incidence of SIDS is well defined however and significantly exceeds the incidence of SADS in young adults or in children over 1 year of age. In the United States, a population-based study revealed an annual incidence of SIDS of 80/100,000 for children <1 year and of SADS of 3/100,000 for children age 1–4 years (13). An Irish national study found similar results with a SIDS rate of 59/100,000 in children <1 year compared to as SADS rate of 1.4/100,000 among children aged 1–4 (14). Risk reduction campaigns have resulted in an unequivocal decrease in incidence by 50-90% (15), most noticeably the 1990s ‘Back to Sleep’ campaign advocating a supine sleep position for infants. However, despite these efforts SIDS rate has plateaued and its current rate is 53/100,000 in the United States and 40/100,000 livebirths in the UK (16,17), positioning SIDS as the leading cause of post-neonatal infant mortality in developed countries (6,15).

**Causes of sudden cardiac death in the young.** Whereas coronary artery disease and myocardial infarction account for over 90% of cases of SCD in the general population (18) SCD in the young – namely below the age of 40 – is caused by a wide variety of causes that can be categorized into structural cardiac diseases and primary electrical disorders (19). Structural causes of sudden cardiac death include: (a) inherited cardiomyopathies such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC) and left ventricular non-compaction; (b) congenital heart diseases; (c) acquired cardiac condition such as coronary artery disease or myocarditis (1). These structural cardiac conditions are usually identified by postmortem examination, but subtle forms of the disease may not be recognized, even by expert pathologists. Primary electrical diseases typically occur in structurally normal hearts and are not recognized by postmortem examination. This includes congenital long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome and idiopathic ventricular fibrillation (20,21). Causes of sudden death in the young are detailed elsewhere in this journal issue (*Davis et al, same issue*).

**MANAGEMENT OF FAMILY MEMBERS**

An algorithm to describe the investigative strategy of families of SCD victims is summarized in Figure 1.

**Rationale of the autopsy.** Postmortem pathological examination may identify an inherited structural heart disease, justifying familial investigations. An autopsy-negative case must lead to investigation of surviving relatives as well, as primary electrical disorders can cause SADS and may be familial. The accurate identification of the cause of sudden death is therefore crucial to determine whether an underlying genetic cardiac disorder is likely and whether there are other potentially at-risk family members. Expert autopsy is recommended as general pathologists may misdiagnose cases, overdiagnosing ARVC, and underdiagnosing SADS (22). Guidelines for autopsy practice exist and include detailed description of postmortem sampling techniques with integration of specialist skills in the evaluation of possible familial disorders (23).

**Molecular autopsy of the victim (the decedent).** Investigations in the family can depend on the results of post-mortem genetic testing, or ‘molecular autopsy’, of the victim. Introduced more than 10 years ago (24), postmortem genetic testing in addition to comprehensive post-mortem examination has proven to be useful in identifying an underlying cause in unexplained SCD. Molecular autopsy of the victim involves the collection of tissue suitable for DNA extraction at autopsy and mutation analysis for selected candidate genes responsible for the main primary electrical disorders. Recent Heart Rhythm Society/European Heart Rhythm Association guidelines recommend the use of targeted postmortem genetic testing in SADS cases especially where clinical evidence suggests a diagnosis of LQTS or CPVT (9,25). Collection of blood and/or suitable tissue for molecular autopsy is also recommended in case of SIDS as an arrhythmia syndrome focused post-mortem genetic testing can be useful (9), although data are still limited. Initial studies targeted a limited number of candidate genes, focusing upon the common causes of LQTS (*KCNQ1*, *KCNH2*, *SCN5A*), BrS (SCN5A) and CPVT (*RyR2*) (26). Recent advances in sequencing technologies (next-generation sequencing) have now made it possible to screen in detail an increasing number of genes in cardiac gene panels at relatively low cost and using a limited amount of DNA. In addition, whole-exome sequencing, where the coding regions of all ~22,000 genes is sequenced, has also been employed in post-mortem genetic testing (27). It is important to note that these technologies extend to the inclusion of genes involved in the inherited cardiomyopathies in addition to the channelopathy genes (28,29). Testing modalities and diagnostic yield of molecular autopsy are presented in details elsewhere in this issue of the journal (*Semsarian et al., same issue*).

**Review of family history.** Evaluation of the surviving family of the SCD victim is performed with a full clinical history with detailed information spanning a minimum of three generations, including the deceased individual. Particular attention should be given to relatives who have suffered suspicious symptoms, such as syncope and seizures, as well as any family history of sudden death at a young age. If necessary, medical records, postmortem reports and death certificates should be reviewed to confirm any suspected diagnoses in relatives. Further information about the family history can often provide useful insight into the genetic heart disease affecting the family (3,30,31).

**Clinical evaluation**. Astandardized approach to clinical evaluation of first-degree relatives is important (1). The strategy of evaluation of family members is staged, as recommended by the Heart Rhythm Society/European Heart Rhythm Association consensus statement for inherited arrhythmia syndromes (9). These recommendations also apply to families of SIDS’ victims although with less certainty of utility (9). Less invasive investigations are first offered and more invasive tests are then considered if a diagnosis is not made. First-degree relatives, obligate carriers, and symptomatic relatives are more likely to be affected and/or at risk of SCD and should be prioritized for evaluation (31).

All relatives should have a comprehensive review of medical and family history, physical examination, resting ECG (with high intercostal space leads), exercise ECG, and a transthoracic echocardiogram. Depending on the clinical situation, further investigations may include 24 h ECG monitoring, signal-averaged ECG, pharmacological provocation tests (such as a sodium channel blocker challenge in suspected BrS patients) and cardiac magnetic resonance imaging (especially in suspected arrhythmogenic right ventricular cardiomyopathy) (1,31). It should be noted that resting and exercise ECGs, cardiac imaging and sodium channel blocker challenge offer the most diagnostic value across studies (31-33). If a diagnosis is made in a proband then genetic testing can be offered targeted to the phenotype (9).

Clinical evaluation alone in relatives of SCD victims may identify an underlying cause in around 30% (range: 13.2% to 52.6%) of selected and comprehensively evaluated families (Figure 2), identifying an inherited arrhythmia syndrome (such as LQTS, CPVT or BrS) or a subtle form of inherited cardiomyopathy (such as HCM or ARVC) (3,26,29-36). Diagnostic yield of familial evaluation is summarized in Figure 2. In a landmark study evaluating 109 first-degree family members of 32 unrelated SADS victims, an inherited cardiac disease was diagnosed in 22% of the families by limited clinical evaluation alone (3). Tan et al. then confirmed a high diagnostic yield of routine, non-invasive cardiac tests in relatives of 43 families of young unexpected sudden death victims, some without autopsies, identifying an inherited cardiac disorder in 40% of families and 8.9 presymptomatic disease carriers per family (30). In a further study, 53% of 57 SADS families were diagnosed with inheritable heart disease using a comprehensive protocol (31).

In a follow-up Dutch series of 140 cases familial cardiological and targeted genetic evaluation gave a diagnostic yield of 33% following SUDS, with inherited conditions comprising 97% (32). In their protocol, investigations beyond resting ECG were performed on clinical suspicion only, which may have reduced the overall yield, but increased the sensitivity of additional investigations. Relatives’ ECGs contributed to a familial diagnosis in 14% of all cases, whereas drug provocation testing and cardiac magnetic resonance imaging showed higher yields, albeit when directed by clinical suspicion. Whilst inherited arrhythmia syndromes represented the majority of causes irrespective of age, the proportion related to cardiomyopathy increased with age (32), reflecting age-related penetrance of the conditions. This confirms the importance of imaging, including cardiac magnetic resonance, in evaluation of families (7). More recently a study from Australia and New Zealand identified a definite diagnosis in 12 of 91 families (13%) of unexplained SCD of children and young adults, consisting of an inherited arrhythmia syndrome in 7 families and in an inherited cardiomyopathy in 5 families (29).

The potential diagnostic utility of investigating the surviving pediatric relatives following SADS had been suggested in a small series with a 19% diagnostic yield (37). This was further confirmed by Wong et al. who demonstrated that cardiac evaluation of pediatric relatives of a SADS victim is useful, especially when focused upon first-degree relatives and on conditions usually expressed in childhood (33). The only useful diagnostic tests were the 12-lead and exercise electrocardiograms and ajmaline provocation tests although provocation testing was often delayed until later teenage years. However young family members may require periodic reassessment even if the initial evaluation is normal as certain diseases such as BrS and cardiomyopathy have age-related penetrance (38).

Only a small minority of evaluated relatives appear to be at sufficiently high risk from an inherited cardiac condition sufficient to require implantation of an implantable cardioverter-defibrillator: usually indicated for only 2% of relatives of SADS cases (31,39). This may reflect the fact that the SADS case was the highest risk individual in each family but was undetected prior to death. Nevertheless, a substantial subset of evaluated relatives required risk modification, medical therapy, and on-going follow-up and advice (31,39). Family members who are clinically screened and found to have no evidence of disease may require follow up at regular intervals dependent upon any disease already identified in the family and the age of the individual. Current guidelines advocate the discharge of asymptomatic negative phenotype adults and follow-up of pediatric cases up to adulthood (9). Based on the knowledge that many genetic heart disorders usually become symptomatic in the second decade of life, it has been proposed that unaffected family members aged 10 to 20 years should be clinically screened on a yearly basis (40). Occurrence of new symptoms in relatives or of additional suspicious sudden deaths within the family should lead to repeat cardiological investigations. Further surveillance of otherwise asymptomatic, clinically unaffected relatives is probably unnecessary.

**Cascade genetic screening.** Cascade genetic screening of blood-related individuals may be considered depending on the results of the proband’s initial genetic testing, in order to clarify whether other family members are silent mutation carriers and thus exposed to the arrhythmic risk (41).

In cases where a genetic diagnosis is made in the decedent, initial familial genetic testing should focus on the parents to determine whether the gene mutation is inherited, or arose *de novo* in the deceased. In SCD cases where the identified mutation in the decedent did not arise *de novo*, the major utility of the genetic result is in cascade screening of at-risk blood relatives. Offering cascade screening to asymptomatic relatives should always be performed in conjunction with clinical evaluation and only alongside comprehensive pre- and post-test genetic counselling (42). Indeed, asymptomatic blood-relatives with a normal ECG should not be considered unaffected because of the variable penetrance of inherited arrhythmia syndromes: genotype-positive, phenotype-negative individuals or so-called silent mutation-carriers (43). Even if these family members may carry a low risk of life-threatening arrhythmia, the risk is not zero and can increase dramatically under specific circumstances such as fever in BrS (44) or drugs that prolong the QT interval (45).

Importantly, in SADS cases where no blood/DNA was collected, genetic testing should not be initiated in any living family relatives unless a clear disease phenotype is present (1). Moreover, the diagnostic yield of genetic test is never 100% so a negative genetic test does not exclude the diagnosis.

**Genetic counselling.** All families in whom a familial cause of SCD is identified should benefit from genetic counselling, even if there is no definite clinical diagnosis (*Ingles et al., same issue*). Underpinning the cardiological evaluation and genetic screening of family members is the presumption that the underlying cause may be an inherited arrhythmia syndrome, most of which display autosomal dominant inheritance (21,42) i.e. first-degree relatives have a 1 in 2 (50%) chance of inheriting the same mutation. However, inherited arrhythmia syndromes are also characterized by a marked phenotypic variability and sometimes age-dependent penetrance (26,42), which means that although the probability of additional blood-related individuals being affected is high, targeting a clinical phenotype can be difficult. It is also thought that not only the causative gene mutation, but also the environment and modifying genes may contribute to some of this variability, stressing the importance of further research aimed at understanding genetic heart diseases.

**Role of cardiac genetic services.** Management of surviving family of a SADS or a SIDS death is complex and requires a multidisciplinary specialized team for managing clinical cardiovascular investigations, molecular autopsy of the decedent, genetic cascade screening of blood relatives, interpretation of results, preventative measures for presymptomatic individuals and psychological support. The specialized multidisciplinary cardiac genetic clinic is a model used worldwide with appropriately trained staff (9,25) providing suitable expertise: cardiologists (adult and pediatric), geneticists, genetic counsellors, forensic pathologists, genetic nurses, and patient support groups (46).

**CONCLUSION**

A significant proportion of cases of SCD in the young are caused by an underlying inherited cardiac condition, which justifies investigation of all surviving relatives in order to identify a definite diagnosis and to prevent further arrhythmic deaths in blood related individuals. Cardiological clinical evaluation of family members is staged and carries a high diagnostic yield. Cascade targeted genetic screening in the family is offered in families where an inherited mutation is identified in the decedent, in order to identify presymptomatic individuals. Specialized multidisciplinary cardiac genetic teams have a key role to manage such families. Further research into understanding the genetic basis of sudden cardiac death and diagnostic modalities for family screening will contribute to improve management and prevention of sudden cardiac death in the young.

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**REFERENCES**

1. Semsarian C, Ingles J, Wilde AA. [Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives.](http://www.ncbi.nlm.nih.gov/pubmed/25765769) Eur Heart J. 2015;36:1290-6.

2. [Morrow W](http://www.ncbi.nlm.nih.gov/pubmed/?term=Morrow%20W), [Berger S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Berger%20S), [Jenkins K](http://www.ncbi.nlm.nih.gov/pubmed/?term=Jenkins%20K), et al. Pediatric sudden cardiac arrest. Pediatrics. 2012;129:e1094-102.

3. Behr E, Wood DA, Wright M, et al. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. Lancet 2003;362:1457–1459.

4. Behr ER, Casey A, Sheppard M, et al. Sudden arrhythmic death syndrome: a national survey of sudden unexplained cardiac death. Heart 2007;93:601–605.

5. Goldstein RD, Kinney HC, Willinger M. [Sudden Unexpected Death in Fetal Life Through Early Childhood.](http://www.ncbi.nlm.nih.gov/pubmed/27230764) Pediatrics. 2016;137. pii: e20154661.

6. [Kinney HC](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kinney%20HC%5BAuthor%5D&cauthor=true&cauthor_uid=19692691), [Thach BT](http://www.ncbi.nlm.nih.gov/pubmed/?term=Thach%20BT%5BAuthor%5D&cauthor=true&cauthor_uid=19692691). The sudden infant death syndrome. N Engl J Med. 2009;361:795-805.

7. Raju H, Behr ER. [Unexplained sudden death, focussing on genetics and family phenotyping.](http://www.ncbi.nlm.nih.gov/pubmed/23128498) Curr Opin Cardiol. 2013;28:19-25.

8. Wong LC, Behr ER. [Sudden unexplained death in infants and children: the role of undiagnosed inherited cardiac conditions.](http://www.ncbi.nlm.nih.gov/pubmed/24585884) Europace. 2014;16:1706-13.

9. Priori SG, Wilde AA, Horie M, et al. [HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013.](http://www.ncbi.nlm.nih.gov/pubmed/24011539) Heart Rhythm. 2013;10:1932-63.

10. [Bowker TJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bowker%20TJ%5BAuthor%5D&cauthor=true&cauthor_uid=12651971), [Wood DA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Wood%20DA%5BAuthor%5D&cauthor=true&cauthor_uid=12651971), [Davies MJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Davies%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=12651971), et al. Sudden, unexpected cardiac or unexplained death in England: a national survey. QJM. 2003;96:269-79.

11. [Margey R](http://www.ncbi.nlm.nih.gov/pubmed/?term=Margey%20R%5BAuthor%5D&cauthor=true&cauthor_uid=21798877), [Roy A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Roy%20A%5BAuthor%5D&cauthor=true&cauthor_uid=21798877), [Tobin S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Tobin%20S%5BAuthor%5D&cauthor=true&cauthor_uid=21798877), et al. Sudden cardiac death in 14- to 35-year olds in Ireland from 2005 to 2007: a retrospective registry. Europace. 2011;13:1411-8.

12. Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. [Sudden death in the young.](http://www.ncbi.nlm.nih.gov/pubmed/16360077) Heart Rhythm. 2005;2:1277-82.

13. [Chugh SS](http://www.ncbi.nlm.nih.gov/pubmed/?term=Chugh%20SS%5BAuthor%5D&cauthor=true&cauthor_uid=19879540), [Reinier K](http://www.ncbi.nlm.nih.gov/pubmed/?term=Reinier%20K%5BAuthor%5D&cauthor=true&cauthor_uid=19879540), [Balaji S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Balaji%20S%5BAuthor%5D&cauthor=true&cauthor_uid=19879540), et al. Population-based analysis of sudden death in children: The Oregon Sudden Unexpected Death Study. Heart Rhythm. 2009;6:1618-22.

14. McGarvey CM, O'Regan M, Cryan J, et al. [Sudden unexplained death in childhood (1-4 years) in Ireland: an epidemiological profile and comparison with SIDS.](http://www.ncbi.nlm.nih.gov/pubmed/22685045) Arch Dis Child. 2012;97:692-7.

15. Moon RY, Horne RS, Hauck FR. [Sudden infant death syndrome.](http://www.ncbi.nlm.nih.gov/pubmed/17980736) Lancet. 2007;370:1578-87.

16. [Matthews TJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Matthews%20TJ%5BAuthor%5D&cauthor=true&cauthor_uid=26270610), [MacDorman MF](http://www.ncbi.nlm.nih.gov/pubmed/?term=MacDorman%20MF%5BAuthor%5D&cauthor=true&cauthor_uid=26270610), [Thoma ME](http://www.ncbi.nlm.nih.gov/pubmed/?term=Thoma%20ME%5BAuthor%5D&cauthor=true&cauthor_uid=26270610). Infant Mortality Statistics From the 2013 Period Linked Birth/Infant Death Data Set. Natl Vital Stat Rep. 2015;64:1-30.

17. Trachtenberg FL, Haas EA, Kinney HC, Stanley C, Krous HF. [Risk factor changes for sudden infant death syndrome after initiation of Back-to-Sleep campaign.](http://www.ncbi.nlm.nih.gov/pubmed/22451703) Pediatrics. 2012;129:630-8.

18. Wellens HJ, Schwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J 2014;35:1642–1651.

19. Ackerman M, Atkins DL, Triedman JK. [Sudden Cardiac Death in the Young.](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/26951821) Circulation. 2016;133:1006-26.

20. [Bezzina CR](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bezzina%20CR%5BAuthor%5D&cauthor=true&cauthor_uid=26044248), [Lahrouchi N](http://www.ncbi.nlm.nih.gov/pubmed/?term=Lahrouchi%20N%5BAuthor%5D&cauthor=true&cauthor_uid=26044248), [Priori SG](http://www.ncbi.nlm.nih.gov/pubmed/?term=Priori%20SG%5BAuthor%5D&cauthor=true&cauthor_uid=26044248). Genetics of sudden cardiac death. Circ Res. 2015;116:1919-36.

21. Cerrone M, Priori SG. Genetics of sudden death: focus on inherited channelopathies. Eur Heart J 2011;32:2109–2118.

22. de Noronha SV, Behr ER, Papadakis M, et al. [The importance of specialist cardiac histopathological examination in the investigation of young sudden cardiac deaths.](http://www.ncbi.nlm.nih.gov/pubmed/24148315) Europace. 2014;16:899-907.

23. [Erck Lambert AB](http://www.ncbi.nlm.nih.gov/pubmed/?term=Erck%20Lambert%20AB%5BAuthor%5D&cauthor=true&cauthor_uid=27113380), [Parks SE](http://www.ncbi.nlm.nih.gov/pubmed/?term=Parks%20SE%5BAuthor%5D&cauthor=true&cauthor_uid=27113380), [Camperlengo L](http://www.ncbi.nlm.nih.gov/pubmed/?term=Camperlengo%20L%5BAuthor%5D&cauthor=true&cauthor_uid=27113380), et al. Death Scene Investigation and Autopsy Practices in Sudden Unexpected Infant Deaths. J Pediatr. 2016;174:84-90.e1.

24. Tester DJ, Spoon DB, Valdivia HH, Makielski JC, Ackerman MJ. Targeted mutational analysis of the RyR2-encoded cardiac ryanodine receptor in sudden unexplained death: a molecular autopsy of 49 medical examiner/coroner’s cases. Mayo Clin Proc 2004;79:1380–1384.

25. Ackerman MJ, Priori SG, Willems S, et al. [HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA).](http://www.ncbi.nlm.nih.gov.gate2.inist.fr/pubmed/21787999) Heart Rhythm. 2011;8:1308-39.

26. [Miles CJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Miles%20CJ%5BAuthor%5D&cauthor=true&cauthor_uid=26143861), [Behr ER](http://www.ncbi.nlm.nih.gov/pubmed/?term=Behr%20ER%5BAuthor%5D&cauthor=true&cauthor_uid=26143861). The role of genetic testing in unexplained sudden death. Transl Res. 2016;168:59-73.

27. [Lahrouchi N](http://www.ncbi.nlm.nih.gov/pubmed/?term=Lahrouchi%20N%5BAuthor%5D&cauthor=true&cauthor_uid=27303672), [Behr ER](http://www.ncbi.nlm.nih.gov/pubmed/?term=Behr%20ER%5BAuthor%5D&cauthor=true&cauthor_uid=27303672), [Bezzina CR](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bezzina%20CR%5BAuthor%5D&cauthor=true&cauthor_uid=27303672). Next-Generation Sequencing in Post-mortem Genetic Testing of Young Sudden Cardiac Death Cases. Front Cardiovasc Med. 2016 May 30;3:13.

28. Hata Y, Kinoshita K, Mizumaki K, et al. [Postmortem genetic analysis of sudden unexplained death syndrome under 50 years of age: A next-generation sequencing study.](http://www.ncbi.nlm.nih.gov/pubmed/27005929) Heart Rhythm. 2016;13:1544-51.

29. Bagnall RD, Weintraub RG, Ingles J, et al. [A Prospective Study of Sudden Cardiac Death among Children and Young Adults.](http://www.ncbi.nlm.nih.gov/pubmed/27332903) N Engl J Med. 2016;374:2441-52.

30. Tan HL, Hofman N, van Langen IM, van der Wal AC, Wilde AA. [Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives.](http://www.ncbi.nlm.nih.gov/pubmed/15998675) Circulation. 2005;112:207-13.

31. Behr ER, Dalageorgou C, Christiansen M, et al. [Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families.](http://www.ncbi.nlm.nih.gov/pubmed/18508782) Eur Heart J. 2008;29:1670-80.

32. [van der Werf C](http://www.ncbi.nlm.nih.gov/pubmed/?term=van%20der%20Werf%20C%5BAuthor%5D&cauthor=true&cauthor_uid=20646679), [Hofman N](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hofman%20N%5BAuthor%5D&cauthor=true&cauthor_uid=20646679), [Tan HL](http://www.ncbi.nlm.nih.gov/pubmed/?term=Tan%20HL%5BAuthor%5D&cauthor=true&cauthor_uid=20646679), et al. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center in The Netherlands. Heart Rhythm. 2010;7:1383-9.

33. Wong LC, Roses-Noguer F, Till JA, Behr ER. [Cardiac evaluation of pediatric relatives in sudden arrhythmic death syndrome: a 2-center experience.](http://www.ncbi.nlm.nih.gov/pubmed/25194972) Circ Arrhythm Electrophysiol. 2014;7:800-6.

34. [McGorrian C](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=McGorrian%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [Constant O](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Constant%20O%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [Harper N](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Harper%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [O'Donnell C](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=O'Donnell%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [Codd M](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Codd%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [Keelan E](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Keelan%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [Green A](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Green%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [O'Neill J](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=O'Neill%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [Galvin J](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Galvin%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23382499), [Mahon NG](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Mahon%20NG%5BAuthor%5D&cauthor=true&cauthor_uid=23382499). Family-based cardiac screening in relatives of victims of sudden arrhythmic death syndrome. Europace. 2013;15:1050-8.

35. [Kumar S](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Kumar%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Peters S](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Peters%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Thompson T](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Thompson%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Morgan N](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Morgan%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Maccicoca I](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Maccicoca%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Trainer A](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Trainer%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Zentner D](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Zentner%20D%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Kalman JM](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Kalman%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Winship I](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Winship%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23973953), [Vohra JK](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Vohra%20JK%5BAuthor%5D&cauthor=true&cauthor_uid=23973953). Familial cardiological and targeted genetic evaluation: low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. Heart Rhythm. 2013;10:1653-60.

.

36. [Mellor G](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Mellor%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25262685), [Raju H](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Raju%20H%5BAuthor%5D&cauthor=true&cauthor_uid=25262685), [de Noronha SV](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=de%20Noronha%20SV%5BAuthor%5D&cauthor=true&cauthor_uid=25262685), [Papadakis M](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Papadakis%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25262685), [Sharma S](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Sharma%20S%5BAuthor%5D&cauthor=true&cauthor_uid=25262685), [Behr ER](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Behr%20ER%5BAuthor%5D&cauthor=true&cauthor_uid=25262685), [Sheppard MN](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed/?term=Sheppard%20MN%5BAuthor%5D&cauthor=true&cauthor_uid=25262685).

Clinical characteristics and circumstances of death in the sudden arrhythmic death syndrome. Circ Arrhythm Electrophysiol. 2014;7:1078-83.

37. Tomaske M, Keller DI, Bauersfeld U. Sudden cardiac death: clinical evaluation of paediatric family members. Europace 2011;13:421–426.

38. Conte G, de Asmundis C, Ciconte G, et al. [Follow-up from childhood to adulthood of individuals with family history of Brugada syndrome and normal electrocardiograms.](http://www.ncbi.nlm.nih.gov/pubmed/25399282) JAMA. 2014;312:2039-41.

39. [Caldwell J](http://www.ncbi.nlm.nih.gov/pubmed/?term=Caldwell%20J%5BAuthor%5D&cauthor=true&cauthor_uid=22505462), [Moreton N](http://www.ncbi.nlm.nih.gov/pubmed/?term=Moreton%20N%5BAuthor%5D&cauthor=true&cauthor_uid=22505462), [Khan N](http://www.ncbi.nlm.nih.gov/pubmed/?term=Khan%20N%5BAuthor%5D&cauthor=true&cauthor_uid=22505462), et al. The clinical management of relatives of young sudden unexplained death victims; implantable defibrillators are rarely indicated. Heart. 2012;98:631-6.

40. Ingles J, Semsarian C. [Sudden cardiac death in the young: a clinical genetic approach.](http://www.ncbi.nlm.nih.gov/pubmed/17199842) Intern Med J. 2007;37:32-7.

41. Schwartz PJ, Ackerman MJ, George AL Jr, Wilde AA. [Impact of genetics on the clinical management of channelopathies.](http://www.ncbi.nlm.nih.gov.gate2.inist.fr/pubmed/23684683) J Am Coll Cardiol. 2013;62:169-80.

42. Wilde AA, Behr ER. Genetic testing for inherited cardiac disease. Nat Rev Cardiol 2013;10:571–583.

43. Schwartz PJ, Dagradi F. [Management of survivors of cardiac arrest - the importance of genetic investigation.](http://www.ncbi.nlm.nih.gov/pubmed/27383078) Nat Rev Cardiol. 2016 Jul 7. doi: 10.1038/nrcardio.2016.104.

44. Mizusawa Y, Morita H, Adler A, et al. [Prognostic significance of fever-induced Brugada syndrome.](http://www.ncbi.nlm.nih.gov/pubmed/27033637) Heart Rhythm. 2016;13:1515-20.

45. Behr ER, Roden D. [Drug-induced arrhythmia: pharmacogenomic prescribing?](http://www.ncbi.nlm.nih.gov/pubmed/23091201) Eur Heart J. 2013;34:89-95.

46. [Spoonamore KG](http://www.ncbi.nlm.nih.gov/pubmed/?term=Spoonamore%20KG%5BAuthor%5D&cauthor=true&cauthor_uid=26582592), [Ware SM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ware%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=26582592). Genetic testing and genetic counseling in patients with sudden death risk due to heritable arrhythmias. Heart Rhythm. 2016;13:789-97.

**FIGURE LEGEND**

**Figure 1.** Algorithm to describe the investigative strategy in the surviving family after unexpected sudden cardiac death, adapted from (9).

**Figure 2.** Causes of sudden arrhythmic death syndrome as determined by various studies of familial evaluation.