REVIEW ARTICLE

Cardiac Gene Defects Can Cause Sudden Cardiac Death in Young People

Silke Kauferstein, Nadine Kiehne, Thomas Neumann,
Heinz-Friedrich Pitschner, Hansjürgen Bratzke

SUMMARY

Background: In Europe, sudden cardiac death (SCD) is one of the most common causes of death. Although sudden cardiac death usually happens in older people, 5% to 10% of the affected individuals are young and apparently healthy. Sudden death in infants, children, and young adults is relatively rare, with an incidence of 1 to 5 per 100 000 persons per year. Nonetheless, up to 7000 asymptomatic children die in the USA each year, almost half of them without any warning signs or symptoms.

Method: Selective literature review.

Results: Although structural cardiovascular abnormalities explain most cases of sudden cardiac death in young people, the cause of death remains unexplained after autopsy in 10% to 30% of cases. Potentially lethal ion channel disorders (channelopathies) such as the long QT syndromes (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and the Brugada syndrome (BrS) may account for at least one-third of these unexplained cases. Most of these diseases are hereditary with autosomal-dominant transmission, i.e., there is a 50% chance that the children of affected individuals will be affected themselves.

Conclusions: Post-mortem genetic screening for sequence variations in cardiac ion channel genes has become an important forensic tool for elucidating the cause of sudden cardiac death. Moreover, it allows the identification of other family members bearing the previously undiagnosed gene defect, who can then undergo a cardiological evaluation if indicated by their clinical history.

Dtsch Arztebl Int 2008; 106(4): 41–7
DOI: 10.3238/arztebl.2009.0041

Key words: sudden cardiac death, ion channel disorder, cardiological diagnosis, molecular biology, family history

Sudden cardiac death is defined as unexpected death in apparently healthy people, which occurs within a very short time interval—usually 1 hour after symptom onset. It is one of the commonest causes of death in Western countries. In Germany alone, some 100 000 people die of sudden cardiac death every year. Although mainly older people are affected, in 5% to 15% of cases sudden cardiac death affects younger people without any prior symptoms.

In older persons, coronary heart disease (about 80%) and dilatative cardiomyopathy (10% to 15%) are responsible for most cases of sudden cardiac death. In young people, the most common pathological substrates are hypertrophic, dilatative, or arrhythmogenic right ventricular cardiomyopathy, myocarditis, or congenital changes to the coronary arteries. However, the cause of death is not detected at postmortem in 10% to 30% of cases (1).

Death without a cause detected at postmortem after the first year of life are known as sudden unexplained death syndrome (SUDS). Death due to unknown cause within the first year of life is known as sudden infant death syndrome (SIDS).

Primary electrical cardiac disorders

Cardiac changes that can result in sudden death in young people often have genetic causes but these are not often diagnosed. In recent years, however, important advances have been made in identifying such cardiac gene defects. More than 40 disorders of this type have been identified, and many are associated with an increased risk of sudden cardiac death.

Cardiac gene defects can be subcategorized into two groups: disorders that are accompanied by structural cardiovascular abnormalities—for example, arrhythmogenic right ventricular dysplasia (ARVD) and hypertrophic cardiomyopathy (HCM). The second group does not have cardiac changes that are detectable at postmortem—their cause is primarily arrhythmogenic. These include the primary electrical cardiac disorders, such as the complex of long QT (LQT) syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT), which may be responsible for a portion of cases of sudden death in young persons that are undetectable at postmortem.

Institut für Forensische Medizin, Johann Wolfgang Goethe-Universität, Frankfurt am Main: Dr. rer. nat. Kauferstein, Dipl.-Biol. Kiehne, Prof. Dr. med. Bratzke

Kerckhoff Klinik, Abteilung für Elektrophysiologie, Bad Nauheim: Dr. med. Neumann, Dr. med. Pitschner

Causes of sudden cardiac death in persons younger than 35 years in Italy from 1979 to 1998, adapted from (2); ARVC, arrhythmogenic right ventricular cardiomyopathy; CHD, coronary heart disease

TABLE

Genetic determinants of sudden cardiac death

Disorder	Gene	Protein	Frequency (%)	Inheritance
LQT1	<i>KCNQ1</i>	Potassium channel (IKs)	35–40	Dominant
LQT2	<i>HERG</i>	Potassium channel (IKr)	30–35	Dominant
LQT3	<i>SCN5A</i>	Sodium channel	5–10	Dominant
LQT4	<i>KCNJ2</i>	Potassium channel (IK ₁)	50	Recessive
Brugada syndrome	<i>SCN5A</i>	Sodium channel	15–30	Dominant
CPVT1	<i>RyR2</i>	Ryanodine receptor	65	Dominant
CPVT2	<i>CASQ2</i>	Calsequestrin	5	Recessive
ARVD-9	<i>PKP2</i>	Plakophilin-2	14–43	Dominant
ARVD-2	<i>RyR2</i>	Ryanodine receptor	No data	Dominant
HCM	<i>βMHC</i>	Heavy β-myosin chain	30–40	Dominant
HCM	<i>MyBP-C</i>	Myosin binding protein C	20–40	Dominant
HCM	<i>TNNT2</i>	Troponin T	5–15	Dominant

Only the most commonly affected genes are listed

Primary electrical cardiac disorders result from pathological changes of cardiac ion channels. These are caused by mutations to the genes that code these ion channels. Ion channels are located in the transmembrane and enable a flow of ions along electrochemical gradients via the membrane through open pores. Many of these ion channels are involved in the development and regulation of the cardiac action potential and therefore in the electrical conduction system of the heart. Mutations in these proteins can result in channel malfunction. The result: cardiac arrhythmias that may eventually cause ventricular fibrillation. Many of these mutated genes have been identified, and their role in the development of cardiac arrhythmias has been confirmed (table).

The penetrance of these disorders—i.e., the probability with which the respective genotype develops from a certain phenotype—is variable. The phenotypes that occur show wide clinical variance, which makes the diagnosis difficult in some cases. Often, electrocardiographic findings are not unequivocally pathological. In some 15% of those affected, a normal, frequency corrected QT interval is seen on the 12 lead ECG, in spite of the presence of the QT syndrome (2). Similarly, unmasking of the Brugada syndrome by using drugs is not absolute proof if the test results are negative (3).

Genetic aspects of cardiac disorders as the cause of sudden cardiac death

The LQT syndrome

Congenital LQT syndrome is a genetically heterogeneous disorder that is often—but not inevitably—characterized on the ECG by a prolonged QT interval (*e-figure 1*). The syndrome is different from acquired LQT syndromes, e.g., in patients who are taking drugs that prolong the QT interval. Nine different genetic locations on the chromosomes 3, 4, 7, 11, 12, 17, and 21 have been identified for congenital LQT syndromes, whose mutations are assigned to the LQT syndromes 1 to 9. Currently, more than 200 mutations are known: in the 5 potassium channel genes *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *KCNJ2*; in the sodium channel gene *SCN5A* (4); and in the adapter protein ankyrin-B (5). Recently, mutations have been identified in the gene of calveolin, *CAV3*, and in a calcium channel, which result in a prolonged QT interval in association with the Timothy syndrome, a multisystem disorder that is accompanied by syncope and sudden cardiac death (6).

Studies by Schwartz et al. (7) of genetic defects and their clinical manifestations (so-called genotype-phenotype relations) have shown that nearly all patients with LQT1 syndrome develop syncope under increased sympathetic nerve stimulation (physical or psychological stress). In a third of persons thus affected, the disorder manifests in childhood and during physical exercise, e.g., swimming (7). A proportion of cases of sudden death during swimming may therefore be due to LQT1 syndrome. In patients with LQT3 syndrome (*figure 2*), the symptoms occur during periods of rest, often while they are sleeping (8). In 12% of all patients with LQT syndrome, sudden cardiac death is the only clinical

Monitor electrocardiogram of a patient with implanted cardioverter defibrillator (ICD) a) with electrical storm in known arrhythmogenic right ventricular disorder and additional *SCN5a* mutation; b) the same patient with polymorphic ventricular tachycardia

manifestation of the disorder. In some 4% of patients, cardiac death occurs within the first year of life (9).

Short QT syndrome

Only in recent years, a further arrhythmia has been associated with sudden cardiac death: the short QT syndrome (SQTS) (10). The ECG of patients with this syndrome shows a shortened QT interval and tall and narrow T waves. Five mutations of the potassium channel genes *KCNH2* (SQTS1), *KCNQ1* (SQTS2), and *KCNJ2* (SQTS3)—which are also associated with the long QT syndrome—have been confirmed as the molecular basis of the SQT syndrome (11). The ion flow in the affected channels increases as a result of each of these mutations, which results in accelerated repolarization and therefore a shortened potential for action (12). Gaita et al. (13) have shown that persons with SQTS have an increased familial risk of sudden cardiac death.

Catecholaminergic polymorphic ventricular tachycardia

In some 60% of patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), mutations are found in the gene of the ryanodine receptor *RyR2*. This is responsible, among others, for regulating the calcium concentration of the endoplasmatic reticulum. However, mutations in the *RyR2* gene have also been found in patients with a subclass of arrhythmogenic right ventricular cardiomyopathy (ARVC) (14). Data about its incidence are, however, lacking.

At 105 exons (areas of the DNA that contain coding information for proteins), the ryanodine receptor is one of the largest proteins in the human organism. Currently, 70 mutations are known, but we can assume that more are yet to be discovered. Mutations in this gene

12 lead ECG of a patient
a) before and
b) after administration of 1 mg/kg BW ajmalin i.v. fractionated over 10 min; development of the J-point elevation and descending ST segment elevation with negative T wave in right precordial leads that are typical of Brugada syndrome

FIGURE 3

result in modified protein and possibly in impaired calcium release from the sarcoplasmic reticulum into the cytoplasm, which can result in arrhythmias, especially in periods of stress. The ryanodine-2 receptor (RyR2) and its accessory proteins calsequestrin-2, FKBP12.6, and triadin-1/junctin, which together form a complex, regulate this process. If mutations occur in the RyR2 gene, adrenergic stimulation—caused, for example, by stress—can result in a decreased affinity of the accessory FKBP12.6 protein to the channel complex. This leads to an increased opening of the ryanodine receptor, which can result in intracellular calcium surplus. This Ca^{2+} overload can result in further depolarizations after completed cardiac repolarization and can therefore enable the induction of ventricular tachyarrhythmias. Persons affected by CPVT have a notably increased risk of syncope and sudden cardiac death. In contrast to the LQT syndromes, the first syncope in untreated patients often manifests at the age of 40; mortality is 30% to 50% (14).

The Brugada syndrome

The Brugada syndrome is an important cause of sudden cardiac death. Its characteristic is a saddle-shaped ST increase on the ECG (*e-figure 2*) in atypical right-bundle branch block in leads V1 to V3 (15). The changes may occur only intermittently. By administering sodium channel blockers such as ajmalin (*figure 3*) it is possible to partly unmask these changes (3). Some 15% to 20% of patients with Brugada syndrome have a mutation in the *SCN5A* gene, which codes the cardiac sodium channel. In patients with the syndrome, genetic mutations have also been found that have a regulatory effect on the sodium channel. Mutations in L type calcium channels have also been found, which points towards a decreased calcium flow as a further cause of the Brugada syndrome, in addition to changes of the sodium flow. However, the genetic foundations have not been sufficiently identified in many cases (15). Patients with Brugada syndrome are at risk of life threatening tachyarrhythmias. After surviving a cardiac arrest or the occurrence of syncope, implantation of a defibrillator is therefore recommended (16).

Molecular biological diagnostics

The constantly increasing number of disorders that are associated with ion channel defects deserve particular attention because the pathophysiology can be explained by combining molecular genetics and electrophysiology to an extent that is not known for other hereditary disorders. Molecular genetic methods enable a targeted search for disease causing mutations in the respective ion channel genes. The first step is DNA extraction from EDTA blood or tissue. Using further molecular biological methods (polymerase chain reaction [PCR]), the coding areas of the respective genes are amplified. Sequence variants in the PCR products are usually confirmed by using special chromatographic separation (DHPLC, denaturing high performance liquid chromatography). Especially for samples with a conspicuous chromatogram, the base sequence is analyzed.

If new mutations are found, electrophysiological methods can be used to investigate whether these affect the gene's function and are therefore potentially pathogenic. Molecular diagnostics of these disorders are currently laborious and expensive, which limits their use in routine diagnostics.

Looking after affected families

Talking to families who have lost one of their own because of sudden cardiac death is a particular challenge for clinicians and forensic doctors alike, because the death has occurred suddenly and unexpectedly. Relatives have feelings of guilt and failure, which are often accompanied by a strong information need with regard to the cause of death. Recent studies have shown that sharing information and talking extensively to affected families results in the diagnosis of the cardiac disorder that is presumably responsible for the sudden cardiac death in some 40% to 53%. In this context, the algorithm presented by Behr and Tan (17) deserves a mention, which provides help on how to proceed after a postmortem examination (figure 4).

The role of postmortem molecular analysis

When starting to look after affected families it is important to gather any available information about the death of the family member. This includes the autopsy report, clinical data, and observations and symptoms preceding the death. Often, death is the first sign of a disease, or else, symptoms had developed that were never investigated.

One of the largest epidemiological studies of unexpected deaths in young people showed that more than half of the deaths were of cardiac origin and in 29% no recognizable cause was identified at postmortem (18). A further study of the Australian army showed an incidence of sudden, unexpected death of 13/100 000 recruits per year; no cause of death was established at postmortem in more than a third (35%) (19).

On the basis of cardiological and clinical data of families in which cases of sudden cardiac death had occurred, two further studies (1) showed that in 22% and 28% of cases, there were signs of a hereditary cardiac disorder. Most were LQT syndromes, but catecholamine induced ventricular tachycardias were also found.

Recent studies have shown that in 35% of sudden deaths, a cardiac ion channel disorder was the underlying cause (figure 5). These studies confirm the importance of the search for potentially life threatening mutations with regard to identifying the cause of death in persons with unexplained deaths. Postmortem molecular analysis is an important diagnostic tool in the forensic assessment of such deaths.

In this context it needs to be mentioned, however, that if no gene defect is found, a cardiac disorder cannot be excluded because 30% of such deaths remain unexplained after using molecular biological methods.

Prevention through postmortem molecular analysis

The primary electrical cardiac disorders are hereditary disorders with autosomal-dominant transmission; this

FIGURE 4

Recommended algorithm for dealing with families affected by sudden cardiac death, adapted from (17)

FIGURE 5

Frequency and distribution of mutations of the ion channel genes in 49 unexplained sudden deaths, adapted from (18)

means that family members have a 50% risk of being carriers of the mutated gene. For this reason, genetic screening is of the utmost importance for the affected family, especially with regard to the prevention of a further cardiac death.

From a forensic perspective it is therefore crucial to inform family members personally about the results of the molecular genetic screening test.

This does not violate the deceased's personality rights or break the doctors' professional secrecy because it is in the deceased's interest that his or her families are informed about potential risks. The "right to remain ignorant" does, however, have to be discussed with the family before any explanations are given.

Genetic family testing is indicated if a positive mutation is found in the deceased and/or the medical history shows the initial clinical symptoms in relatives. This can help to capture persons potentially at risk, and it can also help rule out a disorder. The extent to which asymptomatic gene carriers may benefit from prophylactic treatment is not known.

At the very latest, families should be offered genetic counseling after a conspicuous finding has been confirmed. Affected persons should be told about their prognosis and, if applicable, be offered treatment and be informed about the probability of the disorder manifesting. If clinically healthy family members are examined, genetic counseling should be given even before the examination. This is particularly advisable in disorders that manifest late and cannot or only partially be treated.

The authors are happy to provide details of where molecular genetic tests can be performed.

Conclusions

In summary, identifiable cardiac ion channel disorders are responsible for a third of cases of sudden cardiac death for which no cause is detectable at postmortem. Identifying the genes associated with these disorders, as well as their proteins, has underlined the importance of investigating mutations in these genes, especially with regard to sudden cardiac death. Forensic medical institutions have a particular role in this, since such cases are usually detected in that setting, and specimens for further molecular biological testing are available only there.

Postmortem molecular genetic analysis of the affected ion channel genes (molecular autopsy) in cases of sudden cardiac death are therefore an important aid to explaining such deaths. In case of a positive identification, a need arises for the family to undergo further medical tests. In the context of genetic counseling, an individual risk analysis can be conducted, and in phenotypically and genotypically positive carriers of a gene mutation, life saving prophylactic treatment can be given, e.g., by implanting an ICD (implantable cardioverter defibrillator).

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 21 May 2008, revised version accepted on 27 August 2008.

Key messages

- Primary electrical cardiac disorders are possible causes of sudden cardiac death.
- Such disorders are usually not detected at postmortem.
- For many of these disorders, laborious but ultimately important molecular diagnostics are required.
- Family examinations to identify patients at risk are essential in case of a typical medical history.

Translated from the original German by Dr Birte Twisselmann.

REFERENCES

1. Tester DJ, Ackerman A: The role of molecular autopsy in unexplained sudden cardiac death. *Curr Opin Cardiol* 2006; 21: 166–72.
2. Corrado D, Basso C, Gaetano T: Sudden cardiac death in young people with apparently normal heart. *Cardiovascular Research* 2000; 50: 399–408.
3. Wolpert C, Echternach C, Veltmann C et al.: Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. *Heart Rhythm* 2005; 2: 254–60.
4. Wichter T, Schulze-Bahr E, Eckardt L, Paul M, Levkau B, Meyborg M: Molecular mechanisms of inherited ventricular arrhythmias. *Herz* 2002; 27: 712–39.
5. Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosin S, duBell WH: Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* 2003; 421: 634–39.
6. Splawski I, Timothy KW, Decher N, Kumar P, Sachse FB, Beggs AH et al.: Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. *Proc Natl Acad Sci U S A* 2005; 102: 8089–96.
7. Schwartz PJ: The long QT syndrome. *Curr Probl Cardiol* 1997; 22: 297–351.
8. Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG et al.: Influence of the genotype on the clinical course of the long-QT Syndrome. International Long-QT syndrome Registry Research Group. *N Engl J Med* 1998; 339: 960–65.
9. Schulze-Bahr E, Fenge D, Etzrode W, Haverkamp G, Mönning G, Wedekind H et al.: Long QT-Syndrome and life threatening arrhythmia in a newborn: molecular diagnosis and treatment response. *Heart* 2004; 90: 13–16.
10. Schimpf R, Borggrefe M, Wolpert C: Clinical and molecular genetics of the short QT syndrome. *Curr Opin Cardiol* 2008; 23: 192–8.
11. Roden DM, Balser JR, George AL, Anderson ME: Cardiac Ion Channels. *Annu Rev Physiol* 2002; 64: 431–475.
12. Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman et al.: Idiopathic short QT interval: a new clinical syndrome? *Cardiology* 2000; 94: 99–102.
13. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R: Short QT syndrome: a familial cause of sudden death. *Circulation* 2003; 108: 965–70.
14. Mohamed U, Napolitano C, Priori SG: Molecular and electrophysiological base of catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol* 2007; 18: 791–7.
15. Chen PS, Priori SG: The Brugada syndrome. *J Am Coll Cardiol* 2008; 51: 1176–80.

16. Zipes DP, Camm AJ, Borggrefe M et al.: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006; 48: 247–346.
17. Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tome Esteban MT et al.: Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. Eur Hear J 2008; 29: 1670–80.
18. Tester DJ, Ackerman MJ: Postmortem long QT-Syndrome genetic testing for sudden unexplained death in young. JACC 2007; 49: 240–6.
19. Haverkamp W, Mönning G, Schulze-Bahr H, Wedekind H, Haverkamp F, Eckardt L et al.: QT-Syndrome. J Kardiologie 2001; 8: 402–6.
20. Ingles J, Semsarian C: Sudden cardiac death in the young: a clinical genetic approach. Internal Medicine Journal 2007; 37: 32–7.

Corresponding author

Dr. rer. nat. Silke Kauferstein
Institut für Forensische Medizin
im Klinikum der J. W. Goethe-Universität
Kennedyallee 104
60596 Frankfurt am Main, Germany
kauferstein@em.uni-frankfurt.de

For e-tables please refer to:
www.aerzteblatt-international.de/article09m41

REVIEW ARTICLE

Cardiac Gene Defects Can Cause Sudden Cardiac Death in Young People

Silke Kauferstein, Nadine Kiehne, Thomas Neumann,
Heinz-Friedrich Pitschner, Hansjürgen Bratzke

E-FIGURE 1

12-lead ECG of a patient with congenital long QT syndrome. The frequency-corrected QT interval is 621 ms (ECG writing speed 50 mm/s)

E-FIGURE 2

12-lead ECG of a patient with spontaneous unmasking of ECG changes that are typical for Brugada syndrome in the precordial leads (see also *figure 3*)