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# Molecular autopsy in sudden cardiac death and its implication for families: discussion of the practical, legal and ethical aspects of the multidisciplinary collaboration

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## Summary

Sudden cardiac death (SCD) is a major cause of premature death in young adults and children in developed countries. Standard forensic autopsy procedures are often unsuccessful in determining the cause of SCD. Post-mortem genetic testing, also called molecular autopsy, has revealed that a non-negligible number of these deaths are a result of inherited cardiac diseases, including arrhythmic disorders such as congenital long QT syndrome and Brugada syndrome. Due to the heritability of these diseases, the potential implications for living relatives must be taken into consideration. Advanced diagnostic analyses, genetic counselling, and interdisciplinary collaboration should be integral parts of clinical and forensic practice. In this article we present a multidisciplinary collaboration established in Lausanne, with the goal of properly informing families of these pathologies and their implications for surviving family members. In Switzerland, as in many other countries, legal guidelines for genetic testing do not address the use of molecular tools for post-mortem genetic analyses in forensic practice. In this article we present the standard practice guidelines established by our multidisciplinary team.

*Key words: sudden cardiac death; molecular autopsy; genetic counselling*

## Introduction

Cardiovascular disease is one of the leading causes of death in developed countries [1–3]. The Swiss Federal Statistical Office ranked cardiovascular disease as the number one cause of death in men and women in Switzerland. Although the majority of cardiac death victims are elderly, many children and young adults under the age of 35 die each year due to various cardiac pathologies. Many of these premature cardiac deaths are sudden and unforeseen. Recent progress in the fields of molecular biology and human genetics have enabled identification of the genetic aetiology of many cardiac diseases, including multiple causes of sudden cardiac death (SCD) [4, 5]. Some of the genetically determined cardiac diseases are characterised by morphological changes observed at autopsy, e.g., hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC) [6, 7]. Cardiac diseases related to arrhythmic syndromes, such as congenital long QT syndrome (LQTS), Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT) can only be diagnosed after genetic analysis at postmortem [4, 8]. Previous studies have reported that genetically determined cardiac disease is responsible for more than 50% of SCD cases in children [9, 10]. Preventive treatment exists for many of these diseases, thus iden-

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tifying other family members at risk, is very important. Postmortem evaluation is recommended in all cases of SCD, not only to determine the underlying cause of death, but to prevent future ones in surviving family members. In some cases, if an inherited arrhythmic syndrome is suspected, the phenotype determination of first-degree relatives may help to identify a channelopathy and subsequent genetic analyses can be performed on the index patient or family members.

General practitioners are particularly implicated in the ethical issues surrounding the death and autopsy of SCD victims since they are most often in direct contact with family members. The legal and ethical aspects of genetic analyses in postmortem investigation are complex, especially in a forensic context. This is a very important problem in many countries. The detection and follow-up of familial cases is challenging and requires close collaboration between specialists from different fields. The goal of this paper is to present our experience with forensic autopsy and genetic testing in cases of sudden cardiac death in young individuals.

## Causes of sudden cardiac death

The causes of SCD vary depending on the age of the individuals affected. In individuals over 35 years, ischaemic cardiac disease is most common [11]. Autopsy often reveals coronary artery occlusion or a previously constituted infarct. In individuals under 35 years, cardiomyopathies are ranked above cardiac ischaemic disease, valvular disease and conduction system pathology [12–15]. Sudden death in athletes is often due to undiagnosed structural heart disease. The cause of sport SCD also varies depending on the age of the athlete. Atherosclerotic coronary artery disease remains the most common cause of death in athletes aged 35 years or older; whereas in younger athletes a broad range of cardiovascular causes, including congenital and inherited disorders, have been reported [16–18]. In some cases autopsy investigation is unable to determine the cause of death, despite being performed in accordance with international recommendations [19, 20]. Autopsy negative sudden deaths account for 6 to 40% of all SCDs [12, 13, 15], which are currently considered to be caused by sudden arrhythmic death syndromes [4, 8].

## Cardiac pathologies with a morphological substrate at autopsy

### Hypertrophic cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is a relatively common clinical condition (1 in 500 individuals) characterised by cardiac hypertrophy, myocyte disarray and fibrosis. The clinical course of HCM varies greatly, ranging from a chronically managed condition to sudden death. Symptoms frequently include chest pain, exertion-related dyspnoea, syncope, and progressive exercise intolerance. HCM follows an autosomal dominant inheritance pattern and can be caused by mutations in at least 24 genes encoding for sarcomeric, calcium-handling, and metabolic regulatory proteins. The diagnostic yield of genetic analyses in clinical cases of familial HCM can reach up to 60%, but requires testing by experienced centres [21].

### Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)

ARVC/D is a familial cardiomyopathy that may result in arrhythmias, heart failure and/or sudden death. It is characterised by progressive myocyte loss with fibro-fatty replacement, and has a predilection for the right ventricle [22]. The prevalence is estimated to be between 1 in 5000 to 1 in 10000 individuals. Most cases of ARVC/D follow an autosomal dominant inheritance pattern with variable penetrance and expressivity. To date, eight susceptibility genes encoding different proteins of the desmosome of cardiomyocytes and three additional genetic loci have been identified [5, 23–25].

## Cardiac pathologies without a morphological substrate at autopsy

### Congenital long QT syndrome (LQTS)

Congenital LQTS comprises a distinct group of cardiac channelopathies characterised by delayed repolarisation of the myocardium reflected by QT prolongation (QTc >450 ms in adult males, >470 ms in adult females and >460 ms in individuals <15 yrs old), and an increased risk for syncope and sudden death. Individuals with LQTS may or may not manifest QT prolongation on a resting 12-lead surface electrocardiogram [26]. The heart is structurally normal. The prevalence of LQTS may be as high as 1 in 2500 individuals. LQTS is a genetically heterogeneous disorder usually inherited in an autosomal dominant mode. Autosomal

dominant LQTS was previously known as Romano-Ward syndrome. Although rare, LQTS can be also inherited as a recessive trait, as first described by Jervell and Lange-Nielsen, and is characterised by severe QT prolongation and sensorineural hearing loss. Approximately 5–10% of LQTS cases result from a spontaneous/sporadic germline mutation. To date, several hundreds of mutations have been identified in 12 genes, with ~75% of clinically robust LQTS due to mutations in three genes. Loss-of-function mutations in *KCNQ1*, which encodes $I_{Ks}$ potassium current, cause LQT1 syndrome. Loss-of-function mutations in *KCNH2*, encoding $I_{Kr}$ potassium current, cause LQT2, while gain-of-function mutations in *SCN5A*, encoding $I_{Na}$ sodium current, cause LQT3. These three genes code for ion channel subunits involved in the generation of the cardiac action potential. According to published studies, 75% of patients with a LQTS phenotype are carriers of a specific genetic mutation. In absence of family history or uncertain or "borderline" clinical features according to clinical scoring methods, there is a significant fall-off in the yield of genetic testing to about 45% [5, 24, 27, 28].

### Other rhythms disturbances related to sudden death syndromes

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a syndrome of exercise or emotion-induced polymorphic ventricular tachycardia or ventricular fibrillation in children and young adults. It occurs in a structurally normal heart. In approximately 30% of cases, the family history reveals one or more premature sudden deaths that usually occurred during childhood [29, 30]. Mutations in the RyR2-encoded cardiac ryanodine receptor/calcium release channel represent the most common genetic subtype of CPVT.

Brugada syndrome, first described in 1992, is widely recognised as a form of inherited sudden cardiac arrest. This syndrome is characterised by a specific ECG abnormality and an associated risk of ventricular fibrillation and sudden death. Most of the identified disease-causing mutations have been located in the *SCN5A* gene, which encodes the a subunit of the human cardiac voltage-gated sodium channel. Such mutations, however, can only be identified in approximately 30% of affected individuals [24, 31, 32]. Several hundred *SCN5A* mutations have been reported and the ones that have been functionally tested lead to a loss-of-function of the cardiac sodium channel [33].

## Legal aspects

### Legal aspects of postmortem genetic testing in Europe

Recent advances in the fields of molecular pathology and genetics have resulted in the ability to test for many genetic mutations. In 2007 Borry et al. [34] summarised the legal and ethical aspects of genetic testing and counselling in different European countries. At present there are no existing guidelines for genetic testing in cases of sudden cardiac death in forensic practice in Switzerland or Europe. We recently conducted an international survey, which demonstrated that autopsy practice varies widely between countries and that genetic postmortem testing is performed in only a few academic centres. Responders affirmed that it is very difficult to establish a link between the autopsy of a sudden death victim and the cardiological assessment of their family members. The reasons for this difficulty are numerous, but are largely related to the legal and ethical complexities of postmortem genetic testing.

### Legal aspects of genetic testing in Switzerland

The particularity of the judiciary in Switzerland is the coexistence of different laws at the national (federal) and local (cantonal) levels. In light of the ethical and legal sensitivity of postmortem genetic testing, physicians should have some basic knowledge of the legal aspects involved. A new law on genetic testing (LAGH, Loi fédérale Suisse sur l'analyse génétique humaine) came into force in 2007. In addition to this law there is a larger legal framework that regulates genetic testing, which includes federal laws concerning confidentiality, abortion and data protection (LPD, Loi fédérale sur la protection des données, Swiss federal data protection law [19.6.1992], http://www.admin.ch/ch/f/rs/235_1/), as well as different cantonal laws. This larger framework, however, is broad in scope and of uncertain application for genetic testing and its numerous complexities [35].

A new federal law on human subject research has been recently drafted. It has provoked significant discussion regarding the regulation of research, including genetic testing. The new federal law is not to be expected before 2011. For the time being article 20, al. 2, of the federal law on genetic testing, details the guidelines that apply to genetic research, stipulating that genetic analyses are allowed within a research framework on material that has been obtained for other non-research purposes. The material must be anonymous and the person from who the material stems (or its legal representative if the person is incompetent) must be informed of their rights and not express any opposition to the use of their biological material.

Article 14 of the LAGH states that non-directive genetic counselling must take place before a genetic test is performed, and 4 prohibits genetic

discrimination in line with the principles of art. 119 of the Swiss Constitution. Employers are not allowed to request presymptomatic genetic testing, except if the tests are a valid and recognised means of preventing work-related disease or accidents. Moreover, the law aims to protect individuals who carry morbid genes against discrimination by insurance companies. The latter are not permitted to carry out or require presymptomatic or pre-natal genetic testing before establishing an insurance contract. The only exception refers to private non-obligatory insurance where, in certain cases only, insurance companies may ask clients to send a copy of results from genetic testing previously performed (LAGH, art. 27 et 28). Article 6 of the law guarantees the individual right to decline information related to one's genetic patrimony.

The federal law on genetic testing (LAGH) does not explicitly address the issue of post-mortem genetic testing, leaving only the local (cantonal) laws applicable for autopsy investigation (for example *loi sur la santé publique vaudoise and loi genevoise sur la santé du canton de Genève*).

### Legal aspect of genetic testing after a forensic autopsy

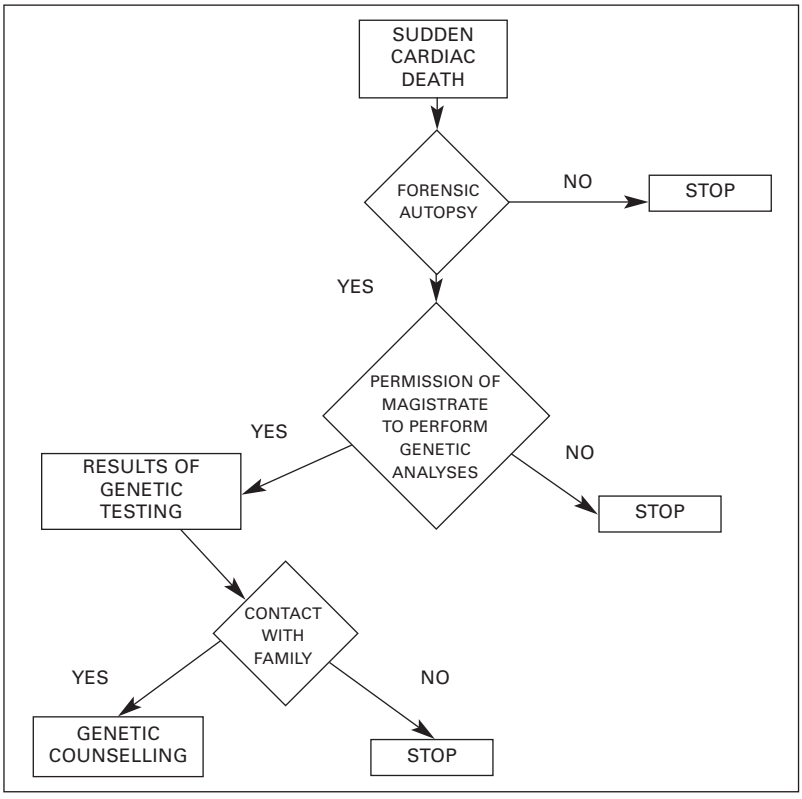
The legal issues surrounding forensic autopsy implicate both the prospective analyses of routine cases and the retrospective analyses for research purposes. The particularity of a forensic autopsy is that the postmortem examination can be carried out without the consent of the deceased or a proxy. The legal guidelines were established after multiple discussions with the lawyers from the legal department of the hospital. The ethical aspects were discussed at length with the ethics committee members. The investigating magistrate can mandate genetic testing on autopsy samples in order to determine the cause of death. Retrospective analyses assimilated to a research activity necessitate consent of the individual prior to death or proxy consent after death, as well as approval by the local ethics committee. In our practice only prospective testing is currently performed.

## Current multidisciplinary collaboration

In Lausanne, the multidisciplinary collaboration "Cardiogene" was established between the departments of cardiology, medical genetics and forensic medicine. Paediatric deaths are autopsied in collaboration with the Institute of Pathology in Lausanne. Sudden death cases are selected on the basis of presumed clinical history, scene investigation and autopsy findings. Cases with a negative autopsy including histological, toxicological, clinical chemistry and microbiological analyses are presumed to be due to an arrhythmic syndrome. Cases of sudden death in which the autopsy reveals a hypertrophic heart are considered as suspect for hypertrophic cardiomyopathy (HCM), even in the absence of typical histological patterns. HCM has been reported as the cause of SCD in children and athletes even in the absence of the left ventricular hypertrophy, as the diagnosis is not always straightforward [36]. Evaluating clinical histories of sudden death in forensic practice can prove very challenging. There is often a blurred history ranging from the individual simply collapsing, to one in which the death takes place in a much more complicated scenario. For example, the sudden arrhythmic event caused by a genetic disease can occur when a person is driving or swimming, resulting in a traffic accident or drowning [37]. The SCD may also be related to a low-level intoxication by antidepressants or antipsychotics known to be linked to drug-induced QT prolongation and the development of torsade de pointes arrhythmias, or to a Brugada syndrome phenotype and the development of polymorphic ventricular arrhythmias [38–40]. Due to the complexities of evaluating clinical histories, our selection sometimes includes some of the aforementioned cases. Once a case is selected, the forensic pathologist informs the investigating magistrate of the possibility of performing genetic analyses. Magistrates are informed that the cause of death

**Figure 1**

Flow chart of genetic testing in SCD in forensic practice.
The genetic analyses in SCD may be performed during the forensic investigation only with the permission of the investigating magistrate. The results of the genetic analyses are transmitted to the investigating magistrate and with his permission to the family. If family members are not contacted or decline to be informed, there is no follow-up.



may be directly or indirectly related to a genetically determined cardiac disease. They occasionally question the cost and time involved in such analyses. If a magistrate orders the genetic analyses, the report of the forensic autopsy notes that "the results of the genetic analyses will follow". With permission of the magistrate, the forensic pathologist is then free to speak with family members of the deceased and to encourage them to seek genetic counselling.

The genetic analyses are performed in order to detect any mutations described in arrhythmic syndromes. In Lausanne, it is currently possible to analyse the following genes implicated in arrhythmic syndromes: *SCN5A*, *KCNQ1* and *KCNH2*. The technical expertise was established through collaboration with the University Hospital of Basel. If HCM is suspected, the genetic testing of 12 genes using resequencing technology is performed in Geneva [41]. The results of the genetic analyses, including a written interpretation, are then transmitted to the investigating magistrate. The forensic pathologist evaluates the results to determine if the initial diagnosis must be modified, and subsequently encourages the family to seek genetic counselling. If family members are not contacted or decline to be informed, there is no follow-up. Genetic counselling of family members can occur at any step of the forensic investigation: at the beginning, after transmission of the results of the molecular autopsy or at a later undetermined date depending on the ability to contact family members or their individual desires. The basic flow chart is presented in figure 1.

## Discussion

Over the past decade, genetic testing for cardiac channelopathies and cardiomyopathies has mostly been performed for the purpose of basic science and to establish genotype–phenotype correlations. There has been great insight into the diagnostic, prognostic, and therapeutic implications of genetic testing. Postmortem genetic testing (molecular autopsy) has been carried out in some academic centres on cases without a morphological explanation for the sudden death [1, 8, 42–46]. These centres identified previously described pathogenic mutations responsible for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia. The molecular autopsies were also performed on cases of sudden infant death syndrome (SIDS); with results indicating that approximately 5–10% of SIDS are due to defective cardiac ion channels [10, 46]. The present recommendation is to perform genetic analyses on any case of SCD with a negative autopsy [47–50].

Studies evaluating the first-degree relatives of SCD victims have shown a high prevalence of genetically determined cardiac pathologies [51–53]. In light of these findings, clinical guidelines state that the investigation of any surviving relatives is crucial in identifying affected individuals and in attempts to decrease the risk of further sudden death [4, 24, 49, 52].

Unfortunately, the link between the postmortem investigation of a SCD victim and the clinical investigation of surviving family members is difficult to establish in most countries. This difficulty may result from legal restrictions, such as lack of consent of the victim or the next of kin, or from the inability to contact the families. From an ethical point of view, family members of SCD victims should have access to the results of the autopsy and genetic tests. The majority of genetic heart diseases show an autosomal dominant inheritance pattern with marked clinical heterogeneity, meaning that the probability of having additional family members affected is high, but the variability in presenting phenotypes is great. Clinical heterogeneity can render obtaining a clinical diagnosis more difficult. Incomplete penetrance and variable expression are common in arrhythmic syndromes, such as LQTS, Brugada syndrome and CPVT, and consequently lead to concealed forms of these disorders [54]. This being said, the clinical assessment of surviving family members alone may not allow for the detection of LQTS or CPVT.

The difficulty in reaching a diagnosis underscores the importance of the interdisciplinary collaboration between forensic pathologists, geneticists and cardiologists. The clinical screening of family members is most effective if any existing mutations of the deceased are found during postmortem genetic testing. In our opinion, genetic counselling and clinical screening of surviving family members should be performed in all cases of SCD, because the clinical history and examination of relatives may reveal a diagnosis of an ion channelopathy or cardiomyopathy that even autopsy failed to detect. The genetic testing of the victim and genetic counselling of surviving family members is also recommended in cases with a morphological substrate found at autopsy or during clinical investigation, such as hypertrophic cardiomyopathy.

Another common problem is that the families often only communicate with the police or with the investigating magistrate. The pathologist, however, is authorised to speak to the family with permission from the judge. Unfortunately, classical police investigations of SCD cases are often unable to properly uncover pertinent facts related to the individuals' medical history. Naturally, it is of the utmost importance that the police or judges direct their investigation to exclude any criminal

activity. For this reason, significant clinical or family history may not be reported to the forensic pathologist. This important information could be obtained during genetic counselling. Occasionally, the results of the autopsy are not properly relayed to the family or are not transmitted with a sufficient explanation. It is of primary importance to improve the system of transmission of autopsy results in cases of sudden cardiac death in order to increase the percentage of families receiving genetic counselling and cardiological assessment, and to identify any asymptomatic carriers of cardiac disease.

SCD cases raise many legal and ethical questions for the forensic pathologist and the general practitioner. The forensic pathologist acts as an expert and has no therapeutic relation with the deceased and his family. It is, however, impossible for forensic pathologists to ignore genetic diseases among the causes for death. From an ethical point of view, determining the cause of death for forensic purposes should be separated from the ethical issues of its implications for the family. An autopsy diagnosis not only determines the cause of sudden death, but may enable the detection of any carriers among family members in order to prevent any future ones. The general practitioners' role is twofold: to demand an autopsy in all cases of SCD, and to refer the family members to a centre specialised in cardiac genetic counselling. Although physicians are not legally bound to inform their patients of the genetic risks of disease, from an ethical standpoint they should inform family members that in a significant percentage of sudden deaths (especially in children and young adults) treatable genetic disorders can be identified. They should respect the family's wish to know or not to know, as expressed during the genetic counselling.

Genetic testing can also be performed many years after the death if the samples are properly collected and stored. EDTA blood and a few grams of cardiac or splenic tissues should be stored at –80 °C, or alternatively stored in RNA later [19, 20, 47]. At present our routine screening concerns only a few genes: *SCN5A*, *KCNQ1* and *KCNH2*. Ryanodine receptor gene mutations related to CPVT are not currently included in routine molecular autopsy practice, although several studies have suggested CPVT as the cause of SCD in young adults, in SIDS, and in a case of unexplained drowning [55, 56]. Further research will certainly permit to uncover more genes implicated in diseases resulting in sudden death and technical advances will render testing more cost effective. For this reason, appropriate sampling and storage is crucial in the anticipation of future technical progress in molecular biology and the overall understanding of the genetic origin of many diseases.

## Conclusion

Independent of its cause, the death of a young individual is tragic for those left behind. When the death is sudden and unexplained, the grief is much more inconsolable. The role of all implicated medical practitioners should be revised in order to make this tragedy easier for families, to prevent additional deaths in surviving family members, and in the interest of public health. A thorough autopsy using the recent advances in medicine and cardio genetics is essential for all individuals involved. International guidelines concerning postmortem genetic testing and transmission of the results to the family members should be proposed for cases of SCD. Appropriate handling of the case requires a multidisciplinary collaboration, including the generalist who certifies the death, the (forensic) pathologist performing the autopsy, the clinical geneticist and the cardiologist who will evaluate the risk of sudden death for family members. This article outlines an ethical and modern approach to all cases of sudden cardiac death.

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