

Genetics and unexplained infant death: genomics in the courtroom

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Sudden unexplained death in infancy, and particularly sudden infant death syndrome (SIDS), remains one of the most troubling situations in paediatrics, given that the etiology and pathophysiology of SIDS remain unknown in the majority of cases. Particularly troubling are the instances of repeated unexplained deaths in young children in one family: the lack of readily identifiable cause of death in the victims of SIDS sometimes raises the suspicion of multiple infanticide, triggering criminal proceedings and long prison sentences, most commonly involving the mother. The history of overturned convictions in the cases of the so-called “killer mums” remains troubling and raises concerns about many parents around the globe facing judicial persecution and incarcerations, on top of the personal and familial tragedies they had endured. Recent advances in genomic technologies allowed affordable access to genetic testing in various fields of medicine, leading to the identification of new genes and new pathogenic variants in known genes associated with various genetic conditions which are often rare and ultra-rare. Research in cardiac genetics provides clues about potential genetic causes of unexplained death in young children, and more importantly causes of recurrent death in one family: pathogenic variants in ion channels can lead to electrical instability of the heart as an underlying mechanism of fatal arrhythmias, where the fatal episode may be the first and only manifestation of the condition. This review summarises what is known about the more common genetic arrhythmias in the context of the recent judicial proceedings in the case of Ms. Kathleen Folbigg in Australia, concluding that thorough genetic investigation is absolutely warranted in criminal proceedings involving multiple unexplained deaths and complex undiagnosed conditions in one family.

Key words: SUDDEN INFANT DEATH; DEATH, SUDDEN; GENETICS; LONG QT SYNDROME; CALMODULIN

INTRODUCTION. UNEXPLAINED DEATH AT A YOUNG AGE AND GENETICS

There is no greater tragedy than that of the loss of a baby or a young child, particularly when there is no readily identifiable reason for the tragic

event. The medical science and literature have come up with various terms (and acronyms) to describe these situations - and most of these terms are phenomenological rather than aetiological, as very often the exact cause of death remains obscure. Sudden Infant Death Syndrome (SIDS, or cot death) is one of the best known

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‘conditions’ which describes the sudden death of an otherwise healthy baby usually under the age of 1 year (and usually in the first 6 months), usually while asleep – where the cause of death remains unclear even after a full investigation, including a complete autopsy with ancillary testing, review of the clinical history and examination of the death scene (1-4). A more general term is Sudden Unexpected Infant Death (SUID) or Sudden Unexpected Death in Infancy (SUDI), describing a broader group of explained and unexplained infant deaths under the age of 1 year (5). Sudden unexpected death in childhood (SUDC) describes sudden death in a child over 12 months of age that is unexplained after thorough clinical investigation, autopsy, and examination of the death scene (4).

The aetiology of SIDS remains obscure, despite decades of intense research. The standing theoretical framework is the ‘triple risk hypothesis’ which suggests interplay between three factors: a critical developmental period in the homeostatic control (peaking at the age of 2–4 months), exposure to stressors (overheating, infection), and underlying susceptibilities (age, sex, race) (2). The incidence of SIDS is estimated at about 1 in 1000 live-born infants and is one of the leading causes of post-neonatal mortality in the developed world.

Genetic factors may play a role in SIDS (in the ‘underlying susceptibilities’ segment), and like in other complex conditions, it is likely that this contribution is polygenic. Importantly, also like in other complex conditions, monogenic forms of fatal diseases likely account for a certain proportion of the ‘otherwise healthy’ children whose death was attributed to SIDS, or to otherwise unexplained death at a young age. The literature suggests the involvement of cardiac, metabolic, and inflammatory genes, as well as genes associated with epilepsy, the serotonin pathway, and ultra-rare conditions (6). Indeed, the contribution of arrhythmogenic heart conditions such as Long-QT syndrome (LQTS), most commonly caused by pathogenic variants in ion channel coding genes *KCNQ1*, *KCNH2*, and *SCN5A* has been speculated and demonstrated over the last two decades. For example, Ackerman et al. showed that pathogenic variants in *SCN5A* may account

for about 2 % of cases (2/93) with SIDS, in a population-based cohort of SIDS cases – as proof of the idea that a proportion of cases of SIDS and/or other forms of unexplained death at a young age of ‘otherwise healthy’ may be due to monogenic conditions, inherited in a Mendelian fashion, mostly autosomal dominant – and with a high recurrence rate (7)!

Of note, inherited cardiac arrhythmias, such as LQTS may manifest with the fatal outcome as the first and only clinical manifestation of the condition, without prior warning in an otherwise healthy person (8). Short of recording an ECG at the moment of the arrhythmic episode (not always possible, particularly if the episode is fatal) – the underlying genetic condition remains undiagnosed given the autopsy morphological findings are usually of a normal heart. Absent genetic testing, the cause of death would remain unclear.

The genetic contribution to SIDS remains an open area of research and there is a growing body of evidence linking cardiac, metabolic, epilepsy as well as inflammation and serotonin pathway genes in the list of potential contributors.

Recent studies using genomic testing provide further insights into the genetic architecture of unexplained death and proof that a percentage of cases of SIDS are indeed fatal outcomes of undiagnosed rare conditions, namely up to 1 in 3 SIDS cases may be explained by familial or genetic diseases such as channelopathies, cardiomyopathies or metabolic conditions (which are not detected by standard forensic procedures) (6). For example, Neubauer et al. investigated a cohort of 161 cases with SIDS of European background with whole exome sequencing focused on 192 genes and found potentially causative variants in about 20 % of SIDS cases – 9 % of channelopathies, 7 % of cardiomyopathies and 1 % of metabolic conditions (9). The same authors also reported on results from exome analysis focusing on 365 genes related to epilepsy in unexplained death (155 SIDS and 45 SUD cases), finding pathogenic and likely pathogenic heterozygous variants in 12,2 % (19/155) of SIDS cases and 13,3 % (6/45) of SUD cases (10). Similarly, Cazzato et al. performed custom panel testing containing sudden cardiac death genes and found likely pathogenic or pathogenic variants in about 5 % of the cases (11). Koh

et al. analysed the genetic determinants of sudden unexpected death in paediatrics (SUDP) in 352 children, mostly with fatal outcomes under the age of 1 year, and found likely contributory variants in about 11 % of cases (12). Of note, the same group published findings on the contribution of chromosomal anomalies in their SUDP cohort and found pathogenic copy number variants in 4,3 % of cases (5/116) and variants of uncertain significance harbouring pathogenic interpretation in another 7,8 % of cases (9/116), for a total of possible chromosomal contribution in SUDP of about 10 % (13).

THE PROBLEM OF RECURRENT INFANT DEATH IN ONE FAMILY

Sir Roy Meadow is a retired British paediatrician who was involved as an expert witness in several criminal cases of alleged infanticide, including the trial of Sally Clark, an English solicitor accused and convicted of murdering her two sons Christopher and Harry. His book 'ABC of Child Abuse' contained a statement that 'in one family one SIDS is a tragedy, two is suspicious and three is murder until proved otherwise' – and this statement later became known as the 'Meadow law'. In the Trial of Sally Clark an erroneous calculation of the likelihood of two occurrences of SIDS in one family yielded a figure of 1 in 73 million for two SIDS cases in one family (square of 8500, the incidence of SIDS in a middle-income non-smoking family in the UK 1 in 8500) – or once every 100 years in the UK (14, 15). This led to the conviction of Sally Clark in 1999. On appeal, she was released in 2003, but her life ended tragically from alcohol intoxication in 2007.

The two sources of the error as judged by the medical statisticians in the Sally Clark case were the application of the "prosecutor's fallacy" and assuming the two events are statistically independent (14, 16). The cases of recurrent sudden and unexpected death in a young child in one family is indeed a rare occurrence, but the rarity of the occurrence can't be taken as proof of guilt (prosecutor's fallacy), given that the cases of multiple infanticides in one family are also exceedingly rare (and on balance perhaps rarer!).

The assumption that both events are independent is the second source of error, given the increased prevalence of SIDS in siblings of index cases with SIDS. Recent literature provides estimates of the rates of recurrence of unexplained death in young children, defined as SIDS or SUDI. As expected from the theoretical principles of formal genetics (empirical risk), and as shown for many other conditions with complex genetics and complex inheritance, the recurrence rate of unexplained death in young children in a relative of an index case is higher than the incidence of unexplained death in young children in the general population. A recent analysis of the incidence of SIDS in siblings of victims of SIDS in a population-based study from Denmark demonstrated a 4 fold increase in the incidence of SIDS in siblings of SIDS victims, consistent with older studies (14, 17). Another UK study analysed data from the CONI (Care of Next Infant Program) registry and reported that the SUDI rate for infants born after one SUDI is 3.93 per 1000 live births, and the rate for the subgroup of unexplained death was 2.27 per 100 live births! Of note, this study reported 3 families (out of 6608) with 3 cases of SUDI, of which in at least one family the three SUDI cases were classified as SIDS (18).

Unlike conditions with complex inheritance where genetic counseling about the recurrence risks relies on these empirical risks, monogenic conditions are inherited in a predictable Mendelian way and recurrences can be calculated more accurately. Most of the monogenic cardiac contributors to SIDS are inherited in an autosomal dominant manner, and the recurrence risks may be much higher: 1 in 4 for two, 1 in 8 for three, and 1 in 16 for four affected children in one family with one affected or non-penetrant carrier parent.

GENETICS OF THE ELECTRICAL INSTABILITY OF THE HEART

The lowering costs of genomic testing using next-generation sequencing (gene panels, whole exome, or whole genome testing) affords genetic testing for an increasing number of patients with suspected genetic conditions who benefit from receiving a genetic diagnosis. The benefits are multiple and depend on the specific clinical sce-

Table 1. Long QT Syndrome: Scoring System for Clinical Diagnosis

FINDING		Points
ECG	QTc ≥ 480 ms	3.5
	460-479 ms	2
	450-459 ms (in males)	1
	≥ 480 ms during 4th minute of recovery from exercise stress test	1
	Torsade de pointes	2
	T wave alternans	1
	Notched T wave in 3 leads	1
	Low heart rate for age	0.5
	Syncope with stress	2
	without stress	1
Clinical history	Congenital deafness	0.5
	Family member(s) with clinical or molecular diagnosis of LQTS	1
Family history	Unexplained sudden cardiac death at age	0.5
	Genetic test Pathogenic variant in a gene known to cause LQTS	3.5
INTERPRETATION		
≤ 1.0 = low probability of LQTS;		
1.5-3.0 = intermediate probability of LQTS;		
> 3.0 = clinical diagnosis of LQTS		

nario, but include offering targeted treatment options, and introducing individual and reproductive risk management – for the proband and their family members. Nowhere is this more true than in the cases of cancer and cardiovascular genetics given the availability of treatment and risk management options – in the case of cardiac genetics this includes various medications and/or implantable cardiac defibrillators/pacemakers. This knowledge is installed in the recommendations of the ACMG for reporting the secondary findings in the analysis of the whole exome or genome – the current list includes 81 genes related to cancer and cardiovascular conditions (19).

Long QT Syndrome (LQTS)

The main electrophysiological feature of LQTS is the prolongation of the QT interval, predisposing to potentially life-threatening arrhythmic episodes, particularly in young individuals. The Schwartz scoring system adopted by the European Society of Cardiology incorporates ECG findings, clinical history, family history, and genetic findings to establish the clinical diagnosis, intermediate probability, or low probability of LQTS, as summarised in Table 1 (20, 21). The prevalence of this condition has been estimated to be 1 in 2000-2500, but may be higher (22).

Cardiac events such as palpitations, syncope, cardiac arrest, or sudden death occur from infancy to adulthood, most commonly in the period preteen to 20-ies, rarely after 40 (usually with the use of medications that prolong QT interval). The symptoms can be misdiagnosed as epileptic fits. The diagnosis relies on careful clinical examination, particular ECG studies, and family history, including ECG studies in family members. Genetic testing may confirm the clinical diagnosis in up to 80 % of cases with LQTS (20, 22).

Genetic studies in LQTS have identified 10-15 genes associated with LQTS, with 3 genes coding ion channel subunits accounting for more than 80 % of genotype-positive cases (22): *KCNQ1* (30-35 % of cases), *KCNH2* (25-30 %) and gain of function *SCN5A* (5-10 % of cases). The list of genes with definitive validity classification (adequate level of evidence of association with the inherited LQTS phenotype), causing less than 1 % of LQTS each also includes gain of function *CACNA1C*, *CALM1*, *CALM2*, *CALM3*, *CAV3*, *KCNJ2* and *TRDN* (20). About 25 % of cases with LQTS do not have an identifiable pathogenic variant in one of these genes (23). Most of the cases with LQTS are inherited from an affected or healthy non-penetrant parent in an autosomal dominant Mendelian fashion and some cases are de novo or result

from rare cases of gonadal (with or without somatic) mosaicism. The clinical expressivity of LQTS is variable and the penetrance of both ECG features and symptoms is reduced and gene-dependent. Generally, it is estimated that about 25 % of cases with identifiable LQTS pathogenic variants have normal QTc on baseline ECG (20, 24).

Asymptomatic individuals are treated with beta-blockers, including individuals with pathogenic LQTS variant and normal QTc interval, however, implantable cardioverter-defibrillator (ICD) is not indicated for asymptomatic individuals, except ones considered very high risk. All symptomatic individuals should be treated with beta-blockers, with a preference for longer-acting nadolol. Patients resuscitated from a cardiac arrest are recommended ICDs, given the high recurrence rate. Other treatment options include left ventricular denervation, for example in patients who refuse an ICD and where beta blockers are contraindicated, not tolerated, or not effective. Patients with LQTS3 due to specific pathogenic variants in *SCN5A* and QTc > 500 msec may benefit from adding sodium channel blockers (such as mexiletine). Drugs that prolong the QT interval should be avoided. Patient education and genetic counseling are essential (20, 25, 26).

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT is a rare inherited channelopathy affecting about 1 in 5000-10000 people. It is characterized clinically by episodes of syncope prompted by exercise/exertion or emotion. Syncope is the first presentation in about half of the patients, and patients may also experience dyspnea, chest pain, dizziness, palpitations, and cardiac arrest. Sudden death may be the first and only symptom. The usual age of onset of symptoms is around age 7-12 years, with a second peak at about 40 years (26 - 29).

The underlying arrhythmia is fast ventricular tachycardia that can resolve spontaneously or deteriorate into ventricular fibrillation resulting in sudden death in a setting of a structurally normal heart. About 30 % of patients with CPVT will have at least one cardiac arrest and sudden unexpected death may be the first and only manifestation of this highly malignant genetic arrhythmia (27,

30). Of note, while the outcome of CPVT may be a fatal arrhythmia, patients are clinically well and have normal heart ultrasound, coronary angiography, and ECG findings between the episodes of arrhythmia, making the diagnosis difficult (27, 28, 30). The diagnosis relies on the careful personal history of emotion or exercise-induced syncope (or epilepsy!), family history of sudden death, clinical examination, and stress electrophysiology studies and is established in patients with a structurally normal heart, normal resting ECG, and exercise- or emotion-provoked bidirectional or polymorphic ventricular tachycardia, or in individuals with a monoallelic pathogenic variant in *RYR2*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, or *KCNJ2* or bi-allelic pathogenic variants in *CASQ2*, *TECRL*, or *TRDN*. Genetic testing can identify family members at risk (27, 30).

Most patients with CPVT and positive genetic findings have a pathogenic variant in the *RYR2* gene (60-70 %). The list of other genes less frequently (<1 % cases) involved in CPVT inherited in autosomal dominant fashion include *CALM1*, *CALM2*, *CALM3*, *KCNJ2*, and *CASQ2* and inherited in autosomal recessive way *CASQ2* (about 5 % of cases), *TECRL*, *TRDN*. About 25 % of patients clinically diagnosed with CPVT have no identifiable pathogenic variant in one of the listed genes (28). CPVT is a condition with variable clinical expressivity and the penetrance for the *RYR2*-related CPVT has been estimated to be 83 % (27). The percentage of probands with de novo variants in *RYR2* is estimated to be about 30-40 % (27, 31).

The recommended treatment of manifestations includes beta blockers (nadolol is considered the most effective), with the inclusion of additional anti-arrhythmic drugs for complex arrhythmia control and implantable cardioverter defibrillator for patients with inadequate arrhythmia control with medications. Left cardiac sympathetic denervation is also an option in CPVT. Competitive sports and intense exercise are contraindicated and digitalis should be avoided (27).

Idiopathic ventricular fibrillation (IVF)

A common cause of sudden (unexpected) death in young adults, IVF is considered in patients who survive an episode of ventricular fibrillation, and

have an otherwise structurally and electrically normal heart (32, 33). Expert consensus statements define IVF as a resuscitated VF victim in whom known cardiac, respiratory, metabolic, and toxicological causes have been excluded (The Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society on inherited primary arrhythmia syndromes) (26, 32, 34). It is considered that 14-23 % of sudden cardiac death in young adults is due to IVF (35).

‘WHEN PIGLETS FLY’: INFANTICIDE OR AN INHERITED HEART CONDITION? A CASE STUDY ON THE ‘FOLBIGG’ GENE

Kathleen Folbigg is a 57-year-old Australian woman, a mother of 4 children who was convicted in 2003 of multiple infanticides of her children Caleb, Patrick, Sarah, and Laura over a period of 10 years and incarcerated for a 40-year jail sentence with a non-parole period of 30 years and labeled ‘Australia’s worst female serial killer’ (36-38). In the 2003 trial there was no direct evidence presented supporting violent or criminal deaths – all children were found dead while asleep in their cots by their mother, no murder weapon was recovered in any instance, there was no admission of guilt, no eye-witnesses of the event, no signs of violence in the autopsy reports (in 3 out of 4 cases the determined cause of death was SIDS), apart from questionably inculpatory extracts from Ms. Folbigg’s diary entries, subjected to interpretations out of context, by non-experts and the lay media. At the time, a psychiatric assessment did not determine a psychiatric condition in Ms. Folbigg. Despite the attempts of the defense to argue natural causes of death as an alternative explanation of the tragic events – the trial found Ms. Folbigg guilty, in support of the closing argumentation of the prosecutor grounded in the “Meadow law” (37-41):

“Caleb may have died from a floppy larynx or SIDS. Patrick may have had an ALTE, which was a first epileptic attack or encephalitis. His death may have been caused by an epileptic attack, an epileptic seizure. Sarah may have had a displaced uvula or SIDS. Laura may have died of myocardi-

tis. Well, yes, ladies and gentlemen, I can’t disprove any of that, but one day some piglets might be born from a sow, and the piglets might come out of the sow with wings on their back, and the next morning Farmer Joe might look out the kitchen window and see these piglets flying out of his farm. I can’t disprove that either. I can’t disprove that one day some piglets might be born with wings and that they might fly. Is that a reasonable doubt? No. Is the hypothesis that the defense advances a reasonable doubt? No. Why not? Because if you look at what they are suggesting, not in isolation, but in totality: There has never ever been before in the history of medicine that our experts have been able to find any case like this. It is preposterous. It is not a reasonable doubt. It is a fantasy, and of course the Crown does not have to disprove a fanciful idea.” (39).

Twenty years later, it fell on a group of geneticists from the Australian National University to prove this “fanciful idea” that sudden unexplained death (and to that end, complex and difficult to diagnose rare genetic disorders) in multiple children in one family is indeed possible, and actually quite possible in the case of an underlying genetic condition, given the recurrence rates of 1 in 2 for autosomal dominant and 1 in 4 for autosomal recessive conditions (38, 40). This complex journey involved a tense interaction of scientists with the New South Wales Australian judicial system – two legal inquiries into Folbigg’s convictions, visits to two different prisons, hours spent in genetic analyses and courtrooms, assembling an international network of experts in the biochemistry and physiology of calmodulin and clinical experts on “calmodulinopathies”, an emerging group rare cardiac conditions, in order to prove that the CALM2 gene variant G114R inherited by Sarah and Laura from their mother was indeed pathogenic and a likely cause of the ‘unexplained’ death they suffered (38).

Calmodulinopathy refers to a group of conditions that manifest with cardiac arrhythmias especially in young individuals due to pathogenic variants in one of the three CALM genes (CALM1, CALM2, and CALM3), and may cause catastrophic arrhythmia resulting in sudden death (42, 43). The three CALM genes code for the identical protein – calmodulin. This protein consists of 149 amino

acid residues and serves as a calcium binding modulator that binds/interacts with a number of enzymes and ion channels, such as the calcium-dependent inactivation (CDI) of cell membrane calcium channel CaV1.2 associated with LQTS and sarcoplasmic reticulum (SR) calcium release channel, RyR2 associated with CPVT. Pathogenic calmodulin variants have been associated with both LQTS and CPVT (42-44). A 2023 review of the international calmodulinopathy registry ICalmR reported on a cohort of 140 subjects (97 index cases and 43 family members), with a median age of 10.8 years. The two most prevalent electrophysiology syndromes associated with pathogenic variants were LQTS (53 % of cases) and CPVT (26 % of cases), IVF phenotype (5 % of cases), and 20 patients manifested primary neurological manifestations unrelated to post-anoxic sequelae. Interestingly, the registry reported an overlapping LQTS/CPVT phenotype in 7 %, and uncertain diagnosis in 8 % of ICalmR individuals. Also, the authors reported on the changing phenotype of calmodulinopathy, from more to less severe – for example, at an earlier time point in 2019 with a smaller number of cases, 85 % of the individuals in the registry had a cardiac event and 27 % had sudden cardiac death, while in 2023 61 % of individuals has a cardiac event and 9 % had sudden cardiac death. In addition, about 30 % of cases had cardiomyopathy or a congenital heart defect (42-44). Further to the growing body of evidence associating pathogenic CALM1, CALM2 and CALM3 gene variants with cardiac phenotypes LQTS (CALM1 LQTS14, CALM2 LQTS15 and CALM3 LQTS16) and CPVT, the American College of Medical Genetics included the CALM genes in the ACMG SF v3.2 list of reportable secondary findings in the context of whole exome or genome testing (19).

Following two Inquiries in 2018/2019 and 2022/2023 and after having spent 20 years in jail, Kathleen Folbigg was pardoned in July 2023 and in December 2023 her convictions were overturned (37, 45).

It is important to highlight some of the challenges in the variant interpretation in general, and particularly in the context of 20-year-old cases with limited clinical information and the evolving understanding of the genetics and clinical features

of calmodulinopathies – from the “tip of the iceberg phenotype” ascertained from the first published cases (all de novo, severe and lethal), to the “iceberg phenotype”, with an increasing number of cases in the international registry and the literature, including less severe, inherited and non-penetrant cases (8, 38).

CONCLUSIONS

Recent developments in human genetics and genomics have brought a new understanding of the genetic architecture of human disease – including sudden and unexplained death, which calls for revising clinical and forensic practices to include comprehensive genetic testing in cases of fatal or survived cardiac arrest / unexplained death. Sudden death may be the first and only manifestation of an underlying genetic arrhythmia, or if symptoms exist they may be misdiagnosed as epilepsy. The benefits of a positive genetic diagnosis include managing the personal and reproductive risk for the index case, but also identification of family members at risk. More extensive genetic testing using gene panels, whole exome, and whole genome testing continuously widens the number of cases with monogenic cardiac conditions and identifies both new genes involved in sudden unexplained death, as well as new clinical presentations of pathogenic variants in genes already associated with specific cardiac clinical presentations – which calls for a move to a gene-based, rather than electrophysiology syndrome/phenotype based disease classification. Scientific approach to unsolved criminal cases, particularly where multiple children are affected or diseased may afford a diagnosis or plausible alternative explanation for natural, as opposed to criminal cause of death usually implicating the mother. Cases such as Kathleen Folbigg’s highlight the importance of building sophisticated criminal justice systems that allow for a fair and criminal review process sensitive to science, particularly in the cases where the defendant or convicted maintains their innocence, as Stephen J Watkins concludes in his article *Conviction by mathematical error?* : “When errors occur we expect them to be admitted, learnt from, and corrected. Should clinical governance extend to the courtroom? Expert witnesses can hold a substan-

tial part of defendants' lives in their hands. Defendants deserve the same protection as patients." (14).

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SAŽETAK

Genetika i neobjašnjena smrt dojenčadi: genomika u sudnici

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Iznenadna neobjašnjiva smrt u dojenčadi, a posebno sindrom iznenadne smrti dojenčadi (SIDS, engl. sudden infant death syndrome), ostaje jedna od najzabrinjavajućih situacija u pedijatriji, s obzirom na to da etiologija i patofiziologija SIDS-a u većini slučajeva ostaju nepoznate. Posebno su zabrinjavajući slučajevi opetovanih neobjašnjivih smrti male djece u jednoj obitelji: nedostatak lako utvrdivog uzroka smrti kod žrtava SIDS-a ponekad pobuđuje sumnju na višestruko čedomorstvo, što pokreće kaznene postupke i duge zatvorske kazne, najčešće uključujući majku. Poništenih presuda u slučajevima takozvanih "majki ubojica" i dalje je zabrinjavajuća i izaziva zabrinutost oko mnogih roditelja diljem svijeta koji se suočavaju sa sudskim progonom i zatvaranjem, povrhom osobnih i obiteljskih tragedija koje su proživjeli. Nedavni napredak u genomske tehnologijama omogućio je pristupačan pristup genetskom testiranju u raznim područjima medicine, što je dovelo do identifikacije novih gena i novih patogenih varijanti u poznatim genima povezanim s različitim genetskim stanjima koja su često rijetka i ultrarijetka. Istraživanja u kardiološkoj genetici pružaju naznake o potencijalnim genetskim uzrocima neobjašnjive smrti u male djece, i što je još važnije, uzrocima ponovljene smrti u jednoj obitelji: patogene varijante u ionskim kanalima mogu dovesti do električne nestabilnosti srca kao temeljnog mehanizma fatalnih aritmija, gdje smrtonosna epizoda može biti prva i jedina manifestacija stanja. Ovaj pregled sažima ono što je poznato o češćim genetskim aritmijama u kontekstu nedavnog sudskog postupka u slučaju gdje Kathleen Folbigg u Australiji, zaključujući da je temeljita genetska istraga apsolutno opravdana u kaznenim postupcima koji uključuju višestruke neobjašnjive smrti i složena nedijagnosticirana stanja u jednoj obitelji.

Ključne riječi: SINDROM IZNENADNE DOJENAČKE SMRTI; SMRT, IZNENADNA; GENETIKA; SINDROM DUGOG QT INTERVALA; KALMODULIN