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Review

# Cardiac ion channel mutations in the sudden infant death syndrome

Eva C. Klaver, G. Marja Versluijs, Ronald Wilders *,[1]

*Heart Failure Research Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

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ABSTRACT

Sudden infant death syndrome (SIDS) is characterized by the sudden death of an infant that occurs during sleep and remains unexplained despite thorough examination. In addition to clinical associations such as prone sleeping and exposure to cigarette smoke, several genetic factors have been identified with regard to SIDS, including autonomic disorders, immunologic polymorphisms and metabolic disorders. In the past decade, postmortem genetic analysis ('molecular autopsy') of SIDS cases has revealed a number of cardiac ion channel mutations that are associated with arrhythmia syndromes, including the long QT syndrome, Brugada syndrome and short QT syndrome. Mutations have been found in genes encoding (subunits of) cardiac potassium, sodium and calcium channels, as well as in genes involved in the trafficking or regulation of these channels. Here, we review the literature on cardiac ion channel mutations in relation to SIDS. Combining data from population-based cohort studies, we conclude that at least one out of five SIDS victims carries a mutation in a cardiac ion channel-related gene and that the majority of these mutations are of a known malignant phenotype. Genetic analysis is therefore recommended in cases of sudden infant death. More research is required to further elucidate the pathophysiology of SIDS and to determine whether genetic or electrocardiographic screening of apparently healthy infants should be pursued.



## 1. Introduction

The term 'sudden infant death syndrome' (SIDS) was first proposed in 1969, to describe "the sudden death of any infant or young child which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death" [1]. Several reconsiderations led to further specification of this definition, limiting the victim's age to <1 year, specifying that death apparently occurred during sleep and stating that thorough examination should include complete autopsy and review of the death scene and clinical history [2]. Also, it has been proposed to classify SIDS cases into different categories according to their features and documentation [2]. Despite these attempts, the definitions and protocols used for diagnosing SIDS have never been fully standardized, and SIDS still remains a diagnosis of exclusion [3].

The prevalence of SIDS has decreased considerably since the 1992 American Academy of Pediatrics recommendation to avoid for babies to sleep in the prone position, and the subsequent international 'Back to Sleep' campaign [4]. Nevertheless, SIDS has until today remained a major cause of infant mortality in developed countries. Accounting for over 2100 deaths, it was the third most important cause of infant mortality in the United States in 2007 [5].

Despite its relatively high prevalence, the exact pathophysiology of SIDS is still poorly understood. Many mechanisms have been suggested and investigated, including infections and several genetic abnormalities. Presumably, SIDS is a multifactorial disorder, with multiple mechanisms resulting in or predisposing to its development. This reinforces the relevance of the search for preventable causes. In line with the presumed multifactorial nature of SIDS, several 'triple risk' hypotheses—with three risk factors contributing to SIDS, e.g. a vulnerable infant, a critical developmental period in homeostatic control, and an exogenous stressor—have been proposed, but none of these have significantly improved our understanding of the cause of SIDS [6].

In this paper, our main aim is to review the literature in which cardiac ion channel mutations are described as a possible cause or predisposing factor of SIDS. Additionally, we will first give a brief overview of several clinical associations and non-cardiac genetic factors that have been reported with regard to SIDS.

## 2. Clinical associations

Risk factors for SIDS include male gender, age two to four months, prematurity, low birth weight, poor prenatal medical care, low socioeconomic status of the family, young age of parents, parental low educational level, short periods between pregnancies, multiple pregnancy, drug intake by pregnant woman, winter months, prone

* Corresponding author. Department of Anatomy, Embryology and Physiology, Academic Medical Center, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5665229; fax: +31 20 6976177.
*E-mail address:* r.wilders@amc.uva.nl (R. Wilders).
[1] PO Box 22700, 1100 DE Amsterdam, The Netherlands.

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sleeping, exposure to cigarette smoke during pregnancy and after birth, and overheating [3]. Most deaths occur during the night and early morning [7]. Additionally, epidemiological studies have reported ethnic differences in the incidence of SIDS; it is significantly higher among indigenous groups than among non-indigenous groups from the same countries [8]. These variations were found to be associated with both genetic and environmental factors.

Already in the 1960s, infections were proposed to contribute to the etiology of sudden unexpected infant death [9], and substantial evidence has since then become available to support this hypothesis. Inflammatory changes are commonly found in SIDS cases, and mild viral infection is an established risk factor for SIDS [7,10]. Several studies have shown that the incidence of SIDS varies in correlation to the incidence of infectious diseases, both on seasonal and yearly bases [10,11]. Among the pathogens that have been specifically reported in association with SIDS are *Staphylococcus aureus*, streptococci and *Escherichia coli* [7].

Additionally, some established risk factors for SIDS are reported to parallel risk factors for susceptibility of infants to infection. These include ethnicity, male gender, prone sleeping, cigarette smoke exposure, overheating, mild respiratory infections, lack of breastfeeding and poor socioeconomic conditions [7].

## 3. Non-cardiac genetic factors

### 3.1. Immunologic polymorphisms

The current most popular hypothesis on the mechanism by which infections provoke SIDS, is that pathogenic toxins give rise to an overwhelming pro-inflammatory cytokine response, ultimately causing physiological changes that lead to death [7]. This hypothesis is supported by the observation that several immunologic polymorphisms which facilitate uncontrolled inflammatory responses are found at a higher proportion in SIDS victims than in controls. Among the altered inflammatory responses that have been suggested to be associated with SIDS, are underproduction of the anti-inflammatory cytokine interleukin-10 (IL-10), overexpression of the powerful cytokines IL-1β and IL-6, and elevated vascular endothelial growth factor (VEGF) [7,10]. Altered cytokine responses have also been hypothesized to be the mechanism by which exposure to cigarette smoke predisposes to SIDS [7].

### 3.2. Autonomic disorders

Several structural and neurotransmitter alterations in the brainstem, consistent with impaired autonomic regulation, have been found in cases of SIDS [12]. These alterations include serotonergic abnormalities in the medulla oblongata [12–14]. Serotonin is a widespread neurotransmitter involved in many functions of the central nervous system, including respiratory and cardiovascular regulation. It has been hypothesized that the mechanism by which serotonergic dysfunction leads to SIDS, is through failure of protective respiratory and autonomic responses to life-threatening hypoxia or hypercapnia during sleep [12,13].

Genetic analyses have identified polymorphisms in the variable tandem repeat sequence in the promoter region of the serotonin transporter (5-HTT) gene. SIDS victims are more likely than matched controls to have the long allele of this gene [15,16]. Increasing effectiveness of the promoter and therefore of serotonin re-uptake by the serotonin transporter, this allele facilitates decreased serotonin concentrations at nerve endings.

Further genetic factors have been identified. Weese-Mayer et al. [17] analyzed several genes pertinent to early embryologic development of the autonomic nervous system. They identified rare protein-changing polymorphisms in association with SIDS in five genes (*PHOX2a*, *RET*, *ECE1*, *TLX3* and *EN1*). After investigating left ventricular and blood samples from nine SIDS cases, Livolsi et al. [18] reported cholinergic abnormalities in the intracardiac part of the autonomic nervous system. Compared with controls, SIDS cases showed an increase in both the density of cardiac muscarinic receptors and the erythrocyte acetylcholinesterase enzyme activity.

### 3.3. Metabolic disorders

In 1976, Sinclair-Smith et al. [19] were the first to investigate the ribs, livers and thymi of children who died of SIDS. In over 90% of 200 SIDS cases, the costochondral junction indicated that death was preceded by retardation in growth velocity. Additionally, 90% of livers showed fatty change indicating a metabolic upset, which in 5% was of severe degree. Postmortem biochemical screening of 313 livers from SIDS cases by Boles et al. [20], implicated abnormalities in several distinct fatty acid oxidation pathways in 14 infants (4.4%).

A well-investigated metabolic disorder studied in relation to SIDS is medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. This relatively common autosomal recessive inherited disease results from a deficiency in the enzyme which catalyzes the first step in β-oxidation of fatty acids. At least nine studies investigated SIDS populations with regard to p.A985G, the most prevalent mutation causing MCAD deficiency [21]. Overall, p.A985G heterozygosity was found in only 0.54% of 2587 SIDS cases, compared with 0.84% of 4636 control cases.

The fact that low birth weight, which is a risk factor for SIDS, is associated with hypoglycemia, has triggered investigation of gene polymorphisms in two key enzymes in blood glucose homeostasis: glucokinase (GK) and hepatic glucose-6-phosphatase (G6PC1). Whereas low G6PC1 expression and activity were found in some SIDS victims [22–24], no significant alterations have yet been identified regarding GK [23].

## 4. Cardiac genetic factors

Already in 1976, the long QT syndrome (LQTS) was proposed as a possible cause of SIDS [25,26]. LQTS is characterized by delayed cardiac repolarization, resulting in QT prolongation on the electrocardiogram (ECG) and a predisposition to syncope, seizures and sudden cardiac death [27,28]. These clinical features are caused by episodic polymorphic ventricular tachyarrhythmias such as Torsades de Pointes (TdP). Especially in young people, LQTS is an important cause of unexpected death. All features of LQTS, including a negative postmortem examination, are compatible with SIDS. In many cases, LQTS is an inherited disorder, caused by mutations in genes predominantly encoding subunits of cardiac ion channels [27,28].

At the cellular level, LQTS is characterized by an increase in action potential duration, as illustrated in Fig. 1A, which may result from an increase in inward current during the plateau phase of the action potential (AP), e.g. due to an increase in the late component of the fast sodium current ($I_{Na}$; 'gain of function'), or a decrease in outward current, e.g. due to a decrease in the rapid or slow delayed rectifier potassium current ($I_{Kr}$ and $I_{Ks}$, respectively; 'loss of function').

Mutations in cardiac ion channel genes may also lead to the Brugada syndrome (BrS) and the short QT syndrome (SQTS) [29,30], which share several clinical features with LQTS, such as a predisposition to sudden cardiac death. The Brugada syndrome is characterized by changes in the ST segment of the ECG rather than QT prolongation, which may result from transmural dispersion in AP duration, in particular in the right ventricle, due to an early repolarization in the epicardial cell layers. On a cellular basis, a decrease in the peak component of $I_{Na}$ due to a loss-of-function mutation in *SCN5A*, i.e. the gene encoding the pore-forming α subunit of the $I_{Na}$ channel, may lead to loss of the AP dome in cells with a large transient outward current, like the right ventricular epicardial cells (Fig. 1B). It should be noted that this explanation of BrS as a