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Review Article

Ion channelopathies associated genetic variants as the culprit for sudden unexplained death

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ABSTRACT

Forensic identification of sudden unexplained death (SUD) has always been a ticklish issue because it used to be defined as sudden death without a conclusive diagnosis after autopsy. However, benefiting from the developments in genome research, a growing body of evidence points to the importance of ion channelopathies associated genetic variants in the pathogenesis of SUD. Genetic diagnosis of the deceased is also a new trend in epidemiological studies, for it enables the undertaking for preventive approach in individuals with high risks. In this review, we briefly discuss the molecular structure of ion channels and the role of genetic variants in regulating their functions as well as the diverse mechanisms underlying the ion channelopathies at gene level.

Contents

1. Introduction

Sudden unexplained death (SUD) constitutes a part of the general sudden death that should not be ignored. Many like to classify SUD as a subtype of sudden cardiac death (SCD) that attributes to abnormal cardiac electrophysiology. Indistinguishable from the majority of SCD, most SUD victims suffered a witnessed death occurred within 1 h of an acute clinical change, or an unwitnessed death occurred within the previous 24 h unexpectedly [1]. Therefore, the electrocardiogram (ECG) or electroencephalogram (EEG) data was often unavailable in these cases. Under this circumstance, identification of death causes for these deceased had long been difficult and controversial through traditional pathology examinations, for the conclusions were mainly based on negative autopsy findings [2].

For decades, understanding the underlying causes of SUD has been an important research target, and much progress has been made at cellular, molecular and genetic levels by means of familial studies, candidate gene analysis, next-generation sequencing

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(NGS) or genome-wide association studies (GWAS) [3,4]. In 2007, a molecular autopsy investigation focused on cardiac channel was performed among 49 SUD cases, and the result suggested that more than one-third of the victims harbored a putative mutation in the cardiac channel genes [5]. Besides, some studies have revealed that the influence of common genetic polymorphisms was rather diversified and remarkable. There is also an emerging concept that a fair amount of SUD is not as simple as one shot disruption but a systematic disease that involves more than one organ, especially heart and brain.

In this review, we present an overview on the genetic and pathological basis of SUD with a focus on ion channelopathy, especially those genetically determined cardio-cerebral channelopathies. Hopefully, the existing information could help investigators establish a systematic risk assessment scale to support diagnoses on molecular level in the prospect of forensic science.

2. Molecular structure of ion channels and the role of genetic variants in regulating their functions

Regular electrophysiological activity is the foundation of physiological function, especially in cardiac rhythm maintenance and neural activation. Since great progress has been made in understanding the genetic and molecular mechanisms of ion channel biophysics, the traditional oversimplified opinion that ionic currents are the expression of distinct intracellular or surface membrane proteins fixed and function independently is no longer tenable. Evidences have proved that an ion channel protein may encounter and interact with hundreds of other proteins during its lifespan [6]. Such complicated situation might explain the diversity of electrocardiographic parameters and its associated variants that extensively distributed in the genome detected by GWAS [7–10]. Admittedly, such a complicated regulation over space and time heralds an important variability for these protein complexes, which are major determinants of cardiomyocyte function, such as excitation–contraction (E–C) coupling, excitability and intercellular communication. Interference in any step of the protein function could be pathological and induce some dangerous symptoms including fibrillation and arrhythmia.

2.1. Sodium channel macromolecular complexes associated variants

Sodium channels are accountable for the generation of action potentials and electrical conduction along the cell membrane. There is no question that sodium channels have important roles in the current rising phase of action potentials, the processes of muscle contraction and the transmission of electrical signals within the nervous system. $Na_V1.5$, encoded by the human *SCN5A* gene, is a main kind of voltage-gated sodium channel highly expressed in cardiac myocytes. It is a large pore-forming protein with 2016 amino acids and a molecular weight of ~220 kDa [11]. $Na_V1.5$ is also named α-subunit, because it has been discovered to have the ability to assemble with β-subunits, which is a clan of small, single transmembrane segment proteins (~30 kDa). In human genome, four of these β-subunits have been testified [12]. The exact stoichiometry between α and β-subunits of the cardiac Na^+ channels is not clear yet. However, it has been reported that in rat brain, α-subunit of the Na^+ channels was co-purified with one β1 and one β2 subunit, suggesting a possible α to β stoichiometry of 1:2 in mammal [13].

According to a summary of Abriel et al., hundreds of mutations in *SCN5A* have been related to cardiac arrhythmic disorders [14], of which, the most famous Brugada syndrome (BrS) has been reported to implicated with approximately 300 possibly pathogenic mutations in *SCN5A* gene alone [15,16]. Although some have concluded that mutations in *SCN5A* may not be the whole story of BrS, and others suggested that the genetic background might take a crucial part in the pathology of this disease [17],*SCN5A* still plays an important role in channelopathies to our knowledge. In addition, mutations in *SCN5A* have been reported to participate in many other disorders, such as long QT syndrome (LQTS), atrial fibrillation (AF), conduction slowing, idiopathic VF, sick sinus syndrome, and dilated cardiomyopathy [18]. Such an impressive list of allelic disorders emphasizes the crucial role that $Na_V1.5$ played in physiology and pathology.

As for the proteins interacted with $Na_V1.5$, about 30 mutations in the genes coding for 6 of those were reported in patients with altered electrophysiological function, which may increase the risk of SCD [19]. Equally important, more than 20 naturally occurring mutations have been described in the genes coding for the 4 β-voltage-gated sodium channel subunits. These mutations were found in SCD patients with a broad spectrum of manifestations including BrS, LQTS, AF and sudden infant death syndrome (SIDS). The underlying molecular mechanisms were diverse among different phenotypes, but the majority of these β-subunit mutations lead to a reduced I_{Na} mediated by $Na_V1.5$ [20]. A briefly overview of disease-related $Na_V1.5$ macromolecular component proteins were listed in Table 1.

2.2. Calcium channel macromolecular complexes associated variants

$Ca_V1.2$, the voltage-gated L-type calcium channel, is the main access for the inflow of calcium into cardiac cells and the core macromolecular calcium channel complex [21]. Among its component subunits, the pore-forming $Ca_V\alpha1$ encoded by the human *CACNA1C* gene carries the primary biophysical or pharmacological properties of $Ca_V1.2$. Therefore, it is pivotal in E–C coupling and the duration of action potential. The $Ca_V\alpha1$ subunit is regulated by different accessory subunits through interacting with them (Fig. 1). It is prevailingly associated with 4 distinct

Table 1
Disease-related $Na_V1.5$ beta subunits and interacting proteins.

Chromosome location	Gene	Protein	Length (aa)	Molecular mass (kDa)	Manifestation of gene defect
19 (q13.11)	SCN1B	β1-subunit	218	24.7	LQTS/BrS/AF
11 (q23.3)	SCN2B	β2-subunit	215	24.3	BrS/AF
11 (q24.1)	SCN3B	β3-subunit	215	24.7	BrS/AF
11 (q23.3)	SCN4B	β4-subunit	228	25.0	LQTS/AF
20 (q11.21)	SNTA1	α1-syntrophin	505	53.9	LQTS/SIDS
3 (p25.3)	CAV3	Caveolin-3	151	17.3	LQTS/SIDS
3 (p22.3)	GPD1L	GPD1L	351	38.4	BrS
17 (p13.1)	RANGRF	MOG1	186	20.4	BrS/AF
3 (p14.3)	SLMAP	SLMAP	811	93.2	BrS
12 (p11.21)	PKP2	Plakophillin-2	837	92.8	BrS
3 (q28-q29)	FGF12	FGF12	243	27.4	BrS
3 (q29)	DLG1	SAP97	926	103.3	BrS