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REVIEW ARTICLE

An overview of the genetic variations associated with the pathophysiology and mechanisms of sudden cardiac death

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Abstract

Sudden cardiac death (SCD) is one of the commonest causes of death among young adults. Cardiac arrhythmias secondary to channelopathies are one of the main causes of SCD. Channelopathies is a condition where there are abnormalities of one or more ion channels involved in the cardiac action potential. These ion channels are strictly regulated and encoded by a specific gene for each channel. As for current knowledge, *KCNQ1, SCN5A, CACN1AC, CALM1*, and *RYR2* are the most studied genetic mutation in inherited sudden cardiac death patient. There are five most common chromosomes involved in this condition namely chromosome 1q42 to q43, 3p21, 7,11, and 12 which encodes RYR*2, SCN5A, KCNH, KCNQ1* and *CACN1AC* respectively. Two most common types of genetic mutation involved are loss-of -function mutation and missense mutations. Any disturbance in channel morphology or function due to genetic mutation will lead to channelopathies for example SCN5A gene gain function mutation in Long QT syndrome. This condition is an inherited disorder and mainly inherited by autosomal dominant. Therefore, genetic linkage study by cascade family screening is important for the early detection of this condition and to reduce the risk of sudden cardiac death among young patients.

Keywords: Sudden cardiac death, *KCNQ1*, *SCN5A*, Long QT syndrome, Cardiac genetic

Sudden cardiac death

Sudden cardiac death (SCD) is defined as an unexpected death of an individual not attributed to the extracardiac disease occurring within 1 hour of symptom onset or within 24 hours after last known to be well (Zipes, Hein, and Wellens 1998). SCD is a devastating condition as it is the only presentation of patients with channelopathies. SCD is unpredictable, and early detection of potentially high-risk patients is mandatory, especially in first-degree relatives. It has been estimated that up to 5 million cases of SCD per year globally, with a higher rate of incidence in western countries than in Asia (Wong et al. 2019). Underreporting and underdiagnosing of SCD in Asia are the reason of the low incidence rate (Roh et al. 2020).

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It is a public health concern globally as young adults are the most affected age group. In patients less than 35-year-old, unexplained causes of death are most prevalent (40%), followed by ischemic heart disease (24%), cardiomyopathy (16%), others (13%,) and myocarditis (3%) (Isbister and Semsarian 2019). An unexplained cause of death is likely to be nonstructural heart disease (Hayashi, Shimizu, and Albert 2015). Usually, it is due to undiagnosed congenital cardiac conditions such as Long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). In this brief overview, we discussed current understanding of the role of genetics in congenital cardiac arrhythmias due to LQTS, BrS, and CPVT and the future direction of genetic study in congenital cardiac arrhythmia.

Overview of action potential physiology

Normally, both atria and ventricles contract synchronously; it requires rapid activations of groups of myocytes (Grant 2009). The propagating

cardiac action potential is an activation mechanism that responds to heart rate and autonomic stimulation (Grant 2009). There are 5 phases of the normal action potential: phase 0, phase 1, phase 2, phase 3, and phase 4. The ion channels play an important role in an ion exchange during each action potential phase. The important properties of ion channels are ion permeation and gating. Ion permeation is defined as the movements of ions from the open channels, and ion gating is a mechanism for opening and closing the ion channels (Grant 2009). The most common ion channels involved in ion exchange are sodium, potassium, and calcium channels. During phase 0, there is rapid depolarization due to the opening of the fast sodium channels and reducing membrane permeability to potassium ions. This is followed by phase 1, which is the partial repolarization phase due to a decrease in sodium ion permeability. In phase 2, there is cardiac action potential plateau due to increased membrane permeability to calcium ions to maintain depolarization. Calcium channels are inactivated towards the end of the plateau with the inward movement of potassium ions, causing repolarization, which is phase 3 of the action potential. The resting membrane potential (phase 4) occurs when there is no movement of ions across the channels (Roh et al., 2020).

Sodium channel is responsible for the rapid upstroke of action potential and rapid impulse conduction through myocytes at phase 0 of the action potential. It has at least three distinct stages in the sodium channel: open, close, and inactivate (DeMarco and Clancy 2016). In the absence of electrical stimuli, the sodium channel will be in the closed state and activated upon membrane depolarization and rapidly become inactivated again. During the closed state, the sodium channel is deactivated during cellular hyperpolarization; meanwhile, during the inactivated state, the channel is unable to open or conduct sodium ions. The difference between the closed and inactivated phase is critical as the upstroke of an action potential depends on the channels' availability to open (DeMarco and Clancy 2016).

The sodium channel consists of primary α and multiple secondary β subunits. There are 10 genes (SCN1A- SCN10A) that encode sodium channel α subunit isoform, and each of them exhibits distinct structures and physiological functions(DeMarco and Clancy 2016). Meanwhile, only 4 genes (SN1B-SCN4B) encode sodium channel β subunits, which are expressed in cardiac tissue that may involve in the facilitation of sodium channel localization and clustering to discrete functional domains via cell-adhesive interaction (Malhotra et al. 2001).

Calcium channels are the principal channel for intracellular signaling ions. They regulate the excitation and contraction coupling of the myocytes (Grant 2009). There are two types of calcium channels known as L- type (low threshold) and T-type (transient) (Mesirca et al, 2015). These channels act as a transporter of calcium ions into the myocytes. The L- type channel is found in all types of myocytes. Meanwhile, a T-type channel is found in the sinoatrial node, atrioventricular node, and Purkinje cells (Mesirca et al, 2015). Five subunits of calcium channel, namely α1, α2, β, γ, and δ had been described. The combination of these subunits forms the native state of the calcium channel (Grant 2009).

The potassium channel is a highly regulated channel and a basis for the change in action potential configuration in response to heart rate. There are three categories of potassium channels, namely voltage-gated (Ito, IKur, IKr and IKs), inward rectifier channels (IK1, IKAch, and IKATP), and the background potassium currents (TASK-1, TWIK-1/2). The voltage-gated channel consists of a principle α subunit and multiple β subunits, generating outward current in the heart during phase 2 of action potential (Grant 2009).

Long QT syndrome (LQTS)

LQTS is the commonest heritable cardiac channelopathies. LQTS is an autosomal dominant inheritance except in Jervell and Lange-Nielsen syndrome. Jervell and Lange-Nielsen syndrome is a combination of LQTS and sensorineural deafness inherited as autosomal recessive (Cerrone et al., 2012). The literature has described that most patients with LQTS have affected parents, and the *de novo* pathogenic variant is low (Alders, Bikker, and Christiaans 2003).

European Society of Cardiology guidelines defines LQTS as a congenital condition where the corrected QT interval is (QTc)≥480 ms in an asymptomatic patient or a QTc≥460 ms in the presence of unexplained syncope (Priori et al. 2015). These changes are not due to medications or electrolyte abnormalities. Prolonged QT interval leads to ion channel dysfunction that causes prolonged repolarization and cardiac arrhythmia. A common manifestation of this syndrome is *torsades de pointes*, ventricular fibrillation, syncope and SCD. These manifestations are triggered by the adrenergic response; however, a small percentage (10 to 15%) experience the symptoms during rest or sleep. The mean age of onset is 12 years old (Cerrone et al., 2012).

The list of genes involved in LQTS keep increasing, and currently, 15 genes have been discovered in

patients with LQTS, but the significance is not well defined yet. There are 3 main genes involved in this syndrome which are *KCNQ1* that is located in the region 11p15.5, *KCNH* located at chromosome 7q35-36, and *SCN5A* located at chromosome 3p21. The three most common types are LQT1, LQT2, and LQT3 (A. Watanabe et al. 2005). LQT1 is caused by the loss of function mutation of *KCNQ1*, which encodes the IKs (slow) channel. Loss of function mutation in *KCNH2*, the gene encoding for the IKr (rapid) channel, occurs in patients with LQT2 leading to failure of trafficking to the cell membrane surface. In LQT3, there is a gain function of mutation of *SCN5A*, gene encoding INa, causing failure of inactivation and increased movement of late sodium ion current (Gray and Behr 2016).

Genotyping in LQTS is important as it will decide which beta blocker is suitable. Different genes involved lead to different patient phenotypes. For example, LQTS1 involves the mutation of *KCNQ1* which responds to non-selective beta-blocker, and LQTS2 occurs in patient with mutation in *KCNH2* only which responds to nadolol. In LQTS3 which gain function mutation of *SCN5A*, mexiletine, a class 1B sodium channel blocker can be used in addition to a non-selective beta-blocker (Li and Zhang, 2018; Watanabe et al., 2005).

Brugada syndrome (BrS)

Brugada syndrome was first described in 1992 (Brugada et al. 2014). It has a high prevalence in Southeast Asia compared to the Western countries. Brugada syndrome is diagnosed in patients who are presented with unexplained syncope and showed Brugada pattern ECG. There are three types of BrS based on ECG pattern which are type 1, type 2, and type 3. We will focus on Type 1 BrS in this overview. Type 1 BrS ECG pattern is characterized by prominent sharp concave ST elevation ≥2 mm, with T wave inversion, in ≥1 right precordial lead V_1 or V_2 in either second, third, or fourth intercostal space (Gray and Behr 2016). Manifestations of BrS include syncopal attack and SCD. Type 1 BrS patient has a high risk of developing malignant arrhythmias such as *torsades de pointes*, ventricular tachycardia or ventricular fibrillation. These malignant arrhythmias mostly occur at rest, during sleep, and after a large meal. It was noted that vigorous exercise worsens the ST elevation in BrS, which may lead to malignant arrhythmias (Masrur, Memon, and Thompson, 2015). The ECG changes in BrS can be unmasked by sodium channel blockers such as ajmaline, propafenone, and flecainide (G. Li and Zhang 2018).

BrS is an autosomal dominant inherited condition, and traditionally, the most common genetic abnormality is an *SCN5A* loss-of-function mutation and mutation in *CACN1Ac* (Gray and Behr, 2016; Mauro et al., 2021). The *SCN5A* gene, which islocated at chromosome 3p21 with 28 exons, encodes the α subunit of the main cardiac sodium channel Nav 1.5 (W. Li et al. 2018). Its main function is to maintain inward sodium current which involve in the fast depolarization phase of action potential. The genetic variants in *SCN5A* loss-of-function mutation would potentially cause disorganization of cardiac electrical system led to arrythmias. Meanwhile, *CACN1AC* gene is located at chromosome 12 and its function is to encode the L-type calcium channel (Gardner et al. 2019; di Mauro et al. 2021b). *CACN1AC* gene mutation is less common as compared to *SCN5A* and research is ongoing to understand *CACN1AC* mutation on BrS. However, based on a recent genetic linkage study, there is no strong association between BrS and *SCN5A* mutation alone except in certain overlap conditions such as LQTS and progressive cardiac conduction defect (PCCD) (Gray and Behr 2016 and Probst et al. 2009).

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT is a highly lethal clinical condition, and the prevalence occurs in 1 in 10,000 in Europe. It is one of the causes of SCD in children and young adults. The mean age of onset is usually 12 years old (Napolitano et al., 2004). The cardinal feature of this condition is bidirectional ventricular tachycardia precipitated by adrenergic stimulation. The patient may present with ventricular fibrillation as the first clinical presentation. The clinical diagnostic criteria include polymorphic or bidirectional ventricular tachycardia during exercise, with normal resting ECG and structurally normal heart (Sumitomo 2016).

Abnormal intracellular calcium handling leading to arrhythmia is the primary pathophysiology of CPVT. Cardiac ryanodine receptor 2 gene (*RYR2*) located on chromosome 1q42 to q43 is the commonest gene involved in CPVT (Laitinen et al. 2001; Sumitomo 2016). Calcium influx during action potential serves to trigger release of calcium from internal sarcoplasmic reticulum by activation of *RYR2*. *RYR2* mutation which is a missense mutation causes calcium channel leakage under adrenergic stimulation leading to excess calcium release into the cytosol in diastole, resulting in increased activation of sodium/calcium channel exchange and delayed after-depolarization (Paavola et al. 2007). Apart from *RYR2* mutation, calmodulin-1 (*CALM1*) missense mutation has also been described in CPVT (Makita et al. 2014). *CALM1* gene

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encodes calmodulin, an essential regulator in calcium handling dependent process. However, its genetic mutation prevalence is lower compared to *RYR2* mutation. The mode of inheritance of *CALM1* and *RYR2* is autosomal dominant (Napolitano et al. 2004).

Beta-blocker without intrinsic sympathetic activity, such as nadolol, is the first-line treatment for CPVT. Class 1C antiarrhythmic agents such as flecainide can be used on top of beta-blocker to reduce cardiac arrhythmia (Baltogiannis et al., 2019). An implantable cardiac defibrillator (ICD) may be considered for primary prevention; however, there is a risk of the electrical storm due to excessive adrenergic stimulation. Left cardiac stellate sympathetic denervation is another option in CPVT patients (N. Li et al., 2017).

Future perspectives

Cascade family screening is important in patients with a family history of sudden cardiac death. Clinical manifestations such as syncope, ventricular arrhythmia, or sudden cardiac death may be the one and only presentation. For patients with clinical features and ECG suggestive of channelopathies, genetic screening is strongly recommended to identify those at risk of SCD. In Malaysia, data on a genetic study among patients with channelopathies is sparse. Therefore, the formation of a nonprofit genetic council body in the country is needed to initiate, encourage, educate and possibly subsidize the cost of genetic family screening in this group of patients. Hence, a proper genetic study registry can be established for further research and development in this area. We propose an initiative for a national action program for genetic screening for channelopathies to be drawn up to prevent unnecessary SCD in young adults.

References

Alders, Mariëlle, Hennie Bikker, and Imke Christiaans. 2003. *Long QT Syndrome*. https://www.ncbi.nlm.nih.gov/books/.

Baltogiannis GG, Lysitsas DN, di Giovanni G, Ciconte G, Sieira J, Conte G, Kolettis TM, Chierchia GB, de Asmundis C, Brugada P. CPVT: Arrhythmogenesis, Therapeutic Management, and Future Perspectives. A Brief Review of the Literature. Front Cardiovasc Med. 2019 Jul 12;6:92.

Brugada R, Campuzano O, Sarquella-Brugada G, Brugada J, Brugada P. Brugada syndrome. Methodist Debakey Cardiovasc J. 2014 Jan-Mar;10(1):25-8.

Cerrone, Marina, Samori Cummings, Tarek Alansari, and Silvia G. Priori. 2012. "A Clinical Approach to Inherited Arrhythmias." *Circulation: Cardiovascular Genetics* 5(5): 581–90.

DeMarco, K. R., and C. E. Clancy. 2016. "Cardiac Na Channels: Structure to Function." *Current Topics in Membranes* 78: 287–311.

Gardner, R. J.Mc Kinlay et al. 2019. "Penetrance and Expressivity of the R858H CACNA1C Variant in a Five-Generation Pedigree Segregating an Arrhythmogenic Channelopathy." *Molecular Genetics and Genomic Medicine* 7(1).

Grant, Augustus O. 2009. "Cardiac Ion Channels." *Circulation: Arrhythmia and Electrophysiology* 2(2): 185–94.

Gray, Belinda, and Elijah R. Behr. 2016. "New Insights into the Genetic Basis of Inherited Arrhythmia Syndromes." *Circulation: Cardiovascular Genetics* 9(6): 569–77.

Hayashi, Meiso, Wataru Shimizu, and Christine M. Albert. 2015. "The Spectrum of Epidemiology Underlying Sudden Cardiac Death." *Circulation Research* 116(12): 1887–1906.

Isbister, Julia, and Christopher Semsarian. 2019. "Sudden Cardiac Death: An Update." *Internal Medicine Journal* 49(7): 826–33.

Laitinen, Päivi J et al. 2001. *Mutations of the Cardiac Ryanodine Receptor (RyR2) Gene in Familial Polymorphic Ventricular Tachycardia*. http://www.ncbi.n-.

Li, Guoliang, and Li Zhang. 2018. "The Role of Mexiletine in the Management of Long QT Syndrome." *Journal of Electrocardiology* 51(6): 1061–65.

Li, Na et al. 2017. "Treatment of Catecholaminergic Polymorphic Ventricular Tachycardia in Mice Using Novel RyR2-Modifying Drugs." *International Journal of Cardiology* 227: 668–73.

Li, Wenjia et al. 2018. "SCN5A Variants: Association with Cardiac Disorders." *Frontiers in Physiology* 9(OCT).

Makita, Naomasa et al. 2014. "Novel Calmodulin Mutations Associated with Congenital Arrhythmia Susceptibility." *Circulation: Cardiovascular Genetics* 7(4): 466–74.

Dhar Malhotra J, Chen C, Rivolta I, Abriel H, Malhotra R, Mattei LN, Brosius FC, Kass RS, Isom LL. Characterization of sodium channel alpha- and beta-subunits in rat and mouse cardiac myocytes. Circulation. 2001 Mar 6;103(9):1303-10.Masrur, Shihab, Sarfaraz Memon, and Paul D. Thompson. 2015. "Brugada Syndrome, Exercise, and Exercise Testing." *Clinical Cardiology* 38(5): 323–26.

Di Mauro V, Ceriotti P, Lodola F, Salvarani N, Modica J, Bang ML, Mazzanti A, Napolitano C, Priori SG, Catalucci D. Peptide-Based Targeting of the L-Type Calcium Channel Corrects the Loss-of-Function Phenotype of Two Novel Mutations of the *CACNA1* Gene Associated With Brugada Syndrome. Front Physiol. 2021 Jan 8;11:616819.

Mesirca, Pietro, Angelo G. Torrente, and Matteo E. Mangoni. 2015. "Functional Role of Voltage Gated Ca2+ Channels in Heart Automaticity." *Frontiers in Physiology* 6(FEB): 19.

Napolitano C, Priori SG, Bloise R. Catecholaminergic Polymorphic Ventricular Tachycardia. 2004 Oct 14 [Updated 2016 Oct 13]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1289/Pa avola, Jere et al. 2007. "Mutant Ryanodine Receptors in Catecholaminergic Polymorphic Ventricular Tachycardia Generate Delayed Afterdepolarizations Due to Increased Propensity to Ca2+ Waves." *European Heart Journal* 28(9): 1135–42.

Priori, Silvia G. et al. 2015. "2015 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)." *European Heart Journal* 36(41): 2793–2867l.

Roh, Seung Young et al. 2020. "Incidence and Etiology of Sudden Cardiac Arrest in Koreans: A Cohort from the National Health Insurance Service Database." *PLoS ONE* 15(11 November).

Sumitomo, Naokata. 2016. "Current Topics in Catecholaminergic Polymorphic Ventricular Tachycardia." *Journal of Arrhythmia* 32(5): 344–51.

Watanabe, Atsuyuki et al. 2005a. "Long QT Syndrome." *Nippon rinsho. Japanese journal of clinical medicine* 63(7): 1171–77.

Wong, Christopher X. et al. 2019. "Epidemiology of Sudden Cardiac Death: Global and Regional Perspectives." *Heart Lung and Circulation* 28(1): 6–14.

Zipes DP, Wellens HJ. Sudden cardiac death. Circulation. 1998 Nov 24;98(21):2334-51.

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