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Mutations of Voltage-Gated Ionic Channels and Risk of Severe Cardiac Arrhythmias

Amir Dehghani-Samani,[1] Samin Madreseh-Ghahfarokhi[2] and Azam Dehghani-Samani[3]

Background: Arrhythmias as important malfunctions of heart are known as abnormal rhythm of heart. Several causes can make arrhythmias and most of them are related to generation and/or conduction of action potential in heart. Action potential in myocytes results from the sequential opening and closing of ion channel proteins that span the plasma membrane of individual myocytes. Action potential's conduction through the heart is depended on electrical coupling between myocytes, which is mediated by gap junctions. Generation and conduction of action potentials are related to perfect action of ionic channels in heart.

Objectives: This novel review comprehensively addressed the ionic mechanisms of the arrhythmogenic mutations in cardiac voltage-gated ionic channels including: *CACNA1C*, *CACNA1D*, *KCNA5*, *KCND2*, *KCND3*, *KCNE1*, *KCNE2*, *KCNE5*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*, *SCN4A*, *SCN5A*, *SCN1B*, *SCN2B*, *SCN3B* and *SCN4B*.

Methods: Current study, for the first time, review and discuses about relation between cardiac arrhythmias and whole of important voltage gated ionic channels from different families, altogether and at the same time.

Results: This review clears that mutations in voltage-gated ionic channels play important roles in generation of severe cardiac arrhythmias, and among them it is looked that mutations in voltage-gated potassium channels are more important.

Conclusions: Most of induced arrhythmias due to voltage-gated ionic channels mutations result in action potentials prolongation and long QT syndromes. Study on ionic channel regulators can be considered as a subject for future research.

Key Words: Arrhythmia • Ion channel • Ionic current

INTRODUCTION

Cardiac arrhythmias, as important kinds of heart malfunctions, are occurring due to abnormal rhythm of the heart. For instance, sometimes the beat of the atria is not coordinated with the beat of the ventricles, so the atria no longer function as primer pumps for the ventricles.[1] Related symptoms to cardiac arrhythmias are including: shortness of breath, weakness, lightheadedness, dizziness and occasionally, chest pain in mild types of arrhythmias, and fainting, loss of conscious, syncope and finally death in severe types of arrhythmias. The causes of the cardiac arrhythmias are usually related to generation and/or conduction of action potentials (APs) in cardiac tissues, which are sharply related to perfect action of ionic channels in heart.[1]

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[1]Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord; [2]Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad; [3]Faculty of Veterinary Medicine, Shahrekord University, Shahrekord, Iran.
Corresponding author: Dr. Amir Dehghani Samani, Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord, Iran. Tel: +98-3814424427; Fax: +98-3814424427; E-mail: amirds2008@gmail.com

DIFFERENT TYPES OF ARRHYTHMIA

According to the specific cause and character, cardiac arrhythmias can divide to different groups. In one

of the best divisions, they are divided into eight different categories.[1] Table 1 shows the causes, mechanisms, sub-divisions and different characteristics of each type of arrhythmias.

Table 1. Different groups of arrhythmias and their characteristics

Type of arrhythmia	Subtypes	Common cause	Characteristics, electrocardiogram (ECG), etc.
Abnormal sinus rhythms[1]	Tachycardia[1]	Increased body temperature, stimulation of the heart by sympathetic nerves, toxic conditions, etc.[1]	Heart rate more than 100 beats/min, ECG: normal, except heart rate.[1]
	Bradycardia[1]	Large and strong heart, vagal stimulation, etc.[1]	Heart rate less than 60 beats/min, ECG: normal, except heart rate.[1]
	Sinus arrhythmia[1]	Alter in strength of the sympathetic and parasympathetic signals to sinus node, etc.[1]	Range of increasing/decreasing in heart rate during the stimulation is more than normal range.[1]
Block of heart signals[1]	Sinoatrial block[1]	Impulse from sinus node is blocked before it enters to atrial muscle, etc.[1]	Sudden cessation of P waves in ECG, with resultant standstill of the atria.[1]
	Atrioventricular block[1]	Decrease the rate of impulse conduction in atrioventricular bundle, etc.[1]	Prolonged P-R or P-Q Interval (First degree), P wave with no QRS-T wave (2nd degree), Dissociated P wave from QRS-T complexes (3rd degree).[1]
	Incomplete intraventri-cular block[1]	Block impulse conduction in the peripheral ventricular Purkinje system, etc.[1]	Replicated increasing/decreasing in height of QRS wave.[1]
Premature contractions[1]	Premature atrial contractions[1]	Mostly result from ectopic foci in heart due to local areas of ischemia; small calcified plaques and toxic irritation of the Atrioventriclar node, Purkinje system or myocardium caused by infection, drugs, nicotine, or caffeine, etc.[1]	P wave occurs soon, P-R interval is shortened.[1]
	Atrioventricular nodal contractions[1]		P wave is missing; instead P wave is superimposed onto QRS-T complex.[1]
	Premature ventricular contractions[1]		Prolonged QRS with high voltage, T wave has electrical potential polarity exactly opposite to QRS.[1]
Paroxysmal tachycardia[1]	Atrial paroxysmal tachycardia[1]	Mostly caused by re-entrant circus movement feedback pathways that set up local repeated self-re-excitation and this focus becomes the pacemaker of the heart, etc.[1]	Inverted P wave is seen before each QRS-T complex.[1]
	Ventricular paroxysmal tachycardia[1]		Series of ventricular premature beats occurring one after another without any normal beats interspersed.[1]
Ventricular fibrillation[1]	Results from cardiac impulses that have gone berserk within the ventricular muscle mass, stimulating first one portion of the ventricular muscle, then another portion, then another, and eventually feeding back onto itself to re-excite the same ventricular muscle over and over, never stopping, etc.[1]		ECG is bizarre and ordinarily shows no tendency toward a regular rhythm of any type.[1]
Atrial fibrillation[1]	Mechanism of atrial fibrillation is identical to that of ventricular fibrillation, except that the process occurs only in the atrial muscle mass, etc.[1]		Numerous small depolarization waves exist. P waves are weak; conversely, QRS-T complexes are normal.[1]
Atrial flutter[1]	Caused by circus movements in the atria. It causes a rapid rate of contraction of the atria, usually between 200 and 350 beats per minute, etc.[1]		P waves are strong, QRS-T complex follows an atrial P wave only once for every two to three beats of the atria.[1]
Cardiac arrest[1]	Results from cessation of all electrical control signals in the heart, etc.[1]		Stop of waves.[1]

NORMAL GENERATION OF ACTION POTENTIALS (APs)

The best introduced mechanism for AP in cardiac cells, which is explained by scientists, indicates that AP in myocytes results from the sequential opening and closing of ion channels span in plasma membrane of individual myocytes. Also differences in the expression and properties of these channels result in heterogeneities in AP wave. Action potential's conduction through the heart depends on electrical coupling between myocytes, which is mediated by gap junctions.[1] The cardiac AP in humans has five different phases (from 0 to 4). Depolarization from the pacemaker cells in Sino-Atrial node brings the membrane potential to the threshold, opening the voltage-activated sodium channels, then the resulting sodium current (I_{Na}) produces a positive feedback loop that causes further sodium channels to open (phase 0). In next step early rapid repolarization results from the activation of the fast and slow transient outward potassium currents, $I_{to,f}$ and $I_{to,s}$, and it is responsible for phase 1 of the AP's generation. This is followed by a prolonged plateau resulting from a balance between the inward currents mediated by the L-type voltage-gated calcium channel ($I_{Ca,L}$) and sodium-calcium exchanger (I_{NCX}), and the outward currents mediated by the delayed rectifier voltage-gated potassium channels (I_K). The rapid and slow currents (I_{Kr} and I_{Ks}, respectively) make up I_K. There is also contribution from the inward rectifying current (I_{K1}). This plateau is responsible for phase 2 of the AP's generation. The driving force for potassium efflux remains high during the plateau phase due to a large difference between the membrane potential and the potassium Nernst potential. As the calcium channels become inactivated, the outward potassium currents predominate, causing further repolarization and bringing the membrane potential towards the potassium equilibrium potential. This is responsible for phase 3 of the AP's generation. The membrane potential returns to its resting value after full repolarization, which corresponds to phase 4 of the AP's generation, and is normally polarized at values between -80 and -64 mV relative to the extracellular space. This resting state is maintained mainly by the inward rectifier current, I_{K1}. The weak inward rectifying ATP-dependent potassium channels ($I_{K,ATP}$) are also active during this phase.[1] Figure 1 shows the different phases of AP's generation in myocytes schematically. Several factor regulate the generation and conduction of APs including:[1] changes in the properties and/or in the functional expression of ionic channels, which are resulted from inherited mutations in the genes encoding these channels,[1] or from cardiac diseases,[1] which can change the AP's waveforms, synchronization, and/or propagation, thereby predisposing the heart to potentially life-threatening arrhythmias.[2]

VOLTAGE-GATED IONIC CHANNELS (VGICs)

VGICs are an important and specific class of transmembrane channels.[1] The first identified VGIC that was voltage-gated sodium channel or (VGSC) was isolated and purified from the eel electroplax.[3] The first voltage-gated potassium channel's sequence was deduced from the Shaker mutant of Drosophila melanogaster.[3] Some functional VGICs are made up a protein with four different subunits like voltage gated potassium channels (VGPCs), or one protein with four homologous domains like VGSCs and voltage gated calcium channels (VGCCs). Each one of the domains or subunits has six trans-membrane segments (S1-6) and a pore loop; the S5, S6 and the pore loop were found to be responsible for ion conduction, S4 contains several basic residues, arginine or lysine and was initially postulated to be the voltage sensor, S2 and S3 contain acidic residues such as aspartate and glutamate. Most of the channels have additional subunits (S1) that modify the basic function but they are not necessary for voltage sensing and ion conduction.[3]

ROLE OF VGICs

VGICs are ion specific, and special types for sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) ions have been identified.[4] Process of opening and closing in the VGICs are triggered by changing ions concentrations, and hence charge gradient, between the sides of the cell membrane.[4] VGICs are activated by changes in the membrane's electrical potential near these channels. The membrane potential alters the conformation of the channel proteins, regulating their opening and

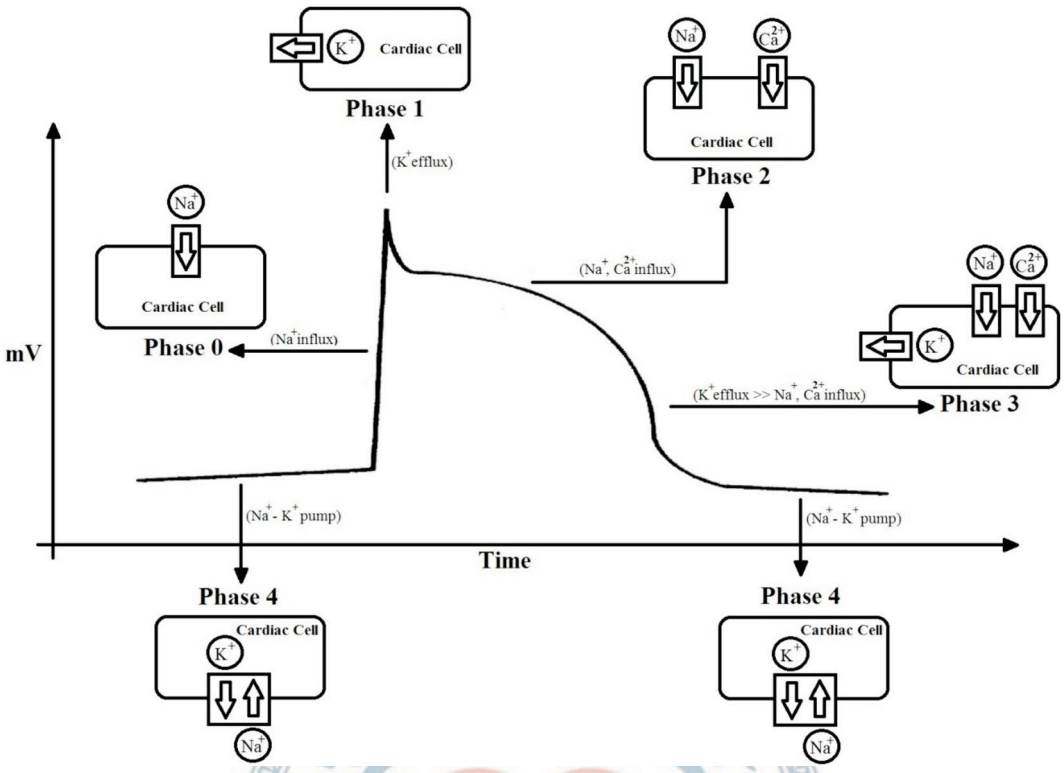

Figure 1. *Different phases of AP's generation in myocytes and different ionic currents in each step.*

closing. Cell membranes are generally impermeable to ions, thus they must diffuse through the membrane through trans-membrane protein channels. They have a crucial role in excitable cells such as neuronal and muscular tissues including cardiac muscles, allowing a rapid and co-ordinated depolarization in response to triggering voltage change. VGICs are found along the axon and at the synapse, they directionally propagate electrical signals.[4] As mentioned in past topics calcium ion, potassium ion and sodium ion are more critical for normal function of cardiac tissues than other ions.[1] In continue role of mutations in *CACNA1C*, *CACNA1D*, *KCNA5*, *KCND2*, *KCND3*, *KCNE1*, *KCNE2*, *KCNE5*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*, *SCN4A*, *SCN5A*, *SCN1B*, *SCN2B*, *SCN3B* and *SCN4B* as important VGICs in generation and conduction of cardiac AP and generation of arrhythmias are discussed in details.

VOLTAGE-GATED CALCIUM CHANNELS (VGCCs)

VGCCs are found in the membrane of excitable cells with a permeability to the calcium ion Ca^{2+} including cardiac muscles.[5] VGCCs are slightly permeable to sodium ions, so they are also called as Ca^{2+}-Na^{+} channels. In normal physiological condition, their permeability to calcium is about 1000 time more than sodium.[1] In normal resting membrane potential, they are physiologically closed, and they are quickly opened at depolarized membrane potentials and this is the source of the voltage-gated epithet. The concentration of Ca^{2+} in outside of cells is normally several thousand times higher than inside of cytosol. Opening of voltage-gated calcium channels allows Ca^{2+} to enter into the cell, this role is more important in cardiac cells where the cells need rapid entrance of calcium ion.[5]

According to the structure different types of VGCCs were identified in mammalians including; L-type, N-type, P/Q-type, R-type and T-type. It is looked that role of L-type channels in normal excitation-contraction in muscles is more important than other types, especially in heart.[5] In cardiac muscle, the major Ca^{2+} currents are distinguished by high voltage VGCCs.[5] These Ca^{2+} currents have been designated by L-type VGCCs.[5]

In cardiac myocytes, VGCC passes Ca^{2+} current inward and triggers calcium release from the sarcoplasmic

reticulum by activating ryanodine receptor 2 (RyR2).[5] The L-type VGCCs that also known as the dihydropyridine channels have four identified subunits including $Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$ and $Ca_v1.4$.[6] Excitation-contraction coupling and regulation of transcription in skeletal muscle are normal function of $Ca_v1.1$,[6] normal functions of $Ca_v1.2$ are including excitation-contraction coupling in cardiac and smooth muscles, endocrine secretion, neuronal Ca^{2+} transients in cell bodies and dendrites, regulation of enzyme activity and regulation of transcription.[6] Normal functions of $Ca_v1.3$ are consisting endocrine secretion, cardiac pace-making, neuronal Ca^{2+} transients in cell bodies and dendrites and auditory transduction,[6] and finally normal function of $Ca_v1.4$ is in visual transduction.[6] $Ca_v1.2$ is encoded by the *CACNA1C* gene, and $Ca_v1.3$ is encoded by the *CACNA1D* gene.

CACNA1C mutations

Missense mutation in the *CACNA1C* was identified in Timothy syndrome patients who are characterized by cardiac arrhythmia, hypoglycemia and neurologic squeals.[7] Presence of this syndrome in the newborn period with no other known affected family members suggests that the inheritance is most probably autosomal dominant.[7] Prolonged QT interval with associated polymorphic ventricular tachycardia, syndactyly, joint contractures, stroke and blindness were reported in *CACNA1C* mutation,[7] also prolonged QT interval and syndactyly involving the 3^{rd}-5^{th} fingers and 2^{nd}-3^{rd} toes in *CACNA1C* mutation patients were reported.[7] Hypertrophic cardiomyopathy,[7] familial sudden cardiac arrest in Brugada syndrome patients[7] were identified in the classic mutation and loss-of-function mutations in *CACNA1C*. Mutations in the *CACNA1C* were detected in a high percentage of probands with J-wave syndromes plus short QT.[7] Different missense mutations in exon 8 of *CACNA1C* gene were identified to have important role in severe cardiac arrhythmias; one is an analogous mutation to that find in exon 8A, and named G406R, other is G402S. Exon 8 encodes the same region as exon 8A, and the two are mutually exclusive. G406R and G402S mutations cause in reduced channel inactivation, maintained depolarizing L-type calcium currents, prolongation of cardiomyocyte APs and delayed after depolarization.[7] Different mutations in *CACNA1C* gene mostly located in C-terminus were identified in patients with idiopathic ventricular fibrillation.[7] Rare mutation of *CACNA1C* in a patient with bipolar disorder and history of Timothy syndrome in childhood was also reported.[7] Novel *CACNA1C* mutations causing QT prolongation and/or fatal arrhythmia attacks in variant phenotypes with larger calcium currents and slower inactivation of APs were also identified.[7] Figure 2 shows the $Ca_v1.2$ topology and position of some mutations which are related to cardiac arrhythmias.[8]

CACNA1D mutations

Losing the function of *CACNA1D* was reported to have important role in sinoatrial node dysfunctions and deafness syndrome with bradycardia and congenital deafness.[7] When presence of ventricular fibrillation in patients with adrenal adenoma was reported,[7] anybody did not expect that *CACNA1D* mutations are responsible for induction of severe hypertension and cardiac arrhythmias.[7] G403D mutation in *CACNA1D* gene were identified in sinus bradycardia and atrioventricular block with prolonged QT-interval and elevated blood pressure patients repeatedly, also presence of mild left ventricular hypertrophy and hypertension were reported from a patients with I750M mutation in *CACNA1D* gene.[7] Same as mutations in *CACNA1C*, mutations in the *CACNA1D* were identified in a high percentage of probands with J-wave syndromes associated with inherited cardiac arrhythmias and sudden cardiac death too.[7] Figure 3 shows the $Ca_v1.3$ topology and position of some mutations which are related to cardiac arrhythmias.[9]

VOLTAGE-GATED POTASSIUM CHANNELS (VGPCs)

As mentioned in last topics, VGPCs play essential roles in APs repolarization,[10] and contribution of individual K^+ channels to repolarization can vary depending on channel density in different cardiac regions.[10] Several types of VGPCs have important function in potassium ion current in cardiac tissues including *KCNA4*, *KCNA5*, *KCND2*, *KCND3*, *KCNE1*, *KCNE2*, *KCNE5*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1* and etc.[10] VGPCs are passing millions of ions per second across the membrane and their gates snap open and shut in milliseconds as they sense changes in voltage or ligand concentration.[10]

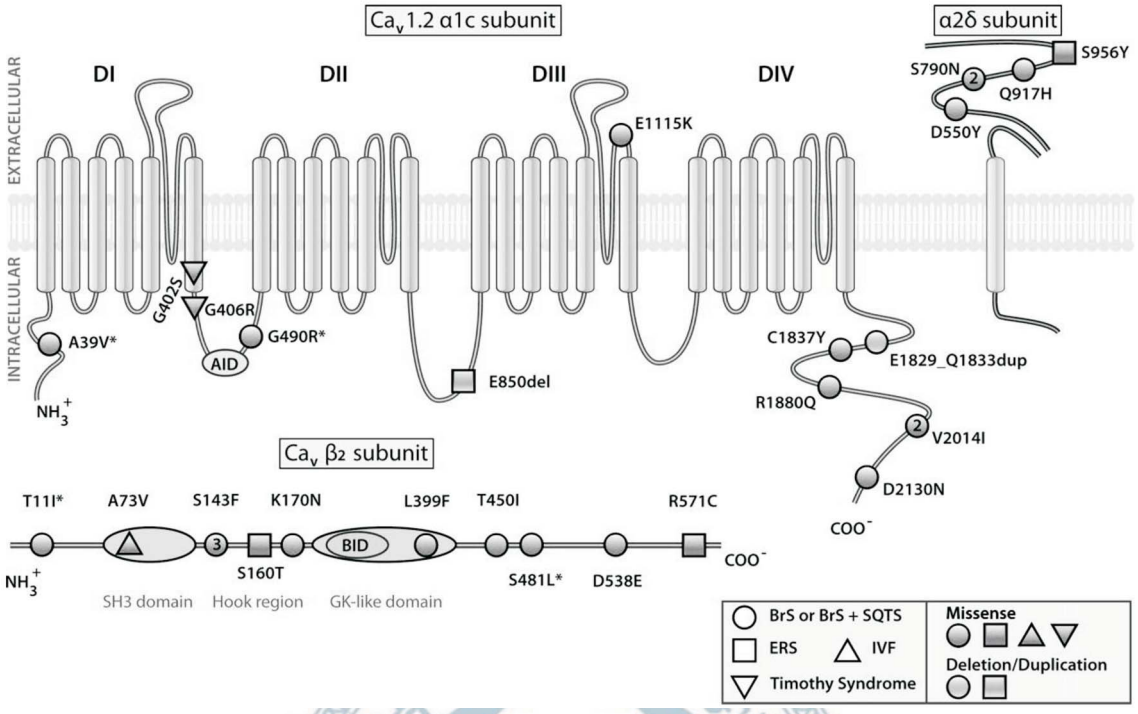

Figure 2. *Cav1.2 topology and position of some mutations which are related to cardiac arrhythmias.*

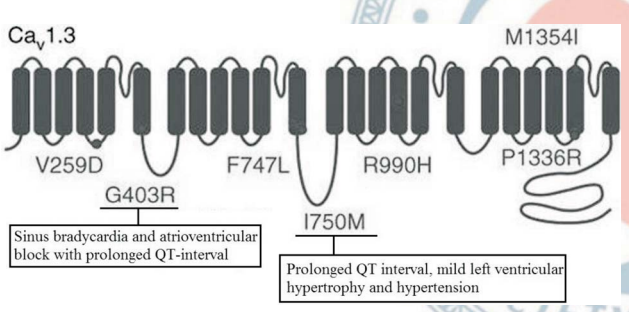

Figure 3. *Cav1.3 topology and position of some mutations which are related to cardiac arrhythmias.*

KCNA5 mutations

KCNA5 mutations (T527M, A576V, E610K, E48G, Y155C, A305T, D322H, D469E, P488S, etc.) cause delayed rectifier potassium currents, APs prolongation, repolarization deficiency and atrial fibrillation.[11] P91L and E33V, which are mutations in *KCNA5*, were also identified in patients with prolonged APs and cardiac arrest.[11] Totally, genetic variation in *KCNA5* promotes multiple mechanisms of arrhythmogenesis for both of gain-of-function and loss-of-function mutations, pertaining to the development of re-entrant excitation and early-after-depolarization. Atrial AP's morphology is demonstrated to be highly sensitive to I_K activation kinetics and had a strong impact on tissue dynamics.[11] Figure 4 shows the K_v1.5 topology and position of some mutations which are related to cardiac arrhythmias.[12]

KCND2, *KCND3* mutations

KCND2 gene mutation (D612N) is associated with J-wave-syndrome and sudden cardiac death due to increase in peak I_{to} current density. This increase in I_{to} results in loss of the epicardial AP dome and predicting an increase in ventricular transmural I_{to} gradient.[11] Gain-of-function mutations in the *KCND3* (L450F and G600R) were identified in Brugada syndrome patients with QT

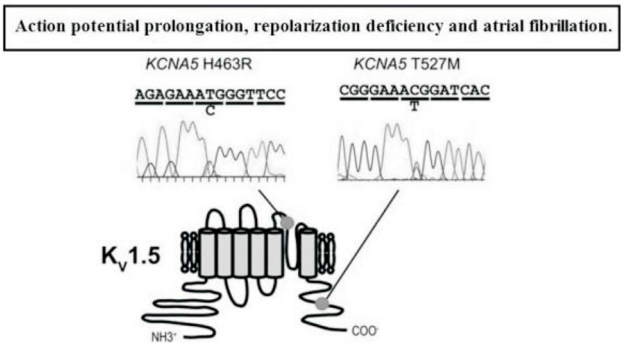

Figure 4. *Kv1.5 topology and position of some mutations which are related to cardiac arrhythmias.*

segment elevation in the leads V1-V3 due to increasing peak I_{to} current density.[11] A novel *KCND3* gain-of-function mutation (A545P) associates with early-onset of persistent lone atrial fibrillation, this association supports the hypothesis that increased potassium current enhances atrial fibrillation susceptibility.[11] Also it was reported that the novel mutations in *KCND3* (p.Val392Ile, p.Ser530Pro, and p.Gly600Arg) may serve as a rare genetic substrate in the pathogenesis of sudden cardiac unexplained death.[11] In contrast, an hypothesis was reported that mutations in the genes *KCND2* and *KCND3*, conducting the cardiac fast transient outward current ($I_{TO,f}$), are not a frequent cause of long QT syndrome and cardiac arrhuthmias.[13]

KCNE1, *KCNE2*, *KCNE5* mutations

KCNE1 missense mutations (S74L and D76N) reduce potassium current (I_{KS}), make delayed cardiac repolarization, prolonged QT syndrome and an increased risk of severe arrhythmias.[11] Also *KCNE1* mutations (G25V and G60D) are associated with early-onset familial atrial fibrillation due to increase in potassium current; agree with hypothesis that increase in potassium current enhances atrial fibrillation susceptibility.[11] M54T and I57T mutated variants of *KCNE2* lead to a gain of function of I_{to} can contribute to generating potential arrhythmogeneity and pathogenesis for inherited fatal rhythm disorders.[11] *KCNE2* deletion (*KCNE2*-null) creates a multisystem syndrome predisposing to aging-dependent QT prolongation, ventricular fibrillation, transient ischemia, atrioventricular block and sudden cardiac death including.[11] Also *KCNE2* deletion (*KCNE2*-null) can promote atherosclerosis and diet-dependent sudden death due to increase in plaque deposition, make premature ventricular complexes and finally results in sudden cardiac death.[11] *KCNE2* gain-of-function mutation (R27C) is also associated with the initiation and/or maintenance of atrial fibrillation in patients with history of familial atrial fibrillation.[11] Also missense mutations in *KCNE2* were identified to have an important role in prolongation of APs and pathogenesis of long QT syndrome.[11]

KCNE5 mutations (p.Y81H, p. D92E and p.E93X) were identified as novel modulators for generation and/or maintenance of Brugada syndrome and idiopathic ventricular fibrillation.[11] Gain of function mutation in *KCNE5* (L65F) is closely associated with non-familial or acquired forms of atrial fibrillation by the mechanism of gain of function in I_{Ks} and disorders of potassium currents.[11] Relation between other mutations in *KCNE5* and atrial fibrillation were reported repeatedly too.[11] In contrast, hypothesis that mutations in *KCNE5* gene have not relation with long QT syndrome was published due to fail in finding of mutations in *KCNE5* gene in patients with long QT syndrome.[14]

KCNH2 mutations

KCNH2 mutation (K897T) was identified as genetic modifier of latent congenital long QT syndrome due to I_{Kr} currents reduction. It was reported that similar mechanism may contribute to the risk for sudden cardiac death too,[11] also other mutations in *KCNH2* were reported in long QT syndrome patients repeatedly.[11] Other *KCNH2* mutation (N588K) is responsible to cause short QT syndrome, paroxysmal atrial fibrillation, ventricular fibrillation and sudden cardiac death.[11] Briefly, it is identified that, like mutations in other members of voltage-gated potassium channels, genetic determinants located in *KCNH2* can also influence QT length in healthy individuals and may represent as risk factors for arrhythmias and/or cardiac sudden death.[11] Figure 5 shows the K_v11.1 topology and position of some mutations which are related to cardiac arrhythmias.[12]

KCNJ2, *KCNJ5* mutations

KCNJ2 mutation (R67W) is responsible to generation of moderate to severe ventricular arrhythmias in Andersen syndrome patients.[11] Andersen syndrome is an autosomal dominant trait with sex-specific variable expressivity. Patients can show dysmorphic features, car-

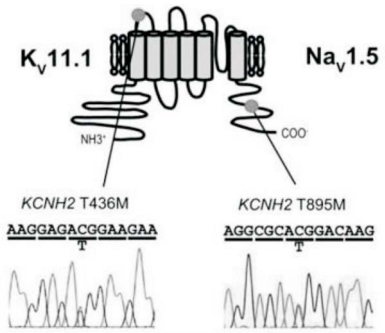

Figure 5. *Kv11.1 topology and position of some mutations which are related to cardiac arrhythmias.*

diodysrhythmic periodic paralysis, cardiovascular malformation (i.e., bicuspid aortic valve, bicuspid aortic valve with coarctation of the aorta, or valvular pulmonary stenosis),[11] same findings were reported repeatedly by different scientists.[11] *KCNJ2* substitution mutation (G514A) is also responsible to cause short QT waves and a greater risk of reentrant arrhythmias.[11] Other *KCNJ2* mutation (T192A) was identified to be related with generation of ventricular dysrhythmia.[11] Loss of function mutations in *KCNJ5* (G387R) and in *KCNJ2* (R67Q, R85W, T305A, T75M) were also identified in patients with long QT syndrome, prominent U-waves, marked ventricular ectopy, and polymorphic ventricular tachycardia without presence of any facial/skeletal abnormalities.[11] Hypothesis that *KCNJ5* mutations aren't apparently involved in the pathogenesis of Sinus node dysfunctions and related arrhythmias including sinus arrest, asystole, or extreme sinus bradycardia was reported after identification of several known single nucleotide polymorphisms in *KCNJ5*, but without presence of any mutations in either of the gene.[15]

KCNQ1 mutations

KCNQ1 polymorphisms can be molecular basis for occurrence of mild I_{Ks} dysfunction, and in the presence of appropriate precipitating factors might predispose potential gene carriers to life-threatening arrhythmias.[11] *KCNQ1* mutation (V307L) in patients with short QT syndrome was identified to make a pronounced shift of the half-activation potential due to gain of function in I_{Ks}.[11] *KCNQ1* novel mutations (W305X, G314C, Q357R, 1338insC and G568A) were identified in patients with familial history of lethal cardiac arrhythmias including: Brugada syndrome, idiopathic ventricular fibrillation and severe long QT syndromes and history of syncope, aborted cardiac arrest and sudden death.[11] Also it is identified that mutations in *KCNQ1* can cause channelopathy co-expressed in heart and brain with aspects of: epilepsy, long QT syndrome, syncope and sudden death.[11] S140G mutation in *KCNQ1* was identified to initiate and maintain atrial fibrillation by reducing APs duration and effective refractory period in atrial myocytes.[11] Other mutations in *KCNQ1* (Y111C, L114P, P117L, L191P, A341V, etc.) were identified in several cases of patients with different aspects of long QT syndromes.[16] Figure 6 shows the $K_v7.1$ topology and position of one mutation which is related to cardiac arrhythmias.[12]

VOLTAGE-GATED SODIUM CHANNELS (VGSCs)

VGSCs have important role in the initiation and propagation of APs in electrically excitable cells such as cardiac cells.[1] VGSCs are large, polymeric complexes, consist of one α subunit and one or more smaller β subunits.[17] The ion-conducting aqueous pore is contained entirely within the α subunit which is the essential element of sodium-channel function and co-expression of the β subunit is required for full reconstitution of the properties of native sodium channels.[18] Nine α subunits ($Na_v1.1$-$Na_v1.9$) have been functionally characterized and a tenth related isoform (Na_x) may also has function as a Na^+ channel.[18] The roles of *SCN4A* ($Na_V1.4$ as primary sodium channel in muscular tissues) and *SCN5A* ($Na_V1.5$) in heart are more important than others but others also have significant levels of expression outside of their primary tissues including in cardiac muscles.[19] Four additional sodium channel β subunits ($Na_V\beta1$-4) also have been identified in total.[19] *SCN1B* and *SCN3B* ($\beta1$ and $\beta3$) are associated non-covalently with α subunits and resemble each other most closely in amino acid sequence, whereas *SCN2B*, *SCN4B* ($\beta2$ and $\beta4$) form disulfide bonds with α subunits and also resemble each other closely. The structure of $Na_v\beta$ subunits resembles a family of cell adhesion molecules,[19] and increasing evidence support their role in localization and immobilization of sodium channels in specific locations in excitable cells.[19]

SCN4A, *SCN5A* mutations

SCN4A mutations (R1448C) were identified to have

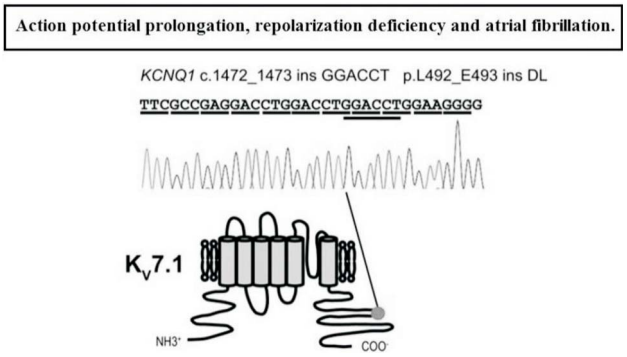

Figure 6. *Kv7.1 topology and position of one mutation which is related to cardiac arrhythmias.*

important role in patients with paramyotonia congenita and repolarization abnormalities.[20] Paramyotonia congenita is a skeletal muscle disorder beginning in infancy or early childhood and usually causes muscle tensing (myotonia).[21] Also cardiac arrhythmia required a pacemaker implantation with 40-90% decrease in compound muscle AP amplitude were reported in patients with the T704M mutation in *SCN4A*.[22] Figure 7 shows the $Na_v1.4$ topology and position of some mutations which are related to paramyotonia congenita and squares sodium channel myotonias.[23] *SCN4A* mutations (R669H) in patients with severe cardiac arrhythmias due to hypokalemic periodic paralysis were also identified.[24] Generation and development of a type 1 electrocardiographic pattern and the occurrence of malignant arrhythmias in patients with Brugada syndrome are closely related to *SCN4A* mutations.[25] Paroxysmal supraventricular arrhythmias during hypokalemic episodes in patients with hypokalemic periodic paralysis were also reported.[26] Generally, mutated *SCN5A* patients are implicated in risk of severe cardiac arrhythmias.[27] *SCN5A* mutation (Y1102) accelerates channel activation, increases the likelihood of abnormal cardiac repolarization and severe cardiac arrhythmias. It is identified that about 13.2% of African Americans carry the Y1102 allele but as Y1102 has a subtle effect on risk then most carriers will never have any arrhythmia.[27] *SCN5A* mutation (M1766L) causes a significant decrease in the sodium channel expression and 10-fold increase in the persistent late sodium currents, contributes to the generation of lethal arrhythmias and displays an overlapping electrophysiological phenotype.[28] *SCN5A* missense mutations (E446K, F1520L, V1279I, D1275N and R222Q) were also identified in patients with dilated cardiomyopathy and sever aspect of supraventricular arrhythmia, sick sinus syndrome, atrial fibrillation, ventricular tachycardia and related APs conduction diseases.[29] Intragenic deletions and missense mutations in *SCN5A* are closely related to generation of long QT syndromes via delay in cardiac sodium channels, fast inactivation or altered voltage-dependence of inactivation.[30] Genetic linkage between special kind of long QT syndrome and polymorphisms within *SCN5A* shows that deleted sequences in *SCN5A* gene resides in a region which is responsible for sodium channels inactivation and delaying in inactivation of sodium channels and finally results in generation of long QT syndrome.[31] *SCN5A* mutations were repeatedly reported to be present in dilated cardiomyopathies, APs conduction disorders and cardiac arrhythmias due to change of sodium currents.[32] Also *SCN5A* mutations were repeatedly identified in patients with different aspects of atrial fibrillation,[33] ventricular fibrillation,[34] and Brugada syndrome.[33] Figure 8 shows the $Na_v1.5$ topology and position of some mutations which are related to cardiac arrhythmias.[35]

SCN1B, *SCN2B*, *SCN3B*, *SCN4B* mutations

Loss of *SCN1B* (*SCN1B*-null) causes increased amplitude of I_{Na}, delayed after-depolarization, triggered beats, delayed Ca^{2+} transients, frequent spontaneous calcium release events and finally increased susceptibility to polymorphic ventricular arrhythmias. Life-threatening arrhythmias in patients with mutations in *SCN1B* can be partly consequent to disrupted intracellular Ca^{2+} homeostasis too.[36] *SCN1B* mutations are associated with Brugada syndrome as well as with other cardiac arrhythmias and familial epilepsy. Several mutation variants

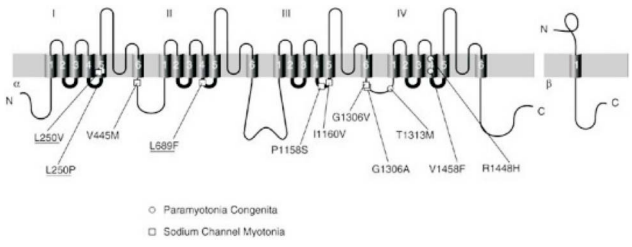

Figure 7. *Nav1.4 topology and position of some mutations which are related to paramyotonia congenita and squares sodium channel myotonias.*

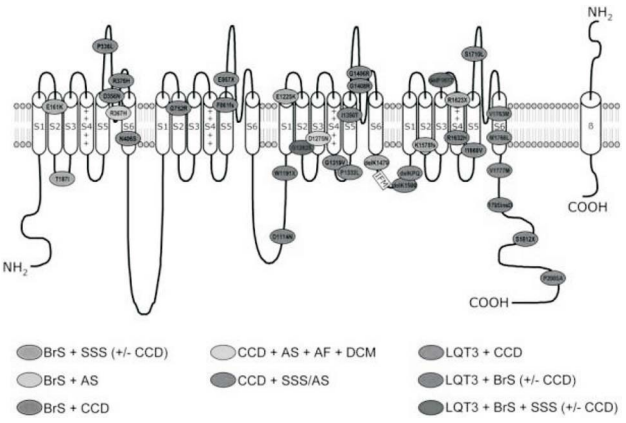

Figure 8. *Nav1.5 topology and position of some mutations which are related to cardiac arrhythmias.*

of *SCN1B* gene are also closely related with Brugada syndrome.[37] Deletion of *SCN2B* (*SCN2B*-null) is also responsible for generation and maintenance of atrial and ventricular arrhythmias via increasing in levels of fibrosis and higher repolarization dispersion.[38] Also novel missense mutation in *SCN2B* was identified to reduce in I_{Na} density and have relation with Brugada syndrome.[39] *SCN3B* mutation (A130V) was identified to associate with atrial fibrillation via induction of dramatically decrease in the cardiac sodium current density,[40] other mutation was reported with same effects on atrial fibrillation.[41] Deletion of *SCN3B* (*SCN3B*-null) was identified to be responsible for abnormal ventricular electrophysiological properties via reduction in Na^+ current densities.[42] Other *SCN3B* mutation (Val110Ile) impairs the cytoplasmic trafficking of Nav1.5 and reduces sodium currents, also it was reported that Val110Ile mutation of *SCN3B* is a relatively common cause of SCN5A-negative Brugada syndrome in Japan.[43] Novel heterozygous *SCN4B* mutations (p.V162G and p.I166L) were identified in patients with atrial fibrillation transmitted in an autosomal dominant pattern. These mutations alter the amino acids evolutionarily highly conserved across species and were both predicted to be disease-causing.[44] Also, a missense mutation in *SCN4B* (L179F) was identified to have role in congenital long QT syndrome via increase in late sodium currents.[45] Figure 9 shows the $Na_v1.5$ and $Na_v\beta1$ topologies and position of some mutations which are related to cardiac arrhythmias.[12]

TREATMENT STRATEGIES FOR CARDIAC CHANNELOPATHIES

It is recommended that β-blockers are the most useful medications for patients with long QT syndrome related to mutations of voltage gated ionic channels.[46] Cardioverter defibrillator implantation is recommended for patients with long QT syndrome and who have/had a cardiac arrest. Also it is also recommended for patients who, even when receiving β-blockers, have experienced repeated syncopal episodes or ventricular arrhythmias.[47-50] In addition, patients who have two or more gene mutations, which can cause long QT syndrome, should be considered for prophylactic cardioverter defibrillator implantation.[51] Individuals with short QT syndrome may also be treated with cardioverter defibrillator implantation to decrease the risk of sudden cardiac death due to ventricular arrhythmias.[46] In some individuals, quinidine may be prescribed to prolong the QT interval; however, the efficacy of this drug is still under clinical evaluation.[52] Patients who are experiencing cardiac arrhythmias due to Brugada syndrome may be treated via cardioverter defibrillator implantation.[46] Patients who experience a cardiac arrest are recommended for cardioverter defibrillator implantation, regardless of any other clinical variables.[46] However, current guidelines do not recommend cardioverter defibrillator implantation in asymptomatic patients with Brugada syndrome, because they are believed to be at low risk for ventricular arrhythmias.[53] Quinidine and isoproterenol increase cellular levels of sodium and calcium while inhibiting potassium levels and may be prescribed to balance the sodium ionic currents within the cardiac myocytes.[46] Several medications are recommended for treatment of cardiac channelopathies but more research is need in this area.

CONCLUSIONS

In this review, roles of voltage-gated channels for calcium, sodium and potassium ions on generation and conduction of cardiac APs are firstly mentioned, and then roles of their gene mutations on occurrence of cardiac arrhythmias as important malfunctions of heart are discussed in detail. This review clears that voltage-gated ionic channels mutations play an important role in generation of severe cardiac arrhythmias and it is suspected

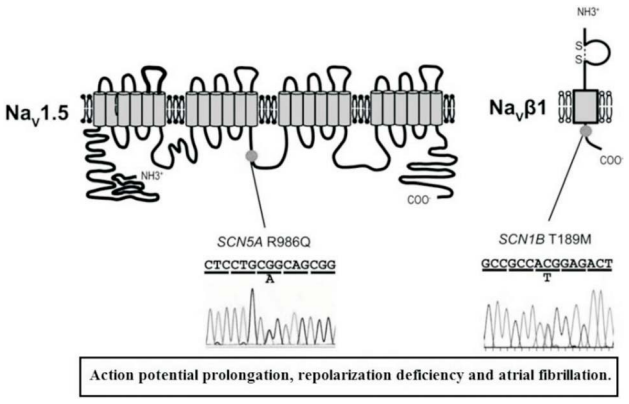

Figure 9. *Nav1.5 and Navβ1 topologies and position of some mutations which are related to cardiac arrhythmias.*

that mutations in voltage-gated potassium channels are more important in generation of arrhythmias. Most of arrhythmias due to mutations in voltage-gated ionic channels result in APs prolongation, different aspects of long QT syndrome and generation of severe cardiac arrhythmias. Study on ionic channel regulators can be considered as a subject for future research.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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