Further insights into inheritable arrhythmia syndromes: Focus on electrocardiograms
Postema, P.G.

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Introduction, based on:
Ion channels involved in cardiac arrhythmias

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*T.T. Koopmann
*P.G. Postema
C.R. Bezzina
A.A.M. Wilde

*These authors contributed equally

Academic Medical Center, Amsterdam, The Netherlands
INTRODUCTION

Normal excitation of the human heart depends on the proper movement of charged ions through special cardiac ion channels across the surface membrane of millions of cardiac cells. Disorders of cardiac ion channels may lead to a heterogeneous group of diseases, also known as cardiac channelopathies, which may predispose to sudden cardiac death (SCD).\(^1\) SCD accounts for up to half a million of deaths yearly in the US,\(^2\) and originates from cardiac arrhythmias which drastically decline cardiac output finally resulting in fatal cerebral ischemia. About 80% of SCD is the result of cardiac ischemia due to coronary artery disease, but in the remaining 20% other causes -like channelopathies- play a causal role. In the last decade there have been major advances in the recognition of pathophysiological mechanisms leading to SCD. Cardiac channelopathies in particular may predispose the young and very young to a premature death. In this chapter we will review the basic biophysical properties of the cardiac ion channels, various cardiac channelopathies and their clinical relevance.

CARDIAC ION CHANNELS

Ion channels consist of specific transmembrane proteins through which ionic currents flow with each cycle of the heart and bring about an electrical signal across the membrane, also known as the ‘action potential’ (figure 1). Each ionic current has its own specific ionic selectivity and time course, which generally means that ion channels are selective for one type of ion over all others in their physiological environment. When the ion channels open, they tend to bring the membrane potential of the cell towards the equilibrium potential of that specific ion.

The cardiac action potential

The cardiac action potential (figure 1) is divided into 5 phases (phase 0 to 4) in which the net effect of different ion currents is described. Phase 0 starts with the voltage-gated sodium channels which open quickly in response to a voltage stimulus from a neighboring cell. This results in the rapid influx of positively charged sodium (Na\(^+\)) ions into the negatively charged cardiomyocyte, also known as the rapid depolarization phase. Then, the sodium channels inactivate quickly and completely. On the surface of the body this depolarization wave can be documented with an electrocardiogram (ECG). The cascade of depolarization of the atrial cardiomyocytes corresponds on the ECG to the P wave and for the ventricular cardiomyocytes it corresponds to the Q, R and S waves.

After the rapid depolarization, a moment of repolarization, phase 1, follows which starts as a result of the closure of the fast sodium channels and outward movement of potassium (K\(^+\)) ions. A plateau phase in the action potential then quickly follows, known
as phase 2, and an almost perfect balance between influx of calcium (Ca^{2+}) ions and outward movement of K^{+} ions maintains the action potential at a relatively constant voltage. Compared to Na^{+} channels, voltage-gated calcium channels inactivate less rapidly and less completely and so they feature prominently in maintaining plateau depolarization. This plateau phase of the ventricular cardiomyocytes corresponds to the first part of the ST-T segment on the ECG. Phase 3, the repolarization phase, is determined by the efflux of K^{+} ions from the cells and corresponds to the last part of the ST-T segment on the ECG. In contrast to the Na^{+} and Ca^{2+} channels which force the potential of the cardiomyocytes to positive levels of at least 40 mV after opening, the K^{+} channels steer the cell to a negative level of -90 mV. Phase 4 is referred to as the resting membrane potential and is determined by the selective permeability of the membrane to various ions, in particular K^{+} ions, keeping the resting membrane potential in the vicinity of the potassium equilibrium potential. On the ECG the T-U-P segment represents phase 4 (i.e. the diastolic phase).

So, depending on which cardiac ion channels are open or closed, the cardiomyocytes

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**Figure 1** ECG, action potential, ion channels

Schematic representation of the ionic currents contributing to the action potential; A. the electrocardiogram (ECG) and the P-QRS-TU segments in time aligned with; B. the ventricular action potential with phase 0 to 4 and the ionic currents originating from; C. the cardiomyocyte displaying (only) those transmembrane ion channels, β-subunits and ionic currents involved in the pathogenesis of the described inherited arrhythmia syndromes. In panel C, ankyrin-B, an adapter protein involved in Long QT Syndrome type 4, is not shown. Abbreviations as in the text.
are either positively or negatively charged. Moreover, type and level of expression of ion channels on the cardiomyocyte membrane differ in the different areas of the heart (e.g. atria vs. ventricles) and in the different myocardial layers (e.g. endocardium vs. epicardium), thereby inducing different action potentials and subsequent potential differences with each heart cycle.

Mutations in the genes encoding ion channels can cause abnormal channel functioning and may thereby lead to changes in the action potential morphology. These action potential changes may subsequently give rise to electrical instability with life-threatening arrhythmias as a direct result.

**Sodium channels**

Voltage-gated Na\(^+\) channels (figure 2) are responsible for the upstroke of the action potential and for the generation of cell-to-cell current which underlies propagation of the action potential in excitable tissues including muscle, nerve and the heart. The channels are composed of pore-forming α subunits of ~260 kDa associated with one or two β subunits of 30–40 kDa that alter the properties of the channel. The α-subunit gene family consists of nine genes\(^3\) (and one additional sodium channel-like gene), that are highly conserved across species. The channels are characterized by differential (in)activation kinetics and by different sensitivities to the sodium channel blocker tetrodotoxin (TTX): highly TTX-sensitive α-subunits (encoded by SCN1A, SCN2A, SCN3A, SCN4A, SCN8A, SCN9A) have faster inactivation kinetics compared to α-subunits that are less sensitive to TTX (encoded by SCN5A, SCN10A, SCN11A).

The four β-subunit isoforms, which are all expressed in the heart, can be divided into 2 groups: β1 (SCN1B)\(^4\) and β3 (SCN3B)\(^5,6\) are most similar in amino acid sequence and are noncovalently associated with the α-subunits\(^6,7\); β2 (SCN2B) and β4 (SCN4B)\(^8\) subunits are also closely related in amino acid sequence to one another but as opposed to β1 and β3 are disulfide-linked to the α-subunits\(^5,8\).

**Sodium channel α-subunits**

The pore-forming α-subunit of the cardiac specific voltage-gated sodium channel (encoded by SCN5A), is a large transmembrane protein that contains four structurally homologous domains (DI-DIV), each composed of six helical transmembrane segments (S1-S6) (figure 2). The S5 and S6 segments and the P-loop between them line the channel pore. The pore contains the selectivity filter also referred to as the DEKA ring (consisting of aspartic acid, glutamate, lysine, alanine; one of these amino acids per P-loop), which attracts positive Na\(^+\) ions and excludes negatively charged ions\(^9\). The lysine residue in the P-loop of DIII is important for discrimination for Na\(^+\) over Ca\(^{2+}\)\(^{10,11}\).

Depending on the membrane potential, voltage-gated Na\(^+\) channels can occupy
three functional states: resting (closed), activated (open), and inactivated (closed). The highly conserved S4 region in each domain has a positive amino acid at every third position, and is considered the voltage sensor. The transition from the resting state to the activated state occurs when a change in transmembrane voltage moves S4 from inside the pore towards the extracellular side of the cell, activating the channel which becomes permeable to ions.\(^{12}\) Inactivation is mediated mainly by the inactivation gate (DIII-DIV linker), that blocks the inside of the channel shortly after it has been activated, and the C-terminal cytoplasmic domain.\(^{13-15}\) During an action potential the channel normally remains open for only a few milliseconds after depolarization before it is being inactivated. When the membrane potential reaches the threshold potential during the repolarization phase, the channels return to their resting state and can be activated again during the next action potential.

**Sodium channel β-subunits**

β-Subunits consist of one transmembrane segment, an intracellular domain and a glycosylated extracellular domain. The structure of the extracellular domain resembles the structure of the V-like family of Ig-fold proteins, containing domains similar to the variable regions of antibodies and including motifs as found in cell adhesion molecules.\(^{16}\) The multifunctional β-subunits modulate channel gating, regulate the level of expression of the α-subunit at the plasma membrane,\(^{17}\) and are involved in cell adhesion through interaction with the cytoskeleton, extracellular matrix, and other cell adhesion molecules that regulate cell migration and aggregation.\(^{18}\)

**Potassium channels**

Many types of K\(^{+}\) channels act together to determine the configuration and duration of the cardiac action potential (figure 1). In the heart, K\(^{+}\) channels include voltage-gated channels, such as the rapidly activating and inactivating transient outward current (I\(_{\text{to}}\)), the ultrarapid (I\(_{\text{Kur}}\)), rapid (I\(_{\text{Kr}}\)) and slow (I\(_{\text{Ks}}\)) components of the delayed rectifier current, and the inward rectifier current (I\(_{\text{K1}}\)).

The delayed rectifier K\(^{+}\) current (I\(_{\text{K}}\)) has a major role in modulating action potential duration and in the heart comprises at least three distinct components: I\(_{\text{Kur}}\), I\(_{\text{Kr}}\) and I\(_{\text{Ks}}\). These currents are easily distinguished on the basis of their pharmacological and biophysical properties. I\(_{\text{Kur}}\) has been recorded in human atria but not in human ventricular tissue. This means that I\(_{\text{Kur}}\) is the predominant delayed rectifier current responsible for human atrial repolarization. This K\(^{+}\) current activates rapidly in the plateau range and inactivates very slowly during the time course of the action potential.\(^{19,20}\) I\(_{\text{Kr}}\) activates rapidly compared to I\(_{\text{Ks}}\), but also partially inactivates. In cardiac myocytes, I\(_{\text{Ks}}\) activates very slowly in response to membrane depolarization. Due to its slow rate of activation, the contribution of I\(_{\text{Ks}}\) to the net repolarizing current is greatest in phase 3 of the cardiac action potential.
Figure 2 Cardiac ion channel proteins

Schematic representation of the cardiac ion channel proteins Nav1.5, Cav1.2, KvLQT1, Kir2.1 and the HCN4 encoded nonspecific cation channel. See text for further explanation. Courtesy of A.C. Linnenbank, PhD, Heart failure research center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.
The transient outward current $I_{to}$ can be divided into two distinct transient outward K\(^{+}\) currents, $I_{to,f}$ and $I_{to,s}$, which are differentially distributed in the myocardium. These currents are differentiated based on their rate of inactivation and recovery from inactivation.

The cardiac inward rectifying potassium current ($I_{Ki}$) stabilizes the resting membrane potential and is responsible for determining the threshold for the initial depolarization and final repolarization of the action potential.\(^{21}\) $I_{Ki}$ is a strong rectifier that passes K\(^{+}\) currents over a limited range of membrane potentials. Upon depolarization, $I_{Ki}$ channels close almost immediately, remain closed during the plateau phase and open again at negative potentials.

**Potassium channel α-subunits**

The membrane-spanning domain of all voltage-gated K\(^{+}\) channels contains two highly conserved parts: the voltage-sensing part that surrounds the central pore and the pore domain itself. The channels are composed of a tetramer of the primary subunits: functional potassium channels are made up of four identical primary subunits, that each contain six transmembrane-spanning domains (S1–S6), with the S4 domain containing six positive charges.\(^{22}\) The pore domain, S5, the P-loop, and S6 all together make up the ion permeation pathway, including the selectivity filter.\(^{23}\) The opening of the channel and generation of the alleged gating current is caused by membrane depolarization, which mediates a movement of the positively charged residues of S4 through the gating channel. However, the voltage sensor of voltage-gated K\(^{+}\) channels is not exclusively S4. Transmembrane segments S2 and S3 (and possibly S1) also contribute to voltage sensing.\(^{24}\)

The human ether-a-go-go-related gene KCNH2 encodes the α-subunit of the $I_{Kr}$ channel (HERG). Similar to other voltage-gated K\(^{+}\) channels, changes in membrane potential induce a sequence of conformational changes within the HERG protein that allow permeation of K\(^{+}\) ions. Opening of the channel involves widening of the inner helices.\(^{23}\) The S6 of HERG has a conserved glycine, which might be involved in channel opening by splaying of the inner helices.\(^{25}\) In the closed state, the four inner helices that line the channel pore create a narrow opening that prevents passage of ions by leaning towards the membrane and interlace near the cytoplasmic border. HERG channels contain a PAS (Per–Arnt–Sim) domain on their cytoplasmic N-terminus that may interact with other regions of HERG such as the S4–S5 linker to affect channel deactivation,\(^{26,27}\) but the exact role of this domain in HERG remains unclear.

KCNQ1, encoding the α-subunit of the $I_{ks}$ channel, has a typical pore loop (figure 2). The structural basis of KCNQ1 channel activation has not been studied, but it is likely that most of the general features of S4 movement and involvement of S6 in channel opening will be similar to HERG. Unlike HERG, KCNQ1 has a motif similar to the S6 proline-X-proline sequence of other voltage-gated potassium channels: proline-alanine-glycine, which is expected to play a role in gating. Furthermore, S6 contains an alanine hinge, a residue
that would favor maintenance of the α-helical structure. Membrane repolarization causes a transient increase in KCNQ1 channel conductance that precedes deactivation. The molecular mechanism of KCNQ1 channel inactivation is poorly understood, but is independent of extracellular K⁺ concentration.²⁸

Kv4.3 is the pore-forming subunit for I_{to}, in human hearts. Voltage-gated K⁺ channels only form homomultimers (multimerize) with members of their own subfamily. This means that Kv4.x genes can only multimerize and form functional channels with other Kv4.x genes. The structural feature responsible for this, is the highly conserved C-terminus of the channel known as the tetramerization domain (T1 domain),²⁹ which is a ~130 amino acid sequence directly preceding the first transmembrane domain. This domain is also thought to play a role in channel gating.

Different gene families (Kir2.1–2.3) have been found in human heart encoding I_{K1}. Similar to voltage gated K⁺ channels, the Kir2.x channels are tetramers.³⁰ However, Kir subunits contain only two transmembrane domains (M1 and M2), which are highly homologous to the S5 and S6 of the abovementioned voltage-gated K⁺ channels (figure 2).³¹ Each Kir subunit has cytoplasmic amino-terminal and carboxyl-terminal regions and a pore loop structure (P or H5 region) between M1 and M2. The P loop contains a selectivity filter that determines K⁺ selectivity.

**Potassium channel and interacting subunits**

Heterologous expression of the pore-forming α-subunits is sufficient to generate functional K⁺ channels. However, the essential role of β-subunits in current characteristics is being increasingly recognized: an expanding family of function-altering β-subunits has been identified, which can modulate functional expression.³²

KCNQ1 encoded subunits interact with KCNE1 encoded minK subunits; small channel subunits (<130 amino acids) that coassemble with α-subunits to form functional channels that considerably alter gating.³³,³⁴ The role of MinK-related protein (MiRP1), encoded by KCNE2, as a physiologically relevant modulator of HERG channels is currently investigated. The structural basis of altered KCNQ1 gating by MiRP subunits has not been determined yet.

Besides several cytoskeletal proteins, Kv4.3 interacts with: (1) K⁺ channel interacting proteins (KChIPs),³⁵ which have a conserved c-terminus that contains four EF-hand-like calcium-binding motifs; (2) NCS-1 (also called frequenin), which increases the current density and slows the rate of inactivation of the Kv4.x current when coexpressed with Kv4.x α-subunits.³⁶,³⁷ In contrast to KChIPs, however, NCS-1 does not affect the voltage dependence of inactivation or rate of recovery from inactivation of the channel; (3) K⁺ channel accessory proteins (KChAPs),³⁸ which can increase current expression, without an effect on current kinetics; (4) dipeptidylaminopeptidase-like protein 6 (DPPX), which causes an increase
in surface expression, an increase of recovery from inactivation, and a shift in inactivation voltage dependence when coexpressed with Kv4.3.\textsuperscript{39,40}

**Calcium channels**

Muscle contraction is regulated by elevation of the intracellular Ca\textsuperscript{2+} concentration mediated by the interaction of two membrane proteins, the L-type voltage-gated calcium channels and the ryanodine receptors. Cardiac muscle contraction requires Ca\textsuperscript{2+} entry with each beat which triggers Ca\textsuperscript{2+} release from the sarcoplasmic reticulum (SR) via Ca\textsuperscript{2+}-release channels, such as the ryanodine receptor, resulting in a cascade of Ca\textsuperscript{2+} ions released into the cytosol, i.e. calcium-induced calcium release. The cardiac L-type calcium channel is assembled from three tissue-specific isoforms; α1 (α11.2), α2δ1, and β isoforms, which are considered the functional minimum core for Ca\textsuperscript{2+} channel assembly (for review see Bodi et al.\textsuperscript{41}). Four hydrophilic and nonglycosylated β-subunit isoforms (β1–β4) have been described, but only β2 and β3 form cardiac L-type voltage-gated calcium channels. The accessory subunits (β, α2/δ) are tightly but not covalently bound to the α1 subunit and modulate the biophysical properties and trafficking of the α1 subunit to the membrane.

**Calcium channel α-subunits**

Like voltage-gated sodium channels, Ca\textsuperscript{2+} channel α1-subunits (170–240 kDa) consist of 4 homologous domains (I–IV), each composed of 6 transmembrane-spanning α-helices (S1 to S6) linked by variable cytoplasmic loops (figure 2). To date, 10 α1 subunit genes have been identified and separated into 4 classes: Cav1.1 (α1S), 1.2 (α1C), 1.3 (α1D), and 1.4 (α1F). Only the α1C (dihydropyridine-sensitive) -subunit is highly expressed in cardiac muscle. The α1-subunit consists of the ion-selective pore, voltage sensor and the binding sites for channel-modulating drugs and is autoregulatory. The S5 and S6 segments and the P-loop between them from each domain line the channel pore. The pore contains the selectivity filter, with one conserved glutamate residue (E) per P-loop.\textsuperscript{42} The positively charged S4 region of each domain is highly conserved and has a positively charged residue (arginine or lysine) at every third or fourth position. Like voltage-gated Na\textsuperscript{+} channels and K\textsuperscript{+} channels, this segment is considered the voltage-sensor.

**Calcium channel β-subunits**

The β-subunit, which does not have a membrane-spanning region, is tightly bound to a highly conserved motif in the cytoplasmic linker between domains I and II of voltage–gated α1-subunit isoforms, called the α-interaction domain (AID), and also to a secondary site.\textsuperscript{43–45} The β-interaction domain (BID), connects with the AID through a α-binding pocket (ABP), a conserved hydrophobic crevice.\textsuperscript{46} Coexpression of β-subunits modulates the biophysical properties of the α1-subunit. A 153-aa sequence in the human cardiac short β2f and β2g-
subunits was recently described as being essential for modulating Ca\textsuperscript{2+} channel function and interaction with the α1C subunit.\textsuperscript{47}

**Calcium channel α2/δ-subunits**

The α2δ-subunits are closely associated with the α1-subunit by surface interaction and are intracellularly linked to the δ-subunit through a disulfide bridge. The α2-subunit is completely extracellular, while the δ-subunit has a single transmembrane region with a short intracellular part. Both subunits are encoded by the same gene, which is separated by proteolytic cleavage.\textsuperscript{48} The in vivo function (and structure) of the α2/δ-subunits is still unknown, however, coexpression of these subunits in heterologous expression systems affects α1 function by increasing channel density with variable minor effects on channel kinetics.\textsuperscript{49}

**HCN channels**

HCN (hyperpolarization-activated cyclic-nucleotide-modulated) channels form a family of nonselective cation channels, which are present mainly in neurons and heart cells, and are responsible for I\textsubscript{f}, the “funny” current in heart tissue, mainly in pacemaker cells (K\textsuperscript{+}-Na\textsuperscript{+} inward current). I\textsubscript{f} is activated upon hyperpolarization and is the main source of depolarizing current and responsible for the duration of diastolic depolarization interval, thereby it controls the heart rate in normal conditions. Because of the functional properties of HCN channels and their presence in sinoatrial node (SAN) cells, the HCN channels are considered pacemaker channels. Four different isoforms have been described and except for HCN3, these isoforms are significantly expressed in the human heart. The dominant HCN isoform in the adult SAN is HCN4.\textsuperscript{50,51} It is thought that the slowly activating HCN4 contributes to the pacemaker activity and the modulation of the heart rate by β-adrenergic stimulation, but the faster activated HCN1 and HCN2 may play a role in maintaining the resting potential of pacemaker cells and other cells.

The HCN channels share a highly conserved core region containing 6 transmembrane segments, with the S4 segment being the voltage sensor (figure 2). The intracellular N and C termini are less conserved between the different HCN channels except for a 120 amino acid long cyclic nucleotide binding domain starting about 80 amino acids downstream of S6. The S1, S1-S2 linker, S2, and S6 C-terminal region are essential for the activation of HCN channels.\textsuperscript{52-54}

**CHANNELOPATHIES AND CLINICAL RELEVANCE**

Normal cardiac functioning is determined by the appropriate timing and functioning of millions of cardiac cells. Loss-of-function or gain-of-function of the above mentioned cardiac ion channels may result in critical changes of the action potential in parts or throughout
the heart, which may subsequently result in abnormal cardiac behaviour. Complete loss-of-function channelopathies are considered to be not compatible with life, so most clinically observed channelopathies will show moderate impairment or attenuation of ion channel function. Importantly, as malignant arrhythmias may only occur once or intermittently during life, day to day functioning of the heart is most often normal, or at least sufficient. This implies that only during certain conditions (such as psychological stress, exercise, auditory stimuli, hyperthermia, use of certain drugs, premature ventricular contractions, bradycardia etc.) and a simultaneously increased vulnerability of the heart, the channelopathy emerges and gives rise to the aforementioned arrhythmias, which may ultimately lead to syncope or, not rarely, SCD.

Most channelopathies follow a Mendelian pattern of inheritance and are classified as either autosomal dominant (most observed) or autosomal recessive (rare). The phenotypic expression of channelopathies is often heterogeneous; where it may give a disastrous outcome in one patient, another may experience no or only minor complaints. Probably, delicate gene-gene interactions and co-existing abnormalities play an important role in determining the ultimate phenotype of the disease. Furthermore, abnormal ion channel functioning may not only alter the cardiac action potential in different ways, but in rare cases may also give rise to other cardiac or extra-cardiac abnormalities.

Cardiac ion channelopathies are often classified according to their phenotypic expression; these include Long QT syndrome, Short QT syndrome, Brugada syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia, Idiopathic Ventricular Fibrillation, Sick Sinus Syndrome and Familial Atrial Fibrillation, all of which will be discussed in the following section.

**Long QT syndrome**

The Long QT syndrome (LQTS) is a cardiac arrhythmia characterized by a prolonged (heart rate corrected) QT interval on the ECG (QTc). LQTS is associated with syncope and sudden death caused by polymorphic ventricular tachycardia also known as torsades de pointes. LQTS is estimated to affect 1 per 2000 to 1 per 5000 individuals. The LQTS phenotype is caused by mutations in different genes which have been classified into different LQTS types (table 1).

The most common form of LQTS inherits in an autosomal dominant fashion, also referred to as Romano-Ward syndrome. Autosomal recessive inheritance is rare and described as Jervell-Lange-Nielsen syndrome in combination with deafness and homozygosity or compound heterozygosity for mutations in KCNQ1 (JLN1) or KCNE1 (JLN2). This latter form particularly is very malignant and has a high incidence of syncope and death during follow-up.

Of importance, the use of many drugs and/or substances is associated with...
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<td>1q42.1-q43</td>
<td>SR Ca$^{2+}$ release</td>
<td>↑</td>
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<td></td>
<td>1p13.3-p11</td>
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<td>Sick sinus syndrome (SSS)</td>
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SR, sarcoplasmic reticulum; NA, not applicable.
prolongation of the QT interval, leading to ‘acquired’ LQTS, which may subsequently result in malignant arrhythmias. Probably, some of these patients exhibit a subclinical form of congenital LQTS, either with mutations or polymorphisms in the LQTS genes. Also hypokalemia and factors influencing pharmacokinetics and pharmacodynamics of the aforementioned drugs, may predispose these patients to prolongation of the QT interval and arrhythmias. Clearly, these provoking factors need to be avoided in all patients with LQTS. The different types of the LQTS mostly have distinct triggers for cardiac arrest. In LQTS type 1, for example, arrhythmias typically manifest during exercise (e.g. swimming), in LQTS type 2 this is true for unexpected auditory stimuli (e.g. arousal by an alarm clock or telephone) and emotional stress and LQTS type 3 is typically bradycardia dependent (e.g. when sleeping). Together, LQTS type 1 to 3 account for up to approximately 95% for LQTS.

Long QT syndrome ion channel mutations
The most common cause of LQTS involve mutations in the genes that encode α-subunits of K⁺ channels that conduct the slow (Iₖₛ, KCNQ1; LQT1) and rapid (Iₖᵢ, KCNH2; LQT2) delayed rectifier K⁺ currents. LQT-causing KCN mutations lead to dominant negative loss of Iₖ function or trafficking defective loss of Iₖ function that results in attenuated outward currents, prolongation of the action potential duration and subsequent prolongation of the QTc interval. Also mutations in KCNE1 and KCNE2, encoding K⁺ channel interacting subunits, have been associated with LQTS (LQT5 and LQT6 respectively).

The 3rd type of LQTS is associated with mutations in SCN5A (LQT3). Gain-of-function mutations in SCN5A result in an increase in the late component of the Na⁺ current by slowing of inactivation or an increase in the reversibility of inactivation, resulting in a small but constant entry of Na⁺ in the plateau phase of the action potential. Because in SCN5A-related LQTS QT-prolongation is most pronounced at lower heart rates, bradycardia presents an important risk factor for developing lethal arrhythmias in LQTS families with mutations in SCN5A. Recently, the first mutation in the SCN4B gene encoding Navβ.4 was presented, which alters sodium channel function. Thus far, over 70 LQTS-causing missense mutations and small (in frame) insertions and deletions have been identified in SCN5A.

Long QT syndrome adaptor protein mutations
Mutations in the gene encoding ankyrin-B (Ank2), a non-ion channel protein, present QT interval prolongation with unusual electrocardiographic features (LQT4). Ankyrin-B has three major isoforms, generated by alternative splicing. The major form of ankyrin-B in cardiac cells is 220 kDa. Ankyrins typically contain three functional domains that consist of the membrane binding domain, the spectrin binding domain, and the regulatory domain. Ankyrins are thought to participate in localization of sodium or calcium channels to the sarcolemma and bind to several ion channel proteins, such as the anion exchanger (Cl⁻/
HCO3-exchanger), Na⁺,K⁺–ATPase, voltage-gated sodium channels and Na⁺/Ca²⁺ exchanger (NCX). How loss of ankyrin-B function can lead to ventricular arrhythmias remains unclear, but it is thought that disturbed Ca²⁺ dynamics may play a role.76

Caveolin-3 is a component of the dystrophin glycoprotein complex, which plays a role in mediating interactions between the cytoskeleton, membrane and extracellular matrix in cardiac and skeletal muscle. CAV3 can form caveolae, small membrane invaginations that participate in signal transduction, protein transcytosis and fluid homeostasis. Interestingly, caveolae have been described to colocalize with SCN5A and thereby may be involved in the formation of a Na⁺ channel macromolecular complex.77 Electrophysiological studies of mutations in LQTS associated CAV3 mutations (LQT9) demonstrated a gain-of-function effect on late sodium current which is quantitatively similar to that reported in LQT3,69,78 suggesting that this may cause the prolonged QT interval and associated arrhythmias. However, the molecular mechanisms between these CAV3 mutations and the changed sodium channel function are not fully defined.

Long QT syndrome and multisystem disorders
Mutations in KCNJ2, encoding the inward rectifier potassium channel Kir2.1 or I\textsubscript{K1}, are associated with QT interval prolongation in the context of the multisystem disorder Andersen Syndrome (LQT7).79 Andersen syndrome (also referred to as Andersen-Tawil syndrome) is a rare skeletal muscle disorder often associated with slight prolongation of the QT interval, with the classical triad of periodic paralysis, cardiac arrhythmias, and congenital dysmorphisms.80,81 Interestingly, the U-wave is pronounced in this syndrome,82 and contrary to other long QT syndromes sudden death occurs infrequently. Andersen-Tawil syndrome associated mutations in KCNJ2 causes dominant-negative suppression of Kir2.1 channel function.79,83 Inheritance of Andersen-Tawil syndrome is autosomal dominant, although penetrance of the disease and disease expression and severity are highly variable. For instance, patients with the heterozygous missense mutation p.Arg67Trp have been found to display nonspecific ECG abnormalities but no QT prolongation, despite a history of syncope and frequent ventricular premature beats.84

Gain-of function mutations in the voltage-gated calcium channel CACNA1c present QT interval prolongation in the context of the multisystem disorder Timothy Syndrome (LQT8).85 This disorder is characterized by multiorgan dysfunction, including lethal arrhythmias, congenital heart defects, immune deficiency, intermittent hypoglycemia, syndactyly, cognitive abnormalities, and autism. De novo mutations were identified in exon 8 and in the alternatively spliced exon 8a of the gene, encoding transmembrane segment S6 of domain I, resulting in a reduction of channel inactivation and thereby leading to maintained depolarizing Ca²⁺ currents during the plateau phase of the action potential.
Short QT syndrome

The short QT syndrome (SQTS) is an inherited syndrome characterized by a QTc ≤ 320 ms and high incidence of ventricular tachycardia/fibrillation in infants, children and young adults.\(^{86,87}\) The first genetic defect responsible for the SQTS (SQT1), involved two different missense mutations resulting in the same amino acid substitution in KCNH2 (p.Asn588Lys), which caused a gain of function in \(I_{Kr}\).\(^{88}\) Hereafter, a missense mutation in KCNQ1 was reported that caused a gain of function in \(I_{Ks}\) (SQT2).\(^{89}\) The third gene to be associated with this syndrome is KCNJ2.\(^{90}\) SQT3 is associated with QTc intervals, around 330-350 ms, not quite as short as SQT1 and SQT2. This mutation in KCNJ2 causes a gain of function in \(I_{K1}\).

Mutations in CACNA2c and CACNB2b, encoding the \(\alpha 1\)- and \(\beta 2b\)-subunits of the L-type calcium channel, have recently been documented in patients with Brugada syndrome and shorter than normal QT intervals (ranging from 330 to 370 ms).\(^{91}\) The clinical significance of moderate shortening of the QT interval is currently under debate.\(^{92}\)

Brugada syndrome

Brugada syndrome is characterized by specific ‘coved type’ or ‘type-1’ ST segments in the right precordial ECG leads (V1 to V3 and leads placed in a higher intercostal space) and is associated with SCD at young age particularly in situations with an augmented vagal tone (e.g. during sleep).\(^{93-95}\) Brugada syndrome has an estimated prevalence of 1 case per 2000 individuals,\(^{93}\) although this is probably too high for the specific ‘type-1’ ECG. It is thought to be more prevalent in Asia than in Europe and the US, but exact figures are uncertain because large prevalence studies are scarce and the typical ECG may often be concealed. It is believed to cause 4 to 12% of all sudden cardiac deaths and ~20% of deaths in patients without gross structural abnormalities.\(^{96}\) However, most patients with Brugada syndrome are -and remain- asymptomatic.\(^{97}\) Furthermore, the pathophysiologic mechanisms determining the vulnerability of the heart for ventricular arrhythmias and the coved type morphology on the ECG are still under debate.

Brugada syndrome displays an autosomal dominant inheritance, but the genetic origin of Brugada syndrome is still largely unraveled with a yield of genetic testing of only 15-30%. Mutations leading to loss of Nav1.5 channel function can result in Brugada syndrome (table 1).\(^{98}\) To date, over 90 mutations in SCN5A (of which ~14 % are nonsense or frameshift mutations, leading to truncation of the protein) have been described in BrS patients.\(^{72}\) These loss-of-function mutations are associated with dysfunctional channels or with a reduction of membrane expression of the channel due to a trafficking defect. Loss of Na\(^+\) channel function reduces the upstroke of the action potential and may slow down action potential propagation. Thus, not surprisingly, patients with Brugada syndrome often present with (progressive) conduction defects.\(^{99,100}\) Furthermore, a haplotype in the promoter region of SCN5A that frequently occurs in Asians was found to be associated with slower conduction in control
patients and also in Brugada patients,\textsuperscript{99,101} suggesting that decreased expression of SCN5A transcripts may contribute to differences in Brugada syndrome prevalence as a function of ethnicity.

As mentioned earlier, mutations in the cardiac voltage-gated Na\textsuperscript{+} channel α-subunit gene SCN5A result in multiple arrhythmia syndromes, among which LQT3, conduction disorders or as overlap syndromes displaying combinations of these disorders.\textsuperscript{102} The same may be true for calcium channel mutations. Genetic and heterologous expression studies recently revealed loss-of-function missense mutations in CACNA1c and CACNB2b in Brugada syndrome patients with shorter-than-normal QT intervals.\textsuperscript{91}

Another gene associated with BrS is in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L).\textsuperscript{103} Mutations in this gene modulate the sodium channel in the heart, but are rare.\textsuperscript{104}

Recent reports indicate that there could be (ultra)structural abnormalities involved in Brugada syndrome.\textsuperscript{105,106} Overlap with arrhythmogenic right ventricular cardiomyopathy has even been suggested before the original report on Brugada syndrome.\textsuperscript{107}

The ECG and arrhythmias associated with Brugada syndrome may -alike LQTS- be provoked by many drugs.\textsuperscript{95} In daily clinical practice this knowledge is used to provoke the type-1 Brugada-ECG with potent sodium channel blockers (e.g. ajmaline or flecainide) in patients suspected of Brugada syndrome who do not spontaneously display the type-1 ECG. These drugs include antiarrhythmic drugs and psychotropic drugs but also substances like cocaine and alcohol. Obviously, these drugs need to be avoided in Brugada syndrome patients. Intriguingly, also hyperthermia\textsuperscript{108,109} (e.g. fever) may provoke the ECG and arrhythmias in a subset of Brugada syndrome patients.

**Conduction disease**

Cardiac conduction disease is most often caused by fibrosis of the conductive tissue in the heart following myocardial infarction, surgery, neuromuscular disease or in combination with congenital cardiac defects. However, cardiac conduction disease may also be caused by channelopathies. Four loci have been described for cardiac conduction disease with an autosomal dominant form of inheritance. Progressive conduction disease is often referred to as Lev-Lenègre’s (or Lenègre-Lev’s) disease.\textsuperscript{110,111} Typical of Lev-Lenègre’s disease is the progression of the disease with aging. One form of progressive cardiac conduction disease or progressive familial heart block is caused by loss-of-function mutations in SCN5A (table 1).\textsuperscript{112,113} The decrease of depolarizing current induced by the SCN5A mutation will slow the upstroke of the action potential and also decrease the depolarizing current to neighboring cells, thereby slowing conduction. Early fibrosis of the conduction system, distinct from the fibrosis observed in normal aging, also seems to be related to the SCN5A mutations.\textsuperscript{112,114,115} The other forms of conduction disease have been described as diseases with different
electrocardiographic characteristics of conduction disturbance, and have been linked to chromosome 19q13.2–q13.3 and 16q23–24. Another locus on chromosome 1q32.2–q32.3 was recently linked to conduction defects in a family with dilated cardiomyopathy. The causative gene in the two latter forms is, however, not yet identified.

**Catecholaminergic polymorphic ventricular tachycardia**

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, autosomal-dominant or -recessive inherited disorder, mainly affecting children or adolescents with structurally normal hearts. It is characterized by (polymorphic) ventricular tachycardia and a high risk of sudden cardiac death (30-50% by the age of 20-30 years) triggered by adrenergic stimuli. Recent studies have identified mutations in genes encoding the cardiac ryanodine receptor 2 (RyR2) or calsequestrin 2 (CASQ2) in patients with this phenotype (table 1). Mutations in RyR2 cause autosomal dominant CPVT, whereas mutations in CASQ2 are responsible for either an autosomal recessive or dominant form of CPVT. It is suggested that RyR2 mutations in the presence of high adrenergic tone can lead to leaking of intracellular Ca$^{2+}$ ions which then generates inward depolarizing membrane currents, delayed after depolarizations and subsequent ventricular arrhythmias. Recently, adaptive changes to CASQ2 deficiency (increased posttranscriptional expression of calreticulin and RyR2) were found to maintain electrical-mechanical coupling, but increase RyR2 leakiness. The central role of RyR2 dysfunction in CASQ2 deficiency therefore merges the pathophysiological mechanism underlying CPVT due to RyR2 or CASQ2 mutations.

**Idiopathic ventricular fibrillation**

Apart from the ion channelopathies mentioned there remains an elusive portion of patients and their families at increased for a sudden and premature cardiac death who do not display a defined arrhythmogenic signature or substrate. Our inability to identify a plausible cause for the SCD that affects these patients is best mirrored in the terminology ‘idiopathic ventricular fibrillation’ or IVF. Because there is no phenotype apart from VF and SCD, these cases are notoriously difficult to manage. The magnitude of this group is estimated at 5% of all SCD, about 9,000 to 12,500 per year in the US. As IVF occurs in families, in those families there will be a trait associated with IVF. Accordingly, it is comprehensible that isolated cases may have similar genetic alterations. When this trait would be uncovered it could serve as the only means to identify patients at risk. However, such a trait has not been discovered yet. Although authors have associated IVF with loss-of-function mutations in SCN5A, as expected this phenotype consisted of severe conduction disease, which can not be accepted as IVF but should be classified as conduction disease.
Sick sinus syndrome (SSS) is an abnormality involving the generation of the action potential by the sinus node and is characterized by an inappropriate atrial rate (too slow) for physiological requirements. The most common clinical manifestations are syncope, presyncope, dizziness, and fatigue. Electrophysiological manifestations include severe sinus bradycardia, sinus pauses or arrest, sinus node exit block and periods of atrial bradyarrhythmias. Many patients with SSS also have atrial tachyarrhythmias (e.g. atrial fibrillation; also referred to as brady-tachy syndrome). Mutations in SCN5A cause a recessive form of SSS (SSS1, Table), which is paradoxical because Nav1.5 is absent in the center of the node. For this reason, it is speculated that the dysfunction is the result of impaired function of Nav1.5 at the periphery of the node. This feature occasionally is part of a SCN5A-related overlap syndrome. Mutations in the cardiac pacemaker channel gene HCN4 cause autosomal dominant SSS (SSS2). The described mutations in this gene are responsible for loss of HCN4 function: the first report showed that the mutated channel is insensitive to cAMP and exhibits altered deactivation kinetics. Most recently, a point mutation in the cyclic nucleotide binding domain in a large family with mild sinus bradycardia was described, which caused a shift of the channel activation to more hyperpolarized potentials, while cAMP modulation remained unaffected [131]. It was suggested that this changed activation behavior decreases the inward diastolic current in SAN cells and consequently slows the heart rate like a mild vagal stimulation.

Familial atrial fibrillation

Atrial fibrillation is the most common cardiac arrhythmia worldwide and is often associated with a poor prognosis (mainly thrombotic events). The majority of patients have atrial fibrillation in association with underlying (cardiac) diseases. However, in 15–30% of the patients an underlying etiology is not found. This condition is referred to as lone atrial fibrillation. Some of these patients have a positive family history for atrial fibrillation (Familial Atrial Fibrillation; FAF) and may have a genetic cause or predisposition. Possible genes responsible for triggering and maintaining atrial fibrillation may include genes that affect automaticity, atrial refractory period duration and conduction. In 2003 Chen et al. published data on a mutation (p.Ser140Gly) in KCNQ1, found in a large Chinese family with autosomal dominantly inherited permanent lone atrial fibrillation. Functional analysis of this mutation revealed a gain-of-function effect on the KCNQ1/KCNE1 and the KCNQ1/KCNE2 currents, thereby reducing the action potential duration and the effective refractory period in atrial myocytes, which consecutively could be the cause for initiation and maintenance of atrial fibrillation. The same group also identified a mutation (p.Arg27Cys) in the KCNE2 gene in 2 Chinese families with lone atrial fibrillation. The age at diagnosis was older than observed in the families with the KCNQ1 mutation and most patients in these families had symptomatic paroxysmal atrial fibrillation and also frequent premature atrial
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complexes. Functional analyses also revealed a gain-of-function effect resulting in both inward and outward KCNQ1/KCNE2 potassium currents resulting in a shortening of the action potential duration, which again may trigger and bring about atrial fibrillation.

SYNOPSIS

Research into inherited arrhythmia syndromes has provided significant insight into the role of various ion channels and mechanisms of arrhythmias. Although many of the disorders discussed in this chapter are quite rare, their understanding is essential to unravel the pathogenesis of arrhythmias in the general population. Also the availability of genetic diagnostic tests has added an important diagnostic tool, providing new opportunities for patient management such as early (presymptomatic) identification and treatment of individuals at risk for developing fatal arrhythmias. The identification of genetic modifiers (such as polymorphisms) is the challenging next step in our understanding of the pathogenesis of arrhythmias. In the next years, our increasing knowledge may lead to better targeted treatment of patients suffering from these disorders.

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