Genetic basis of cardiac ion channel diseases

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Chapter 1

Genetic basis of cardiac arrhythmias

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1.1 Introduction

Normal excitation of the human heart depends amongst others 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 and originates from cardiac arrhythmias which fatally decline cardiac output.[2] About 80% of SCD results from ischemia due to coronary artery disease, but in the remaining 20%, other causes -like channelopathies- play a causal role. Channelopathies (disorders of cardiac ion channels) may lead to cardiac arrhythmias in the absence of structural abnormalities (also known as primary electrical diseases), which hitherto may predispose to SCD. These cardiac arrhythmias are of a hereditary nature and form an extending group of cardiac diseases; they are caused by specific mutations in genes mostly encoding ion channel proteins. The consequences of such mutations are alterations in the biophysical properties of ion channel proteins, which may affect normal cardiac electrophysiology and render the heart susceptible to the development of life-threatening arrhythmias.
In the last decade there have been major advances in the recognition of pathophysiological mechanisms leading to SCD. Primary electrical diseases are often classified according to their phenotypic expression; these include long QT syndrome, Brugada syndrome and sick sinus syndrome.

This thesis focuses on the understanding of the genetic basis of cardiac arrhythmias, which is essential for unraveling the pathogenesis of these arrhythmias. Such knowledge in turn provides new opportunities for patient management such as early (presymptomatic) identification and timely treatment of individuals at risk for developing fatal arrhythmias.

The following chapter and chapter 2 provide overviews of the biophysics of ion channels (with emphasis on the cardiac sodium channel) involved in cardiac arrhythmias and of the clinical and genetic background of these arrhythmias. Chapters 3-7 discuss variants in the cardiac voltage-gated sodium channel α-subunit encoding gene *SCN5A* and in the β1 subunit encoding gene *SCN1B*(*b*), associated with several cardiac arrhythmias. In chapter 8 the first large gene rearrangement in the potassium channel encoding gene *KCNH2* is presented, which is responsible for the long QT syndrome (type 2). This is followed by a discussion and future perspectives of genetics of cardiac ion channel diseases.

1.2 Genetic basis of cardiac arrhythmias

1.2.1 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 activation of 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, may follow 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 TP segment represents phase 4 (i.e. the diastolic phase).

So, depending on which cardiac ion channels are open or closed, the cardiomyocytes 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. endocardial vs. epicardial localized myocardium), 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.

1.2.2 Cardiac ion channels

Individual cardiac myocytes express large numbers of ion-channel encoding genes. Ion channels are membrane proteins which underlie rapid electrical signals among neurons and the spread of excitation in skeletal muscle and heart. Ion channels constitute a class of macromolecular protein tunnels that span the lipid bilayer of the cell membrane, which allow ions to flow in or out of the cell in a very efficient fashion. This flow of ions creates electrical currents large enough to produce rapid changes in the transmembrane voltage, which is the electrical potential difference between the cell interior and exterior. 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. Variability in the expression or function of individual ion-channel genes is an increasingly recognized source of variability in the ion currents recorded in cardiac myocytes under physiological conditions as well as in disease.

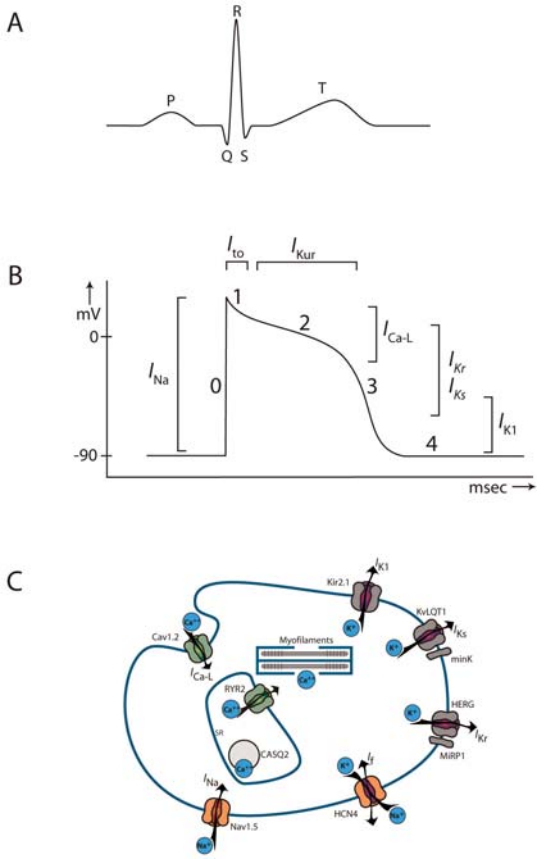

Figure 1: Schematic representation of the ionic currents contributing to the action potential; A. the electrocardiogram (ECG) and the P-QRS-T segments in time aligned with; B. the ventricular action potential with phase 0 to 4 and the ionic currents originating from; C. the cardiomyocyte displaying (only) those transmembrane ion channels, β-subunits and ionic currents involved in the pathogenesis of the described inherited arrhythmia syndromes. Abbreviations as in the text.

Sodium channels

Voltage-gated Na^+ channels are responsible for the upstroke of the action potential (Figure 1) 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]

α-Subunits

The pore-forming α-subunit of the cardiac specific voltage-gated Na^+ 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), which 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.

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,[17,18] and are involved in cell adhesion through interaction with the cytoskeleton, extracellular matrix, and other cell adhesion molecules that regulate cell migration and aggregation.[19]

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_{to1}), the ultrarapid (I_{Kur}), rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier current, and the inward rectifier current (I_{K1}).

The delayed rectifier K^+ current (I_K) has a major role in modulating action potential duration and in the heart comprises at least three distinct components: I_{Kur}, I_{Kr} and I_{Ks}. These currents are easily distinguished on the basis of their pharmacological and biophysical properties.

I_{Kur} has been recorded in human atria but not in human ventricular tissue. This means that I_{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.[20,21]

I_{Kr} activates rapidly compared to I_{Ks}, but also partially inactivates. In cardiac myocytes, I_{Ks} activates very slowly in response to membrane depolarization and activates slower than any other known K^+ current. Due to its slow rate of activation, the contribution of I_{Ks} to the net repolarizing current is greatest in phase 3 of the cardiac action potential.

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_{K1}) stabilizes the resting membrane potential and is responsible for determining the threshold for the initial depolarization and final repolarization of the action potential.[22] I_{K1} is a strong rectifier that passes K^+ currents over a limited range of membrane potentials. Upon depolarization, I_{K1} channels close almost immediately, remain closed during the plateau phase and open again at negative potentials.

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 segment containing six positive charges.[23]

The pore domain, S5 segment, the P-loop, and S6 segment all together make up the ion permeation pathway, including the selectivity filter.[24] 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.[25]

The human ether-a-go-go-related gene *KCNH2* encodes the α-subunit of the I_{Kr} channel (HERG). When *Drosophila* flies with mutations in the ether-a-go-go gene are anaesthetised with ether, their legs start to shake, like dancing.

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.[24] The S6 of HERG has a conserved glycine, which might be involved in channel opening by splaying of the inner helices.[26] 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; Per stands for *Drosophila* period clock protein, Arnt stands for aryl hydrocarbon receptor nuclear translocator and Sim is *Drosophila* single-minded protein) domain on their cytoplasmic N-terminus that may interact with other regions of HERG such as the S4–S5 linker to affect channel deactivation,[27,28] 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 K^+ 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.[29]

$K_V4.3$ is the pore-forming subunit for $I_{to,f}$ in human hearts. Voltage-gated K^+ channels only form homomultimers (multimerize) with members of their own subfamily. This means that $K_V4.x$ genes can only multimerize and form functional channels with other $K_V4.x$ genes. The structural feature responsible for this, is the highly conserved C-terminus of the channel known as the tetramerization domain (T1 domain),[30] 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) encoding I_{K1} have been found in human heart. Similar to voltage gated K^+ channels, the Kir2.x channels are tetramers.[31] 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).[32] 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.

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.[33]

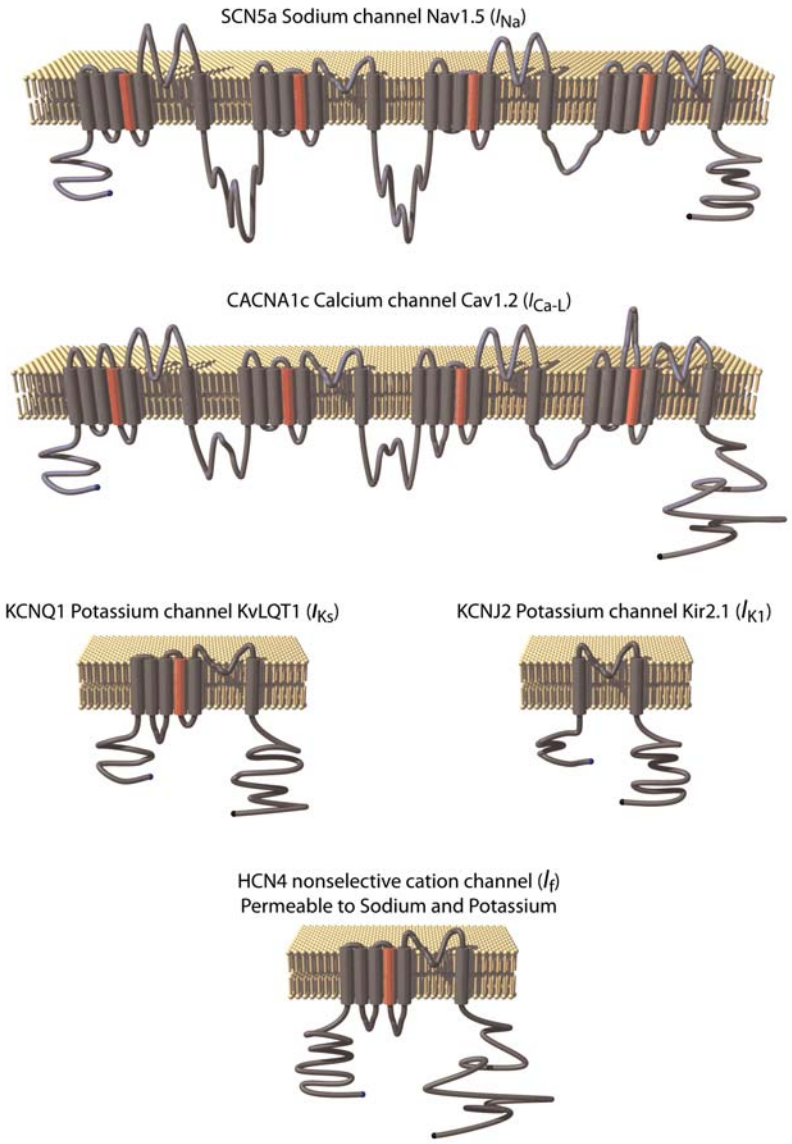

Figure 2: Schematic representation of the cardiac ion channel proteins $Na_V1.5$, $Ca_V1.2$, K_VLQT1, Kir2.1 and the *HCN4* encoded nonspecific cation channel. See text for further explanation. (Courtesy of A.C. Linnenbank)

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.[34,35] The role of MinK-related protein (MiRP1), encoded by *KCNE2*, as a physiologically relevant modulator of HERG channels remains controversial. The structural basis of altered *KCNQ1* gating by MiRP subunits has not been determined yet.

Besides several cytoskeletal proteins, $K_V4.3$ interacts with: (1) K^+ channel interacting proteins (KChIPs),[36] 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 $K_V4.x$ current when coexpressed with $K_V4.x$ α-subunits.[37,38] 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),[39] which can increase current expression, without an effect on current kinetics; (4) dipeptidyl-aminopeptidase-like protein 6 (DPPX or DPP6), which causes an increase in surface expression, an increase of recovery from inactivation, and a shift in inactivation voltage dependence when coexpressed with $K_V4.3$.[40,41]

Calcium channels

Muscle contraction is regulated by elevation of the intracellular Ca^{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^{2+} entry with each beat which triggers Ca^{2+} release from the sarcoplasmic reticulum (SR) via Ca^{2+}-release channels, such as the ryanodine receptor, resulting in a cascade of Ca^{2+} ions released into the cytosol, i.e. calcium-induced calcium release.

The cardiac L-type Ca^{2+} channel is assembled from three tissue-specific isoforms; α_1 ($\alpha_1$1.2), $\alpha_2\delta_1$, and β isoforms, which are considered the functional minimum core for Ca^{2+} channel assembly (for review see: Bodi et al.[42]). Four hydrophilic and nonglycosylated β-subunit isoforms (β_1– β_4) have been described, but only β_2 and β_3 form cardiac L-type voltage-gated Ca^{2+} channels.

The accessory subunits (β, α_2/δ) are tightly but not covalently bound to the α_1 subunit and modulate the biophysical properties and trafficking of the α1 subunit to the membrane.

α-Subunits

Like voltage-gated Na^+ channels, Ca^{2+} channel α_1-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 α_1 subunit genes have been identified and separated into 4 classes: $Ca_V1.1$ (α_{1S}), 1.2 (α_{1C}), 1.3 (α_{1D}), and 1.4 (α_{1F}). Only the α_{1C} (dihydropyridine-sensitive) -subunit is highly expressed in cardiac muscle.

The α_1-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.[43] 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^+ channels and K^+ channels, this segment is considered the voltage-sensor.

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 α_1-subunit isoforms, called the α-interaction domain (AID), and also to a secondary site.[44-46] The β-interaction domain (BID) connects with the AID through a α-binding pocket (ABP), a conserved hydrophobic crevice.[47] Coexpression of β-subunits modulates the biophysical properties of the α_1-subunit. A 153-aa sequence in the human cardiac short β_{2f} and β_{2g}-subunits was recently described as being essential for modulating Ca^{2+} channel function and interaction with the α_{1C} subunit.[48]

α_2/δ-Subunits

The α_2/δ-subunits are closely associated with the α_1-subunit by surface interaction and are intracellularly linked to the δ-subunit through a disulfide bridge. The α_2-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.[49] The *in vivo* function (and structure) of the α_2/δ-subunits is still unknown, however, coexpression of these subunits in heterologous expression systems affects α_1 function by increasing channel density with variable minor effects on channel kinetics.[50]

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_f, the "funny" current in heart tissue, mainly in pacemaker cells (K^+-Na^+ inward current). I_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 sinusnode 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 sinusnode is *HCN4*.[51,52] 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.[53-55]

1.2.3 Channelopathies and their 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 cardiac ion channels may result in critical changes of the action potential in parts of 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, Sick sinus syndrome and Familial atrial fibrillation,[56] 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*.[57] LQTS is estimated to affect 1 per 5000 individuals.[58] 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.[59,60] Autosomal recessive inheritance is rare and described as Jervell-Lange-Nielsen syndrome[61] in combination with deafness and homozygosity or compound heterozygosity for mutations in the α-subunit encoding K^+ channel *KCNQ1* (JLN1) or its interacting subunit encoding gene *KCNE1* (JLN2). This latter form particularly is very malignant and has a high incidence of syncope and death during follow-up.[62]Of importance, the use of many drugs and/or substances is associated with prolongation of the QT interval, leading to 'acquired' LQTS, which may subsequently result in malignant arrhythmias.[63] 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.

Ion channel mutations

The most common cause of LQTS involves mutations in the genes that encode α-subunits of K^+ channels that conduct the slow (I_{Ks}, *KCNQ1;* LQT1) and rapid (I_{Kr}, *KCNH2;* LQT2) delayed rectifier K^+ currents.

More than 200 mutations, mostly missense, have been found in *KCNQ1*. Functional analysis showed that the net effect of LQT1 mutations is a decreased outward K^+ current during the plateau phase of the cardiac action potential. The channel remains open longer, ventricular repolarization is delayed, and the QT interval is prolonged. A multicenter study of 670 LQTS patients of known genotype showed that LQT1 patients (n=371) experience a majority of their cardiac events (62%) during exercise, and only 3% occur during rest or sleep.[64] Of the patients who experienced cardiac events while swimming, 99% had LQT1.

Also over 200 mutations have been reported in *KCNH2*. The majority of the pore region defects are missense mutations, while non-pore defects demonstrate a variety of missense, nonsense, and frameshift mutations. Mutations can result in either structural ion channel defects having dominant-negative effects or intracellular "trafficking" abnormalities causing a reduction in the number of functional ion channels, both leading to loss-of-function. Electrophysiological studies showed that *KCNH2* mutations cause K^+ ion channels to deactivate (close) much faster, blunting the normal rise in I_{Kr} current that results from rapid recovery from channel inactivation/slow deactivation. The I_{Kr} current during the plateau phase is reduced and ventricular repolarization delayed, leading to a prolonged QT interval. Interestingly, unexpected auditory stimuli (e.g. arousal by an alarm clock or telephone) and emotional stress may serve as triggers for arrhythmic events in LQT2 patients, which may be caused by a systemic catecholamine effect or a catecholamine-related shift in the extracellular environment.[65]

A rather relatively uncommon type of LQTS is associated with mutations in *SCN5A* (LQT3). Thus far, over 70 LQTS-causing missense mutations and small (in frame) insertions and deletions have been identified in *SCN5A.*[66] These gain-of-function mutations 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.[67] 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.*[68] The frequency of cardiac events is higher among LQT1 patients (63%) or LQT2 patients (46%) than among LQT3 patients (18%). However, the likelihood of dying during a cardiac event was highest among patients with LQT3.[69]

Mutations (missense or in-frame deletions/insertions) in *KCNE1* and *KCNE2*, encoding K^+ channel interacting subunits, have also been associated with LQTS (LQT5 and LQT6 resp.).[70-72] Furthermore, the first mutation in the *SCN4B* gene encoding $Na_V\beta.4$ was recently presented (LQT10), which altered sodium channel function.[73]

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).[74,75] Ankyrins are thought to participate in localization of Na^+ or Ca^{2+} channels to the sarcolemma and bind to several ion

channel proteins, such as the anion exchanger (Cl^-/HCO_3^- exchanger), Na^+,K^+–ATPase, voltage-gated Na^+ channels and Na^+/Ca^{2+} exchanger (NCX). How loss of ankyrin-B function can lead to ventricular arrhythmias remains unclear, but it is thought that disturbed Ca^{2+} dynamics may play a role: the reported mutations interfere with anchoring of Na^+,K^+–ATPase and NCX, resulting in Na^+ build-up and a compensatory increase in intracellular Ca^{2+} stores.[74]

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.[76] Electrophysiological studies of mutations in LQTS associated *CAV3* (missense) mutations (LQT9) demonstrated a gain-of-function effect on late Na^+ current which is quantitatively similar to that reported in LQT3,[67,77] 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.

Recently, a mutation in the A-kinase anchoring protein 9 (AKAP9; LQT11) has been described that reduces the cAMP-dependent phosphorylation of *KCNQ1*, thereby eliminating the functional response of the I_{Ks} channel to cAMP, resulting in prolongation of the action potential in a computational model of the ventricular cardiomyocyte.[78] Furthermore, mutations in the syntrophin-α encoding gene *SNTA1* were recently reported to be responsible for secondary gain-of-function of the cardiac Na^+ channel (LQT12).[79,80]

Multisystem disorders

Mutations in *KCNJ2*, encoding the inward rectifier K^+ channel Kir2.1 or I_{K1} are associated with QT interval prolongation in the context of the multisystem disorder Andersen syndrome (LQT7).[81] Andersen syndrome (also referred to as Andersen-Tawil syndrome) is a rare skeletal muscle disorder often associated with prolongation of the QT interval, with the classical triad of periodic paralysis, cardiac arrhythmias, and congenital dysmorphisms.[82,83] Contrary to other long QT syndromes, sudden death occurs infrequently in patients with this syndrome. Andersen syndrome associated mutations in *KCNJ2* cause dominant-negative suppression of Kir2.1 channel function, or intracellular "trafficking" defects.[81,83,84] Inheritance of Andersen 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.[85]

Gain-of-function mutations in the voltage-gated Ca^{2+} channel *CACNA1c* have been described that present QT interval prolongation in the context of the multisystem disorder Timothy syndrome (LQT8).[86] This disorder is characterized by multiorgan dysfunction, including lethal arrhythmias, congenital heart defects, immune deficiency, intermittent hypoglycemia, syndactyly, cognitive abnormalities, and autism. Two *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 Ca^{2+} currents during the plateau phase of the action potential.

Treatment

Preliminary clinical studies indicate the possibility for genotype-specific therapy based on abbreviations of the QT interval by agents or other interventions in congenital LQTS. When the genotype cannot be identified, β-blockers are the first choice of therapy in LQTS patients. The international registry of LQTS reported that β-blockers reduce the incidence of syncope and sudden cardiac death in patients with congenital LQTS, especially in LQT1 patients (80 %).[64] However, β-blockers are less effective in LQT2 and LQT3 patients. LQT2 patients could benefit from longterm oral K^+ administration, which was reported to improve repolarization abnormalities in these patients.[87] It was also suggested that K^+ channel openers may be effective when LQTS is secondary to reduced I_{Ks} or I_{Kr}, but not when it is due to augmented late I_{Na} (LQT3). The latter may be given a class Na^+ channel blocker, as first line therapy in LQT3 patients, but should be used at the moment in the presence of β-blockers or in combination with an implantable cardioverter-defibrillator (ICD). Patients with the *SCN5A* mutation p.Asp1790Gly showed an abbreviated QT interval after administration of the class IC Na^+ channel blocker flecainide.[88] However, class IC Na^+ channel blockers might elicit a Brugada syndrome phenotype in LQT3 patients.[89] Pacemaker therapy might also be useful in LQT3 patients: studies have shown that atrial pacing without sympathetic stimulation shortens the QT interval more significantly in patients with LQTS than in control patients, which was specifically clear in LQT3 patients during exercise.[90]

Short QT syndrome

The short QT syndrome (SQTS) is an inherited syndrome characterized by a QTc $\leq$ 320 ms and high incidence of ventricular tachycardia/fibrillation in infants, children and young adults.[91,92] 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}.[93] Hereafter, two missense mutations in *KCNQ1* were reported that caused a gain-of-function in I_{Ks} (SQT2).[94,95] One of these mutations (p.Val141Met) was a *de novo* mutation responsible for SQTS and atrial fibrillation in utero, confirming the hypothesis that gain-of-function mutations in *KCNQ1* channels can shorten the duration of ventricular and atrial action potentials. The third gene to be associated with this syndrome is *KCNJ2*.[96] SQT3 is associated with QTc intervals, < 330 ms, not quite as short as SQT1 and SQT2. Mutations in *KCNJ2* caused a gain-of-function in I_{K1}, leading to an abbreviation of QT interval. Also a shortening of the terminal part of the ST segment can be observed.

Mutations in *CACNA1c* and *CACNB2b*, encoding the α_1- and β_{2b}-subunits of the L-type calcium channel, have recently been documented in patients with Brugada syndrome and somewhat shorter than normal QT intervals (ranging from 330 to 370 ms).[97] The clinical significance of moderate shortening of the QT interval is currently under debate.[98]

Treatment

Because shortening of the QT interval is likely due to an increase in the outward current, blocking the current with class III antiarrhythmic drugs (which are known to increase the QT interval) may be a therapeutic approach for treating SQTS. However, the high incidence of SCD necessitates the implantation of an ICD, especially in symptomatic patients in whom sudden death has been aborted.

Brugada syndrome

Brugada syndrome (BrS) 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).[99-101] BrS has an estimated prevalence of 1 case per 2000 individuals,[99] 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 structural abnormalities.[102] However, most patients with BrS are -and remain- asymptomatic.[103] 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.

BrS displays an autosomal dominant inheritance, but the genetic origin of this syndrome is still largely uncertain with a yield of genetic testing of only 15-30%. Mutations leading to loss of $Na_V1.5$ channel function can result in BrS (Table 1).[104] 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.[66] 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 BrS often present with (progressive) conduction defects.[105,106] Futhermore, 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,[107] suggesting that decreased expression of *SCN5A* transcripts may contribute to differences in BrS prevalence as a function of ethnicity.

As mentioned earlier, mutations in *SCN5A* result in multiple arrhythmia syndromes, among which LQT3, conduction disorders or as overlap syndromes displaying combinations of these disorders.[108] 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 BrS patients with shorter-than-normal QT intervals.[97]

Other genes associated with BrS are the glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*)[109] and the Na^+ β-subunit encoding gene *SCN1B*. Mutations in *GPD1L* can modulate ion channels (probably the Na^+ channel) in the heart, but are rare.[110] Also a mutation in *SCN1B* was found to have an effect on the I_{Na}, leading to BrS and isolated conduction defects.

Recent reports indicate that there could be (ultra)structural abnormalities involved in BrS.[111,112] Overlap with arrhythmogenic right ventricular cardiomyopathy has even been suggested before the original report on BrS.[113]

The ECG and arrhythmias associated with BrS may -alike LQTS- be provoked by many drugs.[101] 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 BrS who do not spontaneously display the type-1 ECG. These drugs include antiarrhythmic drugs, antianginal drugs, psychotropic drugs and also substances like cocaine and alcohol. Obviously, these drugs need to be avoided in BrS patients. Intriguingly, also hyperthermia[114,115] (e.g. fever) may provoke the ECG and arrhythmias in a subset of BrS patients.

Treatment

An ICD should be implanted in BrS patients with a history of cardiac arrest/aborted sudden cardiac death or syncope, because of a high recurrence rate of cardiac events during follow-up periods after the first cardiac event.[116-119] The indication of ICD is still controversial in patients with asymptomatic BrS (i.e. without a history of cardiac arrest/aborted sudden cardiac death and syncope). To reduce the incidence of VF episodes, pharmacological treatment can be considered in symptomatic BrS patients, in combination with ICD therapy. This treatment consists of the administration of agents that reduce outward currents (e.g. I_{to}, $I_{K\text{-}ATP}$, I_{Ks}, I_{Kr}) or induce inward currents (e.g. $I_{Ca\text{-}L}$) at the end of phase 1 of the action potential and as a result attenuate ST segment elevation.

Conduction defects

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.[120,121] 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).[122,123] 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.[122,124,125]

The other forms of conduction disease have been described as diseases with different electrocardiographic characteristics of conduction disturbance[126] and have been linked to chromosome 19q13.2–q13.3[127] and 16q23–24.[128] Another locus on chromosome 1q32.2-q32.3 was recently linked to conduction defects in a family with dilated cardiomyopathy.[129] The causative genes in the three latter forms are, 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.[130] 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*; channel located in the membrane of the sarcoplasmic reticulum that is responsible for the control of calcium release) or calsequestrin 2 (*CASQ2*; the major calcium storage protein in the sarcoplasmic reticulum) in patients with this phenotype (Table 1).[131-134] Mutations in *RyR2* cause autosomal dominant CPVT, whereas mutations in *CASQ2* are responsible for either an autosomal recessive or dominant form of CPVT. To date, more than 70 *RyR2* missense mutations have been identified in CPVT patients. Most of these mutations are clustered in two regions corresponding to the C-terminus of the protein and to the central region, which

is believed to contain regulatory protein FKBP12.6 binding domains. Only 7 mutations have been reported in *CASQ2*. Of these, two mutations are nonsense, two are truncations (small deletions), and three are missense mutations.

Unfortunately, only a limited number of *RyR2* mutations have been functionally characterized and it is for this reason difficult to define whether functional differences exist among mutations and whether they account for severity of the phenotype.[135] 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.[136] The central role of *RyR2* dysfunction in *CASQ2* deficiency therefore merges the pathophysiological mechanism underlying CPVT due to *RyR2* or *CASQ2* mutations.

Treatment

The preferred therapy for CPVT is β-blockers,[130] which may prevent syncope and sudden death because adrenergic activation is the main trigger for cardiac events in these patients.[137] An ICD is required in 30% of patients because of symptomatic recurrence of life-threatening arrhythmias.[138]

Sick sinus syndrome

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),[139] which is paradoxical because $Na_V1.5$ is absent in the center of the node (Table 1). For this reason, it is speculated that the dysfunction is the result of impaired function of $Na_V1.5$ at the periphery of the node. This feature occasionally is part of a *SCN5A*-related overlap syndrome.[140,141]

Mutations in the cardiac pacemaker channel gene *HCN4* cause autosomal dominant SSS (SSS2).[142-144] The few 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.[143] Milanesi et al[142] described a missense mutation in the cyclic nucleotide binding domain in a large family with mild sinus bradycardia, which caused a shift of the channel activation to more hyperpolarized potentials, while cAMP modulation remained unaffected. It was suggested that this changed activation behavior decreases the inward diastolic current in sinusnode cells and consequently slows the heart rate like a mild vagal stimulation.

Treatment

The placement of a pacemaker is currently the treatment of choice for symptomatic bradyarrhythmias in patients with SSS (for overview see: Adàn et al.[145]). In patients who suffer from tachyarrhythmias, a pacemaker may decrease the risk of complete heart block or asystole associated with pharmacotherapy.[146] Importantly, β-blockers should be avoided, since severe sinus bradycardia, sinoatrial arrest, or sinoatrial exit block can occur after administration.[147]

Familial atrial fibrillation

Atrial fibrillation (AFib) is the most common cardiac arrhythmia worldwide and is often associated with a poor prognosis. The majority of patients have AFib 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 AFib.[148] Some of these patients have a positive family history for AFib (Familial Atrial Fibrillation; FAF) and may have a genetic cause or predisposition. Possible genes responsible for triggering and maintaining AFib 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 AFib (Table 1).[149] 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 AFib. The same group also identified a mutation (p.Arg27Cys) in the *KCNE2* gene in 2 Chinese families with lone AFib.[150] The age at diagnosis was older than observed in the families with the *KCNQ1* mutation and most patients in these families had symptomatic paroxysmal AFib and also frequent premature atrial complexes. Functional analyses also revealed a gain-of-function effect resulting in both inward and outward *KCNQ1*/*KCNE2* K^+ currents resulting in a shortening of the action potential duration, which again may trigger and bring about AFib.

Treatment

Patients with lone AFib could benefit from class IC antiarrhythmic drugs, in combination with a Ca^{2+} channel antagonist or a β-blocker to prevent rapid ventricular response in the case of conversion of AFib to atrial flutter. If the sinus rhythm cannot be maintained with pharmacotherapy, the ablation of arrhythmogenic pulmonary veins or the implantation of an atrial defibrillator are alternative therapies.

1.2.4 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, its 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.

Table 1: Inherited arrhythmia syndromes

	Subtype	Gene	Protein	Chromosomal locus	Affected current	Effect on current	OMIM
Brugada Syndrome	BS1	*SCN5A*	Nav1.5	3p21	I_{Na}	↓	601144
	BS2	*GPD1L*		3p22.3	I_{Na}	↓	
	BS3	*CACNA1c*	Cav1.2	12p13.3	$I_{Ca\text{-}L}$	↓	
	BS4	*CACNB2b*	Cavβ2b	10p12	$I_{Ca\text{-}L}$	↓	
	BS5	*SCN1B*	Navβ.1	19q13.1	I_{Na}	↓	
Conduction disease	CCD1	unknown		19q13			113900
	CCD2	*SCN5A*	Nav1.5	3p21	I_{Na}	↓	113900
	CCD3	unknown		16q23-q24			
	CCD4	unknown		1q32.2-q32.3			
	CCD5	*SCN1B*	Navβ.1	19q13.1	I_{Na}	↓	
Catecholaminergic Polymorphic Ventricular Tachycardia	CPVT1	*RYR2*		1q42.1-q43	SR Ca^{2+} release	↑	604772
	CPVT2	*CASQ2*		1p13.3-p11	SR Ca^{2+} release	↑	604772
Sick Sinus Syndrome	SSS1	*SCN5A*	Nav1.5	3p21	I_{Na}	↓	608567
	SSS2	*HCN4*		15q24-q25	I_f	↓	163800
Long QT syndrome	LQT1	*KCNQ1*	KvLQT1	11p15.5	I_{Ks}	↓	607542
	LQT2	*KCNH2*	HERG	7q35-q36	I_{Kr}	↓	152427
	LQT3	*SCN5A*	Nav1.5	3p21	I_{Na}	↑	600163 603830
	LQT4	*ANK2*	Ankyrin-B	4q25-q27	multiple		106410
	LQT5	*KCNE1*	minK, Isk	21q22.1-q22.2	I_{Ks}	↓	176261
	LQT6	*KCNE2*	MiRP1	21q22.1	I_{Kr}	↓	603796
	LQT7	*KCNJ2*	kir2.1, IRK1	17q23.1-q24.2	I_{K1}	↓	600681
	LQT8	*CACNA1C*	Cav1.2	12p13.3	$I_{Ca\text{-}L}$	↑	114205
	LQT9	*CAV3*	Caveolin-3	3p25	I_{Na}	↑	601253
	LQT10	*SCN4B*	Navβ.4	11q23	I_{Na}	↑	608256
	LQT11	*AKAP9*	AKAP9/ yotiao	7q21-q22	I_{Ks}	↓	
	LQT12	*SNTA1*	α-syntrophin	20q11.2	I_{Na}	↑	
	JLN1	*KCNQ1*	KvLQT1	11p15.5	I_{Ks}	↓	220400
	JLN2	*KCNE1*	minK, Isk	21q22.1-q22.2	I_{Ks}	↓	220400
Short QT syndrome	SQT1	*KCNH2*	HERG	7q35-q36	I_{Kr}	↑	609620
	SQT2	*KCNQ1*	KvLQT1	11p15.5	I_{Ks}	↑	609621
	SQT3	*KCNJ2*	Kir2.1, IRK1	17q23.1-q24.2	I_{K1}	↑	609622

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