Channelopathies are diseases caused by dysfunctional ion channels, due to either genetic or acquired pathological factors. Inherited cardiac arrhythmic syndromes are among the most studied human disorders involving ion channels. Since seminal observations made in 1995, thousands of mutations have been found in many of the different genes that code for cardiac ion channel subunits and proteins that regulate the cardiac ion channels. The main phenotypes observed in patients carrying these mutations are congenital long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS) and variable types of conduction defects (CD). The goal of this review is to present an update of the main genetic and molecular mechanisms, as well as the associated phenotypes of cardiac channelopathies as of 2012.

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1. Introduction

1.1. Human channelopathies

Ion channels are essential membrane proteins found in all cell types. They permit the regulated flux of ions across the plasma membrane as well as the membrane of intracellular organelles (Hille, 2001). Since ions are charged molecules, these ionic fluxes produce electrical currents and play a major role in the determination of transmembrane electric potential differences. The cellular resting membrane potential and action potential (AP) of excitable cells largely depend on the function of these ion channels. Basic cellular and tissular processes, such as transepithelial transport, information transmission, muscle cell contraction and hormone secretion are all dependent on ion channel function. The dysfunction of ion channels, also referred to as channelopathies, has been linked to many human diseases (Ashcroft, 2006). Channelopathies are a result of either genetic mutations or acquired malfunctions of ion channels (see Fig. 1). Genetic channelopathies may be caused by mutations in the genes coding for the pore-forming subunit of the ion channels (alpha subunit) or in the genes coding for the regulatory proteins, such as the beta subunit or the enzymes that regulate alpha subunit function. Acquired channelopathies can result from drug exposure, immunoglobulins, or toxins that modify ion channel function. These compounds can inhibit or activate ion channels. It can also be proposed that alterations of the expression and/or regulation of ion channels in the context of primary disease, such as heart failure, may also be classified as secondary cardiac channelopathies.

Since ion channels are expressed in the cells of all tissues and organs of the human body, channelopathies can be at the origin of disease in virtually all fields of medicine. Channelopathies are well recognized in neuro-muscular and cardiovascular disorders since excitable cells harboring voltage-gated ion channels play primordial roles in these systems. Epilepsy, migraines, pain disorders, periodic paralysis and cardiac arrhythmias are some of the most common channelopathy phenotypes seen in these excitable tissues. One of the most prevalent channelopathies, known to be responsible for cystic fibrosis, is caused by loss-of-function of the CFTR chloride channel which disrupts the transepithelial transport of chloride ions (Guggino and Stanton, 2006). Inherited hypertension and tubular renal disorders are also caused by dysfunctional epithelial ion channels (Hubner and Jentsch, 2008).

This review article provides an update on the principal phenotypes associated with genetic cardiac channelopathies. We describe the genetic and pathophysiological mechanisms underlying these cardiac disorders. Clinical aspects, such as prevention and therapeutic strategies, will only be briefly addressed.

1.2. Cardiac channelopathies and their prevalence

The genetic and molecular determinants of cardiac channelopathies were identified over 15 years ago (Priori, 2010) when it was shown that mutated genes in patients with congenital long QT syndrome (LQTS) encode ion channel subunits. Since these seminal findings (Curran et al., 1995; Wang et al., 1995a, 1996), many other inherited electrical disturbances have been linked to mutations in ion channel genes or genes that regulate their function (Fig. 1). The estimated prevalence of cardiac channelopathies in the general population remains ill-defined. Population-based clinical studies often underestimate the prevalence. The incomplete penetrance of channelopathies results in the misdiagnosis of “penetrant” cases as seizure disorders or epilepsy. In addition, many of the severe cases of channelopathies result in sudden cardiac death (SCD). On the other hand, clinical and molecular studies investigating different groups of patients are biased by inclusion criteria and external triggers, i.e. some arrhythmia-triggered drugs. Pathology-based molecular studies of SCD victims overestimate the prevalence because “survivors” with and without disease are not included.

Only a few case reports can be found in the literature from 20 years ago, and these disorders were thought to be very rare. Ten years ago a prevalence of 1:10,000 would have been judged to be an overestimation; whereas the current worldwide prevalence of all cardiac channelopathies is thought to be at least 1:2000–1:3000 per individual in the general population (Schwartz et al., 2009). Channelopathies are likely responsible for about half of sudden arrhythmic cardiac death cases (Behr et al., 2008). The most prevalent and well-known disorder in this group is congenital LQTS. The average prevalence of LQTS has been reported to be 1:2500–1:5000 per individual (Goldenberg et al., 2008; Schwartz et al., 2009; Tester et al., 2006). Much higher LQTS prevalence numbers, 0.8–1.5% of the population, have been found in some ethnic groups with founder effects (Berge et al., 2008; Brink and Schwartz, 2009; Winbo et al., 2011). The second most frequent cardiac channelopathy is Brugada syndrome (BrS) (Benito et al., 2008), for which a prevalence of about 1:10,000 has

![Fig. 1. Simplified classification of human channelopathies.](image-url)
1.3. Role of cardiac ion channels in shaping the cardiac action potential

Since 1995 it has become apparent that the inherited cardiac arrhythmia syndromes are caused by mutations in genes that encode cardiac ion channels (Curran et al., 1995; Wang et al., 1995b). The electrical activity of a cardiac cell is characterized by the cardiac AP generated by ion channel activity (Fig. 2). A depolarizing current is the result of an “inward” flux of positive charges (Na⁺ and Ca²⁺) into the cell, which moves the negative resting membrane potential towards a more positive voltage value. Repolarization is achieved by a delayed “outward” flux of positive charges (K⁺). The particularity of the cardiac AP, as compared to the neuronal AP, is the “plateau” seen with phase 2. The “plateau” phase 2 is mainly due to the inward flux of Ca²⁺ which prolongs the AP duration by ~200–300 ms. The amount of current flowing through the cardiac cell membrane during phase 2 is very small (Weidmann, 1951). As a result, small variations of either depolarizing or repolarizing currents can significantly alter the AP duration (Kass, 1997).

The different phases of cardiac cell electrical activity generate electrical potential differences that can be recorded on the surface of the body as the electrocardiogram (ECG). The QT interval is predominantly determined by the AP duration of ventricular cells. QT interval prolongation, as seen with LQTS, is primarily caused by factors that delay the repolarization phase 3 of the AP (Fig. 3). Recent studies have focused on the individual contributions of ionic currents, related ion transporters, and channels to the generation and alteration of the AP (Fig. 2) (Roden et al., 2002). As of today, the vast majority of the genes coding for the known cardiac ion channel subunits have been found to be mutated in patients with genetic arrhythmias. These mutations modify the properties of these ion channels and, in most cases, alter the depolarization (Brugada et al., 1998) or the repolarization (Keating and Sanguinetti, 2001) phases of the AP.

1.4. Common features of genetic cardiac channelopathies

Cardiac channelopathies are a clinically and genetically heterogeneous group of diseases. Their electrocardiographic features are very different and highly specific but some of their basic clinical expressions are often similar. For example, spontaneous and exercise-triggered syncopes due to ventricular dysrhythmias can be self-terminating or potentially lethal. These disorders are often misdiagnosed as seizures or epilepsy. It is not unusual for patients to be treated with anti-epileptic drugs before obtaining a proper diagnosis. Manifestations can occur at any age, and even prenatal fetal death has been described (Miller et al., 2004). Furthermore, there are numerous secondary conditions with similar ECG phenomena. These phenocopies can accompany a pathological condition and/or be age related. QT interval prolongation can be secondary to many pathologic conditions, such as electrolyte disturbances, cardiomyopathies and subarachnoid hemorrhage (Roden, 2006). Acquired forms of BrS have been described (Shimizu, 2005a), but in these cases the elimination of the causative factors results in the resolution of the rhythm disturbances. Genetically determined arrhythmias usually develop in otherwise normal hearts, and secondary conditions can aggravate but do not drastically change the natural course of the disease. The unusually early manifestation of age-related conditions, such as atrial fibrillation and cardiac conduction defect (Lev-Lenègre disease), should alert the clinician of a possible genetic nature of disease. For family members carrying the same channelopathy mutation, the natural course of disease can vary from SCD to asymptomatic longevity. To date, hundreds of mutations responsible for causing cardiac channelopathies have been described (Anon., 2011b). The vast majority of them were found in a few unrelated families, and some of them are found more commonly in particular ethnic groups (see below). Due to the high rates of genetic polymorphism most affected individuals carry their own “private” rare variant; the causality of which often requires confirmation. There are many criteria that can be used to assess the clinical significance of a novel genetic variant, i.e. statistical analysis of the prevalence in clinical and control groups and predictive bioinformatic analysis of the resulting mutant protein. Functional tests of identified mutations in heterologous in vitro expression systems and comparison to wild-type channel function can provide experimental evidence for the pathological consequences of said mutations and help unravel the molecular mechanisms of arrhythmogenesis. While interpreting functional data one must keep in mind the limitations of each model. The severity of mutant channel dysfunction in model cell lines does not always correlate with the severity of clinical symptoms.
in mutation carriers. The comparison of KCNQ1 mutations p.G314S and p.A341V is an illustrative example (Crotti et al., 2007). The p.G314S mutation shows a strong dominant-negative effect and produces a significantly greater loss in the repolarizing current than the p.A341V mutation, but the clinical manifestations of p. A341V carriers are more severe (Crotti et al., 2007). On the other hand, the generation of genetically-modified animal models is limited as it is both time-consuming and expensive. Nevertheless, in the past decade many genetically-modified mouse lines mimicking mutations found in patients with LQTS, BrS, and CPVT have been very useful to study the pathophysiological mechanisms underlying these syndromes (reviewed by Nilles and London, 2007).

Most channelopathies are characterized by a high risk of SCD, rendering the treatment of affected individuals of the utmost importance. The efficiency of a given anti-arrhythmic drug is dependent on the gene mutated and the functional effect of the mutation. For example, beta-blockers were shown to be effective in reducing the risk of VT and SCD in patients with LQTS (including those with SCN5A mutations), but were inefficient in BrS patients carrying other mutations in the same gene (Zipes et al., 2006). The triggers for life-threatening arrhythmias differ not only between diseases but also within the same syndrome depending on the genetic background (Shimizu, 2005b). For instance, LQTS patients with mutations in KCNQ1 are more prone to arrhythmic events during tachycardia caused by increased sympathetic input, while LQTS patients with mutations in SCN5A are more at risk at rest and during bradycardia (Shimizu, 2005b).

Most of the genes implicated in cardiac channelopathies have wide expression profiles and perform important functions in a variety of tissues. Hence, extra-cardiac involvement is not unusual in cardiac channelopathies. Examples are an increased prevalence of gut motility problems in SCN5A mutation carriers (Locke et al., 2006), seizure and epilepsy in KCNH2 mutation carriers (Johnson et al., 2008), and neuro-muscular symptoms in KCNJ2-associated LQTS (Priori et al., 2005; Tristani-Firouzi et al., 2002). Patients with primary channelopathies require careful clinical examination by multi-disciplinary teams of medical specialists. Genetic counseling is recommended for patients with primary channelopathies and their relatives, and should include a discussion of the risks, benefits, and options available for clinical and genetic testing (Ackerman et al., 2011).

2. Repolarization disorders: long and short QT syndromes

2.1. Clinical presentation

The time elapsed from the beginning of the QRS complex to the end of the T-wave on the ECG is known as the QT interval (Fig. 2). The QT interval depends on the total duration of ventricular electrical activity, and is the integration of all the action potentials from individual ventricular cells. The normal duration of the QT interval varies with the heart rate (HR), thus several normalization formulas have been developed in order to compare QT interval values. Bazett’s formula is the most commonly used: \[ QTc = QT / \sqrt{R-R} \]. QTc is the corrected QT interval, but it is only valid within a limited range of heart rates (50–120 bpm) (Bazett, 1920; Napolitano et al., 2006). Like any other quantitative trait reflecting the influences from multiple sources, the length of QTc has a normal (Gaussian) distribution in the general population. There is no clear cut-off between a normal and abnormal QTc duration. A normal QTc duration is accepted to be within 370–440 ms. Values smaller than 340 ms and larger than 460 ms are considered pathologic and are found in congenital short QT syndrome (SQTS, MIM ID#609620) and congenital long QT syndrome, respectively (LQTS, MIM ID#192500). The grey zone, 340–370 ms and 440–460 ms, may represent either milder forms of congenital QT interval abnormalities or individual variations in the healthy population.

![Fig. 3. Schematic representation of the main ionic currents responsible for the different phases of the cardiac action potential. Red (depolarizing) and blue (repolarizing) shapes indicate relative current amplitude, duration and direction. The shape of the current is aligned with its approximated time of action during the cardiac AP. The phase 0 (upstroke depolarization) is caused by the very rapid activation of voltage-gated sodium channels Na+,1.5. These channels inactivate very rapidly afterwards. The first repolarization phase 1 (notch) is due to the transient outward K+ current Ito. The plateau phase 2 is primarily maintained by an inward Ca2+ current flowing through Cav1.2 voltage-gated channels that inactivate slowly. Repolarization (phase 3) is obtained through the concerted action of three types of outward delayed currents: IKs (slow), IKr (rapid) and IK1. The main pore forming subunit (alpha subunit) of IKs are called KCNQ1 (or K,7.1), of IKr hERG (or K,11.1), and for IK1 Kv2.1. The principal alpha subunits are often found in association with regulatory beta-subunits. A prolongation of the AP duration can be caused by either a reduction in the repolarizing current (blue arrow) or an increase in the depolarizing current (red arrow).](image-url)
The phenotypic appearances of SQTS and LQTS are similar: syncope while at rest or triggered by external stimuli (i.e., emotional stress, shill noise or exercise) and a high risk of polymorphic VT. VT can be non-specific polymorphic VT or, as in the case of LQTS of the torsades de points (Tdp) type. These VT episodes can be either self-terminating or lead to ventricular fibrillation. SCD is often the first symptom of disease.

Electrocardiographic manifestations of LQTS and SQTS are QTc prolongation and QTc shortening, respectively. Alterations of the QTc duration can occur alone or in combination with other cardiac rhythm disturbances, such as sinus bradycardia, atrio-ventricular conduction defects, T-wave alterations, premature ventricular complexes, ventricular tachycardia and atrial fibrillation. Atrial fibrillation is more prevalent in patients with SQTS (Patel et al., 2010). The severity of clinical symptoms (such as the frequency of syncope, age of onset, SCD and grade of arrhythmias) can vary even within the same family.

The diagnostic criteria for LQTS are better defined than those of SQTS, in part because LQTS was identified first. There are some genotype-specific correlations that characterize the three most common variants of congenital LQTS (LQT1, LQT2, and LQT3): i.e. peculiar T-wave morphology, different factors triggering syncope, varying efficiencies of anti-arrhythmic drugs and different risks for SCD (Zareba, 2006; Zhang et al., 2000).

As illustrated in Fig. 4, ECGs of LQT1 and LQT2 patients have often broad-based, prolonged or low amplitude T waves. Bifid or notched T waves are also often found in LQT2 patients. The T wave of LQT3 patients is usually short and follows long ST segment (Moss et al., 1995). Priori et al. (2003) proposed a modern SCD risk stratification in LQTS patients based on genotype, clinical manifestations, and personal data such as age and gender. The lower grey zone of the QTc interval duration is less clear than the upper one, rendering the diagnosis of SQTS more complex. A probabilistic model with a sum score ranging from a “low” to “high” probability of SQTS was recently proposed by Gollob et al. (2011b) to assist in the diagnosis. Their model, however, requires further validation from independent sources. To date, genotype-phenotype correlations and informative genotyping results have only been obtained for a limited number of SQTS families. Fig. 4 shows typical ECG recordings with both prolonged and shortened QT intervals as compared to a normal ECG.

2.2. Inheritance and molecular genetics

Two types of inheritance patterns were originally described for LQTS: autosomal dominant for the Romano–Ward syndrome (Romano et al., 1963; Ward, 1964) and recessive for the Jervell and Lange-Nielsen syndrome (JLNS) (Jervell and Lange-Nielsen, 1957). The latter is characterized by QT interval prolongation with concomitant sensori-neural hearing loss caused by homozygosity or compound heterozygosity in the KCNQ1 or KCNE1 genes. Clinical investigations have revealed mild QT prolongation without hearing loss in the parents of JLNS patients. Reduced IKs current activity in the inner ear cells of patients with JLNS is correlated with an increased risk of SCD, more frequent syncope, atrophy of the stria vascularis and contraction of the endolymphatic compartments (Rivas and Francis, 2005).

At least 15 genes are currently known to carry pathogenic variants that can significantly alter the QT interval duration (Table 1). Mutation screening in coding sequences of these genes yields positive variants in approximately 60–75% of clinically definitive LQTS patients (Napolitano et al., 2005; Zareba, 2006). Mutations in three major genes (KCNQ1, KCNH2, and SCN5A) account for 75–90% of all positively genotyped patients (Kapplinger et al., 2009). Hundreds of rare and relatively common genetic variants have been identified in the genes of interest, and many of these variants have been characterized as disease-causing mutations. Most are “private” single-nucleotide changes (missense mutations or splice errors) found in single or several unrelated families worldwide. Recent studies of copy number variation (CNV) prevalence in LQTS-related genes revealed that 3–5% of patients carry large genomic rearrangements (deletions or duplications) in KCNQ1, KCNH2 and SCN5A genes (Barc et al., 2011; Tester et al., 2010). This percentage of CNV in these three major genes accounts for more LQTS cases than mutations in all other known genes (Barc et al., 2011; Tester et al., 2010). No common mutations or hot-spots have been found in any of the genes of interest, except in a few populations due to a founder effect (Berge et al., 2008; Brink and Schwartz, 2009; Winbo et al., 2011). Mutations in these genes can alter the duration of repolarization, leading to either prolongation or shortening of the QT interval. Mutations in at least 6 genes have been found in patients with congenital SQTS (Table 1), but their prevalence remains unknown (Hedley et al., 2009; Patel et al., 2010). More common genetic variants and their genetic combinations might prove to be of clinical significance. Some may be mutations with low penetrance which are triggered by external factors, such as drugs and toxins. Many of the common genetic variants, i.e. the alleles p.S1103Y-KCNQ1, p.H558R-KCNH2 and p.D85N-KCNE1, have been associated with moderate electrophysiological changes and/or acquired forms of LQTS (George, 2009; Roden, 2004). At present there is no clear boundary between inherited and acquired QT interval alterations. Mutations, functional polymorphisms, as well as many other genetic mechanisms likely contribute to the final phenotypic presentation of channelopathies. Most of these genes have pleiotropic effects due to their expression in many different tissues. They can be subject to epigenetic regulation, and may play broader roles in different processes (i.e. cancers). The KCNQ1 gene, for example, spans a cluster of Beckwith–Wiedemann syndrome (BWS) balanced germ-line chromosomal rearrangement breakpoints and shows maternal expression (Lee et al., 1997). It was shown that KCNQ1 is methylated in most tissues, with the exception of cardiac tissue (Mannens and Wilde, 1997). Thus far there has been neither demonstration of heart rhythm disturbances in BWS nor of overgrowth features in patients with repolarization disorders. In studies with careful pedigree analyses, congenital LQTS is described as a disease with preferential maternal inheritance (Imboden et al., 2006). The inheritance of repolarization disorders may be more complex than originally thought, and many factors must be considered when
dealing with familial data and providing genetic counseling. The QT interval is influenced by genetic and environmental factors. In order to address the genetic heterogeneity of this trait, recent genome-wide association studies (GWAS, i.e. the KORA (Pfeufer et al., 2005) and Rotterdam studies (Newton-Cheh et al., 2009)) were recently performed. It was found that SNPs in the promoter region of the NOS1AP gene are strongly associated with the QTc duration, but no disease-causing mutations or polymorphisms with known functional effects were identified in this area (Newton-Cheh et al., 2009).

2.3. Molecular and cellular pathophysiology

LQTS is the result of delayed repolarization of ventricular cells due to either the reduction in repolarizing (outward) currents or an increase in depolarizing (inward) currents (Fig. 3) (Lu and Kass, 2010). Loss-of-function mutations in the genes coding for K+ channel subunits, and gain-of-function mutations in the genes coding for Na+ and Ca2+ channel subunits and their regulatory proteins have been found in patients with congenital LQTS. The molecular mechanisms for SQTS are very different than those of LQTS. Most of the mutations found for SQTS lead to a gain of function of K+ channels (Patel et al., 2010), resulting in either prolongation or shortening of the QT interval. QT interval prolongation and shortening are not problematic but merely a marker of disease. AP prolongation may induce early after depolarizations at the cellular level and generate TDP, the reasons for which have been cited in this area (Terrenoire et al., 2007).

3. Brugada syndrome

3.1. Clinical presentation

Brugada syndrome (BrS) is genetic cardiac arrhythmic disorder characterized by ST-segment elevation in right precordial leads V1–V2, >2 mm, pseudo right bundle branch block (RBBB), T-wave inversion, and an increased risk of SCD due to polymorphic VT (Brugada et al., 1998). It is estimated to be responsible for 12% of SCD cases and approximately 20% of SCD in patients with structurally normal hearts at autopsy (Juang and Huang, 2004). In some cases, the myocardium of BrS patients has been found to be fibrotic (Coronel et al., 2005), which is in line with the results of mice expressing only one allele of SCN5A (van Veen et al., 2005), the gene coding for Na+ (Fig. 3). However, the link between the reduced function of Nav1.5 and the occurrence of myocardial fibrosis is not yet understood. The characteristic Brugada

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Table 1

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<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Current</th>
<th>Clinical syndromes</th>
<th>References</th>
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Fig. 5. Characteristic BrS1-pattern on ECG. Sinus rhythm, HR 72 bpm, spontaneous BrS pattern (PQ 120 ms; ST-elevation, and negative T-wave in right precordial leads V1–V2, marked by arrows, atypical incomplete RBBB). Male patient 38 y.o., 1st syncope at 36 y.o., ventricular fibrillation and SCD, ICD implanted, carrier of p.E553X mutation in SCN5A gene.
sign on standard ECG leads (Fig. 5) is often transient, and in many cases can only be revealed using drugs which block the sodium current. BrS has a worldwide distribution and the prevalence ranges from 5 to 66 per 10,000 individuals, with the highest rate in South-Asia (Juang and Huang, 2004). The prevalence varies between age groups, with adults having more ECG abnormalities than adolescents (0.05–0.28% vs. 0.005–0.06%, respectively) (Hayashi et al., 2009). The initial manifestations of BrS can appear from the first days of life up to 80 years of age (Campuzano et al., 2010), but the highest risk of SCD is in 35–45 year old males. The majority of life-threatening arrhythmias usually develop during rest or sleep, or during routine daily activities. Syncopes and cardiac arrest can be provoked by hyperthermia (i.e. fever (Keller et al., 2005) or heat exhaustion) and some medications (Barajas-Martínez et al., 2008). At present, there are no approved and efficient anti-arrhythmic drugs that can prevent ventricular tachycardia and fibrillation in BrS patients. There are, however, a series of publications about the successful use of quinidine for the acute suppression of the electrical storm in BrS patients, with no recurrence of VT during prolonged low-dose quinidine administration (Postema et al., 2009). To date, implantable cardioverter-defibrillators (ICD) are considered the only conventional method to prevent SCD in these patients (Benito et al., 2008; Sacher et al., 2006).

### 3.2. Inheritance and molecular genetics

Brugada syndrome is an autosomal dominant trait, but many patients do not have a familial history of BrS or SCD (Kyndt et al., 2001). This may be due to incomplete penetrance, the underdiagnosis of family members, or a high proportion of de novo mutations. Clinical observations show a strong gender disequilibrium with the male to female ratio in an European cohort being 3:1, and up to 9:1 in a South-Asian cohort (Campuzano et al., 2010). The exact mechanisms underlying this gender-specific penetrance have yet to be elucidated. No genes of interest nor evident modifiers have been mapped on the X- or Y-chromosomes. One hypothesis is that the right ventricular myocardium in males is more susceptible to arrhythmias due to gender differences in the myocardial expression of some of the ion channel genes (Barajas-Martínez et al., 2009). The first clinical description of ST-segment elevation was by Martini et al. (1989), and subsequently by Brugada and Brugada (1992). The SCN5A gene was implicated in BrS in 1998 (Chen et al., 1998). Mutations in the SCN5A gene are found in approximately 15–30% of all cases, but the direct causality of these mutations has recently been challenged (Probst et al., 2009) (see below). To date more than 300 individual mutations have been linked to BrS, and only 68 of these were found in different families (Anon., 2011b; Kapplinger et al., 2010). Approximately two thirds of disease-causing variants are missense mutations, with the rest being either frameshifts that result in radical changes in protein structure or translational control, in-frame deletions and insertions, or splicing and nonsense mutations (Kapplinger et al., 2010). Only a relative widening of the PQ interval (>210 ms) and HV time (>60 ms) seem to be predictive of the presence of SCN5A mutations (Smits et al., 2002). A recent study disputed the causative role of SCN5A mutations in BrS pathogenesis based on their findings of the non-segregation of SCN5A mutations and BrS ECG changes in large pedigrees (Probst et al., 2009). One possible explanation of this discrepancy, without disproving the direct role of SCN5A mutations, could be the presence of additional independent genetic variants of BrS in some family members. Additional genes have recently been linked to BrS. Since 2007 the list of genetic variants has increased to 8 (Table 2), but all of them have a low prevalence and explain only a minority of BrS cases.

### 3.3. Molecular and cellular pathophysiology

The correlation between the molecular defects and the clinical phenotypes seen in BrS is still debated. At least two hypotheses have been proposed to explain the ST segment alterations found in BrS patients. Both models point to right ventricular alterations involving either early repolarization (Yan and Antzelevitch, 1999) or late activation (Coronel et al., 2005). The two models are not mutually exclusive, and it is possible that BrS is a mechanistically heterogeneous disease. When studied in expression systems, Nav1.5 genetic variants often show either defective trafficking toward the cell membrane or alterations in their channel intrinsic biophysical properties (Amin et al., 2009). Other more complex mechanisms have also been reported (Keller et al., 2005; Petitprez et al., 2008). Given the central role of the sodium current in cardiac AP propagation/conduction (Kleber and Rudy, 2004), it is not surprising that individuals with sodium channel variants often have delayed ventricular activation with widened QRS intervals on the ECG (Probst et al., 2009; Smits et al., 2002). Other genetic mutations in BrS patients have been shown to either reduce the function of the cardiac sodium channel, as is the case for the beta subunit genes (SCN1B, SCN3B) (Hu et al., 2009; Watanabe et al., 2008) and the protein coded by GPD1-L (London et al., 2007), or alter the balance between the inward and outward currents during the early repolarization phase of the AP (CACNA1C, CACNB2, KCNE3, MOG1) (Antzelevitch et al., 2007; Delpon et al., 2008; Kattygnarath et al., 2011). The genetic and cellular mechanisms underlying BrS are under intense investigation, and it is premature to make any conclusions at this point in time.

### Table 2

Susceptibility genes for Brugada syndrome.

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Current</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrS1</td>
<td>SCN5A</td>
<td>3p21</td>
<td>Nav1.5</td>
<td>hsa</td>
<td>Chen et al. (1998)</td>
</tr>
<tr>
<td>BrS2</td>
<td>GPD1-L</td>
<td>3p22.3</td>
<td>Glycerol-3-phosphate dehydrogenase 1-like</td>
<td>Regulation of hsa</td>
<td>London et al. (2007)</td>
</tr>
<tr>
<td>BrS3</td>
<td>CACNA1C</td>
<td>12p13.3</td>
<td>Cav1.2</td>
<td>l, c</td>
<td>Antzelevitch et al. (2007)</td>
</tr>
<tr>
<td>BrS4</td>
<td>CACNB2</td>
<td>10p12</td>
<td>Cav beta-2</td>
<td>l</td>
<td>Antzelevitch et al. (2007)</td>
</tr>
<tr>
<td>BrS5</td>
<td>SCN1B</td>
<td>19q13.1</td>
<td>Nav beta-1</td>
<td>h</td>
<td>Watanabe et al. (2008)</td>
</tr>
<tr>
<td>BrS6</td>
<td>KCNE3</td>
<td>11q13-q14</td>
<td>MinK-related peptide, Member 3</td>
<td>l</td>
<td>Delpon et al. (2008)</td>
</tr>
<tr>
<td>BrS7</td>
<td>SCN2B</td>
<td>11q23.3</td>
<td>Nav beta-3</td>
<td>h</td>
<td>Hu et al. (2009)</td>
</tr>
<tr>
<td>BrS8</td>
<td>HCN4</td>
<td>15q24-q25</td>
<td>Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4</td>
<td>l</td>
<td>Ueda et al. (2009)</td>
</tr>
</tbody>
</table>
4. Catecholaminergic polymorphic ventricular tachycardia

4.1. Clinical presentation

Catecholaminergic polymorphic ventricular tachycardia (CPVT, MIM ID*604772) is a stress-provoked bi-directional ventricular tachycardia (Fig. 6) that occurs in an otherwise normal heart. There are no other ECG abnormalities, such as QT interval alterations (Liu et al., 2007). About 30% of patients have a positive familial history of SCD. Clinical symptoms begin in childhood or adolescence with syncopal events. The average age of onset is 7–9 years of age (Postma et al., 2005). The cumulative survival before 30 years of age is approximately 50–70% (Swan et al., 1999). The specific ECG pattern is highly reproducible and can be induced using exercise testing. Induction during programmed electrical stimulation is usually ineffective, distinguishing CPVT from familial idiopathic ventricular tachycardia (MIM ID*603829). It was described as a clinical entity by Counel in 1978 and Leenhardt in 1995, who also unveiled moderate QTc prolongation in affected family members (Counel et al., 1978; Leenhardt et al., 1995). The phenotypic overlap between CPVT and LQTS was later found in several CPVT patients (Tester et al., 2005). Nearly 6% of genotype-negative LQTS patients may carry putative CPVT type 1 mutations (Itoh et al., 2010); and about 30% of CPVT cases have a mild QTc prolongation (460–480 ms) which can be misdiagnosed as “concealed LQTS” (Kapplinger et al., 2009). Bi-directional VT has also been described in LQT7 (Andersen–Tawil Syndrome) (Andersen et al., 1971).

Beta-blockers are the most recommended anti-arrhythmic drugs for the treatment of CPVT, despite their limited effectiveness in some cases (Bienacka and Hoffman, 2011; Leenhardt et al., 1995; Pott et al., 2011). A combination of beta-blockers, calcium channels blockers and flecainide for patients resistant to conventional therapy has recently been proposed (Rosso et al., 2007; van der Werf et al., 2011). ICD implantation in patients with a clear diagnosis of CPVT is warranted (Epstein et al., 2008), but it should be kept in mind that PVT can be easily provoked (even with slight physical activity) and cause numerous electrocardiac shocks (Pott et al., 2011).

4.2. Inheritance and molecular genetics

Autosomal dominant, autosomal recessive and sporadic cases of CPVT have all been documented. Molecular genetic testing of the open reading frame of the RYR2 gene encoding the calcium-release channel (CPVT type 1, dominant form) accounts for 50–55% of all cases (Priori et al., 2002). Clinical genetic diagnostic testing of mutations in this gene is difficult due to its large size (105 exons, and ~16.5 kb mRNA encoding 4967 amino acids), but about 65% of mutations in RYR2 can be detected by targeted screening of 16 exons (Medeiros-Domingo et al., 2008). Mutations in the CASQ2 gene encoding the cardiac isoform of calsequestrin can be found in patients with the autosomal-recessive form of CPVT (CPVT type 2) (Lahat et al., 2001). Heterozygous carriers of mutations in the CASQ2 gene appear to be unaffected (di Barletta et al., 2006). An additional autosomal recessive locus (CPVT type 3) was mapped at 7p22-p14 in a single family of Sudanese origin. Three siblings in the family had moderate QTc prolongation and died during physical exercise. The culprit gene has yet to be determined (Bhuiyan et al., 2007a).

4.3. Molecular and cellular pathophysiology

The mutated genes in CPVT patients participate in the handling of Ca2+ in the sarcoplasmic reticulum. Most mutations have been found in RYR2 (Laat enen et al., 2001; Priori et al., 2001), the gene encoding the cardiac rymyodine receptor, an ion channel which permits the outflow of Ca2+ ions from the sarcoplasmic reticulum upon cell membrane depolarization. Mutated RYR2 channels leak Ca2+ when the channel should be closed, resulting in leaky ryomyodine receptors (Wehrens et al., 2005). Using mouse models harboring similar mutations, it was demonstrated that Ca2+ leaks in the cytoplasm of cardiac cells may trigger arrhythmias (Cerrone et al., 2005; Liu et al., 2006). CASQ2, CPVT mutations reduce the Ca2+ buffering capacity of the sarcoplasmic reticulum and alter the biochemical properties of the RyR2 channel, thus increasing the likelihood of spontaneous Ca2+ release into the cytoplasm, triggering delayed after-depolarizations (Priori and Chen, 2011). The details of the mechanisms by which CPVT mutations in calsequestrin proteins (encoded by CASQ2) are generating VT remain poorly understood (Liu et al., 2007).

5. Rare phenotypes

Primary cardiac channelopathies were initially considered to be purely electrical diseases, without significant or observable structural cardiac abnormalities. Molecular and genetic studies have provided new insight into the phenotypic diversity of channelopathies. Uncommon inherited defects and genetic combinations have been linked to rare clinical phenotypes with significant myocardial changes (Table 3). Digenic inheritance was shown for a rare progressive type of atrial cardiomyopathy, atrial standstill (MIM ID*108770), which is characterized by the progressive deterioration of electrical and mechanical activity of the atria, bradycardia, a junctional (narrow) or wide QRS escape rhythm, and the absence of a P-wave on standard ECG (Park et al., 2009). Affected individuals co-inherited rare genetic variants of the SCN5A gene and −44C>T polymorphism in the atrial-specific gap junction protein connexin 40 (Groenewegen et al., 2003). Partial deletion of the RYR2 gene was also recently found in patients with complex (Bhuiyan et al., 2007b) rhythm disturbances, DCM and atrial standstill. At least 4 missense and 1 frame-shift mutation in the SCN5A gene have been shown to cause dilated cardiomyopathy (DCM 1E, MIM ID*601154) and a broad spectrum of rhythm disturbances (sinus node dysfunction, AV block, supra-ventricular and ventricular arrhythmias) (McNair et al., 2004; Olson et al., 2005). Progressive familial heart block (PFHB, Lev-Lenègre disease, MIM ID*113900), an autosomal dominant disorder which is a major reason for pacemaker implantation, can also be categorized as a channelopathy. Progressive ECG changes consistent with right or left bundle branch block and complete A–V dissociation may not only result from altered function of ion channels, but also from primary or age-related sclerotic degeneration of conductive tissue (Viswanathan and Balser, 2006). Mutations in two cardiac ion channel genes, SCN5A (Bezzina et al., 2003) and TRPM4 (Kruse et al., 2009; Liu et al., 2010a), have been implicated in PFHB. Patients carrying SCN5A or TRPM4 mutations who presented with atrial standstill, DCM or His-Purkinje degeneration were shown to have one or more ion permeability defects (Anon., 2011b). The classical model for the functional study of new genetic variants in patients with channelopathies is the expression of the mutant proteins in heterologous cell systems. The link between ion permeability alterations in model cells and the morphological changes in the highly organized myocardium is not always an easy one to make. This is

Table 3

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MIM ID</th>
<th>Gene(s)</th>
<th>Mode of inheritance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial standstill</td>
<td>*108770</td>
<td>SCN5A + GJA5</td>
<td>Digenic</td>
<td>Park et al. (2009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RYR2</td>
<td>Monogenic, dominant</td>
<td>Bhuiyan et al. (2007b)</td>
</tr>
<tr>
<td>DCM with rhythm disturbances</td>
<td>#601154</td>
<td>SCN5A</td>
<td>Monogenic, dominant</td>
<td>McNair et al. (2004), Olson et al. (2005), Bhuiyan et al. (2007b)</td>
</tr>
<tr>
<td>Progressive familial heart block</td>
<td>*113900</td>
<td>SCN5A</td>
<td>Monogenic, dominant</td>
<td>Bezzina et al. (2003)</td>
</tr>
<tr>
<td>Familial sinus node disease</td>
<td>*163800</td>
<td>HCN4</td>
<td>Monogenic, dominant</td>
<td>Kruse et al. (2009), Liu et al. (2010a), Zhang et al. (2000)</td>
</tr>
<tr>
<td>Monogenic, recessive</td>
<td>SCN5A</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
partially why the molecular pathogenesis of myocardial degeneration in many diseases remains unknown despite the localization of a genetic defect. The elucidation of the relationship between a genetic defect and related structural changes will provide new insight into the not-yet-known biological roles of ion channel proteins.

6. Overlapping phenotypes

The concept that distinct phenotypes can be explained by specific genetic mutations encoding ion channels was first challenged by a study describing carriers of the p.insD1795 mutation in SCN5A that presented with either typical LQTS or BrS ECG alterations (Bezzina et al., 1999). Some of the carriers had both alterations. Other studies have shown that not only were LQTS and BrS present in the same carriers, but that they also had cardiac conduction defects (Grant et al., 2002). This led to the development of the SCN5A-overlap syndrome for individuals who present with signs of LQTS, BrS, conduction slowing, sick sinus syndrome or atrial fibrillation either separately or simultaneously (for a comprehensive review see (Remme et al., 2006)). The reasons by which one given mutation can result in a variety of phenotypes remain poorly understood, but may have something to do with the different roles of cardiac sodium channels under different physiological conditions and in different regions of the heart (Abriel, 2007). The pleiotropic effects of genes can be another reason for the observed clinical complexity. The genetic expression in different tissues, the participation in large multi-protein complexes, and the involvement in similar pathways likely broaden the clinical manifestations, and inevitably lead to phenotypic overlapping. Many of the genes linked to cardiac channelopathies, e.g. RYR2, KCNJ2, KCNJ5, CACNA1C, CACNA2B, ANK2, CAV2, etc., are also involved in neurological and neuromuscular disorders. It is now recognized that cardiac channelopathies can be linked to structural heart disease, and neuromuscular and endocrine disorders, and that they rarely result in discrete clinical phenotypes such as LQTS, BrS or isolated electrical disorders of the myocardium. Patients with cardiac channelopathies require complex and versatile medical assistance.

7. Conclusion and perspectives

Since the seminal observations made in 1995 (Curran et al., 1995; Wang et al., 1995b, 1996), the field of cardiac channelopathies has progressed at a very rapid pace. The detailed genotypes, mechanisms, and phenotypic correlations have been discovered thanks to the collaborative efforts between the communities of medical and molecular genetics, cardiology, and the basic sciences (Lehnaert et al., 2007; Priori, 2010). In 2012, the cardiac channelopathies form a particular clinical entity that mainly includes five distinct nosologies (LQTS, SQTs, BrS, CCD, and CPVT) that display a wide range of overlapping phenotypes. The description of new phenotypes is progressing rapidly (Laurent et al., 2012). Despite obvious phenotypic differences between the five syndromes, they also share clear similarities: a pronounced clinical polymorphism (even within a single family), a paroxysmal character and a high risk for SCD. The genetic structure of cardiac channelopathies is complex. Most syndromes may be caused by mutations in many different genes (Tables 1 and 2), and different mutations in one single gene may be at the origin of different phenotypes. As an example, there are thus far 13 genes linked to LQTS, and one of them, SCNSA, is a susceptibility gene for different phenotypes including LQT3 and BrS. All the genes of interests have been found to be highly polymorphic. Several databases are collecting data related to cardiac ion channel gene variants, such as the LVOD database of the Chinese human variome project (Anon., 2011a; Zhang et al., 2010) and “The Gene Connection For The Heart” (Anon., 2011b). There are currently about two thousand identified unique variants in 13 main LQTS genes, half of which are considered pathogenic or possibly pathogenic.

There are still many unanswered questions that are currently being addressed by hundreds of research groups all over the world. The penetrance and expressivity of the cardiac channelopathy phenotypes are particularly fascinating topics. These disorders cannot be classified as “pure” monogenic pathologies, but the detailed interactions between morbid and modifier genes remain unclear. The genetic, molecular and cellular mechanisms underlying these diseases are very heterogeneous. Syndromes previously described to have fairly “homogeneous” phenotypes, i.e. congenital long QT syndrome, are now linked to a myriad of different alterations at all levels of the biological system.

How all of these experimental and clinical findings will impact patient care is a very important issue. Insight into new methods of diagnostic and treatment strategies, such as gene-specific therapy, will hopefully be forthcoming. A study performed in 2010 in 18 European countries showed that genetic testing of inherited arrhythmic syndromes can be locally performed for the majority of cases, and that about half of responding European countries has guidelines for genetic testing (Svendsen and Geelen, 2010). Genetic testing was considered most valuable for LQTS and CPVT, and relatively low for BrS (Svendsen and Geelen, 2010). Risk stratification schemes for patients based on their genotype would prove to be very useful (Crotti et al., 2007; Liu et al., 2010b), but these schemes require detailed knowledge of the individual mutations (Liu et al., 2010b). The development of preventive and therapeutic strategies also requires increased knowledge of the mutations and their consequences (Abriel et al., 2000). New findings of the genetic background and molecular expression mechanisms of mutations, case reports, and data from national and international registries have led to publications of consensus statements (Ackerman et al., 2011; Gollob et al., 2011a) which summarize the current knowledge and recommendations for the genetic testing of patients with inherited cardiac diseases. These documents are considered to be precursors to further guidelines for cardiac genetic testing, and provide new approaches to integrate genetics and technology into clinical practice and personalized medicine.

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