It was only ten years ago that mutations in ion channel genes were first described in patients with the long QT syndrome (LQTS) [1]. Since then, mutations in a total of eight different sarcolemmal ion channel subunit genes (KCNQ1, KCNH2, KCNE1, KCNE2, SCN5A, KCNJ2, HCN4, CACNA1C), two genes encoding sarcoplasmic reticulum (SR) Ca\(^{2+}\) handling proteins (RYR2, CASQ2), and an anchoring protein gene (ANK2) have been linked to a range of primary arrhythmia syndromes. The recognition of abnormal function of these genes in the inherited arrhythmia syndromes has provided remarkable insight into mechanisms of arrhythmias not only in these uncommon syndromes, but has also had very important implications for arrhythmia mechanisms and management more generally. It is therefore very opportune that *Cardiovascular Research* dedicates this spotlight issue to this topic. In this issue, a series of reviews summarizes the current state-of-the-art, and a number of original papers present new data on various aspects of cardiac arrhythmia genetics.

### 1. Monogenic arrhythmia disorders

Estimated to affect up to 1 in 5000 individuals [2], the long QT syndrome (LQTS) is the most frequently encountered of the monogenic arrhythmia syndromes. Since the first description of LQTS-causing mutations, numerous mutations in individuals and families with the disorder have been described. Most often, mutations occur in genes encoding the pore-forming (\(\alpha\)-subunits) of two major repolarizing K\(^+\) channels (KCNQ1, I\(_{Ks}\); KCNH2, I\(_{Kr}\)) or the depolarizing Na\(^+\) channel (SCN5A, I\(_{Na}\)). The LQT registry [3], established in the early 1980s, formed a very important resource for carrying out genotype–phenotype correlation in LQTS patients carrying a causative mutation in these genes. Consequently, of all the primary electrical disorders, it is in this disorder that genetics has perhaps had the greatest impact on patient management. Important aspects of the disease, such as triggers for cardiac events and therapy, were found to be genotype dependent. These and other aspects of genotype–phenotype correlations and their impact on patient management are reviewed by Shimizu [4], in this issue of the journal.

A prolonged QT interval on the surface ECG reflects prolonged ventricular myocardial action potential duration (APD). APD is governed by a delicate balance between inward (Na\(^+\) or Ca\(^{2+}\)) and outward (K\(^+\)) ionic currents. Accordingly, LQTS-associated mutations affecting the Na\(^+\) or Ca\(^{2+}\) channel prolong APD via a “gain-of-function” mechanism, while mutations in genes encoding K\(^+\) channel components cause LQTS by a “loss-of-function” mechanism. The first LQTS-related mutant Na\(^+\) channels that were investigated in vitro by the patch clamp technique exhibited a persistent Na\(^+\) current during the action potential plateau (which explains the prolongation of APD) [1], a phase of the action potential at which wild-type (normal) channels are non-conducting. Eventually, electrophysiological analysis of some SCN5A mutations proved that this was not a universal mechanism by which Na\(^+\) channel mutations prolonged the QT interval. In this issue, the Amsterdam group of Smits et al. present data on two mutations affecting the same amino acid residue within the Na\(^+\) channel which support a mechanism for QT interval prolongation as a consequence...
of changes in Na⁺ window current and postulate that such a mechanism is not so rare [5].

Mutations in KCNH2 and KCNQ1 prolong the QT interval via loss-of-function due to multiple mechanisms. Outward K⁺ current carried by the defective K⁺ channels may be reduced by alterations in channel gating or kinetics. The dominant-type inheritance observed in the majority of cases (recessive-type inheritance is also associated with deafness) often results from “dominant-negative” interactions of mutant with wild-type subunits, both present in a heterozygous individual. Protein trafficking defects that reduce delivery of channels to the cell surface membrane have emerged as a common mechanism of disease in KCNH2-linked LQTS (which would reduce Iₖᵢ). Such mutants may or may not affect the trafficking of the wild-type subunit. In this issue, Paulussen et al. [6] present findings on a trafficking-deficient KCNH2 mutant that they identified in a LQTS family with intriguing counteracting effects (increasing Iₖᵢ) on channel kinetics. In contrast to KCNH2, trafficking defects have only recently been described for KCNQ1 mutations. In this issue, Wilson et al. [7] investigate intracellular trafficking for multiple LQTS-associated KCNQ1 mutants, providing further support for a defective trafficking mechanism in KCNQ1 pathogenesis.

A degree of complexity which is not often taken into consideration in the in vitro study of ion channel mutants is the occurrence of ion channel isoforms arising from alternative splice variants. Thus, mutation effects are often only characterized in the context of one, often the most prevalent, isoform. For KCNQ1, for example, the effect of mutations in the context of isoform 2, which lacks the N-terminal 127 amino acids (with respect to isoform 1), and which exerts a strong dominant-negative effect on isoform 1 [8], have not been extensively investigated. By introducing an LQTS-associated KCNQ1 mutation into both isoforms 1 and 2, Thomas et al. [9] investigated in detail mechanisms of dominant-negative suppression of this mutation, also in the presence of the KCNE1-encoded β-subunit.

While loss-of-function mutations in KCNQ1 and KCNH2 lead to QT interval prolongation, not unexpectedly, gain-of-function mutations result in QT interval abbreviation. The short QT syndrome (SQTS) [10] is the most recently recognized primary electrical disorder, with only few individuals and families with the disorder being reported in the literature. Two articles related to this recently recognized clinical entity are found in this issue. Schimpf et al. [11] review the clinical characteristics, genetics, and therapeutic possibilities of the disorder, while Cordeiro et al. [12] analyze further the electrophysiological characteristics of the KCNH2 N588K substitution, linked to SQTS in 2 families, and propose a mechanism for arrhythmogenesis in patients carrying this mutation.

The discovery in 2003 that an LQTS subtype (LQT4) [13] was caused by mutation in a cytoskeletal (anchoring) protein underscored the importance of proteins other than ion channels themselves in the proper electrical functioning of the heart. This is consistent with an evolving view that ion channels form part of larger complexes, which besides the α- and β-subunits (see the original contribution by Bendahhou et al. [14]) comprise signaling and structural components. In this issue, Meadows and Isom [15] review this emerging field of research with respect to the Na⁺ channel macromolecular complex. Furthermore, using a mouse model of desmin-related cardiomyopathy, Gard et al. [16] demonstrate that a defect in a cytoskeleton protein conventionally thought to fulfill a mechanical function can also lead to electrical abnormalities likely by remodeling gap junctions at intercalated disks.

A disorder that has attracted much attention in the last decade is the Brugada syndrome. First presented as a distinct clinical entity in 1992, it has since been increasingly recognized. Brugada syndrome may be caused by mutations in SCN5A. But unlike those causing the LQTS, SCN5A mutations leading to Brugada syndrome are invariably associated with a loss-of-function. Loss-of-function SCN5A mutations also lead to conduction defects, which not surprisingly often also form part of the clinical picture in Brugada syndrome [18,19].

Fever is known to trigger or exacerbate the clinical manifestations of Brugada syndrome. In this issue, Keller et al. [20] shed further light on mechanisms involved by investigating the characteristics at increased temperature (mimicking fever) of Na⁺ channel mutants identified in patients with a typical Brugada syndrome ECG or ventricular arrhythmias during fever.

Mutations in SCN5A are found in less than a third of patients with the disorder. Other genes for the disorder are yet unknown. Their discovery is greatly anticipated, since they are likely to provide further clues on the mechanism(s) underlying ST segment elevation (signature ECG pattern of Brugada syndrome) and arrhythmogenesis in this disorder, issues which are yet unresolved. In this issue Meregalli et al. [21] provide a detailed explanation of the different hypotheses put forward and review the evidence available for the different mechanisms proposed.

An ongoing discussion also concerns the exact molecular mechanism underlying catecholaminergic polymorphic ventricular tachycardia (Kontula et al. [22]). Mutations in two key sarcoplasmic reticulum (SR) components of the excitation–contraction coupling machinery, the ryanodine receptor (type 2, RYR2) and calsequestrin (CASQ2), have been linked to the disorder, and although in both cases an enhanced SR Ca²⁺ release appears to be involved (which would lead to delayed-after-depolarization-triggered activity), the precise pathophysiological mechanism(s) remains to be resolved.

Also in this issue, Tester and Ackerman [23] review historical developments and ongoing debates surrounding the significance of cardiac channelopathies in the pathogenesis of sudden infant death syndrome (SIDS) and report on potentially causative variants in KCNQ1, KCNH2, and...
that they identified during postmortem genetic testing in cases of SIDS.

2. Modifier genes and polygenic arrhythmia disorders

The identification of the known genes for the monogenic arrhythmia syndromes was in the majority of cases facilitated by the availability of large kindreds with a sufficient number of clearly affected individuals for unambiguous genetic linkage. However, as more and more families were genotyped, it became apparent that as for other monogenic disorders, a large extent of phenotypic variability could exist within families [24]. Hence, relatives carrying an identical mutation to the proband can at times be either unaffected or display more severe or (more likely) milder forms of the disease. Strong evidence in support of a role of phenotypic modulators such as gender, age, and drugs has emerged in particular for the LQTS and a role for such modulators is evident for other disorders, in particular the Brugada syndrome. A widely held hypothesis is that inter-individual genetic variation also plays a role in determination of the ultimate phenotypic manifestation of the disorder. Similar genetic variation is also thought to underlie susceptibility to the more-prevalent arrhythmias such as atrial fibrillation (AF, reviewed by Wiesfeld et al. [25]) and arrhythmias in pathologies such as ischemia and heart failure.

3. Research tools

Thus, one emerging concept is that variation in many genes may contribute to arrhythmia susceptibility in inherited and perhaps “acquired” arrhythmias. This field of research is yet in its infancy (also reflected by the fact that this spotlight issue contains only one original contribution, by Ehrlich et al. [26], on the topic) and is hindered by difficulties inherent to the research tools involved, most importantly the association study design, and the considerable effort entailed in practical aspects among which the enrollment of large numbers of accurately phenotyped study participants. In this issue, Kääb and Schulze-Bahr [27] highlight the salient points to consider in carrying out such research and provide a useful compendium of non-synonymous (associated with amino acid change) DNA variation in genes of interest, while Ehrlich et al. [26] investigate the functional consequences of a non-synonymous KCNE1 gene polymorphism postulated to be associated with increased prevalence of AF. Another concept (reviewed by Roden [28]), also just starting to be tested, is whether such subclinical DNA variants invoke or exacerbate arrhythmias in some individuals undergoing drug therapy.

Animal experimentation (Hewett et al. [29]) has traditionally formed an important tool in arrhythmia research. Expanding knowledge of the molecular substrates for arrhythmias is likely to lead to the generation of more mechanistically faithful animal models (Milan and MacRae [30]), which in combination with the implementation of the evolving “omics” technologies (see Demolombe et al. [31]), are likely to provide important insight into pathways of arrhythmias.

4. The future

The last decade has seen breathtaking progress in identifying mutations that cause unusual congenital arrhythmia syndromes, and in initial studies of the mechanisms involved. There have been surprises: variations in a single gene can cause a wide range of distinct clinical phenotypes; incomplete penetrance is common; misprocessing is a very important mechanism. Is the era of identifying new monogenic arrhythmia syndromes drawing to a close? It would be foolhardy to make this prediction, given the recent emergence of new syndromes and the strong likelihood that “common” diseases, notably AF, include an important genetic component. Indeed, clinical heterogeneity in conditions like AF may simply be telling us that we are treating multiple, mechanistically distinct syndromes the same way because we are not yet smart enough to dissect them apart. Thus, we anticipate that more genes that can harbor arrhythmia-causing mutations remain to be identified. In addition, the idea that the final clinical phenotypes are determined by complex protein–protein and protein–DNA interactions will also be a fertile area for further study.

As progress is made, new questions arise. For example, we are only now beginning to grapple with the question of how new genetic information can be incorporated into diagnosis and therapy. A distinguishing characteristic in contemporary translational science is that progress is best made by studies that include very strong links between clinical scientists – who precisely define phenotypes – and basic scientists. Basic arrhythmia science has traditionally included molecular, cellular, and animal electrophysiology and now increasingly will need to embrace new disciplines like systems biology, genetic epidemiology, and medical ethics. The science of inherited arrhythmia syndromes has come a very long way in the last decade, and we anticipate an equally breathtaking next decade as these advances begin to be applied clinically.

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