Inherited cardiac arrhythmia syndromes have received a lot of attention in recent years, particularly the molecular genetic basis, which has been unraveled to a great extent in the past years. Disease entities have been subdivided based on their causal gene defect, which, indeed, has been shown to impact on disease expression, clinical characteristics, prognosis and treatment. This particularly holds for the long QT syndrome. Studies in other, more recently described, disease entities, such as Brugada syndrome, catecholaminergic polymorphic ventricular arrhythmias and the short QT syndrome, are ongoing. For some of them the heterogenetic nature has just very recently been established. For these reasons, genetic testing has been introduced to clinical practice in several countries, which enables timely treatment of affected individuals and reassurance of those not inheriting the causal gene defect. Presymptomatic testing, however, is not without drawbacks. Psychosocial studies are needed in this field and should be promoted. It is likely that this development will further increase the knowledge of the (patho-) physiology of these disease entities, but also of more common arrhythmia syndromes. (Circ J 2007; Suppl A: A-12–A-19)

Key Words: Arrhythmias; Genes; Genetics; Ion channels; Sudden cardiac death
### Table 1 Summary of Genes and Chromosomal Loci for Inherited Cardiac Arrhythmia Syndromes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene</th>
<th>Protein/aliases</th>
<th>Chromosomal locus</th>
<th>Inheritance</th>
<th>Ionic current affected</th>
<th>Effect on current</th>
<th>Reference(s)</th>
<th>OMIM#</th>
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<tr>
<td><strong>Long QT syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>KvLQT1</td>
<td>11p15.5</td>
<td>Dominant</td>
<td>Is</td>
<td></td>
<td>64, 65</td>
<td>192,590</td>
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<td>LQT2</td>
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<td>HERG</td>
<td>7q35-q36</td>
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<td>Is</td>
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<td>66, 67</td>
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<td>SCN5A</td>
<td>Nav1.5</td>
<td>3p21</td>
<td>Dominant</td>
<td>Is</td>
<td></td>
<td>66, 68</td>
<td>603,830</td>
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<td>LQT4</td>
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<td>Ankyrin-B</td>
<td>4q25-q27</td>
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<td>Multiple</td>
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<td>21q22.1-q22.2*</td>
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<td>Is</td>
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<td>70</td>
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<td>MiRP1</td>
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<td>SCN4B</td>
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<td>Is</td>
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<td>KCNQ1</td>
<td>KvLQT1</td>
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<td>KCNH2</td>
<td>HERG</td>
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<td>Dominant</td>
<td>Is</td>
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<td>KvLQT1</td>
<td>11p15.5*</td>
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<td>17q23.1-q24.2*</td>
<td>Dominant</td>
<td>Is</td>
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<td><strong>Brugada syndrome</strong></td>
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<td>BS1</td>
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<tr>
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<td>Cav1.2</td>
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<td>Cav1.2b</td>
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<td>ICa-L</td>
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<tr>
<td><strong>Catecholaminergic polymorphic ventricular tachycardia</strong></td>
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<td>CASQ2</td>
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<td>1p13.3-p11</td>
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<td>SR Ca&lt;sup&gt;2+&lt;/sup&gt; release</td>
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<tr>
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<tr>
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<tr>
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<td>Recessive</td>
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<tr>
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<td>Nav1.5</td>
<td>3p21</td>
<td>Dominant</td>
<td>Is</td>
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<tr>
<td><strong>Familial atrial fibrillation</strong></td>
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<td>FAF1</td>
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</tr>
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<td>KvLQT1</td>
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<tr>
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<td></td>
<td>5p13</td>
<td>Recessive</td>
<td></td>
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</tr>
<tr>
<td>FAF6</td>
<td>KCNJ2</td>
<td>Kir2.1, IRK1</td>
<td>17q23.1-q24.2*</td>
<td>Dominant</td>
<td>Is</td>
<td></td>
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<td></td>
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<tr>
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<td>HERG</td>
<td>7q35-q36*</td>
<td>Dominant</td>
<td>Is</td>
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<tr>
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<td>GJA5</td>
<td>Connexin 40</td>
<td>1q21.1*</td>
<td>Somatic</td>
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<td></td>
<td>55</td>
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</tr>
<tr>
<td>FAF9</td>
<td>KCNA5</td>
<td>Kv1.5</td>
<td>12p13*</td>
<td>Dominant</td>
<td>Is</td>
<td></td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

*Although mutations have been described in this gene in individuals with this disorder, genetic linkage to this locus has not yet been demonstrated.

†Subtypes numbered according to date of publication of finding.


‡‡Although described only in sporadic patients, in vitro functional studies provide evidence for a Dominant effect for the mutation.

‡All probands described carried the same de novo mutation with the exception of two siblings who inherited the mutation from their unaffected mother who was mosaic for the mutation.

SR, sarcoplasmic reticulum.
rent during the plateau phase of the action potential delays repolarization, thereby prolonging the action potential and the QTc interval. LQTS 3 and 8 involve the cardiac sodium and calcium channels, respectively. In these subtypes, the causes are gain-of-function mutations, which lead to increased inward current during the action potential plateau phase and, consequently, prolongation of the QTc interval. LQTS 10 relates to a subunit of the cardiac sodium channel (SCN4B), whereas LQTS 4 and 9 are based on variations in the proteins ankyrin and caveolin, which are involved in ion channel trafficking and localization, respectively.\(^5\) It is important to realize that the putative causality of the genetic findings is not based on sound linkage data in all subtypes. In particular, single individuals or small families with just a few affected individuals form the basis of the suggested causal relationship in LQTS 5, 6, 9, and 10.

The current subdivision is not unimportant, because there appears to be a strong genotype–phenotype relationship. Shortly after the identification of heterogeneity in LQTS, gene-specific T-wave morphologies were described for the 3 most common subtypes, which account for 85% of the genotyped population\(^8\) (ie, LQTS 1, 2, and 3). In the years that followed, these observations were extended.\(^9\) Moreover, gene-specific clinical parameters were also identified.\(^10\) In particular, the triggers for symptoms received a lot of attention. Indeed, highly gene-specific triggers are present for LQTS 1 (swimming and diving) and LQTS 2 (auditory stimuli).\(^11\)–\(^14\) In addition, exercise- or stress-related arrhythmias are frequently observed in LQTS 1 and 2, whereas the majority of events in LQTS 3 occur at rest.\(^14\)

Based on these observations, it is evident why anti-adrenergic interventions, in particular, \(\beta\)-adrenoceptor blockade, are typically effective in LQTS 1 and 2, but less so in LQTS 3.\(^14,15\) Based on the biophysical consequences of altered sodium current in LQTS 3, it has been speculated that sodium-channel blockers may be beneficial.\(^16\) Indeed, a very significant reduction in QTc-interval during sodium-channel blocker treatment has been shown. However, it should be stressed that, at present, long-term follow-up of patients on this drug class is lacking. At the same time, failure of such therapy has been reported.\(^17\) Implantation of a pacemaker or an implantable cardioverter-defibrillator

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**Fig 1.** (A) Example of an arrhythmia that occurred during an exercise test in an LQT1 patient (6-lead recording, extremity leads). Note the absence of any pause preceding the arrhythmia. (B) Example of a pause-dependent arrhythmia as typically seen in LQT2 patient (as this patient; 12-lead recording). Not infrequently, 1 episode is followed by the next episode of torsades de pointes arrhythmia. Calibration in both ECGs is standard.
(ICD) is occasionally required in all 3 subtypes, maybe more so in LQTS 3 patients. Data on the other subtypes are scarce, although it is generally recognized that, in particular, LQTS 8 may be a highly malignant subtype.

The age of onset of symptoms is another clinical variable that displays some gene-specific features. In LQTS 1, the age of onset is between 5 and 15 years in most, but is typically at puberty in LQTS 2 and 3 (in LQTS 3, it is somewhat later than in LQTS 2). These observations may affect the decision about when to start treatment. In particular, in asymptomatic LQTS 3 patients, it may be beneficial to delay the onset of treatment (which may involve ICD implantation). However, prospective studies are lacking, so in general practice prophylactic treatment is usually started immediately after the diagnosis is made.

Other gene-specific features relate to extracardiac features in LQTS 7 and 8. In LQTS 7 (‘Andersen syndrome’), these include episodic paraplegia, and facial and skeletal deformities. In LQTS 8 (‘Timothy syndrome’), syndactyly, congenital heart defects, and autism are found. In LQTS 4, atrial arrhythmias and sinus node dysfunction are part of the phenotype.

Finally, we recently described that the type of arrhythmia onset may also be gene-specific. That is to say, the hallmark tachyarrhythmia of LQTs, torsade de pointes ventricular tachycardia (VT), is most often tachycardia-dependent in LQTS 1 (Fig 1A), whereas in LQTS 2, it is almost always preceded by a pause, which gives rise to the typical short–long–short initiating sequence of RR intervals (Fig 1B). Whether these gene-dependent characteristics reflect gene-dependent arrhythmogenic mechanisms remains to be determined.

**Short QT-Interval Syndrome**

SQTS may be regarded as the mirror image of LQTS. Indeed, gain-of-function mutations in 3 LQTS-associated potassium-channel encoding genes have so far been found to cause SQTS. SQTS is a rare disease characterized by short QT-intervals on the ECG, short refractory periods throughout the heart, and a high arrhythmogenic potential (atrial and ventricular arrhythmias). Disease onset seems to be at a young age in the few families/individuals that have been described so far. The gain-of-function mutations cause an increased outward current during the plateau phase of the action potential with concurrent abbreviation of the action potential and the QTc interval.

Because the number of reported patients is still so small, information on possible gene-specific clinical properties and/or therapy is lacking. Quinidine has been shown to normalize (ie, lengthen) the QTc intervals in individuals with a KCNQ2 mutation (SQTS 1). Sotalol was ineffective, probably because the familial mutation in the reported family resided in the sotanol-binding domain. Hence, the lack of effect may be family-specific. In general, ICD therapy is currently considered the only effective treatment.

**Brugada Syndrome**

BS was first described in 1992 by Pedro and Josep Brugada as a clinical entity consisting of right bundle branch block, right precordial ST segment elevation and SCD. In recent years, it is increasingly recognized as a familial arrhythmia syndrome, particularly prevalent in South-East Asia and Japan, with a presumably high prevalence of SCD. The ECG signature of the syndrome is the right precordial ST segment elevation. Right bundle branch block may be present, but is not mandatory. Instead, conduction delay can be present at different cardiac levels, evidenced by prolonged PR intervals, abnormal electrical axis and, frequently, right ventricular conduction delay. BS patients are not often symptomatic (presyncope and syncope). On the other hand, SCD is, unfortunately, not infrequently the first manifestation. SCD may also be present in family members.

The diagnosis is based on the presence of the above-described ECG signature, either spontaneously or after drug infusion, and 1 or more clinical parameters which include documented ventricular fibrillation (VF), self-terminating polymorphic VT, a family history of SCD (<45 years of age), coved-type ST segment elevations in family members, inducibility of ventricular tachyarrhythmias during electrophysiological study (EPS), syncope or nocturnal agonal respiration. In the absence of one of these factors, the ECG is referred to as Brugada pattern. There should be no other factor(s) that can account for the ECG abnormality.

In the absence of typical ECG changes at baseline, the precordial leads may be placed in higher intercostal spaces (3rd and, sometimes, 2nd), and several drugs may be used to unmask the required ECG pattern. These include class I antiarrhythmic drugs such as flecainide, amiodarone and procainamide, and, in Japan, pilsicainide. Ajmaline seems to be the drug with the best specificity/sensitivity.

The pathophysiological basis of the ECG changes is heavily discussed. The main theory revolves around the postulated heterogeneity in action potential morphology across the (right) ventricular wall (for review see Antzelevitch). In the presence of an abbreviated action potential in the epicardial layer and an unaffected action potential in the endocardial and mid-mural layers, electrotonic current will flow from endocardium to epicardium during the plateau phase. This will generate ST segment elevation in the electrodes that overlie this area. The differences in action potential morphology are most prominent in the right ventricular outflow tract, because the expression of relevant ion channels (the transient outward potassium current, Ito, in particular) differs between these regions, with the Ito channel being functionally most prevalent in the right ventricular outflow tract myocardium. An alternative theory considers right ventricular conduction delay as critically important. Long conduction delays are, however, needed to explain the right precordial conduction delay. For both theoretical explanations, clinical evidence has been provided over the years, but neither theory has been proven beyond doubt. In the end, a combination of both theories may turn out to be pertinent. Of particular relevance in this discussion is the recent evidence that some BS patients have subclinical structural cardiac abnormalities, which may escape routine clinical imaging modalities and only become evident with microscopy. In fact, all studied pathoanatomical samples of deceased BS patients to date harbor structural cardiac abnormalities. In South-East Asia and Japan, with a presumably high prevalence of SCD. The ECG signature of the syndrome is the right precordial ST segment elevation. Right bundle branch block may be present, but is not mandatory. Instead, conduction delay can be present at different cardiac levels, evidenced by prolonged PR intervals, abnormal electrical axis and, frequently, right ventricular conduction delay. BS patients are not often symptomatic (presyncope and syncope). On the other hand, SCD is, unfortunately, not infrequently the first manifestation. SCD may also be present in family members.

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In the absence of typical ECG changes at baseline, the precordial leads may be placed in higher intercostal spaces (3rd and, sometimes, 2nd), and several drugs may be used to unmask the required ECG pattern. These include class I antiarrhythmic drugs such as flecainide, amiodarone and procainamide, and, in Japan, pilsicainide. Ajmaline seems to be the drug with the best specificity/sensitivity.

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a SCN5a mutation have been described. All mutations harbor a loss of function effect (ie, less sodium inward current during the upstroke (phase 0) of the action potential).40 In the transmural heterogeneity theory, it is assumed that a loss of the plateau phase may ensue if reduced inward current is present to oppose a given amount of Ito. In the delayed conduction theory, reduced inward sodium current directly translates into reduced conduction velocity. The second gene was very recently identified in a family in which the gene defect was previously linked to a locus on chromosome 3, next to SCN5a.42 The gene product, GPD1L, seems to affect sodium channel function, leading to a decrease in current amplitude with similar consequences as described above.43 Very recently, 2 other genes, which both affect the amplitude of the calcium current, have been identified in individual patients. Biophysical data reveal a reduction in the calcium inward current which will also affect the duration of the action potential plateau phase.44

Another issue that is heavily discussed is the appropriate treatment of BS patients. Whereas there is consensus that symptomatic BS patients (including those who have been resuscitated) should receive an ICD, there is controversy on how to manage asymptomatic patients with a spontaneous type 1 ECG (coved-type ECG). Reported cardiac death risks vary among different studies, ranging from 1–2% to 14% at approximately 3 years of follow-up.45–47 Some authors use an EPS for risk stratification. According to these investigators, inducible patients are considered at high risk and are treated with an ICD, whereas non-inducible patients are considered safe and receive careful follow-up.48 However, others do not consider the EPS outcome as a parameter with sufficient predictive power and consider asymptomatic patients at low risk, based on relatively long-term follow-up data.46–47 A recent meta-analysis appeared to support the latter approach by showing that the EPS is not sufficiently predictive.48 In general, patients should be advised to refrain from using drugs that may elicit a type 1 ECG, and to seek medical attention in the case of fever.29,30 Hyperthermia has been shown to elicit a type 1 ECG and is not infrequently associated with malignant arrhythmias.

**Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)**

CPVT is an inherited arrhythmia disorder characterized by polymorphic VT or VF that is elicited by increased adrenergic tone. This syndrome was first described by the late Philippe Coumel and associates in the 1970s and more extensively in a seminal paper in 1995.49 Physical and/or emotional stress are the typical symptom triggers. Often, the disease presents in young children, and the family history is frequently characterized by premature SCD, which is associated with the above-mentioned, typical, triggers. When left untreated, the risk of SCD is quite high.50 The diagnosis is easily made by an exercise test or 24-h Holter monitoring. At baseline, bradycardia is usually observed.31 During exercise, isolated ventricular extrasystoles appear at a patient-specific heart rate. With ongoing exercise, the arrhythmias become more complex (ie, bigeminy, bidirectional VT and, occasionally, VF).50 Similar observations can be made on Holter recordings where, in particular, the relationship between the occurrence of arrhythmias and the heart rate should be studied.

Based on the causal genes involved, it appears that impaired cellular calcium homeostasis is central in this disorder. In the early years of this century, the human ryanodine receptor gene (hRyR2) and the calsequestrin gene (CASQ2), both key players in the calcium homeostasis of myocardial cells, were unmasked as causal genes for this disorder.52–54 The first gene was identified in various small families with many de novo mutations, and in a large Finnish family with autosomal dominant inheritance.52,53 A CASQ2 mutation was found in a large Bedouin family as an autosomal recessive trait.54 Calcium overload secondary to malfunctioning gene products underlies the arrhythmias.

The cornerstone of therapy is β-blocker treatment. In addition, lifestyle advice should be an integral part of therapy; in particular, the avoidance of strenuous exercise (eg, competitive sports). An ICD might be occasionally needed, but the β-blocker therapy should not be discontinued.

**Other Inherited Arrhythmia Disorders**

There are a few other arrhythmia syndromes that segregate as an autosomal dominant trait, including atrial fibrillation, sinus node dysfunction and/or atrial standstill. Ion channel genes seem to be involved with or without modifier genes. For atrial fibrillation the number of genes is rapidly increasing. At present, at least 4 genes have been shown to be causal, together with 3 loci with unknown genes (Table 1). Several of the identified genes encode for potassium-channel subunits (Table 1). Interestingly, somatic mutations in the gene encoding for connexin 40, the main atrial connexin and an important player in atrial conduction, have been recently detected in cardiac tissue of lone atrial fibrillation patients.55 The familial forms seem rather rare. Familial sinus node dysfunction is, not surprisingly, caused by a dysfunction of the pacemaker channel, but SCN5a may also be involved when present as compound heterozygous mutations (Table 1). Finally, isolated conduction disease has been linked to mutations in SCN5a and a number of other, as yet unknown, genes (Table 1).56

**Genetic Testing in Inherited Arrhythmia Disorders**

As discussed earlier the identification of causal genes for inherited arrhythmia syndromes has enabled the possibility of identifying asymptomatic carriers. This process, referred to as presymptomatic counseling, has been the subject of a lot of debate, in particular when it includes children, as will be the case for several of the primary arrhythmia syndromes (for review see van Langen et al57). There is a lack of relevant experience in the field of cardiogenetics, whereas geneticists and associated professionals do have experience with presymptomatic testing in neurological diseases and malignancies (neurogenetics and oncogenetics, respectively).57 The few studies performed in LQTS patients reveal significant psychosocial disturbances, in particular in parents of affected children.58,59 Before genetic testing becomes widely available in routine clinical practice, much more research in this field is needed.

The yield of molecular genetic testing varies between different diseases. It seems highest in LQTS, with a worldwide (mean) yield of 60–70%.60–62 With a proven familial nature (ie, more than 1 family member clinically affected and/or with a young (<40 years) deceased family member) the yield is significantly higher.52 Also, usage of the gene-specific features increases the yield.53 In BS the percentage is considerably lower, with a value somewhere between...
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20% and 30% SCN5a involvement.6 The impact of the recent identification of new genes in the latter disease entity remains to be established. For the other inherited arrhythmia syndromes no reliable numbers are available.

Summary

In recent years the molecular basis of many inherited arrhythmia syndromes has been unraveled and to date new causal genes are identified. The number of truly idiopathic arrhythmias is decreasing with every gene identified. Although small, the proportion of arrhythmias that are hereditary is not insignificant. In particular, these diseases underlie a substantial number of cases of premature sudden death, and identification of the causal genes allows for timely and tailored treatment of eventually affected family members (gene carriers). This development has also markedly increased the basic knowledge of ion channel physiology and pathophysiology and it is likely that many more patients (suffering from more common arrhythmia syndromes) will benefit from this development in future years.

References


