A Clinical Approach to Inherited Arrhythmias

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In the past decade, the discovery that cases of ventricular arrhythmias and sudden cardiac death (SCD) in young individuals potentially could be caused by an unrecognized genetic substrate has defined a new subset of cardiac conditions: inherited arrhythmogenic diseases (IADs). Although rare in clinical practice, these diseases are more common than previously thought. They represent a challenge for the arrhythmia specialist in terms of diagnosis and clinical management. The correct diagnosis of IADs, as well as the use and interpretation of the results of genetic testing, are not straightforward and require a specific expertise such as that provided by specialized and dedicated centers. Here we will review the general issues arising from the correct interpretation of genetic testing and its indications. We also will focus on the clinical management and use of genetic information in different inherited arrhythmias.

Cardiac Channelopathies

The term “channelopathies” defines a group of inherited arrhythmias syndromes caused by mutations on genes encoding for ion channel proteins and proteins that regulate ion channels. These mutations disrupt the balance of currents in the cardiac action potential, favoring the onset of life-threatening arrhythmias in the absence of structural heart defects.

The Long QT Syndrome

The long QT syndrome (LQTS) is a heritable channelopathy characterized by an exceedingly prolonged cardiac repolarization that may trigger ventricular arrhythmias and SCD. LQTS is one of the first channelopathies in which clinical and genetic features have been discovered, and a large series of patients have been collected and followed over the years. Thanks to these studies, LQTS management takes into account a patient’s genetic background and has become a paradigm for the use of genetic information applied to the clinical practice.

Clinical Characteristics and Diagnosis

Long QT syndrome can manifest with syncope and cardiac arrest. These commonly are triggered by adrenergic stress; however, roughly 10% to 15% of patients experience symptoms at rest or during the night. The mean age of onset of symptoms is 12 years, and earlier onset usually is associated with a more severe form of the disease.

The diagnosis of LQTS is based on the ECG and the measurement of the heart rate corrected QT interval (QTc). Cut-off values have been established based on the use of Bazett formula. Normally, QTc should not exceed >440 ms in males and >460 ms in postpuberal females. Additionally, patients affected by congenital LQTS show frequent abnormalities in the T wave morphology (Figure 1), ie, diphasic T waves, notches, low amplitude, or very slow onset. Macroscopic T wave alternans is rare, but it correlates with poor prognosis. The evaluation of QT interval duration during the diagnostic process requires a trained eye and the availability of several examples at different heart rates. To avoid over- or underestimation, we suggest measuring the QT interval and choosing traces in which the RR interval is constant for at least 10 to 20 beats. Considering the limitation of Bazett formula, that it is nonlinear at fast or slow heart rates, we prefer to exclude from the evaluation traces with heart rate >100 bpm or <50 bpm.

The QT interval is the most important indicator of risk. Patients who present with QTc >500 ms repetitively are considered at high risk for arrhythmias and SCD.

The syndrome can present with incomplete penetrance, and 10% to 35% of genetically affected patients show a normal QTc interval despite being genetically affected by the disease (Figure 2). The identification of these individuals within a family often can be established only through genetic testing; the clinical value of identifying silent carriers is based on the evidence that these patients may experience arrhythmic events. In our series of patients, approximately 10% of silent carriers of a disease-causing mutation experienced symptoms mainly when they were treated with QT prolonging drugs.

The first therapeutic approach for all patients is β-blocker therapy. Using the evidence that 10% of silent gene carriers are at risk of cardiac events in spite of presenting with normal QT intervals, and LQTS patients remain at risk of experiencing symptoms after age 40, we initiate prophylactic
β-blocker therapy at the time of diagnosis. No data are available to establish if there are differences in the efficacy of different β-blockers, nor are systematic dose-response curves available. It is our practice to preferentially use nadolol (with a dose of 1 mg/Kg/d) over other β-blockers given its long half-life and efficacy. In the presence of recurrent symptoms while on therapy or in high-risk patients, an implantable cardioverter-defibrillator (ICD) should be considered.4

Genetic Substrate
Long QT syndrome presents with 2 different modes of transmission.1 The autosomal dominant form (Romano Ward syndrome) is the most common. The rare autosomal recessive form (Jervell-Lange-Nielsen syndrome) is associated with concomitant neurosensorial deafness. Only 2 genes (KCNQ1 and KCNE1) have been linked to this form and should be suspected if consanguinity is present in the family in addition to deafness.10

The list of LQTS genes causing the autosomal dominant variant is expanding constantly, and currently totals 13 genes.1,10,11 All encode for ion channel proteins or for proteins such as chaperons and modulators that regulate ion channels. Therefore, the final common consequence of LQTS mutations is the disruption of 1 or more ionic currents of the cardiac action potential, ultimately resulting in abnormally prolonged repolarization. Despite the remarkable heterogeneity...
of LQTS, the 3 forms that were first described (LQT1, LQT2, and LQT3) account for >90% of genotyped patients (Table 1). These 3 forms represent the variants from which it has been possible to perform genotype-phenotype correlations and genotype-based risk stratifications studies. Mutations on the KCNQ1 gene encoding for the α-subunit of the channel for the IKs repolarizing current cause LQT1. The LQT2 form is linked to mutations on the gene KCNH2 for the α-subunit of the channel for the IKr repolarizing current. In both cases, mutations cause a loss of function in the protein, leading to reduced repolarizing potassium current. The LQT3 variant is caused by mutations on the SCN5A gene encoding for the alpha subunit of the cardiac sodium channel. These mutations increase the late INa depolarizing current, thus ultimately resulting in prolonged action potential duration.

**Genotype-Phenotype Correlations**

Initial observations noted that T waves in LQTS patients showed gene-specific differences. This prompted investigators to study if additional specific differences could be identified among LQT1, LQT2, and LQT3, and applied to the clinical practice. It was discovered initially that triggers for cardiac events are different among the 3 forms. LQT1 patients have the highest incidence of arrhythmic events during exercise. LQT2 patients are more sensitive to strong emotions, particularly to startling noises. LQT3 patients experience most of their events at rest or during sleep. However, it is important to keep in mind that overlap may exist and that these data are only 1 of the parameters to be taken into account in the patients’ evaluation. The evaluation of genotype/phenotype correlations in our large Italian population highlighted that genotype is an independent risk predictor (Figure 3), and also may influence the response to treatment with β-blockers. The 2 studies showed that, although LQT1 patients respond very well to β-blockers (Figure 4), in patients with LQT2 and LQT3 arrhythmic events recur more frequently despite β-blockers. The influence of the genetic substrate on the clinical course of LQTS also has been availed by the American College of Cardiology, American Heart Association, and European Society of Cardiology 2006 Guidelines for the prevention of SCD. That sparked the consideration of ICD implantation as primary prevention of cardiac arrest for LQT2 or LQT3 patients with QTc >500 ms. It is, however, our advice that physicians use a multiparametric and individualized approach in the assessment of their patients and avoid using genotype as the only indicator of risk. Accordingly, a patient with LQT1 and a very prolonged QT interval is most likely at higher risk of life-threatening arrhythmias than an individual with LQT3 and a borderline QTc.

Novel therapeutic approaches targeting the genetic defect also have been proposed. Considering the incomplete protection afforded by β-blockers in LQT3 and the reduced influence of adrenergic stress as an arrhythmic trigger, sodium channel blockers, such as mexiletine or flecainide, were suggested as potential therapy. Initially, the use of sodium channel blockers in all LQT3 patients was considered of potential benefit, though it later became evident that not all LQT3 patients respond to mexiletine with QTc shortening. In vitro studies demonstrated that specific mutations have different responses to the drug, suggesting that in vitro testing of the response to sodium channel blockers might be helpful to guide management of LQT3 patients. These studies in cell systems are among the first to demonstrate the role bench studies can have in the clinical assessment of inherited arrhythmias toward tailoring appropriate treatment to each individual.

It is worth highlighting that given the small number of LQT3 patients at present time there is no evidence that therapy with sodium channel blockers influences outcome in this group.

**Indications and Use of Genetic Test in Long QT Syndrome**

Genetic testing is especially useful in LQTS in the presence of a clear clinical phenotype. If the patient shows a prolonged...
QTc, the identification of the specific genotype can orient treatment and risk stratification. As an example, the effectiveness of β-blockers in controlling recurrent arrhythmic episodes is higher in LQT1 patients (Figure 4), whereas a QTc >500 ms, a history of symptoms, and a LQT2 or LQT3 genotype may prompt a more aggressive approach.4

Due to the incomplete penetrance of LQTS, the use of genetic testing to diagnose silent gene-carriers among family members is highly recommended. In the same perspective, genetic test also can identify those family members who are not carriers of the disease, providing a conclusive diagnosis and limiting the need of periodic clinical evaluations and prophylactic therapy.

More blurred are the indications for genetic testing in borderline cases, where the yield of the test is low and the absence of a mutation is not sufficient per se to exclude the diagnosis. Additionally, the yield of the test in diagnosing the newer and rarer LQTS variants, beyond LQT1, LQT2, and LQT3, is still low, and the interpretation of the results remains challenging (Table 1).

An emerging issue is the correct interpretation of the effect of novel unreported variants and their potential to cause the phenotype. In this perspective, data from the literature, functional studies, and cosegregation of genotype/phenotype in large pedigrees when available are all elements that one should consider when assessing the significance of a genetic test.

The Brugada Syndrome

In the early 1990s, Pedro and Josep Brugada described a new disease characterized by familial transmission, structurally normal heart, and high incidence of ventricular arrhythmias and SCD, which now bears their name.18 The Brugada syndrome (BrS) is an IAD characterized by a peculiar surface ECG and arrhythmias mostly occurring at rest, during sleep, in the presence of fever, and after large meals.19,20 As described below, it is a condition that continues to puzzle electrophysiologists and cardio-geneticists because of its challenging diagnosis and treatment.

Clinical Characteristics and Diagnosis

The BrS is characterized by arrhythmias mostly occurring at rest or during sleep. Patients present with ST-segment elevation in the right precordial leads, often in the presence of right bundle-branch block on the surface ECG, in the absence of acute cardiac ischemia.18 The ST segment morphology, considered diagnostic, is indicated as type 1 and presents a “coved” aspect21 (Figure 5). However, the patterns indicated as type 2 (saddle-back, elevation >2.5 mm) or type 3 (coved or saddle-back with ST elevation <2.5 mm) should be considered suspect for the disease21 and prompt medical attention.

One of the challenges in recognizing BrS is the transitory nature of the ECG pattern as it is often intermittent and difficult to detect in a single ECG tracing (Figure 5). For that reason, to diagnose affected patients, 12-lead ECG Holters should be performed, allowing for prolonged monitoring of the right precordial leads.

A diagnostic pattern may be unmasked by the infusion of sodium channel blockers flecainide, procainamide, and ajmaline.21,22 Different reports suggested that ajmaline and flecainide might have increased sensitivity in unmasking Brugada syndrome if compared with procainamide, which is the only injectable sodium channel blocker available in the

Figure 4. Different event-free survival in β-blocker therapy in catecholaminergic polymorphic ventricular tachycardia (CPVT) and in long QT 1, showing the high rate of recurrences in CPVT. Data are derived from the authors’ database TRIAD (Transatlantic Registry of Inherited Arrhythmogenic Diseases).
United States. To shed some light on this controversy, a Food and Drug Administration approved evaluation aimed to compare the diagnostic sensitivity of flecainide versus procainamide infusion is now ongoing in our center.

The type 1 pattern also may appear after abundant meals or during fever, both of which have been indicated as potential arrhythmic triggers. Supraventricular arrhythmias and atrial fibrillation are common also.

The disease has autosomal dominant transmission. Despite 50% of the carriers of disease-causing mutations being female, the vast majority of clinically affected patients are men, even though it is still unknown how gender influences the manifestation of the disease.

At variance with other IADs, symptoms tend to not manifest in childhood, but they appear in the second to third decade, and the arrhythmic risk then remains prevalent throughout adulthood. Family history for cases of sudden death during sleep in young men may direct the diagnosis.

At present, no medical therapy has proven effective in BrS, and the only treatment remains the ICD implant. Quinidine has been proposed as a potential therapy based on preliminary encouraging data showing that it could reduce the incidence of inducible ventricular tachycardia (VT)/ventricular fibrillation (VF) and ICD shocks in a subset of patients. Two clinical trials are now ongoing to test the effect of quinidine in BrS (NCT00789165 and NCT00927732). Awaiting more conclusive evidence on the efficacy of quinidine, its use is currently limited to ICD carriers experiencing repeated appropriate device therapies.

Risk stratification is based on clinical parameters, and the results of genetic testing at present time do not contribute to the risk stratification process. The combined presence of history of syncope with the presence of a spontaneous type 1 ECG is considered a marker of higher risk of SCD. Patients presenting with type 1 ECG only during pharmacological challenge are at lower risk to experience symptoms. Neither a family history, nor the presence of a mutation in the SCN5A gene have been shown to be risk indicators. The predictive value of programmed electric stimulation has been initially controversial, however, several recent studies on different series of patients agreed that it should not be used as a parameter for risk stratification. The multicenter prospective PRELUDE study, led by our group, recently has confirmed the limited predictive value of programmed electric stimulation in a large series of BrS patients, who all underwent the same stimulation protocol.

Genetic Bases and Genotype-Phenotype Correlations

Only an exiguous number of BrS patients are genotyped successfully. At present, 7 genes have been linked to the disease, but altogether mutations are detected in only 25% to 30% of patients (Table 1). Among the causative genes, 2 account for the majority of genotyped patients: SCN5A and \( \text{CACN1Ac} \). Other less represented genes (\( \text{SCN1B} \), \( \text{SCN3B} \), and \( \text{GPD1-L} \)) causing BrS participate in the regulation of the sodium current, which has been shown to play an important role in the pathophysiology of the disease. The second most prevalent BrS gene is \( \text{CACN1Ac} \), encoding for the \( \alpha \)-subunit of the cardiac calcium channel. Few cases have been attributed also to mutations on the \( \text{CACNB2} \) gene, encoding for the \( \beta \)-subunit of the same channel. In both cases, mutations cause a loss of function that reduces the current. Interestingly, loss of function mutations on these genes also have been associated with another IAD, the short QT syndrome (SQTS). An intermediate phenotype sharing features of both diseases has been reported as well.

Genotype-phenotype correlation studies have provided limited results in the setting of BrS; therefore, as of today the presence or absence of a mutation does not exert a prognostic role nor contribute to the selection of treatment.
identified hallmark of the presence of a mutation on the SCN5A gene is the higher incidence of conduction defects.37

Patients carrying mutations on the genes encoding for the calcium channel subunits, on the contrary, tend to have an abbreviated repolarization and usually present a QTc <360 ms.35

Indications for Genetic Test
Genetic testing in BrS has the general indications to allow diagnosing of affected family members and allowing prenatal and reproductive counseling.

When the test is positive, extension to family members is very useful as it allows identifying affected individuals with a concealed clinical phenotype or to exclude non-carriers. However, as in all IADs, a negative genetic test cannot exclude the clinical diagnosis as it simply indicates that the currently identified genes are not abnormal in a given patient.

The Short QT Syndrome
One of the latest channelopathies to be reported is the SQTS, characterized by an abnormally reduced cardiac repolarization (Figure 1) that is associated with a high incidence of arrhythmias and SCD. Its description in 200038 introduced the concept that genetic alterations that affect cardiac repolarization, either prolonging or reducing its duration, result in increased arrhythmogenesis.

Clinical Characteristics and Diagnosis
The first SQTS family was described in 2000.38 As is common in all new conditions, these first cases fall into the extreme spectrum of clinical manifestations, and the QTc interval found in the early families was often <300 ms. With the increase of symptomatic patients diagnosed with short QT, the cut-off for the definition of QTTS has been raised to values between 340 to 360 ms (Figure 1). Most patients show tall, peaked, and narrow T waves, with an almost absent ST segment and a relative long Tpeak-Tend interval.39 Analogous to measuring the QT interval in LQTS, isolated recordings are not sufficient for the diagnosis, and the QTc should be measured in several instances, at different values of HR, and mostly around 60 bpm.

Short QT syndrome patients have a high incidence of atrial fibrillation and supraventricular arrhythmias, which also are reported to occur in children.40 In several cases the first manifestation of symptoms is cardiac arrest, and a family history of SCD is frequent.

The electrophysiological study can help in the diagnostic process because SQTS patients tend to present with very short atrial and ventricular refractory periods, and it is common to induce ventricular tachycardia by mechanical contact of the catheters.40

Genetic Bases and Indications for Genetic Testing
When the SQTS was described initially, investigators tested if the same genes implicated in the LQTS also could have a role in the pathogenesis of the SQTS. Indeed, mutations on 2 LQTS genes, KCNH2 and KCNQ1, were found in patients affected by SQTS.41,42 In vitro functional studies revealed that SQTS mutations determine a gain of function of the IKr or IKs channel, respectively, thus increasing the repolarizing potassium current and shortening repolarization. Therefore, as in the case of LQT3 and BrS, the SQTS and LQTS are allelic diseases. In 200543 our group identified the KCNJ2 gene, which encodes for the channel for the inward rectifier IK1 current, as the third gene that causes SQTS. Interestingly, in the first patients identified with SQT3 the T wave morphology differed from that described for the other 2 forms of SQTS, showing an asymmetrical shape, with a normal ascending phase followed by a rapid terminal end.

At present, very few SQTS patients have been diagnosed and genotyped (Table 1); therefore, genetic testing contributes to clinical management to confirm the diagnosis and to facilitate identification of affected family members.

Catecholaminergic Polymorphic Ventricular Tachycardia
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a peculiar channelopathy linked to mutations on genes implicated in the regulation of intracellular calcium homeostasis.44,45 The study of the disease and of its arrhythmogenic mechanisms recently has provided important advancements that also could be applied to acquired cardiac conditions presenting with calcium disregulation.

Clinical Aspects and Diagnosis
Catecholaminergic polymorphic ventricular tachycardia manifests with stress-induced syncope and cardiac arrest, leading often to SCD.44,46,47 Occasionally, idiopathic VF also could be the first clinical manifestation of the disease. The mean age of onset of symptoms is approximately 12 years.47,48 These common clinical features often raise issues of differential diagnosis between CPVT and LQTS with modest prolongation of QT interval. The importance of distinguishing between the 2 diseases, however, centers on the evidence that CPVT patients have more severe clinical manifestations than LQTS and present a reduced response to β-blockers.44 (Figure 4). Additionally, in CPVT, the role of adrenergic stress in triggering symptoms is even more relevant than in LQTS because the occurrence of cardiac arrest at rest is an unusual event in CPVT.

At variance with LQTS, most CPVT patients become symptomatic, and therefore the penetrance of the disease is higher than that of LQTS. In our historical population of patients we observed that in the absence of medical therapy, 80% of patients are symptomatic before age 40.49

In CPVT patients, baseline ECGs are unremarkable, while the morphology of arrhythmias is peculiar and may orient the diagnosis. The disease is characterized by bidirectional VT, a tachycardia in which the QRS complexes of the ectopic beats have a 180° rotation on the frontal plane (Figure 6). Polymorphic VT is common, too, while monomorphic VT is much less frequent.47

Despite the fact that the lack of signs in the surface ECG may affect the diagnosis, the arrhythmias easily are reproducible during exercise stress test in the majority of patients (Figure 6). There is a typical pattern of arrhythmia development during exercise that progresses from the occurrence of supraventricular and ventricular beats or couplets toward the
development of bidirectional polymorphic VT. Arrhythmias usually promptly decrease at the interruption of exercise. Interestingly, supraventricular arrhythmias and short runs of atrial fibrillation are common and may facilitate the onset of ventricular arrhythmias. For this reason, exercise test and Holter monitoring are important diagnostic tools and also are useful to monitor the course of the disease and the antiarrhythmic efficacy of medical therapy.

The mainstay of treatment of CPVT is represented by β-blockers. Even though therapy often is increased to the maximal tolerated dose, the incidence of recurrences is high, around 30% to 40% (Figure 4), and therefore consideration of additional treatments becomes indicated.47,49 Considering the high lethality of the disease, and the evidence that often SCD may be the first manifestation, CPVT is an IAD in which the use of ICD in primary prevention often is considered when β-blockers fail to control arrhythmic episodes. Recent studies derived from experiments in animal models suggest that flecainide could be an effective addition to β-blockers in limiting β-blockers leakage from the SR either by loss of the binding capacity or by altering RyR2 open probability.

Even though the disease has a genetic etiology, most reported cases are sporadic. This could be attributed to its high lethality and to the fact that patients may not reach reproductive age unless correctly diagnosed and effectively treated. When the disease is observed in familial cases there often is family history for juvenile SCD during adrenergic stress that may help in the diagnosis.

**Genetic Bases and Indication to Genetic Testing**

Catecholaminergic polymorphic ventricular tachycardia can present with an autosomal dominant or with an autosomal recessive transmission. Our group identified in 2001 the gene involved in the more common, dominant form of CPVT, the *RyR2* gene, which encodes for the cardiac ryanodine receptor. It is the main protein controlling the release of calcium from the sarcoplasmic reticulum (SR) during the cardiac excitation-contraction coupling.44 The rare, recessive form is caused by mutations on the *CASQ2* gene, coding for calsequestrin, a protein that controls SR calcium by binding free calcium ions.45 Investigators were prompted in exploring genes coding for SR proteins as a potential substrate for CPVT by the morphology of arrhythmias. As a matter of fact, bidirectional VT initially was observed during digitalis toxicity, a condition in which patients experience calcium overload. The discovery of the genetic bases of CPVT suggested its arrhythmogenic mechanisms, and the study of knock-in mice demonstrated that in CPVT, as in digitalis toxicity, delayed after depolarizations-induced triggered activity underlies the arrhythmias.53,54

Mutations on RyR2 cause dysfunction of the channel that becomes more prone to release calcium from the SR in the diastolic phase, thus favoring development of delayed after depolarizations. Similarly, *CASQ2* mutations cause calcium leakage form the SR either by loss of the binding capacity or by altering RyR2 open probability.

Among IADs, CPVT is one in which the yield of genetic testing is encouraging, with values of 60% to 70% positive results in the presence of clinical phenotype55 (Table 1; Figure 7). Once more, extending genetic testing to family members allows the identification of gene carriers before they begin developing symptoms, thus allowing the initiation of β-blockers. Gene testing also may be useful for prenatal diagnosis and reproductive counseling. Considering the malignancy of this condition, the possibility of starting prophylactic treatment based on the genetic diagnosis bears important implications in the management of a patient’s family.

Mutations on the *RyR2* gene also have been discovered in cases of stress-related idiopathic VF,56 even if in these cases a positive outcome of the test is less likely.58 In the absence of clinical signs pointing toward a specific condition that could have caused the adrenergic-mediated cardiac arrest, screening on this gene may represent a reasonable approach.

Because RyR2 is one of the largest human genes, with 105 exons, it has been advocated59 to limit sequencing of the gene only to the regions that account for most of the identified mutations. However, data from our laboratory showed that among 82 RyR2-positive probands, 14% of the probands had mutations outside the regions conventionally examined.57 Family screening in these cases identified 4 additional gene
Genetic testing generally produces a good yield in CPVT, with an average cost of $9170 per positive test, reduced to $5263 when the clinical diagnosis is conclusive. However, its use in borderline situations, in the absence of strong clinical indicators, is less advisable, considering that the probability of a positive result could decrease from 62% to 5%.

On the other hand, considering the low yield of genetic analysis in Brugada syndrome, the cost per positively genotyped individuals is higher than that of other IADs; therefore, genetic screening mainly is justified in cases with clear clinical presentations to improve the chances of a positive outcome.

Conclusions
The clinicians’ ability to better care for patients continues to improve as novel genes continue to be identified. The limiting factor, which was once lack of data, now seems to be shifting to the costs of testing. Further understanding of the genotype-phenotype correlations not only assists in improvements in treatment, but more importantly, prevention. The clinicians’ understanding of the importance of genetic testing in not only diagnosis but in risk stratification, and treatment is paramount. This new knowledge emphasizes the need of a specialized expertise in the field of cardiovascular genetics to manage complex information derived from the clinic, as well as from the basic research laboratory to grant the patients all the benefits linked to the genetic results.

Disclosures
None.

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