Long-QT syndrome (LQTS) has been the first inherited arrhythmogenic syndrome to be extensively characterized in clinical cardiology. Its genetic bases were disclosed in the early 1990s by Keating’s group, opening the field of molecular arrhythmology.1–3 The publication of Keating’s works generated a great deal of excitement among those involved in the care of LQTS patients because it became clear that the possibility of identifying in the clinic the DNA variants that cause LQTS would affect the clinical management of families affected by the disease.

A major breakthrough in the application of clinical genetics to clinical practice came shortly after the discovery of the genes for the 3 most prevalent variants of the disease (ie, LQT1, LQT2, and LQT3) when Moss and colleagues4 showed that the morphology of the ST-T–wave complex presents a remarkably distinctive shape in each of the genetic variants of LQTS. This study generated the view that LQTS is not 1 disease but rather represents a group of pathologies characterized by prolongation of cardiac repolarization that are caused by different genes and therefore should be regarded as distinct entities. The publication of this seminal article stimulated the search for genotype-phenotype correlations that dominated the field for the subsequent 15 years.

Investigators around the world started performing genetic testing in LQTS families and describing the distinguishing clinical manifestations of patients with mutations in each of the 3 key genes. Among the pivotal observations that have shaped the field is the report by Schwartz et al5 that showed that each genetic variant of LQTS has a distinguishing trigger for initiation of life-threatening arrhythmias. The study showed that patients affected by LQT1 are more prone to develop arrhythmias during physical exercise, whereas patients with LQT2 have most of their events during emotional stress and patients with LQT3 become symptomatic at rest and during sleep. Data from Wilde et al6 added to this concept, showing that in the LQT2 subgroup auditory stimulation is often a trigger for cardiac arrest. Similarly, Ackerman and coworkers7 reported that, among all physical activities, swimming is associated with higher risk of cardiac events in LQT1 patients.

The next challenge in the assessment of genotype-phenotype correlations was the investigation of the severity of clinical manifestations for each genetic form of LQTS. In 2003, we reported a very large cohort of patients genotyped as LQT1, LQT2, and LQT3 and searched for independent predictors of cardiac arrhythmic events.8 Our data showed that the duration of the corrected QT interval is the most important metric for risk assessment and that the genetic background is the next major factor that determines the likelihood of having life-threatening arrhythmias in the first 40 years of life. The evidence that the severity of the disease is influenced by the genetic substrate prompted the question of whether the molecular substrate also could influence the response to therapy.

An early study from Vincent et al9 observed that patients with LQT1 have a better response to β-blockers than patients with other genetic forms of LQTS. We expanded on this observation and in 2004 reported data on 335 genotyped LQTS patients showing that failure of β-blockers to prevent arrhythmias was observed more frequently in patients with early onset of symptoms (first manifestations before 7 years of age) and in patients with LQT2 and LQT3.10

Overall, the 10 years between 1995 and 2005 were characterized by extensive investigation of the differences among the genetic variants of the disease. This collective effort produced solid data that allowed revising the risk stratification and management of LQTS in light of the genetic background. Some of the concepts expressed in those studies were incorporated into guidelines for clinical practice.11,12

Once again, the innovative Dr Moss and his team made a further step and ventured into the investigation of whether the position of a mutation within a given gene would allow more accurate risk stratification and more refined genotype-phenotype correlation. Since 2002, studies from the International Registry of LQTS have highlighted that the location of a mutation in the KCNH213 or the KCNJ144 gene is associated with severity. An interesting finding of this research was the identification that mutations in the transmembrane domain region of the 2 channels were more malignant than mutations localized in other areas. These data provided some hints for the identification of those patients who, despite being in the lower-risk category of LQT1, still manifest with a severe form of the disease.

When we look at the field today, in light of the advancements made and with the understanding of their limitations, it becomes clear that to further refine the ability to define...
genotype-based prognostic metrics, we need to characterize the severity of individual mutations. Although this personalized approach might remain out of reach for quite some time, we could certainly approximate this target by defining the arrhythmic risk in clusters of mutations based on several features such as their position or the type of amino acid replacement.

In this issue of the Circulation, Barsheshet et al.15 present interesting data in support of the view that within the cDNA sequence of the KCNQ1 gene there are 44 amino acids (between residues 171–195 and 242–262) that, when replaced, confer a much higher risk of death than almost any other mutation in the gene. The study is intriguing in that it represents an attempt to identify higher-risk individuals in the lower-risk population of LQT1 patients. It should be noted, however, that the number of patients affected by mutations in such a restricted portion of the gene, which corresponds to 7% of the entire coding region, is likely to be small. The “vulnerable” region identified by the authors corresponds to the cytoplasmic loops (C loops) that group the 2 intracellular linkers between the transmembrane domain S2 to S3 and S4 to S5 in the predicted topology of the protein (the Figure).

The relevance of this KCNQ1 region in arrhythmogenesis has been well described in an important evolutionary study that compared the distribution of pathogenic mutations in KCNQ1 and in KCNH2.16 That study provides compelling evidence that although arrhythmogenic mutations are localized mainly in the pore region and in the extracellular loops in KCNH2, they preferentially localize in the pore region and in the intracellular loops in KCNQ1. The percentage of KCNQ1 mutations located in the small C-loop region is hard to define; it likely corresponds to a small proportion of probands. According to the Gene Connection for the Heart database (www.fsm.it/cardmoc), of 357 KCNQ1 mutations, only 54 (15%) are in the C loop (Figure 1); this number confirms the estimate reported in the study by Barsheshet et al.15 A most interesting part of the study relates to the in vitro characterization of KCNQ1 mutations. Functional investigations performed by the authors show that, analogous to what observed in all LQTS-related mutations in the KCNQ1 gene, the I _Ks_ current is decreased in all the C-loop mutations. However, the novel finding is the evidence that, on exposure to forskolin, which mimics adrenergic activation, only C-loop mutations fail to increase I _Ks_. The inability of C-loop mutations to increase I _Ks_ during adrenergic activation supports the view that these mutations may be particularly malignant because, besides inducing a marked prolongation of QT interval at rest, they worsen QT duration during adrenergic activation. This hypothesis is indeed fascinating, even if it remains unclear why mutations located outside the C loop do not have a blunt response to adrenergic stimulation even if in patients they also present an inability to shorten QT interval during exercise.

Despite being innovative, the mechanistic interpretation of the malignancy of C-loop mutations provided by Barsheshet et al.15 needs to be taken with a word of caution given that in vitro functional characterization of mutations may yield different results when performed in different laboratories. For example, when expressed by Chouabe et al.17 the R190Q mutation was unable to form functional homomeric channels. Of course, such an observation does not support the explanation that this mutation has an attenuated response to adrenergic stimulation.

In conclusion, the study by Barsheshet et al.15 represents an important step toward refining risk stratification for LQT1 patients based on the information provided by molecular genetics. The study raises some controversies compared with previously published data and provides an opportunity for expressing an important methodological consideration. As we approach the ambitious goal of establishing clinically applicable risk stratification schemes that affect patients with life-threatening conditions in uncommon arrhythmogenic diseases, we should discuss how to ensure that only robust and reproducible data18 are incorporated into clinical practice. For example, it may be proposed that only findings that are concordantly reported by >1 registry should enter recommendations for patients’ management. In this respect, we should support the existence of at least 3 or 4 independent worldwide databases for inherited arrhythmogenic diseases so that the field would be ready for cross-validation of results as new hypotheses are advanced. Such an approach would lead to the introduction of robust data in the clinics to the benefit of patients and their families.
Disclosures

None.

References


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