Commentary
Clinical applicability of molecular biology: the case of the long QT syndrome
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Abstract

The clinical applicability of molecular cardiology has been questioned at length and by many clinical investigators. The congenital long QT syndrome (LQTS) provides an excellent example of how tight the relationship can be between molecular biology and clinical cardiology. The advent of molecular diagnosis has demonstrated how low the penetrance can be in LQTS; this implies that there are many gene carriers who do not show the clinical phenotype and may have a normal QT interval despite being at risk. There is also a gene-specific predisposition to be at risk for cardiac arrest under different circumstances, and this provides additional basis for a gene-specific approach to therapy.

Keywords: genetics, long QT syndrome, molecular biology, sudden death

Introduction
When the initial excitement for molecular biology settled down, we all faced the same question: what about clinical applicability? There are, as a matter of fact, numerous examples of the clinical applicability of molecular biology but one of the most impressive is certainly represented by the leading cause of sudden death below age 20, namely the congenital LQTS. Indeed, LQTS probably represents the best example so far of how molecular biology can modify the traditional clinical approach and allow a more sophisticated clinical management tailored toward the specific, genetically controlled, characteristics of each patient.

This brief essay will first review the current information on the LQTS genes and will then discuss how this new wealth of knowledge is affecting the diagnostic and therapeutic process.

LQTS genes
Six loci have so far been related to LQTS, and five genes have been identified. Two of these genes, *KCNE1* and *Mirp1*, respectively responsible for LQT5 and LQT6, are rare. The most common forms, respectively responsible for LQT1, LQT2, and LQT3, depend on mutations on *KvLQT1* (encoding the I_{Ks} current), on *HERG* (encoding

LQTS = long QT syndrome.

the I$_{Kr}$ current), and on *SCN5A* (encoding the Na$^+$ current). The data available for genotype–phenotype correlation studies on adequate numbers are limited to LQT1, LQT2, and LQT3. A new terminology has therefore now to be used in order not to miss these differences that are important for a molecular understanding of the underlying defects and mechanisms, and for a more specific and effective clinical management [1–4].

Diagnosis

The cornerstone of the diagnosis of LQTS has always, and dutifully so, been represented by the presence of a prolonged QT interval on the electrocardiogram. This was always an integral part of the diagnostic criteria proposed in 1985 [5] and later in 1993 [6]. It is true that, in 1980 [7] and then again in 1985 [5], it had already been proposed that patients affected by LQTS who had a normal QT interval must have existed. This unorthodox hypothesis was received with skepticism and, despite growing supportive data, was eventually proven correct when our group provided conclusive evidence for low penetrance in LQTS [8]. Penetrance represents the percentage of gene carriers who show the clinical phenotype of any given genetic disease. Penetrance for LQTS had been generally assumed to be close to 90%, thus implying that very few gene carriers could exist without showing the main clinical characteristic, namely QT prolongation. We studied nine genotyped probands who were considered 'sporadic cases of LQTS' (ie no other member of these nine families was thought to be affected by LQTS), and 46 family members considered to be 'non-affected'. Four of nine probands proved to have *de novo* mutations, thus confirming the clinical impression that they were indeed 'sporadic' cases of LQTS. In the remaining five families, however, several other members were found to be gene carriers. Penetrance in these families ranged between 14 and 33%, thus suggesting that, at least in some families, there are two to four additional individuals who are gene carriers for each patient identified as clinically affected.

This finding has major clinical implications. When visiting members of a LQTS family and, for example, when discussing with the parents of a truly affected child the clinical status of some of his/her siblings with a normal QT interval, it will no longer be possible to state, based on clinical data alone, that they are 'certainly not affected by LQTS'. This has *per se* become a most important reason to attempt genotyping in all LQTS probands (the proband is the first family member seeking medical attention). In the 50–60% of patients in whom genotyping will be successful (by current standards), it will become easy, fast, and cheap to screen for the culprit mutation in all the remaining family members. The silent gene carriers, who certainly have a reduced 'repolarization reserve' [9], should avoid conditions that produce hypokaliemia or drugs that block I$_{Kr}$. This concept creates a novel responsibility for their

physicians, who should now alert these individuals to the large number of drugs, cardiac and non-cardiac, that block potassium currents.

Therapy

The recent realization that the arrhythmogenic 'triggers' (conditions associated with the onset of cardiac events, such as syncope or cardiac arrest or sudden death) are, to a large extent, gene specific will lead to specific management strategies aimed at reducing the risk of major cardiac events. The data come from a unique cooperative effort [10] based on almost 700 patients of known genotype, and all with prior cardiac events. The same study investigated the efficacy of beta-blockers.

Three main arrhythmogenic triggers were defined at the outset of the study: exercise, emotions, and rest/sleep without arousal. The analysis focused on the three major subgroups, LQT1 ($n = 371$), LQT2 ($n = 234$), and LQT3 ($n = 65$), and striking differences emerged.

LQT1 patients had almost all of their events (88%) during conditions associated with increased sympathetic activity, especially during exercise (62%). When the analysis was limited to lethal events, exercise accounted for 68% of the patients. There is specificity also within the different types of physical activity. Indeed, 33% of the cardiac events suffered by LQT1 patients occurred while swimming. Conversely, 99% of the LQTS patients suffering cardiac events while swimming did belong to the LQT1 subgroup. Besides the direct clinical implications, this finding strengthens the concept that reduction or block of the I$_{Ks}$ current predisposes to life-threatening arrhythmias under conditions of increased sympathetic activity [11]. On this basis, it follows that competitive sports should not be allowed for LQT1 patients, and that they should avoid strenuous exercise, with special attention to swimming.

It came as no surprise when this analysis was completed that beta-blockers were particularly effective in this large subgroup. Indeed, 81% of the patients had no recurrences once therapy was initiated. The incidence of sudden death and resuscitated cardiac arrest was 4% in the entire LQT1 population, and it was 23% among those who had recurrences. Beta-blockers can clearly be expected to be an effective and sufficient therapy for most LQT1 patients.

The pattern shown by LQT2 and LQT3 patients was quite different from that of LQT1 patients and showed unexpected similarities, particularly the relatively low incidence of major cardiac events during exercise. These figures are strikingly low when the analysis is limited to the lethal events: none of the LQT2 and only 4% of the LQT3 patients died during exercise. A probable explanation lies in the common feature shared by LQT2 and LQT3

patients of a preserved I_{Ks} current. It is worth remembering that I_{Ks} is activated by catecholamines, and facilitates shortening of action potential duration when cycle length shortens, a key factor in reducing the probability of re-entrant arrhythmias.

LQT2 patients suffered most of their events during emotions or while at rest. Their predisposition to suffer these arrhythmic events in association with auditory stimuli, such as those produced by telephone calls or alarm clocks, especially when they are asleep, is of interest. This auditory trigger accounts for 26% of the cardiac events for LQT2 patients. Conversely, 80% of the events triggered by acoustic stimuli occur in LQT2 patients. It follows that removal of telephones and alarm clocks from the bedrooms of LQT2 patients could be considered as the simplest, but nonetheless quite effective, of the gene-specific therapies now available for patients affected by LQTS.

Beta-blockers are effective in LQT2 patients, but not so strikingly as in LQT1 patients. Only 59% of the LQT2 patients had no more recurrences. Only 4% of the entire group, however, suffered cardiac arrest and none suffered sudden death. The combined incidence of cardiac arrest and sudden death was 11% among the patients with recurrences.

LQT3 patients are different, not only because they represent the most uncommon subtype of the three (not including the rare LQT4, LQT5, and LQT6), but also because the current affected is that carrying Na^+ inside cardiac cells, and because the consequence of most mutations is a 'gain of function' resulting in an excess of delayed sodium inward current. They are different because of a uniquely high risk of sudden death during their first episode (20% versus 4% among LQT1 and LQT2 patients) [12] and because of additional clinical features disclosed by our study of the genotype–phenotype correlation. The most striking is the propensity of the LQT3 patients to have their cardiac events while at rest or asleep without arousal. The incidence of these events is 38% when syncope is included, and reaches 62% when only lethal events are considered. The underlying pathophysiologic mechanism is represented by an excessive QT prolongation when cycle length is prolonged; the best evidence of this phenomenon is represented by the changes occurring during night-time [13], when LQT3 patients have QTc prolongation that is markedly prolonged compared with those observed among LQT1 (almost absent) and LQT2 patients. Conversely, they tend to shorten the QT interval during exercise much more than the other two subgroups.

The outcome with beta-blockers within this group is also not completely surprising, given the observations already discussed. Clearly, LQT3 patients do not manage well when their heart rate slows down. As this is a primary con-

sequence of treatment with beta-blockers, their questionable efficacy could have been anticipated. Indeed, 56% of the treated patients become asymptomatic and the incidence of cardiac arrest and sudden death among treated patients is very high (11% in the entire group and 25% among those with recurrences). Indeed, left cardiac sympathetic denervation as a means to prevent a major release of norepinephrine at the ventricular level is recommended for these patients. The implant of an implantable cardioverter-defibrillator is also a very reasonable therapeutic option.

Because of the evidence that most mutations on *SCN5A* lead to an excess of sodium inward current, the LQT3 patients represent the first group for which a gene-specific (or, more precisely, a mutation-specific) therapy can be implemented. Our group provided initial evidence in 1995 [14] that the sodium channel blocker mexiletine was able to shorten the QT interval to a larger extent than in the other subgroups. These data have been expanded and confirm our initial impressions [15]. This finding may not apply to all sodium channel blockers. Flecainide, for example, has recently been suggested as a long-term therapy for LQT3 patients. We have, however, recently observed that when flecainide is administered intravenously to LQT3 patients, it not only shortened the QT interval but also produced ST segment elevation in six of 13 patients in leads V1–V3, that are typical of the Brugada syndrome [16]. This of course raises concerns for its chronic use. Finally, it is important to remember that there is no evidence whatsoever to indicate that the QT shortening, albeit reassuring and encouraging, translates into a clinical benefit for the patients.

Conclusion

Taken together, it seems unavoidable to admit and recognize that molecular biology does indeed have clinical applicability, and that the long QT syndrome represents a prime example of this concept.

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