New Insights Into the Long-QT Syndrome

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Long QT Syndrome (LQTS) is an arrhythmogenic disease in which prolongation of cardiac repolarization alters electrical stability of the heart predisposing affected individuals to cardiac arrest. The first arrhythmic manifestations occur during adolescence and largely are triggered by increased sympathetic activity. Mutations in genes encoding ion channels or ion channels' controlling proteins have emerged as the basis for the LQTS. The dissection of the LQTS at the molecular level has boomed in the mid nineties. Today, 70% of the LQTS population can be genotyped. Researchers intensively hunt for other causal genes and even move to the non-coding regions of the LQTS genes in attempt to genotype the remaining 30% of LQTS patients. Additionally, strategies have been developed to implement genotyping into clinical practice. On the clinical level, tremendous efforts of large international registries on the LQTS are now paying off and provide us with new data on the natural history of the LQTS and the response to therapy of genotyped LQTS patients. This editorial and the accompanying review article in this issue of *Revista Española de Cardiología* will address recent advances relevant to clinical management of affected patients.

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Genetics of the LQTS

Genetic Basis

Although inheritance of the LQTS is autosomal dominant (Romano-Ward syndrome),[1,2] female predominance is often observed. Besides a positive selection of mutant alleles being transmitted, it has been shown recently that mutant alleles are transmitted more often to female offspring.[3] LQTS in combination with deafness is inherited as an autosomal recessive trait (Jervell-Lange-Nielsen syndrome, J-LN),[4] although it has been reported that the Romano-Ward variant can also be transmitted as a recessive disorder.[5,6] Autosomal dominant LQTS occurs with an estimated frequency of about 1 in 5000 people in the general population.[7] The J-LN is far less common with an estimated incidence of 1.6 to 6 cases per million.[8]

Whereas the Romano-Ward syndrome depends on mutations affecting at least 5 genes, all encoding for subunits of cardiac sodium and potassium channels (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2), the J-LN depends on homozygous or compound heterozygous mutations on either 1 of 2 genes (*KCNQ1* and *KCNE1*)[9-11]. It is not yet known if the simultaneous presence of a heterozygous defect in *KCNQ1* and in *KCNE1* would result in the J-LN.

One gene, *ANK2*, encoding for cardiac ankyrin-B, a structural protein that anchors ion channels to the cell membrane, has been shown to cause LQTS subtype 4. The latter form of LQTS is extremely rare and few carriers of mutations in the *ANK2* gene have been described.

Since patients with *ANK2* mutations can display varying degrees of cardiac dysfunction including bradycardia, sinus arrhythmia, idiopathic ventricular fibrillation and catecholaminergic polymorphic ventricular tachycardia, and since prolonged QTc intervals are not a consistent feature in *ANK2* mutation carriers, it is reasonable to consider ankyrin-B dysfunction as a clinical entity, distinct from classic LQTS, as also suggested in a study by Mohler et

al.[12] Recently, the functional characteristics of all *ANK2* variants identified to date were assessed in primary cardiomyocytes and a range of in vitro phenotypes have been detected, including wild-type, simple loss-of-function, and severe loss-of-function activity, seen with the variants causing severe human phenotypes.

This study reinforces the role of ankyrin-B-dependent protein interactions in regulating cardiac electrogenesis.[13]

Two other syndromes have been described in which LQTS is associated with extra-cardiac manifestations. These features should be looked for when clinically assessing LQTS patients. Andersen syndrome is a rare, clinically pleiotropic disorder characterized by mild prolongation of the QTc interval (but often marked prolongation of the QUc interval), ventricular arrhythmias, periodic skeletal muscle paralysis, and dysmorphic skeletal features.[14,15] Characteristic physical features are low-set ears, micrognathia, clinodactyly, and dysmorphic features. Arrhythmias include frequent premature ventricular contractions, bigeminy, and ventricular tachycardia, typically nonsustained, and bidirectional. Degeneration into lethal ventricular arrhythmias is relatively uncommon. The syndrome is inherited in an autosomal dominant fashion, although many cases are sporadic. It is caused by mutations in *KCNJ2*, the gene encoding for the inward rectifier K^+ channel Kir2.1.[14] *KCNJ2* mutations account for nearly 2 thirds of reported cases, with the molecular basis of the remaining third still undefined. The full triad of clinical features (ventricular arrhythmias, periodic paralysis, and characteristic dysmorphic features) is present in only 58% to 78% of mutation-positive patients.[14]

Timothy syndrome is another multi-organ dysfunction in which a prolonged QT interval, ventricular arrhythmias, and congenital heart disease are associated with extra-cardiac manifestations including webbing of fingers and toes, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism.[16-18] The gene responsible for Timothy syndrome is *CACNA1C*, encoding for calcium channel $Ca_v1.2$.[18] The inheritance pattern of Timothy syndrome is sporadic in all but 1 family described so far. In the latter family, it was demonstrated that siblings were affected by the same mutation and that 1 unaffected parent was mosaic for the mutation.[18] To date only 2 mutations in *CACNA1C* have been identified in Timothy syndrome patients.[18,19]

Recently, 4 novel mutations in *CAV3*-encoded caveolin-3 have been identified in 905 unrelated LQTS patients: suggesting that this new genetic form of LQTS is extremely uncommon. Caveolae are known membrane micro-domains whose major component in the striated muscle is caveolin-3. Cardiac sodium channels localize in the caveolae. Electrophysiological analysis of sodium current demonstrated that mutant *CAV-3* results in a 2- to 3-fold increase in late sodium current compared with wild-type *CAV-3*, a pathophysiological mechanism well established to cause QT prolongation.[20]

Distribution of LQTS Mutations

Based on the current knowledge about the molecular substrate of LQTS, 70% of Romano-Ward probands can be successfully genotyped by standard methods.[21] Today, LQTS has been associated with hundreds of different mutations in the aforementioned genes (see http://www.fsm.it/cardmoc). The vast majority of mutations is found in *KCNQ1* and *KCNH2*, accounting for 84% of identified mutations in a study of Tester et al,[22] in which a pool of 541 unrelated LQTS patients was tested for mutations in *KCNQ1, KCNH2, SCN5A, KCNE1,* and *KCNE2*.[22] *SCN5A* mutations counted for 15% of mutations.[22] In the same study, missense mutations were most common, followed by frameshift mutations, non-sense, splice-site mutations, and in-frame deletions.[22] Of note, almost all mutations are private mutations although some mutational hot spots have been described.[23,24] The existence of so many private mutations on several genes mandates systematic screening of entire coding regions. Recently, we reported the feasibility of an effective alternative strategy that may help bring genotyping closer to routine clinical practice.[21] We observed in a prospective study that 180 (58%) of 310 genotyped LQTS probands carried mutations on 64 nonprivate codons. These codons cover 3.5% of the *KCNQ1*, 2.2% of the *KCNH2*, 0.4% of the *SCN5A* coding regions. Based on the evidence that in our study 88% of successfully genotyped patients carry mutations in the *KCNQ1* and *KCNH2* genes, it would seem logical that DNA of patients who test negative for the search for mutations in the 64 codons (first step) should be analyzed by assessing the coding regions of *KCNQ1* and *KCNH2* genes (second step). Only patients who test negative to the first 2 steps, would then move to the last level of this 3-tier approach for LQTS genotyping and their DNA would be screened for mutations on *SCN5A*, *KCNE1*, and *KCNE2* genes.

Compound mutations, both in the same gene and in different genes, are relatively common in LQTS.[25] Tester et al[22] identified 5% of the patient group as carriers of 2 pathogenic mutations (ie, 10% of genotype-positive group).[22] In another recent study, it was reported that 20 of 252 LQTS probands (7.9%) had 2 variants in the ion channel genes *KCNQ1, KCNH2, SCN5A,*

or *KCNE1*.[26] In the group with 2 mutations, QTc intervals were longer, the incidence of cardiac arrhythmia was higher and symptoms were more severe.[26] These data favor a systematic screening of all LQTS genes, even if a causal mutation is found in a certain gene.

Genetics in Sudden Infant Death Syndrome and Sudden Unexplained Death Syndrome

A molecular study in 201 Norwegian sudden infant death syndrome (SIDS) victims showed that genetic variants in LQTS genes are present in 9.5% of SIDS victims.[27] A very recent study implicated *CAV3* mutations as a pathogenic basis of SIDS: 3 distinct *CAV3* mutations were identified in 3 of 50 black infants but no *CAV3* mutations were detected in 83 white infants.[28] Given the growing consistency of these and other[29] molecular autopsy reports, the challenge is to find a cost-effective and efficient means for presymptomatic detection of LQTS to reduce the morbidity and mortality of the subset of SIDS etiologically related to LQTS genes and to determine whether newborn ECG screening is appropriate.[30]

Another recent comprehensive postmortem study performed genetic testing in 49 sudden unexplained death (SUD) victims with an average age of death of 14.2 years.[31] Over one-third of decedents harbored a putative cardiac channel mutation: 7 hosted mutations in the *RyR2*-encoded calcium release channel and 10 carried LQTS susceptibility mutations.[31] Accordingly, postmortem cardiac channel genetic testing should be pursued in the evaluation of autopsy-negative SUD in order to provide reliable genetic counseling to the relatives of a SUD victim.

Genetic Modifiers in the LQTS

A potential explanation for the clinical heterogeneity among LQTS patients sharing the same disease-causing mutation is the coexistence of modifier gene alleles, altering arrhythmia susceptibility. This concept has been demonstrated in a family segregating a novel, low-penetrant *KCNH2* mutation (A1116V) along with a common single nucleotide polymorphism (K897T) in *KCNH2*.[32]

Recently, a genome-wide association study on 200 normal subjects at the extremes of the KORA-cohort based QT interval distribution,[33] identified NOS1AP (CAPON), a regulator of neuronal nitric oxide synthase, as a new target that modulates cardiac repolarization.[34] This study indicated that approximately 60% of subjects of European ancestry carry at least one minor allele of the *NOS1AP* genetic variant, which can explain up

to 1.5% of QT interval variation.[34] To date, it is unknown whether this genetic variant modulates the QT interval prolongation in LQTS patients.

Identification of the genetic modifiers, that will ultimately determine the final phenotype in LQTS patients, undoubtedly constitutes one of the current challenges for researchers in the field.

"Non-Genotyped" LQTS Patients

In the approximately 30% of LQTS patients in whom conventional mutation screening fails to uncover a mutation, recent anecdotal studies report other genetic defects than the commonly found point mutations or small insertions and deletions in coding regions.

Using a quantitative multiplex approach, a large gene rearrangement consisting of a tandem duplication of 3.7 kb in *KCNH2* has been found to be responsible for LQTS in a Dutch family.[35] The rearrangement is undetectable by current polymerase chain reaction-based exon-scanning methodologies. It has to be determined in a larger series whether analysis for large gene alterations in routine genetic testing may provide a genetic diagnosis in a number of non-genotyped patients.

It is well known that base pairs around the exon-intron boundaries (donor and acceptor splice sites) are essential for normal splicing.[36] Sequence alterations at these locations are potentially disease-causing by disruption of the splice site and, subsequently, exon skipping.[37,38] So far, it has been shown in 2 studies that disease-causing aberrations can be detected at less highly conserved nucleotide positions than either the obligatory GT or AG of the donor and acceptor splice sites. In one family, an intronic variant in *KCNH2*, T1945+ 6C, was identified. Splicing assay showed T1945+ 6C causing downstream intron retention. Complementary deoxyribonucleic acid with retained intron 7 failed to produce functional channels.[39] Another study described the pathophysiological role of an A to G branch point substitution in *KCNH2* in intron 9 at position -28 (IVS9-28A>G).[40]

Cost-Effectiveness of Genetic Screening

As genetic analysis leaves the research arena and enters into practice it becomes critical to provide information to prioritize access to genetic testing based on cost/benefit considerations. We performed a retrospective analysis[41] on 559 patients consecutively referred over a 5 year period and divided them into three groups according to the QTc duration: group 1: QTc <440 ms (n=95) including

family members of sudden death victims with normal heart, patient with idiopathic ventricular fibrillation and patients with drug induced Torsades de Pointes (TdP); group 2: 440 ≤QTc <470 ms (n=160) including patients with unconfirmed LQTS diagnosis; group 3: QTc ≥470 ms (n=304) ie, patients with conclusive clinical diagnosis of LQTS. The cost per positive genotype in each group was derived based on cost of commercially available LQTS genotyping of 5400 dollars per screening of the LQTS genes 1 to 5. The yield of LQTS genotyping was 2% in group 1, 14% in group 2, and 64% in group 3. Based on the current cost of 5400 dollars per screening, the cost per positive genotype is 256 500 dollars in patients with normal QTc, 37 565 dollars in patients with borderline QTc and 8418 dollars in patients with QTc ≥470 ms (*P*<.0001). These cost considerations suggest to prioritize genetic testing in LQTS patients with clinical diagnosis in whom genotyping is used for risk stratification and to guide treatment. Screening of patients with uncertain LQTS diagnosis and of patients with normal QT and risk factors for LQTS is still too expensive to justify its use outside the research lab. In another study, the incremental cost-effectiveness of genetic testing compared with no genetic testing for symptomatic index cases has been determined. The authors found that genetic testing is more cost-effective than not testing for symptomatic index cases at an estimated cost of 2500 dollars per year of life saved.[42]

Genotype-Phenotype Correlations

Despite some overlap, the 3 major subtypes of LQTS (LQT1, LQT2, and LQT3) have their own clinical profile. Phenotypical differences in genetically distinct forms of LQTS may include every aspect of the clinical presentation: ECG characteristics, QT dynamics during exercise, arrhythmia related triggers, onset of arrhythmias, natural history, pregnancy-related cardiac events, and response to β-blocker treatment. We'll review recent insights in the latter 4 correlations.

Genotype-Specific Onset of Arrhythmias

The onset of TdP may differ among LQTS patients, being pause dependent in some but not all. This disparity may point to different arrhythmia mechanisms and may affect therapy strategies (see below). It seems that pauses preceed TdP significantly more often in LQT2 than in LQT1, and that the interval immediately before TdP (pause interval) is significantly longer in LQT2 than in LQT1.[43]

Natural History

General LQTS population. In 2003, we reported natural history data on 647 genotyped patients of 193 unselected families.[44] The mean age of the first cardiac event was not different among the LQT1, 2, and 3 subgroups, the risk of becoming symptomatic was lowest among LQT1 patients and a significantly higher number of events for LQT2 than LQT1 patients was reported together with a trend toward more events among LQT3 than among LQT1 patients.[44] Cumulative mortality rate was different among the groups: it was significantly higher among LQT2 patients than LQT1 patients and there was a trend toward a higher cumulative mortality rate among LQT3 patients than among LQT1 patients.[44] In the same study, we stratified risk according to the genotype, in conjunction with other clinical variables such as sex and length of QT interval and proposed a risk stratification scheme to be used in the management of asymptomatic patients whenever genotype is available.[44]

Specific Subgroups

ADOLESCENCE. Since analyses of predictors of cardiac events have primarily considered syncope as the predominant end point, a specific study has been performed in 2772 LQTS patients to identify risk factors associated with aborted cardiac arrest and sudden cardiac death during adolescence.[45] Significant independent predictors of aborted cardiac arrest or sudden cardiac death during adolescence were reported to be syncope, QTc interval, and sex. Those patients with 1 syncopal episode in the last 2 years had an adjusted hazard ratio (HR) of 11.7 (95% confidence interval [CI, 7.0-19.5; *P*<.001) and those with 2 or more syncopal episodes in the last 2 years had an adjusted HR of 18.1 (95% CI, 10.4-31.2; *P*<.001) for life-threatening events. Irrespective of events occurring more than 2 years ago, QTc of ≥530 ms was associated with increased risk (adjusted HR, 2.3; 95% CI, 1.6-3.3; *P*<.001) compared with those having a shorter QTc. Males between the ages of 10 and 12 years of age had higher risk than females (HR 4.0; 95% CI, 1.8-9.2; *P*=.001), but there was no significant risk difference between males and females between the ages of 13 and 20 years.

ADULTHOOD. In a very recent study, female gender, QTc interval, LQT2 genotype, and frequency of cardiac events before age 18 years were associated with increased risk of having any cardiac events between the ages of 18 and 40 years in 812 mutation-confirmed LQTS patients age 18 years or older.[46] In the same group, female gender, QTc interval ≥500

ms, and interim syncopal events during follow-up after age 18 years were associated with significantly increased risk of life-threatening cardiac events in adulthood. The severity of LQTS in adulthood can thus be risk stratified with information regarding genotype, gender, QTc duration, and history of cardiac events. Unfortunately, no data exist on the clinical behavior of LQTS in the elderly population.

LOCALIZATION OF THE MUTATION IN THE CHANNEL. It has been reported that LQT2 patients with mutations in the pore region of the *KCNH2* gene are at markedly increased risk for arrhythmia-related cardiac events compared to patients with non-pore mutations.[47] Besides mutations in the pore, those in the PAS domain of the KCNH2 channel may also have a deleterious impact.[48] Similarly, LQT1 associated mutations involving the transmembrane spanning domains and/or pore regions of the KCNQ1 channel were associated with a worse outcome than those LQT1 patients harboring mutations in the C-terminus.[49]

JERVELL-LANGE-NIELSEN SYNDROME. This subgroup is the most severe variant of LQTS, with a very early onset and major QTc prolongation.[50] Subgroups have been identified in a study on 186 J-LN patients: females, patients with a QTc ≤550 ms, those without events in the first year of life, and those with mutations on *KCNE1* are at relatively lower risk for aborted cardiac arrest and sudden cardiac death.[51]

Pregnancy Related Cardiac Events

The clinical course of women with LQTS during and after pregnancy has been investigated in a recent study: women with LQTS have a reduced risk for cardiac events during pregnancy, but an increased risk during the 9-month postpartum period, especially among women with the LQT2 genotype.[52]

Response to β-Blocker Treatment

Beta-blockers (β-BRs) are considered the treatment of choice in LQTS patients although this is primarily based on nonrandomized trial evidence.[53]

An observational, retrospective study of the LQTS registry[54] indicated a significant reduction in the mean rate of cardiac events after starting β-BR therapy. However, patients who had symptoms before β-BR therapy had a high likelihood of experiencing recurrent cardiac events (32% within 5 years) despite being on treatment. Furthermore, 14% of patients with an aborted cardiac arrest before β-BR therapy are expected to experience recurrent cardiac arrest or death within 5 years while on β-BRs. In the same study, the concept

was introduced that response to β-BR therapy may be modulated by genetic substrate. Given the high incidence of cardiac events during exercise in LQT1 patients, it is reasonable to hypothesize that β-BRs are particularly effective in the LQT1 subgroup.[55] In a large β-BR treated LQTS cohort, a gradient of risk from LQT1, LQT2 to LQT3 was reported: cardiac events occurred in 19 of 187 (10%) LQT1 patients, 27 of 120 (23%) LQT2 patients, and 9 of 28 (32%) LQT3 patients.[56] These findings suggest that more aggressive therapy such as the prophylactic implant of an ICD may be warranted in LQT2 and LQT3 patients.[53,56]

Recently, data on β-BR treatment in specific LQTS populations came to light. In the study of the natural history of LQTS in adolescents, β-BR therapy was associated with reduced risk among patients with recent syncope.[45] In the study of the behavior of LQTS in adults, β-BRs effectively reduced but did not eliminated the risk of both syncopal and life-threatening cardiac events in adult patients with mutation-confirmed LQTS.[46] Among J-LN patients treated with β-BRs, the cumulative probability of LQTS-related death was 35% in one study.[50] In a second study, 51% of J-LN patients had events despite therapy.[51] It can thus be concluded that β-BRs have limited efficacy in J-LN. Finally, β-BRs were associated with a reduction in cardiac events during the high-risk postpartum time period.[52]

The favorable clinical effects of β-blockers in LQT1 are not fully elucidated. Remarkably, treatment with β-BRs reduces arrhythmic events in LQT1 without a known influence on QT interval duration. A recent analysis of 24-h electrocardiographic recordings from 24 LQT1 patients obtained before and during the treatment with β-BRs indicated a decrease in both the diurnal maximal T-wave peak to T-wave end interval and the maximal ratio between late and early T-wave peak amplitude, which are electrocardiographic counterparts of transmural dispersion of repolarization and early afterdepolarizations, respectively. Additionally, abrupt maximal QT intervals at heart rates higher than 85 beats/min were decreased under β-BR therapy, whereas QT intervals measured at steady-state conditions remained unchanged.[57] As indicated above, pause-dependence of TdP onset in LQTS seems to be genotype specific, being predominant in LQT2 but absent in LQT1.[43] Most likely, pause-dependent TdP are triggered by early after depolarizations (carried by L-type Ca^{2+} channels) and TdP following the relatively fast heart rate in LQT1 may be compatible with delayed afterdepolarizations (secondary to intracellular Ca^{2+} overload). Either way, the proposed involvement of both early and delayed afterdepolarizations provides a rationale for the use of β-BRs as these drugs counteract loading of intracellular Ca^{2+} stores by cAMP-dependent processes.[43]

Summary of Recent Advancements in the Understanding of LQTS

This editorial has highlighted the impressive advancement in the field of LQTS made in last 10 years. Among the most important aspects that mark a departure from previous knowledge is the concept that the genetic substrate identifies distinct forms of LQTS that present specific characteristics and require different management. Accordingly, LQT1, LQT2, LQT3, LQT5 are the 4 types of Romano Ward LQTS, and JLN1 and JLN2 are the 2 types of Jervell and Lange-Nielsen LQTS. In addition to those, several LQTS-spectrum disorders have been identified in which specific cardiac or extracardiac manifestations are present. This group includes LQT4, LQT7, and LQT8 that have been discussed in the previous sections. Some very uncommon genetic variants such as LQT7 and LQT9 identified in a handful of patients worldwide remain anecdotal reports and it is impossible to tell whether they present distinguishing features.

Given the role of the identification of the genetic substrate for LQTS patients' management, the most important challenge in the field is now that of increasing access to and reimbursement of genetic analysis for LQTS. In this respect it is important that in each country referral centers are established so that the still expensive and time consuming effort of genotyping can become part of diagnostic routine in cardiology thus allowing all patients to be genetically characterized and treated accordingly.

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