Genotype–Phenotype Relationship in the Long QT Syndrome

Brimming With Knowledge but Thirsting for a Therapeutic Solution*

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Since it was first reported 50 years ago, the long QT syndrome (LQTS) is now recognized as a genetic disease caused by mutations of ion channel genes encoding a cardiac channel essential for the control of ventricular repolarization (1). The LQTS is not only the most common and extensively researched genetic cardiac arrhythmia (2,3), it has also attracted premier scientists and scholars in single-cell electrophysiology and molecular genetics. In turn, they have produced seminal discoveries that shaped our understanding of the syndrome. The mutated genes in LQTS patients cause delayed repolarization and, in turn, prolong the QT interval on the surface electrocardiogram; these abnormalities are associated with torsade de pointes and/or ventricular fibrillation, resulting in the clinical manifestation of syncope and/or sudden death (2,3).

Currently, there are hundreds of mutations in 10 genes linked to LQTS, which have been genetically subtyped into LQT1 through LQT8 (3). However, 95% of these cases involve LQT1 through LQT3. These common forms of LQTS have different genes coding various ion channel subunits, making an impact on the diagnosis and management of LQTS patients. The most common form is LQT1, which is caused by the loss-of-function mutation in KCNQ1, which encodes IKs, an adrenergic-sensitive potassium current of the cardiac myocytes. Thus, LQT1 patients usually have symptoms after emotional or physical stress, notably diving or swimming. Not surprisingly, LQT1 patients respond very well to β-blockade treatment, and exercise may aggravate QT prolongation. The LQT2 subtype is caused by loss-of-function mutations in KCNH2 (HERG), which encodes IKr; the triggering event is usually by a sudden loud noise such as an alarm clock. In contrast, LQT3 is caused by the disruption of fast inactivation of the cardiac sodium-channel SCN5A, resulting in persistence of the inward sodium current during the plateau of the cardiac action potential as well as the prolongation of repolarization and QT interval. LQT3 patients usually have symptoms at rest or during sleep and respond poorly to β-blockade therapy, but respond very well to mexiletine, a sodium-channel blocker. Furthermore, LQT3 has the highest prevalence of sudden cardiac death. Clinical data derived from genotyped LQTS patients clearly underscore the differences in risks and responses to treatment among the variants of LQTS patients. The advances of our understanding of the electrophysiological consequences of these gene mutations make the phenotype–genotype correlation of LQTS patients possible and enable physicians to tailor their care of the patients in a more logical and less empirical manner.

One of the vital elements of the said advances in LQTS is the well-known international registry that was created many years ago. The International LQTS Registry catalogues both talented researchers and LQTS patients from both sides of the Atlantic, expediting an otherwise arduous research process, especially if done by a single center. Subsequently, physicians and scientists from other offspring LQTS registries, created by several renowned institutions, joined those from the original international registry in working on this fascinating inherited genetic arrhythmia. This collaboration establishes a new way of studying genotype–phenotype correlation and its impact on diagnosis, treatment, and risk stratification.

Identifying high-risk asymptomatic LQTS patients for cardiac arrest or syncope remains an important task for the scientist and the registry alike. One does not have to be reminded that when young, otherwise healthy LQTS patients suddenly die, it devastates family, friends, and loved ones. The key questions are these: What is the risk for my daughter/son? What can I do to protect my family in the future? Some parents would demand an implantable cardioverter-defibrillator (ICD), even though data show a family history of sudden death does not specifically determine other cardiac events. Consequently, subjecting a young asymptomatic patient to long-term β-blockade therapy or to ICD treatment is not necessarily an easy task. Therefore, a robust risk-stratification paradigm is desirable in selecting patients for long-term treatment.

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Thus far, corrected QT (QTc) duration (≥500 ms) and symptoms of syncope or aborted sudden cardiac death are the best predictors for future events. In asymptomatic patients, QTc duration is the only useful variable for risk stratification (4). However, recent data suggest that mutations in the transmembrane portion of the ion channel protein and the degree of ion channel dysfunction are important independent risk factors for LQT1 patients (5). In the same vein, preliminary data from the international registry suggest an increased risk of arrhythmic events for LQT2 patients if they have a mutation in the pore region of the hERG gene when compared with those who have mutations in the nonpore region (6). The investigators from the international registry then collaborated with the other registries—Japan, the Netherlands (Amsterdam), and the Mayo Clinic—to further explore the influence of the location, coding type, and topology of the channel mutation on the clinical manifestation and outcomes of LQT2 patients in their registries. Their findings, reported by Shimizu et al. (7) in this issue of the Journal, have brought a new level of understanding to the genotype-phenotype relationship in LQT2 patients.

Shimizu et al. (7) found that LQT2 patients who have missense mutations either at the transmembrane pore (S5-loop–S6) or at the N-terminus region of the hERG gene, carry a higher risk of syncope or cardiac arrest (hazard ratio: 2.87 and 1.86, respectively), whereas those with the same type of mutation, but at the transmembrane nonpore location, have a lower risk. When the investigators further explored mutation-location interaction for risk stratification, they ascertained that LQT2 patients with nonmissense mutation in the C-terminal region were at significantly higher risk than were patients with the missense mutation at the same region, a fascinating discovery. Mutations located in alpha-helical domains are associated with a higher risk of cardiac events than mutations located in beta-sheet domains. In short, Shimizu et al. (7) are the first to document that the type, location, and topology of mutations of the KCNH2 plays an important role in the magnitude of repolarization abnormality, leading to occurrences of life-threatening cardiac arrhythmias.

The question then arises: How does this new observation affect our approach in managing asymptomatic LQT2 patients? For example, if there is a patient who has QTc >500 ms but has nonmissense mutation at the N-terminal, then, is withholding treatment the correct path? But what if an LQT2 patient has a missense mutation at the transmembrane pore region but the QTc is <500 ms (albeit this is not a likely scenario)? Should one recommend a beta-blocker and a potassium supplement? The study by Shimizu et al. (7) is not really designed to answer this question, for it is a retrospective observational study to determine genotype-phenotype relationships. The report does not have protocols for determining the effects of any therapeutic modalities on the clinical outcomes. Nevertheless, beta-blocker treatment in this study reduced the risk of first cardiac events by 63%; unfortunately, the drug was mostly effective in preventing syncope but not lethal ventricular arrhythmias. It is a quandary, unless one is willing to implant an ICD in all of these patients.

Cardioverter-defibrillator implantation in young, otherwise healthy persons has vices and virtues. While undoubtedly an ICD is effective in converting ventricular fibrillation to sinus rhythm and may save lives, an ICD does not reduce the risk of recurrences in ventricular arrhythmias and may deliver unpleasantly frequent shocks to patients, causing a negative impact. A combination of beta-blocker therapy and potassium supplements as well as an ICD could be a rational approach to preventing lethal arrhythmias, and perhaps the drug would minimize ICD discharges. However, long-term ICD treatment of the young is known to be associated with inappropriate shocks or device malfunctions (i.e., lead fractures, insulation breaks, infection). Evidence in the current study reveals significant differences in ICD use among the 4 registries in this study.

Shimizu et al. (7) enrich our knowledge and understanding of the genotype-phenotype relationship. This enhances our ability to identify high-risk LQT2 patients, but leaves us with a therapeutic dilemma of treatment for the patient. It is possible that a prospective multicenter study involving the consortium of these LQTS registries is required to determine whether beta-blockade therapy and potassium supplements are effective in reducing sudden death in this high-risk LQT2 population or whether an ICD is required. Based on what we have witnessed with the kind of work done by collaborators such as Shimizu et al. (7), I am optimistic that we are on our way to finding the optimal solution for our high-risk LQTS patients in the near future.

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REFERENCES

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