Genotyping Has a Minor Role in Selecting Therapy for Congenital Long-QT Syndromes at Present

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Genotyping has led to enormous advances in understanding the phenotype and clinical course of the congenital long-QT syndromes (LQTS). In the most common LQTS forms, LQT1, LQT2, and LQT3, genotyping a clearly affected person in each family provides the ability to easily identify family members with reduced penetrance of the QTc and symptoms phenotypes, thus, providing also the opportunity to prevent sudden death and cardiac arrest by administering presymptomatic therapy.

Response by Moss and Goldberg see p 233

The role of genotyping in selecting the therapy for LQTS is, on the other hand, unclear. Data from the literature and from the Salt Lake City LQTS database will be presented to show that genotyping has only a minor role in selecting therapy for LQTS. The discussion will primarily address the LQT1, LQT2, and LQT3 forms (caused by mutations of the LQT1, 2, 3, 5, and 6 genes) and the rare LQT4, LQT7, and LQT8 forms will be discussed briefly, and because so little is known about the new LQT9-11 forms they are not ready for a discussion of genotyping for therapy decisions. The pleural term “Long-QT syndromes” is indeed now very appropriate because of the diversity (both molecular and phenotype) of the conditions caused by the 11 accepted or proposed LQTS genes.

What Is the Role of Genotyping for Selecting Therapy for Congenital Long-QT Syndrome?
The idea of genotype-based therapy has been discussed for some time, being encouraged by the experimental findings with mexiletine and flecainide in LQT3 and potassium supplementation in LQT2, plus other laboratory findings. The concept has received additional attention recently as some details outlining the complexity of the molecular substrate of LQTS are being reported.

There are several concepts that are important for the discussion of this controversy. First, what we really want to accomplish by treatment is to prevent sudden death and aborted cardiac arrest. Most publications have reported the rate of all events combined, the majority of which are syncope. Fortunately, sudden death and cardiac arrest specific data from a large number of patients from the International LQTS Registry database are now available. Second, there are only 3 or perhaps 4 therapies proven to reduce sudden death and cardiac arrest in LQTS; β-blockers, the implantable cardioverter defibrillator (ICD), left cardiac sympathetic denervation (LCSD), and possibly pacemaker therapy. Third, for genotyping to have an important role in selection of therapy, genotype-based treatments must be proven to reduce sudden death and cardiac arrest significantly more in patients with the target genotype than does any nonspecific therapy. No prospective, comparative trials of any therapy for LQTS have been performed.

For convenience, the evidence to support the position that genotyping has only a minor role in selecting therapy is compiled into the following categories:

1. Current treatments rely on genotype to only a minor degree, yet are quite effective.
A. β-blockers, LCSD, and behavior modification.
B. ICD’s and pacemakers.

2. Genotype is not a risk factor for sudden death or cardiac arrest, and the rate of these events is similar in each genotype.

3. LQTS is a very complex disorder and genotype does not accurately predict clinical outcome.
   A. The tremendous genetic heterogeneity.
   B. The high degree of reduced penetrance and variable expressivity of symptoms and QTc intervals.

4. The demographics of long-QT syndrome are different than initially perceived.
   A. The high number of asymptomatic gene carriers.
   B. The low rate of sudden death and aborted cardiac arrest in all 3 genotypes.

**Current Treatments Rely on Genotype to Only a Minor Degree, Yet Are Quite Effective**

**β-blockers, LCSD, and Behavior Modification**

β-blockers are quite effective in LQT1 and LQT2 in general and are very effective if they are taken daily and persistently and QT prolonging drugs are avoided.28 They are less effective in LQT3, and, thus, they have a degree of genotype specificity. Behavior modification similarly is most helpful in LQT1 and LQT2. For practical purposes, however, this apparent genotype specificity influences therapy in only a very small number of patients. Because the LQT1 and LQT2 forms constitute roughly 95% of LQT1-3 patients, β-blocker and behavioral modification treatments could reasonably be given to all patients except those with a typical LQT3 phenotype without knowing the DNA-based genotype and without harm. β-blockers could potentially be given also to the 15% or so of LQT3 patients who have cardiac events with exercise or emotion,29 but its effectiveness in this group has not been tested. Asymptomatic patients with the LQT3 phenotype may best be treated with “watchful waiting” as roughly 80% remain asymptomatic through at least age 40.30 Symptomatic patients with the LQT3 phenotype would be candidates for an ICD. The minor role of genotyping could be used in the small number of patients who do not fit into these described categories. One example would be patients with unusual ECG findings, often due to multiple mutations.1,14,31

The location of the mutation or the ethnic background of patients may influence risk for events,16,17,32 but there is no evidence that patients with these genotypic features do better with one therapy versus another. Regarding LCSD, although it seems particularly suited to patients with adrenergic-mediated events (most, if not all, LQT1 and many LQT2 patients), its mechanisms of effect are not fully defined and its’s effectiveness in LQT2 and LQT3 patients with rest/sleep events has not been defined. There have been a number of publications on this procedure,31-44 but involving relatively few patients, and often the genotype was not known or not reported. Thus, the degree of genotype specificity of LCSD is unknown.

**Implantable Cardioverter Defibrillator**

Certainly, this effective therapeutic modality is not genotype specific. All patients could be provided ICD implantation without genotype knowledge. Pacemakers have been used in a modest number of patients, and shown to be effective, often in conjunction with β-blocker therapy, perhaps particularly in patients with pause dependent torsade.45 I conclude, however, there is too little experience to know if pacemakers have any important genotype specificity. Pacemakers appear to receive limited use in this era of ICD implantation in LQTS and are less effective than β-blockers or ICDs.

The 2 common treatment strategies, β-blockers and ICDs, would both quite effectively diminish the rate of sudden cardiac death and aborted cardiac arrest with no or little genotype information.

**Genotype Is Not a Risk Factor for Sudden Death and Cardiac Arrest, and the Rate of These Events Is Similar in Each Genotype**

The International LQTS Registry data show that genotype is not a risk factor for sudden cardiac death or cardiac arrest,20-22 and that the rates of sudden death and cardiac arrest events are similar in all 3 genotypes.30 Thus, it would be unlikely that genotyping would be useful to select therapy to prevent these events.

**LQTS Is a Very Complex Disorder and Genotype Does Not Accurately Predict Clinical Outcome**

**The Tremendous Genetic Heterogeneity**

A big impediment to reaching the goal of patient specific therapy based on genotype is the progressively expanding evidence of the high degree of complexity of the syndrome. More than 600 mutations of the 5 genes causing LQT1, LQT2, and LQT3 have been identified so far, yet about 30% of phenotypically affected patients/families have no mutation found in the currently screened genes.46-48 Genotyping offers no aid in selecting therapy for this important subset of LQTS patients. Of those families that do have a gene mutation found, most have their own novel mutation,1,49 yet within each genotype the expression of the disease is basically the same in each family. Further, the degree of functional impairment of the channel involved does not correlate well with the severity of the phenotype. These observations indicate that there is much we do not know about the pathophysiology, particularly the risk and protective factors. Because the clinical course of individual patients is not accurately defined by the genotype, the genotype is unlikely to be helpful for selecting therapy.

**The High Degree of Reduced Penetration and Variable Expressivity of Symptoms and QTc Intervals**

One of the most interesting features of LQTS, and one that really complicates diagnosis and therapy decisions, is the high degree of reduced penetrance and variable expressivity. These characteristics have been known for quite some time and are very pertinent to this discussion. The first
genotype-phenotype study of LQTS revealed that about 30% of the 83 affected members of the 3 families studied were life-long asymptomatic, 4 members (5%) had a prior cardiac arrest, and affected members exhibited a range of QTc intervals from 410 to 590 ms. About 12% had a QTc of 440 ms or less, commonly defined as normal, and about 20% had a borderline QTc of 450 to 480 ms that overlapped with those of the unaffected family members. Thus, approximately 30% of carriers had normal or borderline (nondiagnostic) QTc intervals. Further, the QTc was quite variable among the carriers in each family, and that immediately indicated that there were many modifier factors that were not known, most still not identified today. The genetic locus that was identified in these members, the Harvey ras-1 gene, was subsequently found to be a novel potassium channel gene, now termed KCNQ1, thus, these families had LQT1. In 1998, data from the International LQTS Registry showed that 38% of LQT1, 54% of LQT2, and 82% of LQT3 patients were asymptomatic through 40 years of age, and that the rate of death or cardiac arrest over that time frame was essentially the same in each genotype, being 11% in LQT1, 10% in LQT2, and 9% in LQT3. Other studies have also confirmed the reduced penetrance and variable expressivity features of LQTS. Figure 1 demonstrates an example of the variability of QTc expression among 836 LQT1, LQT2, and LQT3 patients from the Salt Lake City LQTS database, showing a range of QTc intervals from 400 to 690 ms. Figure 2, also from the Salt Lake City LQTS database, expands the earlier observation that variability of QTc values exists among members of single families, each member having the same genotype and mutation type. In my experience, a generally similar degree of variability of the QTc interval is seen in almost all families with the

![Figure 1. Distribution of the baseline, resting ECG QTc values in 836 LQT1, LQT2, and LQT3 patients. The QTc range is from 390 to 700 ms, which demonstrates the high degree of variable expressivity of this feature. The figure also shows the reduced penetrance of the QTc phenotype, with about 25% of patients having a QTc interval between 390 to 460 ms, values that overlap completely with those of normal subjects.](http://circep.ahajournals.org/)

![Figure 2. Distribution of baseline, resting ECG QTc values among affected members of individual LQT1, LQT2, and LQT3 families. In each family there is substantial variability of the QTc value among members.](http://circep.ahajournals.org/)
LQT1, LQT2, and LQT3 genotypes when a large number of affected members are evaluated. Similar to the QTc variability shown in these figure, and as noted above, there is a large variability of symptoms and outcomes. Only a small percentage of members of any family, if any, will experience sudden death or cardiac arrest; others will have few to many syncopal spells, although the majority will be asymptomatic. The prominent variability of QTc and symptoms emphasizes that due to the many unknown factors that influence the pathophysiology and clinical course of each person, the genotype is not helpful for predicting outcome nor for selecting therapy.

The Demographics of LQTS Are Different Than Originally Perceived

The High Number of Asymptomatic Gene Carriers

Before genotyping and the resultant genotype-phenotype correlations, the majority of patients that came to medical attention were those with serious cardiac events (sudden death, cardiac arrest, or frequent or severe syncpe) or an obviously long-QT interval. Consequently, the literature reported that LQTS carried a high risk for sudden death or cardiac arrest. Those with reduced penetrance of the symptoms and QTc phenotypes were, of course, not detected because it was neither known that they existed nor were tools available for their diagnosis. Once genotyping became available and genotype-phenotype studies led to improved accuracy of phenotyping, the interest in screening of extended family members increased and the average number of gene carriers identified per family increased, as shown in Figure 2, and in reports by others. Figure 3 shows an example of how LQTS patients were identified in a contemporary evaluation, demonstrating the large number, 69%, that were asymptomatic at diagnosis. This distribution is more representative of the spectrum of patients now being identified than what was present in many prior studies.

The Low Rate of Sudden Death and Aborted Cardiac Arrest

As noted above, the early reports on LQTS contained primarily highly symptomatic patients and/or those with very long-QTc intervals. Few of the asymptomatic and remotely symptomatic patients or those with reduced penetrance were included. Thus, it appeared that the rate of sudden death and cardiac arrest was quite high. Over time as more of the asymptomatic, the remotely symptomatic, and those with reduced penetrance of the phenotype have been included, the reported rates of these events have declined. Table 1 shows the most recent LQTS Registry data. These annualized rates are quite low and are particularly noteworthy in that only 20% to 30% of the patients in these studies received β-blockers, and just 2% to 3% received an ICD or LCSD. Of added importance, it is now evident that β-blocker noncompliance and use of QT prolonging drugs are the major causes of cardiac events in patients prescribed β-blockers, rather than β-blocker failures. Patients who are compliant with β-blockers and take no QT prolonging drugs have a dramatic reduction in sudden death and cardiac arrest (Table 2). The rate of sudden death or cardiac arrest in these patients was 3 to 5 times less than the already low rates reported from the Registry data, compare Table 2 with Table 1.

Genotyping for Selecting Therapy in the “Atypical” LQTS Forms LQT4, LQT7, and LQT8

I prefer to call the LQT1, LQT2, and LQT3 forms the ‘classic LQTS’ forms, and the remainder ‘atypical’ because they all have clinical features such as noncardiac abnormalities and/or molecular substrate that make them somewhat different than classic LQTS.

LQ4? Ankyrin B Syndrome

This rare disorder is due to mutations of the ankyrin-B gene, from a family of anchoring proteins. The phenotype was initially reported to include QT prolongation, along with sinus node dysfunction, sinus bradycardia, atrial fibrillation, and sudden death. Subsequent observations indicate that the reported QT prolongation was really QU prolongation, and that QT prolongation occurs in only a minority of gene carriers. Not more a U wave disease than QT disorder. Ankyrin-B affects many channel processes rather than encoding for a single gene product, and Ankyrin-B mutations

Table 1. Rates of Sudden Death and Cardiac Arrest in LQT1, LQT2, and LQT3 Patients by Age Group, Reported From the International LQTS Registry Database

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. with SCD/ACA</th>
<th>Percent with SCD/ACA</th>
<th>Duration in Years</th>
<th>Percent with SCD/ACA/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldenberg et al, 1–13 y</td>
<td>3015</td>
<td>53</td>
<td>1.8</td>
<td>12</td>
<td>0.15</td>
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<tr>
<td>Hobbs et al, 10–20 y</td>
<td>824</td>
<td>26</td>
<td>3.1</td>
<td>10</td>
<td>0.31</td>
</tr>
<tr>
<td>Sauer et al, 18–40 y</td>
<td>812</td>
<td>50</td>
<td>6.1</td>
<td>22</td>
<td>0.28</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death; ACA, aborted cardiac arrest.
have been found in healthy subjects and others\(^6\) raising questions about their functional significance. For these reasons, the designation LQT4 may not be appropriate and the term “Ankyrin-B syndromes” may be the preferred designation. \(^5\) Genotyping is available for this syndrome and is useful for identification of those without a clear phenotype, but appears to be not useful for selecting therapy.

**LQTS7? Andersen Syndrome, Andersen-Tawil Syndrome Type 1, ATS1**

Andersen et al\(^{46}\) reported in 1971 on an 8-year-old with short stature, hypertelorism, broad nasal root, and defects of soft and hard palate. The term “Andersen syndrome” was used for the first time in 1994 by Tawil et al\(^{47}\) in patients with the clinical findings as described by Anderson, plus periodic paralysis, and ventricular arrhythmias, which include frequent PVCs and ventricular tachycardia, particularly, bidirectional ventricular tachycardia. This constellation plus QT prolongation was proposed as Andersen-Tawil syndrome and as LQT7 by Tristani-Firouzi\(^{48}\) in 2002. They demonstrated that mutations of the KCNJ2 gene are responsible for this disorder and designated it ATS1. Clinically, this disorder is unlike classical LQTS in that the phenotype shows a variety of features including periodic paralysis, a number of skeletal anomalies, high frequency PVCs, bidirectional ventricular tachycardia rather than torsade de pointes, and uncommon sudden death despite the very frequent ventricular arrhythmias. The molecular defect and the substrate for arrhythmia susceptibility in ATS1 are distinct from the “classic” forms of inherited LQTS also.\(^6,8,9\) Further, it appears that U waves were included in the “QT” measurement in some of the early publications, and that the QTc is actually uncommonly prolonged in ATS1.\(^7,0\) Thus, the designation as LQT7 may not be appropriate. Commercial genotyping is available for ATS1, but the diagnosis is generally quite apparent by the presence of one or more of the characteristic clinical findings and treatment is not influenced by knowing the genotype.

**LQT8. Timothy Syndrome, TS, Syndactyly-related LQTS**

The rare syndactyly-LQTS relationship was first reported in 1995.\(^7,1,2\) Mutation of the CACNA1c gene affects the Cav1.2 calcium channel (Splawski, 2004 #2989) producing a multisystem syndrome called Timothy syndrome after Katherine Timothy who had first contact with an affected family and described the clinical findings. The constellation of the phenotype include pronounced QT prolongation, syndactyly of fingers and toes, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism. The risk for arrhythmias and sudden death is high and the events often occur early in life. Though rare and few patients have been identified, the ICD appears to be the treatment of choice. Verapamil has been reported to improve ventricular tachyarrhythmias in 1 patient. This rare disorder has a characteristic phenotype that appears to be diagnostic, and the high mortality evident to date indicates that ICD implantation is appropriate. Therapy is not aided by knowing the genotype at this time.

In summary, there is substantial evidence that genotyping contributes only to a minor degree in selecting therapy at present, and despite that, our current treatment options lead to quite good outcomes. Future discoveries may yield an “enhanced and more comprehensive” genotype that defines which individual patients are at risk for sudden death or cardiac arrest, allowing us to move into the personalized medicine era of congenital long-QT syndromes.

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None.

## References

Response to Vincent

Arthur J. Moss, MD; Ilan Goldenberg, MD

Dr Vincent is a good friend and colleague, and he has been involved as a co-investigator in the International Long QT Syndrome Registry for more than 25 years. Although we have somewhat differing viewpoints on the optimal approach to selecting life-saving therapy in patients with long-QT syndrome (LQTS), careful reading of our somewhat opposing positions in the two associated articles reflects more a matter of degree than substance. Dr Vincent takes the viewpoint that genotyping has only a minor role in selecting therapy for patients with LQTS, largely because the life-threatening event rate is relatively low when β-blockers are universally administered to patients with LQTS. He further buttresses his position by highlighting the variable penetrance of family members with the same LQTS genotype using the broad categories of LQT1, LQT2, and LQT3. However, he does not discuss knowledge from the recent literature in which subjects with different mutations within a given genotype can have very different clinical courses, with some mutations associated with a high risk for cardiac events, whereas other mutations have a truly benign clinical course. In addition, Dr Vincent fails to mention that genotype risk in affected subjects is age and gender specific. Thus, genetic risk stratification and the aggressiveness of LQTS therapy, in terms of the dose of the β-blockers, the extent of behavioral modification, the use of genotype-specific therapy (such as mexiletine, flecainide, or ranolazine), and the appropriate use of implanted defibrillator therapy, require full knowledge of the clinical and genetic risk profile of each individual patient if we are going to eliminate even a low mortality risk while minimizing adverse therapeutic side effects in this relatively young, vulnerable group of at-risk patients. Our opinion is that one size does not fit all, especially as we gain new and expanding information about the differential, mutation-specific, risk profile that is now being uncovered as more patients and families with specific LQTS-related mutations are being studied and followed up.
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