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EDITORIAL COMMENT

Genetic Testing in Subjects With No Clinical Abnormality

The Tip of a Huge Iceberg*

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Genetic testing for individuals with manifest long QT syndrome (LQTS) has become part of routine care to confirm the clinical diagnosis and to stratify risk. A spinoff of such testing has been the identification of proband relatives with normal QT intervals who nevertheless are mutation carriers. A report in this issue of the *Journal* (1) addresses risk in this group. More generally, as described in the following, we are on the precipice of very widespread genetic testing using new sequencing approaches. The present study points to issues we will have to consider as we increasingly identify subjects with genetic variants and no clinical abnormalities.

See page 51

The congenital LQTS was first recognized as a clinical entity in the late 1950s and the early 1960s. Over the next 3 decades it came to be characterized largely as a rare condition in which children, adolescents, and young adults displayed striking QT interval prolongation and susceptibility to sudden death, generally with exercise, emotional stress, or exposure to sudden loud noises; the incidence of syncope or sudden death seemed to diminish with beta-blocker therapy (2). Exceptions to this general pattern were noted, such as occasional subjects who died in their sleep or without apparent provocation. The real breakthrough in management arose from fundamental scientific discovery: the identification of disease genes in which mutations cause the congenital LQTS (3). Initial studies in relatively small numbers of families were able to establish that the 3 major subtypes differ in electrocardiographic patterns, provokers of arrhythmias, response to beta-blocker therapy, and even prognosis (4,5). These advances in translating basic molecular and genetic information to the care of patients were only possible with the aggregation of large numbers of affected patients and their families into large registries.

The last decade and a half has seen not only advances in defining subtype-specific management, but also an increasing awareness of the disease among cardiologists and internists, and the increasing availability of genetic testing. One consequence of these advances is the increasing recognition of the phenomenon of incomplete penetrance (6), that is, subjects who are carriers of the causative mutation in a member of their family and yet who display normal electrocardiographic results. Previous studies have demonstrated that among those with prolonged QT intervals, the greater the prolongation the worse the prognosis (7). Thus, mutation carriers with normal QT intervals ought to be at low risk. The present study supports that contention but does not totally erase risk in such subjects, raising new questions about management.

Summary of the Present Study

The new study reports the incidence of aborted cardiac arrest (ACA) or sudden cardiac death (SCD) from birth through age 40 years in 3,386 subjects from 552 families from U.S., Western European, and Japanese centers. Among these subjects, 1,392 were mutation carriers with long QT intervals (defined here as a corrected QT [QTc] interval >440 ms), 469 were mutation carriers with QTc interval ≤440 ms, and the remaining 1,525 family members did not carry the proband's mutation and had normal QT intervals. Among those with long QTc intervals, the risk for ACA or SCD was 15% over the 40 years of follow-up (about 209 events), compared with 4% (17 events) in mutation carriers with normal QT intervals and 0.4% among unaffected family member controls.

Previous studies have identified risk factors for ACA or SCD in those with long QTc intervals: female sex, non-LQTS type 1 (LQT1) genotype, longer QT intervals, and (as discussed further in the following) mutation location. In this and previous studies, a family history of ACA or sudden death did not increase risk for these events in the study subjects. An interesting question is whether previous predictors of ACA or SCD also apply in mutation carriers with normal QTc intervals, and neither female sex nor QTc duration did. In the present study group, the prognosis was unexpectedly worse in those with LQT1; it is conceivable that the infrequent use of beta-blockers contributed (8).

In addition to specific genetic subtype (LQT1, LQT2, or LQT3), recent studies, using essentially the same study subjects as those reported here, have suggested that the predicted functional properties of individual mutations may be important in determining prognosis. Thus, for example, in patients with LQT1 and in those with LQT2, the common potassium channel-linked forms of the disease, prognosis appeared to be more severe among those patients with mutations predicted to affect transmembrane segments

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of the encoded channel protein, and less severe for mutations predicted to affect N- or C-termini (9–11). One possibility is that mutations affecting transmembrane segments are more likely to disrupt the permeation pathway of the channel (as suggested in the present report); more generally, mutations in transmembrane segments may be more likely to exert dominant negative effects in vitro, that is, to suppress potassium current by more than the 50% expected from a "simple" autosomal dominant disease. Interestingly, in the present study, this relationship of transmembrane versus N- or C-terminal mutations did not hold up in patients with manifest QT prolongation but did appear to be a predictor in those with normal QT intervals. Overall, there are fewer data available for LQT3 (the sodium channel-linked form of the disease), and although dominant negative suppression of channel function has been observed in vitro (12), the mechanisms and extent of the phenomenon are not so well understood; variants of uncertain significance seem more common in the cardiac sodium channel gene (*SCN5A*) than in the two potassium channel genes (*KCNQ1* and *KCNH2*) (13).

Caveats to the Interpretation of the Present Study

The common criticism directed against registry studies in any setting is their observational nature; these are not randomized clinical trials. However, randomized clinical trials are very difficult to accomplish in a rare disease such as the congenital LQTS because of the logistics that such an undertaking would require, the heterogeneous nature of the disease (many mutations), and, importantly, the likely lack of equipoise among large numbers of investigators around the world. So, although the approach is imperfect, it is what we have.

Given this limitation, it is appropriate to think a bit more about how mutation carriers with normal QTc intervals get into the registry and are followed. The study group was accumulated by several large registries, as well as a series of smaller centers across Europe. In this effort to be inclusive, the investigators run the risk of introducing errors because of differences in case ascertainment. This is particularly germane to the study group. For example, one could easily envision a situation in which a proband's children are more likely to undergo genetic testing than the parents. Follow-up and therapy for those with normal QTc intervals might be different from those with long QTc intervals; medication histories are unavailable for some of the study centers. Indeed, we do not know if a normal QTc interval once means a normal QTc interval on subsequent recordings. Genetic ancestry plays a strong role in modulating risk in other settings, and so inclusion of multiple racial groups—desirable from a clinical point of view—may further confound interpretation of the study outcome.

Among the 469 mutation carriers with normal QTc intervals, there were 17 ACA or SCD events. Therefore, it would be very imprudent to draw sweeping management conclusions on the basis of this small number and, in particular, on the basis of subsets of this small number. Thus, for example, the investigators' conclusion that prognosis may be worse with mutations in certain locations of the channel protein must be tempered by the very small number of events.

Finally, some comment must be offered on the single "illustrative" case presented: a mutation carrier with completely normal electrocardiographic results and episodes of non–pause-dependent, non–heart rate change–dependent polymorphic ventricular tachycardia. These tracings are typical of so-called idiopathic ventricular fibrillation initiated from a single focus (note the identical morphology of the initiating tachycardia beat) (14). Thus, this may well not represent a manifestation of LQTS; alternatively, this could be a new manifestation of LQTS, but absent other supporting data (such as a demonstration of how the mutation could generate this rhythm in the absence of QT prolongation), this is a difficult conclusion to support. The presentation of the intracardiac recordings adds further uncertainty. The top strip in Figure 4C shows rapid ventricular tachycardia, but with a relatively late coupled onset, unlike the clinical episodes presented. The bottom strip shows wide complex rhythm that is not a tachycardia, but rather simply atrioventricular pacing. Dwelling on a single case in an analysis of 3,386 subjects may seem pointless until one recognizes that misclassification of even 1 or 2 of the 17 ACA or SCD events could easily refute the conclusions of this study.

What Is Needed Next?

Genetic testing for the congenital LQTS, and many, many other conditions, is now beginning to be accepted into the fabric of modern health care. One naïve hope might be that such testing could be deterministic; that is, a genetic test could tell a clinician what to do in a given situation. However, as large datasets accrue relating genotypes to a variety of outcomes, the lesson that genetics is probabilistic is being reinforced: genetic variation modulates susceptibility to important clinical phenotypes, such as ACA or SCD. A reasonable way forward, therefore, might be to simply grow the current databases in size and duration of follow-up, but even with much larger study sets, genetics will never become deterministic.

I cling, therefore, to the hope that understanding the mechanisms whereby individual mutations cause channel dysfunction, and more importantly how common and rare genetic variants and the environment conspire to modulate those clinical phenotypes, is more likely to provide us with directions about how to manage vexing patients. The comparison of transmembrane versus nontransmembrane mutations is a wonderful start, but surely this must be followed by more detailed exploration of individual mutations and the channel dysfunction they confer. Recent studies describing the role of variation in the *NOS1AP* gene

as a potential modifier of risk highlight the potential of mechanistic approaches (15,16).

What should a physician do with mutation-positive patients with normal QT intervals? I am inclined to suggest following these individuals with serial electrocardiograms, avoiding QT-prolonging drugs, and deploying beta-blockers. I do not think the data on mutation location are robust enough to make this part of clinical decision-making yet.

The issue of genetic testing in individuals with no apparent phenotype is a general problem in modern genomics. Current estimates, derived from "next-generation" sequencing of whole human genomes, are that each of us harbors tens of thousands of deoxyribonucleic acid (DNA) variants that are present only in us and our immediate families (17), and that hundreds of these "personal" DNA variants are nonsynonymous, that is, they are predicted to alter amino acid sequence (18). As an example, the fully annotated genome of Steven Quake (a founder of Helicos, one of the companies developing next-generation DNA sequencing hardware) was published earlier this year (19). The Quake genome included 3 rare variants, in myosin-binding protein C, desmoplakin, and TMEM43, that could predispose to an increased risk for SCD. Whether variants such as these, discovered in an asymptomatic subject (although Quake actually has a family history of SCD), are biologically important or merely incidental findings is very much up in the air (20). This highlights the potential advantages and drawbacks of a vision of future health care in which whole genome sequences are included pre-emptively as part of each patient's medical record. It is possible that this approach will discover polymorphisms that are actionable, but the downside is a very high likelihood that many variants will be largely irrelevant.

Interventional cardiology continues to struggle with the oculostenotic reflex – the overwhelming urge to do something about an abnormality even in the absence of evidence that an intervention will be beneficial (21). One conclusion I draw from the present study is that we need more data (and ultimately guidelines) to address the management of patients with genetic variants and no detected clinical abnormalities. Otherwise, we will generate a 21st century equivalent of the oculostenotic reflex whose implications for health care may be enormous.

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