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Should Genetic Testing be Recommended for Long QT Syndrome Patients and Their Relatives?

Menachem Braun

Menachem Braun graduated with a BS in Biology in September 2017.

Abstract
The Long QT Syndrome (LQTS) is a familial, potentially fatal cardiac arrhythmia. Traditionally, it has been diagnosed by ECG. Molecular studies have provided evidence that LQTS can be caused by a range of underlying molecular abnormalities. Genetic research has proven that different forms of LQTS have different genotypic bases. Therefore, it has become possible to diagnose the specific type of disease genetically. This study examines the advancements made in the past thirty years in understanding LQTS and research regarding the use of genetic testing in order to determine the benefits of genetic testing for this disease. A survey of original studies which produced the information is presented here, and provides the reader with an understanding of the mechanics of the disease and how they differ in the several genetic variants. Research shows that the benefit of genetic testing must be weighed against the personal implications in may have for a particular patient and his or her family.

Introduction
In the year 1856, the German scientist Freidrich Ludwig Meissner described what may have been the first recorded case of the Long QT syndrome (LQTS). He recorded a case in which a deaf female student died suddenly during a moment of emotional stress. There had been two other children in her family who had died previously under similar circumstances. Since a diagnosis of LQTS requires an electrocardiogram, and at that time the ECG had not yet been invented, (Rivera-Ruiz, 1927) it is not known for certain that these cases were an example of LQTS (Vincent, 2002). Over a hundred years later, a study was performed on a family of 10 children. Four of the children had profound deafness and would often faint during moments of emotional or physical stress (Jervell, Lange-Neilson, 1957). Later, a similar familial tendency to faint during stress was observed in case studies (Ward, 1964). A prolonged QT interval was observed in the ECGs of subjects. At that time, two familial heart diseases known collectively as Long QT Syndrome were fully discovered and defined.

The advent of molecular and genetic science has revolutionized the medical world’s approach to this disease, as it has done for that of many others. Molecular studies have divided the cases of LQTS, which seemed in the past like one basic condition, into larger categories differentiated based upon molecular mechanism. Genetic differences were discovered between these types in the lab, and since genetic testing became available to the public in 2004, 15 categories including over 1500 different mutations have been found to be the underlying cause of a prolongation of the QT interval. This study focuses on the three categories which make up the overwhelming majority of cases. In some cases, certain genetic origins and molecular mechanisms have been linked to certain phenotypic characteristics, and some believe that genetic diagnosis may aid in recommendations and treatment for LQTS patients. This study aims to give a full description of the physiological and molecular mechanisms of LQTS based upon the latest research, and analyze the contribution of genetic research to the understanding and treatment of the disease. Most importantly, the primary objective of this study is to answer the question: Should genetic testing be universally recommended to LQTS patients and their relatives?

Methods
The Touro library system was an invaluable source of recent, high-quality academic papers. In addition, the National Institutes of Health and NCBI provided excellent references to PubMed articles which provided useful information. The author sought out independent studies and other primary sources to provide up-to-date reports of developments in the molecular and genetic understanding of the disease. Studies regarding recent attempts at gene-specific treatments and current academic medical surveys are considered in determining when genetic testing is indicated.

Discussion
Physiology of LQTS
The QT interval indicates the length of time from the beginning of the depolarization of the ventricles to the end of their repolarization. A prolonged QT interval will mean that the ventricles are taking too long to repolarize. This usually does not interfere with cardiac function, but occasionally can cause life-threatening ventricular fibrillation. The major mechanism of ventricular fibrillation which is brought about by a prolonged QT interval is the result of Early Afterdepolarizations (EADs). The plateau curve caused by the delay in repolarization can cause some of the heart’s cells to begin depolarizing while others are in the process of repolarizing. This can cause heterogeneous activity in the heart tissue, especially the ventricles, with some regions contracting and others relaxing. The result is a quivering or fibrillating heart, which cannot produce sufficient blood output and quickly leads to syncope and death (January, et. al. 2000).

Clinical Manifestation
Normally, depolarization and excitation of the cells of the heart are caused by a quick flow inwards of positively charged ions. These are usually Sodium and Calcium ions. However, the repolarization of the cells is not the result of those same ions flowing back out; it is an outward current of positively charged Potassium ions which causes repolarization. As the Potassium outflow increases, it overtakes the Sodium inflow, and the cell begins to repolarize. In all forms of LQTS, the symptoms are caused by a surplus of positive charges remaining within the cell. When some channels malfunction, the extra positive charge is caused
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by reduced outward Potassium current. When other channels malfunction, the extra positive charge is caused by increased or unchecked inward Sodium current. In either case early afterdepolarizations can result, meaning that depolarization may still be going on after the effects of repolarization have subsided. This can cause what is called a U wave (Roden, et. al. 1996). This U wave, however, is not a homogenous contraction of the heart. Some of the cells will show this depolarization, and others will not. If this EAD is still going on when the next beat occurs, it can cause the heart to contract in an uneven way (Antzelevitch, Sicouri, 1994). This leads to a characteristic ECG graph known as Torsades de Pointes. This is French for “Twisting of the Points,” and is named for the peculiar way the wave form seems to twist around the isoelectric line (El-Sherif, et. al. 1996).

Torsades de Pointes is not able to sustain a sufficient stroke volume of blood to support brain function. After some time with this abnormal ECG morphology, the patient will faint. Most of the time, the heart will overcome the Torsades and regain a normal heartbeat. At other times, the heart will not be able to “snap out of it” and the rhythm will deteriorate to ventricular fibrillation, without providing any meaningful output of blood. Unfortunately, this situation leads to death within minutes.

A patient who presents with Torsades is considered a medical emergency due to the risk of ventricular fibrillation which may result. However, the situation rights itself in the vast majority of cases. Therefore, DC shock defibrillation is not used as a primary course of action since it can cause recurrent arrhythmias.

One of the major aspects of treatment is preventing the patient from returning to a state of Torsades; whatever caused it the first time might cause it again. Therefore, it is urgent to remove or mitigate the effects of any drugs which may have caused the Torsades. It is also advisable to take measures to suppress EADs, among other things. Magnesium is effective at suppressing EADs (Viskin, 1999).

Since the danger resulting from a prolonged QT interval depends not only on the actual length of the interval but also the way it interacts with the surrounding segments of the ECG wave, it is important to have a method with which to accurately measure the clinical significance of any particular QT prolongation. To this end, the concept of QTc was developed, in which the actual length of the QT interval is mathematically corrected to take heart rate into account (Bazett, 1920). Since that time, many other methods have been proposed, and the medical community is currently in debate over which is most useful and accurate.

**Molecular Mechanisms**

To understand the cellular and molecular mechanics of Long QT Syndrome, we must understand the process of the action potential itself. At rest, nerve cells have a higher level of positive charge outside the cell than they do inside. When a nerve cell is stimulated, the chemical or electrical impulse it receives activates voltage- or ligand-gated Sodium channels. This creates an influx of positive current (depolarization). After a certain amount of positive flow is admitted to the cell, voltage-gated Potassium channels are activated, creating an outflow of Potassium ions and returning the cell to its resting state with more positive charge on the outside. Many different types of channels are involved in these processes. Cardiac muscle cells are unusual in the sense that they act to carry an action potential as efficiently as nervous tissue can, and therefore depend upon a similar set of ion channels (Sanguinetti, Jurkiewicz, 1990). We will delve deeper into this process shortly.

Some years ago, a groundbreaking study uncovered information about the process of repolarization in cardiac tissue. The goal was to understand electrophysiological differences between different areas of the heart. Microelectrodes were used to measure delays in repolarization found in certain canine heart cells, known as M cells. These cells, which had been previously found to show markedly longer repolarization times, are found in the deep sub-pericardial and mid-myocardial regions. The researchers measured the durations of their action potentials to have a mean of 358 ms, as opposed to 282 ms or 287 ms found in other regions of cardiac muscle. Upon further examination of the M cells, it was shown that they show differences in IK when compared to other cells. IK means Potassium ion current, which is the current responsible for the repolarization that ends every action potential. There are two distinct currents found in cardiac cells, the IKr, or rapid-activating current, and the IKs, or slow-activating current. These currents are mediated by two separate transmembrane voltage-gated protein channels. The M cells have smaller IKs (Slow-acting Potassium current) than the other cells, while IKr (Rapid-acting Potassium current) is generally the same. Of course, the mechanism for the rate of an action potential has many factors, and depends upon the inward rectifier (IK1), Calcium ion inward current, Sodium-Potassium pump inward current, Sodium-Calcium inward current, and others.) (Sanguinetti, Jurkiewicz, 1990). The IKs in the M cells was measured using a selective IKr blocker, E-4031. The Potassium current was measured in the cells with E-4031 and in the cells without E-4031. The difference between the two measurements was the IK due to IKr, and the common portion was the IK due to IKs. It was found that the IKr in different cell types was essentially the same, and reduced IKs current was responsible for the delayed repolarization in the M cells. It was discovered in this study that IKr differs from IKs in its kinetics of activation, more negative threshold for activation, and different protein structure suggested by its selective blockage by methane sulfonamide class III agents like E-4031. However, studies of M cells demonstrated that delayed IKs can play a principle role in delayed repolarization. The researchers predicted that the M cells may be found to be the culprits of diseases such as LQTS (Liu, Antzelevitch, 1995).
Later the same year, it was shown that the plateau portion of repolarization is accomplished principally by the IKs protein. It was also discovered that in the heart in general, blocking either IKr or IKs can prolong duration of the action potential by the same degree. This means that either protein can be a target for antiarrhythmic drugs for tachycardia. By the same token, either protein could also be the culprit of an arrhythmia with extended action potentials, such as LQTS (Zeng, et. al. 1995.) As we will see soon, genetic studies have confirmed that LQTS can result from mutations in the genes which code for either of the proteins, and others as well.

Genetic Variation

It has been known for many years that not all cases of LQTS have the same symptoms. For example, some cases of LQTS are dangerous specifically under situations of emotional stress. Other cases are set off especially by exercise, whereas some cases seem to cause syncope specifically during swimming. It was established that in these cases it was not the stress or exercise of swimming which caused the ill effects, but rather the actual immersion of the face in cold water (Mayumi, et.al. 1995).

Genetic research has since shown that mutations in several genes, coding for several proteins, can cause LQTS. Different types of the disease have been linked to different genes, and over 1500 different novel mutations have thus far been discovered on 15 different genes which code for 15 different proteins. One such gene is the KCNQ1 gene. This gene on chromosome 11 codes for the alpha subunit of the voltage-gated Potassium channel. It has six transmembrane domains. Even though there is an ion pore function for this protein alone, some of the functioning of the channel requires it to be co-assembled with the beta subunit. This subunit is called KCNE1. The two subunits together account for the cardiac IKs. Mutations in different segments of this protein channel cause varying degrees and kinds of diseases. The S4 domain contains a voltage sensor, and loss of function mutations in this area can cause LQTS. In addition, there is a pore helix selectivity filter segment which can, when its shape is altered, severely affect the functioning of the IKs current. In this segment, certain mutations cause more loss of function than others. For example, an I313K mutation in the selectivity filter segment can cause all of the symptoms of LQTS, including syncope and risk of death, whereas an I313M mutation will prolong the QT interval, but the patient will be otherwise asymptomatic. All KCNQ1 and KCNE1 mutations are included in the category LQT1 (Ikrar, et. al. 2008).

LQT2 is a result of a loss of function in the HERG channel. HERG stands for Human Ether a go go related gene, so named for the fact that a mutation in its homolog in fruit flies causes them to “dance” when exposed to ether. More than 80 mutations were known in this gene in 2000, and many more are known today. HERG is a gene located on chromosome 7 that codes for the pore-forming subunit for the IKr channel. There are several mechanisms by which HERG mutations cause reduced IKr. One of them is that a certain degree of codominance exists in heterozygous individuals with certain mutations. The protein which comprises the HERG channel is actually a tetrameric structure formed by the co-assembly of four copies of the HERG gene product. Depending on how the subunits combine, the mutant gene products might be excluded from the ion pores, causing a 50% reduction in pore function. On the other hand, the mutants might be included in some of the complete proteins, causing more than 50% to be defective. Other mutations in the HERG gene are truly dominant, and produce channels which activate at voltages which are more negative than usual. One mutation, N629D, was found to make the pore channel nonselective and allow ions other than K+ to pass through. Interestingly, many mutations in the HERG protein affect not the actual functioning of the ion pore, but its “trafficking,” i.e. its ability to be properly packaged and transported to the plasma membrane. In these cases, the mutant proteins are marked as abnormal by the cell’s quality control systems and are kept in the endoplasmic reticulum and degraded. In these scenarios, applying E-4031 to affected cells was shown to allow trafficking of the proteins to the plasma membrane, and the drug could later be washed off. Applying this method in vivo is still an area of study for these particular mutant forms. This is a form of gene-specific therapy for LQT2. Another form may be increasing serum K+ concentration, since HERG current is highly sensitive to extracellular K+ concentration. (January, et. al. 2000)

More work was done recently on attacking the gene-specific therapy problem from the trafficking angle. It has been shown that certain mutations cause misfolding of the protein, and this is what prevents it from leaving the endoplasmic reticulum. This was discovered by causing chemical unfolding of several different mutant forms and measuring the difference between the stabilities of each mutant’s folding. It was found that there was a direct correlation between the conformational stability of the protein and its degree of trafficking deficiency (Harley, et. al. 2012).

LQT3 is has a very different molecular basis from that of both LQT1 and LQT2. The first two forms of Long QT syndrome are caused by malfunction of Potassium channels. These channels function to create an outflow of positive current during repolarization of the heart’s muscle cells. These mutations are examples of what is known as “loss of function” mutations. In other words, the protein coded for by the gene does not work as well with the mutation as it does in the wild type. LQT3, however, is a “gain of function” mutation. It causes the Sodium channel pores to become more effective than in the wild type. This means that the depolarization process lasts longer, thereby slowing repolarization and extending the QT interval (Mazzanti, et. al. 2016).
Gene-Specific Recommendations and Therapies

Phenotypic differences have been found between LQT1 and LQT2. Heterogeneity has been noticed among LQTS patients regarding the effect that exercise has in precipitating Torsades de Pointes and ventricular fibrillation. It was discovered that patients matched for age and gender showed differing QT adaptation patterns during exercise. Patients with LQT1 showed a steady QTc prolongation, even at higher heart rates. Since each heart beat occurs at a faster rate, and the QT prolongation remains the same, it is more likely that the repolarization process will interfere with the following QRS complex, bringing about Torsades de Pointes and ventricular fibrillation, causing syncope or death. In LQT2, however, the QT interval prolongation is actually reduced as the heart rate increases, meaning that the QT interval occupies the same proportion of the total ECG sequence that it does at lower heart rates, such as during rest. Therefore there is no greater risk of syncope in LQT2 during exercise than at any other time. This is consistent with the molecular and genotypic understanding of the differences between these two disease types. Exercise creates an increase in sympathetic activity, i.e. the heart is being driven not only by its internal pacemaker, but also by hormonal and systemic nervous impulses and stimulants, such as epinephrine and other adrenergic agents. In this situation, the predominant current for the increase in the rate of repolarization has been proven to be the IKs current, precisely that one which is affected by LQT1. Therefore, it is understand able that LQT1 patients will be more susceptible to syncope brought on by exercise-related stress. These differences are generalizations; actual recommendations to patients still must be based upon observation and testing under different types of stress (Sy, et. al. 2010).

In addition, many symptoms have been found to be associated with different forms of LQTS. As stated, LQT1 is associated with syncope brought on by exercise, with swimming being a particular stimulus in certain cases. LQT2 is associated with cardiac events connected with mental stress such as fear or anger. LQT2 patients also faint when they hear sudden noises such as alarm clocks and phones. LQT3 seems to be associated with attacks which come while a person is resting or sleeping. Knowledge of the genetic basis of the disease can thus be helpful in advising the patient which activities to avoid. However, even though statistically there is a significant association of these properties with these forms of the disease, a genetic diagnosis is by no means conclusive of a specific expression. Among the 1500 variations discovered thus far, most do not exactly fit the general trend. Therefore, although genetic testing can be helpful in planning an avoidance or treatment plan, clinical manifestation is the ultimate deciding factor (Mangset, Hoffman, 2014).

Several gene-specific therapies have been proposed for LQTS. Beta Blockers are effective for LQT1 and LQT2, whereas they can have negative effects in the case of LQT3. Potassium supplements also are suggested for LQT2, since an elevated blood potassium level has been shown to enhance the activity of the HERG channels. Mexiletine, a methane sulfonamide Sodium channel blocker, may be effective for LQT3, as described before. Although some of these have shown promise, comprehensive and clear proof of their efficacy and safety has not yet been established (Viskin, 1999.) Recent studies have shown Mexiletine to be effective at reducing the QTc of more than two thirds of patients with LQT3. These studies had certain limitations, however, and were not sufficient basis for widespread use of this gene-specific therapy (Mazzanti, et. al. 2016).

Implications of Genetic Testing

Since 2004, genetic testing has been made available on symptomatic people to discover what the genetic source of their syncopal episodes may be. However, in many cases there is a dilemma for the patient. Most cases of LQTS do not require genetic testing for diagnoses, and if pathology is suspected in a newborn based on heredity, risk of serious effects can usually be effectively determined by ECG. In addition, even if the genetic testing comes up clear, preventive measures will still be taken for anyone whose QTc is over the limit of .45 ms. Therefore, the primary justification for genetic testing is not identification, but rather the possibility that gene-specific therapy will be available. As explained, most gene-specific therapies which require a genotypic diagnosis are still not available to the public. Those therapies and recommendations which are available can be safely used without genetic testing. This creates a dilemma for many patients and their relatives. On the one hand, there is the patient’s right to know. A clear, empirical knowledge of the source of their disease helps some patients adjust and cope psychologically. On the other hand, who would want to know for certain that they carry a gene which may or may not have deleterious effects on their children? Since there are effective screening methods, and this knowledge can be a significant source of fear and anxiety as well as causing moral dilemmas, many people are uncomfortable going for testing. Sensitivity to this discomfort has been termed by some as “the patient’s right not to know.” This consideration is rarely addressed by health care providers, and the National Society of Genetic Counselors is making an effort to educate providers about the psychological impact of genetic testing (Mangsett, Hoffman, 2014).

A longitudinal study was done to observe the long-term effects of congenital LQTS. Individuals from 328 families with multiple cases of LQTS were observed over the course of several years. The probands had usually fainted at some time during their childhood years, with an episode of fainting or death occurring in 50% of them by age 12. The majority were women, showing that the effects of the gene are more serious in females. The yearly rate of fainting spells till age 50 was 5.0% per year for those enrolled in the study, and the rate of death was .9%. This
was higher not only than the rates in unaffected family members, but also higher than the rates in affected family members. This shows that LQTS genes can have a variable level of expression even among affected people (Moss, et al. 1996). Since the disease can have varying levels of effect even among those who are stricken by it, it may be true that testing of all family members can help in discovering mildly affected people.

More recently, however, a survey was taken to determine the effects of genetic abnormalities on people who were otherwise clinically normal in terms of ECG and symptoms. Interestingly, no ill effects were found to be associated with genetic defects alone, even in situations where those same genetic defects produced significant disease in other patients. Some suggest that this might be affected by the fact that genetically positive patients tend to take care to avoid activities which bring on syncopal episodes. This information was not part of the study however, and it is therefore unclear whether clinically normal but genetically abnormal individuals need to take any action at all to protect themselves from syncope or death (Lampert, 2015).

One other argument has been made in favor of genetic testing of family members of affected individuals. Some drugs which are administered by psychiatrists to relieve psychological symptoms either function directly through changing the electrophysiological workings of the heart, or have side effects which can affect or alter the action potential of the heart cells. It is suspected that an increased rate of sudden death among psychiatric patients may be caused by underlying QT interval abnormalities which may, when augmented by the effects of the drugs, come to have deadly effects upon the heart's rhythm (Sayako, et al. 2014.) However, the effects were only observed in a small percentage of the psychiatric population.

Certain specific mutations have been identified as conclusive-ly pathogenic. Individuals who carry these variants are advised to take beta blockers as a prophylactic measure. Although these are official recommendations due to an abundance of caution, there is still no evidence that these mutations pose a significant risk in unaffected people, and the testing of relatives is not universally required (Vincent, 2001).

Conclusions

The Long QT Syndrome is a great example of how a little information can be a dangerous thing. This is an area in which there has been a recent surge in pure information: exact mutation types, statistics, symptoms, etc. However, the tying together and understanding of this information is lagging far behind its production, and that which exists is ambivalent and confusing. Since people rely on their healthcare providers not only for information, but also for confidence and reassurance, it can be difficult for the provider to respond appropriately to questions about this disease. One patient commented that he gets different recommendations from the same doctor on different occasions. In these situations the doctor must try to convey confidence to the patient while honestly admitting that he or she does not know the full significance of genetic results, and possibly nobody in the world knows (Mangsett, Hoffman, 2014).

Genetic testing is definitely a powerful tool in the understanding of LQTS. However, both methods of interpreting the genetic data and the treatments that might be tailored to the specific types have not yet been developed in a way which provides institutionally recognized necessary medical benefit. In addition, in most cases, only minor benefits have been shown to come from testing unaffected relatives for identification purposes. This makes it difficult to argue that all patients and relatives should universally submit to genetic testing, since research has observed emotional and ethical difficulties which can arise from the testing itself. However, a specific genetic diagnosis can influence the recommendations and, to some degree, the treatment that a patient will be provided with. In addition, since treatment is recommended for some variants even in the absence of ECG symptoms, relatives of individuals with those variants have more reason to submit for genetic testing. A physician and genetic counselor should therefore discuss the benefits as well as the pitfalls of testing with the patient or relative, and the patient or relative should decide whether or not to submit to testing. In the coming years, the approval of developing gene-specific treatments may make genetic testing more important for affected individuals.

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