What about genetic testing?

Since the original genetic discovery that defective ion channels can cause LQTS in 1995, LQTS genetic testing has been performed in select research laboratories throughout the world as a discovery-based research genetic test whereby the patient (research subject) may or may not be a direct beneficiary of his/her research participation. Since 2004, LQTS genetic testing has been commercially available, clinical diagnostic test. This test is called FAMILION and is provided by PGxHealth. The FAMILION test searches for genetic misspellings in the five major LQTS-susceptibility genes that cause approximately 70 – 80% of LQTS. Your physician may order the initial test on one family member (so-called index case). Once/if the index case has a gene mutation identified, testing of other family members for that mutation is available, and can assist in clarifying those family members with non-definitive ECG findings. In fact, if a genetic diagnosis of LQTS is established for the index case, the ONLY definitive test to rule in or rule out LQTS for family members and relatives is the LQTS genetic test.

What is the treatment and who should be treated?

All symptomatic patients should receive treatment. All children and young adults should be treated even if they do not have symptoms. This is because symptoms might occur and sudden death may be the first symptom. Thus, preventative treatment is required in all. Most often, the usual treatment involves taking beta-blocker medications daily. This approach is effective for the majority of patients with LQTS. The dose needs to be monitored closely carefully balancing the prevention of LQTS spells with unwanted side effects related to energy level and mood.

Patients who continue to have symptoms in spite of appropriate doses of beta-blockers may also require additional medications or devices. Patients who have experienced a cardiac arrest usually receive an ICD (implantable defibrillator). With LQTS genetic testing, treatment strategies can be guided by the underlying genetic cause. For example, beta blockers are generally extremely protective in type 1 LQTS (LQT1) but may not afford sufficient protection in type 3 LQTS (LQT3). Thus, patients with LQT3 may therefore require alternative medical therapy and/or an ICD. Patients with very aggressive LQTS experiencing recurrent sudden death episodes may also benefit from a surgery known as left cardiac sympathetic denervation (LCSD) surgery or long QT syndrome. Increasingly, all LQTS families are being advised to obtain their own personal automatic external defibrillator (AED) as a standard part of their family’s sudden death prevention arsenal.

Persons over 40 years of age at the time of diagnosis, who have been asymptomatic (without symptoms) all their life (or for many, many years), may not need treatment as their risk of developing symptoms at these later ages is very low. As with all patients with LQTS, these seemingly low-risk older patients need to avoid low blood potassium (caused by diuretic drug use, vomiting or diarrhea) and drugs which aggravate the heart’s recharging system and prolong the QT interval. This combination of an otherwise dormant LQTS genetic substrate plus a ‘second hit’ can provide a fatal 1-2 punch. For a complete list of drugs that prolong the QT interval and/or induce torsade de pointes, visit www.sads.org or www.qtdrugs.org.

Medication compliance

It is very important that LQT-directed medical therapies be taken every day and not missed or omitted. The medications are not cure-all, they only provide protection while being taken and the protective effect is gone within a day or two of stopping the medication. After that, the risk of cardiac events is the same as if the patient had not taken the medication at all. Parents should teach their children about the importance of daily medication, and should make sure each daily dose is taken. Physicians need to discuss this directly with all patients, but particularly pre-teens and teenagers. The most common reason for cardiac events while on medication may be that the medication has been missed or stopped.

How can parents protect their kids?

• Make sure the children take their medication daily, no missing doses.
• See the doctor regularly for follow-up. Growing children need medication dose changes regularly. Make sure you see the doctor at least once a year, more frequently during very rapid growth, and discuss the need for dose changes.
• Be supportive if the doctor advises “no competitive sports for your child.” Support this advice, and help the child to understand that usual physical activities are suitable, but that competition may be dangerous. Channel their energies into sports without intense physical demands (golf, for example), or non-physical activities.
• Insist upon a “QT safety check” with any prescription given to your child. Besides the provided list of at-risk medications, the physician ordering the medication and the pharmacist dispensing it should conduct their own surveillance.
• Get additional medical advice if you are not comfortable with how things are going. Ideally, every patient/family with LQTS should be cared for by a heart rhythm specialist (cardiac electrophysiologist) or even a long QT syndrome specialist. Do not hesitate to obtain a second opinion if you have any questions about your child’s treatment.
• Make sure your family has their own AED (automatic external defibrillator) and encourage your child’s school district to adopt an AED program in their schools.
Patients and Parents need to know:

- What is LQTS?
- Who to see for proper testing.
- How to develop a family pedigree and screen family members.
- About genetic testing for LQTS and other SADS conditions.
- When to refer patients for diagnosis & treatment.
- When to consider LQTS as a possible diagnosis.

We estimate that 1 in 2500 people in the United States have LQTS. LQTS-predisposed sudden deaths continue to claim otherwise healthy infants, children, adolescents, and adults at an unacceptably high rate. However, with increased awareness, genetic testing, and effective treatment options, LQTS can be diagnosed early and sudden death prevented. Still, this condition is often undetected prior to death and not recognized as the cause of death. Family members of individuals with unexplained death should be tested for LQTS and other genetic arrhythmias. LQTS is a highly treatable disorder and, with correct diagnosis and common treatments, most deaths are preventable.

Physicians need to know:

- When to consider LQTS as a possible diagnosis.
- When to refer patients for diagnosis & treatment.
- About genetic testing for LQTS and other SADS conditions.
- How to develop a family pedigree and screen family members for LQTS.

Patients and Parents need to know:

- The warning signs and symptoms of LQTS.
- Who to see for proper testing.
- How to protect their children and themselves.
- How to expand their family pedigree and contact other family members who may be at risk.

What is LQTS?

QT is a disturbance of the heart’s electrical system. It is caused by abnormalities of microscopic pores in the heart cells called ion channels. Ions such as potassium, sodium, calcium and chloride pass back and forth across the cell membrane through ion channels. As they do, they generate the electrical activity (depolarization and repolarization) that controls the heart’s beating. Our window to this electrical activity of the heart is through an electrocardiogram (EKG or ECG). Potassium and sodium ion channels are two of the major sites affected in LQTS.

The abnormal channels prolong the repolarization (“recharging”) process and the QT interval, thus predisposing patients to certain cardiac arrhythmias. Thus, LQTS is a glitch in the electrical recharging phase of the heart.

What is the QT interval?

The QT interval is a time interval on the ECG. It represents the time from the electrical stimulation (depolarization) of the heart’s pumping chambers (ventricles) to the end of the recharging process of the electrical system (repolarization). It is measured in milliseconds and closely approximates the time from the beginning of the ventricles’ contraction until the end of relaxation.

The QT interval varies in each person and between persons—such as most physiologic parameters—such as blood pressure or heart rate. In particular, the QT varies with the heart rate. It shortens as the rate increases and lengthens as the rate decreases. Therefore, there is a range of normal or healthy QT intervals. In contrast, the long QT heart often recharges sluggishly or inefficiently as evidenced by a “prolonged QT interval” on the ECG.

To determine if a given QT is normal for a given heart rate, the QT is corrected for the heart rate using a simple mathematical formula, and the resultant quantity is called the QTc. The QTc is the value that doctors generally use when assessing for LQTS.

The “normal” QTc varies from approximately 350 to 480 milliseconds. About 90% of people have a value between 380 and 440 ms, which is the range doctors generally consider as the “normal” range. However, this “normal” range is affected by age and gender. For example, women tend to have slightly longer QT intervals than men and while a QTc of 440 ms represents the top 2.5 percentile in a 4-day-old infant, that same value represents the top 15-20th percentile for a 40-year-old woman. The diagram below provides an example of a normal and a prolonged QTc interval. The RR interval determines the heart rate.

In this diagram, since the heart rate (RR) is the same for both examples but the QT interval is longer in the lower panel, the QTc is longer in the lower panel example.

What are the symptoms of LQTS?

Nearly half of patients with LQTS NEVER have a symptom. However, if/when the LQTS heart “spins” electrically out of control into its trademark cardiac arrhythmia called torsade de pointes, sudden, temporary, loss of consciousness (syncope) is the most common event. These events usually occur without warning and are triggered by exertion or auditory stimuli. Typically, the onset of symptoms is earlier in boys than in girls. Statistically, the greatest risk window includes the first three decades of life (the first two decades in males and the second and third decades in females). However, there are tragic exceptions to these trends and LQTS-related events can continue during the 40’s and 50’s. When presenting later, a second hit, due to a medication that further aggravates the QT interval or low potassium, is often present.

In patients who experience syncope only, the potentially dangerous rhythm spontaneously returns to normal, usually within about one minute, and the patient quickly regains consciousness without disorientation or confusion. Some patients may experience slight fatigue Afterwards, others feel fine and resume their regular activities. If this bad LQTS rhythm persists longer, patients may then manifest a generalized seizure. In fact, some patients with LQTS have been misdiagnosed initially with epilepsy or a benign reaction to a medication. In both the syncope and seizure presentations, the long QT heart eventually caught itself, reverted back to normal sinus rhythm, and the “spell” ended. On the other hand, in a minority of patients, the torsade rhythm persists, then degenerates into the heart rhythm known as ventricular fibrillation, which rarely reverts back to a normal rhythm without medical intervention. If the ventricular fibrillation is not converted, usually by electrical defibrillation, the outcome is sudden cardiac death or sudden cardiac arrest.

When should the diagnosis be suspected?

In any young person with unexplained syncope (fainting), unexplained seizures, or unexplained cardiac arrest or sudden death.

Usually, a careful history of the events surrounding the syncope differentiates LQTS-induced syncope from the common faint, known as vasovagal or neurocardiogenic syncope. The LQTS syncope is usually precipitous and without warning. It often occurs during or just after physical exertion, emotional excitation or sudden auditory arousal (such as a doorbell or alarm clock), but may occur during sleep or at rest. Conversely, in vasovagal syncope, most times there are warning symptoms, such as dizziness, blurring or blackening of vision, tingling or sweating, for seconds to even minutes prior to the syncope. Also, a precipitating event is usually present, commonly pain, injury, nausia, or an unpleasant or stressful experience.

When there is a family history of unexplained syncope, unexplained seizures, or sudden death in young people. As noted above, at least one-third to one-half of individuals never exhibit symptoms, and, therefore, the lack of prior symptoms does not exclude a person or family from having LQTS.

When the autopsy is normal following the sudden and unexpected death of a young person.

How is the diagnosis made?

LQTS is diagnosed primarily upon recognition of a prolonged QT interval on the ECG. A QTc of 470 milliseconds (ms) in males and 480 milliseconds in females is generally considered strongly suspicious for LQTS, in the absence of other evidence of medications, which prolong the QT interval or other forms of heart disease. A QTc of less than 440 ms in males and 410 ms in females makes the diagnosis extremely unlikely. The computer generated QTc may be incorrect, so when the diagnosis of LQTS is considered, the physician should verify the computer measurement.

Not all LQTS patients have a prolonged QT on the initial ECG. However, in about 30 – 50% have a QTc that overlaps with the normal range and over 10% have a QTc < 440 ms. QTc’s in this range are inconclusive, therefore, and must be clarified by additional testing such as exercise stress testing, the epinephrine QT stress test, and genetic testing.

How is LQTS inherited, and who in a known or suspected family should be tested?

LQTS is usually inherited by autosomal dominant transmission. This means that it generally affects boys and girls equally, and that each child of an affected parent has a 50% chance of inheriting the genetic abnormality. In a really large family, close to 50% of the children would inherit the disease-causing gene. In average size families, it can range from all to none as each child has an independent 50/50 chance of inheriting the “genetic defect.” Once a family member is identified with LQTS, it is extremely important that other family members be tested for the syndrome. It is especially important to know which parent and grandparent has the abnormality, since brothers and sisters, aunt’s, uncles, nieces, and cousins on the affected side are potentially at risk.

This prospective screening, by ECG, is extremely important so that all affected family members are identified and treated early in order to prevent the tragic and unnecessary sudden deaths that may occur.