

How to make the diagnosis of Long QT syndrome in patients with reduced penetrance of the prolonged QT phenotype when DNA testing is not available or is negative.

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The inherited Long QT syndrome (LQTS) is notable for genetic and phenotypic heterogeneity. Reduced penetrance of both the ECG and symptoms phenotype is prominent in LQTS. Approximately 50% of gene carriers never have symptoms and about 33% have a normal to borderline prolonged QTc interval (≤ 460 msec) on the baseline ECG. The diagnosis of LQTS is difficult in those patients without a prolonged QT interval on baseline ECG, whether symptomatic or asymptomatic, and particularly problematic when DNA testing is either unavailable or is negative (DNA testing is negative in about 30% of LQTS patients tested).

This manuscript will discuss strategies for clarifying the diagnosis in these patients.

As is often the case in medicine, the answer is in the details.

- The History
- The ECG
- The Family Pedigree



The History

The primary symptom in LQTS is syncope, with aborted cardiac arrest and sudden death the other symptoms. Importantly, about 50% of gene carriers never have any symptoms throughout their entire life yet they can pass the gene on to their children who can have symptoms, including sudden death. Thus, it is important to identify the asymptomatic carriers in addition to those with symptoms, particularly the asymptomatic children as they may not have had any symptoms by the time of the evaluation, but may do so subsequently. Obviously, the absence of symptoms does not exclude the diagnosis of LQTS, nor does the absence of a family history of LQTS or early sudden death. For those patients with syncope a careful history of the event(s) may disclose features that are consistent or inconsistent with an LQTS event. If consistent, that history adds suspicion to the diagnosis of LQTS. The details of the history of syncope usually clarify the differential diagnosis.

The differential diagnosis of LQTS

- Vasovagal/neurocardiogenic syncope: Usually preceded by progressive presyncopal symptoms including lightheadedness, visual blurring and darkening, sweating, and recognition of impending faint. Often aborted by sitting or lying down. Typically very brief period of unconsciousness. Usual precipitators are pain, injury, seeing blood or getting a shot, nausea, among others. In some cases the syncope is precipitous and more difficult to differentiate from LQTS syncope. Brief syncope and absence of impaired breathing are clues to the correct diagnosis. Further, most patients with a precipitous vasovagal event have other episodes with typical presyncopal feelings, assisting the physician in making the correct diagnosis.

- Seizures: May be preceded by aura, the events are usually precipitous but accompanied by rigidity, major or minor motor movements, incontinence, and post ictal signs and symptoms.
- Orthostatic hypotension: Surprisingly, this diagnosis is often missed because the details of the event are not asked in the history. Recognition that the syncope occurs after rising from bed or a chair easily clarifies the diagnosis.
- Other tachyarrhythmias: Palpitations are usually the predominant symptom and may persist for some time prior to the syncope.
- LQTS: Syncope is usually precipitous and without warning. Palpitations and presyncope are uncommon, though not unheard of. When palpitations are present they usually indicate a different tachyarrhythmia than LQTS. Loss of consciousness is usually 1 to 2 minutes, breathing is impaired or absent, and there is no pulse. Upon awakening the patient is alert and oriented, and usually resumes their daily activity after a short time. Typical precipitators include exercise, and emotion such as startle, fright, or anger. Some episodes occur during sleep or at rest while awake. Rigidity and major motor movement are uncommon, however, seizures are a common misdiagnosis in LQTS patients. A careful history usually reveals minor and non-repetitive jerks, more like myoclonic jerks rather than seizure movements. The myoclonic type jerks are often interpreted by the lay observer as a seizure. If the medical person accepts that conclusion from the observer without further questioning for clarification, the misdiagnosis is perpetuated. There are no post ictal symptoms in LQTS. A small minority of LQTS patients have a typical major motor seizure. My experience suggests this usually occurs several minutes after the loss of consciousness, and probably is due to cerebral anoxia from the cardiac arrest. A careful history, if observers were present and can be questioned usually clarifies the time sequence of events. The major motor movements are immediate in a seizure but delayed by several minutes in a hypoxic seizure and the patient is usually cyanotic when the seizure begins.

The reason why palpitations and presyncope are uncommon in LQTS events is shown in the ECG strip below, Figure 1. Within less than one second following the initiating PVC the rate is over 300/minute. Since the heart does not contract at such a rate palpitations are not perceived. The immediate cessation of cerebral perfusion apparently does not allow time for presyncope symptoms to occur. Some of few patients I've seen who do experience palpitations or presyncope have had slower rates of torsade.

Figure 1

ECG strip showing the onset and rate of torsade de pointes



The ECG

The QTc criteria for the diagnosis of LQTS

The QTc criteria for diagnosis of LQTS in the literature are somewhat variable, but are generally similar. From our extensive database we have developed the following criteria. These criteria can be applied to ECG records from any of the several sources mentioned below except for ambulatory ECG recordings. They require a longer QTc for diagnosis (see section on ambulatory ECGs for details).

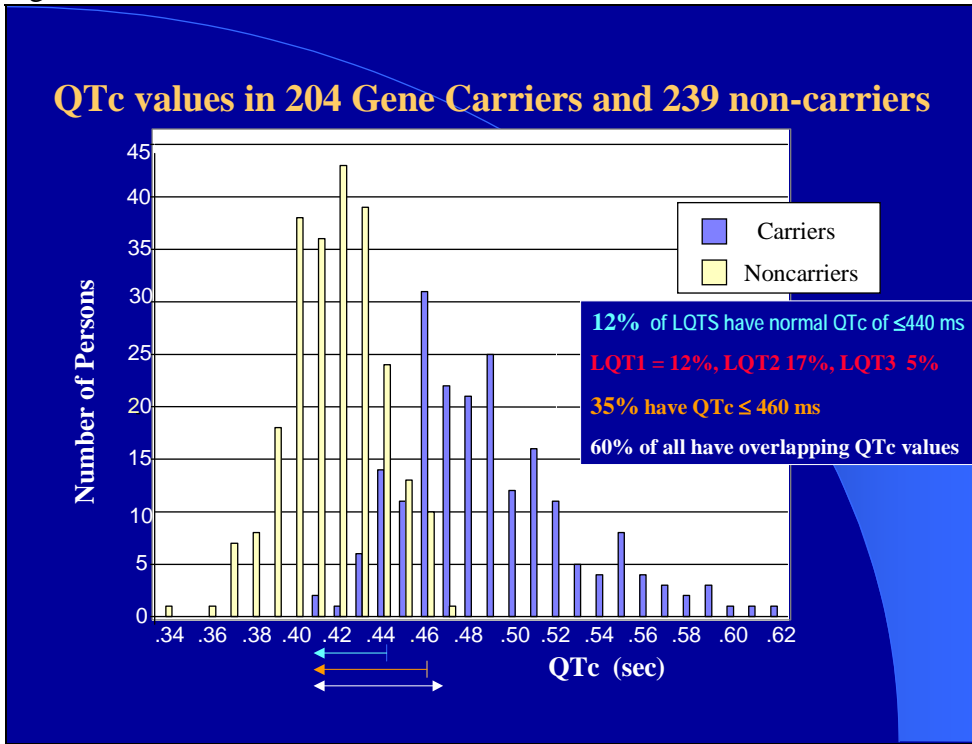
QTc Criteria for Diagnosis

- QTc ≥ 0.48 sec in females = LQTS, in the absence of QT prolonging drugs or any other disease that could lengthen QT interval
- QTc ≥ 0.47 sec in males = LQTS, in the absence of QT prolonging drugs or any other disease that could lengthen QT interval
- QTc < 0.39 sec in males and < 0.40 in females = No LQTS
- In presence of LQTS type symptoms or known family history:
 - QTc 0.46 sec in females and 0.45 sec in males = high probability LQTS
- QTc of 0.39 to 0.45 in males and 0.40 to 0.46 sec in females = uncertain. Requires further clarification

The Baseline ECG

As noted above, about 1/3 of LQTS gene carriers have a QTc on baseline ECG of ≤ 460 msec, range 390 to about 700 msec. About 12% have a QTc ≤ 440 msec. The diagnosis will be routinely missed in these patients unless the strategies discussed here are employed for clarification of the diagnosis. The graph below, Figure 2, is from several years ago and shows the QTc distributions in a group of LQTS gene carriers and non-carriers. More recent graphs of much larger numbers from my database include a few LQTS gene carriers with QTcs of 390 and 400 msec and some with QTcs up to 640 msec but are otherwise similar. Note the large degree of overlap between normals and LQTS carriers.

Figure 2

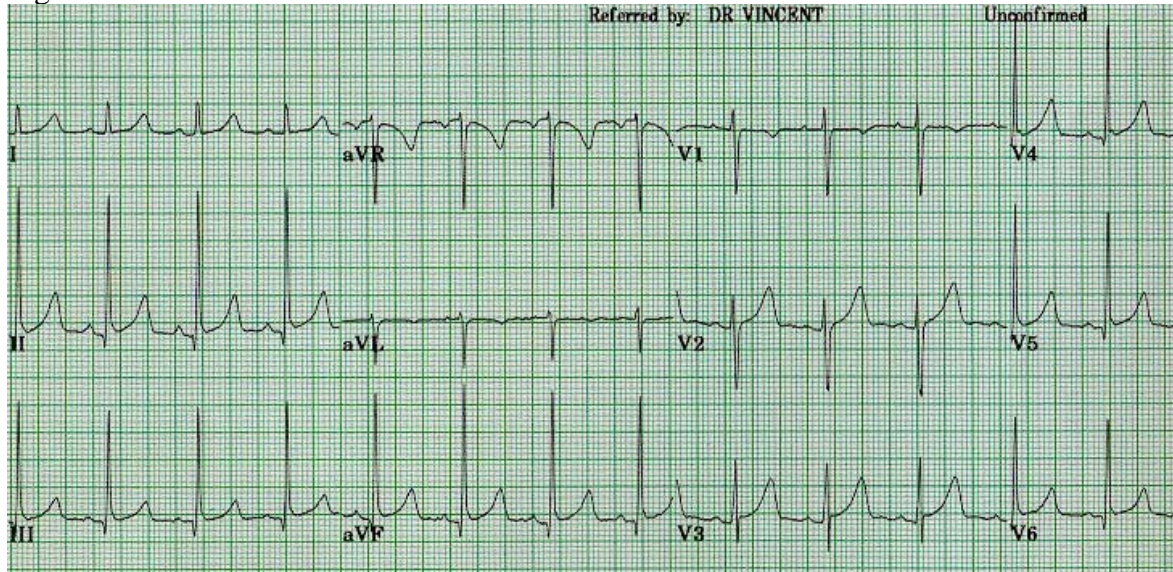


The average QTc in LQTS patients is about 485 msec. This degree of QT prolongation is not real obvious and it's easy to drop the ball on the diagnosis.



Many patients are missed because the QTc prolongation is not recognized. The ECG below, Figure 3, is from an LQTS gene carrier and shows a QTc of 470 msec and normal T waves. I think you would agree that it would be easy to miss this degree of QT prolongation and the diagnosis of LQTS, although 470 msec is highly suspicious for LQTS, and from our data is diagnostic in a male. One needs to have a careful eye and pay particular attention to the QT interval if a reasonable index of suspicion exists that the patient may have LQTS.

Figure 3



What ECG strategies can be used to clarify the LQTS diagnosis in a patient with a normal to borderline QTc?

Ambulatory ECGs: Holter or event monitoring

The QTc varies over time in normals and LQTS subjects. In perhaps 60-70% of the gene carriers with a non-diagnostic QTc on baseline ECG the QTc becomes diagnostically prolonged at some point during an ambulatory recording. The literature indicates that normal subjects may have QTc values up to 500 msec on ambulatory ECG, so a QTc > 500 msec is used to indicate LQTS, the higher the value the more confident is the diagnosis.

Serial 12 lead ECGs

I've recognized over many years that the QTc of LQTS patients varies from one ECG to the next, as do those of normals. Recently we examined this in a study of 40 LQT1 patients on whom I had obtained serial ECGs of a period of 12 ± 7 years. Age at first ECG was 12.8 ± 13.5 years, and there were 262 ECGs for review, 6.5 ± 4.1 per patient. The QTc on baseline ECG was 487 ± 39 msec. Importantly, 33%, 13/40, had a QTc on the first ECG of ≤ 460 msec, so are of particular interest to this discussion. In serial ECGs of individuals the QTc varied by 10 to 100 msec, mean 51 ± 25 msec. At baseline 65% had a diagnostic QTc using the criteria given above. After the second ECG that percent had increased to 80%, and after the third ECG had increased further to 88%. Thus, 65% (8/13) of those with non-diagnostic QTc intervals at baseline revealed a diagnostic QTc by the third ECG.

Analysis of T wave morphology

A characteristic T wave morphology for each of the LQTS 1-3 genotypes were reported by Moss, et al. These observations were expanded by Zhang, et al, who found 10 characteristic patterns in these genotypes, four in LQT1, four in LQT2 and two in LQT3. These patterns can be used to assist in the clarification of those patients with non-diagnostic QTc intervals. The images below, Figures 4, 5 and 6, show how this can be done.

Figure 4

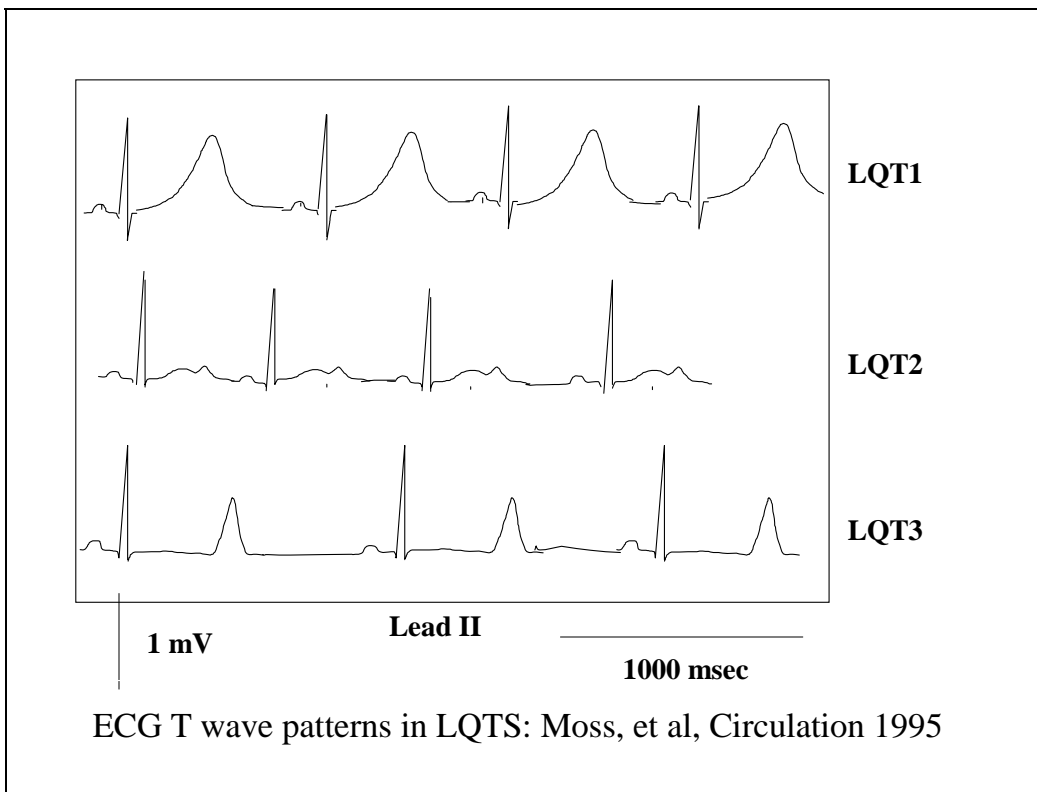
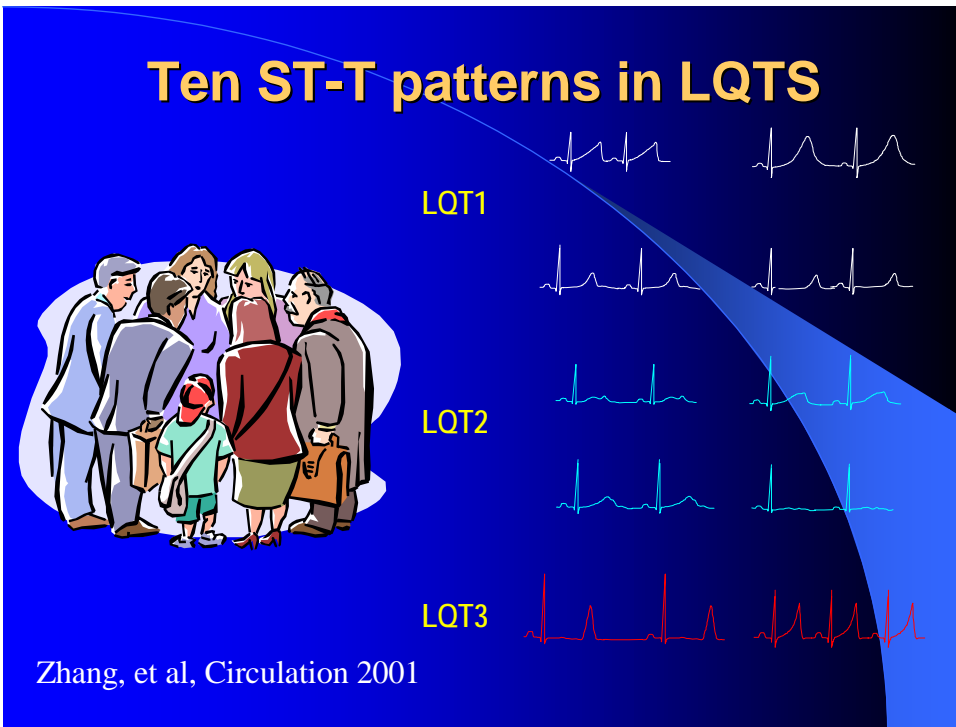


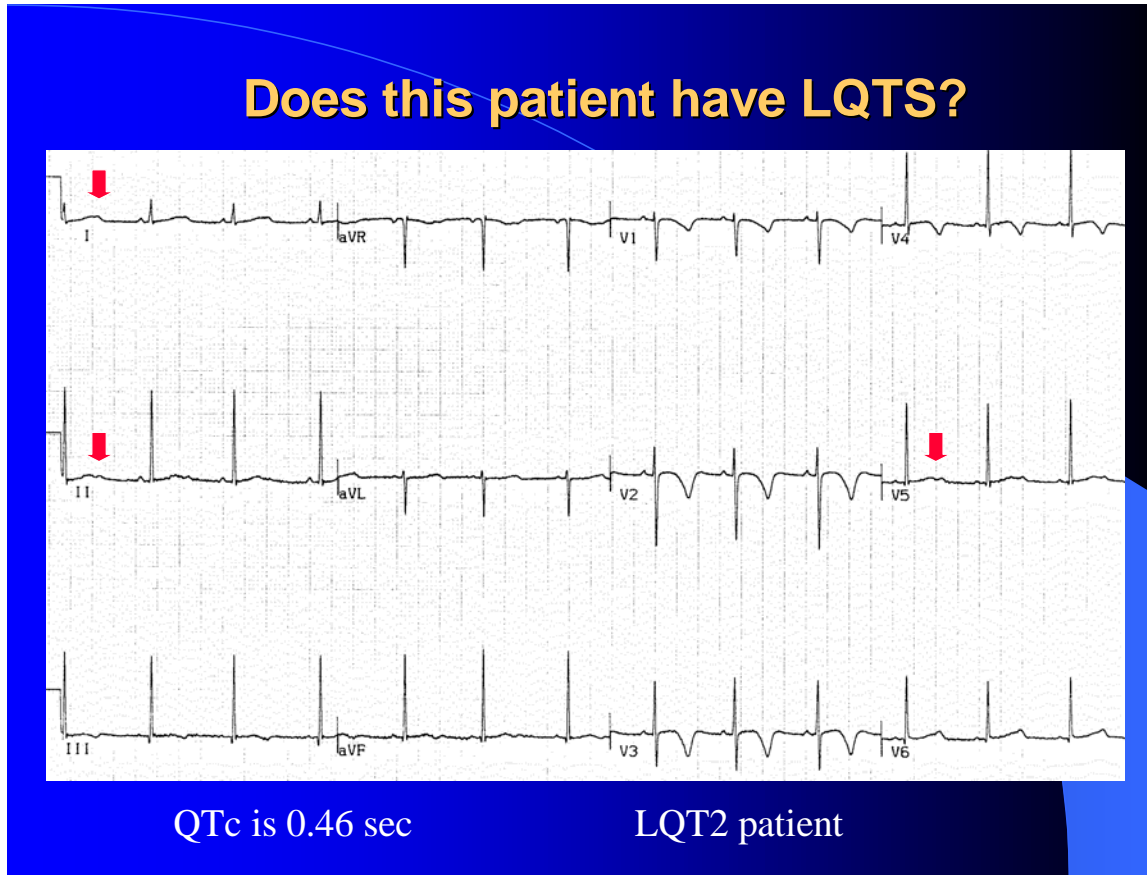
Figure 5



In this figure from the Zhang, et al publication, additional ST-T patterns were identified for each genotype. Four ST-T variants were identified for the LQT1 genotype including the large area, broad based pattern. Added were a normal ST-T pattern, one that looked somewhat like LQT3, and, in children under age 5 a pattern with immediate upsloping ST segment going directly into the T wave. For the LQT2 genotype, four variations of the bifid T wave pattern were identified. In LQT3 a pattern with a more normal ST segment and taller T waves was found in young LQT3 children in addition to the long ST segment and narrow T wave found in adults.

The next image, Figure 6, shows the importance of T wave pattern in influencing diagnostic decisions. Does this patient have LQTS? The QTc is 0.46 sec.

Figure 6.



In this figure, the ECG of a child from a known LQTS family is shown. The QTc at 460 msec is non-diagnostic though certainly suspicious in a member of a known LQTS family. However, the bifid T waves shown by the red arrows are consistent with the LQT2 genotype of this family, and influenced a decision to label this patient as a gene carrier, subsequently confirmed by additional ECG studies.

These characteristic ST-T patterns have been shown to be quite accurate in predicting the correct genotype of patients and families, and are very useful for stratifying genetic studies by indicating which gene should be screened first.

Exercise ECG studies

The observation that QTc may become more abnormal during adrenergic stimulation was reported in the earliest publications on LQTS. The observations were made with both epinephrine injection and exercise. Exercise testing for evaluation of LQTS patients has been used extensively for many years. The use of epinephrine or other catecholamine infusion is now being investigated again after many years during which it was not used. This section will discuss the use of exercise testing only. The ECG examples below show the response commonly seen in LQT1, and the two responses commonly seen in LQT2. Exercise ECG testing does not appear to be of value in the LQT3 genotype, so no ECG examples are presented but a graph showing the QTc response of the three genotypes compared to normals is presented.

Figure 7, LQT1

This example from a genotyped LQT1 patient is very characteristic of this genotype. The QTc increases during exercise and is typically longest at about 1 minute after exercise. In this case the T wave merges with and almost encompasses the P wave at peak exercise, and is further prolonged at 1 minute recovery. This response of QTc increase is almost always seen in LQT1 making exercise a very valuable tool for the clarification of subjects with uncertain QTc intervals. The normal response is for the QTc to remain relatively constant during exercise and recovery, see the graph below. Note also the large and apparently broad-based T wave in the exercise and recovery tracings, even more prominent than seen in the baseline record, which also adds to the diagnostic power.



Figure 7A, baseline ECG, QTc 0.47

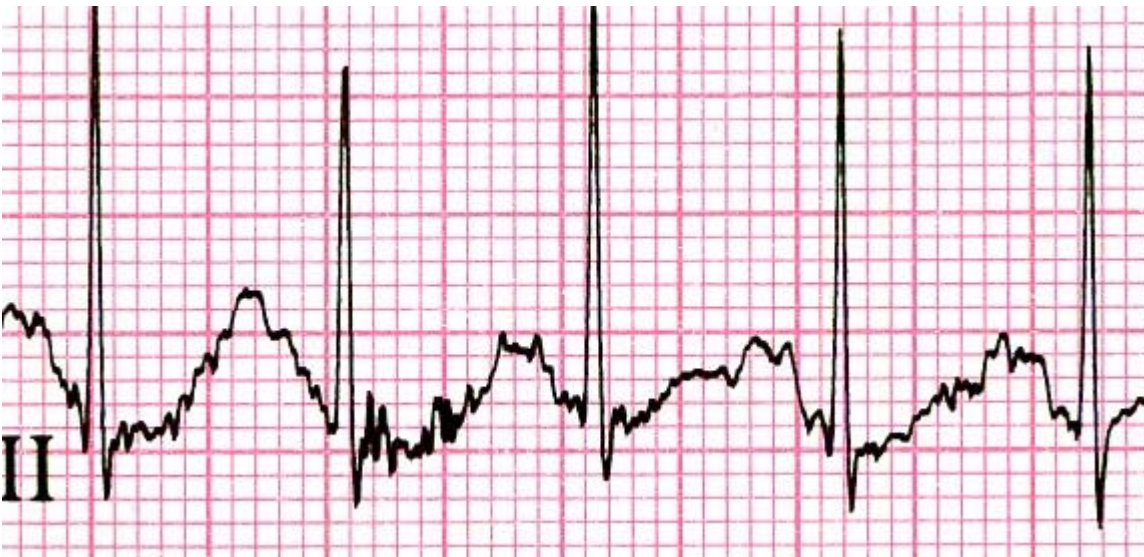


Figure 7B, peak exercise, QTc 0.52 sec

The T wave now merges with and nearly encompasses the P wave.



Figure 7C, 1 minute recovery.

QTc is further prolonged at 0.55 sec

Fig. 8, LQT2

This example of a genotyped LQT2 patient shows a borderline prolonged QTc at baseline, an appropriate case for this discussion, with little change during exercise and early recovery. About one-half the time the QTc does not prolong or shortens somewhat during exercise and early recovery, but then often becomes longer in later recovery. In this case the QTc at 8 minutes of recovery was 0.47 seconds. This case also shows the usefulness of T wave morphology changes during exercise and recovery. Note in the 1 minute recovery tracing the broad and flat top to the T wave, shown by the arrow. This represents a subtle bifid T wave and when it occurs it assists in the diagnosis of the LQT2 patient even if the QTc does not become abnormal. Often the bifid T wave is more obvious than the one shown here. I used this example thinking that if you can see this subtle bifid T wave you will certainly see the more obvious examples if you look for them.



Fig. 8A. QTc 0.46



Fig. 8B. QTc 0.45



Fig. 8C QTc 0.44

Fig. 9, LQT2

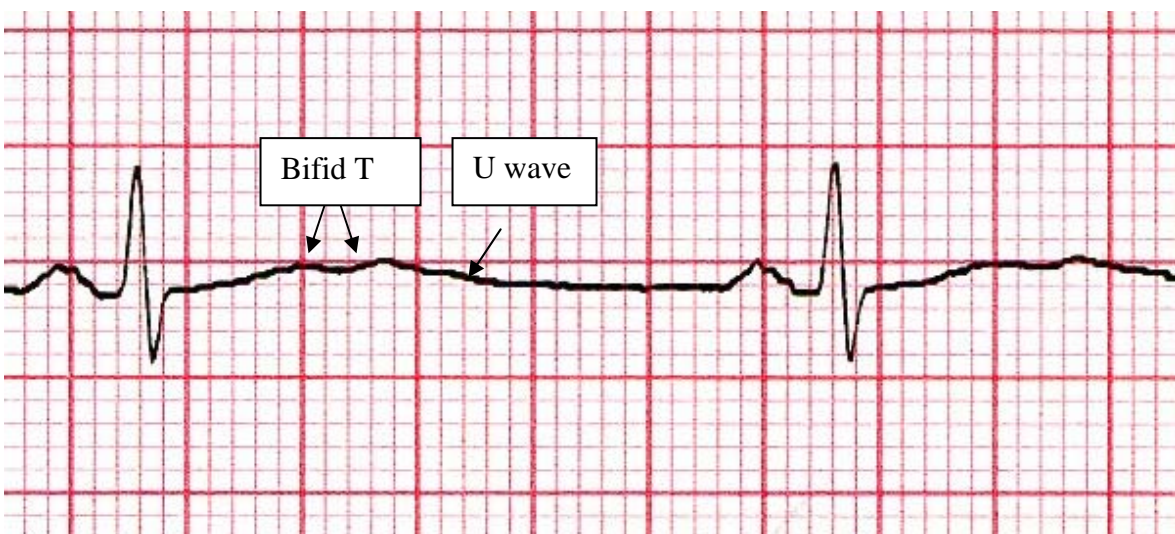


Fig. 9A.



Figure 9B, during exercise

The T morphology has become very complex, with the second component of the T wave becoming very large and probably encompassing the U wave. The QTc (arrow) is 0.58 seconds.

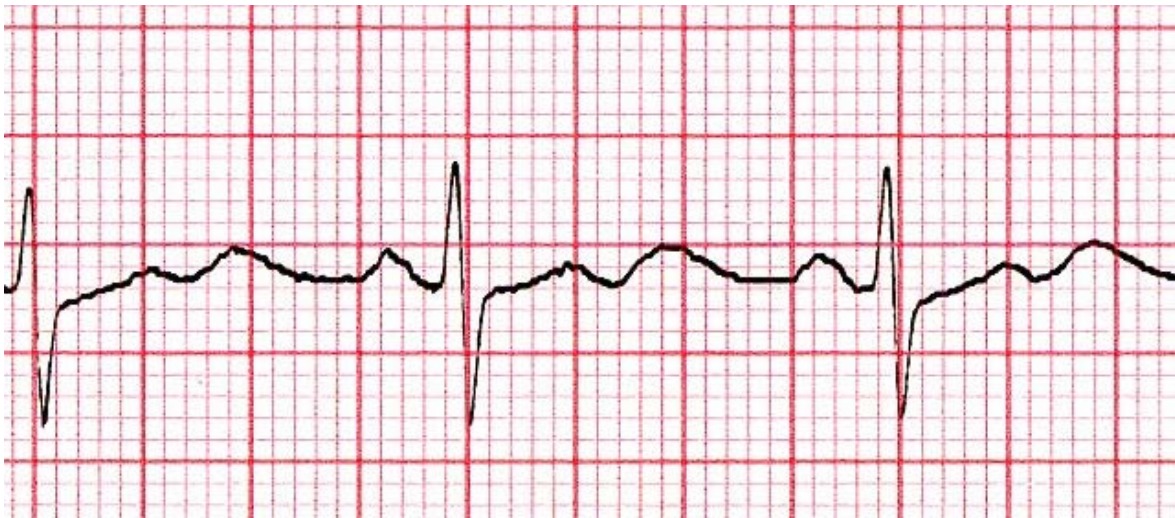
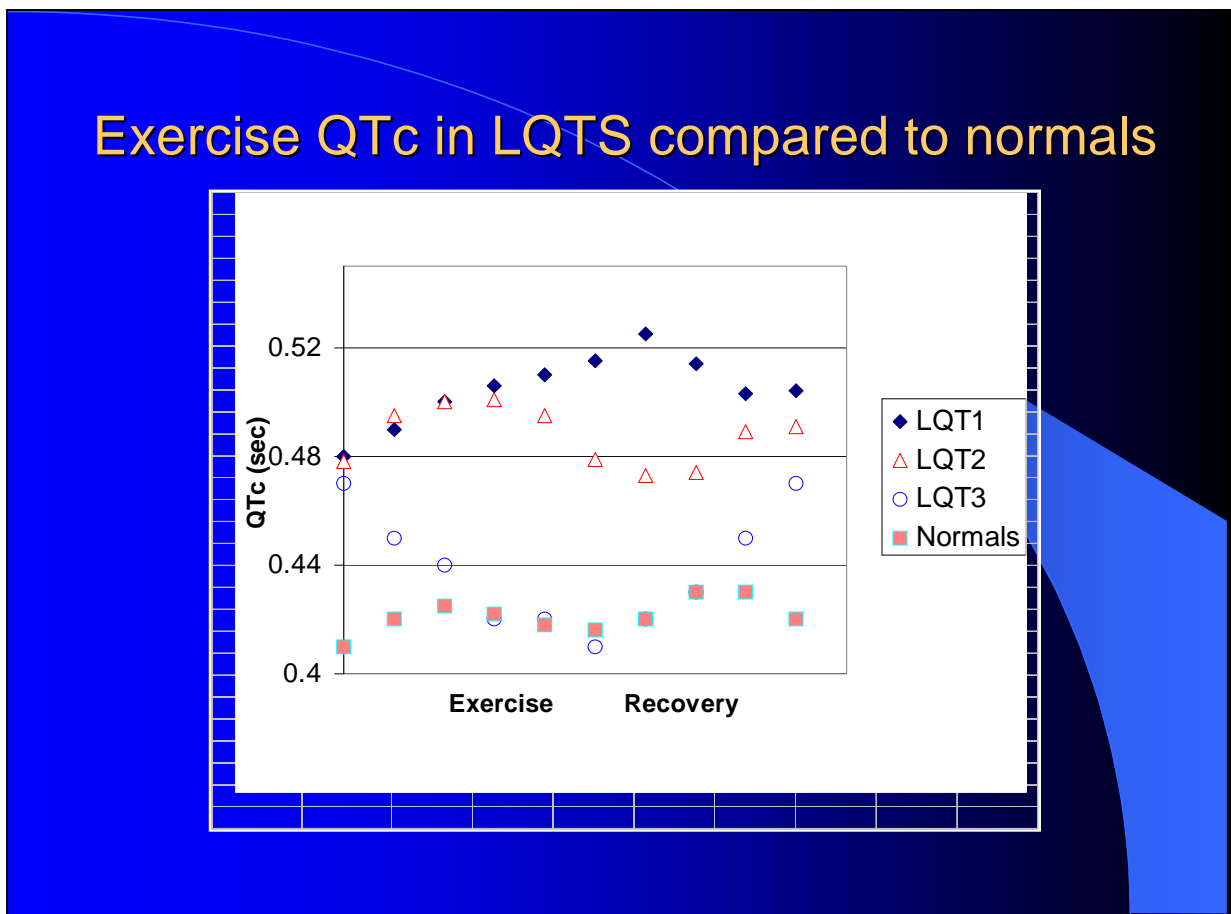


Figure 9C, 1 minute after exercise

The second component of the T wave is still very large, QTc is 0.54 sec.

This ECG is not a diagnostic dilemma because even though the QTc is borderline, the QT interval at 0.52 seconds is abnormal for this degree of bradycardia, HR is 49/min. Equally important, there are obvious bifid T waves in the baseline tracing, making it clear that this is an LQT2 patient. This example of a genotyped LQT2 patient shows the other response in LQT2 patients, an increase in QTc during exercise and early recovery, similar to the LQT1 response. This response occurs about one-half the time. In LQT1 and these cases of LQT2 the QT most often shortens during exercise but not to an appropriate amount for the degree of shortening of the cycle length, so the QTc increases. In some cases, particularly LQT1, the QT actually lengthens as the cycle length shortens, leading to a big increase in QTc interval, similar to this example.

Graph showing the average QTc response in the LQT1, LQT2 and LQT3 genotypes compared to normals. The LQT2 pattern is a composite of the two different responses demonstrated in the examples above. LQT3 patients often show an exaggerated shortening of the QTc compared to normals.

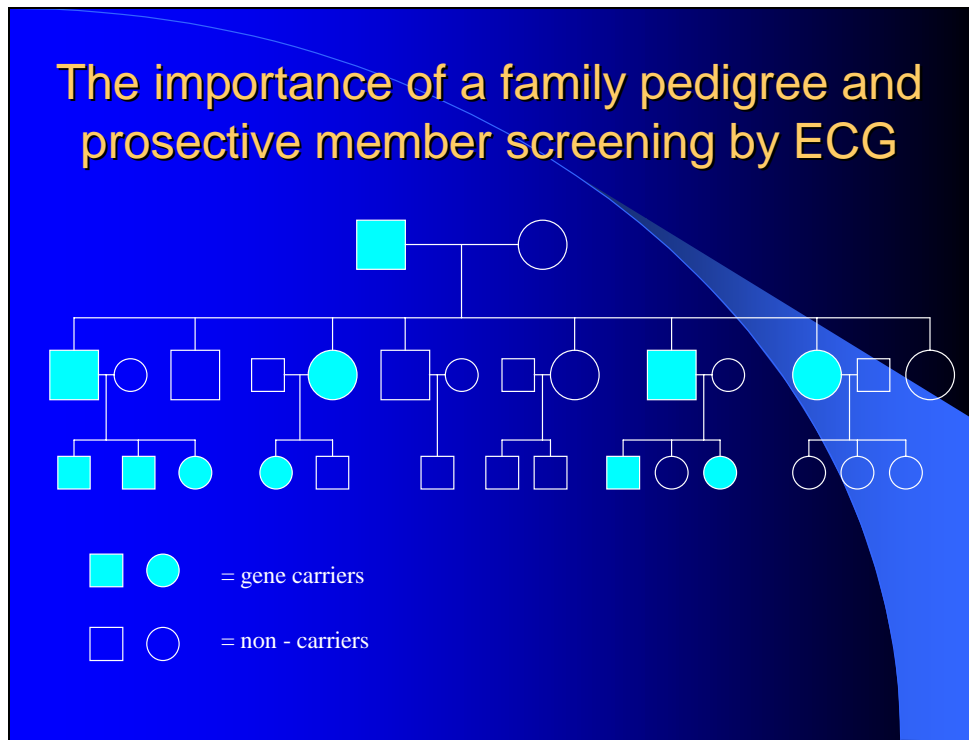


Vincent, et al, Circ, abstract.

The Family Pedigree

I have found it very helpful to construct a family pedigree consisting of at least the proband, their two parents and the proband's siblings, the grand parents, and if possible the siblings of the parents. ECGs are obtained on those members and the QTc placed on the pedigree. This provides several very important opportunities.

1. Since this is a genetic disease, autosomal dominant in transmission, other family members of the proband are going to have the mutated gene. In the vast majority of cases one parent will have it, of course. As demonstrated in the stylized pedigree below, other siblings are likely to have it too, since each child of an affected parent has a 50% chance of getting the abnormal gene allele. Similarly, it is likely that some of the affected parent's siblings and their children will have LQTS. In well less than one percent of cases the proband has a de novo mutation and neither parents nor siblings are affected. The degree of pedigree expansion noted above is not very difficult and is critical for identifying the closely related presymptomatic affected family members and providing prophylactic treatment. Of course, the pedigree can be expanded much farther than this, but it takes quite a bit of work.



This pedigree shows the possible rates of transmission from an affected parent to children with a usual number of children given autosomal dominant transmission. The percent of children affected range from none of the children to all of the children. Of course if there were a large number of children, say 50 or more, there would be equal numbers who inherited the gene and who did not inherit it, since each child has a 50% chance of inherited the mutant or the normal allele.

The review of ECGs of family members in the pedigree is very helpful in determining if the patient with an uncertain QTc interval has LQTS or not. Since other family members will very likely have LQTS also if the proband patient does, and about 70% of LQTS patients have a prolonged QTc on baseline ECG and about 80% have typical T waves, finding a prolonged QTc and/or a typical T wave pattern on the ECGs of other family

members makes it clear that the proband patient is at risk for having the disease. This makes interpretation of the various studies described above even more meaningful and changes how the QTc is interpreted.