

Medical Policy



Title: Genetic Testing for Congenital Long QT Syndrome

Professional

Original Effective Date: August 12, 2009

Revision Date(s):

Current Effective Date: August 12, 2009

Institutional

Original Effective Date: August 12, 2009

Revision Date(s):

Current Effective Date: August 12, 2009

DESCRIPTION

Congenital long QT syndrome (LQTS) is an inherited disorder characterized by the lengthening of the repolarization phase of the ventricular action potential, increasing the risk for arrhythmic events, such as torsades de pointes, which may in turn result in syncope and sudden cardiac death. Management has focused on the use of beta blockers as first-line treatment, with pacemakers or implantable cardiac defibrillators (ICD) as second-line therapy.

Congenital LQTS usually manifests itself before the age of 40 years, and may be suspected when there is a history of seizure, syncope, or sudden death in a child or young adult; this history may prompt additional testing in family members. It is estimated that more than one half of the 8,000 sudden unexpected deaths in children may be related to LQTS. The mortality of untreated patients with LQTS is estimated at 1%–2% per year, although this figure will vary with the genotype, discussed further here. (1) Frequently, syncope or sudden death occurs during physical exertion or emotional excitement, and thus LQTS has received some publicity regarding evaluation of adolescents for participation in sports. In addition, LQTS may be considered when a long QT interval is incidentally observed on an EKG. Diagnostic criteria for LQTS have been established, which focus on EKG findings and clinical and family history (i.e., Schwartz criteria, see following section, "Clinical Diagnosis"). (2) However, measurement of the QT interval is not well standardized, and in some cases, patients may be considered borderline cases. (3)

In recent years, LQTS has been characterized as an "ion channel disease," with abnormalities in the sodium and potassium channels that control the excitability of the cardiac myocytes. A genetic basis for LQTS has also emerged, with 7 different variants recognized, each corresponding to mutations in different genes as indicated here. (4) In addition, typical ST-T-wave patterns are also suggestive of specific subtypes. (5)

LQT1 is associated with mutations in the gene *KNQ1* located on chromosome 11. LQT1 is responsible for about 50% of all LQTS, and arrhythmic events prompted by exercise

may occur most commonly in this subtype. Therefore, patients with LQT1 may be advised to minimize exercise.

LQT2 is associated with mutations in the gene *KCNH2* located on chromosome 7 and is seen in 45% of patients with LQTS. Arrhythmic events appear to be precipitated by auditory stimuli, and these patients may be advised to avoid clock alarms, etc.

LQT3 is associated with mutations in the gene *SCN5A* located on chromosome 3. This subtype is seen in 3%–4% of patients with LQTS. In this subtype, the majority of cardiac events occur during sleep. LQT3 variant is also known as the Brugada syndrome.

LQT 4-7 involve *KCN* genes located on chromosomes 21 and 17. These variants each account for less than 1% of LQTS.

Clinical Diagnosis

The Schwartz criteria are commonly used as a diagnostic scoring system for LQTS. (3) The most recent version of this scoring system is shown in the Table. A score of 4 or greater indicates a high probability that LQTS is present; a score of 2–3 an intermediate probability; and a score of 1 or less indicates a low probability of the disorder. Prior to the availability of genetic testing, it was not possible to test the sensitivity and specificity of this scoring system; therefore, the accuracy of this scoring system is ill-defined.

Table. Diagnostic Scoring System for LQTS (Adapted from reference 3)

| Criteria | Points |
|--|--------|
| Electrocardiographic findings | |
| *QT _c >480 msec | 3 |
| *QT _c 460-470 msec | 2 |
| *QT _c <450 msec | 1 |
| History of torsades de pointes | 2 |
| T-wave alternans | 1 |
| Notched T-waves in three leads | 1 |
| Low heart rate for age | 0.5 |
| Clinical history | |
| *Syncope brought on by stress | 2 |
| *Syncope without stress | 1 |
| *Congenital deafness | 0.5 |
| Family history | |
| *Family members with definite LQTS | 1 |
| *Unexplained sudden death in immediate family members younger than 30 years of age | 0.5 |

Genetic Testing

The Familion® test describes the analysis of the genes responsible for subtypes LQT 1-5. The test is offered in a variety of ways. For example, if a family member has been diagnosed with LQTS based on clinical characteristics, complete analysis of all 5 genes can be performed to both identify the specific mutation and identify the subtype of LQTS.

If a mutation is identified, then additional family members can undergo a focused genetic analysis for the identified mutation. If a specific type of LQTS is suspected based on the EKG abnormalities, genetic testing can focus on the individual gene.

All of the LQTS genes are large, and genetic testing has revealed multiple different mutations along their length. The pathophysiologic significance of each of the discrete mutations is an important part of the interpretation of genetic analysis. PGxHealth (New Haven, CT), the laboratory offering the Familion test, compares the results to the PGxHealth Cardiac Ion Channel Variant Database, which includes data from over 750 individuals of diverse ethnic backgrounds. Therefore, the chance that a specific mutation is pathophysiologically significant is increased if it is the same mutation as that reported in several other cases of known LQTS. However, there may be many instances when the detected mutations are of unknown significance. Variants are placed into four classes, based on the probability that the variant identified represents an actual deleterious LQTS mutation (6):

- Class I – Deleterious and probable deleterious mutations. These are either mutations that have previously been identified (deleterious mutations), represent a major change in the protein, or cause an amino acid substitution in a critical region of the protein(s) (probable deleterious mutations).
- Class II – Possible deleterious mutations. These variants encode changes to protein(s) but occur in regions that are not considered critical. Approximately 5% of patients without LQTS will exhibit mutations in this category.
- Class III – Variants not generally expected to be deleterious. These variants encode modified protein(s), however, these are considered more likely to represent benign polymorphisms. Approximately 90% of patients without LQTS will have one or more of these variants, therefore patients with only class III variants are considered 'negative.'
- Class IV – Non-protein-altering variants. These are not considered to have clinical significance and are not reported in the results of the Familion® test.

The absence of a mutation does not imply the absence of LQTS; it is estimated that mutations are only identified in 60%–70% of patients with a clinical diagnosis of LQTS. (7) For these reasons, the most informative result of testing would probably occur when a family member undergoes genetic testing for a specific genetic mutation that has been identified in symptomatic relatives known to have LQTS. Interpretation of the results will likely be improved as the database grows. Other laboratories have investigated different testing strategies. For example, Napolitano and colleagues propose a three-tiered approach, first testing for a core group of 64 codons that have a high incidence of mutations, followed by additional testing of less frequent mutations. (8)

Another factor complicating interpretation of the genetic analysis is the penetrance of a given mutation or the presence of multiple phenotypic expressions. For example, approximately 50% of carriers of mutation never have any symptoms. There is variable

penetrance for the LQTS, and penetrance may differ for the various subtypes. While linkage studies in the past indicated that penetrance was 90% or greater, more recent analysis by molecular genetics has challenged this number (9), and suggested that penetrance may be as low as 25% for some families.

POLICY

Genetic testing* in patients with suspected congenital long QT syndrome may be considered **medically necessary** for individuals with signs and/or symptoms indicating a moderate-to-high pretest probability** of LQTS.

Genetic testing for LQTS to determine prognosis and/or direct therapy in patients with known LQTS is considered **experimental / investigational**.

*Genetic testing may be non-covered by member contract based on family history indication alone.

**Determining the pretest probability of LQTS is not standardized. An example of a patient with a moderate to high pretest probability of LQTS is a patient with a Schwartz score of 2–3.

RATIONALE

The following discussion of the evidence is based on a 2007 TEC Assessment, "Genetic Testing for Long QT Syndrome." (10)

Validation of the clinical use of any genetic test focuses on 3 main principles: 1) the analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or excluding a mutation that is absent; 2) the clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and 3) the clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Analytic validity

The Familion test for LQTS sequences the entire length of the potentially affected genes in the forward and reverse directions. Full genetic sequencing is the gold standard laboratory procedure for identifying genetic mutations.

The following information on analytic sensitivity and specificity was obtained from the Web site of PGxHealth (New Haven, Conn.) (6), the manufacturer of the Familion® genetic test for LQTS. Additional unpublished data were supplied by PGxHealth in response to a list of structured questions. (11)

The PGxHealth Web site states that the analytic sensitivity of the test is greater than 99%: This analytic sensitivity is based on an independent analysis of 21 "unknown" samples by PGxHealth, which had been previously characterized and supplied to the company by a research lab at the University of Rochester. Of these 21 samples, 20 contained various types of mutations, including

nonsense, missense, splice site, and insertions/deletions, and one sample was a "wild type," containing no mutations. According to the manufacturer, all of the mutations were correctly identified (11), thus leading to their reporting of analytic sensitivity of greater than 99%.

The PGxHealth Web site (6) states the following concerning the analytic specificity of the test: "The chance of a falsely detected genetic variant is minimized by requiring that each variant be seen in sequence traces for both forward and reverse directions and that two trained technicians independently examine each trace. Chances of false positives are minimized by the use of a validated sample tracking system that uses robotics and barcodes. For each positive finding of a Class I or Class II variant, a second round of PCR amplification and sequencing is performed to confirm the initial finding."

Abnormal results from the commercial test are reported as Class I or Class II mutations, and the analytic specificity for each class of mutations will differ. Approximately 75% of all reported deleterious mutations are Class I and the remaining 25% are Class II mutations. (12) For Class I mutations, data from the validation sample reported by the manufacturer indicate that false positive results are expected to be extremely uncommon, so that analytic specificity will approach 100%. For Class II mutations, false positive results are more likely to occur. Analysis of non-LQTS patients revealed that variants reported as Class II mutations are found in approximately 5% of patients without LQTS. (11) Therefore, the analytic specificity of Class II mutations is expected to be approximately 95%.

Clinical Validity

The true clinical sensitivity and specificity of genetic testing for LQTS cannot be determined with certainty as there is no independent gold standard for the diagnosis of LQTS. The clinical diagnosis can be compared to the genetic diagnosis, and vice versa, but neither the clinical diagnosis nor the results of genetic testing can be considered an adequate gold standard.

Hofman et al (13) performed the largest study comparing clinical methods with genetic diagnosis, using registry data. This study compared multiple methods for making the clinical diagnosis, including the Schwartz score, the Keating criteria, and the absolute length of the QTc (corrected QT) with genetic testing. These data indicate that only a minority of patients with a genetic mutation will meet the clinical criteria for LQTS. Using the most common clinical definition of LQTS, a Schwartz score of 4 or greater, only 19% of patients with a genetic mutation met the clinical criteria. Even at lower cutoffs of the Schwartz score, the percentage of patients with a genetic mutation who met clinical criteria was still relatively low, improving to only 48% when a cutoff of 2 or greater was used. When the Keating criteria were used for clinical diagnosis, similar results were obtained. Only 36% of patients with a genetic mutation met the Keating criteria for LQTS.

The best overall accuracy was obtained by using the length of the QTc as the sole criterion; however, even this criterion achieved only modest sensitivity at the expense of lower specificity. Using a cutoff of 430 msec or longer for the QT interval, a sensitivity of 72% and a specificity of 86% was obtained.

Tester et al (14) completed the largest study that evaluated the percent of individuals with a clinical diagnosis of LQTS that are found to have a genetic mutation. The population in this study was 274 consecutive patients referred for genetic testing and found to have a LQTS mutation.

The genetic diagnosis was compared to the clinical diagnosis, defined as a Schwartz score of 4 or greater. Of all patients with a clinical diagnosis of LQTS, 72% were found to have a genetic mutation.

The above data indicates that genetic testing will identify more individuals with possible LQTS compared with clinical diagnosis alone. It may often not be possible to determine with certainty whether patients with a genetic mutation have the true clinical syndrome of LQTS. The data also demonstrates that approximately 30% of patients with a clinical diagnosis will not be found to have a known mutation, suggesting that there are additional mutations associated with LQTS that have not been identified to date. Therefore, a negative genetic test is not definitive for excluding LQTS at the present time.

Clinical Utility

For diagnosing LQTS, the clinical utility of genetic testing is high. LQTS is a disorder that may lead to catastrophic outcomes, i.e., sudden cardiac death, in otherwise healthy individuals. Diagnosis using clinical methods alone may lead to underdiagnosis of LQTS, thus exposing undiagnosed patients to the risk of sudden cardiac arrest. For patients in whom the clinical diagnosis of LQTS is uncertain, genetic testing may be the only way to further clarify whether or not LQTS is present. Patients who are identified as genetic carriers of LQTS mutations have a non-negligible risk of adverse cardiac events even in the absence of clinical signs and symptoms of the disorder. Therefore, treatment is likely indicated for patients found to have a LQTS mutation, whether or not other signs or symptoms.

Treatment with beta blockers has been demonstrated to decrease the likelihood of cardiac events, including sudden cardiac arrest. Although there are no controlled trials of beta blockers, there are pre-post studies from registry data that provide evidence on this question. Two such studies reported large decreases in cardiovascular events and smaller decreases in cardiac arrest and/or sudden death after starting treatment with beta blockers. (15, 16) These studies reported a statistically significant reduction in cardiovascular events of greater than 50% following initiation of beta-blocker therapy. There was a reduction of similar magnitude in cardiac arrest/sudden death, which was also statistically significant.

Treatment with an implanted automatic implantable cardioverter-defibrillator (AICD) is available for patients who fail or cannot take beta-blocker therapy. One published study reported on outcomes of treatment with AICDs. (17) This study identified patients in the LQTS registry who had been treated with an AICD at the discretion of their treating physician. Patients in the registry who were not treated with an AICD, but had the same indications, were used as a control group. The authors reported that patients treated with an AICD had a greater than 60% reduction in cardiovascular outcomes.

For determining LQTS subtype or specific mutation, the clinical utility is less certain. The evidence suggests that different subtypes of LQTS may have variable prognosis, thus indicating that genetic testing may assist in risk stratification. Several reports have compared rates of cardiovascular events in subtypes of LQTS. (1, 15, 18, 19) These studies report that rates of cardiovascular events differ among subtypes, but there is not a common pattern across all studies. Three of the four studies (15, 18, 19) reported that patients with LQT2 have higher event rates than patients with LQT1, while Zareba and colleagues (1) reported that patients with LQT1 have higher event rates than patients with LQT2.

However, there is not sufficient evidence to conclude that the information obtained from genetic testing on risk assessment leads to important changes in clinical management. Most patients will be treated with beta-blocker therapy and lifestyle modifications, and it has not been possible to identify a group with low enough risk to forego this conservative treatment. Conversely, for high-risk patients there is no evidence suggesting that genetic testing influences the decision to insert an AICD and/or otherwise intensify treatment.

Some studies that report outcomes of treatment with beta blockers also report outcomes by specific subtype of LQTS. (15, 19) Priori and colleagues (15) reported pre-post rates of cardiovascular events by LQTS subtypes following initiation of beta-blocker therapy. There was a decrease in event rates in all LQTS subtypes, with a similar magnitude of decrease in each subtype. Moss and colleagues (16) also reported pre-post event rates for patients treated with beta-blocker therapy. This study indicated a significant reduction in event rates for patients with LQT1 and LQT2, but not for LQT3. This analysis was also limited by the small number of patients with LQT3 and cardiac events prior to beta-blocker treatment (4 of 28). Sauer and colleagues (20) evaluated differential response to beta-blocker therapy in a Cox proportional hazards analysis. These authors reported an overall risk reduction in first cardiac event of approximately 60% (hazard ratio: 0.41, 95% CI: 0.27-0.64) in adults treated with beta blockers, and an interaction effect by genotype. Efficacy of beta-blocker treatment was worse in those with LQT3 genotype ($p=0.04$) compared with LQT1 or LQT2. There was no difference in efficacy between genotypes LQT1 and LQT2.

These data suggest that there may be differences in response to beta-blocker therapy, particularly for patients with LQT3. However, the evidence is not consistent in this regard, with one of three the studies demonstrating a similar response for LQT3 compared to other subtypes. In addition, even if differential response is present, it is not clear how this would influence management. Although response to beta-blocker therapy may be less for patients with LQT3, the data still suggest that there may be a benefit. Whether beta-blocker therapy should be withheld, or replaced with AICD treatment, cannot be determined from these data.

Indications for Testing

Indications for testing will depend on a variety of factors, including family history, presence or absence of a known mutation in the family, symptoms, length of the QTc interval on EKG, etc. For diagnostic testing, patients with a moderate-to-high pretest probability of LQTS, but in whom the diagnosis cannot be made by clinical methods, will derive the most benefit from testing. Table 1 gives a framework for categorizing patients into testing categories; however, as indicated in the table, there may be substantial uncertainty on the benefit of testing for a number of these categories.

For individuals with a known LQTS mutation in the family but who do not themselves meet the clinical criteria for LQTS, genetic testing will improve outcomes. These individuals have a high pretest probability of disease and LQTS can be diagnosed with certainty if the test is positive. Treatment of these individuals with beta blockers will reduce the incidence of subsequent cardiovascular events. Furthermore, because the specific mutation is known prior to testing, the disease can be ruled out with certainty if results are negative.

For diagnosis of LQTS in other patient populations, there may be a benefit as well. For patients who have some signs and symptoms of LQTS, but no known mutation in the family, testing may be beneficial. In this situation, LQTS can be diagnosed with reasonable certainty if a class I mutation is identified; however, the likelihood of false-positive results is higher than if a known mutation were present in the family. In patients with lower pretest probabilities of disease, the utility of testing declines, although precise risk/benefit thresholds cannot be established.

Table 1. Potential patient indications for genetic testing

| | Meets clinical criteria for LQTS | Some signs/symptoms of LQTS; does not meet clinical criteria | No signs/symptoms of LQTS |
|--|----------------------------------|--|---------------------------|
| FH positive and known mutation in family | - (?) | ++ | + |
| FH positive but family mutation status unknown | - (?) | + | + |
| FH negative | - | + (?) | - |

++ definite benefit of genetic testing, + probable benefit of genetic testing,
? uncertain benefit of genetic testing, - no benefit of genetic testing

Clinical criteria for LQTS – Schwartz score 4 or greater (other definitions possible as well)
FH+ – family history positive for sudden death at age younger than 30; or clinical diagnosis of LQTS in family (without known mutation)

Signs/symptoms of LQTS – long QT interval on EKG; syncope; aborted cardiac arrest
Genetic testing has also been proposed to determine LQTS subtype and/or the specific mutation present. For individuals who meet clinical criteria for LQTS, genetic testing for this purpose has not been demonstrated to improve the patient's own health outcomes. Once diagnosed with LQTS, most, if not all patients should be treated with beta-blocker therapy and lifestyle modifications. There is no evidence to suggest that genetic testing influences clinical decisions whether or not to treat with beta-blocker therapy, nor does the evidence indicate that knowledge of genetic testing results influences the decision to implant an AICD. Therefore, it is not possible to conclude that genetic testing for LQTS improves outcomes when used to direct therapy or determine prognosis.

Based on the above evidence, it can be concluded that genetic testing for LQTS improves health outcomes for the following patient groups:

1. Individuals who do not meet the clinical criteria for LQTS, but who have:
 - a close relative (i.e., first-, second-, or third-degree relative) with a known LQTS mutation; or
 - a close relative diagnosed with LQTS by clinical means whose genetic status is unavailable; or
 - signs and/or symptoms indicating a moderate-to-high pretest probability of LQTS.

2008 Update

A literature search was performed for the period of April 2007 through November 2008. There were no clinical trials identified that directly evaluated the utility of genetic testing. There were

also no trials that evaluated the benefit of treatment in individuals with a LQTS-related genetic mutation who do not have a clinical diagnosis of LQTS.

Numerous studies reported on the identification of new genetic mutations associated with LQTS. (21, 22) These and similar studies may eventually reduce the percentage of patients with known LQTS who are not found to have a known LQTS mutation, effectively increasing the clinical validity (sensitivity) of genetic testing.

Two studies evaluated the psychological effects of genetic testing for LQTS. Hendriks et al studied 77 patients with a LQTS mutation and their 57 partners. (23) Psychological testing was performed after the diagnosis of LQTS had been made and repeated twice over an 18-month period. Disease-related anxiety scores were increased in the index patients and their partners. This psychological distress decreased over time but remained elevated at 18 months. Andersen et al conducted qualitative interviews with 7 individuals found to have LQTS mutations. (24) They reported that affected patients had excess worry and limitations in daily life associated with the increased risk of sudden death, which was partially alleviated by acquiring knowledge about LQTS. The greatest concern was expressed for their family members, particularly children and grandchildren.

Another line of research attempts to explain the variability in clinical expression for patients with a LQTS mutation. (25) While in the past, this was felt to be largely a matter of incomplete penetrance, researchers have begun to identify other non-genetic factors that may modify the risk of clinical symptoms, including sudden death. Sze et al (26) reported that the presence of coronary artery disease increased the likelihood of LQTS-related cardiovascular events by a factor of 2.24 (95% CI: 1.23-4.07; $p < 0.008$). Dalageorgou et al. (27) reported that the length of the QT interval was modified by the presence of other genetic markers associated with resting heart rate, suggesting that autonomic tone may be a significant modifier of LQTS risk.

In summary, genetic testing for LQTS continues to be an active area of research.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- | | |
|-------|--|
| S3860 | Genetic testing, comprehensive cardiac ion channel analysis, for variants in 5 major cardiac ion channel genes for individuals with high index of suspicion for familial long QT syndrome (LQTS) or related syndromes (new code effective 10/1/08) |
| S3861 | Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada syndrome (new code effective 10/1/08) |
| S3862 | Genetic testing, family-specific ion channel analysis, for blood-relatives of individuals (index case) who have previously tested positive for a genetic variant of a cardiac ion channel syndrome using either one of the above test configurations or confirmed results from another laboratory (new code effective 10/1/08) |

ICD-9 DIAGNOSIS

426.82 Long QT syndrome

746.89 Congenital anomalies; other specified anomalies of the heart

REVISIONS

| | |
|------------|--|
| 08-12-2009 | Policy added to the bcbsks.com web site. |
|------------|--|

REFERENCES

1. Zareba W, Moss AJ, Schwartz PJ et al. Influence of genotype on the clinical course of the long QT syndrome. *N Engl J Med* 1998; 339(14):960-5.
2. Schwartz PJ, Moss AJ, Vincent GM et al. Diagnostic criteria for the long QT syndrome. An update. *Circulation* 1993; 88(2):782-4.
3. Al-Khatib SM, LaPointe NM, Kramer JM et al. What clinicians should know about the QT interval. *JAMA* 2003; 289(16):2120-8.
4. Khan IA. Long QT syndrome: diagnosis and management. *Am Heart J* 2002; 143(1):7-14.
5. Zhang L, Timothy KW, Vincent GM et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation* 2000; 102(23):2849-55.
6. PGxHealth, New Haven, CT, Web page, <http://www.pgxhealth.com/genetictests/familion/physicians/howitworks.cfm> , accessed 5/10/07.
7. Chiang CE. Congenital and acquired long QT syndrome. *Cardiol Rev* 2004; 12(4):222-34.
8. Napolitano C, Priori SG, Schwartz PJ et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 2005; 294(23):2975-80.
9. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 1999, 99(4):529-33.
10. 2007 TEC Assessments. Genetic Testing for Long QT Syndrome.
11. PGxHealth, New Haven, CT; personal communications, 7/20/07, and 8/09/07.
12. Tester DJ, Salisbury BA, Carr JL et al. The effect of mutation class on QTc in unrelated patients referred for the Familion™ genetic test for long QT syndrome. Abstract presented at Heart Rhythm Society Meeting, May 11, 2007, Denver, CO.
13. Hofman N, Wilde AA, Kaab S et al. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? *Eur Heart J* 2007; 28(5):575-80.
14. Tester DJ, Will ML, Haglund CM et al. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol* 2006; 47(4):764-8.
15. Priori SG, Napolitano C, Schwartz PJ et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA* 2004; 292(11):1341-4.
16. Moss AJ, Zareba W, Hall WJ et al. Effectiveness and limitations of beta-blocker therapy in congenital long QT syndrome. *Circulation* 2000; 101(6):616-23.
17. Zareba W, Moss AJ, Daubert JP et al. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol* 2003; 14(4):337-41.
18. Priori SG, Schwartz PJ, Napolitano C et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003, 348(19):1866-74.

19. Schwartz PJ, Priori SG, Spazzolini C et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; 103(1):89-95.
20. Sauer AJ, Moss AJ, McNitt S et al. Long QT syndrome in adults. *J Am Coll Cardiol* 2007; 49(3):329-37.
21. Eddy CA, MacCormick JM, Chung SK et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. *Heart Rhythm*, 2008; 5(9):1275-81.
22. Zhang S, Yin K, Ren X et al. Identification of a novel KCNQ1 mutation associated with both Jervell and Lange-Nielsen and Romano-Ward forms of long QT syndrome in a Chinese family. *BMC Med Genet* 2008; 9:24.
23. Hendriks KS, Hendriks MM, Birnie E et al. Familial disease with a risk of sudden death: a longitudinal study of the psychological consequences of predictive testing for long QT syndrome. *Heart Rhythm* 2008; 5(5):719-24.
24. Andersen J, Oyen N, Bjorvatn C et al. Living with long QT syndrome: a qualitative study of coping with increased risk of sudden death. *J Genet Couns* 2008; 17(5):489-98.
25. Scicluna BP, Wilde AW, Bezzina CR. The primary arrhythmia syndromes: same mutation, different manifestations. Are we starting to understand why? *J Cardiovasc Electrophysiol* 2008; 19(4):445-52.
26. Sze E, Moss AJ, Goldenberg I et al. Long QT syndrome in patients over 40 years of age: increased risk for LQTS-related cardiac events in patients with coronary disease. *Ann Noninvasive Electrocardiol* 2008, 13(4):327-31.
27. Dalageorgou C, Ge D, Jamshidi Y et al. Heritability of QT interval: how much is explained by genes for resting heart rate? *J Cardiovasc Electrophysiol* 2008; 19(4):386-91.