LONG QT SYNDROME

Bottom line: Long QT syndrome (LQTS) is one of several inherited heart disorders than can lead to sudden cardiac death (SCD). LQTS is a rhythm disorder that can predispose to fast, chaotic heart rhythms which may trigger a sudden fainting spell, seizure or SCD. It is treatable if diagnosed. The ECG is neither sensitive nor specific for hereditary LQTS. A QTc ≥ 500ms is considered high risk for LQTS. Individuals with clinical features such as syncope, and repeated corrected QT interval (QTc) of >450ms for men and >470ms for women, should be referred to a cardiac arrhythmia specialist and a genetics clinic for assessment and genetic testing where indicated. Family physicians can play a crucial role in referring first degree relatives to cardiac genetics specialist services following the death of a young person in whom an autopsy did not identify cause of death or in whom a heritable cardiac disorder was suspected.

WHAT IS LONG QT SYNDROME?

Long QT syndrome (LQTS) is a disorder involving the cardiac ion channels resulting in prolongation of the ventricular action potential during cardiac repolarization (i.e. prolonged QT interval on electrocardiogram (ECG)). It occurs in approximately 1 in 2,000 to 1 in 2,500 people. LQTS predisposes to syncope and/or sudden cardiac death and is one of the leading causes of sudden death in otherwise healthy young people. LQTS is one of numerous causes of sudden infant death syndrome (SIDS).

The diagnosis of LQTS usually relies on clinical and family history, in addition to a corrected QT interval (QTc). Determination of an absolute value for an abnormal QTc is difficult as there is a considerable borderline range and the data cut-offs are not clear. Acceptable cut-off values to balance a high positive predictive value and a lowered false positive rate are shown in Table 1.

Table 1. Corrected QT interval (QTc) cut-offs which should prompt referral to cardiac arrhythmia specialists and genetics clinic for assessment [Waddell-Smith *et al,* 2016 – see online for full reference].

	Corrected QT interval cut-off (in ms)
Women	>470
Men	>450
Children >12 years Female…… Male ……	 >460 >450
Children <12 years (female and male)	>450

In 20-40% of individuals the ECG may be inconclusive. Since a normal ECG cannot completely "rule out" LQTS, **it is recommended that patients be referred to a cardiac specialist for evaluation** (which may involve manual calculation of QTc and additional testing) if symptoms, signs or family history are present (Box 1).

WHAT DO I NEED TO KNOW ABOUT THE GENETICS OF LONG QT SYNDROME?

Most forms of LQTS are hereditary, usually autosomal dominant. LQTS can also be acquired due to other causes such as anorexia nervosa, or induced by certain medications (see Surveillance and Management).

At least 15 genes have been implicated in LQTS. Some genotype-phenotype correlations may be drawn. The three most common genes, accounting for over 90% of known LQTS mutations, are:

- *LQT1* (*KCNQ1*) on chromosome 11, which encodes potassium channel subunits
- *LQT2* (*HERG, KCNH2*) on chromosome 7, which encodes potassium channel subunits
- *LQT3* (*SCN5A*) on chromosome 3, which encodes sodium channel subunits

Box 1. Clinical symptoms, signs and family history which should prompt referral to cardiac arrhythmia specialists and genetics clinic for assessment.

- Syncope (*loss of consciousness*) or near syncope spells triggered by:
  1. Physical exertion
  2. Auditory stimuli e.g. fire alarm
  3. Emotional stress/distress
     - Repetitive events more concerning
     - Excluding events that are likely due to vasovagal events is difficult but necessary (e.g. those occurring during abrupt postural changes, exposure to heat and dehydration, emotional reactions to events such as blood draw, etc.)
- Family history of unexplained sudden death in otherwise healthy persons at a young age (< 40 years)
  - Attention to unexplained death during swimming, death during seizures, a family history of "seizure" disorders and other unexplained deaths
    - Sodium-channel abnormalities may be precipitated by fever. These cardiac events may appear seizure-like and may be mislabelled as epilepsy.
- Corrected QT interval of:
  - Men: >450ms
  - Women: >470ms

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

Consider referral to your local genetics centre for:

- Individuals with clinical symptoms (see Box 1) of LQTS or a suggestive ECG
- First degree family members of individuals clinically diagnosed with LQTS
- First degree relatives of an individual with a known mutation in a LQTS gene
- Individuals with a family history of sudden death in a first degree relative under the age of 40

All of the above individuals **should also be referred to a cardiac arrhythmia specialist.**

SUDDEN ARRHYTHMIC DEATH IN THE YOUNG : OTHER DISORDERS

In addition to LQTS, there are other cardiac disorders, some of them heritable, which can cause sudden death in young people. These include arrhythmogenic and hypertrophic cardiomyopathies, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT). Review of individuals who have experienced cardiac arrest and their first degree relatives may identify a cause in up to~40% of cases. Family physicians may play a crucial role in referring first degree relatives to cardiac genetics specialist services following the death of a young person in whom autopsy did not identify cause of death or in whom a heritable cardiac disorder was suspected. Please refer to Ellison (2015) for an overview of other inherited cardiac disorders that can cause SCD.

WHAT DOES THE GENETIC TEST RESULT MEAN?

LQTS is autosomal dominant. A man or woman with LQTS due to a single faulty gene has a 50% chance of passing the genetic risk for arrhythmia to each child.

LQTS demonstrates reduced penetrance (*not every individual who inherits a mutation in a LQTS gene will develop LQTS*) and variable expressivity (*clinical presentation can vary between affected individuals even within a family*).

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

Genetic testing for LQTS can provide:

- Clarification of LQTS risk status for individuals with borderline clinical investigations
- Identification of individuals in whom a particular mutation confers a higher risk for SCD
- Assistance with life planning (e.g. decisions about careers, participation in competitive sports)
- Relief from worry, for those who test negative for a known family mutation, (a true negative result), as they will not develop the disease in the future and know that their children are not at risk of inheriting the disease

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

Genetic testing can result in:

- Adverse psychological reaction, particularly due to potential for risk of sudden cardiac death, family issues, distress
- Uncertainty due to a genetic variant of unknown significance
- Uncertainty due to limited sensitivity of genetic testing. About 1/4 of LQTS families do not have a recognizable gene mutation
- Insurance/job discrimination

The perceived benefits and limitations of genetic testing may vary with an individual's personal and family experience of LQTS. The perspective of an individual who has lost a family member to LQTS contrasts significantly with the perspective of an otherwise healthy individual whose prolonged QT interval was picked up incidentally on routine ECG.

SURVEILLANCE AND MANAGEMENT

LQTS is treatable with beta-blockers, implantable cardioverter defibrillators, and avoidance of competitive sports, electrolyte imbalances, and QT-prolonging medications [see www.crediblemeds.org for a comprehensive list (free access, one-time registration required)].

Risk stratification takes into consideration factors such as QTc duration, genotype, gender and age.

For a recent review article on sudden cardiac death see Ellison S. Sudden cardiac death in adolescents. *Prim Care Clin Office Pract* 2015: 42: 57–76. See online for complete reference list. **Other LQTS resource**: The Canadian Sudden Arrhythmia Death Syndromes (SADS) Foundation website http://www.sads.ca/

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