



The Cardiac Society of Australia and New Zealand

## Guidelines for the diagnosis and management of Familial Long QT Syndrome

These guidelines were revised by Dr Jonathan Skinner and members of the Cardiovascular Genetic Diseases Council Writing Group.

The guidelines were reviewed by the Continuing Education and Recertification Committee and ratified at the CSANZ Board meeting held on Wednesday, 10th August 2011.

### 1. Clinical Characteristics

#### 1.1 Definition and prevalence

Long QT syndrome (LQTS) is a familial condition causing syncope and sudden death through rapid ventricular tachycardia (torsade de pointes), which can deteriorate to ventricular fibrillation, in otherwise fit and healthy young people. Prevalence is approximately 1 in 2,500.<sup>1</sup> Clinical diagnosis is made from a combination of suspicious history, family history and the twelve lead ECG, which typically reveals a heart-rate corrected QT interval ( $QT/RR$  interval= $QTc$ ) of greater than 0.46 in women and 0.45 in men. QT interval behaviour after exercise testing is often helpful in making the diagnosis.

#### 1.2 Clinical presentation

LQTS most commonly presents with syncope or sudden death during or following exercise or stress in a young person. QT prolongation can present on an incidental ECG or during family screening following a sudden unexplained death.<sup>2 3</sup> Misdiagnosis of LQTS as epilepsy, particularly “familial epilepsy,” is common.<sup>4</sup> Seizures following exertion or arousal, and during sleep, must raise the suspicion of LQTS.

#### 1.3 Clinical diagnosis

The diagnosis is usually made on clinical grounds (table 1).<sup>5</sup> If the presentation is with syncope or resuscitated sudden cardiac death, the ECG shows  $QTc$  prolongation and the T-wave morphology is frequently abnormal. QT prolongation due to drugs or biochemical imbalance (low potassium, calcium or magnesium), hypothermia and myocardial disease must be excluded.

Features suggesting arrhythmic syncope include collapse associated with exercise, sudden emotional stress or loud noise, and physical injuries indicating failure to make protective movements when falling - particularly facial injury. Syncope associated with swimming is due to LQTS until proven otherwise. Syncope secondary to pain or nausea or syncope preceded by nausea is more commonly neurocardiogenic.<sup>6</sup> The implantable digital loop recorder (“reveal device”) can be valuable in detecting or excluding arrhythmia at time of syncope if others tests are inconclusive.

**Table 1: Clinical diagnostic criteria for LQTS\***

Electrocardiogram Findings†	Points	
Corrected QT interval, seconds		* from Schwartz et al. <i>Circulation</i> 1993,88:782-4.
≥0.48	3	Scoring: ≤1 point, low probability of LQTS; 2 to 3
0.46-0.47	2	points, intermediate probability of LQTS; and ≥4
0.45 (in males)	1	points, high probability of LQTS.
Torsades de pointes‡	2	† Findings in the absence of medications or
T-wave alternans	1	disorders known to affect these electrocardiogram
Notched T wave in 3 leads	1	findings. The corrected QT interval (QTc) is
Low heart rate for ages§	0.5	calculated by the Bazett formula: $QTc = QT/\sqrt{RR}$ ,
<b>Clinical history</b>		where R-R is the time interval between 2
Syncope‡		consecutive QRS complexes on electrocardiogram.
With stress	2	‡ Torsades de pointes and syncope are mutually
Without stress	1	exclusive.
Congenital deafness	0.5	§ Resting heart rate below the second percentile for
<b>Family history</b> ¶		age.
Family members with definite LQTS	1	¶ The same family member cannot be counted in
Unexplained sudden cardiac death	0.5	both categories
at under 30 years among immediate		
family member(s)		

*Family history:* A detailed family history looks for a history of syncope or sudden unexplained death at a young age in a close relative. Directed questioning is essential, with a family tree being drawn. Consider unexpected drowning in a strong swimmer, or road traffic accidents on a straight road. Document age and mode of death, or syncope in all close relatives. Familial epilepsy and sudden infant death are suspicious. Any sudden unexpected natural death with a negative post-mortem should trigger a family investigation for LQTS.

*Family screening:* ECGs should then be obtained on all first-degree relatives. Up to one third of asymptomatic gene mutation carriers have QTc values within the normal range. QTc values of ≥0.44 sec are treated as suspicious. Values below 0.41 sec are uncommon in gene carriers. The length of the QT interval is linked to the risk of syncope and sudden death, but all gene carriers are at an increased risk, and can still pass on the mutation to 50% of their children.

Certainty for many family members often requires genetic testing. Holter testing is of limited value for making the diagnosis unless torsade de pointes or T-wave alternans is documented. Exercise testing can be very helpful. After exercise, QT intervals of LQT mutation carriers and non-carriers tend to separate more than at rest. (An absolute QT interval of over 0.37sec at a heart rate of 100 post exercise is highly suggestive of LQTS types 1 or 2; a value below 0.34 sec makes it unlikely.)<sup>7</sup> Also watch for QTc prolongation for at least nine minutes post exercise; a QTc >0.445ms at end recovery distinguishes 92% of LQT 1 and 2 subjects from controls.<sup>8</sup>

## 2. Molecular Genetics

### 2.1 Familial LQTS disease genes

LQTS is most commonly inherited in an autosomal dominant manner and is sometimes called Romano-Ward syndrome. A single mutation in any one of the *LQT1 through LQT12* genes results in this autosomal dominant form of LQTS. Each child of an affected parent has a 50% chance of inheriting a disease-causing gene mutation.

The commonest genotypes are types 1 and 2; about 8% are type 3. In each, a dysfunctional cardiac cell channel results in prolongation of the cardiac action potential, and thus the QT interval (table 2). Many of the hundreds of mutations found to date are unique to a family or very rare; and detail about pathogenicity may be lacking. About quarter of families with LQTS do not yet have a recognised genetic locus

Approximately 5% of families have two mutations, family members with both mutations tend to be more severely affected. The presence of 2 mutations on opposite chromosomes in either the *LQT1* or *LQT5* gene results in a severe autosomal recessive form of LQTS with associated sensorineural deafness (Jervell and Lange-Nielsen syndrome).<sup>9</sup>

Studies of the three commonest genotypes (Types 1, 2 and 3) have shown that the life-threatening cardiac events (syncope or sudden death) tend to occur under specific circumstances in a gene-specific manner, and have characteristic T wave morphologies,<sup>10</sup> see table 3.

Mutations in the cardiac sodium channel gene *SCN5A*, cause long QT type 3 if the cardiac sodium channel ( $\text{Na}_v1.5$ ) is overactive (leaking sodium and prolonging the action potential), and cause Brugada syndrome if it is underactive.<sup>11</sup> Both clinical conditions tend to cause nocturnal sudden death as their first symptom, and families exist where both of these conditions are present in different family members, with the same genetic mutation. *SCN5A* mutations are the commonest single-gene cause of sudden unexplained death in infancy (about 6% of all cases).

Subjects with long QT types 1 and 2 tend to have several “warning” syncopal episodes before a sudden death, whereas in long QT3 the first presentation is typically sudden death.<sup>12</sup>

**Table 2: Long QT genes**

Clinical name	Chromosomal locus	Gene name	Current Affected	Proportion of mutations <sup>^</sup>
<i>LQT1</i>	11p15.5	<i>KCNQ1 (KVLQT1)</i>	$\text{K}^+$ ( $\text{I}_{\text{Ks}}$ )	38%
<i>LQT2</i>	7q35-36	<i>HERG (KCNH2)</i>	$\text{K}^+$ ( $\text{I}_{\text{Kr}}$ )	42%
<i>LQT3</i>	3p21-24	<i>SCN5A</i>	$\text{Na}^+$ ( $\text{I}_{\text{NA}}$ )	12%
<i>LQT4</i>	4q25-27	Ankyrin B	$\text{Na}^+$ ( $\text{I}_{\text{NA}}$ )	1%
<i>LQT5</i>	21q22.1-22.2	<i>KCNE1 (minK)</i>	$\text{K}^+$ ( $\text{I}_{\text{Ks}}$ )	5%
<i>LQT6</i>	21q22.1-22.2	<i>KCNE2 (MiRP1)</i>	$\text{K}^+$ ( $\text{I}_{\text{Kr}}$ )	1%
LQT7 (Anderson)	17q23	<i>KCNJ2</i>	$\text{K}^+$ ( $\text{K}_{\text{ir}2.1}$ )	<0.1%
<i>LQT8 (Timothy)</i>	12p13.3	<i>CACNA1C*</i>	$\text{Ca}^{++}$ ( $\text{I}_{\text{Ca-L}}$ )	<0.1%
<i>LQT9</i>	3p25	<i>CAV3 (Caveolin)</i>	$\text{Na}^+$ ( $\text{I}_{\text{NA}}$ )	<0.1%
<i>LQT10</i>	11q23.3	<i>SCN4B</i>	$\text{Na}^+$ ( $\text{I}_{\text{NA}}$ )	<0.1%
<i>LQT11</i>	7q21-q22	<i>AKAP9 (A -anchor protein 9)</i>	$\text{K}^+$ ( $\text{I}_{\text{Ks}}$ )	<0.1%
<i>LQT12</i>	20q11.2	<i>SNTA1 (alpha-1 syntrophin)</i>	$\text{Na}^+$ ( $\text{I}_{\text{NA}}$ )	<0.1%

<sup>^</sup> From Modell, 2006<sup>13</sup>

\*Calcium channel, voltage-dependent, L type, alpha 1C subunit

LQT7-Anderson syndrome is a rare neurological disorder characterized by periodic paralysis, skeletal developmental abnormalities, and QT prolongation.

LQT8-Timothy syndrome is a rare condition characterised by syndactyly, facial dysmorphism, autism and severe LQTS.

**Table 3 Phenotypic characteristics of LQT types 1, 2 and 3**

LQT type	T-wave morphology	Events triggered by exercise %	Events triggered by excitement %	Events during rest or sleep%	Reduction of risk of SCD by beta blockers	Group most severely affected	Percentage of LQT gene positive SUDI cases*
1	Broad based	62	26	3	75%	Boys aged 5-15	10%
2	Low voltage, double bump	13	43	29	50%	Adult women	10%
2	Late onset high amplitude	13	19	39	No established benefit	Adult male and infants	68%

\*SUDI- sudden unexplained death in infancy

## 2.2 Genetic screening

The main value of genetic testing lies in family screening. Following the identification of a proband who unequivocally has LQTS, molecular diagnosis is then sought through screening the known genes. Hundreds of mutations within the genes have been identified, and these genes carry many polymorphisms (harmless genetic variations), so that this first molecular diagnosis is time consuming. However, once the mutation is found, screening for this point mutation in the family is relatively quick.

Careful counselling prior to testing is essential, and confidentiality of results needs to be assured. Some people will not want their own GP or their family to know their result. Negative aspects of a positive genetic diagnosis include potential insurance and employment and psychological problems.

Genetic screening for LQTS as part of a molecular autopsy in autopsy-negative young sudden death can reveal a diagnosis in 15-20% of cases.<sup>14 15</sup>

## 3. Management

### 3.1 Affected individuals

#### *Removal of triggers*

All gene carriers must avoid medications which prolong the QT interval, can cause torsade de pointes or lower serum potassium levels. A constantly updated list is available at [www.qtdrugs.org](http://www.qtdrugs.org).

#### *Assessing level of risk of sudden cardiac death*

Management must be guided by an assessment of risk. Data from the international long QT registry show that the most important features are:

1. Length of the QT interval on serial resting ECGs;
2. History of arrhythmic syncope or cardiac arrest; and
3. Gender.<sup>16-18</sup>

For example, an 18 year old with a  $QTc > 550ms$  has a 19% chance of cardiac arrest by aged 40, compared to a 2% risk with  $QTc$  less than 470ms.<sup>18</sup> In adults, females are at much higher risk than males; the reverse in childhood. A 6-year old boy with a history of syncope has a 15% risk of cardiac arrest by age 12, compared to 0.6% risk in an asymptomatic 6-year old girl.<sup>17</sup> Women, especially those with LQTS type 2, are at particular risk in the nine months post partum (risk is reduced during pregnancy).<sup>19</sup>

LQT gene carriers, like the general population, may suffer from neurocardiogenic syncope. Risk stratification depends on correctly assigning the nature of the syncope.

Whilst adrenaline challenge and exercise testing can help clarify gene carriage state, there is as yet no evidence supporting the use of such recordings to assess risk. Although the death of a family member may understandably bring a perception of increased risk, there is no evidence that it does.<sup>17 20</sup> Careful evaluation has demonstrated for example that death of a sibling does not increase risk.<sup>20</sup>

#### *Measuring the $QTc$*

Despite the failings of the Bazett heart-rate correction formula ( $QT$  divided by square root of preceding R-R interval), it is still in popular use, and all outcome data are based on its use. Measure in lead II and V5,<sup>21</sup> take the longest on serial ECGs.<sup>22</sup> The end of the  $QT$  interval is determined by extrapolating the steep curve of the T wave down to the baseline (“teach the tangent”).<sup>23</sup>

#### *Lifestyle modifications*

With all forms of LQTS, where there is a long  $QT$  interval (and not necessarily just gene carriage), some degree of limitation in sporting activity is recommended. The limitation needs to be more severe with LQT1, or those who have already experienced events during exercise, than LQT2 and 3. They should not become professional athletes, and all highly competitive sports are to be discouraged. With LQT 1, and subjects with a history of exercise induced syncope, swimming and diving are contraindicated. With LQT 2, or those with a history of auditory evoked events, remove loud alarm clocks and turn down the volume on the phone at night.

#### *Beta Blockade*

Beta blockade should be initiated in those who have had symptoms, and those with a definite long  $QT$  interval, particularly in pre-adolescent boys, including infants. Overall reduction of risk of sudden cardiac death in high risk subjects is 67% in LQT 1 males and 71% in LQT 2 females.<sup>24</sup> No benefit is yet established with long  $QT$  3. Long acting agents are preferred to aid compliance, such as nadolol or slow release propranolol. Once started, they should not be stopped; there is a period of high risk after stopping beta-blockers due to up-regulation of beta-receptors on treatment.

LQT3 patients are at higher risk at slower heart rates, and the  $QT$  interval shortens at faster heart rates. This raises concerns, not yet supported by evidence, regarding the use of beta-blockers. The prevention of noradrenaline release remains important, but it may be more safely achieved with selective left cardiac sympathetic denervation, which does not reduce heart rate. LQT3 patients may benefit from pacemakers, which would also allow the safe use of beta-blockers. There is a high mortality rate despite therapy even at the first episode, especially in males with a long  $QT$  interval. Early consideration of AICD is reasonable if the  $QTc$  is greater than 500ms.

No gene-specific therapies have proven effect in reducing risk of death, nor are they yet known to be safe.  $QT$  interval can be shortened experimentally with potassium pump enhancing agents, such as nicorandil, in LQT type 1 and spironolactone combined with oral potassium in LQT type 2. In LQT type 3 sodium channel blockers, such as flecainide, can shorten the  $QT$  interval, but may induce a Brugada phenotype.<sup>25</sup>

### *Automated Intracardiac Cardioverter-defibrillators (AICD)*

This issue is reviewed by the Heart Rhythm UK sudden death group recently.<sup>26</sup> These devices are not without morbidity and patients must be selected carefully. AICDs are considered to be indicated for:

1. Resuscitated cardiac arrest,
2. Persistent arrhythmic syncope whilst on beta blockers,
3. When beta blockers are contra-indicated and high risk is established.

A relative indication is the presence of a very long QT interval ( $QTc > 0.55\text{sec}$ ) even without symptomatology, particularly adult females and males with LQT 3. Unless inserted for contraindication to beta-blockers, it is important that beta-blockers are continued because of the risk that a defibrillation shock may cause an adrenergic surge and precipitate a further event or electrical storm.

### *Left cervical sympathectomy*

Minimally invasive selective left cardiac sympathectomy<sup>27,28</sup> may be considered for:

1. Those with severe disease and in whom beta blockers are contra-indicated or AICD cannot be placed or is not wanted.
2. Controlling VT storms in those with an AICD,
3. LQT3 or a personal or family history of events during rest or sleep.

Some individuals at intermediate risk may choose this option rather than take beta blockers, and it may be considered as a primary prevention, particularly boys with LQT1. Those at high risk should continue beta blockers after the sympathectomy when feasible.

### **3.2 Asymptomatic family members**

If LQTS cannot be excluded, the individual should avoid medications contra-indicated in LQTS. Those with a long QT interval ( $>500\text{ms}$ ), especially young males and adult females need to be treated much as someone who has already presented with syncope. Beta blockers should be proposed and sensible limitations placed on sporting activities and particularly swimming.

The role of beta blockers in those without symptoms, a normal QT interval and yet a positive genetic diagnosis is controversial, since evidence is not yet strong to establish a reduction in risk. Those with a family history of adrenergic induced cardiac events, or known to have LQT1, are most likely to benefit. It should be remembered that intermittent adherence to beta blocker therapy may carry its own risk; when the medication is stopped, the up-regulated beta-receptors may lead to an increased risk for a few days after stopping.

### **3.3 Genetic counselling and psychological counselling.**

The main aim of the clinician is to prevent sudden death through medication and life-style changes. A secondary aim is to assist the family in their adjustments that have to be made. Time and skilled psychological and genetic counselling is required. This is often more than the busy cardiologist can provide and suitable professional assistance should be offered when appropriate. Genetic counselling is particularly important *prior* to testing an asymptomatic individual with a normal ECG. A positive result may have adverse psychological, social, employment and insurance effects.

Some of those at highest risk are adolescents and teenagers. Beta blockers and the limitations on activities are both hard pills to swallow, and whilst encouraging adherence, it is important not to alienate the patient. They will need to feel some retention of control in their lives.

## 4. Further Information

### Useful Websites

[www.sads.org](http://www.sads.org) (International site of the Sudden Arrhythmic Death Society)

[www.sads.org.au](http://www.sads.org.au) (Australian site)

[www.cidg.org](http://www.cidg.org) (Cardiac Inherited Disease Group, New Zealand)

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