The clinical and electrophysiological spectrum of cardiac sodium channel mutations
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CHAPTER 4.1

THE LONG QT SYNDROME

4.1.1 INTRODUCTION

The congenital form of the long QT syndrome is a primary electrical disease of the heart, like the Brugada syndrome (BS) and inherited cardiac conduction disease (ICCD). Similar to these two diseases one form of the congenital long QT syndrome, LQT3, has been causally associated with mutations in the SCN5A gene. An important difference with BS and ICCD is that for long QT syndrome an acquired form exists, next to the congenital inherited form, as a clinically important disease.

As the name suggests the long QT syndrome is characterized by a prolonged QT interval on the 12 lead electrocardiogram (figure 1). The QT interval is an indicator of the duration of the ventricular action potential. If the repolarization process of the action potential is abnormally delayed, beyond its normal duration, this will show as prolongation of the QT interval. When repolarization is delayed inhomogeneously in the different regions of the heart this will, in addition to QT prolongation result in an abnormally shaped T-wave. This inhomogeneity, or transmural dispersion of repolarization (TDR), can induce and maintain a life threatening ventricular tachyarrhythmia called torsades de pointes (TdP).

Therefore, QT prolongation, or as we shall discuss later QTc prolongation, the QT interval corrected for heart rate, should always be considered a warning sign for a potentially life threatening cardiac disease.

Congenital long QT syndrome was first described in 1957 by Jervell and Lange-Nielsen as an autosomal recessive disease in patients that additionally suffered from congenital deafness. After this discovery autosomal dominant inherited forms of the long QT syndrome were described by Romano in 1963 and Ward in 1964. These patients, suffering from Romano-Ward syndrome, do not have congenital deafness.

The inherited nature of some forms of the long QT syndrome was thus already recognised at that time, but it was not until 1995 that mutations in ion channel genes, ‘LQT genes’ (Table 5.1), were found to be involved. The Jervell-Lange-Nielsen syndrome is caused by homozygous loss of function mutations in KVLQT1 or in MinK, reducing the repolarizing potassium current. Patients suffering from the Romano-Ward syndrome can have a mutation in one of seven different genes.

Acquired long QT syndrome is caused by QT-prolonging cardiac and non-cardiac drugs. In some patients with acquired long QT syndrome, mutations or polymorphisms in LQT genes can be found that do not give a long QT phenotype unless repolarization is further delayed by QT prolonging drugs (www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm).
The LQT genes encode for several different ion channels and accessory subunits and, in one LQT type (LQT4) for a structural cell protein (Table 4.1). Ion currents that have been found to be affected by mutations are the sodium current, \( I_{\text{Na}} \), and the potassium currents, \( I_{\text{Ks}} \), \( I_{\text{Kr}} \), and \( I_{\text{Kir}} \). The ECG, clinical phenotype and prognosis have been shown to be different depending on the affected ion current. Presently 7 genetic forms of the Romano-Ward type inherited long QT syndrome have been identified and subsequently named LQT1-7. Each LQT subtype is linked to mutations in a specific gene. The autosomal dominant inheritance of LQT1 to 7 means that if patients are heterozygous for the mutation they will also have 1 normal allele.

Except for LQT3 and LQT4, genes encoding cardiac potassium channels are involved. Potassium channels are formed by co-assembly of four \( \alpha \)-subunits (either KvLQT1 or HERG) and therefore several combinations of normal and abnormal subunits, forming a functional channel are possible, resulting in functionally different ion channels. Additionally the \( \alpha \)-subunits associate with modulating \( \beta \)-subunits (minK and MiRP1) which may affect current characteristics. The action potential prolonging mechanism in these forms of LQT is a reduction in repolarizing potassium currents, \( I_{\text{Ks}} \), \( I_{\text{Kr}} \), and \( I_{\text{Kir}} \).
### Table 4.1

<table>
<thead>
<tr>
<th>LQTS type</th>
<th>Gene</th>
<th>Chromosomal Locus</th>
<th>Affected Ion current</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1 (KVLQT1)</td>
<td>11p15.5</td>
<td>IKs ↓ (slow activating delayed rectifier)</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2 (HERG)</td>
<td>7q35-36</td>
<td>IKr ↓ (rapid activating delayed rectifier)</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>3p21-24</td>
<td>INa ↑ (increased or prolonged INa)</td>
</tr>
<tr>
<td>LQT4</td>
<td>Ankyrin B</td>
<td>4q25-27</td>
<td>↑ late INa (possibly)</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1 (minK)</td>
<td>21q22.1-22.2</td>
<td>IKs ↓ (slow activating delayed rectifier)</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2 (MiRP1)</td>
<td>21q22.1-22.2</td>
<td>IKr ↓ (rapid activating delayed rectifier)</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>17q23</td>
<td>IKir2.1 ↓ (inward rectifier)</td>
</tr>
</tbody>
</table>

In LQT3, the simultaneous expression of normal and abnormal sodium channel α-subunits will occur. The mutations in the SCN5A gene in LQT3 are gain-of-function mutations (Figure 2), increasing the depolarizing sodium current, as shall be discussed.

The effects of many mutations in LQT genes have been studied using cellular expression models such as HEK, tsA, COS-cells or Xenopus oocytes. By doing so the QT prolonging effect of the majority of mutations can be explained and the effect of mutations in the same gene predicted. Some mutations and their effects on channel gating may additionally enable us to gain insight in structure function relationships of the ion channel and interacting, subunit, proteins. Elucidating such relationships and mechanisms has increased our understanding of the function of ion channels and their role in the normal and abnormal cellular electrophysiology of the heart.

Because LQT1, 2 and 3 make up approximately 95% of all inherited long QT syndromes, the present knowledge on the pathophysiology and treatment of the long QT syndrome is based on these three forms of the disease. Therefore this introductory chapter will only deal with these three forms of the Romano-Ward syndrome and especially the long QT syndrome type 3.
Chapter 4.1

Effects of LQT3 SCN5A mutations on sodium channel kinetics when studied in cell expression models

4.1.2. Clinical characteristics and diagnostic criteria

The hallmark of the long QT syndrome is the prolonged QT interval on the body surface ECG.6,7,8 However, the ECG and the clinical presentation may not always be typical and
directly lead to the diagnosis long QT syndrome. Not infrequently patients suffering from long QT syndrome have first been (mis-)diagnosed with other diseases, among which epilepsy, that were thought to explain their symptoms of (recurrent) fainting. Because of this, in 1992, Schwarz et al. have proposed diagnostic criteria for the long QT syndrome based on electrocardiographic, clinical data and the family history.\(^{6,7}\) By assigning points to several criteria the probability of the diagnosis long QT syndrome can be established (Table 4.2).\(^7\) In a patient with a score less than 1 the diagnosis is very unlikely while a score of more than 4 (the maximum score is 9) the probability of the diagnosis long QT syndrome is very likely.\(^7\) In patients with a score between 1 and 4 the probability of the diagnosis is intermediate and further diagnostics, follow up and screening of more ECG’s, and in familial long QT syndrome screening of family members is helpful.\(^7\)

**Table 4.2**
Diagnostic criteria in the long QT syndrome

<table>
<thead>
<tr>
<th>Electrocardiographic findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td></td>
</tr>
<tr>
<td>&gt;480ms</td>
<td>3</td>
</tr>
<tr>
<td>460-470ms</td>
<td>2</td>
</tr>
<tr>
<td>450-460ms (men)</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes(^*)</td>
<td>2</td>
</tr>
<tr>
<td>T wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T wave in three leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age(^\dagger)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>with stress</td>
<td>2</td>
</tr>
<tr>
<td>without stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Family members with established LQTS(^\ddagger)</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained SCD age &lt;30 y among immediate family members</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(^\ast\)not in the presence of QT prolonging drugs, \(^\dagger\) resting heart rate below the second percentile for age , \(^\ddagger\) the same family member cannot be counted twice (from Schwartz PJ et al. Circulation. 1993; 88:782-4)
After the diagnosis is made a further evaluation of the patient is needed for several reasons. First it should be established if the disease is acquired or familial in nature. If the disease is familial in nature, a genetic diagnosis may be possible in 70% of cases and family screening for the disease should be offered.\footnote{22} If the disease is acquired a provocative drug may be identified. Furthermore the study of long QT syndrome in individual patients and families is of scientific interest because it may increase our knowledge of the pathophysiological basis of the disease.

### 4.1.2.1 Index event and arrhythmia triggers

The long QT syndrome patient may present with (recurrent) syncope or aborted sudden cardiac death (SCD).\footnote{6,7,8} If ECG recordings of the event are available they may show torsade de pointes or ventricular fibrillation (VF). Torsade de pointes is usually self-terminating and is only lethal when it develops into VF.\footnote{1,2}

For the congenital long QT syndrome types 1, 2 and 3 gene-specific triggers have been identified (Table 4.3). Arrhythmias in LQT1 are triggered by physical or emotional stress and swimming, in LQT2 stress also plays a role and especially (loud) acoustic stimuli. In LQT3 arrhythmias mainly occur at rest.\footnote{1,21}

The age at which the first symptoms occur shows a gene specific-pattern. The first event in LQT1 occurs at a median age of 9 years while this is 12 and 16 years for LQT2 and LQT3 respectively.\footnote{1,21} The limitation of these observations is already evidenced by the A1330P LQT3 mutation that presented as sudden infant death syndrome.\footnote{24}

### Table 4.3

<table>
<thead>
<tr>
<th></th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>affected gene</td>
<td>KCNQ1</td>
<td>HERG</td>
<td>SCN5A</td>
</tr>
<tr>
<td>prevalence (%)</td>
<td>42\footnote{10}</td>
<td>45\footnote{10}</td>
<td>8</td>
</tr>
<tr>
<td>arrhythmia trigger</td>
<td>physical stress</td>
<td>auditory stimuli</td>
<td>rest</td>
</tr>
<tr>
<td>ECG morphology</td>
<td>broad T wave</td>
<td>small or notched T wave</td>
<td>delayed T wave onset</td>
</tr>
<tr>
<td>median age at first event (yr)</td>
<td>9</td>
<td>12\footnote{10}</td>
<td>16\footnote{10}</td>
</tr>
<tr>
<td>lethality (%)</td>
<td>4\footnote{22}</td>
<td>4</td>
<td>20\footnote{22}</td>
</tr>
</tbody>
</table>

4.1.2.1 Patient and family history
The history of a long QT patient may reveal symptoms of cardiac arrhythmias such as syncope. Similar events, and especially an unusually high incidence of SCD may be present in the patient's family. When acquired long QT syndrome is suspected a complete list of drugs, prescription and over the counter drugs, used by the patient should be recorded.
Physical examination of the patient and laboratory tests, excluding other cardiac and systemic diseases and especially electrolyte abnormalities, which may cause syncope and/or arrhythmias and QT prolongation, should be performed.

4.1.2.2 The electrocardiogram
The ECG is the most important diagnostic tool in the long QT syndrome. Heart rate, conduction parameters, and the QT interval should be measured. Using the latter the heart rate corrected QT interval can also be calculated. The QT interval is measured in the ECG lead in which the T-wave and especially the terminal part of the T-wave can be evaluated most accurately. Amplification of the ECG recording and the drawing of a tangent can be useful in defining the T wave end. The QTc interval can be calculated by using the Bazett formula (QTc=QT/√RR). The QTc interval should be ≤440 milliseconds in male adults and ≤450 milliseconds in adult females and children. The Bazett formula is most accurate at heart rates between 50-90 beats/min. The T-wave shape in the long QT syndrome has been shown to have genotype-specific characteristics. LQT1 patients have a broad T-wave, LQT2 patients have a low amplitude and sometimes notched T-wave while LQT3 patients have a peaked T-wave with a delayed onset (Figure 1). Sometimes T-wave alternans may be observed. During T-wave alternans the T-wave shows transient beat-to-beat changes in its shape, amplitude and polarity during sinus rhythm. T-wave alternans is a sign of electrical instability and thus a sign of increased risk for the development of arrhythmias.
In addition to prolonged QT intervals, long QT syndrome patients often have a lower heart rate, both during rest and during exercise. Bradycardia may be particularly present in LQT3. In addition to bradycardia, sinus node dysfunction, sinus pauses and atrioventricular and intraventricular conduction disturbances have been reported.

4.1.2.3 Genetic screening
When a case of familial long QT syndrome is suspected several screening approaches are possible. All seven LQT genes can be screened in a random fashion or they can be screened
in the order of the gene that is most often involved (HERG ≈ 45%, KCNQ1 ≈ 42% and SCN5A ≈ 8%). Both these options are labour intensive and expensive.\textsuperscript{22} The most efficient screening option is to make an educated guess of the gene involved based upon the phenotypical characteristics of the patient. Family screening should be offered to all family members at risk and not only to those with suspect ECG’s as the abnormalities may appear and disappear in time.

4.1.3 Therapy

The necessity of treatment of asymptomatic patients, without syncope or TdP, is a matter of debate. Life-style advice about eliminating arrhythmia triggers must be given in both symptomatic and asymptomatic patients. Therapy for symptomatic congenital long QT syndrome, especially pharmacological therapy, should be genotype-specific.\textsuperscript{26-31} Arrhythmias in long QT syndrome type 1 and 2, are triggered by adrenergic stimuli.\textsuperscript{1,20,21} In accordance with this observation the number of arrhythmic events can be reduced by beta-blocker therapy.\textsuperscript{26-28} Significant reductions in the incidence of arrhythmias and mortality rates have been reported in symptomatic patients after the start of beta-blocker therapy, however, in long QT syndrome type 3 beta-blockers are not effective.\textsuperscript{29}

Sodium channel blockers, eg. mexiletine, lidocaine and tocainide (class 1b anti-arrhythmic drugs), would theoretically be helpful in long QT syndrome type 3, in shortening the action potential, and have been shown to do so in experimental models.\textsuperscript{29-31} Because beta-blockers are not effective and the long-term efficacy of sodium channel blockers is unknown, implantation of an implantable cardioverter defibrillator (ICD) may be warranted.\textsuperscript{32,33} The initiation of TdP is often preceded by a pause and LQT patients often have relatively low heart rates, and may require additional beta-blocker therapy. In these cases the implantation of an artificial pacemaker may be a necessity.\textsuperscript{34-38} In some families pacemaker therapy has been shown to be effective. Pacemaker implantation may additionally prevent SCD due to complete heart block.\textsuperscript{34}

4.1.5 The molecular mechanism of QT prolongation in the long QT syndrome type 3

QT prolongation may result from increased depolarizing or reduced repolarizing current. Accordingly, LQT3 associated SCN5A mutants produce increased Na\textsuperscript{+} current. The exact biophysical changes identified by patch-clamp studies of SCN5A mutants in LQT3 is summarized in Figure 2.\textsuperscript{39-62,64,65,71,72} Their almost universal pathophysiological mechanism is
enhanced persistent Na\(^+\) current.\(^{39-45,62,64,65}\) While normal Na\(^+\) channels have virtually complete fast inactivation shortly following opening, these mutant channels exhibit a resistance to inactivation. An enhanced propensity for reopening from the inactivated state causes a persistent current during the action potential plateau.\(^{47,57}\) The first biophysically characterized LQT3-related SCN5A mutant, ΔKPQ,\(^{39}\) provides a plausible explanation for this gating change: the three residue deletion in the linker between domains III and IV, the putative fast inactivation lid, may destabilize its binding to its receptor at the inner vestibule of the channel pore. Similarly, the next reported LQT3 associated mutants are located in the S4–S5 linkers and in close proximity to the docking site for the fast inactivation lid.\(^{66}\) Regions of the C terminus may also be involved in fast inactivation, as engineered mutations here disrupt fast inactivation\(^{67}\) and enhance persistent Na\(^+\) current,\(^{68}\) and some LQT3 associated mutants are clustered here. While the persistent current is relatively small (not exceeding 5% of peak Na\(^+\) current), it may cause significant action potential prolongation, afterdepolarizations, and torsade de points, because it occurs during a phase of the cardiac cycle when the membrane potential is governed by a delicate balance of depolarizing and repolarizing forces, and the membrane resistance is high. Thus, small disruptions of this balance may profoundly affect membrane potential.\(^{69}\)

Clinical studies in LQT3 patients indicate that QT prolongation is most severe and arrhythmias most prevalent at slow heart rates, and that there is abnormally strong QT shortening upon heart rate increases.\(^{29}\) Accordingly, the persistent Na\(^+\) current is prominent at slow heart rates\(^{39,51,69}\) and reduced at fast rates, because, in some SCN5A mutants, its recovery from inactivation is slow and therefore incomplete at fast rates.\(^{35,24,51}\) Conversely, many LQT3 patients (30–40%) experience cardiac arrest during exercise or emotional stress.\(^{18,21}\) Enhanced adrenergic tone during these circumstances may facilitate the early afterdepolarizations that trigger their tachyarrhythmias. Accordingly, these patients may have QT prolongation at fast heart rates, because their SCN5A mutants do not cause QT prolongation by enhancing persistent Na\(^+\) current with a slow recovery from inactivation, but by other mechanisms. Challenging this view, however, is a study in transgenic mice (knock-in of ΔKPQ, a mutant with pronounced persistent Na\(^+\) current), where sudden pacing-induced heart rate increases caused paradoxical QT prolongation.\(^{42}\) While this observation is of obvious clinical relevance, its underlying mechanism is unclear. Functional AV block was also reported. Here, repolarization delay is so excessive that the action potential duration exceeds the beat-to-beat interval of the underlying rhythm. Thus, cardiac excitability is not
restored when the wavefront of the following beat arrives. The site of AV block is the ventricular working myocardium or the specialized conduction system (Purkinje fibers, bundle branches), but not the AV node. Some mutants do not exhibit enhanced Na$^+$ current in patch-clamp studies, but seem to exert electrophysiological effects only in conjunction with environmental factors (acquired LQT syndrome).
4.1. REFERENCES

18. Wilde AAM, Jongbloed RJ, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KvLQT1-related patients (LQTS1). J Am Coll Cardiol. 1999;33:327-332
55. Nagatomo T, January CT, Makielski JC. Preferential block of late sodium current in the LQT3 KPQ mutant by the class IC antiarrhythmic flecainide. Mol Pharmacol. 2000;57:101-107


The Long QT syndrome