HEREDITARY, CONGENITAL, FAMILIAL SHORT-QT SYNDROME or “GUSSAK SYNDROME”

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• Gene mutation •
Abstract

Hereditary, congenital or familial short QT syndrome is a clinical electrocardiographic, familial hereditary channelopathy, autosomal dominant or sporadic, genetically heterogeneous of the electrical system of the heart that consists of a constellation of signs and symptoms, as syncope, sudden death, palpitations and dizziness with high tendency to paroxysmal atrial fibrillation (AF) episodes, short QT interval on ECG (QTc ≤ 300 ms) that doesn't significantly change with heart rate, tall, narrow-based and peaked T waves that are reminiscent of the typical T waves in "desert tent" of hyperkalemia, structurally normal heart, short refractory periods in atrial and ventricular myocytes and inducible ventricular fibrillation to programmed electrical stimulation. A few affected families have been identified. There are sporadic cases. Familial short QT syndrome is a clinical and genetic counterpart, the long-QT syndrome. Both syndromes reflect the close, but opposite relationship of potassium channel dysfunction in the setting of normal repolarization.

Chronology of the discovery

**Year 1993:** The first data suggesting that not only too long but also too short a QT interval (<400 ms) may be associated with increased risk of sudden death (SD)\(^1\).

**Year 2000:** Proposed as a new inherited clinical syndrome by Gussak et al.\(^2\): We propose the just eponym “Gussak syndrome”.

**Year 2004:** January Ramon Brugada et al. from the Masonic Medical Research Laboratory identified the first genetic defect in this new clinical entity. The study was the result of a collaborative effort among researchers in Europe, and the United States\(^3\).

**Year 2004:** May: Bellock et al identified the second genetic defect in this new clinical entity. The SQT2 variant with mutation in slow delayed rectifier \(I_Ks\);
Year 2005: Prof. Silvia Priori et al identified the third genetic defect in this new clinical entity. This variant was named SQT3 variant. The mutation was observed in inward rectifier K+ current $I_{K1}^−$.

Etiology and pathogenesis

In hereditary or familial short QT syndrome (SQTS) there are specific mutations in one of three different potassium channels involved in cardiac repolarization. Three different gain-of-function mutations in genes encoding for cardiac outward potassium channels could be observed. The table 1 and the figures 1, 2 and 3 shows the mutation identified until today.

Table 1 and the figures 1, 2 and 3

The SQTS is a paradigm to understand the role of potassium channels in ventricular fibrillation$^6$. The principal gene candidates proposed to underlie these syndromes were gain of function mutations of $I_{K_{r}}(\text{SQT1})$, $I_{K_{s}}(\text{SQT2})$, $I_{K1(\text{SQT3})}$, $I_{K-\text{ACh}}$ and $I_{K-\text{ATP}}^7$. $I_{K-\text{ACh}}$ gain of function or other means by which the influence of the parasympathetic nervous system could be exaggerated was considered as the most likely mechanisms to explain the deceleration-dependent variant of the SQTS$^8$. A current hypothesis is that SQTS is due to increased activity of outward potassium currents in phase 2 and 3 of the cardiac action potential (AP). This would cause a shortening of the plateau phase of the AP (phase 2), causing a shortening of the overall AP, leading to an overall shortening of refractory periods and the QT interval.

Although the gain of function (increased activity) for KCNH2 shortened AP in the SQTS, a simulation model of the KCNH2 channel with the N588K mutation in the cardiac $I_{Kr}$ ion channel associated with the SQTS study suggested that arrhythmogenesis is associated not only with gain of function, but also with accelerated deactivation of KCNH2. Unexpectedly, 1 parameter change alone, which caused gain of function, could shorten the AP duration (APD) but failed to
induce early after-depolarizations (EADs). Only the condition with the combined gating defects could lead to EADs.\(^9\)

Preferential abbreviation of APD of either endocardium or epicardium appears to be responsible for amplification of transmural dispersion of repolarization (TDR) in the SQTS. The Long QR syndrome (LQTS), SQTS, Brugada and catecholaminergic polymorphic ventricular tachyarrhythmia are pathologies with very different phenotypes and aetiologies, but which share a common final pathway in causing SD.\(^{10}\) Much of the experimental work seems to show that arrhythmogenic action results mostly from an increase in the heterogeneity of the refractory periods, whether this involves a prolonged, short or even normal repolarization time. Knowledge of the mechanisms responsible for arrhythmias due to primary anomalies of ventricular repolarization could provide a model for secondary anomalies.\(^{11}\)

The possible main substrate for the development of VT/VF may be a significant TDR due to a heterogeneous abbreviation of the APD. Shortening of the effective refractory period combined with increased TDR is the likely substrate for re-entry and life-threatening tachyarrhythmias.\(^{12}\)

**Incidence:** Although only a few cases have been reported, it is possible that the incidence is underestimated, as so far little attention has been focused on short QT interval on the ECG.

**Symptoms and signs** There are major and minor cardiac events:

Major cardiac events:
1) Resuscitated cardiac arrest;
2) Syncope;
3) SCD.

Minor cardiac events
1) Palpitations;
2) Dizziness.
3) Atypical fainting spells.

It is very important to recognize this ECG pattern, because it is related to a high risk of SCD in infants, children and young adults, otherwise healthy individuals. The short QT syndrome is a new congenital entity associated with familial paroxysmal AF and/or SD or unexplained syncope, dizziness and palpitation. Individuals have family members with a history of unexplained or SD at a young age (even in infancy), palpitations, or AF. Resuscitated cardiac arrest in the presence of a positive family history for SD is frequent.

SD occurs in all age groups and even in newborns. Usually affects young and healthy people with no structural heart disease and may be present in sporadic cases as well as in families. Approximately 5-10% of SDs hit patients without structural disease of the heart. The proportion of young patients (< 40 years of age) in this group is even higher (10-20%). In younger patients significantly more diseases like hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia and primary electrical diseases of the heart could be observed such as LQTS, SQTS, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. The primary electrical diseases are different concerning their electrocardiographical pattern, clinical triggers of arrhythmias, results of invasive diagnostics and therapy. Meanwhile, molecular genetic screening can reveal specific mutations of ion channels and can identify consecutive functional defects. Short QT syndrome is associated with an increased risk of SD, most likely due to ventricular fibrillation. SQTS can be acquired and heritable.

**Acquired Short-QT Syndrome**

Analogous to the acquired long QT syndrome and acquired Brugada syndrome, SQTS can be induced by drugs, electrolytes unbalance, and pathophysiologic
states. However, little is known about prognostic implications of SQTS, which can causes SD in otherwise healthy individuals. The ECG of affected patients displays a very short QT interval and tall symmetrical T waves. Table 2 summarizes the most common etiologic mechanisms of Short-QT Syndromes.

Table 2

Diagnosis

The diagnosis of SQTS consists of characteristic history and findings on ECG and electrophysiologic testing. There are currently no set guidelines for the diagnosis of SQTS.

Electrocardiogram

All patients have a constantly and uniformly short QT interval at ECG. The characteristic findings of short QT syndrome on ECG are a short QTc interval, typically ≤ 300 ms\cite{14}, that doesn't significantly change with the heart rate. There is a lack of adaptation during increasing heart rates.

QT interval is shortened when QTc is less than 350 ms (1st degree of shortening). In children with QTc below 330 ms (2nd degree of shortening) short QT syndrome should be excluded. Normal variability of absolute QT value during sinus arrhythm on ECG at rest does not exceed 40ms\cite{15}.

Shortened QT interval is characteristic for children with family history of SD at young age. Registration of QT duration equal to or shorter than 88% of predicted value requires exclusion of diseases and syndromes with increased risk of SD. Values of QTc 88 370 ms and 350 ms were considered minimal for heart rates above and below 78 bpm, respectively. QT shortening to the level of QT(p)80 at heart rates above 70 bpm corresponded to QTc values < 330ms\cite{16}.

When looking at the ECG, we should pay attention not only to too long but also to too short a QT interval. We should not forget that a short QT interval found on the ECG may only be a reflection of external factors influencing ECG morphology, such as digoxina use, Hipercalcemia, hyperthermia, Hiperonasemia, acidosis,
autonomic imbalance and thus does not represent a real short QT syndrome and SD risk.

T wave: tall, peaked, pointed, narrow, and symmetrical T waves may also be noted.

It is frequently associated with Left Anterior Fascicular Block (LAFB), Individuals may also have an underlying atrial rhythm or AF.

Atrial fibrillation: It is a common cardiac arrhythmia whose molecular etiology is poorly understood. Familiar AF is an infrequent arrhythmia, usually well tolerated, that follows a dominant autosomic hereditary pattern. The association of a short QT interval with familial AF was first described by Gussak et al\(^2\).

In 1997 Brugada et al\(^17\) identified three families of whom some members had AF which segregated as an autosomal dominant disease. The disease was mapped to chromosome 10q22-q24 and 10q32. One of the genes mapped to the 10q22 region is DLG5, a member of the MAGUKs (Membrane Associated Gyanylate Kinase) family which mediates intracellular signaling. Shah et al\(^18\) identified two distinct alternately spliced transcripts of this gene. The genomic sequence of the DLG5 gene spanned 79 KB with 32 exons and was shown to have ubiquitous human tissue expression including placenta, heart, skeletal muscle, liver and pancreas. Molecular research of AF has focused on two main fields, identification of the genes that play a role in the initiation of the event in the acute form and altered gene expression during the disease state that perpetuate the arrhythmia and convert it into a chronic form\(^19\).

Chen et al\(^20\) studied a family with hereditary persistent AF and identified the causative mutation (S140G) in the KCNQ1 (KvLQT1) gene on chromosome 11p15.5. The KCNQ1 gene encodes the pore-forming alpha subunit of the cardiac I(Ks) channel (KCNQ1/KCNE1), the KCNQ1/KCNE2 and the KCNQ1/KCNE3 potassium channels. Functional analysis of the S140G mutant revealed a gain-of-function effect on the KCNQ1/KCNE1 and the KCNQ1/KCNE2 currents, which
contrasts with the dominant negative or loss-of-function effects of the KCNQ1 mutations previously identified in patients with long QT syndrome. Thus, the S140G mutation is likely to initiate and maintain AF by reducing action potential duration and effective refractory period in atrial myocytes.

**Stress testing**

The response to stress testing is a slight reduction of the QT interval during the physiological increase in heart rate with exercise.

**Programmed electrical stimulation (PES)**

In the electrophysiology lab, individuals with SQTS are noted to have short refractory periods, both in the atria as well as in the ventricles. During PES, atrial and ventricular effective refractory periods are shortened, and in a high percentage, VF is inducible. The significance of PES is at present unclear concerning risk stratification in patients with SQTS\(^{21}\).

The possibility of the recurrence of numerous shocks while the patient is conscious must always be explained to the patients. These shocks are sometimes inappropriate, and may lead to psychological problems and suicide in teenagers.

Clinicians need to be aware of this deadly ECG patterns as it portends a high risk of SD in structurally normal hearts in otherwise healthy subjects.

**Autopsy diagnosis**

Autopsy do not reveal any structural heart disease in SQTS. Most of the recent progress in autopsy diagnosis of sudden unexpected death comes from molecular biology, especially in case of SD without significant morphological anomalies. New syndromes have been described by cardiologists, such as SQTS and revealed in some cases by a SD. Molecular biology is now needed when limits of morphological diagnosis have been reached\(^ {22} \).

The table 3 show the main entities without structural heart disease and SD tendency
Table 3
Patients without structural heart disease and SD tendency\textsuperscript{23}.

**Treatment**

The best form of treatment is still unknown, but the implantable cardioverter-defibrillator (ICD) appears to be the safest and most effective therapy. Therapy for choice seems to be the ICD because of the high incidence of SD\textsuperscript{25}. However, ICD therapy may be associated with an increased risk of inappropriate therapies for T wave oversensing, which, however, can be resolved by reprogramming ICD detection algorithms.

In patients with SQTS and implanted ICD, increased risk for inappropriate therapy is inherent due to the detection of short-coupled and prominent T waves. Careful testing of ICD function and adaptation of sensing levels and decay delays without sacrificing correct arrhythmia detection are essential\textsuperscript{26}.

The use of certain antiarrhythmic agents, particularly quinidine, may be of benefit in individuals with short QT syndrome due to their effects on prolonging the action potential and by their action on the $I_K$ channels\textsuperscript{1}. The ability of quinidine to prolong the QT interval has the potential to be an effective therapy for short QT patients because effectively suppressed gain-of-function in potassium channel, along with prolongation of the QT interval. Quinidine block the fast Na\textsuperscript{+} current; $I_{Io1}$ channel or transient outward current, inward rectifier $I_K1$, delayed rectifier: $I_{KS}$, $I_{Kr}$ and $I_{KUR}$, $I_{KATP}$ or adenosine triphosphate ATP sensitive potassium channel, $I_{K-Ach}$, alpha 1 and alpha 2 adrenergic receptors and M\textsubscript{2} muscarinic receptor. This QT prolongation is particularly important because these patients are at risk of SD from birth, and ICD implant is not feasible in very young children. Quinidine may serve as an adjunct to ICD therapy or as possible alternative treatment especially for children and newborns\textsuperscript{27}. While the use of these agents alone is not indicated at present, there may be benefit of adding these agents to individuals who have
already had ICD implantation to reduce the number of arrhythmic events. Furthermore, in patients with a mutation in HERG (SQT1), quinidine rendered ventricular tachyarrhythmias noninducible and restored the QT interval/heart rate relationship toward a reference range. Oral quinidine is effective in suppressing the gain of function in IKr responsible for SQTS1 with a mutation in HERG and thus restoring normal rate dependence of the QT interval and rendering VT/VF noninducible\textsuperscript{28}.

Prevention of AF has been accomplished by the class Ic agent propafenone\textsuperscript{12}. It drug could be effective to prevent episodes of paroxysmal AF in patients with\textsuperscript{29}.

References

16)Makarov OM, Chuprova ON, Kiseleva OI. QT Interval Shortening in Families With History of Sudden Death at Young Age Kardiologiia. 2004; 44:51-56.


<table>
<thead>
<tr>
<th>DATE OF DISCOVERY</th>
<th>SQT1</th>
<th>SQT2</th>
<th>SQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004 Jan 6(^{3})</td>
<td>2004 May 25(^{4})</td>
<td>2005 April 15(^{5})</td>
</tr>
<tr>
<td>GENE MUTATION</td>
<td>KCNH2 (human ether-a-go-go gene HERG channel) (N588K missense mutation resulting in the same amino acid change (N588K) in the S5-P loop region of the cardiac potassium outward rectifying channel, (Mutation V307L)</td>
<td>KCNQ1, KvLQT1 g919c substitution in KCNQ1 encoding pore-forming alpha subunit of the cardiac I(Ks). S140G mutation KCNQ1 gain-of-function mutation in familial AF.</td>
<td>KCNJ2. The affected members of a single family had a G514A substitution in the KCNJ2 gene that resulted in a change from aspartic acid to asparagine at position 172 (D172N). KCNJ2 gene locus (region 17q23.1–q24.2). LQT7 Andersen syndrome was found on the long arm of chromosome 17 (lod score, 3.23 at ( \varphi=0 )) and overlapped the</td>
</tr>
<tr>
<td>POTASSIUM CHANNEL INVOLVED</td>
<td>$I_{Kr}$</td>
<td>$I_{Ks}$</td>
<td>$I_{K1}$</td>
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<td></td>
<td>Rapid component of the delayed rectifier K+ current</td>
<td>Slow component of the delayed rectifier K+ current</td>
<td>Inwardly rectifying Kir2.1</td>
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<tr>
<td><strong>KCNJ2 gene locus</strong></td>
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<td>(region 17q23.1–q24.2)</td>
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Table 2. Short-QT Syndromes

<table>
<thead>
<tr>
<th>A) Acquired and Drug-related Short-QT Syndrome:</th>
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<tbody>
<tr>
<td>• Acidosis;</td>
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<tr>
<td>• Alterations of the autonomic tone;</td>
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<tr>
<td>• Digoxin toxicity and digoxin effect</td>
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<tr>
<td>• Hypercalcemia;</td>
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<tr>
<td>• Hyperthermia;</td>
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<td>• Increased potassium plasma levels;</td>
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<tr>
<th>B) Hereditary or familial short-QT Syndrome:</th>
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<tr>
<td>SQT1: Ikr or rapid component rectifier $K^+$ channel</td>
</tr>
<tr>
<td>SQT2: Iks slow component rectifier $K^+$ channel</td>
</tr>
<tr>
<td>SQT3: $I_{k_1}$ or inward rectifier $K^+$ current.</td>
</tr>
</tbody>
</table>
Table 3

Patients without structural heart disease and SD tendency\textsuperscript{23}.

1) Long QT syndrome;
2) Short QT syndrome
3) The Brugada syndrome;
4) Idiopathic ventricular fibrillation.
5) Short-coupled torsade de pointes;
6) Catecholaminergic polymorphic ventricular tachyarrhythmia.
7) Short PR interval, bradycardia and polymorphic ventricular tachycardia: Shortening of PR interval -110 ms without signs of Wolf-Parkinson-White syndrome. There are not QT interval prolongations, or ST segment elevations in right precordial leads. It is associated with frequent attacks of syncope high risk of malignant ventricular tachyarrhythmia and SD\textsuperscript{24}.
8) Mixed forms, or overlapping clinical phenotypes:
   a) Brugada disease associated with LQT3
   b) Brugada syndrome associated with Lenègre disease\textsuperscript{i}
   c) Brugada syndrome associated with sinus node dysfunction\textsuperscript{i}
   d) Brugada syndrome associated with atrialstandstill\textsuperscript{i}
9) Some sudden unexpected nocturnal death syndrome (SUNDS)
10) Some sudden infant death syndrome (SIDS).
Opposite relationship of potassium channel dysfunction in the setting of normal repolarization. SQT1 has a gain of potassium channel function and LQT2 a loss of potassium channel function.

CONGENITAL SQT1

CONGENITAL LQT2

N588K missense mutation on KCNH2

Long QTc > 470ms affected
Figure 2

MUTATION IN KvLQT1:
SLOW “DELAYED RECTIFIER CURRENT” KvLQT1
Gen: KCNQ1 - Harvey ras-1 gen

CONGENITAL SQT2

T WAVE
Tall, peaked, pointed, narrow and symmetrical.

GAIN OF FUNCTION RECTIFIER CURRENT

Mutation V307L on KvLQT1 g919c substitution in KCNQ1 encoding pore-forming alpha subunit of the cardiac I(Ks).

CONGENITAL LQT1

BROAD-BASED PROLONGED T WAVE
GIANT U WAVE
REDUCED RECTIFIER CURRENT

60% of all Congenital LQTS.

Opposite relationship of potassium channel dysfunction in the setting of normal repolarization. SQT2 has a gain of potassium channel function and LQT1 a loss of potassium channel function.
MUTATION IN KCNJ2: THE OPERATION OF THE CHANNEL IS INDEPENDENT FROM VOLTAGE.

Inward K+ rectifier channel, IK1, Kir or background current It belongs to a subfamily of channels known as Kir2.x, with several types having been identified: Kir2.3, Kir2.2 and Kir2.1

CONGENITAL SQT3

This is an inward K+ channel, which is predominant in the final part of phase 3 within the cell in hyperpolarized state. It remains open until phase 4 in the face of very negative membrane potentials (hyperpolarization) with the aim of keeping the rest potential, because it is responsible of the balance state of rest transmembrane potential (RTP) or E1.

SQT3 and Andersen syndrome (LQT7) reflect the close, but opposite relationship of potassium channel dysfunction in the setting of normal repolarization. SQT3 has a gain of potassium channel function and Andersen syndrome a loss of potassium channel function. It was found on the long arm of chromosome 17 and overlapped the KCNJ2 gene locus (region 17q23.1–q24.2).