ไขความลับโรค long QT syndrome ชนิดที่ 3: ข้อมูลเชิงลึกทางพันธุกรรม การค้นพบทางสรีรวิทยาไฟฟ้า และความก้าวหน้าทางการวิจัยในปัจจุบันและอนาคต (unveiling the mysteries of long QT syndrome type 3: Genetic insights, electrophysiological discoveries and advancements in current and future research)

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Introduction

Long QT syndrome type 3 (LQTS3) stands as an enigmatic cardiac disorder that has intrigued scientists, clinicians, and researchers for decades. This hereditary condition, characterized by prolonged ventricular repolarization, poses a substantial risk of life-threatening arrhythmias, leading to syncope, cardiac arrest, and sudden cardiac death[1]. Understanding the intricate mechanisms underlying LQTS3 has been a challenging pursuit, but recent strides in genetic insights, electrophysiological discoveries, and advancements in research have started to shed light on its elusive nature.

LQTS3 is a subtype of the broader Long QT Syndrome (LQTS), a group of inherited cardiac disorders associated with abnormalities in cardiac ion channels. It is primarily caused by gain-of-function mutations in the *SCN5A* gene, encoding the α-subunit of the cardiac sodium channel $Na_V1.5$ [2]. Unlike other subtypes of LQTS, LQTS3 is characterized by a persistent inward sodium current during the plateau phase of the cardiac action potential, which disrupts the delicate balance of ion channel currents and significantly prolongs ventricular repolarization[3].

The clinical manifestations of LQTS3 often differ from those of other LQTS subtypes, as patients frequently experience arrhythmias during rest or sleep, rather than during exercise or stress[4]. This unique clinical phenotype, combined with the distinct underlying molecular and electrophysiological mechanisms, presents challenges in diagnosis, risk stratification, and management of affected individuals.

Recent advancements in genetic sequencing technologies have provided crucial insights into the genetic architecture of LQTS3. By identifying novel *SCN5A* mutations and studying their functional consequences, researchers have deepened their understanding of the complex genotype-phenotype relationships in LQTS3. These discoveries have paved the way for improved diagnostic techniques, including genetic testing and cascade screening of at-risk family members.

Furthermore, the advent of sophisticated electrophysiological tools and experimental models has allowed researchers to unravel the intricate workings of the cardiac sodium channel $Na_V1.5$ and its aberrations in LQTS3. High-resolution cellular and molecular studies have elucidated the pathophysiological mechanisms that underlie the sustained inward sodium current, facilitating the development of targeted pharmacological interventions and gene therapies.

In this article, we delve into the captivating realm of LQTS3, exploring the recent advance-

ments in genetic insights, electrophysiological discoveries, and the emerging research avenues. We will delve into the intricate genetic landscape of LQTS3, the clinical manifestations and challenges in its diagnosis and management, and the exciting therapeutic prospects on the horizon. By unraveling the mysteries of LQT3, we aim to foster a deeper understanding of this complex disorder and contribute to the ongoing efforts in preventing sudden cardiac death in affected individuals.

Through the integration of genetic, molecular, and clinical research, the collective knowledge gained in recent years holds tremendous promise for unraveling the mysteries surrounding LQTS3. As scientists and clinicians join forces, armed with groundbreaking advancements, we inch closer to improved diagnostics, individualized treatments, and ultimately, a brighter future for individuals affected by LQTS3.

Long QT Syndrome

LQTS is a cardiac disorder characterized by abnormal electrical activity within the heart. Patients with LQTS exhibit QT prolongation on their electrocardiogram (ECG), which can lead to various symptoms such as loss of consciousness and acute heart failure due to ventricular tachyarrhythmias, particularly torsades de pointes. These arrhythmias could result in cardiac arrest, syncope, or be mistaken as a consultive disorder caused by hypoxia-induced cerebral seizures[5, 6].

According to the diagnostic criteria outlined by the European Society of Cardiology, individuals are classified as having LQTS when their QT duration exceeds 480 ms, regardless of gender (Figure 1)[7]. However, for screening purpose, the definition of QT prolongation differs slightly, with males considered to have QT prolongation if their QT duration exceeds 450 ms and females if it exceeds 460 ms[8].

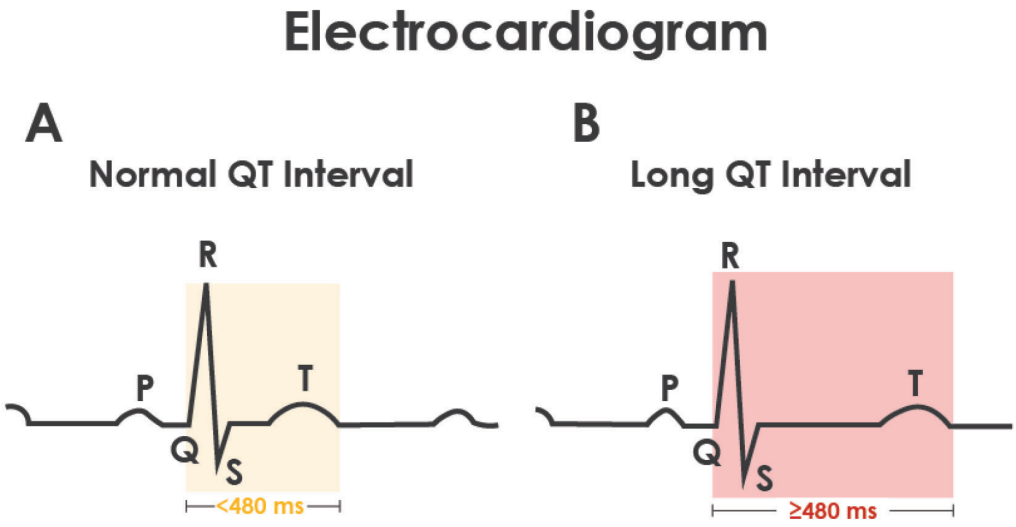


Figure 1. Electrocardiogram of A. Normal QT interval B. Long QT interval

1. Prevalence of LQTS

While the exact prevalence of this condition in the overall population remains scarce, a study by Schwartz *et al.* (2009) illustrates the prevalence of LQTS specifically among Caucasians. Their findings indicated a prevalence rate of approximately 1 case per 2,534 individuals, equating to 0.04%. Interestingly, this study also revealed a higher incidence of LQTS in females compared to males, as reported by the National Heart, Lung, and Blood Institute in 2022[9].

Research conducted by Trithiphen *et al.* in 2019 examined the occurrence of LQTS in the Thai population by analyzing 2,456 electrocardiograms (ECGs). The study revealed that 14% of the ECGs demonstrated QT prolongation. Furthermore, the subject with a prolonged QT interval were observed to be 12.5% in males and 17.7% in females. Following an 18-year follow-up period, it was found that 10.5% of individuals with prolong QT experienced cardiovascular events[10].

2. Clinical manifestation

Symptoms associated with LQTS encompass a range of manifestations, including episodes of fainting or loss of consciousness, palpitations, seizures, rapid or irregular heartbeat, sudden death, chest pain, breathing difficulties, as well as paleness or cyanosis. The severity can vary among individuals and differ depending on the specific genetic mutation involved.

While some individuals may exhibit symptoms from birth, others may experience them later in life, although the condition generally affects younger individuals. A retrospective analysis of the medical history of 647 untreated LQTS patients over a span of 28 years revealed that approximately 13% experienced cardiac arrest or sudden death before reaching an average age of 40.3 years. Certain triggers, such as physical activity (particularly swimming), emotional and auditory stimulation, as well as sleep, can precipitate symptoms[11].

The diagnosis of LQTS primarily relies on the examination of various factors, including the ECG readings, presence of QT-prolongation, assessment of the patient's clinical history, and consideration of their family history. However, the key symptom that often leads to suspicion of LQTS is unexplained fainting. Additionally, some patients may also experience accompanying symptoms such as blurred vision, mild headache, seizures, rapid heartbeat, weakness, and other related manifestations. Diagnosis is made by calculating an LQTS score with the score of 3.5 or above indicating high probability for congenital LQTS [11] (Figure 2).

	Points
ECG findings	
QTc	
• ≥480 ms	**3**
• 460-470 ms	**2**
• 450 ms (in men)	**2**
Torsades de pointes	**2**
T-wave alternans	**1**
Notched T wave in three leads	**1**
Low heart rate for age	**0.5**
Clinical history	
Syncope	
• With stress	**2**
• Without stress	**1**
Congenital deafness	**0.5**
Family history	
Family members with definite LQTS	**1**
Unexplained sudden cardiac death at age <30 years	**0.5**

Figure 2. Diagnostic criteria for LQTS in 1993[1]

3. Type of LQTS

There are several types of LQTS. The most common are three groups: type 1, type 2, and type 3, which have different etiology and pathophysiology.

3.1 Type 1 LQTS (LQTS1) is primarily attributed to a mutation in the *KCNQ1* gene, leading to the loss of function of the voltage-gated potassium channel type 7.1 ($K_V7.1$). This genetic abnormality results in a diminished slow delayed rectifier current generated by the flow of potassium ions (I_{Ks}). Notably, LQTS1 displays a higher prevalence in males, usually occurs during childhood, and episodes of arrhythmia are commonly triggered by physical exertion or exercise. Patients with type 1 LQTS account for 35% of all LQTS cases[4].

3.2 Type 2 LQTS (LQTS2) arises from a mutation in the *KCNH2* gene, leading to the deactivation of the voltage-gated potassium channel type 11.1 ($K_V11.1$). This genetic alteration disrupts the rapid delayed rectifier current potassium ions (I_{Kr}), resulting in a decreased efflux of these essential ions. LQTS2 exhibits a higher incidence among the female population, usually occur during puberty, and arousal is the main trigger events. It accounts for 30% of all LQTS cases[4].

3.3 Type 3 LQTS (LQTS3), is caused by a genetic mutation in cardiac sodium channel gene (*SCN5A)*, leading to an enhanced function of the voltage-gated sodium channel type 1.5 ($Na_V1.5$). This genetic alteration results in an increased activity of $Na_V1.5$, altering the delicate balance of sodium currents (I_{Na}) within the heart. Type 3 LQTS demonstrates a higher prevalence among the puberty female, the main trigger event is rest. It accounts for about 10% of the LQTS population[4] (Figure 3).

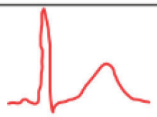
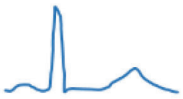
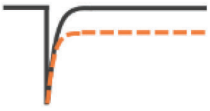
LQTS	Type 1	Type 2	Type 3
Gene	*KCNQ1*	*KCNH2*	*SCN5A*
Protein	$K_v7.1$	$K_v11.1$	$Na_V1.5$
Frequency among LQTS	35%	30%	10%
ECG			
QT change when exercise	Failure to shorten	Normal	Supranormal
Main trigger events	Exercise	Arousal	Rest
Age of onset arrhythmia	Childhood	Puberty	Puberty
Gender most at risk	Male	Female	Female
Effect on current			
Effect on action potential			

Figure 3. The relation between genotype and phenotype of LQTS in the three primary sub-categories, types 1, 2, and 3[4].

While studying all types of LQTS is important, focusing on LQTS3 specifically can offer several unique advantages and opportunities for research and clinical advancements. LQTS3 is distinguished from other types of LQTS due to its association with a specific mutation in *SCN5A*, which is responsible for the creation of sodium channels in the heart. Genetic mutation in *SCN5A* not only contributes to LQTS3 but also has the potential to cause various other disorders, including Brugada syndrome, dilated cardiomyopathy, and atrial fibrillation. By studying mutation in this gene, researchers can enhance their understanding of the physiology of ion channels. Furthermore, LQTS3 exhibits a primary trigger event, rest, which is an unavoidable aspect of human life, so studying LQTS3 could emphasizes the importance of customized treatment approaches that take into account the specific needs of individuals affected by LQTS3. Therefore, in this article we will mainly focus on LQTS3.

Long QT syndrome type 3 (LQTS3)

4. Cause of LQTS3

As mentioned above, LQTS3 is a result of a mutation occurring in the *SCN5A* gene, which is responsible for generating the cardiac sodium channel called $Na_V1.5$. This mutation alters the influx of sodium ions into cells, leading to changes in the sodium current (I_{Na}). Given the intricate nature of the mutation's impact, this article will commence by elucidating fundamental knowledge concerning the voltage-gated sodium channel in mammalian myocardial cells. This introduction aims to provide a solid foundation for comprehending the complex effects of mutation.

4.1 Voltage-gated sodium channel in myocardial cells of mammals

The gene *SCN5A* can be found on chromosome 3p21 and comprises a total of 28 exons. It undergoes transcription and translation to produce the primary cardiac isoform, $Na_V1.5$, which belongs to the family of voltage-gated sodium channels. $Na_V1.5$ comprises four distinct domains referred to as DI to DIV. Each domain is composed of six segments that span the cell membrane, namely S1 to S6. The region between S5 and S6 within each domain forms a pore and ion selectivity filter. [12] Within these segments, segment 4 contains a concentration of positive charges, which is believed to be involved in detecting changes in electrical potential. The N-terminal and C-terminal regions connect all four domains to the peptide chain[13, 14] (Figure 4).

The voltage-gated sodium channel exists in three states: open, closed (resting), and inactivated. These state transition from closed to open when the membrane depolarizes.

The channel remains open for a very short duration before becoming inactivated. When the cell membrane potential returns to its hyperpolarized resting potential, the inactivated state reverts back to the resting state. The current flowing through the sodium channels corresponds to their cycling through the resting, open, and inactivated states[15] (Figure 5).

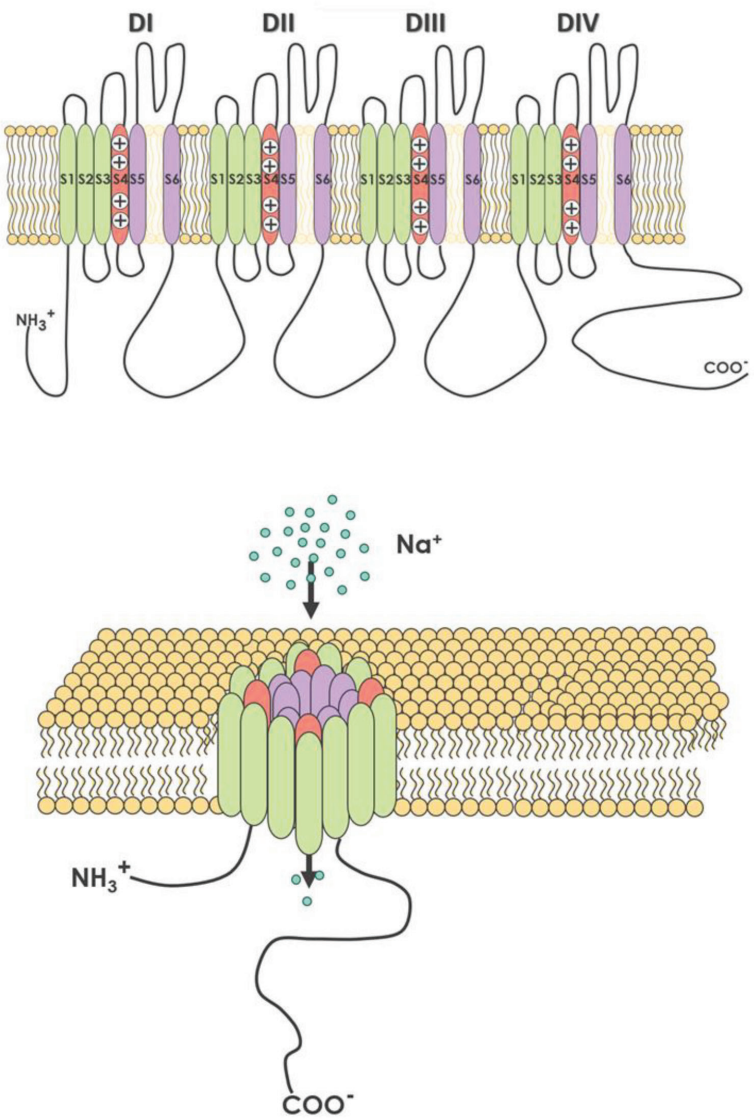


Figure 4. Molecular arrangement of the sodium channel in the heart. **A.** Illustration of the α-subunit ($Na_v1.5$). $Na_v1.5$ is composed of four sections (DI-DIV), each containing six segments that span the cell membrane (S1-S6). The S4 segments possess a positive charge and serve as voltage sensors. **B.** The four sections of $Na_v1.5$ fold around a pore responsible for ion conduction, which is lined by the connecting segments between the S5 and S6 segments[2].

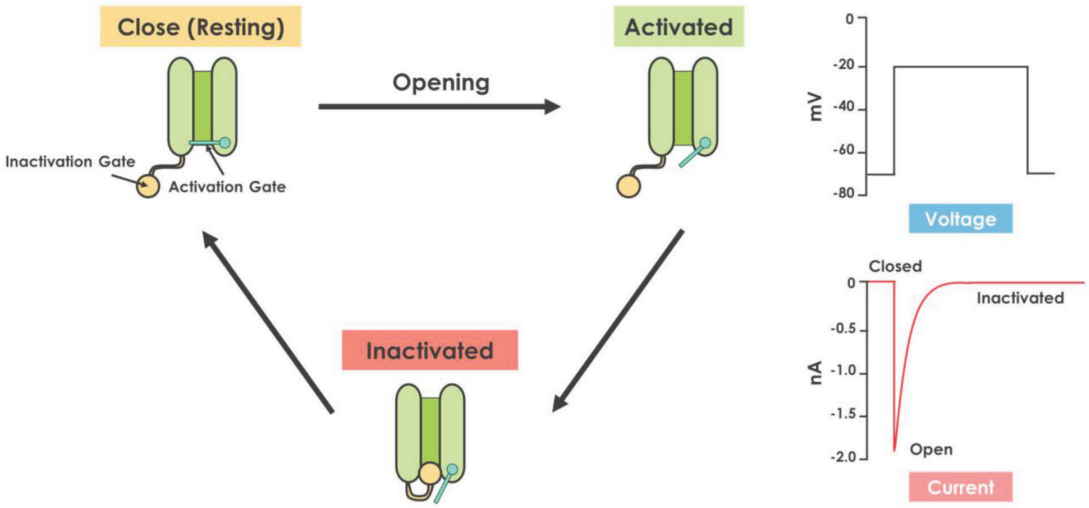


Figure 5. Sodium channels exhibit three different states: open, closed (resting) and inactivated, undergoing cycles between them. These channels transition from the closed (resting) state to the open state when the cell membrane experiences depolarization. The channel remains open for a very brief period, lasting less than a millisecond, before entering the inactivated state. Once the cell membrane potential returns to a hyperpolarized resting level, the inactivated state transitions back to the resting state. The current flowing through sodium channels corresponds to the cycling of these channels through the resting, open, and inactivated states[15].

4.2 Sodium current from sodium influx through voltage-gated sodium channels

When cardiomyocytes are activated by electrical signals originating from neighboring cells or artificially induced stimuli during patch-clamp experiments, their initial membrane potential (around -85 mV) becomes less negative, a process known as depolarization. This depolarization initiates the outward displacement of the positively charged voltage sensors (S4 segments). Subsequently, these sensors' movement prompts the activation of ion channels, leading to the opening of these channels and facilitating the passage of ions. Simultaneously with the onset of activation, the channels initiate their inactivation process, resulting in their closure. Nonetheless, inactivation occurs at a slower pace compared to activation, allowing the channels to remain briefly open for the passage of inward sodium currents (I_{Na}) during phase 0 of the action potential. (Figure 6A, 6B). Inactivation occurs in different conformational states, including fast, intermediate, and slow inactivation[2, 16].

The fast inactivation process is interconnected with activation and commences when the S4 segment of DIV moves outward. This movement serves as a stimulus for specific amino acids (isoleucine, phenylalanine, and methionine) known as the IFM motif, along with nearby glycine and proline, to obstruct the channel's pore. These amino acids bind with multiple amino acids in the cytoplasmic loops situated between the S4 and S5 segments of DIII and DIV, effectively obstructing the channel[2, 16].

The molecular processes leading to slow inactivation are not as well understood. However, mutations in certain parts of the channel, such as the P-loops, S6 segments, and C terminus, have been observed to influence this state. Regardless, more than 99% of sodium channels are inactivated by the end of phase 1 of the action potential, and they can only be reactivated after a recovery period during phase 4. Slow inactivation requires much longer recovery times compared to fast inactivation [2, 17].

In some cases, a very small portion of sodium channels may reactivate during phase 3 of the action potential. This reactivation generates a current that is referred to as the window current (Figure 6C, 6D), which is less than 1% of the peak I_{Na}. It is called the window current because it occurs when the cell membrane reaches a depolarized potential that is sufficient to reactivate some channels, but not enough to cause complete inactivation. In a healthy heart, the voltage range for the window current is highly limited and precise, giving it a minor role during the cardiac action potential[2].

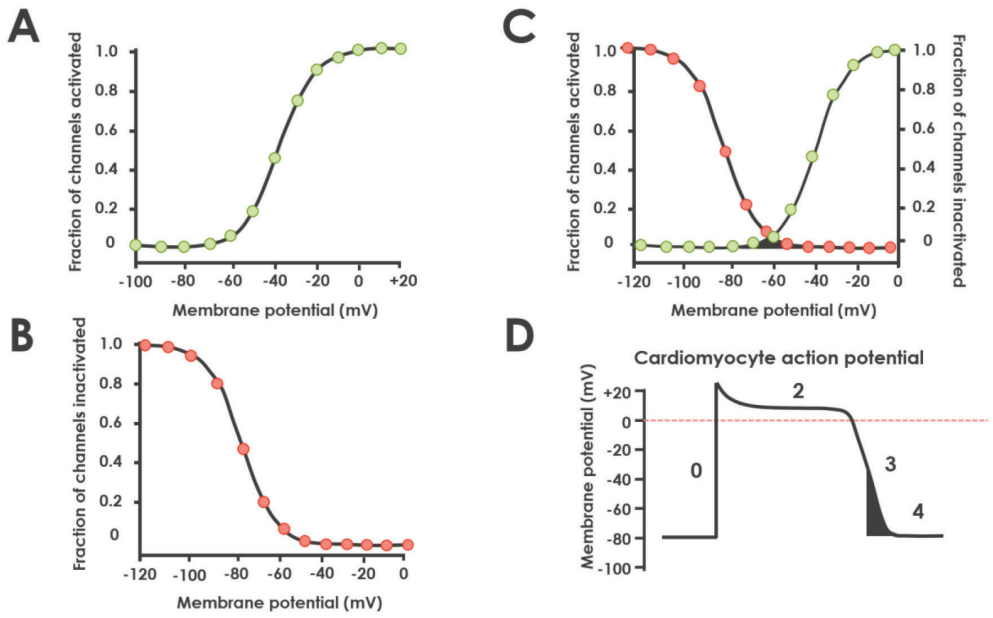


Figure 6. Investigation of voltage-dependent activation and inactivation of the cardiac sodium channel by using the patch-clamp experiment. A. Activation properties are examined by applying 50 ms voltage steps from a holding potential of −120 mV. The resulting sodium current amplitudes are normalized to the maximum peak sodium current amplitude and plotted against the corresponding voltage, forming the activation curve. B. Inactivation characteristics are studied by applying 500 ms voltage steps from a holding potential of −120 mV to induce channel inactivation (prepulse). The fraction of channels remaining uninactivated is measured using a 20 mV test pulse, and the amplitude of sodium current at each test pulse is divided by the maximum peak sodium current amplitude, resulting in the inactivation curve. C. The region shaded in gray illustrates the presence of a window current, which arises when the sarcolemma attains a membrane potential that enables partial reactivation of channels without undergoing complete inactivation. D. The window current is typically observed during phase 3 of the ventricular action potential, within a narrow voltage range.[2]

4.3 *SCN5A* mutations that cause LQTS3

LQTS3 is associated with mutations in *SCN5A* and affects around 13% of genotyped individuals with LQTS[18, 19]. To date, over 80 *SCN5A* mutations have been discovered in LQTS3 patients, with almost half of them undergoing heterologous study[3]. The majority of these genetic alterations are missense mutations, which result in a gain-of-function in sodium

channels by interfering with the process of rapid inactivation. This disruption leads to an abnormal sustained sodium current that does not properly inactivate (I_{sus} or I_{pst})[20] (Figure 7B, 7C). These mutations are primarily concentrated in specific regions of the $Na_V1.5$ sodium channel, including the S4 segment of DIV, the DIII-DIV linker, and the cytoplasmic loops between the S4 and S5 segments of DIII and DIV. Additionally, mutations in the C terminus are involved in stabilizing fast inactivation by interacting with the DIII-DIV linker.[3, 18, 21, 22]

Less frequently observed mechanisms through which mutations in *SCN5A* lead to LQTS3 involve the augmentation of the window current[23, 24]. (Figure 8B), slower inactivation[24, 25], faster recovery from inactivation[26, 27] (Figure 8A), and larger peak sodium current density[28] (figure 8C). The window current is increased when mutant sodium channels fail to inactivate at positive potentials, widening the voltage range where the channel can reactivate without inactivation[23, 24]. Slower inactivation leads to longer channel openings, resulting in a slowly inactivating sodium current known as the late sodium current (I_{NaL})[25] (figure 8D). In certain literature, there is a tendency to use terms like I_{sus}, I_{pst}, and I_{NaL} interchangeably. The window current, along with I_{NaL}, shares similarities with I_{sus} and influences phases 2 and 3 of the action potential, which usually exhibits minimal or no sodium current. Accelerated recovery from inactivation and higher peak sodium current density both involve an enhanced influx of sodium ions during phase 0 of the action potential. The impact of these mutations disrupts the equilibrium between depolarizing and repolarizing currents, favoring depolarization. This delay in the repolarization process can trigger early afterdepolarizations during other phases of the action potential as well, such as phases 2 and 3. Purkinje fiber myocytes, which naturally have longer action potential durations, are particularly susceptible to these early afterdepolarizations[17, 29]. The induction of torsades de pointes, a specific type of arrhythmia, is believed to be initiated by these early after depolarizations specific phases of the action potential[2, 30].

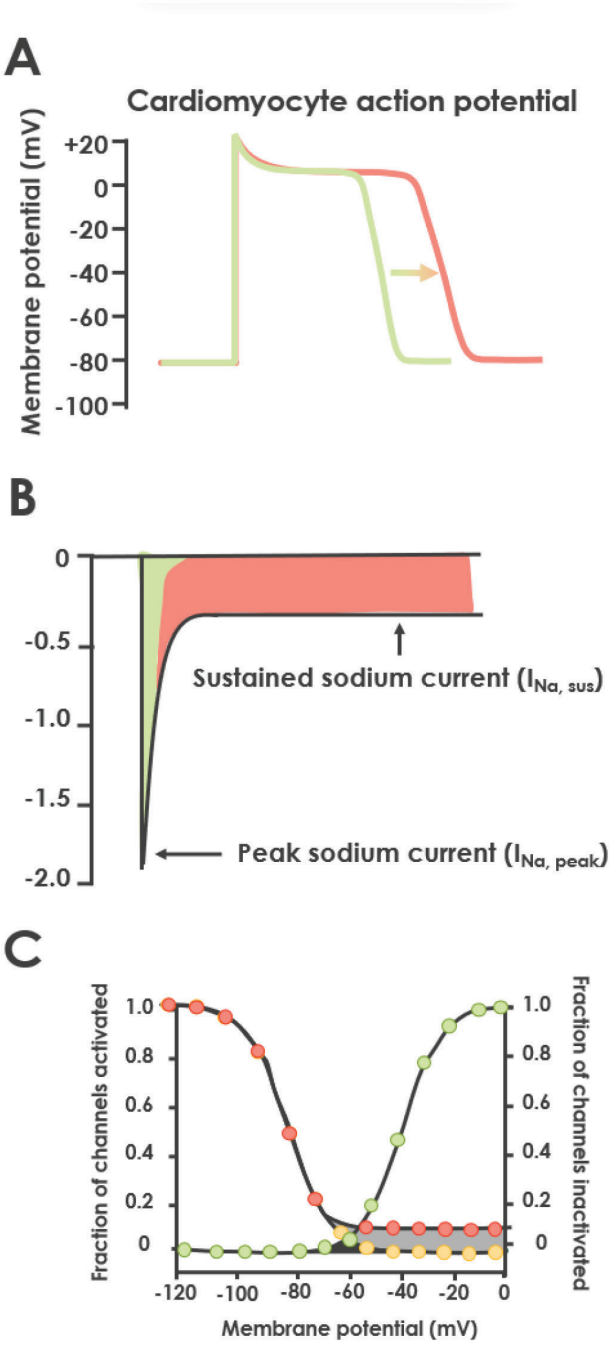


Figure 7. Long QT Syndrome type 3 A. Prolonged QT interval attributed to delayed repolarization of ventricular action potentials. B. Presence of abnormal sustained non-inactivating sodium current (red area) contributing to delayed repolarization in LQTS3. C. Sustained current resulting from incomplete inactivation of sodium channels (red circles)[2].

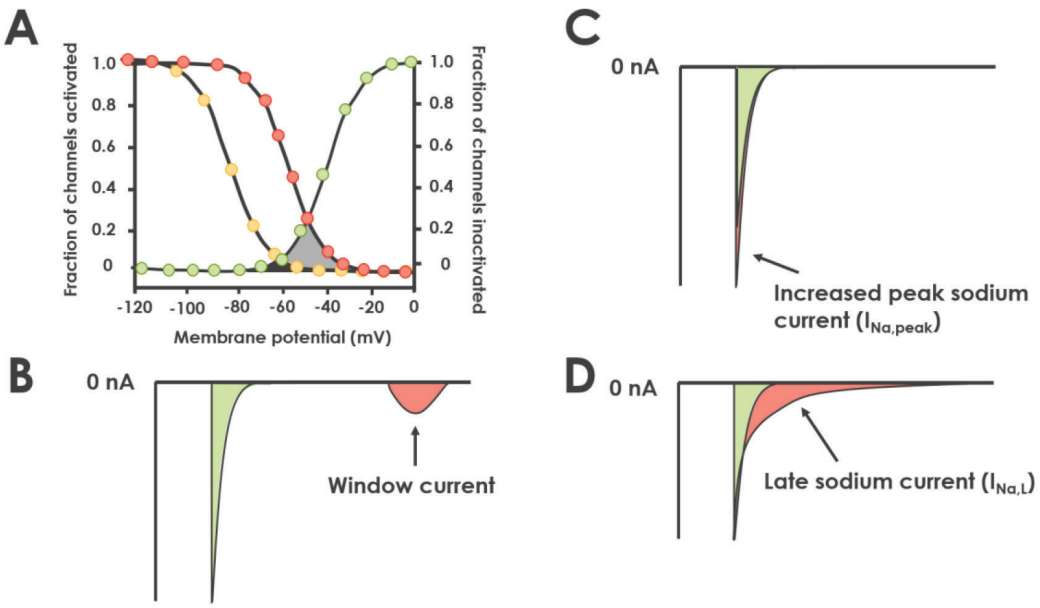


Figure 8. Alternative mechanisms leading to sodium channel gain-of-function LQTS3 A. Evident augmentation of the window current arising from delayed inactivation of cardiac sodium channels (depicted as red circles). B. The increased window current is observed during phases 2 and 3 of the ventricular action potential (depicted as the red area), C. The peak sodium current observed during phase 0 (depicted as the red area). D. Slower inactivation leads to the generation of a late sodium current (depicted as the red area)[2].

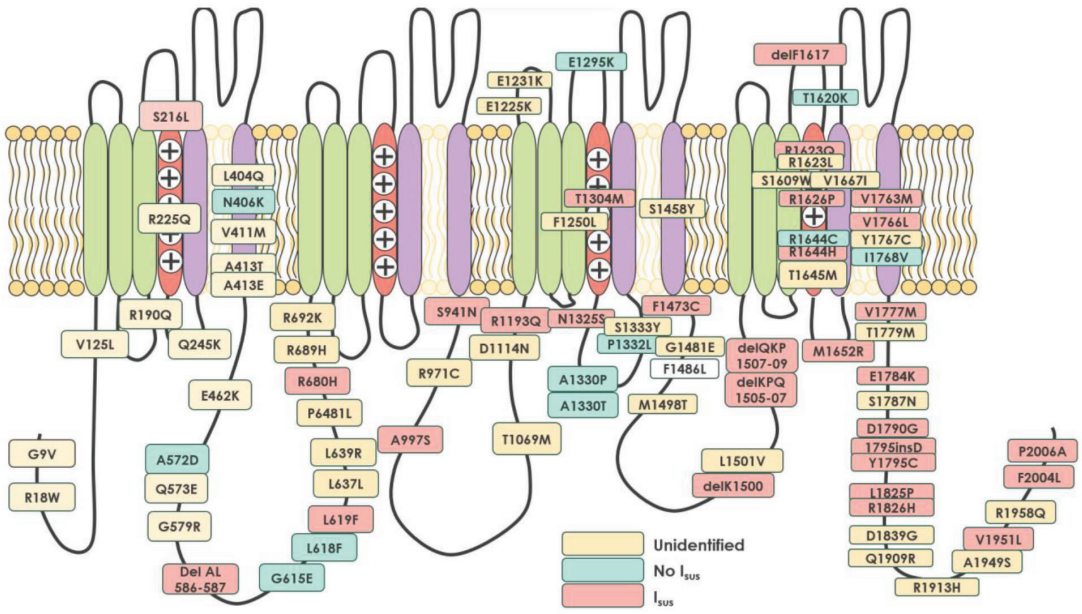


Figure 9. SCN5A mutations associated with LQTS3[3] (more information on table 1)

Table 1. Examination of LQTS3 mutant channels and their electrophysiological properties, highlighting the assessment of increased window current through shifts in steady-state activation and inactivation curves, and experimental confirmation using a ramp protocol[3].

LQTS3 Variant	I_{sus}	I_{window}	I_{peak}	Current decay	Recovery time	References
S216L	↑	↑	↔	Faster	Faster	(31)
N406K		↔	↓		↔	(32)
A572D		↔	↔		Faster	(22, 26)
delAL586-587	↑	↔	↑	Faster	Faster	(31)
G615E	↔	↔	↔		Faster	(22, 26, 31)
L618F	↔	↔	↔			(33)
L619F	↑	↑	↔	↔	Faster	(34)
R680H	↑	↔	↔	Faster	↔	(31)
S941N	↑	↔	↔	Slower	↔	(35, 36)
A997S	↑			Slower		(37)
R1193Q	↑	↓	↔	Faster		(38)
F1250L	↔	↔	↔			(33)
E1295K	↔	↑ (shifted)	↔	slower	Faster	(39)
T1304M	↑	↑	↔	Faster	Faster	(31)
N1325S	↑	↑		Slower	Slower	(23)
A1330P	↔	↑	↔	Slower	Faster	(24)
A1330T	↔	↑ (shifted)	↔	↔	Faster	(40)
P1332L	↔	↔	↔	Slower	Slower	(35, 41)
F1473C	↑	↑	↔		Faster	(42)
F1486L	↑	↑	↔	Slower	Faster	(31)
delK1500	↑	↓		Slower		(43)
delKPQ1505-1507	↑	↑	↔	Slower	Faster	(20, 23, 44)
delQKP1507-1509	↑		↔	Faster	Faster	(45)
delF1617	↑ at +40 mV or ↓ at -60 mV	↓	↓	Slower	Slower	(46)

LQTS3 Variant	I_{sus}	I_{window}	I_{peak}	Current decay	Recovery time	References
T1620K	↔	↑	↔	Slower	Faster	(47)
R1623Q	↑	↑	↔	Slower	↔	(48, 49)
R1626P	↑		↔	Slower	↔	(25)
R1644H	↑	↑		Slower	↔	(23)
R1644C	↔	↑	↔	↔	Faster	(50)
M1652R	↑	↑	↔	Slower	Faster	(25)
V1763M	↑		↔		Faster	(51)
M1766L	↑	↑	↓			(52)
I1768V	↔	↑	↔	↔	Faster	(28)
V1777M	↑	↓				(27)
E1784K	↑	↓	↓	↔, Faster	Faster	(53-55)
D1790G	↑	↓	↔	Faster	Faster	(56, 57)
1795insD	↑	↓	↓	↔, Slower	Slower, ↔	(58-61)
Y1795C	↑	↓, ↔	↑	Slower	↔	(28)
L1825P	↑	↔	↓	Slower	↔	(62, 63)
R1826H	↑	↑		Slower		(37)
V1951L	↑ (delQ1077)	↔	↑	Faster	↔	(31)
F2004L	↑	↑	↔	Slower	Faster	(31)
P2006A	↑	↑	↔	↔	Faster	(31)

4.4 How to examine the functioning of the sodium channel?

Based on the provided information, extensive research has been conducted over an extended period to investigate the function of sodium channels. To examine the function of sodium channels over time, scientists have introduced a modified form of the *SCN5A* gene into cultured cells using a plasmid. This resultes in the expression of mutant sodium channels within the cells. By utilizing patch clamp electrical stimulation, researchers have studied the behavior of these channels when subjected to a specific voltage, comparing them to the non-mutated sodium channels. Among the various cell types utilized for transfection, HEK293 cells are the most frequently employed.

HEK293 cells, short for human embryonic kidney 293, are derived from human embryonic kidney cells and are extensively utilized in cell biology research. These cells are favored in scientific studies due to their consistent growth characteristics and high transfection efficiency with minimal cell death. HEK293 cells have become a popular choice for investigating channel gene mutations, assessing the impact of drugs on channels[64], exploring RNA interference systems[65], examining protein-protein interactions[66], and studying nuclear signaling involved in protein production regulation[67], among other applications.

Previously, it was widely believed that HEK293 cells did not express voltage-gated ion channels. Electrical stimulation often did not elicit any electrical current, or if it did, the occurrence was extremely rare. However, recent research has challenged this belief by demonstrating the expression of specific channels in HEK293 cells. These channels include $Na_V1.7$, presumed Ca^{2+} channels (such as $Ca_V1.2$ and $Ca_V1.3$), and outward rectifier K+ channels (such as $K_V1.1$, $K_V1.2$, $K_V1.3$, $K_V1.6$, or $K_V3.1$), among others, as illustrated in Figure 10. These channels are also observed to exhibit low levels of expression. Consequently, when introducing other genes responsible for channel formation, such as *SCN5A*, into HEK293 cells, no significant changes in potential difference or electrical activity are detected during electrophysiology studies[68]. To ensure consistency in the investigation of channel-forming genes, it is crucial to include negative controls where no genes are transfected into the cells.

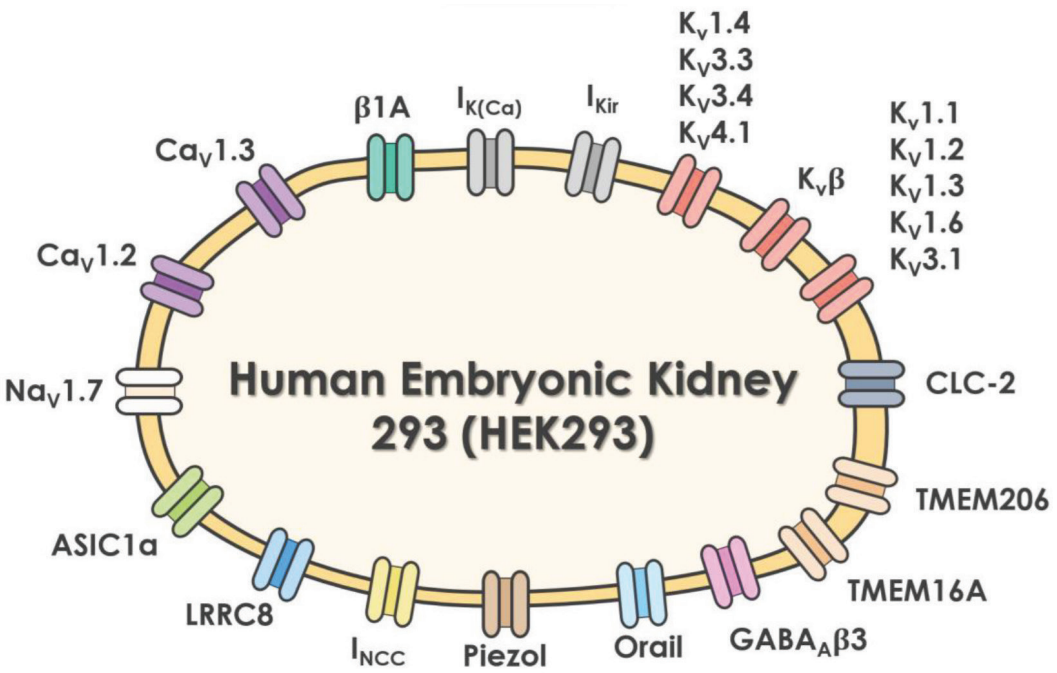


Figure 10. The presence of various ion channel subunits that may naturally occur in HEK-293 cells. These subunits encompass voltage-gated Na^+ channels (potentially encoded by NaV1.7), the β1A subunit, Ca^{2+} channels (potentially encoded by $Ca_V1.2$ and $Ca_V1.3$), outward rectifier K^+ channels (potentially encoded by $K_V1.1$, $K_V1.2$, $K_V1.3$, $K_V1.6$, or $K_V3.1$), transient outward K^+ channels (potentially encoded by $K_V1.4$, $K_V3.3$, $K_V3.4$, or $K_V4.1$), Kvβ, Ca^{2+}-activated K^+ channels, voltage-gated Cl^- channels (potentially encoded by CLC-2), TMEM16A-mediated Ca^{2+}-activated Cl^- channels, TMEM206-mediated proton-activated Cl^- channels, the β3 subunit for GABAA receptors, LRRC8A/C swelling-activated Cl^- channels, transient receptor potential (TRP) channels, nonselective cation channels, acid-sensitive ion channels (ASIC1a), store-operated Ca^{2+} channels (Orail 1), and mechanically activated channels (Piezo1). It should be noted that the activation of Ca^{2+}-activated K^+ channels and Cl^- channels can occur through Ca^{2+} influx via voltage-gated Ca^{2+} channels, TRP channels, nonselective cation channels, Orail 1 channels, and Piezo1 channels[68].

Nowadays, the use of HEK293 cells is widespread for the examination of channel mutations. Numerous investigations have been conducted to explore the effects of the SCN5A gene mutation on HEK293 cells. For example, A study conducted by Mikiyama et al. in 2008 examined a family of patients with atrial fibrillation and identified a mutation in the SCN5A gene at amino acid position 1875, where methionine was replaced by threonine

(M1875T). The researchers employed the whole cell patch clamp technique to compare HEK293 cells transfected with a plasmid containing the wildtype SCN5A gene and cells transfected with a mutated version at position M1875T. The findings revealed that mutations in the SCN5A gene at this specific location resulted in an increased peak I_{Na} and slower inactivation compared to the wildtype cardiac sodium channels, indicating a gain-of-function effect[69]. This study shed light on the potential role of this mutation in causing atrial fibrillation and related disorders. Consequently, it offers valuable insights for disease prognosis, such as identifying individuals with the mutation who may be at risk of developing atrial fibrillation. Subsequently, researchers have delved deeper into this mutation by employing CRISPR-Cas9 to edit the genes of experimental mice, introducing mutations at the same location. They then have studied various aspects such as the heart's characteristics, cardiac action potential in the left atrium, and the I_{Na} from cardiomyocytes. The outcomes indicated that the physical appearance and cardiac rhythms of the mutant mice resembled those of the normal mice. However, there were noticeable differences in the action potential of the left atrium. The mutant mice exhibited a higher peak upstroke velocity, shorter action potential duration, and elevated peak I_{Na}. While the mice with the mutation did not display atrial fibrillation symptoms, their left atrium and cardiomyocytes were affected. These alterations in electrical current suggested a potential inclination toward atrial fibrillation. Moreover, the researchers have explored the effectiveness of flecainide, a sodium channel blocker, in reducing atrial fibrillation in these mutant mice. Interestingly, it was observed that flecainide diminished the refractory period of the action potential in the left atrium to a greater extent in the mutant mice compared to the normal mice. This indicates that sodium channel mutations at these specific sites render cardiomyocytes less responsive to flecainide.[70] This study represents a previous investigation that aimed to understand the impact of SCN5A mutations on cardiac function by conducting experiments on animals. The findings from this study are valuable as they provide a foundation for future research on the functional consequences of mutated sodium channels associated with LQTS3.

5. Clinical characteristics of LQTS3

In Wilde's 2016 study, general characteristics of 391 LQTS3 patients, including baseline patient characteristics, electrocardiographic parameters, and genetic variables, were studied from three area: the United States of America, Europe and Japan. (Table 2)[71]

Table 2. Clinical Characteristics of 391 LQT3 Patients[71]

Characteristics	USA	Europe	Japan	Missing	Total
No. of patients	208	155	28	-	391
Male, n (%)	85 (41)	72 (46)	17 (61)	-	174 (45)
Age at ECG, year	26±19	31±20	25±19	33	28±20
ECG, mean±SD					
RR, ms	865±240	896±206	946±213	33	884±225
PR, ms	159±36	162±28	165±30	84	161±33
QRS, ms	83±13	104±112	387±81	35	92±73
QTp, ms	353±78	362±70	387±81	36	359±75
QT, ms	442±87	443±84	473±89	35	445±86
QTc, ms	479±50	471±63	487±62	35	476±57
QTc males, ms	487±52	475±60	487±69	9	482±57
QTc females, ms	473±48	466±67	486±54	26	471±56
Treatment, n (%)					
Beta-blockers	77 (38)	31 (21)	3 (11)	8	111 (29)
Left cardiac sympathetic denervation	1 (0)	5 (3)	0 (0)	3	6 (2)
Pacemaker	13 (6)	6 (4)	0 (0)	3	19 (5)
Internal cardiac defibrillator	49 (24)	16 (10)	4 (14)	-	69 (18)
Location of mutation, n (%)					
N Terminus	1 (0)	0 (0)	0 (0)	-	1 (0)
Transmembrane	77 (37)	77 (50)	15 (54)	-	169 (43)
C Terminus	59 (28)	44 (28)	12 (43)	-	115 (29)
Transmembrane spanning	71 (34)	34 (22)	1 (4)	-	106 (27)
Mutation type, n (%)					
Missense	153 (74)	147 (95)	22 (79)	-	322 (82)
Deletions	55 (26)	8 (5)		-	169 (43)
C Terminus	59 (28)	44 (28)	12 (43)	-	115 (29)
E1784K	47 (23)	10 (6)	12 (43)	-	69 (18)

6. Therapy for LQTS3

β-Blocker therapy has been proven to significantly reduce the risk of cardiac events in patients with LQTS1 by more than 95% and in patients with LQTS2 by 70% to 80%. However, initial genotype-phenotype studies did not show clear efficacy of β-blockers in LQTS3. In vitro cellular studies raised concerns about potential proarrhythmic effects of β-blockers in LQTS3, leading to the premature belief that β-blockers might be contraindicated for this subtype. Consequently, a significant number of LQTS3 patients have received prophylactic ICD therapy over the past decade due to these concerns. Theoretical arguments, based on limited cases, suggested that β-blockers should be avoided in LQTS3, particularly in patients with longer QT intervals at slow heart rates and associated events during rest or sleep. Mechanisms such as atrioventricular block, bradycardia, sinus pauses, and sinus arrest were proposed as possible causes of death in LQTS3. However, Wilde *et al.* (2016) found that β-blocker therapy did not have proarrhythmic effects but, in fact, demonstrated a clear and significant protective effect against cardiac events. The beneficial effect was especially pronounced in females, while in males, the lower event rate prevented a clear demonstration of efficacy. Notably, there was no evidence of harmful effects of β-blocker therapy in males with LQTS3. Only a small percentage of patients (3%) experienced mortality while on β-blockers during a median follow-up of over 7 years. The absolute risk of LQTS3 related arrhythmia-related death in asymptomatic individuals by the age of 40 is less than 15%. The risk is influenced by factors such as QTc duration and the presence of symptoms. High-risk patients with prior syncope or aborted cardiac arrest or those with QTc in the 500-ms range may require additional therapies such as left cardiac sympathetic denervation, ICD implantation, or LQTS3-targeted pharmacotherapy with medications like mexiletine, flecainide, ranolazine, or experimental drugs. However, the precise timing for initiating these therapies cannot be determined from this study. Treatment decisions in high-risk patients should be made based on clinical judgment, weighing the disease risk against the risk/benefit profile of the selected therapy in each patient, taking into account age, sex, QTc duration, prior symptoms, and the patient's response to β-blocker therapy[71].

Conclusion

The integration of electrophysiological studies and experimental models has provided invaluable insights into the intricate workings of the cardiac sodium channel $Na_V1.5$ and its dysregulation in LQTS3. These discoveries have not only deepened our understanding of

the disease but have also paved the way for the development of novel pharmacological agents and potential gene therapies aiming at restoring the delicate balance of ion channel currents.

Although the best treatment or prevention is not yet available for LQTS3. However, the combined efforts of genetic insights, electrophysiological discoveries, and advancements in current and future research have paved the way for significant progress in our understanding of LQTS3. The ongoing exploration of this complex disorder holds great promise for refined diagnostics, targeted therapies, and ultimately, the prevention of life-threatening arrhythmias and sudden cardiac death. By unraveling the mysteries of LQTS3, we embark on a path towards transforming the lives of individuals affected by this condition and providing hope for a future where its impact is minimized through precision medicine and improved clinical care.

As we uncover more about LQTS3, it is crucial to emphasize the collaborative efforts among scientists, clinicians, and affected individuals and their families. By fostering interdisciplinary collaborations, sharing knowledge and resources, and prioritizing translational research, we can continue to unravel the mysteries surrounding LQTS3 and strive towards improved outcomes and better quality of life for those affected.

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