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Long QT syndrome — a genetic cardiac channelopathy

Zespół długiego QT — genetycznie uwarunkowana kanałopatia

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INTRODUCTION

Long QT-syndrome (LQTS) is a genetic cardiac channelopathy characterised by a prolonged QT interval on a surface electrocardiogram (ECG), syncope, T-wave abnormalities, ventricular tachycardia of the torsades de pointes (TdPVT) type (Fig. 1) and an increased risk of sudden death [1]. LQTS has variable clinical presentation and is genetically characterised by incomplete penetrance, as seen in many other cardiac genetic conditions [2].

Historically, LQTS is divided into a congenital and an acquired form. Four clinical types of congenital LQTS (cLQTS) have been defined. The commonest is the Romano-Ward syndrome (RWS), with autosomal dominant inheritance and a prevalence of approximately 1 in 2,500 [1]. The other three variants known are much rarer. These are: Jervell-Lange Nielsen syndrome (JLNS), wherein LQTS is associated with congenital deafness and the pattern of inheritance is autosomal recessive; Andersen syndrome (AS), where LQTS is variably present together with other arrhythmias, periodic paralysis and malformations; and the very rare Timothy syndrome (TS), characterised by a more malignant form of LQTS, cardiac and other somatic malformations, and autism [3, 4].

The acquired form of LQTS (aLQTS) presents itself with a normal QT-interval on the ECG under normal conditions, but a prolonged interval under the influence of drug-intake or structural heart disease [5]. The aLQTS occurs much more frequently than cLQTS, and (interestingly) may have a genetic element that makes the individual more susceptible to certain drugs.

The clinical diagnosis of LQTS is made using the diagnostic criteria given in Table 1 [6]. As seen, it comprises ECG findings, a clinical history of syncope and a family history of LQTS or sudden cardiac death. Importantly, the QT interval increases with decreasing heart rate, making it necessary to use a rate-corrected QT interval termed QT_c ($QT_c = QT/\sqrt{RR}$) when assessing whether the interval is prolonged or normal [7]. Presently, the diagnostic criteria do not involve the results from genetic testing, but such testing is necessary to identify asymptomatic carriers and relatives of affected individuals who may otherwise present clinically with sudden death as the first symptom [8]. As beta-adrenergic blockade or the application of an ICD unit may dramatically reduce the risk of cardiac events, there exists a real treatment option in LQTS [9].

The aim of this review is to give an update on the expanding number of genes known to be associated with LQTS and their pathophysiological mechanisms.

GENES INVOLVED IN LQTS

Changes in the QT interval duration are caused by an altered time course of the cardiac action potential (AP). An AP consists of depolarisation, plateau and repolarisation phases which reflect the electrical activity across the cardiomyocyte plasma membrane during one contraction, i.e. from systole until the next diastole. This activity is generated by a number of ion channels and can be influenced by various effector systems such as the autonomous nervous system. The most significant ion channels involved in forming the AP are given in Figure 2, along with their individual time-voltage relationship. The LQTS can be described as a cardiac channelopathy resulting from elevated inward depolarising currents or diminished outward repolarising currents of the AP that lead to a prolongation of the QT interval [10].

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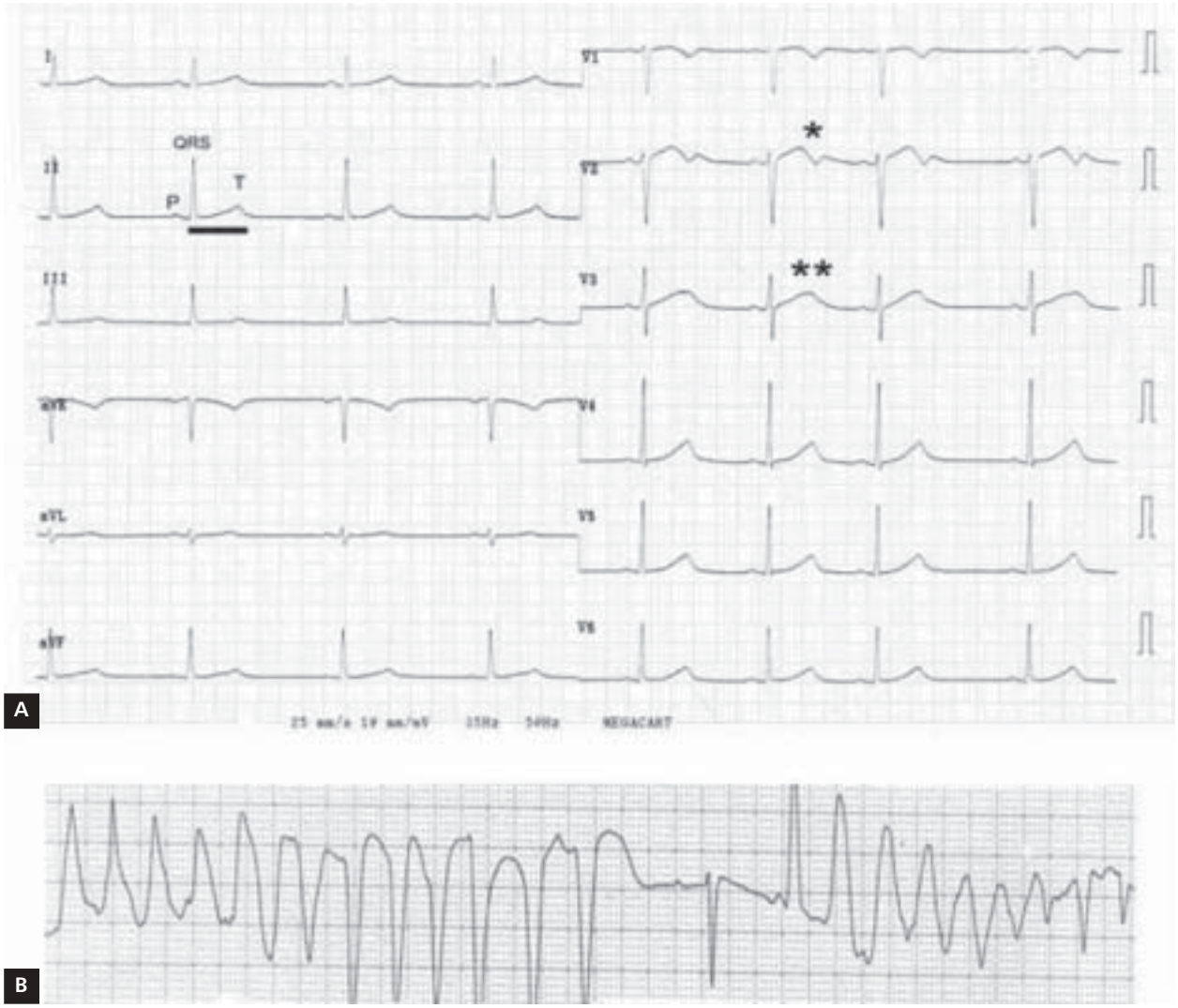

Figure 1. A. An ECG of an LQT2 patient with prolonged QT-interval (underlined), and bifid T-wave (*) and notched T-wave (**); **B.** An ECG showing the characteristic ventricular tachycardia of torsades de pointes type

To date, 12 different genes have been associated with LQTS. These include sodium, potassium and calcium channels as well as interactors of the various channels and channel subunits. Mutations in these genes may result in the loss [11–22] or gain of function [23, 24] and are summarised in Table 2.

METHODS OF MUTATION SCREENING

A variety of techniques are employed to detect the genetic variants in LQTS. For the application of these methods in a clinical setting, it is important that they are inexpensive, rapid and that their sensitivity as well as their specificity exceeds 97%. Direct sequencing by capillary array electrophoresis (CAE) is still considered the 'gold standard' although it is too expensive to be a first line mutation detection method. Single strand conformation polymorphism (SSCP) analysis and denaturing high performance liquid chromatography (DHPLC) provide cheaper options [25–27]. These techniques can be optimised and modified for greater sensitivity and specificity and to cut down the labour required, although in certain cases it still takes a lot of time for analyses. Resources required for screening can be reduced by sensibly selecting genes for analysis [28]. However, compound heterozygotes, digenic inheritance, and modifying genes highlight the importance of a comprehensive screening strategy including all genes [29, 30].

Table 1. Diagnostic criteria of long QT syndrome

	Points
ECG findings*	
QT_c**	
≥ 480 $ms^{1/2}$	3
460–470 $ms^{1/2}$	2
450 (males)	1
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 before the age of 30 among immediate family members	0.5

*In the absence of medications or disorders known to affect these electrocardiographic features; **QT_c calculated by Bazett's formula, where $QT_c = QT/\sqrt{RR}$; ***Mutually exclusive;****Resting heart rate below the second percentile for age; *****The same family member cannot be counted in A and B. Low probability of LQTS is defined by an LQTS score ≤ 1 point; an intermediate probability of LQTS is defined by an LQTS score of 2 to 3 points; ≥ 4 points indicates a high probability of LQTS (Modified from Schwartz et al. [6])

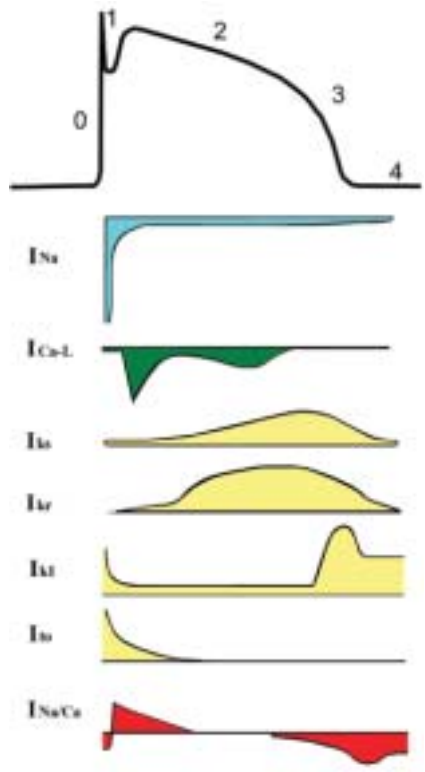

Figure 2. Ionic channels involved in formation of action potential. The sodium current (I_{Na}) is represented by blue, the long lasting calcium current (I_{Ca-L}) by green, four different potassium currents (I_{Ks}, I_{Kr}, I_{K1}, I_{to}) by yellow, and the sodium calcium exchange current ($I_{Na/Ca}$) by red

GENOTYPE-PHENOTYPE CORRELATION

Correlations between the genotype and phenotype in the LQTS are complicated by the fact that in many LQTS genes, very few mutations have been identified. Intra-allelic heterogeneity also plays a role, as mutations in the same gene may confer different risks of cardiac events due to the location of the mutation, and the phenotype of the LQTS-gene associated with the disease may vary between affected family members. Complex phenotypes such as BrS, CCD as well as structural heart disease, (such as DCM), involving LQTS have been reported [31, 32].

For LQT1, LQT2 and LQT3 correlations of the genotype with prognosis and risk of cardiac events have been performed [33]. These three types of LQTS also have characteristic T-wave differences on the ECG [34]. Repeating these investigations with other LQT types is difficult, as there is limited data available. However, LQT7 patients exhibit a distinct ECG with characteristic U-waves [35]. JLNS and TS (LQT8) carry a particularly high risk of sudden cardiac death from early childhood onwards [23, 36].

CLINICAL SIGNIFICANCE OF MUTATION IDENTIFICATION IN LQTS-ASSOCIATED GENES

The simple findings of mutations in LQTS-associated genes are not sufficient to claim that they are the cause of the disease. Apart from single mutations, there are numerous polymorphisms which contribute to the number of sequence variants observed. Many of these variants have been associated with repolarisation as well as cardiac conduction defects and have been proposed as disease-modifying factors. The pathological significance of a mutation is only very occasionally supported by genetic linkage. Evidence for pathogenicity can be obtained if functional analysis is performed to determine the effect of a particular LQTS-associated mutation. This can be achieved by doing electrophysiological studies of mutated ion channel subunits expressed *in vitro* in order to compare it to known pathophysiological mechanisms.

Table 2. The genes associated with long QT syndrome

Type	Syndrome	Gene	Protein	Function	Mechanism	Characteristics and triggers	Prevalence in LQTS patients
LQT1	RWS, JLNS	*KCNQ1*	Kv7.1	α subunit I_{Ks}	Loss-of-function	Arrhythmia triggered by exercise, swimming and emotion	40–55%
LQT2	RWS	*KCNH2*	Kv11.1	α subunit I_{Kr}	Loss-of-function	Arrhythmia triggered by sound or emotion	35–45%
LQT3	RWS	*SCN5A*	Nav1.5	α subunit I_{Na}	Gain-of-function	Arrhythmia triggered by sleep, rest and emotion	2–8%
LQT4	RWS	*ANK2*	Ankyrin B	Adaptor (I_{Na-K}, I_{Na-Ca}, I_{Na})	Loss-of-function	Arrhythmia triggered by exercise	< 1%
LQT5	RWS, JLNS	*KCNE1*	minK	β subunit I_{Ks}	Loss-of-function	Arrhythmia triggered by exercise and emotion	< 1%
LQT6	RWS	*KCNE2*	MiRP1	β subunit I_{Kr}	Loss-of-function	Arrhythmia triggered by rest and exercise	< 1%
LQT7	AS	*KCNJ2*	Kir2.1	α subunit I_{K1}	Loss-of-function	Syndromic, arrhythmia triggered by rest and exercise, frequent ectopy	< 1%
LQT8	TS	*CACNA1C*	Cav1.2	α subunit I_{Ca}	Gain-of-function	Syndromic, early onset and death from arrhythmia	< 1%
LQT9	RWS	*CAV3*	M-Caveolin	Adaptor (I_{Na})	Loss-of-function	Rest and sleep triggers arrhythmia	< 1%
LQT10	RWS	*SCN4B*	Navβ4	β subunit I_{Na}	Loss-of-function	Exercise triggers arrhythmia	< 0.1%
LQT11	RWS	*AKAP9*	Yotiao	Adaptor (I_{Ks})	Loss-of-function	Exercise triggers arrhythmia	< 0.1%
LQT12	RWS	*SNTA1*	α_1-Syntrophin	Scaffolding protein (I_{Na})	Loss-of-function	Rest triggers arrhythmia	< 0.1%

RWS — Romano-Ward syndrome; JLNS — Jervell and Lange-Nielsen syndrome; AS — Andersen syndrome; TS — Timothy syndrome. Modified from Hedley et al. [9]

LQTS-ASSOCIATED GENES AND THE PATHOPHYSIOLOGICAL MECHANISM OF MUTATIONS

KCNQ1

The first reported LQTS-associated mutations were found in the potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*) gene (MIM# 607542). The *KCNQ1* gene is located on the short arm of chromosome 11 and contains 16 exons which range in size from 47 to 1,122 bp [37]. This gene belongs to a large family of genes that provide instructions for making potassium channels. It encodes a 75 kDa protein consisting of 676 amino acids [37]. This is an alpha-subunit of the slow producing voltage-gated potassium channel (Kv7.1) (Fig. 3A) which conducts the slow delayed rectifier K^+ current (I_{Ks}) (Fig. 2). It contributes to the repolarisation of the cell, terminating the plateau phase of cardiac action potential (AP) and thereby also the heart's contractions [38]. Kv7.1 co-assembles with a beta subunit called minK which plays an important role in modulating the current of this channel [38].

To date, more than 250 mutations in *KCNQ1* have been implicated with LQTS type 1 (LQT1 – MIM# 192500) [9]. It has been shown that mutations of Kv7.1 alter the function of

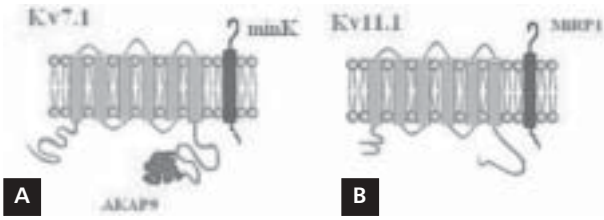

Figure 3. Schematic drawings of voltage-dependent potassium channels Kv7.1 (**A**) and Kv11.1 (**B**) with intracellular C- and N-terminus and six trans-membrane domains

I_{Ks} due to defective trafficking and dominant-negative loss-of--function effects [39, 40]. Moreover, several mutations have been reported that affect the binding of interacting proteins [41].

KCNH2

Another frequently mutated gene in LQTS is *KCNH2*, a potassium voltage-gated channel, subfamily H, member 2 gene (MIM# 15427). This gene was mapped to chromosome 7 and contains 15 exons [13, 42]. It encodes a protein consisting of 1,159 amino acids and is highly expressed in the he-

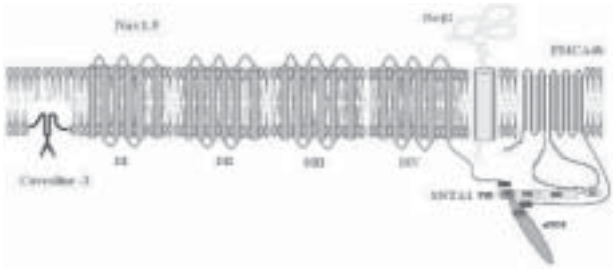

Figure 4. Schematic drawing of the sodium voltage-gated channel Nav1.5 containing four homologous domains, DI-DIV, each of which has six putative membrane-spanning regions. DI-IV — domains 1-4; PDZ — PDZ structural domain; PH1 — pleckstrin homology domain1; PH2 — pleckstrin homology domain2; SU — syntrophin unique domain

art [42]. This protein is an alpha-subunit of the voltage-gated potassium ion channel Kv11.1 (previously known as HERG) (Fig. 3B) which conducts the repolarising cardiac rapidly activating delayed rectifier K^+ current (I_{Kr}) (Fig. 2) [43]. Kv11.1 co-assembles with the beta subunit MiRP1 which modulates the potassium current of this channel, drastically affecting the length of the plateau phase of the cardiac action potential [11]. When this channel's ability to conduct electrical current across the cell membrane is inhibited or compromised by the application of drugs or by occurring mutations, it can result in LQTS [43].

To date, more than 300 mutations have been reported in *KCNH2* associated with LQTS type 2 (LQT2 – MIM# 152427) [9]. Mutations in *KCNH2* result in many different dysfunctions of the Kv11.1 channel, including trafficking deficiencies and the formation of non-functional channels or channels with altered gating properties [44].

SCN5A

Sodium channel dysfunctions in congenital LQTS are largely due to mutations in the *SCN5A* gene. This sodium voltage-gated channel, type V, alpha subunit gene (MIM# 600163) was mapped to chromosome 3 by fluorescence in situ hybridisation [45]. It consists of 28 exons that span approximately 80 kb, and 65% of LQT3-causing mutations are found in exons 20–28 [46]. *SCN5A* encodes a protein of 2,016 amino acids which is structurally very similar to that of other depolarising sodium channels. This protein forms the α-subunit of the cardiac sodium channel Nav1.5 (Fig. 4). Nav1.5 conducts the sodium inward current (I_{Na}) (Fig. 2) which is responsible for the initial depolarisation of cardiomyocytes [9].

Mutations in *SCN5A* that are associated with LQTS (LQT3 – MIM# 603830) characteristically produce an increased late I_{Na} and consequently prolonged repolarisation [47]. The *SCN5A* LQTS-associated mutations mainly act through a gain-of-function mechanism which means that although the mutant channel functions normally, certain properties are altered, the most frequent being fast inactivation [47].

ANK2

The first protein implicated in a congenital long QT syndrome that is not an ion channel or channel subunit is called Ankyrin B. It is coded for by *ANK2* (MIM# 600919). The *ANK2* gene is located on the long arm of chromosome 4 and consists of 46 exons, of which exon 38 is brain-specific [48]. Ankyrin B is a member of a larger family of versatile membrane adapters (ankyrin-R, ankyrin-B, ankyrin-G and tissue-specific splice forms) required for organising, transporting and anchoring membrane protein complexes to the actin/spectrin cytoskeleton. Among other molecules, ankyrins bind a number of ion motive proteins essential for cardiac electrophysiology in general including the Na^+/Ca^{2+} exchanger; inositol 1,4,5--triphosphate receptor and Na^+/K^+ ATPase [49].

The loss-of-function mutations identified in *ANK2* (LQT4 – MIM# 600919) are associated with dominantly inherited type LQT4 in humans [50]. All these mutations result in abnormal co-ordination of multiple functionally-related ion channels and transporters such as the Na^+/Ca^+ exchanger which is involved in Ca^{2+} release during cardiac excitability and can lead to a complex of phenotypes including LQTS, sinus bradycardia, cathecolaminergic polymorphic ventricular tachycardia, idiopathic ventricular fibrillation and sudden death [15, 51].

KCNE1 and KCNE2

Two other genes involved in the congenital long QT syndrome encode ion channel beta-subunits of the KCNE family. Their protein products form single trans-membrane domain ancillary subunits that co-assemble with voltage-gated potassium (Kv) channel α-subunits modifying their function. The first one is called *KCNE1,* which is the potassium voltage-gated channel, IsK related subfamily member 1 gene (MIM# 176261). *KCNE1* is located on the long arm of chromosome 21. It consists of three exons, with the third exon encoding the 129 amino acid protein [37, 52]. This protein, called the minimal potassium channel (minK), co-assembles with α-subunits of Kv7.1 (Fig. 3A) forming channels that conduct the slowly activating delayed rectifier K^+ (I_{Ks}) current (Fig. 2) [38].

Mutations in the *KCNE1* gene that are associated with LQTS (LQT5 – MIM# 176261) are characterised by reducing the potassium flux. There is evidence to suggest that KCNE1 plays a role in channel recycling which alters the I_{Ks} current [53]. The importance of minK in regulating the function of the Kv7.1 channel is emphasised by the fact that a number of inherited mutations in *KCNE1* result not only in long QT syndrome but also in deafness due to the reduced I_{Ks} in the inner ear [17, 54]. The combination of deafness with LQTS is called JLNS and has a very poor prognosis [36].

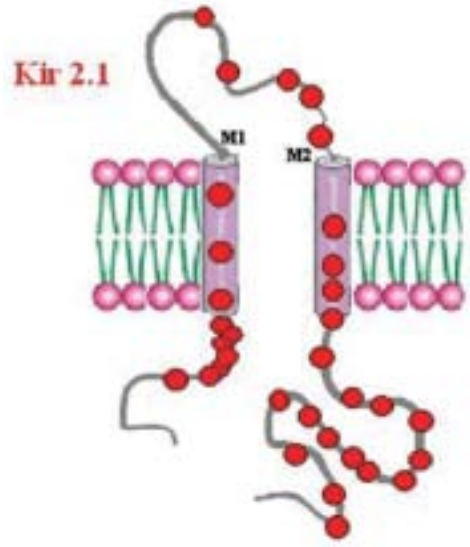

Figure 5. Schematic drawing of the voltage-dependent inwardly rectifying potassium ion channel Kir 2.1 composed of two trans-membrane domains (M1 and M2) separated by a pore-associated extracellular domain. The location of known LQTS-associated mutations is indicated by red spots

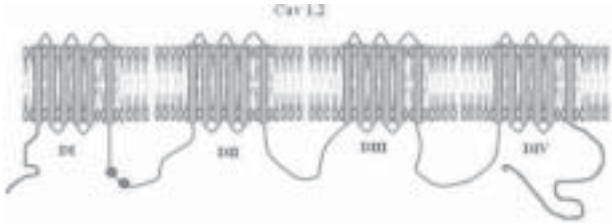

Figure 6. Schematic drawing of the calcium voltage-dependent channel composed of four homologous domains (DI-DIV) each consisting of six trans-membrane segments. The location of the two LQTS-associated mutations is indicated by red dots

The second member of the KCNE family is *KCNE2*. *KCNE2* is the potassium voltage-gated channel, IsK-related subfamily, member 2 gene (MIM# 603796). This gene is located on the long arm of chromosome 21 and consists of two exons. The second exon encodes the 123 amino acid protein [11]. This protein, known as the minimum potassium ion channel related peptide 1 (MiRP1), functions as a small integral membrane β-subunit associated with the α-subunits of the Kv11.1 ion channels (Fig. 3B). Together, these subunits conduct the rapidly activating delayed rectifier (I_{Kr}) current (Fig. 2) [11, 55].

Mutations in *KCNE2* associated with LQTS (LQT6 – MIM# 603796) are characterised by a reduction of the potassium flux generated by the I_{Kr} current resulting in delayed repolarisation [11, 17]. Furthermore, *KCNE2* mutations may also cause the acquired form of the LQTS [56].

KCNJ2

A further potassium channel involved in LQTS and influencing the cardiac action potential is encoded by the *KCNJ2* gene. *KCNJ2* is the potassium inward rectifying channel, subfamily J, member 2 gene (MIM# 600681). This gene is located on the long arm of chromosome 17 and contains two exons which span approximately 10 kb [57]. The *KCNJ2* gene encodes a 427 amino acid protein (Kir2.1) (Fig. 5) which forms a voltage-dependent inwardly rectifying potassium ion channel responsible for conducting a significant part of the inwardly rectifying I_{K1} current (Fig. 2). I_{K1} is important for stabilising the resting membrane potential, defining the excitation threshold and modulating repolarisation [58]. The activity of the Kir 2.1 channel is highly dependent on the integrity of channel interactions with phosphatidylinositol 4,5-bisphosphate (PIP2) [59].

By genetic linkage studies in a large family, Plaster et al. [16] identified mutations in *KCNJ2* that were also associated with Andersen syndrome (LQT7 – MIM# 170390). Andersen syndrome (AS) is inherited in an autosomal dominant fashion and is characterised by periodic paralysis, cardiac arrhythmias and dysmorphic features [60]. Furthermore, there is a high variability and incomplete penetrance in AS. LQTS is the primary cardiac manifestation, present in 71% of patients with AS, and dominant-negative loss-of-function mutations in *KCNJ2* result in malfunctioning Kir2.1 channels [3]. This is also the reason that LQT7 remains the name of this type of LQT. However, it should be noted that LQT7 is associated with bidirectional ventricular tachycardia (VT), premature ventricular contraction (PVC) and extrasystoles [35]. Sudden death is rare when compared to other LQT-types.

CACNA1C

Calcium channel dysfunctions in the congenital LQTS are related to mutations in *CACNA1C*, the calcium voltage-dependent channel, L type, alpha-1C subunit gene (MIM# 114205). *CACNA1C* is located on the short arm of chromosome 12 and contains 50 exons [61]. This gene encodes an α-1 subunit of a voltage-dependent calcium channel, known as CaV1.2 (Fig. 6) which mediates the depolarising influx of calcium ions ($I_{L,Ca}$ current) (Fig. 2) into the cell and contributes to the plateau phase of the cardiac action potential. Multiple isoforms of the α-1 subunit protein exist and they often have different electrophysiological and pharmacological properties [62].

Mutations in *CACNA1C* have been described in patients with Timothy syndrome (LQT8 – MIM# 601005) [4, 23]. Timothy syndrome (TS) is a rare autosomal dominant disorder characterised by physical malformations, as well as neurolo-

gical and developmental defects, including heart QT-prolongation, heart arrhythmias, structural heart defects, immune deficiency, intermittent hypoglycaemia, syndactyly, autism and baldness at birth. Timothy syndrome often results in early death [4]. Mutations in *CACNA1C* associated with LQTS were identified in differentially spliced exons 8 and 8A. The complete lack of voltage-dependent inactivation in these mutants results in prolonged Ca^{2+} inward current during the plateau phase of the AP. This leads to Ca^{2+} overload and delayed repolarisation [23].

CAV3

As previously mentioned, LQTS is also associated with mutations in genes encoding proteins that interact with the ion channel subunits. The second interacting protein, other than ankyrin B, which has been implicated with the LQTS is encoded by the caveolin-3 (*CAV3*) gene (MIM# 601253). *CAV3* is located on chromosome 3 and consists of two exons [63]. It encodes a 196 amino acid protein called M-caveolin (CAV3) (Fig. 4) a principal protein in caveolae which are membrane invaginations that participate in localising membrane proteins at the membrane surface [64]. It is only expressed in the heart and skeletal muscle. Among other functions, such as intracellular sorting of lipids or proteins, CAV3 modulates the I_{Na} current by interactions with membrane components including the α-subunit of Nav1.5 [65].

Vatta et al. [21] analysed the *CAV3* gene in 905 unrelated patients with LQT (LQT9 – MIM# 611818) and identified loss-of-function mutations in six of them. It has been shown that the interaction of the mutant caveolin-3 with the Nav1.5 ion channel results in a two to five-fold increase in the late I_{Na} which is consistent with pathological mechanisms previously described in LQT3 [66].

SCN4B

Another sodium channel involved in LQTS is encoded by the *SCN4B* gene. This is the sodium voltage-gated channel, type IV, beta subunit gene (MIM# 608256). *SCN4B* is located on chromosome 11 and contains five exons [67]. Its protein product consists of 228 amino acids and forms the β4-subunit of the cardiac sodium channel (Fig. 4) responsible for the conduction of the I_{Na} current (Fig. 2). Yu et al. [67] determined that the biophysical function of the β-subunit is to modify the function of Nav1.5 by slightly inhibiting the I_{Na}.

Medeiros-Domingo et al. [14] analysed the *SCN4B* gene in a Mexican-mestizo family with LQTS (LQT10 – MIM# 611819) and they identified a mutation which, when expressed in HEK293 cells stably expressing the Nav1.5 ion channel, causes a dramatic eight-fold increase in the late sodium current. This effect is very similar to that observed with LQT3-associated mutations in *SCN5A*.

AKAP9 and SNTA1

Recently, two additional genes with LQTS-associated mutations involved in controlling ion channels function have been identified. The first encodes a protein which is a member of the A-kinase anchor proteins (AKAPs), while the second is a member of the syntrophin protein family.

AKAP proteins are a group of structurally diverse proteins which target cAMP-dependent protein kinase A (PKA) to facilitate PKA mediated phosphorylation [68]. LQTS-associated mutations were reported in one of the AKAP members known as the A-kinase anchor protein 9 (*AKAP9*) gene (MIM# 604001). *AKAP9* is located on chromosome 7 and comprises 51 exons [69]. This gene encodes two proteins, the human homologue of the rat protein, AKAP120 and a 1,626 amino acid protein also known as yotiao (Fig. 3A) [69]. In the heart, yotiao is involved in the phosphorylation of a number of proteins including the ryanodine receptor, the L-type Ca^{2+} channel and the potassium channel responsible for the slow repolarising current, I_{Ks} [70–72].

Chen et al. [12] analysed the *AKAP9* gene in 50 LQTS families where no mutations were detected in the other known LQTS-associated genes. They discovered a single mutation located in close proximity to the C-terminal Kv7.1 binding site (LQT11 – MIM# 611820). Further investigation showed that this inherited mutation reduces, but does not eliminate, the interaction between yotiao and Kv7.1. It reduces the cAMP-dependent phosphorylation of Kv7.1 and alters the functional response of I_{Ks} channels to cAMP, resulting in delayed repolarisation of the ventricular action potential [12].

Syntrophins are cytoplasmic sub-membranous proteins that are components of the dystrophin-associated protein complex containing multiple protein interaction motifs. LQTS-associated mutations were identified in the syntrophin, α1 (*SNTA1*) gene (MIM# 601017) which forms part of this group. The *SNTA1* gene is located on chromosome 20 and consists of eight exons [73]. It encodes a 505 amino acid protein called α1-syntrophin (Fig. 4) which acts as a scaffolding protein for neural nitric oxide synthase (nNOS), plasma membrane Ca^{2+}-ATPAse (PMCA) and the α-subunit of Nav1.5 at the C-terminus [74].

The *STNA1* gene was analysed in 50 unrelated LQTS patients for whom no mutations have been reported in the other LQTS-associated genes. One missense mutation was identified in a patient with a seriously prolonged QTc interval on the ECG (LQT12- MIM# 601017) [20]. Functional studies showed that the mutation causes increased nitrosylation of Nav1.5 and increases the late sodium current. This is consistent with previous reports about LQT3-associated mutations in *SCN5A*. Additionally, the mutation disrupts the link between Ca^{2+} transporting, plasma membrane 4 (PMCA4b) and the Nav1.5/α1-syntrophin complex [20].

CONCLUSIONS

To date, mutations in 12 genes have been associated with LQTS. The spectrum of genes involved is rapidly increasing, and recent findings point to the significance of proteins interacting or modulating cardiac ion channels. Identification of disease-causing mutations is important as it may help identify asymptomatic gene carriers that could benefit from prophylactic beta-adrenergic blockade or application of an ICD unit.

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