Pregledni rad / Review article

Sindrom dugog QT intervala — uzrok iznenadne smrti

Long QT syndrome — a cause of sudden death

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SAŽETAK: Sindrom dugog QT intervala (LQTS) je primarni aritmijski poremećaj koji može dovesti do pojave malignih ventrikularnih aritmija tipa *torsades de pointes* (TdP) i iznenadne srčane smrti. Obilježja u elektrokardiogramu (EKG) uključuju produljenje korigiranog QT intervala i abnormalnosti T-vala. Do danas identificirana genetska osnova za LQTS uključuje trinaest podložnih gena: *KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1*, i *KCNJ5*. Najčešći genotip su mutacije *KCNQ1* te gotovo polovica pacijenata ima tu vrstu mutacije. Navedeni geni kodiraju ionske kanale i regulatorne proteine koji su uključeni u modulaciju struja srčanog akcijskog potencijala. Stečeni oblici LQTS-a mogu također biti uzrokovani genetskim mutacijama, u tim slučajevima nositelji mutacija razvijaju aritmije isključivo u određenim uvjetima (npr. uporaba određenih lijekova). Trenutna terapija uključuje primjenu beta-blokatora, ugradnju implantabilnog kardioverter defibrilatora (ICD) te simpatičku denervaciju srca. LQTS mutacije povezane su s iznenadnom srčanom smrti kod mladih i veoma mladih; a post-mortem genetska testiranja LQTS gena mogu biti korisna kod procjene uzroka iznenadne neobjašnjive smrti (*sudden unexplained death*). Kaskadni probir koristan je za identificiranje asimptomatskih članova obitelji koji mogu biti pod povećanim rizikom od iznenadne smrti. U ovom preglednom članku prikazali smo gene povezane s LQTS-om zajedno s opisom povezanih patofizioloških mehanizama.

KLJUČNE RIJEČI: sindrom dugog QT intervala, aritmije srca, iznenadna srčana smrt.

SUMMARY: Long QT syndrome (LQTS) is a primary arrhythmic disorder that may lead to the precipitation of torsades de pointes (TdP) and sudden death. Electrocardiogram (ECG) features include prolongation of the corrected QT interval and T-wave abnormalities. The genetic basis of LQTS identified to date includes thirteen susceptibility genes: *KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1*, and *KCNJ5*. Mutations in *KCNQ1* are by far the most frequent genotype with nearly half of the patients carrying K*CNQ1* mutations. These genes code for ion channels and regulatory proteins that are involved in the modulation of the currents of the cardiac action potential (AP). Acquired forms of LQTS may also have underlying genetic mutations, in these cases mutation carriers develop arrhythmias only under certain conditions (e. g. use of certain medications). Current therapies include use of beta-blockers, implantable cardioverter defibrillators (ICD) and left cardiac sympathetic denervation. LQTS mutations have been associated with sudden death in the young and very young; and postmortem genetic testing in LQTS genes can be useful when assessing the cause of a sudden unexplained death. Cascade screening is also useful to identify asymptomatic family members that may be at risk of sudden death. Here we have reviewed the genes associated with LQTS along with the description of the related pathophysiological mechanisms.

KEYWORDS: long QT sindrome, arrhythmia, sudden cardiac death.

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Uvod

Sindrom dugog QT intervala (LQTS) nasljedna je bolest srca obilježena produljenim QT intervalom u EKG, abnormalnostima T-vala, ventrikularnom tahikardijom tipa *torsades de pointes* (TdP), sinkopama i povećanim rizikom od iznenadne smrti[1]. Tipično, LQTS ima varijabilnu kliničku prezentaciju i nepotpunu penetraciju, tj. neki nositelji patogenih mutacija su asimptomatski i ne manifestiraju produljenje QT intervala, a moguće je da prva manifestacija bolesti budu sinkopalne epizode koje rezultiraju srčanim zastojem i iznenadnom smrti[2]. Stoga je veoma važno identificirati nositelje mutacija, zato što čak i ako su asimptomatski mogu imati povećani rizik od iznenadne smrti.

Definirana su četiri klinička tipa kongenitalnog LQTS-a koja uključuju: (1) Romano-Ward sindrom, najučestaliji tip uz pojavnost od 1 : 2.500 i autosomno dominantan uzorak nasljeđivanja[3,4]; (2) Jervell-Lange Nielsen sindrom, rjeđi, s autosomno recesivnim nasljeđivanjem i kongenitalnom gluhoćom[5]; (3) Andersenov sindrom, obilježen učestalim aritmijama, paralizom i malformacijama[6]; (4) veoma rijedak Timothy sindrom, obilježen teškim LQTS-om, srčanim i somatskim malformacijama te autizmom[7]. Kod stečenih oblika LQTS-a, produljeni QT interval pojavljuje se u određenim okolnostima kao što su korištenje specifičnih lijekova, hipokalemiji, hipomagnezemiji i strukturnim bolestima srca. Postoje genetski elementi koji također mogu predisponirati razvoju stečenog LQTS[8]. Trenutne opcije liječenja uključuju beta-adrenergijsku blokadu, ugradnju implantabilnog kardioverter defibrilatora (ICD) ili simpatetičku denervaciju. Dokazano je da i učinak beta-blokatora ima genetsku komponentu[9].

Trajanje ventrikularne depolarizacije i repolarizacije označeno je QT intervalom, što je uzrokovano transmembranskim protokom ionskih struja (npr. depolarizacijske, ulazne struje koje dovode do utoka natrija (Na^+) i kalcija (Ca^{2+}) u stanicu i repolarizacijske, izlazne struje koje dovode do izlaska kalija (K^+) iz stanice). Ova stanična aktivnost naziva se akcijski potencijal (**Slika 1**).

Introduction

Long QT syndrome (LQTS) is an inherited heart disease characterized by prolonged QT interval on the ECG, T-wave abnormalities, ventricular tachycardia of the torsades de pointes (TdP) type, syncope, and an increased risk of sudden death[1]. Typically, LQTS has a variable clinical presentation and incomplete penetrance, i.e. some carriers of a pathogenic mutation are asymptomatic and do not manifest QT interval prolongation and often the first manifestation of the disease can be syncopal episodes that result in cardiac arrest and sudden death[2]. Therefore, it is very important to identify mutation-carriers, because even if they are asymptomatic they may still be at risk of sudden death.

Four clinical types of congenital LQTS have been defined and they include: (1) Romano-Ward syndrome, by far the most common type with a prevalence of 1: 2,500 and autosomal dominant pattern of inheritance[3,4]; (2) Jervell-Lange Nielsen syndrome, more rare, with an autosomal recessive inheritance and congenital deafness[5]; (3) Andersen syndrome, characterized by frequent arrhythmias, paralysis and malformations[6]; and (4) the very rare Timothy syndrome, characterized by a severe LQTS, cardiac and somatic malformations, and autism[7]. In acquired forms of LQTS, long QT-intervals arise under particular circumstances such as use of specific drugs, hypokalemia or hypomagnesaemia, and structural heart diseases. There are genetic elements that may also predispose to acquired LQTS[8]. Treatment options currently include beta-adrenergic blockade, insertion of an implantable cardioverter defibrillator (ICD) or sympathetic denervation. The effect of beta-blockers has also been shown to have a genetic component[9].

The QT interval indicates the duration of ventricular depolarization and repolarization, which is caused by transmembrane flows of ion currents (e.g. inward depolarizing sodium (Na^+) and calcium (Ca^{2+}) currents and outward repolarizing potassium (K^+) currents. This cellular activity is called the action potential (**Figure 1**).

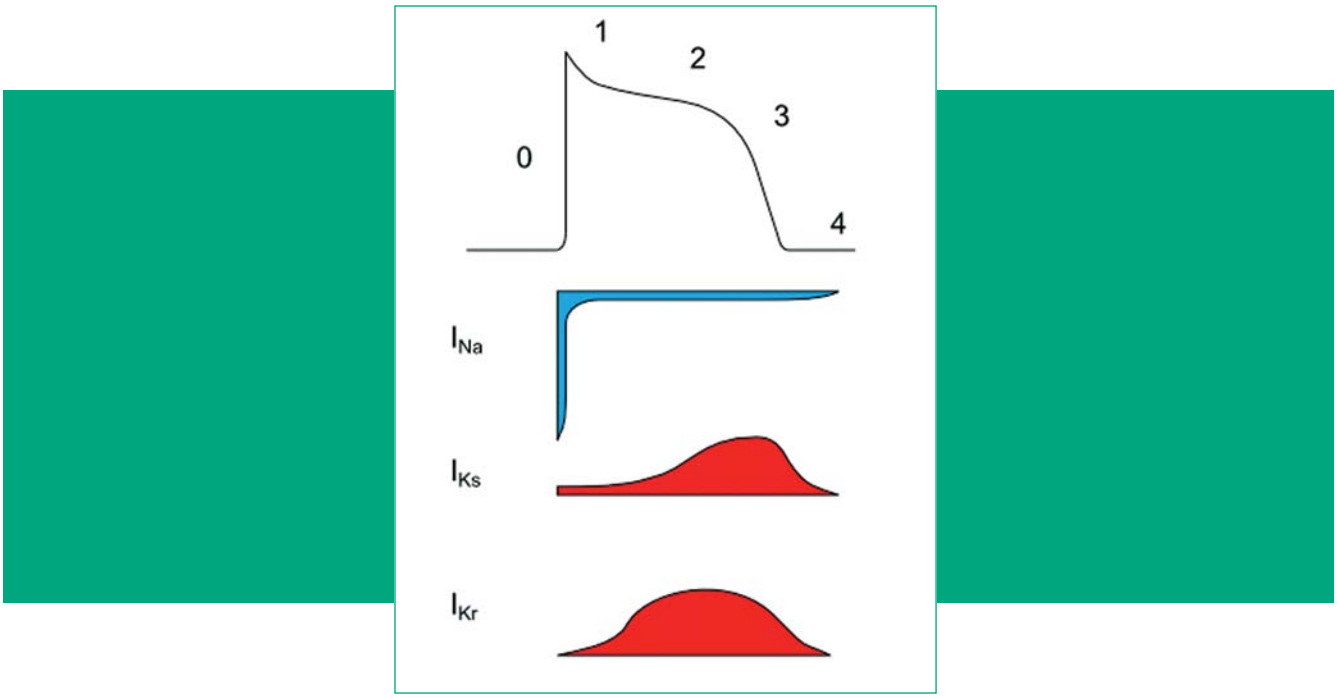

Figure 1. *Schematic representation of the action potential, inward (INa), and outward (IKs, IKr) currents that contribute to its generation. The currents are conducted by the Na^+ channel Nav1.5, and the K^+ channels Kv7.1 and Kv11.1 respectively.*

Produljeni QT interval može biti rezultat smanjene ukupne repolarizirajuće struje (npr. smanjene repolarizirajuće, izlazne K^+ struje ili povećane depolarizirajuće, ulazne Na^+ i Ca^{2+} struje). Naime, ustanovljeno je da je LQTS povezan s mutacijama gena koji uzrokuju gubitak funkcije repolarizirajućih K^+-ionskih kanala i njihovih podjedinica ili mutacijama koje uzrokuju pojačanu funkciju depolarizirajućih Na^+- i Ca^{2+}-ionskih kanala i njihovih podjedinica. Neki pacijenti koji nose genetske mutacije povezane s LQTS-om mogu imati normalan QT interval, no istovremeno i smanjenu repolarizacijsku rezervu te viši rizik za nastup tahikardije i iznenadne smrti.

Kriteriji za dijagnosticiranje LQTS-a sastoje se od EKG nalaza i pozitivne obiteljske anamneze (**Tablica 1**)[10]. Kod procjene QT intervala, neophodno je koristiti korigirani QT interval (QTc) kao što je onaj izračunat pomoću Bazett-ove formule (**$QTc = QT/\sqrt{RR}$**), budući da se QT interval povećava smanjenjem frekvencije srca. Visokorizični pacijenti s LQTS-om obično imaju QTc intervale ≥500ms. Iako je trenutna klasifikacija LQTS-a genetski bazirana, najvažnija klinička značajka kod LQTS-a je produljenje QT intervala (**Slika 2**)[11,12]. Genetska osnova LQTS-a dokazana je kad se otkrilo da mutacije u Na^+ i K^+ ionskim kanalima uzrokuju produljenja repolarizacije[13,14]. Do današnjeg dana opisan je velik broj mutacija što je omogućilo klasifikaciju LQTS-a na temelju genetske etiologije u 13 podtipova (**Tablica 2**).

Prolonged QT intervals can result from a reduced net repolarizing current (e.g. lower outward repolarizing K^+ currents or higher inward depolarizing Na^+ and Ca^{2+} currents). Indeed, LQTS is found associated with loss-of-function mutations in genes encoding for K^+-ion channels subunits or regulating proteins and gain-of-function mutations in genes encoding depolarizing Na^+- and Ca^{2+}-ion channels and subunits. Some patients carrying LQTS-related gene mutations can actually have a normal QT but also a reduced repolarization reserve and higher risk of tachycardia and sudden death.

Criteria to diagnose LQTS consist of ECG findings and clinical family history (**Table 1**)[10]. When evaluating the QT interval, it is necessary to use a rate-corrected QT interval such as calculated using Bazett's formula (**$QTc = QT/\sqrt{RR}$**), since the QT interval increases with decreasing heart rate. High-risk patients with LQTS usually have QTC intervals ≥500ms. Although the current classification of LQTS is genetically based, the most important clinical characteristic in LQTS is QT-interval prolongation (**Figure 2**)[11,12]. Genetic causes of LQTS were established when mutations in proteins forming Na+ and K^+ ion channel were shown to delay repolarization[13,14]. Since then many more mutations have been reported enabling a classification of 13 subtypes of LQTS, based on genetic aetiology (**Table 2**).

Table 1. *Diagnostic criteria of long QT syndrome.*

	Points
ECG findings[1]	
A. QTc[2]	
≥480 ms$^{1/2}$	3
460–470 ms$^{1/2}$	2
450 (males)	1
B. Torsades de pointes[3]	2
C. T-wave alternans	1
D. Notched T-wave in three leads	1
E. Low heart rate for age[4]	0.5
Clinical history	
A. Syncope	
With stress	2
Without stress	1
B. Congenital deafness	0.5
Family history[5]	
A. Family members with definite LQTS	1
B. Unexplained sudden cardiac death below age 30 years; among immediate family members	0.5

[1]In the absence of medications or disorders known to affect these electrocardiographic features.
[2]QTc calculated by Bazett's formula, where $QTc = QT\sqrt{RR}$
[3]Mutually exclusive.
[4]Resting heart rate below the second percentile for age
[5]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, high probability of LQTS.
Modified from Schwartz et al. [1993] [10].

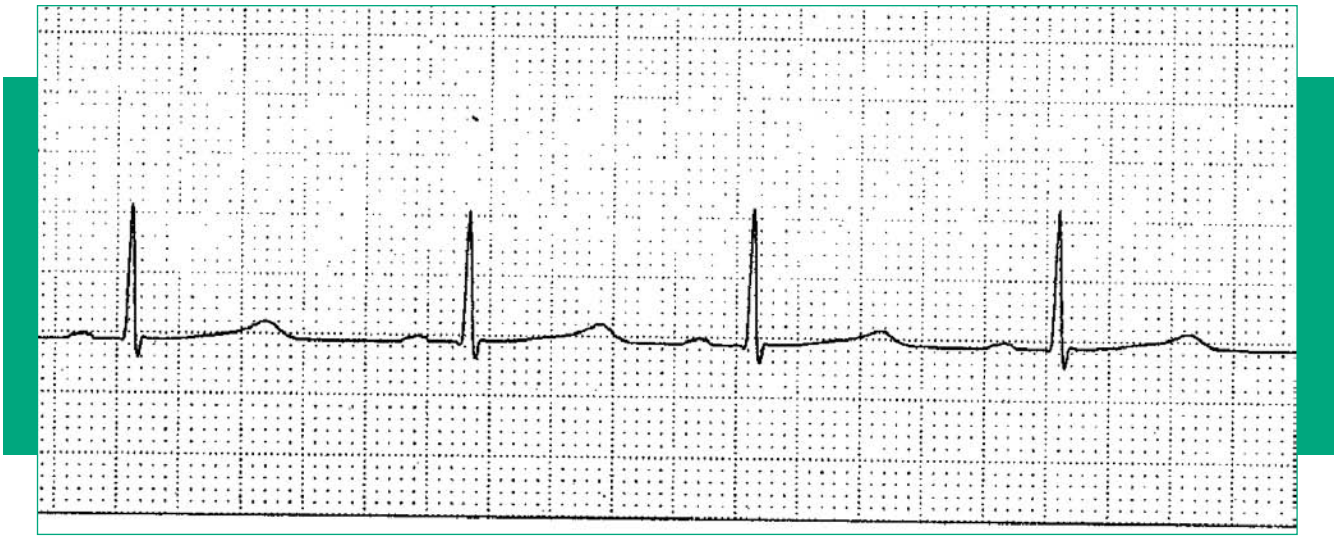

Figure 2. *Electrocardiographic patterns that can be found in the patients with long QT syndrome.*

Table 2. *The genes associated with long QT syndrome.*

Type	Syndrome	Gene	Chromosomal localization	Protein	Function	Current alterations	Characteristics and triggers	Prevalence in LQTS patients (%)
LQT1	RWS, JLNS	*KCNQ1*	11p15.5	Kv7.1	α-subunit	↓ IKs	Arrhythmia triggered by exercise, swimming and emotion	40–55
LQT2	RWS	*KCNH2*	7q35–36	Kv11.1	α-subunit	↓ IKr	Arrhythmia triggered by sound or emotion	35–45
LQT3	RWS	*SCN5A*	3p21	Nav1.5	α-subunit	↑ INa	Arrhythmia triggered by sleep, rest and emotion	2–8
LQT4	RWS	*ANK2*	4q25-27	Ankyrin B	Adaptor	↓ (INa-K, INa-Ca, INa)	Arrhythmia triggered by exercise	< 1
LQT5	RWS, JLNS	*KCNE1*	21p22	minK	β-subunit	↓ IKs	Arrhythmia triggered by exercise and emotion	< 1
LQT6	RWS	*KCNE2*	21p22	MiRP1	β-subunit	↓ IKr	Arrhythmia triggered by rest and exercise	< 1
LQT7	AS	*KCNJ2*	17q23-24	Kir2.1	α-subunit	↓ IK1	Syndromic, arrhythmia triggered by rest and exercise, frequent ectopy	< 1
LQT8	TS	*CACNA1C*	12p13.3	Cav1.2	α-subunit	↑ ICa	Syndromic, early onset and death from arrhythmia	< 1
LQT9	RWS	*CAV3*	3p25	Caveolin 3	Adaptor	↓ INa	Rest and sleep triggers arrhythmia	< 1
LQT10	RWS	*SCN4B*	11q23	Navβ4	β-subunit	↓ INa	Exercise triggers arrhythmia	< 0.1
LQT11	RWS	*AKAP9*	7q21–22	Yotiao	Adaptor	↓ IKs	Exercise triggers arrhythmia	< 0.1
LQT12	RWS	*SNTA1*	20q11.2	α1-Syntrophin	Scaffolding protein	↓ INa	Rest triggers arrhythmia	< 0.1
LQT13	RWS	*KCNJ5*	11q23-24	Kir3.4	β subunit	↓ IKAch	Arrhythmia triggered by exercise and emotion	< 0.1

RWS: Romano-Ward syndrome; JLNS, Jervell and Lange-Nielsen syndrome; AS, Andersen syndrome; TS, Timothy syndrome
Modified from Hedley et al. 2009 [23]

Cilj ovog članka je pružiti ažurirani popis gena, fenotipa i patofizioloških mehanizama koji su uključeni u nasljedni LQTS.

Genotipska-fenotipska korelacija

Među 13 trenutno poznatih LQTS podtipova, više od 90% osoba pripada u tri prvo otkrivena oblika: LQT1, LQT2 i LQT3[1]. Ova tri oblika uključuju genetske mutacije gena *KCNQ1, KCNH2 i SCN5A*. Razlike u mutacijama i elektrofiziološkim mehanizmima među LQTS podtipovima imaju tendenciju stvaranja jasnih razlika u morfologiji T-vala; LQT1, LQT2 i LQT3 imaju karakteristične razlike T-vala[15], a

The aim of this review is to provide an updated list of genes, phenotypes, and pathophysiologic mechanisms involved in inherited LQTS.

Genotype-phenotype correlation

Among the 13 LQTS subtypes currently known, more than 90% of individuals belong to the three forms that were first identified: LQT1, LQT2 and LQT3[1]. These three forms include genetic mutations in *KCNQ1, KCNH2* and *SCN5A* genes, respectively. Differences in mutations and electrophysiological mechanisms among the LQTS subtypes tend to produce distinctive differences in the T-wave morphology; LQT1,

LQT7 pokazuje karakteristične U-valove[16]. Međutim, EKG obrasci mogu imati značajnu interfamilijarnu i intra-alelnu varijaciju, što čini nemogućim njihovo korištenje kao zamjenu za genotipiranje[17,18]. Okidači za aritmiju značajno se razlikuju ovisno o tipu LQTS: tjelovježba i plivanje za LQT1, glasna buka i emocionalni stres za LQT2, dok kod LQT3 većina pacijenata ima srčane događaje tijekom spavanja ili odmora[19]. Genotip može biti snažan indikator rizika te može predvidjeti odgovor na antiadrenergijsku terapiju. Intenzitet disfunkcije ionskih kanala i lokacije mutacija utječu na QT interval i klinički intenzitet kliničkog fenotipa[20,21]. Stratifikacija rizika može se također mijenjati starenjem[12]. Nadalje, postoje izvješća o složenim fenotipovima kao što su Brugada sindrom (BrS), disfunkcija sinusnog čvora i strukturalna bolest srca koji uključuju i LQTS[22].

Indikacije, ishodi i klinički značaj genetskog testiranja

Genetsko testiranje je analiza DNK sekvence s namjerom da se identificiraju patogene mutacije u genima prethodno povezanim s bolesti. Postoje nekoliko tehnika koje omogućavaju genetski probir, kapilarna zonska elektroforeza (KZE) se smatra "zlatnim standardom" zbog svoje visoke osjetljivosti, iako uključuje veći trošak.

Genetski probir općenito se razmatra u slučajevima kada pojedinac ima jasnu kliničku dijagnozu i posebice u slučajevima pozitivne obiteljske anamneze. Genetski probir posebno je koristan za identifikaciju asimptomatskih nositelja mutacija. Postoje nekoliko ishoda početnog genetskog probira. U prvom slučaju, može se identificirati mutacija koja uzrokuje promjenu u nizu aminokiselina (*missense* mutacija), u jednom ili više testiranih gena. Međutim, sami pronalazak takve mutacije nije dovoljan za njeno povezivanje s bolesti. Stoga je potrebno zadovoljiti cijeli niz kriterija koji će potvrditi da genetska varijacija zaista jest mutacija koja uzrokuje bolest. Ti kriteriji uključuju: dokazivanje bolesti kod članova obitelji, odsutnost u kontrolnoj populaciji, pozicija mutacije u evolucijski očuvanom dijelu niza aminokiselina, prethodna izvješća o navedenoj mutaciji i funkcionalne elektrofiziološke *in vitro* studije. Potonje, ako su u skladu s patogenim mehanizmom, su snažna potpora pretpostavki da je određena mutacija patogena. Preuranjeni završetak u sekvenci aminokiselina (*stop codon*) ili mutacije sto uzrokuju pomak okvira čitanja genetičke šifre (*frame shift*) su najrazornije vrste mutacija te ih je obično lakše klasificirati kao patogene. Svi ovi dokazi, zajedno s kliničkim nalazima, doprinose ispravnoj klasifikaciji genetskih varijacija. Još jedan mogući ishod genetskog probira je slučaj u kojem se ne pronađe mutacija. Razlog tome može biti, između ostalog, da se štetna mutacija nalazi u genu ili regiji za koje se još nije otkrila povezanost s bolesti. Obično će provođenje mutacijskog probira rezultirati identifikacijom patogene mutacije u 70% do 80% LQTS slučajeva[23]. Genetski probir je bitan za identificiranje asimptomatskih nositelja koji bi se mogli klinički manifestirati kao iznenadna srčana smrt te pridodaje važne informacije za predviđanje ishoda i odabir terapije.

KCNQ1 (LQT1)

Naponom regulirani K^+ kanal, KQT-like podobitelj, gen člana 1 (*KCNQ1*) nalazi se na 11p15.5, a rasprostire se na 404 kilo baza (kb) i sadrži 16 egzona u rasponu od 16 do 1.122 parova baza (bp)[24]. *KCNQ1* kodira α-podjedinicu K^+ ionskog kanala (Kv7.1), koja provodi I_{Ks} struju. Kv7.1 (α-podjedinica)

LQT2 and LQT3 have characteristic T-wave differences[15] and LQT7 exhibits characteristic U-waves[16]. However, ECG patterns display considerable interfamilial and intra-allelic variation, making it impossible to use as a substitute for genotyping[17,18]. Triggers for arrhythmia are prevalently different according to the type: exercise and swimming in LQT1, loud noise and emotional stress in LQT2 and in LQT3 most patients experience cardiac events during sleep or at rest[19]. Genotype can be a strong indicator of risk and it can predict response to antiadrenergic therapy. The severity of ion-channel dysfunction and sites of mutation affect the QT interval and the clinical severity of the clinical phenotype[20,21]. Risk stratification can also change with increasing age[12]. Complex phenotypes such as Brugada syndrome (BrS), sinus node dysfunction, and structural heart disease involving LQTS have also been reported[22].

Indications, outcomes and clinical significance of genetic testing

Currently several techniques are used in genetic screening, the process of analysing the DNA sequence of disease-associated genes in order to identify pathogenic mutations. Direct sequencing by capillary array electrophoresis is considered the "gold standard" for its high sensitivity; regardless of its relatively high cost.

Genetic screening is generally considered when an individual has a definite clinical diagnosis, particularly in cases of positive family history. The major significance of the genetic screening is the identification of mutation carriers, especially if asymptomatic. There can be several outcomes of the initial genetic screening. In the first case, a mutation that includes a change in the amino acid sequence (missense mutation) is found in one or more genes tested. However, the mere finding of such mutation is not sufficient to associate it with disease. Therefore, a number of criteria must be fulfilled to support that a genetic variant is a disease-causing mutation. These criteria include segregation with disease in family members, absence in a control population, location of the variant in an evolutionary conserved part of the amino acid sequence, previous reports of the mutation and functional electrophysiological in vitro studies. The latter, if consistent with a pathogenic mechanism, is a strong support to the pathogenic role of the mutation. Premature stops in the amino acid sequence or frame shift mutations are more disruptive mutations and usually easier to classify as pathogenic. All this evidence, together with clinical findings, contribute to the correct categorization of the genetic variants. Another possible outcome of the genetic screening is the case where no mutations are identified. There are several explanations for this among which that the disease-causing mutation is present in a gene or region not yet discovered to be disease-associated. Usually, mutation screening will result in the identification of a disease-causing mutation only in the 70% to 80% of LQTS cases[23]. Genetic screening is useful to identify asymptomatic carriers who may otherwise present clinically with sudden death and adds important information for predicting outcome and selecting therapy.

KCNQ1 (LQT1)

The K+ voltage-gated channel, KQT-like subfamily, member 1 gene (*KCNQ1*) is located at 11p15.5, it spans over 404 kb, and contains 16 exons ranging in size from 16 to 1122 bp[24]. *KCNQ1* encodes for the alpha-subunit of the K^+ ion channel (Kv7.1), which conducts the I_{Ks} current. Kv7.1 (α-subunit)

veže se na akcesorne proteine, proizvode gena *KCNE1* i *KCNE3* (β-podjedinice) koje reguliraju njegovu funkciju (**Slika 3**)[25-27].

binds to accessory proteins encoded by *KCNE1* and *KCNE3* (beta-subunits) and is regulated by them (**Figure 3**)[25-27].

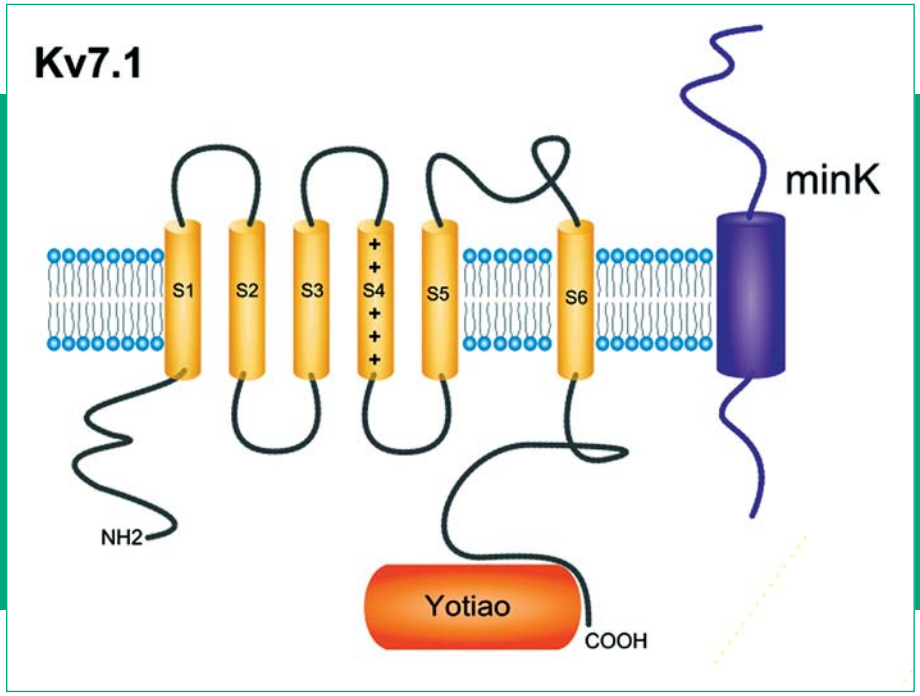

Figure 3. *Schematic drawing of the K⁺ channel Kv7.1.*

Do sada je opisano preko 250 mutacija u *KCNQ1* koje uzrokuju LQT1. *KCNQ1* mutacije se javljaju kod 42-54% LQTS bolesnika[28]. LQT1 i LQT5 su oboje rezultat redukcije I_{Ks} struje zbog mutacija u *KCNQ1* i *KCNE1*. LQT1 karakteriziran je sinkopom, adrenergijski-induciranom TdP i učinkovitošću liječenja β-blokerima[29]. Patofiziološki mehanizam je gubitak funkcije zbog: dominantne negativne supresije, defektnog prometovanja, stvaranja nefunkcionalnih ili disfunkcionalnih kanala[24]. Smanjena I_{Ks} struja dovodi do povećane transmuralne disperzije repolarizacije stjenke lijevog ventrikula. *KCNQ1* mutacije su također pronađene kod sindroma kratkog QT intervala (SQTS)[30,31], familijarne atrijske fibrilacije (AF)[32], sindroma iznenadne smrti dojenčeta i odraslih (SIDS i SADS)[33,34] te stečenog LQTS.

KCNH2 (LQT2)

Naponom regulirani K^+ kanal, podobitelj H, gen člana 2 (*KCNH2*) drugi je najučestaliji gen pogođen kod LQTS-a te se pojavljuje u 35-45% genotipiziranih pacijenata s LQTS-om[28]. *KCNH2* (7q35-7q36) je dugačak 33 kb, sadrži 15 egzona i kodira protein od 1.159 aminokiselina: alfa-podjedinicu naponom reguliranog K^+ ionskog kanala Kv11.1. Kv11.1 provodi odgođenu brzo aktivirajuću ispravljačku K^+ struju (IKr). Kv11.1 vezuje *KCNE2*-kodirani protein MiRP1 te je moduliran njime (**Slika 4**).

Trenutno je poznato preko 300 *KCNH2* mutacija, koje rezultiraju LQT2 podtipom. Patogeni mehanizam LQT2 je gubitak funkcije Kv11.1 što rezultira smanjenom I_{Kr} strujom. Smanjene I_{Kr} struje usporava repolarizaciju, povećava transmuralnu disperziju repolarizacije te produljuje akcijski potencijal naročito u sredini miokarda. LQT2 u većini slučajeva nastaje zbog neispravnog prometovanja Kv11.1, a rjeđe zbog pro-

Over 250 mutations have been described in *KCNQ1* causing LQT1, which occurs in 42-54% of known genotyped patients with LQTS28. LQT1 and LQT5 both result from I_{Ks} reduction due to mutations in *KCNQ1* and *KCNE1*, respectively. LQT1 is characterized by syncope, adrenergic-induced TdP, and effectiveness of beta-blocker treatment[29]. The mechanism responsible for that is a loss-of-function due to: dominant-negative suppression, defective trafficking, failure to assemble or dysfunctional channels[24]. Reduced I_{Ks} increases the transmural dispersion of repolarization in the left ventricular wall. *KCNQ1* mutations have also been found in short QT syndrome (SQTS)[30,31], familial atrial fibrillation (AF)[32], sudden infant and adult death syndromes (SIDS and SADS)[33,34], and acquired LQTS.

KCNH2 (LQT2)

The K^+ voltage-gated channel, subfamily H, member 2 gene (*KCNH2*) is the second most common gene involved in LQTS and it occurs in 35-45% of genotyped patients with LQTS[28]. *KCNH2* (7q35-7q36) spans over 33 kb, contains 15 exons and encodes for an 1.159 amino acid protein, the alpha-subunit of the voltage-gated potassium ion channel Kv11.1. Kv11.1 conducts the cardiac rapidly activating delayed rectifier K^+ current (IKr). Kv11.1 binds *KCNE2*-encoded protein MiRP1 and is modulated by it (**Figure 4**).

Currently over 300 *KCNH2* mutations, resulting in LQT2, are known. The pathogenic mechanism of LQT2 is loss-of-function of Kv11.1 which results in reduction of I_{Kr}. Reduced I_{Kr} slows repolarization, and increases transmural dispersion of repolarization and prolongs the action potential especially in the midmyocardium. LQT2 is due to defective trafficking of Kv11.1, in the vast majority of cases, and more rarely, to alterations of gating[35].

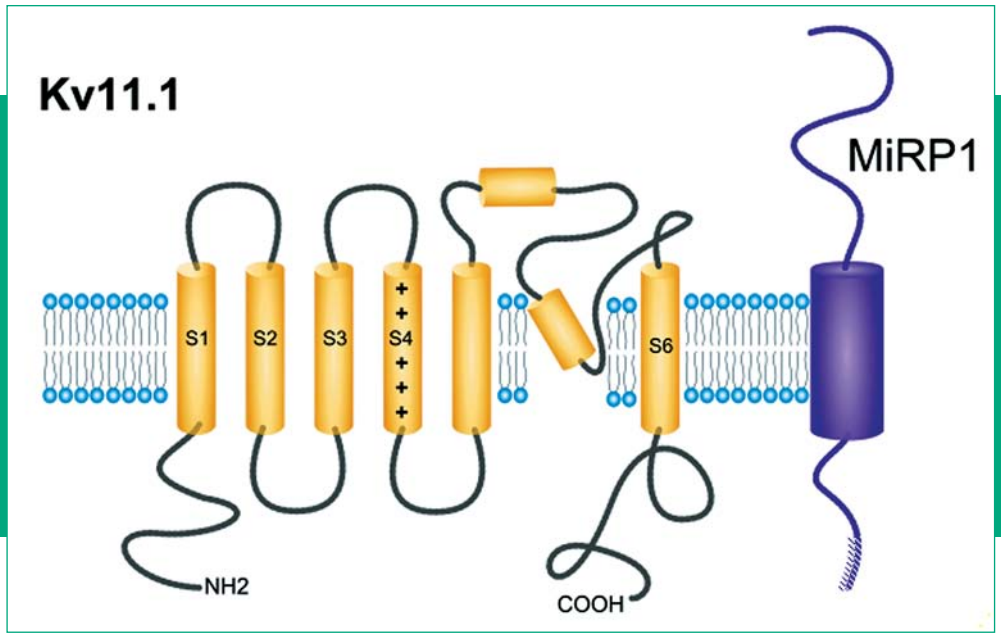

Figure 4. *Schematic drawing of the K⁺ channel Kv11.1.*

mjena u gatingu, odnosno dinamici otvaranja i zatvaranja kanala[35].

Mutacije u *KCNH2* također su povezivane sa SIDS-om[36]. Nadalje, najčešći uzrok stečenog LQTS-a je inhibicija I_{Kr} lijekovima koji blokiraju Kv11.1 kanal[37].

SCN5A (LQT3)

Naponom regulirani Na^+ kanal, tip V, gen alfa podjedinice (*SCN5A*) treći je najučestaliji gen povezan s LQTS, koji se pojavljuje u 2-8% genotipiziranih pacijenata[28]. *SCN5A* kodira za alfa-podjedinicu srčanog Na^+ kanala Nav1.5, koji provodi depolarizirajuću I_{Na} struju prema unutrašnjosti stanice[38]. *SCN5A* (lokus 3p21) sadrži 28 egzona koji se rasprostiru na 80 kb[39]. *SCN5A* se alternativno prekraja što treba uzeti u obzir pri lokaliziranju mutacija. Nav1.5 je dug 2.106 aminokiselina te je organiziran u četiri homologne domene od kojih svaka ima šest transmembranskih regija (**Slika 5**)[40].

Mutations in *KCNH2* have also been associated with SIDS[36]. Furthermore, the most frequent cause of acquired LQTS is inhibition of I_{Kr} by drugs that block the Kv11.1 channel[37].

SCN5A (LQT3)

The Na^+ voltage-gated channel, type V, alpha subunit gene (*SCN5A*) is the third most common gene involved in LQTS, occurring in 2-8% of the genotyped LQTS patients[28]. *SCN5A* encodes for the alpha-subunit of the cardiac Na^+ channel Nav1.5, which conducts the depolarizing inward current I_{Na}[38]. *SCN5A* (locus 3p21) contains 28 exons spanning over 80 kb[39]. Several splice forms exist and this should be taken into account when mutations are located. Nav1.5 is 2106 amino acids long and it is organized in four homologous domains each of which has six transmembrane regions (**Figure 5**)[40].

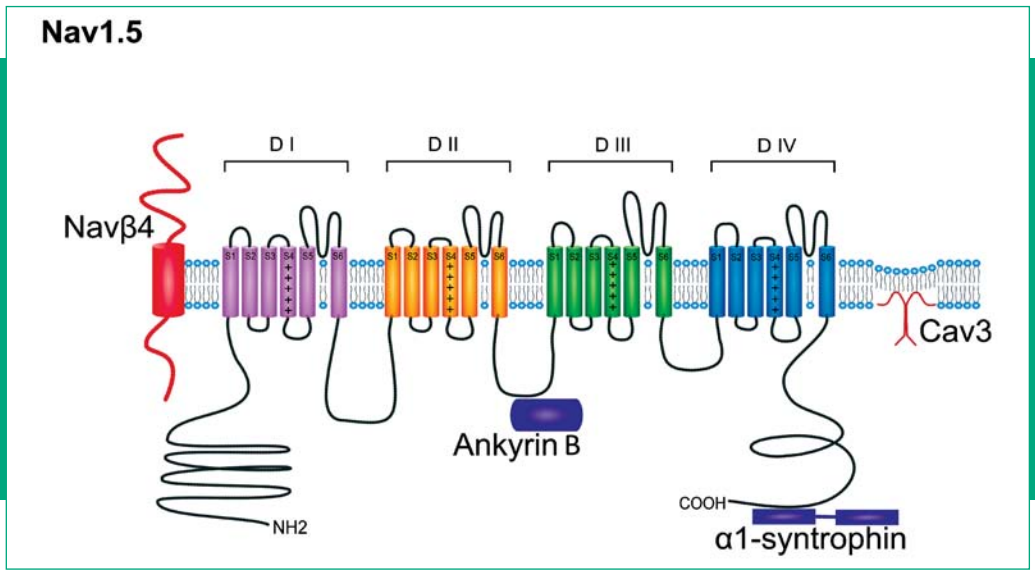

Figure 5. *Schematic drawing of the Na⁺ channel Nav1.5 and interacting proteins involved in long QT syndrome. Nav1.5 contains four homologous domains, DI-DIV, each of which has six putative membrane-spanning regions.*

SCN5A mutacije uključene u LQT3 tipično dovode do pojačane Nav1.5 funkcije odnosno povećanja kasne I_{Na} struje i, posljedično, produljena repolarizacije. Mehanizam može biti usporen stupanj inaktivacije, brži oporavak od inaktivacije, promjene gatinga i abnormalne interakcije s beta-podjedinicama[41]. Većina *SCN5A* mutacija uključenih u LQT3 nalaze se u egzonima 20-28 i nalaze se u regijama koje su ključne za brzu inaktivaciju Nav1.5[23].

Pored LQTS-a, mutacije *SCN5A* povezane su i s drugim srčanim poremećajima uključujući sindrom bolesnog sinusnog čvora, BrS, bolestima provodnje srčanog impulsa, fibrilaciji atrija, dilatativnoj kardiomiopatiji, aritmijama povezanim s akutnim infarktom miokarda i miješanim fenotipovima uključujući i strukturalne bolesti srca[42]. Nadalje, opisani su uobičajeni polimorfizmi koji modificiraju klinički fenotip[43]. Liječenje beta-blokatorima manje je učinkovito kod LQT3, a budući da pojavnost srčanih događaja kod LQT3 nije učestala, nije poznato da li su beta-blokatori štetni[19,29].

ANK2 (LQT4)

Ankirin-2 gen (*ANK2*) kodira ankirin B, adaptor koji pozicionira ionske kanale i druge molekule na specijalizirane membranske mikrodomene[44]. Gen *ANK2* (4q25-4q27) ima 46 egzona, rasprostire se na više od 560 kb i karakterizira ga tkivno-specifično alternativno prekrajanje[45]. Srčani izooblik je protein od 220 kDa. Mutacije gena *ANK2* proizvode gubitak funkcije ankirina B sa složenim i različitim fenotipovima koji uključuju bradikardiju, sinusnu aritmiju, idiopatsku ventrikularnu fibrilaciju, kateholaminergičnu polimorfnu ventrikularnu tahikardiju i iznenadnu smrt. LQT4 je obilježen dugim QT intervalom kojeg pogoršava tjelovježba i emocionalni stres. Smatra se da stupanj gubitka funkcije ankirina B može biti povezan s kliničkim intenzitetom bolesti[46].

KCNE1 (LQT5)

Naponom regulirani K^+ kanal, Isk-povezana podobitelj, gen člana 1 (*KCNE1*) kodira minimalni K^+ ionski kanal (minK). MinK je pojedinačna transmembranska β-podjedinica koja modulira α-podjedinicu naponom reguliranog Kv7.1 kanala, kodiranog od *KCNQ1*. *KCNE1* je mapiran na 21q22.1-21q22.2, ima tri egzona i kodira protein od 129 aminokiselina[47,48]. Mutacije *KCNE1* gena rezultiraju smanjenom IKs strujom s rezultirajućim produljenjem QT intervala. LQT5 obično pokazuje blage kliničke fenotipove iako, homozigotne mutacije *KCNE1* ili miješane heterozigote *KCNQ1* i *KCNE1* stvaraju fenotip JNLS obilježen LQTS-om i gluhoćom[25,49].

KCNE2 (LQT6)

Naponom regulirani K^+ kanal, IsK-povezana podobitelj, gen člana 2 (*KCNE2*) kodira minimalni peptid 1 (MiRP1) povezan s K^+ ionskim kanalom. *KCNE2* je mapiran na 21q22.1, sadrži dva egzona i kodira protein od 123 aminokiseline. MiRP1 je β-podjedinica Kv11.1 (kojeg kodira *KCNE2*) te stoga doprinosi provođenju I_{Kr} struje. Kao što je za očekivati, mutacije u *KCNE2* rezultiraju smanjenjem I_{Kr} struje. Bolesnici s LQT6 su rijetki, imaju blagi fenotip s niskom penetracijom[50]. Mutacije u *KCNE2* također mogu uzrokovati stečene oblike LQTS-a[37,51].

SCN5A mutations involved in LQT3 typically produce a gain-of-function of Nav1.5 resulting in an increased late I_{Na} and, consequently, prolonged repolarization. The mechanism can be due to slowed rate of inactivation, faster recovery from inactivation, gating shift, and abnormal interactions with beta-subunits[41]. The majority of the *SCN5A* mutations involved in LQT3 are found in exons 20-28 and they map in regions that are crucial for the fast inactivation of Nav1.5[23].

Apart from LQTS, mutations in *SCN5A* are associated with other disorders including sick sinus node syndrome, BrS, cardiac conduction disease, AF, dilated cardiomyopathy, arrhythmia in association with acute myocardial infarction and mixed phenotypes including structural heart disease have been identified[42]. Furthermore, common polymorphisms that modify the clinical phenotype have been described[43]. Beta-blocker treatment is less effective in LQT3 and, since the occurrence of cardiac events is not frequent in LQT3, it is unknown whether beta-blockers are harmful[19,29].

ANK2 (LQT4)

The Ankyrin-2 gene (*ANK2*) codes for ankyrin B, an adaptor that localizes ion channels and other molecules at specialized membrane microdomains[44]. The *ANK2* gene (4q25-4q27) has 46 exons, spans over 560 kb and it is present in several, tissue specific, splice forms[45]. The heart specific isoform is a protein of 220 kDa. Mutations in the *ANK2* gene produce a loss-of-function phenotype with complex and varied set of phenotypes including bradycardia, sinus arrhythmia, idiopathic ventricular fibrillation, catecholaminergic polymorphic ventricular tachycardia, and sudden death. LQT4 is characterized by a long QT interval aggravated by exercise and emotional stress. The degree of functional loss of ankyrin B seems to be correlated with clinical severity of the disease[46].

KCNE1 (LQT5)

The K^+ voltage-gated channel, Isk-related subfamily, member 1 gene (*KCNE1*) encodes the minimal K^+ ion channel (minK). MinK is single transmembrane β-subunit that associates with and modulates the α-subunit of the voltage-gated Kv7.1 channel, encoded by *KCNQ1*. *KCNE1* maps to 21q22.1-21q22.2, has three exons and encodes for a 129 amino acid protein[47,48]. Mutations in KCNE1 result in a reduced IKs current and thus prolonged QT interval. LQT5 usually shows mild clinical phenotypes although, homozygous mutation in *KCNE1* or compound heterozygotes of *KCNQ1* and *KCNE1* produce the JNLS phenotype, characterized by LQTS and deafness[25,49].

KCNE2 (LQT6)

The K^+ voltage-gated channel, IsK-related subfamily, member 2 gene (*KCNE2*), encodes the minimum K^+ ion channel-related peptide 1 (MiRP1). *KCNE2* maps to 21q22.1, comprises two exons and codes for a 123 amino acid protein. MiRP1 is the beta-subunit of Kv11.1 (encoded by *KCNE2*) and thus contributes to the generation of the I_{Kr} current. As expected, mutations in *KCNE2* result in a reduction of the I_{Kr} current. Patients with LQT6 are rare and present mild phenotypes with low penetrance[50]. Mutations in *KCNE2* may also cause acquired forms of LQTS[37,51].

KCNJ2 (LQT7)

KCNJ2 je K^+ ulazni ispravljački kanal, podobitelj J, gen člana 2. Gen se nalazi na dugom kraku kromosoma 17; sadrži dva egzona koji se rasprostiru na 10 kb[52]. *KCNJ2* kodira naponom regulirani ulazni ispravljački K^+ ionski kanal Kir2.1 odgovoran za provođenje značajnog dijela ulazne ispravljačke I_{k1} struje. I_{k1} stabilizira potencijal pri odmoru, određuje prag podražaja membrane u mirovanju i modulira repolarizaciju[53]. *KCNJ2* mutacije odgađaju kasnu repolarizaciju faze-3, posebice u subendokardu, što uzrokuje blago produljenje QT-a. Produljenje akcijskog potencijala izaziva preopterećenje Ca^{2+}, što naposljetku potiče TdP. Mutacije *KCNJ2* uzrokuju Andersenov sindrom koji se često povezuje s ventrikularnom tahikardijom, preuranjenom kontrakcijom ventrikula i ekstrasistolama. Iznenadna smrt rijetko je posljedica ovih mutacija[16].

CACNA1C (LQT8)

CACNA1C je o naponu ovisan Ca^{2+} kanal, L tip, gen podjedinice alfa-1C. Kodira alfa-podjedinicu dugodjelujućeg (L-tipa) naponom reguliranog kanala Cav1.2 koji provodi ulaznu $I_{Ca,L}$ struju, što je važno tijekom plato faze AP-a. *CACNA1C* je veliki gen koji se rasprostire na 640 kb, nalazi na kromosomu 12p13.33, sadrži 50 egzona te je prisutan u višestrukim oblicima alternativnog prekrajanja. Prevladavajući oblik Cav1.2 sastoji se od 2.138 aminokiselina[54]. Struktura Cav1.2 sadrži četiri homogene domene, svaka s po šest transmembranskih regija (S**lika 6**)[55].

KCNJ2 (LQT7)

KCNJ2 is the K+ inward rectifying channel, subfamily J, member 2 gene. The gene is located on the long arm of chromosome 17; it contains two exons that span over 10 kb[52]. *KCNJ2* encodes the voltage-dependent inwardly rectifying K^+ ion channel Kir2.1 responsible for conducting a significant part of the inwardly rectifying I_{k1} current. I_{k1} stabilizes the resting potential, defines the membrane threshold and modulates repolarization[53]. *KCNJ2* mutations delay late phase-3 repolarization, especially in the subendocardium, causing mild QT prolongation. The prolongation of AP induces Ca^{2+} overload, which ultimately triggers TdP. Mutations in *KCNJ2* cause Andersen syndrome, frequently associated with ventricular tachycardia, premature ventricular contraction and extrasystole. Sudden death is rarely associated with these mutations[16].

CACNA1C (LQT8)

CACNA1C is the Ca^{2+} voltage-dependent channel, L type, alpha-1C subunit gene. It encodes for the alpha-subunit of the long-lasting (L-type) voltage gated channel Cav1.2., which conducts the inward $I_{Ca,L}$, important during the plateau phase of AP. *CACNA1C* is a large gene that spans 640 kb at chromosome 12p13.33 and contains 50 exons and is present in multiple splice forms. The predominant splice form of Cav1.2 comprises 2138 amino acids[54]. Cav1.2 structure contains four homologous domains, each with six transmembrane regions (**Figure 6**)[55].

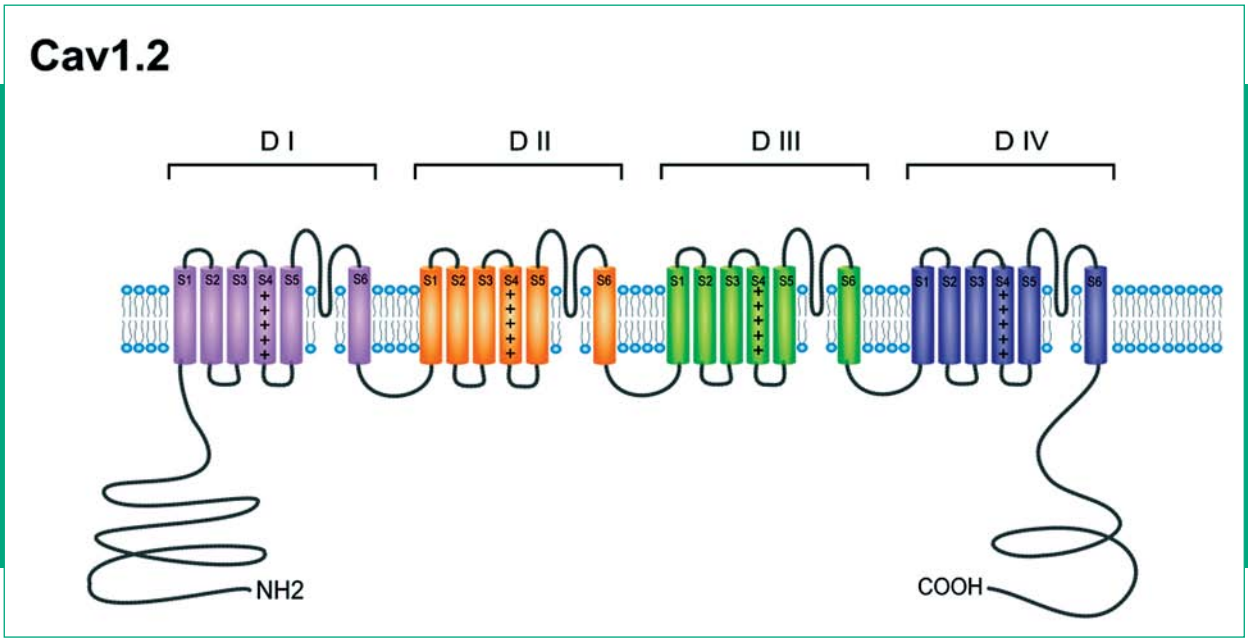

Figure 6. *Schematic drawing of the Ca2⁺ channel Cav1.2 alpha-subunit. Cav1.2 also has four homologous domains, DI-DIV, each consisting of six membrane-spanning regions.*

Samo dvije mutacije gena *CACNA1C* (p.G402S i p.G406R) su opisane u LQTS. Uzrokuju Timothy-ev sindrom, rijetku i tešku bolest obilježenu produljenim QT intervalom, sindaktilijom, imunodeficijencijom, hipoglikemijama, kognitivnim oštećenjima, autizmom i višeorganskim malformacijama. Patogeni mehanizam je pojačana funkcija Cav1.2 zbog gubitka inaktivacije što dovodi do produljenja ulazne $I_{Ca,L}$ struje, pro-

Only two mutations in the *CACNA1C* gene have been described (p.G402S and p.G406R). They are the cause of Timothy syndrome, a rare and severe condition characterized by prolonged QT interval, syndactyly, immune deficiency, hypoglycaemia, cognitive impairment, autism, and malformations in multiple organs. The pathogenic mechanism is gain-of-function and it involves loss of Cav1.2 inacti-

duljenja AP-a i preopterećenja Ca^{2+}. U genu *CACNA1C* opisane su još dvije mutacije ali povezane sa BrS i SQTS[56].

CAV3 (LQT9)

Gen kaveolin-3 (CAV3) nalazi se na kromosomu 3p25, sadrži dva egzona, rasprostire se na 13 kb i proizvodi protein od 151 aminokiseline, M-kaveolin (CAV3)[57]. Protein CAV3 posrednik je endocitoze uz formaciju kaveola. Poznati ionski kanali koji su u interakciji sa CAV3 uključuju kanale koje kodiraju geni *KCNH2, SCN5A i CACNA1C*[58-60]. Mutacije CAV3 gena povezane su s LQT9 i SIDS-om. Druge bolesti koje su uzrokovane mutacijama u CAV3 uključuju mišićnu distrofiju "*limb-girdle*" tipa[61], mišićnu distrofiju povezanu s distrofin-glikoprotein-kompleksom[62], idiopatsku hiperkreatinkinazemiju[63] i "*rippling*" mišićnoj bolesti[64]. Smatra se da mutacije u CAV3 uzrokuju LQTS učinkom na *SCN5A*-kodirane Nav1.5 kanale, no noviji dokazi dovode u sumnju da li CAV3 mutacije stvarno uzrokuju LQTS[65].

SCN4B (LQT10)

SCN4B je naponom regulirani Na+ kanal tipa IV, gena beta podjedinice. Kodira beta-podjedinicu (Navβ4) kompleksa Na+ kanala (Nav) te regulira njegovu funkciju. *SCN4B* sastoji se od pet egzona i rasprostire na 19.5 kb kromosoma 11q23[66]. Jedina mutacija identificirana na *SCN4B*, p.L179F, ima *in vitro* učinak povećanja kasne INa struje[67]. LQT10 je nalik LQT3.

AKAP9 (LQT11)

A-kinaza sidro protein 9 gen (*AKAP9*) kodira dva proteina, yotiao protein od 1.626 aminokiselina i AKAP120. Oba proteina članovi su obitelji AKAP proteina podupirača, koji su uključeni u podstaničnu lokalizaciju protein kinaze A (PKA)[68]. *AKAP9* se nalazi na kromosomu 7q21-7q22, sastoji se od 51 egzona koji se rasprostiru na 170 kb[69]. U *AKAP9* pronađena je jedna mutacija (p.S1570L) povezana s LQTS-om koja uključuje yotiao protein. Mutacija kompromitira mjesto na kojem se yotiao veže na *KCNQ1*-kodirani kanal Kv7.1 i uzrokuje smanjenje funkcijskog odziva IKs na cAMP stimulaciju[70].

SNTA1 (LQT12)

Sintrofin, alfa-1 gen (*SNTA1*) kodira alfa-1-sintrofin, protein podupirač načinjen od 505 aminokiselina. Sintrofini su citoplazmatički sub-membranski proteini, organizirani u multiproteinske komplekse, gdje dolaze u interakciju sa distrofinom i ostalim proteinima[71]. *SNTA1* ima 8 egzona koji pokrivaju 36 kb kromosoma 20[72]. *SNTA1* mutacija p.A390V pronađena je pri analizi od 50 LQTS bolesnika koji nisu u krvnom srodstvu. Mutacija izaziva povećanje kasnih INa struja, a budući da je alfa-1-sintrofin u interakciji s više ionskih kanala nije moguće ustanoviti egzaktni patogeni mehanizam[73].

KCNJ5 (LQT13)

KCNJ5 je najnovije otkriveni LQTS gen. *KCNJ5* je gen člana 5, podobitelji J, ulaznog ispravljačkog K^+ kanala, dug je 27 kb, ima tri egzona i mapiran je na kromosomu 11q24.3[74]. Kodira 419 aminoiselina dug, G-proteinom aktiviran, ulazni ispravljački K^+ kanal 4 (Kir3.4). Podjedinice Kir3.4 i Kir1.3 spajaju se kako bi formirale heterotetramerijske K^+ kanale

vation leading to prolonged inward $I_{Ca,L}$, AP prolongation, and Ca^{2}+ overload . Two other *CACNA1C* mutations have also been described in BrS and SQTS[56].

CAV3 (LQT9)

The caveolin-3 gene (CAV3) is located on chromosome 3p25, it consists of two exons, it spans 13 kb and it produces a 151 amino acids protein, the M-caveolin (CAV3)[57]. The CAV3 protein mediates endocytosis through formation of the caveolae. Multiple ion channels have been found interacting with CAV3 in the caveolea, including channels encoded by *KCNH2, SCN5A*, and *CACNA1C*[58-60]. Mutations in CAV3 are associated with LQT9 and SIDS. Other diseases caused by CAV3 mutations include limb-girdle muscular dystrophy[61], dystrophin-glycoprotein-complex-associated muscular dystrophy[62], idiopathic hyperCKemia[63], and rippling muscle disease[64]. Mutations in CAV3 have been suggested to cause LQTS based on an effect on the *SCN5A*-encoded Nav1.5 channel, but recent evidence makes it doubtful whether CAV3 mutations do really cause LQTS[65].

SCN4B (LQT10)

SCN4B is the Na+ voltage-gated channel, type IV, beta subunit gene. It encodes for the beta subunit (Navβ4) of the Na+ channel (Nav) complex, and it regulates its function. *SCN4B* is composed of five exons and it spans 19.5 kb at chromosome 11q23[66]. The only mutation identified in *SCN4B*, p.L179F, has been demonstrated to have an in vitro effect of increasing the late INa current[67]. LQT10 resembles LQT3.

AKAP9 (LQT11)

The A-kinase anchor protein 9 gene (*AKAP9*) codes for two proteins, the yotiao protein of 1626 amino acids and AKAP120. Both proteins are members of the AKAP family of scaffolding proteins involved in subcellular localization of protein kinase A (PKA)[68]. *AKAP9* is located on chromosome 7q21-7q22, it consists of 51 exons spanning more than 170 kb[69]. A single LQTS-associated mutation was found in *AKAP9* (p.S1570L) involving the yotiao protein. The mutation compromises the binding site of yotiao to *KCNQ1*-encoded channel Kv7.1, and it causes the reduction of the functional response IKs to cAMP stimulation[70].

SNTA1 (LQT12)

The syntrophin, alpha-1 gene (*SNTA1*) encodes alpha-1-syntrophin, a 505 amino acid scaffolding protein. Syntrophins are cytoplasmatic sub-membranous proteins,components of the dystrophin-associated protein complex, where they interact with multiple targets[71]. *SNTA1* has 8 exons covering 36 kb of chromosome 20[72]. A single LQTS-associated mutation was found in *SNTA1*, p.A390V, in an analysis of 50 LQTS unrelated patients. Functional studies showed that the mutation has the effect of increasing late INa, however the mechanism underlying this effect could not be established due to interactions of alpha-1-syntrophin to multiple ion channels[73].

KCNJ5 (LQT13)

KCNJ5 is the most recently discovered gene to be involved in LQTS. *KCNJ5* is the K^+ channel, inwardly rectifying, sub-

koji provode acetilkolinski induciranu K^+ struju (I_{KACh}). Opisana je samo jedna *KCNJ5* mutacija (p.G387R) vezana za LQTS i to s nepotpunom penetracijom[75]. Mutacija p.G387R utječe na regiju Kir3.4 odgovornu za navođenje kompleksa Kir3.4/Kir3.1 na staničnu membranu. *In vitro* studije pokazale su da mutacija kompromitira formiranje funkcionalnih Kir3.4/Kir3.1 kompleksa, što uzrokuje drastično smanjene ulazne I_{KACh} struje.

LQTS i iznenadna smrt

Dugo vremena se sumnjalo da je LQTS mogući uzrok SIDS-a[76], a prvo veliko prospektivno istraživanje na tu temu pokazalo je da je produljeni QT interval bio prisutan kod polovice SIDS slučajeva[77]. Potvrda da LQTS značajno doprinosi iznenadnoj smrti došla je s identifikacijom prve LQTS mutacije u žrtvi SIDS-a, a naknadne studije su to potvrdile. U prvoj studiji, obavljenoj postmortem na 93 novorođenčeta, ustanovljeno je da je 2% žrtava imalo mutacije u evolucijski visoko očuvanim regijama *SCN5A*[78]. Drugo istraživanje, obavljeno na 201 žrtvi SIDS-a u Norveškoj, identificiralo je kod 9,5% žrtava funkcijske mutacije LQTS gena[33]. U analizi 57 engleskih obitelji žrtava nagle smrti, Behr i suradnici[79], pronašli su u više od polovice slučajeva mutacije povezane s nasljednim bolestima srca od kojih 38% su bile LQTS mutacije.

Osim povezanosti LQTS i iznenadne smrti također su ustanovljeni i visokorizični genotipovi iznenadne smrti. Smatra se da je rizik od srčanih događaja znatno manji kod nositelja LQT1 nego kod nositelja LQT2 i LQT3 te da su nositelji LQT1 češće asimptomatski u usporedbi s nositeljima LQT2 i LQT3. Međutim, rizik od nastupa srčanih događaja (sinkope, srčani zastoj, iznenadna smrt) varira prema točnoj lokaciji mutacije, što komplicira procjenu rizika temeljenu na genotipu[12]. Također postoje drugi bitni čimbenici, kao QTc interval i spol, koje je potrebno uzeti u obzir kod procjene rizika. Muški je spol pod većim rizikom u ranijoj dobi, no srčani se događaji kod ženskih bolesnica postupno povećavaju s dobi[80]. Za druge LQT podtipove za sada su dostupni samo ograničeni podaci, no homozigotne ili miješane mutacije (tj. Jervell-Lange Nielsen sindrom) te bolesnici s Timothy sindromom doimaju se pod naročito visokim rizikom od iznenadne smrti od ranog djetinjstva[81,82].

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family J, member 5 gene, it is 27kb long, has three exons and maps on chromosome 11q24.3[74]. It encodes for the 419 amino acid long, G protein-activated, inward rectifier K^+ channel 4 (Kir3.4). Kir3.4 and Kir1.3 subunits assemble to form heterotetrameric K^+ channels that mediate the acetylcholine induced K^+ current (I_{KACh}). Only one *KCNJ5* mutation (p.G387R) is described relative to LQTS and it was detected in a large Chinese family with incomplete penetrance[75]. p.G387R seems to affect a region of Kir3.4 involved in surface targeting of the Kir3.4/Kir3.1 complex. *In vitro* studies showed that the mutation compromises the formation of functional Kir3.4/Kir3.1 complexes, causing drastically reduced inward I_{KACh} currents.

LQTS and sudden death

It has been suspected for a long time that LQTS is a cause of SIDS[76] and one of the first studies performed showed that half of SIDS cases had prolonged QT interval[77]. The identification of the first LQTS-causing mutations in a victim of SIDS, and subsequent studies, confirmed that LQTS is a significant contributor in sudden death. In the first study, performed postmortem on 93 infants, 2% of the victims were found to harbour mutations in highly conserved regions of *SCN5A*[78]. Another study, performed on 201 SIDS victims in Norway, identified in 9.5% of the victims functional mutations in LQTS genes[33]. Behr et al.[79] analysed 57 English families of SADS victims and found in over half of them mutations related to inherited heart disease of which 38% were LQTS mutation.

While more and more evidence is gathered on the relationship between LQTS and sudden death, several efforts have also been made in attempt to identify high-risk genotypes for sudden death. The risk of cardiac events was found to be considerably smaller in LQT1 carriers than in LQT2 and LQT3 carriers, and LQT1 carriers are more often asymptomatic as compared to LQT2 and LQT3 carriers. However, the risk of occurrence of cardiac events (syncope, cardiac arrest, sudden death) varies according to the precise location of the mutation, which complicates risk estimation based on genotype[12]. Likewise there are other modifying factors, like QTc interval and gender, which have to be taken into account when evaluating risk. Male sex seems to be a high risk at an early age, but cardiac events in female patients gradually increases with age80. Limited data are available for the other LQT subtypes, but homozygous or compound mutations (i.e. Jervell-Lange Nielsen syndrome) and Timothy syndrome patients seem to be at particularly high risk of sudden death from early childhood[81,82].

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