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Molecular genetic markers of QT interval duration and sudden cardiac death: literature review

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ABSTRACT

The study of sudden cardiac death (SCD) and its etiopathogenesis in cardiology practice remains one of the most pressing public health problems. In Western countries, SCD accounts for 20% of the total mortality and 50% of mortality associated with cardiovascular diseases. Considering the electrical instability in the myocardium as one of the main reasons for the development of life-threatening arrhythmias (ventricular tachycardia / ventricular fibrillation) and SCD, one should be aware of such provoking factors as ischemic heart disease, myocarditis, valvular heart disease, pharmacological influences, cardiomyopathy, and channelopathy. An increase or decrease in the duration of the QT interval, which reflects the work of ion channels, as well as ventricular depolarization and repolarization, increases the risk of SCD.

The aim of this review was to study and analyze the available literature data on the relationship of molecular genetic markers with the duration of the QT interval.

Currently, there is a number of genetic studies that allow to identify a large number of mutations and polymorphisms of known genes that affect the variability of the QT interval, showing their significance in risk stratification of sudden arrhythmic death and choosing the right tactics for managing, preventing, and treating patients, thus reducing the risk of SCD. The predictive value of genetic testing is the highest for long QT syndrome (LQTS), for which a gene-specific risk profile has been established, and lower for other channelopathies. A large amount of genetic data may be a promising approach to quantifying the risk of SCD, especially at a young age, which will be facilitated by further study of this problem.

Keywords: sudden cardiac death, duration of the QT interval, long QT syndrome, short QT syndrome, single nucleotide polymorphism, molecular genetic marker

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Молекулярно-генетические маркеры длительности интервала QT и внезапная сердечная смерть: обзор литературы

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РЕЗЮМЕ

Изучение внезапной сердечной смерти (ВСС) и ее этиопатогенетических факторов в кардиологической практике остается одной из наиболее актуальных проблем здравоохранения. В западных странах ВСС составляет 20% общей летальности и 50% летальности, связанной с сердечно-сосудистыми заболеваниями. Рассматривая электрическую нестабильность миокарда в качестве одной из главных причин развития жизнеугрожающих аритмий (желудочковая тахикардия/фибрилляция желудочков) и ВСС, следует помнить о таких провоцирующих факторах, как ишемическая болезнь сердца, миокардит, клапанные пороки сердца, фармакологические влияния, кардиомиопатии и каналопатии. Увеличение или уменьшение длительности интервала QT, который отражает работу ионных каналов, процессы деполяризации и реполяризации миокарда желудочков, повышает риск ВСС.

Цель данного обзора – изучение и анализ имеющихся данных литературы о взаимосвязи молекулярно-генетических маркеров с длительностью интервала QT.

На сегодняшний день существует ряд генетических исследований, позволяющих идентифицировать большое количество мутаций, полиморфизмов известных генов, оказывающих влияние на вариабельность интервала QT, показывая их значимость в стратификации риска внезапной аритмогенной смерти, выборе верной тактики ведения, профилактики и лечения пациентов, уменьшая вероятность ВСС. Прогностическая ценность генетического тестирования наиболее высока для синдрома удлиненного интервала QT (LQTS), для которого установлен ген-специфический профиль риска, и в меньшей степени определена при других каналопатиях. Большой объем генетических данных может стать многообещающим подходом для количественной оценки риска ВСС, особенно в молодом возрасте, чему способствует дальнейшее изучение данной проблемы.

Ключевые слова: внезапная сердечная смерть, длительность интервала QT, синдром удлиненного интервала QT, синдром укороченного интервала QT, однонуклеотидный полиморфизм, молекулярно-генетический маркер

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

The study of sudden cardiac death (SCD) and its etiopathogenetic factors is of particular interest in cardiology practice. In Western countries, SCD accounts for 20% of the total mortality and 50% of mortality associated with cardiovascular diseases [1]. According to the epidemiological register, the following parameters of annual SCD prevalence among all age groups are noted: Australia – from 34.6 to 99.4 per 100,000 population, which corresponds to the parameters in New Zealand; China – 41.8 per 100,000 population; Japan – 14.9 per 100,000 population; South Korea – 20.1 per 100,000 population; USA – from 50 to 100 per 100,000 per 100,000 population; Europe – 84.0 per 100,000 population per year, respectively [2].

To date, a number of studies have been carried out in the Russian Federation on the prevalence of SCD in various regions. In 2011, the results of a large-scale, cross-sectional study "REZONANS" (Ryazan, Voronezh, Khanty-Mansiysk) including 285,736 patients with coronary heart disease (CHD) were published, according to which the incidence of SCD was 156 per 100,000 male population and 72 per 100,000 female population per year, which is 2.3 and 2.8 times higher than the rates registered in medical institutions [3].

In 2016, R.M. Linchak et al. published data from the "GERMINA" register on the structure and frequency of SCD among the working-age population of the Bryansk region for 2012 [4]. The study involved 417,740 people aged 25–64 years. According to the results, the frequency of SCD was 25.4 per 100,000 population, of which about 85% were males and 15% were females. In the structure of the overall and cardiovascular mortality, the share of SCD was 2.9% and 7.3%, respectively [4].

It should be noted that the incidence of SCD increases with the age of the population included in the study. This is especially noticeable after 45 years, which is associated with an increased risk of developing CHD. Middle-aged men have a 4 times increased risk of SCD compared with women of the same age. However, as the age increases, this difference between the sexes decreases, and disappears at the age of ≥ 85 years [5, 6].

Among people under 35 years of age, the highest frequency of SCD is observed in the age group of 0–5 years. The above age-specific characteristics of the SCD prevalence, taking into account gender, are described by C.X. Wong et al. [2]. It is known that people of African American descent have a higher level of SCD compared to people of Hispanic or Caucasian descent [6]. According to the results of the study by J. Ghobrial et al., the average age in the groups of people of African American and Asian descent with a SCD episode was less than that recorded in the group of Hispanic descent [7]. In the same groups, a lower socioeconomic level and a lower survival rate after performed cardiopulmonary resuscitation were observed. Among concomitant diseases, diabetes mellitus, arterial hypertension and end-stage renal failure were more common ($p < 0.001$) [7].

The main cause of SCD is considered to be electrical instability in the myocardium as a possible consequence of CHD, acquired valvular heart disease, cardiomyopathy, drug toxicity, and hereditary channelopathies (Fig. 1) [2, 5, 8, 9]. Accordingly, the prognostic factors of SCD in men and women, first of all, are risk factors for CHD, including arterial hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, etc. [5, 10, 11].

According to the Oregon SUDS study, 58% of subjects aged 5–34 years who experienced community-acquired SCD had at least one risk factor for cardiovascular disease. Moreover, the prevalence of obesity among these young people was 39% [12]. Subsequently, data were published on the relationship of other comorbidities, such as atrial fibrillation, chronic kidney disease, obstructive sleep apnea, depression, anxiety disorder, psychosis, as well as physical activity and other lifestyle factors with the risk of SCD [13–15].

A burdened family history of SCD is an important predictor of SCD development [16]. As a rule, in 5% of SCD cases, no cardiovascular pathology is detected in survivors after successful resuscitation or during autopsy of the deceased [9]. In children and people under 35 years of age, CHD accounts for a much smaller proportion of deaths, with hypertrophic cardiomyopathy, coronary artery anomalies, myocarditis, arrhythmogenic right ventricular cardiomyopathy, and primary ion channelopathies accounting for a significant proportion. SCD can often be the first manifestation of the disease in a family. Clinical and genetic assessment of survived family members plays a key role in the diagnosis of underlying heart disease, relying on the fact that most hereditary heart diseases are characterized by autosomal dominant inheritance, which, in turn, provides a 50% chance of verifying the same disease substrate among survived family members [11].

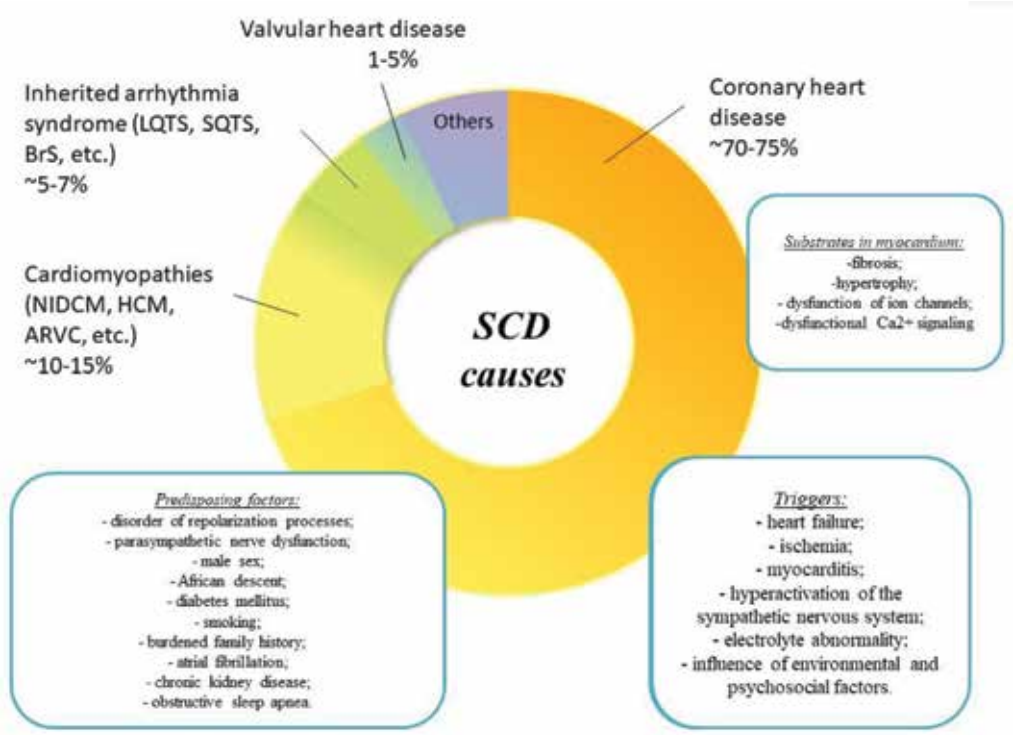

Fig. 1. Main causes of and risk factors for sudden cardiac death.

Focusing on the arrhythmogenic nature of SCD, one should be aware of the following primary nosologies: long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, the molecular and genetic aspects of which are considered as alternative criteria for SCD risk stratification along with electrophysiological and ultrasound parameters, MRI diagnostic parameters (areas of ischemia, foci of fibrosis, ejection fraction, etc.), such biomarkers as B-type natriuretic peptide, troponin, galectin-3, and soluble ST2 [1]. A molecular and genetic analysis reveals predictors in 65% of cases of long QT syndrome (LQTS), in 20% of cases of Brugada syndrome (primary electrical diseases), and in 20–52% of cases of cardiomyopathies [17–20].

Thus, the aim of this literature review was to study and analyze the available literature data on the relationship of molecular and genetic factors with QT interval duration.

LONG QT SYNDROME

QT interval is an electrocardiographic parameter reflecting depolarization and repolarization of the ventricular myocardium, the electrophysiological basis of which is the state of the ion channels in the cardiomyocyte membrane. The balance between calcium, potassium, and sodium ion channels determines the duration of the action potential in cardiomyocytes (Fig. 2) [21–23].

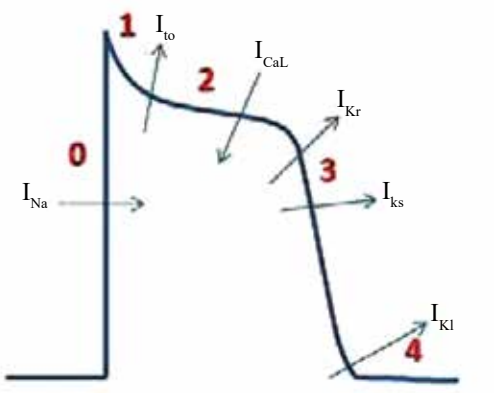

Fig. 2. Action potential and transmembrane ion currents

A decrease in repolarizing outward K^+ currents (mainly I_{Ks}, I_{Kr}, I_{K1}) or an increase in depolarizing inward Na^+ or Ca^{2+} currents (mainly I_{Na} and I_{Ca}) in cells can lead to lengthening of the QT interval, which is a pathophysiological substrate for LQTS [23, 24]. The QT interval duration primarily depends on the cardiac cycle duration. Therefore, to assess this interval, the Bazett formula is used and the term “corrected QT”

or "QTc" is introduced [21]. The Bazett formula has been repeatedly criticized. However, other calculation methods such as Framingham, Fredericia, and Hodges formulas have not become widespread [25, 26].

Prolonged QTc, defined as a QTc value > 450 ms in men and > 460 m in women in lead II or V5 on a standard 12-lead ECG, predisposes to functional re-entry, torsades de pointes form of ventricular tachycardia, and SCD. Otherwise unexplained, baseline QTc ≥ 500 ms should be associated with inherited LQTS. In addition, a drastic increase in QTc (ΔQTc > 60 ms) indicates an increased risk of torsades de pointes form of ventricular tachycardia / SCD in drug-induced LQTS [21].

LQTS is the most common hereditary ion channelopathy characterized by a prolonged QT interval on a 12-lead electrocardiogram and an increased risk of malignant arrhythmias in patients without structural heart disease [27, 28]. Clinical symptoms of LQTS include palpitations, syncope, and convulsions, more often as a consequence of torsades de pointes form of adrenergic tachycardia [29].

LQTS can be diagnosed if the following criteria are met (HRS / EHRA / APHRS, 2013):

1) The risk of LQTS is > 3.5 points on the Schwartz scale and there are no secondary causes of QT interval prolongation;

2) A characteristic pathogenic mutation in one of the LQTS genes;

3) QTc interval according to Bazett formula ≥ 500 ms on repeated 12-lead ECGs and no secondary causes of QT interval prolongation.

However, already in 2015, the updated LQTS criteria were published in the clinical guidelines of the European Society of Cardiology, which used QTc values ≥ 480 ms or a risk assessment on the scale of more than 3 points [30]. As mentioned above, genetic screening plays a key role in the LQTS diagnosis, which makes it possible to identify a pathogenic mutation and determine a further patient management strategy. Currently, there are 17 different LQTS subtypes associated with monogenic mutations in 15 autosomal dominant genes (Table) [29].

Table

The main LQTS subtypes according to P.J. Schwartz et al. [31]

LQTS type	Gene	Locus	Mutation frequency among LQTS cases (%)	Effect
LQT1	*KCNQ1*	11p15.5	40–55	$\downarrow K_{v7.1}$
LQT2	*KCNH2*	7q35–36	30–45	$\downarrow K_{v11.1}$
LQT3	*SCN5A*	3p21–24	< 1	$\downarrow Na_{v1.5}$
LQT4	*ANKB*	4q25–27	< 1	↓Ankyrin B
LQT5	*KCNE1*	21q22.1	< 1	↓MinK
LQT6	*KCNE2*	21q22.1	< 1	↓MiRP1
LQT7	*KCNJ2*	17q23	< 1	↓Kir2.1
LQT8	*CACNA1C*	12p13.3	< 1	↑L-type calcium channel
LQT9	*CAV3*	3p25	< 1	↓Caveolin 3
LQT10	*SCN4B*	11q23.3	< 1	↓Sodium channel – β4
LQT11	*AKAP9*	7q21–22	< 1	↓Yotiao
LQT12	*SNTA1*	20q11.2	< 1	↓Syntrophin α1
LQT13	*KCNJ5*	11q24	< 1	↓Kir3.4
LQT14	*CALM1*	14q32.11	< 1	Calmodulin 1 (dysfunctional Ca^{2+} signaling)
LQT15	*CALM2*	2p21	< 1	Calmodulin 2 (dysfunctional Ca^{2+} signaling)
JLN1	KCNQ1	11p15.5	< 1	$\downarrow K_{v7.1}$
JLN2	KCNE1	21q22.1–22.2	< 1	↓MinK

Causal gene mutations are detected in approximately 70% of patients with LQTS [32]. Approximately 75% of all pathogenic variants are found in the genes *KNCQ1, KCNH2,* and *SCN5A*, which are responsible for the LQTS 1–3 subtypes in patients with the Schwarz.scale score of ≥ 4, while in 25% of cases, the genotype remains unidentified after extensive genetic testing based on various panels [27, 33, 34]. It is possible that a small proportion of patients with genotype-negative LQTS may have an as yet unknown Mendelian disorder, but the existence of a different, more complex inheritance pattern in this subgroup cannot be denied (Fig. 3).

Thus, a genome-wide association study (GWAS) comparing cases of rare arrhythmia syndrome with a control group has shown that it can identify mod-

current, I_{Kr} current. LQT2 mutations in the hERG potassium channel entail amplitude reductions; they are loss-of-function mutations that decrease I_{Kr} amplitudes and prolong repolarization. On the electrocardiogram, it is recorded in the form of a bifurcated or notched T wave, which has low amplitude and is asymmetric. Potential triggers include emotional stress. A more aggressive phenotype is observed in patients with mutations in the pore region (S5–loop–S6).

LQT3 is caused by mutations in the *SCN5A* gene located at position 3p21–24. The *SCN5A* gene encodes $Na_V1.5$, an α-subunit of the voltage-dependent Na^+

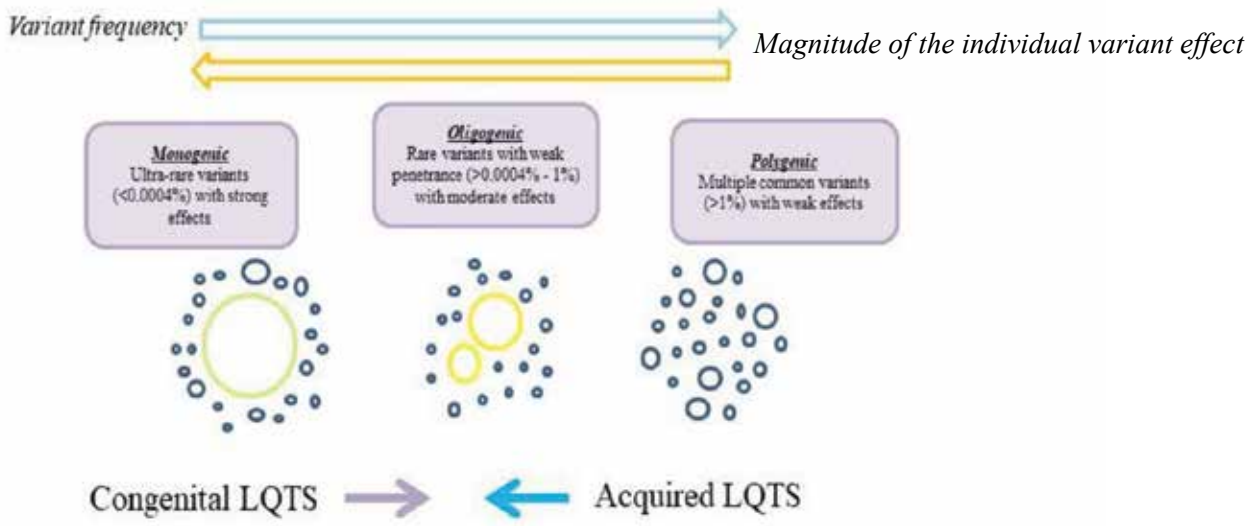

Fig. 3. Genetic models underlying acquired and congenital forms of long QT syndrome.

ulators of susceptibility to the disease and suggest its polygenic etiology. In their case-control study, N. Lahrouchi et al. identified the important role of common genetic variation in LQTS susceptibility and confirmed the complex (polygenic) architecture of genotype-negative LQTS, which was consistent with an earlier publication by J.R. Giudicessi et al. [34, 35].

For LQT1–3, the phenotype – genotype correlation is evident. In about 85% of LQTS cases, a patient with a positive genotype carries a mutation inherited from one of the parents, and in the remaining 15%, a *de novo* mutation is appropriate. Approximately 50% of patients with the LQTS genotype are asymptomatic throughout their lives, while 10–50% of these patients do not show any obvious prolongation of the QT interval. Complex mutations (≥ 2 mutations) are found in 10% of patients with a positive genotype. As a rule, the clinical manifestations of the disease in such patients are more severe [33].

LQT1 is the most common subtype and is verified in > 40% of individuals with LQTS. The main substrate is the loss of / decrease in the function of the *KCNQ1* gene located at the 11p15.5 locus, encoding the α-subunit of the voltage-gated potassium channel, K_V 7.1. K_V 7.1 consists of 4 α-subunits, which, together with the β-subunits of KCNE1, generate a slowly activated delayed rectifier potassium current (I_{Ks}). I_{Ks} physiologically increases due to sympathetic influences in order to adapt the QT interval to a certain heart rate (HR). With a decrease in I_{Ks}, the QT interval is not shortened, which leads to the development of arrhythmia. On the electrocardiogram of a patient with LQT1, a wide and symmetrical T wave is recorded against the background of a prolonged QTc interval. Accordingly, the main trigger for syncope or SCD in LQT1 is exercise. The incidence of life-threatening events is the lowest in LQT1 compared with LQT2 or LQT3. Heterozygous KCNQ1 mutations cause dominant Romano – Ward syndrome of LQT1 and are the most common LQTS genotype. Homozygous mutations in KCNQ1 or complex heterozygous mutations can cause autosomal recessive Jervell and Lange – Nielsen syndrome.

LQT2 is the second most common subtype, affecting 30% of individuals with LQTS. LQT2 is caused by mutations in the *KCNH2* or *hERG* gene located at position 7p35–36, which encodes voltage-gated pores that form the α-subunit of the K_V 11.1 potassium channel. α-subunits form a complex with the transmembrane protein KCNE2, homologous to KCNE1, thereby generating a fast component of the delayed rectifier

channel and a mediator of the I_{Na} depolarizing current. Mutations in this gene, present in 10% of genetically diagnosed LQTS patients, increase the duration of the action potential plateau phase by increasing late depolarizing currents. The trigger for this subtype is sleep (bradycardia). On the electrocardiogram, LQT3 is recorded as a prolonged isoelectric interval and a relatively normal T wave.

Another 6 relatively rare forms of LQTS are associated with a defect in ion channels due to mutations in the corresponding genes:

– *KCNE1* (LQT5) encodes the β1 subunit of the voltage-gated potassium channel K_V 7.1; participates in the generation of current I_{Ks};

– *KCNE2* (LQT6) encodes the β2 subunit of the voltage-gated potassium channel K_V11.1; participates in the generation of current I_{Kr};

– *KCNJ2* (LQT7 or Andersen – Tawil syndrome) encodes the Kir2.1 potassium channel as the mediator of the inward rectifier current, I_{Kl};

– *CACNA1* (LQT8 or Timothy syndrome) – α1C-subunit of the voltage-gated Ca^{2+} L-type channel, Ca_V1.2, the defect of which increases the inward depolarizing calcium current and leads to prolongation of the action potential plateau phase and a prolonged QT interval;

– *SCN4B* (LQT10) encodes the β4 subunit of voltage-gated Na_V 1.5;

– *KCNJ5* (LQT13) is responsible for the work of the potassium channel, Kir3.4, which is activated by the G-protein.

The following three rare forms of LQTS include causal genes encoding adapter proteins that bind the cell membrane to the cytoskeleton:

– *ANK2* (LQT4) – ankyrin-2, which coordinates the work of Na^+ / K^+-ATPase, Na^+ / Ca^{2+-} exchanger and inositol triphosphate receptor, which leads to abnormal restoration of the initial state of ions;

– *CAV3* (LQT9) – caveolin-3, which regulates ion channels in caveolae, including membrane expression of Na_V1.5 / Kir2.1;

– *SNTA1* (LQT12), encoding α-syntropin, which binds Na_V1.5 channels to the NOS-PMCA4b complex.

Other rare genes of LQTS subtypes are associated with kinase activity, such as *AKAP9* (LQT11), encoding binding of the kinase-9 anchor protein A to the protein kinase A regulatory subunit, resulting in a decrease in I_{Ks}; *CALM1* (LQT14), *CALM2* (LQT15), and *CALM3* (LQT16) are responsible for the calmodulin protein, an important intracellular Ca^{2+} sensor that transmits a signal and modulates Ca_V1.2. A mutation in one of the three genes, even when heterozygous, is sufficient to result in an early and severe form of LQTS with an extremely long QTc interval. A mutation in the *TRDN* gene encoding the triadin protein, known as a regulator of RyR receptors and Ca_V1.2 calcium channels, also increases I_{CaL}. Mutations of two more genes, *TRPM4* and *RYR2,* in individuals with LQTS are mentioned in the literature; their mechanisms of influence require further study [23–35].

SHORT QT SYNDROME

Short QT syndrome (SQTS) is a rare, inherited, autosomal dominant cardiac channelopathy associated with malignant ventricular and atrial arrhythmias. The syndrome was first described in 2000 by Gussak et al. as an inherited disease, when idiopathic persistently short QT intervals were recorded in 4 members of the same family on an electrocardiogram. In the future, the goal of many studies was to search for diagnostic criteria. In 2011, Gollob et al. proposed SQTS criteria based on 4 components, including electrocardiographic data, medical history, family history and genotype.

Genetic testing only detects a causal mutation in < 25% of SQTS cases. According to O. Campuzano et al., no more than 200 cases have been diagnosed worldwide; accordingly, the prevalence of SQTS is estimated at 0.02–0.1% [36, 37]. Currently, according to the European Society of Cardiology 2015 clinical guidelines, the clinical diagnosis of SQTS can be made with a decrease in QTc duration ≤ 340 ms and should be considered at QTc values ≤ 360 ms if one or more of the following criteria are met: a confirmed pathogenic mutation; cases of SQTS detection in the family; family history of sudden cardiac death at the age of < 40; a history of syncope of unknown origin or documented ventricular tachycardia / ventricular fibrillation in the absence of structural heart disease [30].

The pathogenetic mechanisms of SQTS are associated with abnormalities of the heart ion channels that regulate the action potential in cardiomyocytes, affecting the duration of repolarization. Major mutations are associated with increased function in voltage-gated potassium channel subunits (KCNH2, KCNQ1, KCNJ2) and decreased / lost function of voltage-gated calcium channels (CACNA1C, CACNB2B, and CACNA2D).

Analysis of 32 gene variants described in the literature showed that only 9 of them (28.12%) have a decisive pathogenic role. All definitively pathogenic variants are located in KCNQ1, KCNH2 or KCNJ2, encoding potassium channels. Other variants, located

in the genes encoding calcium or sodium channels, are associated with electrical disturbances accompanied by shortened QT intervals, but do not guarantee the development of SQTS.

The only previously known pathogenic variant of CACNA2D1, p. (Ser755Thr), associated with a BrS-like phenotype and a short QT interval, was considered by O. Campuzano et al. as a variant with an ambiguous effect on the phenotype, as it did not show significant changes in ionic current. In the *KCNH2* gene, only four variants play a definitely pathogenic role: p. (Asn588Lys) c. (1764C > A), p. (Asn588Lys) c. (1764C > G), p. (Thr618Ile), and p. (Ile560Thr); 3 variants, p. (Glu50Asp), p. (Ser631Ala), and p. (Trp-927Gly), were classified as likely pathogenic due to a lack of functional data. Two more options in *KCNH2*, p. (Arg1135His) and p. (Arg164Cys), remain indeterminate as both were identified in patients with Brugada syndrome and a shortened QT interval but were not consistent enough with the SQTS diagnosis.

Of the three *KCNJ2* variants associated with SQTS, all three, p. (Met301Lys), p. (Glu299Val), and p. (Asp172Asn), are classified as pathogenic, the negative role of which is confirmed by all currently published data. In *KCNQ1,* one variant, p. (Val307Leu), remains classified as pathogenic, while the variant p. (Phe279Ile) is currently classified as likely pathogenic. Finally, the potentially pathogenic variant p. (Arg370His), found in the *SLC4A3* gene, suggests an association of a new gene with SQTS and represents a previously underestimated mechanism for the development of malignant arrhythmia [37].

There are 8 subtypes of SQTS, SQT 1–8, the development of which is based on the following mechanisms:

1) SQT1, is associated with mutations in the *KCNH2* / *hERG* gene, the role and mutations of which were described above. The hERG channels are uniquely rapidly inactivated depending on the voltage, which promotes a certain contribution of the I_{Kr} current to ventricular repolarization. The linker region of the hERG S5 pore plays a role in inactivating the hERG current. Mutations are mainly associated with a shift in the inactivation peak depending on voltage and an increase in the I_{Kr} current, which leads to a decrease in duration of the QT interval, which is electrophysiologically a substrate both for atrial fibrillation / flutter and for ventricular tachycardia / ventricular fibrillation.

2) SQT2 is caused by mutations in the *KCNQ1* gene, the product of which, together with KCNE1, forms functional proteins, affecting the I_{Ks} current. Mutations in the gene lead to rapid activation or delayed inactivation of potassium channels, which are often the cause of accelerated ventricular repolarization.

3) SQT3 is the result of mutations in the *KCNJ2* gene encoding the Kir2.1 protein, the function enhancement of which affects the duration of the final part of the action potential repolarization.

4) SQT4 and SQT5 include mutations in the *CACNA1C* and *CACNB2b* genes encoding the α1C and β2 subunits of L-type voltage-gated calcium channels that provide the I_{Ca} current. Mutations in *CACNA1C* have been identified as shortening the action potential by slowing down the movement of the α1C subunit towards the membrane. A mutation in *CACNB2b* drastically reduces I_{CaL} without affecting the speed of subunit movement. Both mutations, by decreasing internal I_{Ca} currents, cause transmural and epicardial dispersion of repolarization, resulting in SQTS combined with Brugada syndrome.

5) SQT6 is caused by a mutation in the *CACNA2D1* gene encoding the α2δ1 subunit of L-type voltage-gated calcium channels. The proposed mechanism for reducing I_{CaL} currents through $Ca_V1.2$ turned out to be doubtful, since it was not possible to register shortening of the QT interval in genotype-positive relatives.

6) SQT7 is associated with mutations in the *SCN5A* gene, which encodes the α-subunit of sodium channels, affecting late sodium current, the loss of function of which can affect both depolarization and repolarization. The *R689H* mutation increases late sodium flow, which raises doubts about its isolated effect on the SQT phenotype.

7) SQT8 is associated with mutations in the *SLC4A3* gene, which encodes the AE3 protein, which facilitates transport of Cl^- ions into cardiomyocytes in exchange for HCO_3 transport. According to a number of authors, p.(Arg370His) in the gene should be attributed to a likely pathogenic variant, which leads to a decrease in metabolism and an increase in pH, which induces shortening of the QT interval [23, 37–39].

Conducting a number of genetic studies, including case-control studies using the polymerase chain reaction method, studies using next generation sequencing methods, and genomic association studies, made it possible to identify and study a large number of polymorphisms of known genes that affect the QT interval variability, thereby showing their importance in risk stratification of sudden arrhythmogenic death.

In the course of a meta-analysis, involving 13,685 individuals of European descent from three prospective cohort studies, the Framingham Heart Study (FHS, n = 7,650), the Rotterdam Study (RS, n = 4,606), and the Cardiovascular Health Study (CHS, n = 1,429), C. Newton-Cheh et al. found an association of single-nucleotide polymorphisms (SNPs) of the known genes *NOS1AP* (rs12143842, rs12029454, rs16857031), *KCNQ1* (rs2074238, rs12576239), *KCNE1* (rs1805128), *KCNH2* (rs4725982, rs2968864), and *SCN5A* (rs12053903), which are involved in cardiomyocyte repolarization, with the QT interval duration. Associations at five new loci included 16q21 near *NDRG4* and *GINS3*, 6q22 near *PLN* (rs11756438), 1p36 near *RNF207*, 16p13 near *LITAF*, and 17q12 near *LIG3* and *RIFFL*. Collectively, 14 independent variants at 10 loci accounted for 5.4–6.5% of the QT interval variations [40].

Continuing the search for pathogenic variants in individual cohorts, based on the New Zealand Cardiac Inherited Disease Registry, in 273 patients with LQTS, 4 out of 29 SNPs associated with an increased risk of cardiac events were identified, *NOS1AP* (rs12143842, rs16847548) and *KCNQ1* (rs0798, rs8234). Patients homozygous for the risk allele rs12143842 had an increased risk of sudden cardiac death (odds ratio (-OR) = 10.15; 95% confidence interval (CI) 2.38–43.34, p = 0.045). Several other SNPs showed tendencies toward associations with QT interval duration and clinical events [41].

In a recent GWAS case-control study, separately for the European (1,238 cases vs. 8,219 controls) and Japanese populations (418 cases vs. 1,617 controls), three statistically significant polymorphisms were found: rs12143842 (OR = 1.32; 95% CI 1.21–1.42; $p = 1.09 \times 10^{-11}$), rs179405 (OR = 1.38; 95% CI 1.23–1.54; $p = 1.92 \times 10^{-8}$) in the KCNQ1 intron; and rs17061696 (OR = 1.25; 95% CI 1.15–1.35; $p = 4.33 \times 10^{-8}$) in the KLF12 intron. All 3 loci were previously associated with the QT interval duration, a marker of myocardial repolarization on the electrocardiogram, in the general population. The low-frequency missense variant in *KCNE1*, p.Asp85Asn (rs1805128, OR = 2.78; 95% CI 1.67–3.90; $p = 5.31 \times 10^{-7}$), reached the expected threshold of statistical significance in the European population and had a more pronounced effect in polygenic inheritance of genetically elusive LQTS variants (OR = 7.64; 95% CI 3.66–15.95; $p = 5.99 \times 10^{-8}$) [34].

In 2007, in a population-based study carried out in a cohort of 2,008 apparently healthy subjects, 200 of which had the shortest QT interval and 200 people – the longest, the known variants of the *KCNH2*, *SCN5A*, *KCNQ1*, *KCNE1*, and *KCNE2* genes were analyzed. The minor allele *SCN5A* IVS24 + 116 "A" was more common in the group with the shortest QTc, while the minor alleles *KCNQ1* rs757092 "G" and *KCNH2* rs3815459 "A" were more common in the group with the longest QTc. There were no significant differences for *KCNE1* IVS2–128 G > A and *KCNE2* rs2234916 between the two groups. A genotype analysis showed a twofold increase in the risk of QTc prolongation for carriers of the genotype combining the "C" and "A" alleles of the 2 *KCNE1* SNPs, IVS2–129 C > T (rs2236609) and rs1805127 (G38S), respectively [42]. In the work by S.F. Qureshi et al., the AA genotype and the "A" allele rs1805124 in the *SCN5A* gene were more frequent in patients with LQTS compared with the control group (OR = 2.43; 95% CI of 1.23–4.79, p = 0.01), which indicates its role in the LQTS etiology [43]. In the publication by N.A. Bihlmeyer et al., there are already about 45 single nucleotide variants (SNVs) associated with ventricular repolarization, 10 of which were previously unknown [44].

CONCLUSION

A significant proportion of SCD cases in young people is associated with primary arrhythmia syndrome. Considering the electrical instability in the myocardium as one of the main reasons for the development of life-threatening arrhythmias (ventricular tachycardia / ventricular fibrillation) and SCD, one should be aware of such provoking factors as coronary heart disease, myocarditis, valvular heart disease, pharmacological influences, cardiomyopathy, and channelopathy. It is known that an increase or decrease in the duration of the QT interval, which reflects the work of ion channels and the processes of ventricular depolarization and repolarization, increases the risk of SCD.

Along with diagnosis and treatment strategies, one of the objectives of genetic testing for arrhythmia syndromes is to improve prediction of a risk of adverse events in each individual patient based on their own genotype. Therefore, the study of the relationship of molecular genetic markers with the QT interval duration contributes to better understanding of the pathophysiological mechanisms, correct choice of management strategy, and prevention and treatment of the patient, reducing the likelihood of SCD. The predictive value of genetic testing is the highest for LQTS, for which a gene-specific risk profile has been established, and to a lesser extent for other channel-

opathies. The large amount of genetic data may be a promising approach to quantifying the risk of SCD, especially at a young age, which is facilitated by further study of this problem.

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