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Genetic diagnostics in cardiology: Impact of heredity on risk of developing cardiovascular disease

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SOUHRN

Genetické aspekty vzniku kardiovaskulárních onemocnění jsou důležité kvůli jejich významnému přínosu k celkové struktuře srdeční patologie a rozšíření diagnostických možností molekulárních technologií. Cílem studie bylo systematizovat současné znalosti o roli dědičných faktorů ve vývoji kardiovaskulárních patologií a posoudit klinickou účinnost genetických metod pro jejich diagnostiku. Po uplatnění kritérií pro zařazení a vyloučení zahrnoval přehled literatury 60 vědeckých studií. Analýza prokázala, že primární a sekundární strukturální poškození myokardu, srdeční arytmie a aterosklerotické komplikace jsou často způsobeny komplexními polygenními interakcemi spíše než jednotlivými monogenními defekty. Dědičné formy kardiomyopatií jsou spojeny s variacemi v genech sarkomerních a cytoskeletálních proteinů, přičemž klinické projevy se liší v závislosti na přítomnosti dalších modifikujících polymorfismů. Poruchy srdečního rytmu, jako je syndrom dlouhého a krátkého QT, syndrom Brugadových a katecholaminergní polymorfní tachykardie, vykazují vysokou genetickou heterogenitu a neúplnou penetranci. Geneticky determinované hodnoty lipoproteinu(a) (Lp(a)) jsou podstatné v patogenezi nejen aterosklerózy, ale i mnoha dalších onemocnění postihujících kardiovaskulární systém, souvisejících s polymorfismy lokusu Lp(a) na chromosomu 6q27 a ovlivňujících riziko trombotických komplikací. Navzdory prokázané účinnosti metod panelového a exomového sekvenování při identifikaci genetické predispozice je jejich klinické využití omezeno vysokými náklady a nedostatkem jednotných interpretačních kritérií, což omezuje možnost hromadného screeningu a personalizovaného přístupu k léčbě pacientů.

Keywords:
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ABSTRACT

The genetic aspects of cardiovascular disease formation are of relevance due to their significant contribution to the overall structure of cardiac pathology and the expansion of the diagnostic capabilities of molecular technologies. The study aimed to systematise current knowledge about the role of hereditary factors in the development of cardiovascular pathologies and to assess the clinical efficacy of genetic methods for their diagnosis. The literature review, after implementing the inclusion and exclusion criteria, included 60 scientific studies. The analysis demonstrated that primary and secondary structural myocardial damage, cardiac arrhythmias and atherosclerotic complications are often caused by complex polygenic interactions rather than single monogenic defects. Hereditary forms of cardiomyopathies are associated with variations in sarcomeric and cytoskeletal protein genes, with clinical manifestations varying depending on the presence of additional modifying polymorphisms. Cardiac rhythm disorders, such as long and short QT syndrome, Brugada syndrome and catecholaminergic polymorphic tachycardia, demonstrate high genetic heterogeneity and incomplete penetrance. Genetically determined levels of lipoprotein(a) (Lp(a)) are substantial in the pathogenesis of not only atherosclerosis but also many other diseases affecting the cardiovascular system, associated with polymorphisms of the *LPA* gene on chromosome 6q27 and influencing the risk of thrombotic complications. Despite the proven effectiveness of panel and exome sequencing methods in identifying genetic predisposition, their clinical implementation is constrained by high costs and the lack of unified interpretation criteria, which limits the possibility of mass screening and a personalised approach to patient management.

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Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality and disability in most developed countries, with modern research increasingly pointing to a significant contribution from genetic factors, even in cases where environmental or metabolic origins have long prevailed. External factors like obesity, hypertension, alcohol consumption, and lifestyle habits can amplify or mitigate the genetic predisposition to cardiovascular disease (CVD), they can worsen these genetic risks. For instance, obesity can exacerbate genetic susceptibility to heart disease, meanwhile hypertension can trigger heart damage in genetically vulnerable individuals. It highlights the need for a comprehensive approach to cardiovascular risk assessment that considers both genetics and lifestyle factors. The availability of next-generation sequencing methods, the expansion of representative epidemiological samples and the improvement of bioinformatics algorithms have greatly facilitated the search for and analysis of rare and common genetic variants that determine varying degrees of susceptibility to CVD, from hypertension and coronary heart disease to various forms of cardiomyopathy and arrhythmias.

As indicated by Townsend et al.,[1] epidemiological data in several European countries show that in approximately 30% of cases, genetic mutations or polymorphisms are detected in a group of patients with severe cardiac complications capable of increasing the risk of early heart failure (HF) or life-threatening arrhythmias to varying degrees. At the same time, as mentioned by Zhao,[2] several Asian regions have a higher prevalence of certain rare genetic variants, including mutations associated with lipid metabolism and endothelial function disorders, which affect age-related morbidity rates and the overall prognosis for coronary complications. These observations emphasise that the role of hereditary factors in populations needs to be completely reassessed, addressing ethnic and socio-economic differences, and confirm the need for targeted screening programmes.

As highlighted by Yadav et al.,[3] the contribution of heredity to the formation of some forms of hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) can exceed 50%, while in some cases associated with primary channelopathies, the presence of a pathogenic mutation is not always accompanied by a pronounced phenotype (incomplete penetrance), which leads to the presence of a wide cohort of carriers of defective genes. This heterogeneity in the clinical picture is explained by complex interactions between specific genes that affect the electrophysiological properties of the heart, vascular tone, and metabolic chains. The individual combination of such variants can either increase or decrease the overall risks, which stimulates interest in identifying subclinical carriers and expanding diagnostic protocols.

Genetic diagnostics is a hot topic in the scientific community as Schultheiss et al.[4], Ahmad et al.[5] and Mio et al.[6] write, the systematic introduction of panel testing and exome sequencing in cardiology opens new opportunities for both more accurate individual prognosis and preventive measures in families with a history of early cardiac death or severe forms of cardiomyopathy. The widespread implementation of these methods in clinical practice is significantly limited by economic barriers. As highlighted by Grosse and Gudgeon,[7] a significant share of the cost of exome analysis is made up of interpretation costs, infrastructure and qualified personnel, and list prices often do not reflect the actual cost of the study. Moreover, as noted by Addissouky et al.,[8] access to the genetic technologies (including pharmacogenomics and precision medicine) in actual practice remains limited due to uneven distribution of resources, lack of compensation mechanisms, and low awareness among primary care professionals.

A common shortcoming of current research, regardless of country or methodology, is that most projects focus on a single group of disorders (e.g., channelopathies) or single genes (e.g., *SCN5A*, *KCNQ1*), without considering the complex polygenic contribution. In addition, scattered data is not always suitable for a systematic assessment of the role of environmental factors (diet, comorbidities, lifestyle) that potentiate or attenuate the effect of heritable variants. Often, the statistical characterisation of the series under study is insufficient, especially when analysing rare mutations, and this makes it difficult to formulate reliable recommendations for the general population.

The study aimed to systematise current research on the role of hereditary factors in the development of CVDs and to assess the potential of molecular genetic methods in clinical cardiology. To achieve this goal, the following tasks were set in the review: to analyse the current literature on the molecular mechanisms of inheritance of various forms of cardiomyopathies and primary arrhythmias; to characterise the features of the pleiotropic and polygenic influence of genetic variants on the phenotypic manifestations of diseases; to consider modern methods of genetic diagnosis and their prognostic significance; and to identify the main limitations and prospects for the integration of genetic data into the system of personalised medicine and prevention.

Materials and methods

The design of the present study is a targeted (narrative) literature review aimed to summarise and analytically interpret current scientific data on genetic predisposition to CVD, with a focus on molecular mechanisms, diagnostic approaches, and prospects for clinical application of personalised medicine in cardiology. In this study, to obtain a comprehensive view of the current theoretical and empirical data on the problem under study, a literature review was conducted. It included peer-reviewed scientific articles, monographs, conference proceedings, dissertations, and official documents. Publications from 2015 to 2024 were used to cover the most up-to-date data and approaches. Sources were selected based on their scientific relevance and availability of the full text, as well as on a preliminary analysis of abstracts and key findings.

Initially, a search plan was developed for several international and national databases, including Scopus and Web of Science. Additionally, Google Scholar was used to refine the list of references, providing free access to

several publications. This strategy expanded the coverage of potentially relevant materials, minimising the risk of missing relevant research. When forming search queries, logical operators ("AND", "OR", "NOT") were used to combine terms that reflect the essence of the problem under study.

The keywords and phrases were identified based on an analysis of terms frequently encountered in contemporary papers and included several thematic groups. The first group covered the main research issues and included terms such as "exome sequencing in cardiology", "polygenic interactions in arrhythmia development", "genetic predisposition to CVDs", "hereditary risk factors for atherosclerosis", "genetic markers of heart failure", and "molecular genetic diagnostics of cardiomyopathies". The second group was related to methodological aspects such as "experimental design", "statistical analysis" and "data quality". The third group reflected contextual and regional specifics. This multi-level system of keywords fine-tuned search and prioritised the most relevant aspects of the topic.

A multi-stage selection process was used to objectively assess the relevance of the publications found. The first stage involved analysing titles and abstracts (title/abstract screening), which removed irrelevant papers and duplicates. The second stage was reading the full text of the articles, which assessed the quality of the methodology and statistical tools used, as well as the relevance of the research objectives to the stated results. Sources were excluded if they contained methodological inaccuracies, insufficient evidence of conclusions or contradictory interpretation of data.

As a result, more than 100 of the 250 initially selected papers were excluded due to duplication or non-compliance with quality criteria. The final pool of 60 articles formed the basis of the analysis, ensuring the breadth of coverage and methodological reliability of the data obtained. This approach to the formation of the database collected the most relevant and high-quality materials reflecting current trends and prospects for further research on the stated topic. This provided additional verification of the reliability and reproducibility of the results presented in the publications. Finally, each article was subjected to a final critical analysis for compliance with generally accepted standards of scientific reporting and research transparency.

Results and discussion

Hereditary CVD: Evolution of views

Modern research in the field of genetic predisposition to CVD is largely based on the Human Genome Project and the experience of using high-throughput DNA sequencing technologies, which have significantly changed the notion of this aspect of cardiology.[9] Early hypotheses regarding the heredity of primary diseases such as cardiomyopathy suggested that most of these pathologies have a strictly monogenic basis: a single mutation in a "master" gene directly leads to a particular disease, such as HCM or DCM. However, as more genetic studies have been carried out, increased evidence has been found that the classic "one gene, one disease" scheme does not reflect the complexity of the actual molecular mechanisms of heart disease. Thus, it was discovered that several cardiomyopathies are formed with the participation of several genetic loci, from rare variants with a moderate effect (low-frequency, rare variants) to common, but "small" in terms of the strength of the effect of associated single nucleotide polymorphisms (SNPs); also, many "structural" genes or "channel" genes can exhibit pleiotropy, leading to diverse phenotypes affecting not only the myocardium but also the arterial system, connective tissue, and sometimes other organs as part of complex syndromes.[10]

An example of this kind of evolution of views is HCM, which was initially considered a typical example of a classical monogenic hereditary pathology. Studies in the early 1990s suggested that HCM was associated with mutations in sarcomeric protein genes (*MYH7*, *MYBPC3*, etc.).[11,12] It was assumed that in patients with a confirmed mutation in *MYH7*, encoding the heavy chain of beta-myosin, the form of cardiomyopathy was supposed to be explained by this single cause. However, a detailed analysis of familial cases of HCM revealed a highly variable degree of hypertrophy, time of onset, and risk of complications (e.g., sudden cardiac death).[13] Some mutation carriers showed an aggressive form of the disease, while relatives with an identical mutation may have minimal symptoms.[14] This led to the assumption that there are additional modifier genes whose variants (including common SNPs) can enhance or attenuate the manifestations of HCM.[15] Subsequently, sequencing of an expanded set of genes and meta-analysis of population data confirmed the association of several SNPs with various forms of cardiomyopathy, and described cases of "overlapping" phenotypes, when a combination of mutations in sarcomeric proteins and regulators of calcium homeostasis leads to more severe hypertrophy or early manifestations.[16]

Another example is DCM, the development of which has been associated mainly with mutations in cytoskeletal proteins (*LMNA*, *TTN*, etc.). *TTN* mutations, especially truncating variants, are quite common in healthy carriers; therefore, a pathogenic *TTN* mutation alone does not always lead to severe DCM. The key factor may be the "load" of additional variants in other genes or the combination of these variants with external influences (e.g., toxic or metabolic). This is confirmed by families in which carriers of the same *TTN* variant have different clinical manifestations: some develop a malignant form of dilatation and progressive HF at a young age, while others remain subclinical for many years.[17] Genetic analyses (including panel and exome sequencing) are increasingly revealing a polygenic basis of DCM in several patients: none of the "major" mutations alone explains the nature of the lesion, but their combination forms a stable predisposition.[18]

In parallel, knowledge about the pleiotropy of genes responsible, among other things, for the development of primary myocardial lesions has been expanding. Classically, it was believed that genes encoding structural elements (sarcomeric, desmosomal, cytoskeletal) exclusively affect the mechanical and morphological features of the myocardium, while "ionic" genes (*SCN5A*, for example) affect only the electrical function.[19,20] However, it has

been found that mutations in the desmosomal protein *PKP2*, which were previously described exclusively in the context of arrhythmogenic cardiomyopathy (ARC), sometimes lead to dilated form or moderate hypertrophy, and the pathology itself can affect the electrophysiological characteristics of the myocardium.[21] The model of *PKP2* pleiotropy is shown in **Table 1**. *SCN5A*, usually associated with conduction disorders, is in some cases associated with severe structural remodelling up to left ventricular dilatation. Thus, the differences in the clinical spectrum often depend not only on the "central" defect, but also on a combination of modifying variations that determine the extent to which cardiac mechanical properties, repolarisation, calcium homeostasis, and ultimately the formation of cardiomyopathy are affected.

From a diagnostic standpoint, the shift from a monogenic to a polygenic approach means that a patient suspected of having a genetically determined CVD often needs to undergo broader genetic screening. Standardised panels already include genes encoding major sarcomeric proteins (*MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*), cytoskeleton (*DES*, *LMNA*, *FLNC*), and extracellular matrix-related genes (*FBN1*, *COL3A1* in certain syndromes).[22] However, it is often necessary to perform exome or whole-genome analysis to identify rare deep variants, insertions/deletions, variations in promoter and enhancer regions (regulatory regions), and to assess the cumulative contribution of SNPs. In family-based analysis, it is possible to perform a Polygenic Risk Score (PRS), which incorporates dozens or hundreds of SNPs that individually have a small effect but in aggregate have a statistically significant impact on the risk of HF, fibrosis, or adverse outcomes.[23] It is equally necessary to consider exogenous factors such as gender, age, comorbidities, and lifestyle. Polymorphisms in genes related to lipid metabolism, inflammatory factors, and ion transport disorders can, in some cases, exacerbate the progression of cardiomyopathy, although without a "substantial" primary mutation in a key structural protein, these polymorphisms rarely lead to severe changes.[24–26]

Thus, the scientific focus is gradually shifting to the concept that most primary CVDs are the result of subtle interactions between a monogenic "core" (the mutation that determines the main cardiomyopathic phenotype) and many additional genetic factors that shape clinical severity and rate of progression. This complicates the task of prediction: even the detection of a mutation in *MYBPC3* does not always mean a severe course, and the absence of pathogenic variants in the baseline panel does not yet exclude a genetic nature. In addition, pleiotropy is also observed: a single mutation can affect several molecular processes, i.e., affect sarcomeric function, ionic regulation, and the extracellular matrix, all of which lead to a variety of phenotypic manifestations.

All the aspects highlight the need to revise diagnostic algorithms: instead of a strict search for "one mutation of one gene", exome/genomic techniques are relevant, along with a multi-level assessment of polygenic risk. The transition to systemic genetics (including transcriptomic, epigenetic, and proteomic analysis) can clarify the complex network of interactions and suggest potential targets for therapy or prevention. This requires a concerted effort: the creation of large international consortia that combine DNA samples from thousands of patients and link specific genetic signatures to detailed clinical pictures. This is the only way to obtain statistically reliable data on rare variants and to compare several "minimally pathogenic" polymorphisms that together cause severe disease.

In practice, this perspective can be used in personalised medicine: specific "vulnerability zones" are identified in individual patients, observation schemes are adjusted, and preventive measures are more actively taken at a young age with a high cumulative genetic load. From a clinical point of view, cell models based on induced pluripotent stem cells (iPSCs) are also useful, being used *in vitro* reproduction of pathological changes in the myocardium (both hypertrophy and dilatation) and selection of individualised drug combinations. However, a real transformation of patient management on a large scale is only possible with the simultaneous development of affordable sequencing technologies, analytical algorithms for polygenic risk, and educational programmes that create awareness among physicians of the importance of comprehensive genetic assessment in cardiomyopathies.

Lipoprotein(a): The genetic basis of metabolic predisposition to CVD

Lipoprotein(a) (Lp(a)) is a unique lipoprotein particle in terms of structure and function, whose role in cardiology is increasingly recognised as critical due to its close association with genetic predisposition to CVD.[27]

Table 1 – The *PKP2* model of pleiotropy[19–21]

PKP2 function	Physiological process	Consequences of dysfunction	Associated diseases	Final phenotype
Integrity of slotted contacts	Electrical communication	Violation of the conduct	Brugada syndrome	Arrhythmias + sudden cardiac death
Sodium channel function	Sodium current	Reduced excitability	Brugada syndrome	Arrhythmias + sudden cardiac death
Cell adhesion	Mechanical integrity of the cell	Impaired contractility and cell death	Dilated cardiomyopathy	Dilated cardiomyopathy / reparative fibrosis
Transcriptional regulation	Calcium homeostasis, metabolic and mechanical regulation	Trigger activity	Catecholaminergic polymorphic ventricular tachycardia	Arrhythmias + sudden cardiac death

Lp(a) is structurally similar to low-density lipoprotein (LDL), as it contains a significant proportion of cholesterol and has a modified apoB100 linked by disulfide bridges to apolipoprotein(a) (apo(a)).[28] The percentage of cholesterol in Lp(a) can reach 45%, and the apo(a) molecule itself contributes 27% to 50% to the total protein composition of this lipoprotein particle. Apo(a) is encoded by the *LPA* gene on chromosome 6q27, has a kringle domain and a protease domain, and the kringles in apo(a) show significant similarity (78-100%) to similar structural elements of plasminogen. However, it is the variability in the number of copies of kringle IV type 2 (KIV2) that is one of the central factors determining both the size of the apo(a) isoform and the level of Lp(a) in the blood: a small number of KIV2 repeats correlates with a higher Lp(a) content, while a longer isoform usually corresponds to a relatively low concentration.[29] Since up to 90% of the variation in Lp(a) levels is due to hereditary factors, genetic studies focused on the *LPA* gene and SNPs confirm a direct causal relationship between elevated Lp(a) concentrations and an increased risk of atherosclerotic events.[30] In parallel, ethnic differences indicate that people of African descent usually have significantly higher Lp(a) than Caucasians or Asians, and Japanese in the Asian cohort often have levels that exceed those of Indians and Chinese. Dietary and environmental factors account for only 10% of Lp(a) levels, which further emphasises the crucial role of heredity.

Studies have shown that Lp(a) increases the probability of development of several cardiovascular conditions, including coronary heart disease, aortic stenosis (AS, AVS), peripheral arterial disease (PAD) and ischaemic stroke.[31] In terms of mechanism, the main contribution of Lp(a) to atherogenesis is explained by its structural similarity to LDL, which helps to carry a significant proportion of cholesterol that causes deposition in the vessel wall. However, no less significant is the presence of apo(a) homology with plasminogen, which leads to competition for binding to fibrin and attenuation of fibrinolysis. Thus, Lp(a) complements the atherosclerotic process both through direct transport of "excess" cholesterol and by increasing thrombotic complications.[32] Thus, the study determined that oxidised phospholipids (OxPL) present in Lp(a) activate the CD36/TLR2 signalling pathway, causing endoplasmic reticulum stress (ERS). Excessive ERS results in the formation of foamy macrophages subject to apoptosis, which leads to the vulnerability of atherosclerotic plaques and increases the risk of acute coronary syndromes.[33] OxPL covalently bound to lysine residues in the K5 fragment of apo(a) has also been found to stimulate the secretion of interleukin-8 (IL-8) by macrophages, thereby creating an additional pro-inflammatory environment in the vascular wall.[34]

Numerous single-nucleotide polymorphisms, such as rs10455872 and rs3798220, are significant. Their presence leads to an increase in Lp(a) and a higher probability of developing CHD, with odds ratios of 1.70 and 1.92, respectively.[35] The more Lp(a) concentration increases, the higher the chance of negative coronary outcomes, and this relationship is robust to adjustments for other risk factors, such as LDL cholesterol. Lp(a) levels above 30 mg/dl have been shown to triple the risk of complications after coronary artery bypass grafting (CABG).[36] People whose Lp(a) values fell into the 90th–95th percentile were almost 90% more likely to have a myocardial infarction (MI), and those above the 95th percentile were 160% more likely to have one. A meta-analysis of 30,000 patients taking statins found that the effect of Lp(a) may be exacerbated by such therapy, increasing the residual risk of atherosclerotic complications.

In addition, several studies have analysed ethnic differences, as the variability of the *LPA* gene largely determines the differences in Lp(a) concentrations between different racial groups. In individuals with familial hypercholesterolaemia (FH), Lp(a) levels are also often elevated, which significantly increases their overall cardiovascular risk. With certain "severe" mutations in LDLR, the level of Lp(a) rises by 30%, and at concentrations above 500 mg/l, the risk of heart attack increases several times. However, it remains unclear how useful it is to consider Lp(a) as part of additional risk stratification in patients with FH.[37,38]

In the context of PAD, individuals with high Lp(a) concentrations, low molecular weight apo(a) phenotypes and the rs10455872 allele have been found to be at higher risk of both symptomatic intermittent claudication and asymptomatic reduction in blood flow (as assessed by ABI). Moreover, Lp(a) can cause calcification of the aortic valve, leading to stenosis (AVS) and, according to the gene association (rs10455872), is associated with a threefold increase in risk in people with Lp(a) >90 mg/dL. OxPL is one of the key mediators that increase inflammation and disrupt valve structure.[39]

The mechanisms of thrombosis at high levels of Lp(a) are explained by the parallel with plasminogen, but in some groups of patients, a reduced probability of major haemorrhage was also found, suggesting a complex balance. Nevertheless, especially in the arterial bed, competition of apo(a) with plasminogen inhibits natural fibrinolysis and increases the risk of arterial thrombosis.[40] For coronary pathology, this may mean more frequent heart attacks and related complications.

Lp(a) is also closely associated with HF; the presence of large isoforms of apo(a), significant accumulation of Lp(a), and concomitant aortic stenosis increase the likelihood of developing HF, partly due to valve and myocardial damage. In Chinese patients, high Lp(a) was found to be associated with an increased incidence of recurrent HF in the setting of pre-existing coronary heart disease. Interesting racial differences have been noted, as a clear correlation is not always found in African Americans, while in Caucasians, this relationship is more evident.[41,42]

Another substantial aspect is the issue of major adverse cardiovascular events (MACE). Elevated Lp(a) levels are an independent predictor of MACE, including myocardial infarction, stroke, and cardiovascular mortality. In patients with severe inflammation (hs-CRP $\geq$2 mg/l), the negative impact of Lp(a) increases.[43] It was found that with a 1 unit increase in logLp(a) and the presence of high hs-CRP, the risk of MACE increases by 13%. Such findings suggest that the combination of genetically determined high levels of Lp(a) and systemic inflammation increases the likelihood of atherosclerotic complications. However, the question

of whether this relationship is valid for individuals with low cardiovascular risk remains unresolved and requires further study.

For instance, Lp(a) is a largely hereditary determinant of CVD risk, where the varying number of copies of KIV2, *LPA* gene SNPs and associated factors (FH, race, LDLR mutations) create pronounced interindividual heterogeneity. Research on the genetic aspect does not demonstrate why some people have abnormally high levels of Lp(a) with relatively good profiles of other lipids but also highlights the prospects for early genetic testing to predict the risk of heart attack, stroke, aortic valve stenosis, and peripheral arterial disease. In the near future, gene therapy, innovative molecules (e.g., inhibitors of apo(a) synthesis) and comprehensive consideration of polymorphisms in *LPA* may help to accurately correct Lp(a) levels, further expanding the toolkit of personalised cardiology.

Molecular genetic basis of heart rhythm disorders

The molecular genetic aspects of inherited cardiac rhythm disorders are being actively studied due to the development of next-generation sequencing and improved methods for functional assessment of ion channels. There are several large groups of such pathologies, including long QT syndrome (LQTS), Brugada syndrome (BrS), short QT syndrome (SQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT).[44] Each of the above nosological forms has characteristic electrocardiographic features, but their underlying cause is largely associated with mutations in genes encoding ion channel proteins or their regulatory subunits. In some cases, the pathogenic variant is detected in classical "channel" genes (*SCN5A*, *KCNH2*, *KCNQ1*, etc.), in other situations, "modifier" genes (*KCNE1*, *KCNE2*, *CACNA1C*, etc.) associated with adaptive or auxiliary functions may be involved.[45,46] Incomplete penetrance of mutations is often noted, and the phenotype itself depends on a combination of genetic and environmental factors.

Long QT syndrome is one of the most studied channelopathies. For the purpose of this study, we use the term channelopathies to refer to genetic disorders caused by mutations in ion channel genes, leading to abnormal ion flow and contributing to arrhythmias, which are the observable electrical disturbances in the heart's rhythm that result from such mutations. Most researchers point to at least 17 genes involved in the development of LQTS (subtypes LQT1–LQT17). LQT1, LQT2 and LQT3 account for most cases (over 90%). LQT1 is usually associated with defects in the *KCNQ1* gene, which encodes the α-subunit of the potassium channel that provides a slowly activated inward rectifying current (IKs). Mutations can affect the pore domain, voltage sensor, or regions required for interaction with β-subunits (*KCNE1*) or an adaptor protein (*AKAP9*). These mutations impair the channel's ability to open fully, decrease ion conductance, and disrupt the assembly of functional subunits, thereby increasing the risk of arrhythmias. The result is insufficient activation of IKs and delayed repolarisation, especially during sympathetic stimulation.[47] This explains the clinical observation that arrhythmias in LQT1 carriers are provoked by stress, exercise, or swimming. Variants in *KCNE1* (LQT5) and *AKAP9* (LQT11) act in a similar way, disrupting the coordinated assembly and regulation of the IKs channel. Mutations in *KCNQ1* can affect the pore domain, voltage sensor, or interaction sites with regulatory β-subunits (such as *KCNE1*), leading to insufficient activation of the IKs current.[48–50] This reduced activation of IKs results in delayed repolarization, particularly during sympathetic stimulation, which can be triggered by stress or physical activity. These mutations impair the channel's ability to open fully, decrease ion conductance, and disrupt the assembly of functional subunits, thereby increasing the risk of arrhythmias.

The LQT2 subtype (*KCNH2*) is associated with a defect in the fast delayed rectifier potassium current (IKr) formed by the hERG protein. The *KCNH2* and *KCNE2* genes are involved in the assembly of this channel, with *KCNE2* encoding a small auxiliary subunit.[51] A decrease in IKr leads to a significant prolongation of repolarisation, and for LQT2, the most typical clinical trigger is a sharp sound stimulus or emotional stress. In contrast, the LQT3 subtype (*SCN5A*) is characterised by an increase in the late sodium current (INa), which causes an additional influx of positive ions in the plateau phase.[52] Mutations in *SCN5A* can lead to a "current window" by delaying the inactivation of the sodium channel. In contrast to *LQT1-LQT2*, LQT3 syndrome more often manifests episodes of arrhythmias during sleep or rest.[53–55] In addition to *SCN5A*, there are several additional sodium channel-related genes (*SCN4B*, *CAV3*, *SNTA1*), mutations in which lead to less frequent subtypes of LQTS (LQT9, LQT10, LQT12).[56] There are also rare forms of LQTS associated with calcium channels

Table 2 – Genes with confirmed pathogenicity involved in the development of LQTS and their mechanisms of action[51,52,56]

Genetic locus	*KCNQ1*	*KCNH2*	*SCN5A*	*CALM1*	*TRDN*	*KCNJ2*	*CACNA1C*
Chromosomal position	11p15.5	7q35-36	3p21-p24	14q32.11	6q22.31	17q24.3	12p13.3
Related syndromes	LQT1, JLNS	LQT2	LQT3	LQT14	LQT17 (TKOS)	LQT7, ATS	TS, LQT8
Encoded protein	Kv7.1 (KCNQ)	Kv11.1 (hERG)	Nav1.5	Calmodulin	Triadin	Kir2.1	Cav1.2
Physiological effects	Reduced IKs	Reduced IKr	Increase in INa1.5	ICa-L amplification	ICa-L amplification	Reduced IK1	ICa-L amplification
Frequency of occurrence	40–55%	30–45%	5–10%	<1%	<1%	<1%	<1%

(*CACNA1C*, *CACNB2*, *CALM1/2/3*, etc.), such as Timothy syndrome (LQT8), calmodulin subtypes (LQT14–16) and cases associated with triadin deficiency (*TRDN*, LQT17).[57] These genes reflect the diversity of pathways involved in the regulation of action potential and contractility. The genes with confirmed pathogenicity involved in the development of LQTS and their mechanisms of action are shown in **Table 2**.

According to current clinical criteria, Brugada syndrome is diagnosed in the presence of a specific ST-segment elevation in the right precordial leads (V_1-V_2, often in the 2nd or 3rd intercostal space).[58] Initially, it was assumed that the loss of Nav1.5 is central in BrS (*SCN5A*) function, which reduces the fast sodium current and changes the balance of depolarisation and repolarisation in the right ventricular outflow tract.[59] However, other genes (*SCN10A*, *SCN1B*, *CACNA1C*, *CACNB2*, *CACNA2D1*, etc.) were also contributing to the pathogenesis. Molecular analysis shows that some patients do not have the pathogenic variant in *SCN5A* at all, which indicates genetic heterogeneity. The diagnosis of BrS in children is rare, but there are observations where high risks of sudden death are recorded as early as 19 years of age. Substantial prognostic factors are the spontaneous form of BrS type 1 on the ECG, syncopal episodes in the history and the presence of pathogenic variants (e.g. c.2131A>T in *SCN5A*).[60] We found that 75% of LQTS cases could be attributed to mutations in genes associated with the LQT1–LQT3 subtypes, while only about 20% of BrS cases were genetically confirmed, with most cases associated with the *SCN5A* mutation.

Short QT syndrome (SQTS) is considered relatively rare and was first described about 20 years ago. Genetic data indicate about 15% of detectable mutations in patients, although the spectrum of genes involved is wide (*KCNQ1*, *KCNH2*, *KCNJ2*, *CACNA1C*, *SLC4A3*, *CACNA2D1*, *CACNB2*, etc.). As a rule, a shortened QT reflects accelerated repolarisation due to excessive potassium currents or a decrease in calcium currents. Mutations in *KCNQ1* (SQT2), *KCNH2* (SQT1) and *KCNJ2* (SQT3) lead to an increase in the corresponding IKr, IKs or IK1 potassium currents, while variants in *CACNA1C*, *CACNB2*, *and CACNA2D1* (SQT5-SQT7) reduce calcium entry, ultimately shortening the action potential and QT interval. It is believed that males may additionally shorten the QT after puberty, increasing the risk of severe arrhythmias. Due to the low prevalence of SQTS, genetic studies are fragmentary, but several pathogenic loci have been identified, including *KCNH2*, *KCNQ1*, and *KCNJ2*.[61]

Catecholaminergic polymorphic ventricular tachycardia is characterised by the occurrence of ventricular arrhythmias under the influence of physical activity or emotional stress in the presence of normal rest. It is caused by mutations in genes that regulate calcium homeostasis in the sarcoplasmic reticulum. The most common cause of CPVT (up to 55% of cases) is defects in *RYR2* (R4496C and others), which encodes a type 2 ryanodine receptor.[62] Impaired control of Ca^{2+} release provokes delayed postdepolarisation and, consequently, polymorphic VEs (ventricular extrasystoles), which develop into dangerous tachycardias. Of patients, 5% have *CASQ2* (calsequestrin-2), in which the disease is autosomal recessive and usually occurs in a particularly severe manner. There are also additional genes *CALM1*, *CALM2*, *CALM3*, *and TRDN* involved in the regulation of the response to β-adrenergic stimulation.[63] Genetic approaches to CPVT therapy (allele-specific silencing, restoration of normal *RYR2* expression) are currently being tested using animal models.[64]

Modern data also describe several other, rarer forms of hereditary supraventricular rhythm disorders, where the contribution of genetic factors is only beginning to be clarified. In the atrioventricular nodal recurrent tachycardia syndrome (AVNRT), mutations in genes associated with sympathetic regulation, sodium/calcium channels, and Purkinje fibre structure are thought to be involved.[65] Although the specific genes responsible for familial AVNRT remain unidentified, next-generation sequencing is increasingly revealing rare variants at *SCN1A*, *SCN2B*, *RYR2*, *ATP2A2* and some other loci in patients with recurrent episodes. It is likely that AVNRT, similarly to many channelopathies, involves a polygenic basis and interacts with autonomic regulation.

Thus, in all these hereditary arrhythmia syndromes (LQTS, BrS, SQTS, CPVT, etc.), a common principle remains genetic heterogeneity, incomplete penetrance, and often multigene character. Currently, genetic testing is recommended in cases of obvious or suspected hereditary arrhythmia to clarify the type of mutation (or several) and determine the risks for families.[66] Most of the known channelopathies follow an autosomal dominant pattern, but autosomal recessive or even X-linked forms are also found. Given the progress of NGS, routine gene panels for LQTS, BrS, SQTS, CPVT or mixed phenotypes contain dozens of key loci, including *SCN5A*, *KCNQ1*, *KCNH2*, *CACNA1C*, *KCNE1/2*, *RYR2*, etc. Nevertheless, some cases remain "mutation-negative", which indicates unexplored regions of the genome (regulatory regions, deep introns, rare structural rearrangements) or the influence of multiple polymorphisms in combination.

Clinical guidelines suggest that, in addition to genetic analysis of the proband, first-line relatives should be screened: some silent carriers may not have a QT interval or ST-elevation potential, but the risk of malignant episodes under certain stressful conditions remains high.[67] In addition, by correctly determining the genetic subtype, it is possible to individualise the approach to treatment: for example, in LQT3, it is advisable to place a wider emphasis on late sodium current blockers (mexiletine or ranolazine), in LQT1, beta-blockade is primarily substantial, and in BrS, implantation of a cardioverter-defibrillator is often discussed to prevent sudden death. In rarer cases (calmodulin forms of LQTS), standard methods may be ineffective, which emphasises the importance of a clear molecular analysis.

Gene therapy remains one of the most promising areas, especially for CPVT, where the possibility of restoring normal *RYR2* function or suppressing the mutant allele using AAV vectors and silencing RNA in animals has already been demonstrated.[68–70] Although the study has not yet progressed beyond the preclinical stage, the results are noteworthy. In an experimental mouse model of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) carrying the heterozygous RYR2 R4496C mutation, researchers delivered a cardiactargeted viral vector expressing a mutantspecific small RNA (miRYR2U10)

to selectively silence the mutant allele via RNA interference (RNAi). Following treatment, the ratio of wildtype to mutant RYR2 mRNA doubled, total RyR2 protein in the heart was only modestly reduced (~15 %), and the intervention abolished adrenergically induced delayed afterdepolarizations, prevented stresstriggered ventricular tachycardia, and reversed ultrastructural abnormalities of calciumrelease units and mitochondria.[71] Similar projects should be expected in the foreseeable future for forms of SQTS and some severe variants of LQTS.

As the use of genetic testing becomes more widespread in clinical cardiology, ethical considerations about genetic privacy, data storage, and informed consent will become increasingly important. Ensuring that patients fully understand the implications of genetic testing, including how their data will be used and stored, is crucial to maintaining ethical standards in genetic medicine.[72–74]

In summary, the genetic basis of hereditary arrhythmias includes a very wide range of loci encoding potassium, sodium, and calcium channels and proteins involved in ion transport or regulatory mechanisms (*RYR2*, *CASQ2*, *AKAP9*, *SNTA1*, etc.). Given that a detailed diagnosis (including the identification of precise mutations) not only explains the phenotype in a particular patient but also provides substantial information about the risks for family members, genetic testing is central to modern cardiology. Even if the mutation has incomplete penetrance, the carrier needs regular monitoring and prevention.

Conclusions

Modern research shows that hereditary CVDs are often complex and polygenic in nature, and as a result, a single mutation does not always explain the full range of clinical manifestations. For example, in cases of LQTS syndrome, genetic defects can be detected in approximately 75% of patients, with more than 90% of the mutations detected being concentrated in the LQT1–LQT3 subtypes. On the other hand, only about 15% of SQTS cases have detectable changes (most commonly in the *KCNH2* and *KCNQ1* genes), and BrS, which is associated mainly with loss of *SCN5A* function, is confirmed by genetic analysis in only 20% of cases. At the same time, *RYR2* mutations are found in about 55% of CPVT cases, and about 5% of *CASQ2* mutations.

An additional target of study is Lp(a), which can contain up to 45% of cholesterol in a particle and is encoded by the *LPA* gene (6q27); an increase in its level correlates with atherosclerosis and thrombosis, indicating the role of not only structural but also metabolic factors. Such heterogeneity confirms that a single "monomutation" cannot explain the entire set of clinical manifestations, so the emphasis is shifting to polygenic combinations, including "modifier" polymorphisms. The latest panel and exome sequencing methods, as well as functional tests (e.g., IKs, IKr, late INa), provide a more systematic risk assessment and adaptation of therapy.

The main limitation of this review is the disparity of primary sources and the lack of a single database, which makes a unified meta-analysis difficult. Due to the pleiotropic effects of several genes and the polygenic nature of many hereditary CVD pathologies, it is advisable to compile a list of analysed loci and use wider genetic panels for a full assessment of genetic risk. This has a significant potential to address the combined contribution of not only the main pathogenic variants, but also modifier polymorphisms that can significantly affect the clinical picture. Such a strategy can help improve the accuracy of diagnosis and create prerequisites for a more targeted correction of therapy, considering the complex nature of the pathology. Further research in this area should focus on the formation of international registries integrating genomic, phenotypic and environmental data, as well as the development of high throughput bioinformatic tools for their clinical application. In addition, it is necessary to study the combined phenotypes of mutations in structural proteins and ion channels, unify diagnostic approaches and functionally validate new genetic variants.

Conflict of interest
All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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