REVIEW

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GENETIC BASIS OF DILATED CARDIOMYOPATHY: RECENT EVIDENCE AND FURTHER CHALLENGES

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Abstract. *Dilated cardiomyopathy (DCM) is a heterogeneous disorder of cardiac muscle leading to a common phenotype, characterized by dilatation of the left or both ventricles and reduced contractile function. This type of cardiomyopathy is the most common, often leading to clinically manifested heart failure and sudden cardiac death. In recent years, a wide range of pathogenic variants in genes related to the pathogenesis of DCM have been identified through genetic studies. There are several major groups of genes involved, depending on the functional belonging and cellular compartmentalization: genes encoding sarcomeric, cytoskeletal, mitochondrial proteins, and the nuclear envelope. A significant portion of the genetic variations leading to DCM is located in the TTN gene, which encodes the large sarcomeric protein titin. Despite advances in next-generation sequencing technologies that facilitate extensive genetic testing in patients with DCM, challenges exist regarding interpreting genetic variants and correlating them with certain phenotypic expression and clinical courses. In addition, epigenetic factors modify the genetic predisposition and complicate clinical presentation, highlighting the complexity of DCM and the need for more detailed study of genotype-phenotype relationships. Future therapeutic directions in DCM emphasize precision medicine approaches, including genome editing technologies, such as CRISPR/Cas9, gene therapy, and pharmacogenomics, that aim to target specific genetic and molecular causes of disease.*

Key words: *dilated cardiomyopathy, genetic basis, personalized medicine*

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INTRODUCTION

Definition and pathophysiology of DCM

Cardiomyopathies represent a large group of primary myocardial diseases that can lead to structural and functional disorders of the heart and are independent of myocardial loading conditions [1]. This type of cardiac muscle disease is heterogeneous and is divided into several major subgroups, depending on the cause of occurrence and how the cardiovascular system is affected: dilated, hypertrophic, and arrhythmogenic cardiomyopathy [2].

Dilated cardiomyopathy (DCM) is a clinical diagnosis characterized by left ventricular or biventricular dilatation. It is characterized by reduced contractile function in the absence of loading conditions that can explain the changes in cardiac structure and function (e.g., arterial hypertension, valvular disease, ischemic heart disease, etc) [3]. Early diagnosis and follow-up of DCM is important, as it may present with a clinical picture of heart failure and/or rhythm pathology, including sudden cardiac death (SCD) [1]. The disease is characterized by extreme heterogeneity in terms of etiology, and its development is attributed to genetic or non-genetic causes, as well as their interaction, which leads to the development of an end pathway common phenotype of dilated dysfunctional cardiac chambers [4]. Genetic factors contribute to about 30-40% of the total occurrence of DCM in patients at risk, with the responsible genes encoding diverse groups of molecules involved in different physiological mechanisms. It has been reported that these genes encode several proteins that are involved in transcription, cytoskeletal and nuclear architecture, sarcomere integrity, and mitochondrial function [5].

Dysfunctional structural proteins are the cause of impaired contractility, progressive dilatation of the cardiac ventricles leading to dilatation of the valve rings, impaired coaptation of the leaflets and secondary failure of the mitral and tricuspid valves of the heart (secondary ventricular valve failure), which worsens haemodynamics and further leads to volumetric burden of the cardiac cavities with their subsequent dilatation, deterioration of haemodynamics and closure of the "vicious circle". This mechanism is associated with a decrease in ejection fraction and an increase in ventricular wall stress and end-systolic volumes [6]. What follows is a decrease in stroke volume (the volume of blood ejected from the left ventricle during each contraction), cardiac output (the amount of blood pumped from the heart per minute), impaired ventricular filling, and an increase in diastolic pressure (the amount of blood in the ventricle during diastole and used as an indicator of ventricular dilatation) [3, 7]. Left ventricular dilatation is associated with changes such as fibrosis and remodeling, whereby its shape changes to spherical [3, 7]. Fibrotic remodelling, along with potential concomitant channelopathies, is the cause of increased risk of rhythm disturbances and sudden cardiac death.

Early mechanisms that are observed in the cardiovascular system to compensate for its malfunctioning are sympathetic stimulation, stimulation of the renin-angiotensin-aldosterone system, and neurohumoral stimulation. This leads to an increase in heart rate and venous return and venous pressure, with a following increase in ventricular filling, due to the Frank-Starling mechanism and to the Treppe phenomenon – compensatory enhancement of the contraction [6]. In the initial phases, these changes have a compensatory effect, but after a certain point (probably genetically or hemodynamically determined), they have a negative, additional damaging effect on the myocardium associated with structural and electrical changes leading to remodeling of the cardiac ventricle [6]. It is yet unclear how much the structural cardiac alterations that take place in the myocardium may also impact the expression of specific genes, changing clinical expression.

Prevalence, classification, and clinic

Dilated cardiomyopathy is one of the most common forms of cardiomyopathy, with an incidence of 1 in 250-400 among people with heart failure [8]. Approximately 5-7 cases of DCM occur per 100,000 people each year, although precise determination of the incidence is difficult due to incomplete penetrance, late presentation of the disease, and an asymptomatic course [9, 10]. According to statistics from a study conducted by Codd et al. in Minnesota, USA, between 1975 and 1984, the prevalence of DCM was higher in males compared to females, with a ratio of 3:1 [11], resulting in gender being a risk factor for the development of the disease. According to the International Society for Heart and Lung Transplantation, DCM is the leading cause of heart failure (HF) and heart transplantation in adults and children [12]. Patients often start exhibiting symptoms of the disease between the ages of 20 and 60 [7]. Dilated cardiomyopathy is the leading cause of death in the pediatric population, accounting for 55% of total cardiomyopathy cases in this group [13]. Compared to adults, children have a far lower incidence of the disease. The Pediatric Cardiomyopathy Registry reports that there are 0.53 incident cases of DCM for every 100,000 children [13]. The main classifications differ: the American Heart Association classifies DCM into several groups: genetic (familial), mixed or acquired, while the European Society of Cardiology divides

DCM into non-genetic (non-familial) and genetic (familial) forms [14, 15]. According to the National Institutes of Health, dilated cardiomyopathy is classified as either primary (idiopathic) or secondary, and a diagnosis of idiopathic DCM requires the exclusion of all secondary causes [16].

A characteristic feature of the clinical course of DCM is the heterogeneity that results from the broad spectrum of genetic and non-genetic factors [17]. The possible phenotypic overlap of different groups within a classification should be considered, e.g., acquired forms of DCM may occur in individuals with genetic predisposition, heterozygosity for certain genes, or incomplete penetrance.

Non-genetic forms of DCM can be caused by a variety of sources, for example, myocardial inflammation due to the presence of an infectious disease (most commonly viral). In addition, autoimmune and endocrine diseases, exposure to harmful chemicals, toxins, and allergens can also contribute to the development of DCM [18]. It should be stressed that not all patients with myocardial involvement from the above external factors develop DCM, and it is assumed that there is a genetic predisposition where full recovery may occur, and some patients might slide towards the DCM phenotype.

According to the British Heart Foundation, the most common clinical symptoms in patients with DCM are chest pain (due to elevated filling pressure and end-diastolic volume) and those of overt heart failure: leg swelling, paroxysmal nocturnal dyspnea, orthopnea, shortness of breath on exertion, fatigue [19]. Consequently, some of the complications seen in patients with more severe forms of DCM are congestive heart failure, secondary valvular heart disease, cardiac rhythm disturbances, thromboembolism, and IHD [16]. The heterogeneity in etiology and clinical symptomatology associated with DCM can complicate the timely and accurate diagnosis.

Genetics of dilated cardiomyopathy

Mendelian inheritance patterns

Dilated cardiomyopathy can have genetic, acquired, or mixed etiologies, and familial and sporadic cases can be seen [20]. Sporadic forms occur in patients with no family history associated with the disease and in patients with affected family members. The presence of a familial form of DCM is confirmed when two or more relatives meet the criteria for DCM or when the primary patient (proband) meets them and has a first-degree relative who has suffered a SCD under the age of 35 [21].

Between 20-35% of familial cases of DCM are due to the presence of a genetic variant that causes the development of the disease [20]. In addition, over 50 disease-responsible genes have been described to date, with the major inheritance mechanism in monogenic forms of DCM being autosomal dominant (56%) [9, 22, 23, 24]. In the pediatric population, there are differences in inheritance, with the autosomal recessive type being most common in children [22]. Cases of X-linked and mitochondrial inheritance of DCM have been reported, but they are not prevalent [25]. In addition to monogenic forms of inheritance of DCM, the disease may be part of a genetic syndrome that affects other organs and systems [10].

The incomplete and age-dependent penetrance, as well as variable expressivity, are characteristic and may influence the expression of the disease, both between different families and between relatives from the same family [26]. The severity of DCM, as well as environmental factors, also play an important role in the development and course of the disease [22].

Common genes and genetic variants

Due to the growing interest in molecular genetics, many genes and genetic variants associated with the DCM phenotype have been discovered in recent years (Table 1). These genes are responsible for the synthesis of multiple proteins involved in different genetic pathways [9]. Next-generation sequencing (NGS) technologies, in particular, have a fundamental role to play in revealing genome and exome sequences associated with the development of DCM [18].

The genes associated with the DCM phenotype are diverse and can be divided into several broad groups, depending on the functional disorders they cause:

Sarcomeres are the main contractile units of skeletal and cardiac muscle. Variations in the genes encoding sarcomeric proteins account for 5-10% of DCM cases. Variants in sarcomeric genes sometimes cause overlapping phenotypes with other cardiomyopathies [27]. Titin is the largest sarcomeric protein in the myocardium, and genetic changes that lead to its truncation occur in 25% of the most severe cases of DCM [24]. Orphanou et al [27] reported that 20-25% of familial and 18% of sporadic cases of DCM are caused by genetic variations in the *TTN* gene. Over 60,000 missense alterations in the titin gene have been identified using next-generation sequencing, many of which are variants with uncertain significance [28].

Truncating genetic variants in the *TTN* gene identified in patients with DCM are represented in the A-band and absent in the Z-disk and M-band regions [28]. Pugh et al. [29] confirmed the presence of this type of alteration in the general population (1.65%) and demonstrated that those localized in the A-band are more common in patients with DCM compared

to controls. Genetic variants in the *TTN* gene (nonsense, frameshift, splicing, and copy number variations) can significantly alter titin structure, occurring more frequently in patients with DCM than in patients with hypertrophic cardiomyopathy (HCM) and controls, respectively [29].

Identification of pathogenic variations in the *TTN* gene is essential for patient monitoring and genetic counseling. This helps to assess the individual risk of developing cardiomyopathy and allows the implementation of personalized treatment. Establishing the relationship between variants in the *TTN* gene and phenotypic expression in affected patients is key to conducting molecular genetic diagnosis.

Between 5-13% of DCM cases are due to genetic variations in *LMN* genes. Variants in the *LMNA* gene are the second most prevalent genetic cause of the disease [30]. The proteins encoded by the *LMNA* and *LMNC* genes, known as lamins, are major components of the nuclear lamina in the structure of the nuclear membrane [31]. Genetic changes in *LMNA* leading to DCM are missense and frameshift mutations [1]. The mechanisms characterizing the autosomal dominant form of inheritance of DCM caused by changes in lamin genes may be due to several factors, e.g., dominant-negative effect or haploinsufficiency [1].

Dilated cardiomyopathy associated with the presence of genetic variations in *LMNA* is characterized by a severe phenotype, a predisposition to ventricular arrhythmias, and cardiac conduction abnormalities [24]. Cardiovascular diseases caused by variants in *LMNA* are associated with a high incidence of clinical progression, arrhythmic, and non-arrhythmic events [32].

LMNA-associated DCM manifests with variable penetrance concerning age, with onset between the 3rd and 4th decades. By the 7th decade, penetrance is high and reaches about 90-95% [30].

Pathogenic genetic variants in genes encoding cytoskeletal proteins have been associated with an inherited form of DCM [34-37]. Filamins, dystrophin, and desmin are included in this group of cytoskeletal proteins [24].

The *FLNC* gene encodes filamin C, which plays an important role in the attachment of sarcomeres to the plasma membrane. It has been reported that autosomal dominant inheritance is associated with very high penetrance (97%) in patients over 40 years of age [24]. Dungu et al [38] present a case of a family affected by DCM caused by a pathogenic variant in the *FLNAC* gene that caused sudden cardiac death at a young age and heart failure due to left ventricular and myocardial damage [34].

The *DES* gene encodes the protein desmin, which is a key subunit and part of the intermediate filament in cardiac muscle, skeletal muscle, and smooth muscle [24]. Pathogenic changes in *DES* have been reported in patients suffering from a wide range of skeletal and cardiovascular diseases with overlapping phenotypes [24]. Some of the cardiovascular diseases are dilated cardiomyopathy, restrictive cardiomyopathy, and conduction disorders [24, 39].

Next-generation sequencing

In recent years, next-generation sequencing has proven to be a method that leads to the discovery of both novel and known genes and genetic variants associated with the DCM phenotype [45]. This widely used methodology significantly accelerates the process of genetic diagnosis in affected individuals and makes it possible to establish genotype-phenotype relationships, which in most cases is crucial for disease follow-up [46].

It is known that the diagnostic yield of the familial cases (47.6%) of DCM discovered by a panel of tar-

Table 1. Prevalence of gene variants associated with dilated cardiomyopathy

Gene	Estimated contribution to DCM	References
TTN (Titin)	25%	[29]
LMNA (Lamin A/C)	5-8%	[36]
MYH7 (β-myosin heavy chain)	10%	[36]
TNNT2 (Cardiac troponin T)	2.9%	[37]
TNNI3 (Cardiac troponin I)	<1%	[38]
DSP (Desmoplakin)	3-4%	[39, 40]
DES (Desmin)	<1-2%	[41]
SCN5A (Sodium channel)	1.7%	[42]
BAG3	2.3-3.6%	[43]
FLNC (Filamin C)	1-4.5%	[44]

get genes (target sequencing) associated with DCM is higher compared to sporadic cases (25.6%) [47]. In a study of 122 Romanian patients with DCM, the diagnostic yield of analysis using a gene panel was 50.8% [46], which is high compared to results from other studies (23.5%, 35%, 37%) (Table 2) [48]. There is increasing evidence that whole-exome testing leads to significantly high diagnostic yield and is the preferred method in rare disease diagnostics [49]. Performing whole-exome sequencing to elucidate genetic diagnosis in the pediatric population is associated with a 50% diagnostic yield [50], and in adult individuals ranges between 22%-57% depending on the studied cohort (Table 2) [51].

There are some advantages and disadvantages regarding the strategies based on NGS. They are divided into targeted sequencing and whole-genome (WGS)/whole-exome (WES) sequencing. Whole-genome and exome sequencing have an advantage in terms of their comprehensiveness and detection of an extremely large number of genetic variants compared to gene panel sequencing [52]. Another advantage is that they can identify modifier genes, as well as analyse non-coding regions and detect structural variants (in WGS) [53]. A known disadvantage of WES/WGS may be the lower coverage of some parts of DNA compared to targeted sequencing, which may result in important genetic variants being missed. The reporting of variants of uncertain significance and the analysis time are increased by approximately 2.5-fold when applying WES/WGS compared to targeted sequencing due to the significantly larger volume of data [53].

Therapeutic aspects in the treatment of patients with DCM

Dilated cardiomyopathy is a complex disease with genetic and acquired causes and thus requires a multimodal and complex therapeutic approach. Current therapeutic approaches focus on symptom control, prevention of disease progression, as well as prevention of subsequent complications and life prolongation. Emerging therapeutic approaches aim to address the underlying causes leading to the disease and modify its course by genetic and molecular interventions.

Genetic testing and personalized medicine are becoming increasingly important treatments for individual patients, and new therapies, such as stem cell therapy and CFTR enhancers, represent promising future interventions.

Genetic and personalized approaches

Genetic testing is critical for risk stratification and therapeutic decision-making in DCM, as different genetic variations may lead to different prognoses and responses to the conducted treatment. For example, variants in lamin A/C and filamin C are associated with poor prognosis and arrhythmic phenotypes [59].

Personalized medicine based on genotype-phenotype correlations is becoming a key aspect in the follow-up of DCM, allowing for more targeted and effective treatment [52].

Stem cell therapy, especially with mesenchymal stem cells, was a promising option for the treatment of DCM. These cells can differentiate into cardiomyocytes, potentially restoring normal heart function. However, studies have not had the desired effect so far, and research is ongoing to determine the most effective stem cell types and treatment protocols [61].

Pharmacological interventions

Traditional pharmacological treatment of chronic HF focuses on controlling symptoms and reducing myocardial remodeling. The main classes of medications used according to current recommendations include: beta-blockers, ACE inhibitors, SGLT2 inhibitors, neprilysin inhibitor in combination with an angiotensin II receptor blocker (Sacubitril/Valsartan), aldosterone antagonists, and, in the presence of peripheral/central stasis, diuretic therapy [62]. Recent studies highlight the importance of adherence to guideline-recommended drug therapies for improving patient outcomes [63].

Novel pharmacological therapies, such as CFTR enhancers, have shown potential in preclinical models

Table 2. Comparison of diagnostic yields across genetic testing approaches in DCM studies

Study/Cohort	Sample size	Diagnostic yield	Testing type
[54], [47], [48]	766, 145, 230	**23,5%-50.8%**	Targeted gene panels
[55]	2088	**24.6%**	
[48]	42	**22%-57%**	Whole-exome sequencing (WES)
[56]	363	**25.07%**	
[57]	49	**31-70%**	Whole-genome sequencing (WGS)
[58]	15	**39%**	

to affect cardiac dilation and improve cardiac function, indicating a new direction for therapeutic development through a shift in the phenotypic expression of molecular mechanisms [64]. However, such options are still under investigation.

Myosin modulators are pharmaceutical drugs that have shown promising results in recent years in the treatment of various forms of HF, in particular cardiomyopathies. They are a new class of drugs, small molecules, and their mechanism of action is by targeting myosin in the muscle fibers of the heart, thereby being able to modulate muscle contractions [65]. There are two main types of modulators, depending on the mechanism of action: activators (omecamtiv, danicamtiv) and inhibitors (mavacamten, aficamten), and they directly affect the rate of cardiac contractions by binding to β-myosin [66]. For the moment, the first type – myosin activators – have a role in the treatment of the phenotypic expression of DCM.

Dilated cardiomyopathy and hypertrophic cardiomyopathy are characterized by opposing effects on cardiac contractile function, with the former showing an impaired LV ejection fraction, whereas in the latter, the underlying mechanism is diastolic dysfunction with an „excessively high" (at least in the first steps) ejection fraction (due to increased LV hypercontractility), which is partly explained by genetic defects affecting sarcomeric function [66].

Several inotropic therapies (adrenergic agonists and phosphodiesterase inhibitors) are known to cause adverse side effects that increase mortality and are not suitable for long-term use [67].

Myosin activators that enhance ATPase activity have shown efficacy in patients with systolic HF of various etiologies. Through different mechanisms of action, myosin activators have been shown to treat the hypocontractile phenotype in DCM and increase left ventricular systolic function in preclinical animal models and humans [68, 69].

Multidisciplinary and follow-up care of patients with DCM

A comprehensive multidisciplinary approach, including regular follow-up and reassessments, is essential to optimize the treatment of DCM. This includes the use of advanced imaging techniques and genetic testing to monitor disease progression and tailor treatment accordingly [63].

Although current treatments for DCM are primarily aimed at controlling symptoms and preventing complications, the integration of genetic knowledge and new therapies promises more effective and personalized interventions. However, challenges remain in translating these advances into widespread clinical practice, and further research is needed to validate and refine these approaches.

Personalised medicine and target therapies

Personalized medicine aims to adapt treatments based on individual genetic profiles, potentially improving outcomes and reducing unnecessary interventions [70]. Also, techniques such as CRISPR-Cas9 gene editing, antisense therapies, and RNA therapies are being explored to correct genetic defects and modulate pathophysiological pathways. Advances in gene editing, such as the use of CRISPR-based editors, show potential for correcting genetic variants associated with DCM. However, there remain challenges associated with reaching the target site, as well as the manifestation of off-target effects that must be overcome in order to have clinical application [71].

In addition, expression of microRNAs, such as miR-208, has been associated with adverse clinical outcomes in DCM, suggesting potential targets for therapeutic intervention [72]. Although translational medicine offers promising treatment options for DCM, challenges remain in this field. The complexity of genetic variation and environmental factors complicates the development of universally effective therapies. Furthermore, the transition from research models to clinical application requires careful validation to ensure safety and efficacy.

Gene therapy is emerging as a promising approach for the treatment of DCM. This innovative treatment strategy aims to address genetic alterations in DCM, offering the potential for more effective and durable interventions compared to traditional therapies. Recent studies have investigated various gene therapy techniques, including gene replacement, gene editing, and RNA-targeted therapies, to improve cardiac function and prevent disease progression in models of DCM. Key aspects of gene therapy applications in DCM are presented below.

Gene replacement and editing

Gene therapy with *PHGDH*: Gene therapy with phosphoglycerate dehydrogenase (*PHGDH*) is a promising method to improve cardiac function in models of dilated cardiomyopathy. This approach uses the modulation of serine biosynthesis and one-carbon metabolism to improve cardiac dysfunction and halt disease progression. Therapy involves the use of an adeno-associated virus (AAV) vector to deliver the *PHGDH* gene specifically into cardiomyocytes, resulting in significant improvement in cardiac struc-

ture and function. As previously mentioned, *PHGDH* gene therapy improves serine biosynthesis and one-carbon metabolism, which are critical for cell growth and repair processes. This metabolic rewiring is cardioprotective, as it improves glucose metabolism in the heart, thereby increasing energy production and reducing stress on cardiac cells. Therapy prevents the development of interstitial fibrosis and cardiomyocyte hypertrophy, which are common pathological features of DCM. This structural improvement is related to the metabolic changes induced by *PHGDH* expression [73].

Gene therapy with *BIN1*: Gene therapy with c*BIN1* in canine models of ischemic dilated cardiomyopathy has shown promising results in improving overall hemodynamics and left ventricular filling pressures, indicating its potential to restore cardiac function. This therapy is aimed at restoring cardiac function by correcting the underlying molecular abnormalities, particularly the organization of T-tubule microdomains, which are critical for calcium handling in cardiac cells. The therapy involves transfer of the *cBIN1* gene using an adeno-associated viral vector, which has been shown to improve various cardiac parameters in affected dogs [74].

Gene therapy using nexiline: Gene therapy using nexiline (NEXN) represents a promising approach for the treatment of DCM, often associated with changes in the *NEXN* gene. Studies have shown that systemic delivery of nexiline can restore cardiac function in animal models, suggesting potential for clinical application. This therapy aims to address the genetic basis of DCM by offering a more targeted treatment compared to traditional symptom management. Nexilin is critical for stabilizing the sarcomeric Z-disc in cardiac muscle cells, and its deficiency leads to DCM by destabilizing these structures. Gene therapy involves the use of adeno-associated virus (AAV) vectors to deliver functional *NEXN* genes into affected cells, restoring normal protein function and cardiac structure [75].

RNA-targeted therapies

Cas13b-mediated RNA knockdown

RNA-targeted therapies for dilated cardiomyopathy are emerging as a promising approach to address the genetic and molecular basis of this disease. Recent studies in the field of RNA-targeted therapies, particularly using the CRISPR-Cas13 system, have shown the potential to ameliorate genetic forms of DCM by targeting aberrant RNA transcripts. The goal of these therapies is to modulate gene expression and improve cardiac function by addressing specific genetic variations associated with DCM. The CRISPR-Cas13b system has been used effectively to remove mutant RNA transcripts in models of DCM. Specifically, PspCas13b was delivered using adeno-associated virus vectors to target the TNNT2(R141W) genetic variant in transgenic DCM mice, resulting in improved cardiac function and reduced myocardial fibrosis. This approach highlights the potential of RNA-targeted therapies to specifically address the genetic variations that contribute to DCM, offering a targeted intervention that can improve cardiac function [76].

Innovative methods using viral vectors

Adeno-associated viral vectors (AAVs) have emerged as promising gene therapy tools for DCM, offering potential therapeutic benefits by targeting genetic variants and metabolic pathways associated with the disease. Adeno-associated vectors can deliver therapeutic genes directly into the heart, potentially altering disease progression and improving cardiac function. The application of AAV vectors in DCM involves various strategies, including gene addition and metabolic modulation, which have shown promising results in preclinical models. Adeno-associated viral vectors are commonly used to deliver therapeutic genes, including *PHGDH*, c*BIN1*, and Cas13b, due to their effectiveness in targeting cardiac tissues [73, 74, 76].

Although gene therapy holds considerable promise for the treatment of DCM, challenges remain, including understanding the complex genetic structure of the disease and the variable expressivity of genetic variations. Precision medicine approaches that tailor treatments based on individual genetic profiles are being explored to enhance the efficacy of gene therapies. In addition, the integration of advanced imaging and multiomics could lead to further refinement of these therapies, potentially shifting the focus from treating symptoms to preventing the onset of disease [70].

Translational medicine in DCM

Translational medicine is a rapidly evolving field that aims to bridge the gap between molecular research and clinical application. This approach focuses on understanding the genetic and molecular basis of DCM to develop targeted therapies and improve outcomes for patients with this disease. Recent advances in genomic medicine, stem cell technology, and precision medicine are central to these translational efforts and approaches. These innovations are paving the way for personalized treatment strategies that target the specific genetic and molecular profiles of DCM patients, potentially changing the management and prognosis of this disease. There are several directions, including the following factors:

Genetic and molecular insights into DCM

Genetic variants are associated with approximately 35% of DCM cases, often affecting genes related to cytoskeletal, sarcomeric, and nuclear proteins [10]. The identification of novel causative genes has provided insights into the molecular mechanisms of DCM, highlighting the role of calcium and protein homeostasis in cardiomyocytes as well [77]. Advances in genomic medicine would improve understanding of the genetic architecture of DCM, facilitating the development of genotype-specific therapies [70].

Innovative research models

Human inducible pluripotent stem cells (hiPSCs) are used to model inherited cardiomyopathies, allowing researchers to study patient-specific disease mechanisms in vitro. These cells offer a promising alternative by providing a more accurate representation of human cardiac physiology. They enable the study of genetic and molecular mechanisms specific to human cardiomyocytes, potentially improving the relevance of preclinical results [78]. Animal models, particularly genetically modified mice and large animal models, are critical for studying the pathophysiology of DCM and testing potential therapies [79].

CONCLUSION

Dilated cardiomyopathy is a highly complex and multifactorial disease that is influenced by both hereditary and non-genetic variables, as well as external factors like alcohol, toxins, infections, etc. Establishing a precise genetic profile in DCM is important in terms of phenotypic and clinical overlap of different types of cardiomyopathies, which creates obstacles in the follow-up and implementation of appropriate therapy. Due to the development and advancement of molecular genetic studies related to dilated cardiomyopathy, genotype-phenotype correlations are being demonstrated to help scientists and clinicians control the disease in affected individuals. More in-depth studies on the genetics of DCM are needed, as are studies involving large cohorts and families. This will contribute to the interpretation of genetic variants associated with the disease, especially those of uncertain significance, which in some cases remain a major challenge.

Abbreviations: *DCM (dilated cardiomyopathy), HF (heart failure), SCD (sudden cardiac death), NGS (next-generation sequencing), HCMP (hypertrophic cardiomyopathy), WGS (whole-genome sequencing), WES (whole-exome sequencing) CFTR Enhancers, ACE Inhibitors, Adenoassociated Virus (AAV), Human Inducible Pluripotent Stem Cells (hiPSC)*

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