Title

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Journal

Structural Heart, 7(5)

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Publication Date

2023-09-01

DOI

10.1016/j.shj.2023.100200

Peer reviewed

Structural Heart 7 (2023) 100200

Articles and Issues Available at ScienceDirect

Structural Heart

journal homepage: www.structuralheartjournal.org

Review Article

The Genetic Evaluation of Dilated Cardiomyopathy

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ARTICLE INFO

Article history:
Submitted 19 November 2022
Revised 7 April 2023
Accepted 19 April 2023
Available online 15 July 2023
Guest Editor: Luisa Mestroni, MD

Keywords:
Arrhythmias
Cardiovascular genetics
Dilated cardiomyopathy
Genetic cardiomyopathy
Genetic testing
Heart failure

ABSTRACT

Dilated cardiomyopathy (DCM) is a common cause of heart failure and is the primary indication for heart transplantation. A genetic etiology can be found in 20-35% of patients with DCM, especially in those with a family history of cardiomyopathy or sudden cardiac death at an early age. With advancements in genome sequencing, the understanding of genotype-phenotype relationships in DCM has expanded with over 60 genes implicated in the disease. Subsequently, these findings have increased adoption of genetic testing in the management of DCM, which has allowed for improved risk stratification and identification of at risk family members. In this review, we discuss the genetic evaluation of DCM with a focus on practical genetic testing considerations, genotype-phenotype associations, and insights into upcoming personalized therapies.

ABBREVIATIONS

DCM, dilated cardiomyopathy; GDCM, genetic dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; VUS, variant of uncertain significance; WGS, whole genome sequencing.

Introduction

Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) dilation and systolic dysfunction. When ischemic and nonischemic etiologies have been ruled out, DCM is labeled as idiopathic.[1] However, with the increased availability of genetic testing, a growing proportion of patients (20-35%) previously labeled as idiopathic have been found to have an associated genetic variant.[2–4] The most common inheritance pattern seen in genetic DCM (GDCM) is autosomal dominant although other modes (i.e., autosomal recessive, X-linked, and complex polygenic) have been observed.[5]

Red flags for GDCM include a strong family history with 2 first-degree relatives having idiopathic DCM or sudden cardiac death at age <35 years. Furthermore, GDCM should be suspected if 3 or more of the following criteria are met: unexplained ventricular or supraventricular arrhythmias, LV dilation >112% of the expected value, LV dysfunction (EF <50% or fractional shortening <28%), unexplained sudden death before the 5th decade, and segmental wall motion abnormalities.[1,6,7] Other features concerning for GDCM include the presence of significant atrioventricular block, implantable cardioverter-defibrillator (ICD) or pacemaker before the age of 50 years and LV assist device or heart transplant before the age of 60 years.[8–10] When these red flags are present, genetic testing is recommended to evaluate for GDCM. It is important to recognize that the absence of red flags does not rule out genetic causes of DCM since sporadic mutations can occur; therefore, genetic testing should still be pursued if clinical suspicion remains high.

Recently, tools have been developed to aid the clinician in deciding whether to pursue genetic testing in patients with suspected GDCM. The Madrid Genotype Score estimates the probability of receiving a significant genetic test result using 5 criteria: pre-existing family history of DCM, low voltage on electrocardiogram, presence of skeletal myopathy, absence of hypertension, and absence of left bundle branch block.[11] When 4 or more of these criteria were met, a pathogenic or likely pathogenic variant was identified in 79% of patients.[11]

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https://doi.org/10.1016/j.shj.2023.100200

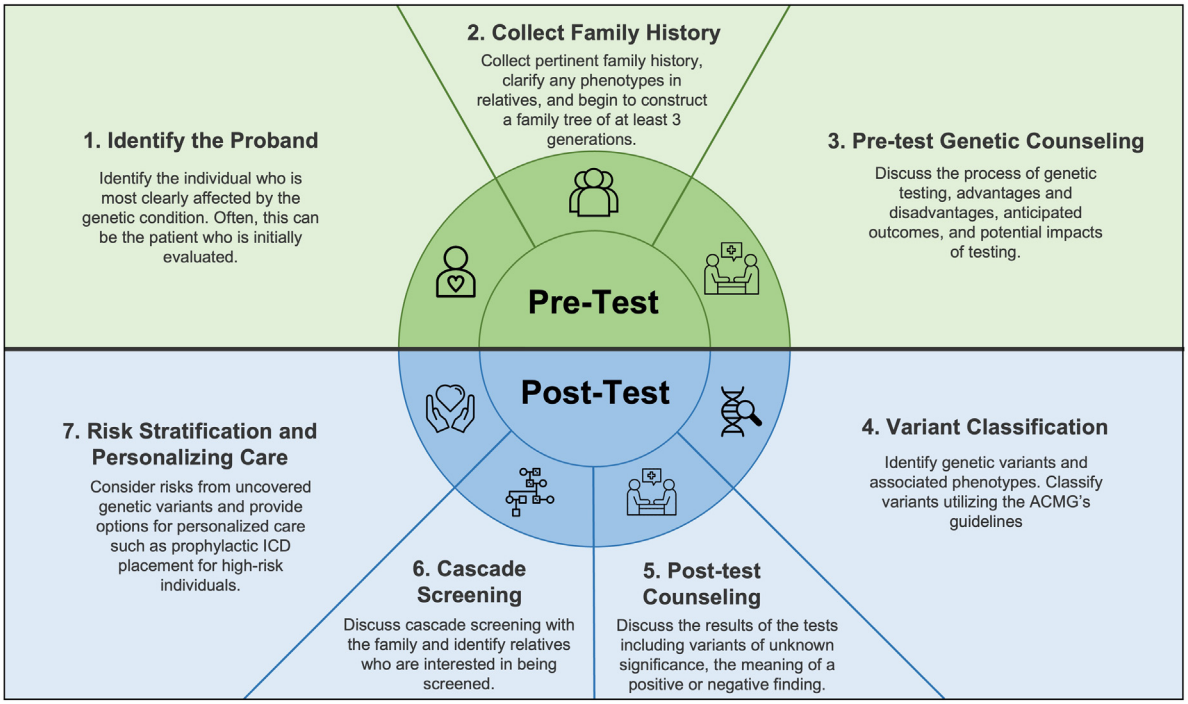

Figure 1. Practical framework for genetic evaluation of dilated cardiomyopathy.

Genetic Evaluation

Family History

The first step in the genetic evaluation of patients with suspected GDCM begins with identifying the proband and taking a detailed family history (Figure 1). Providers should create a family tree of at least 3 generations to establish the mode of inheritance (i.e., autosomal dominant/recessive, X-linked etc.).[9] The cause and circumstances of every death for every family member before the age of 50 years should be recorded. A detailed family tree will help determine the pretest probability of genetic testing and identify other potential at risk family members. However, before obtaining genetic testing, it is important to perform genetic counseling.

Genetic Counseling

Genetic counseling involves helping patients understand the medical, psychological, and familial implications of genetic disorders. Genetic counseling is often broken down into pregenetic and postgenetic testing concerns.[9]

Pretest counseling is critical for patient informed consent and providers should discuss the process, benefits and limitations of genetic testing, including anticipated outcomes.[12] Other discussion points should include potential for incomplete penetrance, genetic heterogeneity, incidental findings, insurance and employment discriminations, and implications for other family members. Fortunately, with the Genetic Information Nondiscrimination Act passed in 2008, individuals are protected from discrimination for health insurance and employment (only applies to employers with 15 or more employees) based on genetic test results.[9] However, there are no laws prohibiting long-term care, disability, and life insurance companies from using these genetic test results. Additional pretest considerations include choosing the appropriate genetic test and identifying the best individual to test.

Post-test counseling is important to provide accurate result interpretation, including explanations of variants of undetermined significance (VUS), and any incidental findings.[9] Furthermore, post-test responsibilities include initiation of cascade screening of family members if indicated and providing psychosocial support to patients and families when needed. Providers must also be adept with genetic interpretation which is challenging since genetic tests are not binary and the pathogenicity assessment is extremely difficult in the background of variable expressivity and incomplete penetrance.[9] A "negative" genetic test does not guarantee that the disease is not genetic, but only that a mutation was not detected by that test.[9] A VUS also has a wide range of confidence for likelihood of being pathogenic (10-90%).[13] Therefore, it is important for cardiovascular genetic experts to re-evaluate results especially VUS in the patient's clinical context and consider possible reclassification, particularly if the patient is of a racial or ethnic group which may be under-represented in current genomic databases, or if there is high suspicion that a variant will lead to a functional protein defect. Additionally, genetic testing can often lead to incidental findings that are unrelated to the initial indication for which the genetic test was ordered.[14] This is more common with nontargeted genetic testing which includes whole genome or exome sequencing and genetic panel testing. Problems lie in the ethics of reporting incidental findings, especially when many of these findings are not clinically actionable. In 2021, the American College of Medical Genetics and Genomics published clarifications on which incidental findings have actionable outcomes and thus should be discussed in pretest and post-test genetic counseling sessions.[14,15] These include DCM-related genes such as LMNA, filamin C (FLNC), PAG3, desmin, and RBM20. Providers should periodically check in with genetic testing laboratories, review current interpretations in ClinVar, and consider re-testing to ensure that management decisions are based on the most up-to-date genetic information.[9]

Benefits of Genetic Testing

Genetic testing is often most useful to determine at risk family members and does not have a direct health benefit to the proband, although it can help to determine the etiology of disease.[12] Therefore, the primary benefit of genetic testing is cascade screening of family members to potentially identify subclinical disease.[9,16] Other benefits include differentiating diseases that appear phenotypically and morphologically

similar, prognostication, phenotypic risk stratification, potential for early treatment, and personalized recommendations.[9]

The practical applications to genetic testing in DCM are limited but are expected to grow as we learn more. There is increasing evidence for the use of genotype—rather than phenotype-based classification for risk stratification of patients with cardiomyopathies.[17] Paldino et al. found that a genotype-based classification more accurately identified patients at risk for malignant ventricular arrhythmias and sudden cardiac death compared to a phenotype-based one. This has important clinical implications as it suggests that patients with high-risk genetic variants (i.e., LMNA, FLNC, desmoplakin [DSP], and plakophilin-2) should be considered for ICD independent of phenotype or LV systolic function. Currently, the Heart Failure Society of America extends consideration of ICD in patients with LV ejection fraction (LVEF) >35% in the presence of LMNA mutation.[18] Moreover, other variants such as FLNC and PLN also show a similar propensity for developing serious arrhythmias independent of LV dilation and function. Subsequently, the Heart Rhythm Society extends consideration of ICD in these patients with LVEF <45%.[16] Finally, in the 2022 European Society of Cardiology guidelines for prevention of sudden cardiac death, primary prevention ICDs are recommended in DCM patients with a LVEF <50% and more than 2 of the following risk factors (syncope, late gadolinium enhancement on cardiac MRI, inducible sustained monomorphic ventricular tachycardia at programmed electrical stimulation and pathogenic variants in LMNA, PLN, FLNC, and RBM20).[10,19]

Genetic Testing

Genetic panel testing is the most widely used method of testing.[20] With recent advancements in sequencing technologies, it has become easier and cheaper to add genes to these panels while still preserving sensitivity and specificity.[21] Genetic panel testing is particularly advantageous in DCM because of genetic heterogeneity with multiple gene candidates.[20] It is important that genetic panels be periodically updated to include the most current, medically actionable variants.[14,15]

Next generation sequencing has driven the costs of whole genome sequencing (WGS) or whole exome sequencing down significantly where they are feasible in the clinical setting. WGS is the gold standard for sequencing of the genome as it illuminates all variant types, including single nucleotide polymorphisms, insertions-deletions, splice-site variants, and genomic rearrangements.[22] WGS is particularly attractive in the context of DCM as pathogenic variants can exist outside the exon.[23] Therefore, WGS may be useful when genetic panel testing is unrevealing and clinical suspicion remains high for GDCM.

Variants Implicated in GDCM

GDCM is diverse with more than 60 genes implicated (Table 1). The most common variants involve titin (TTN) and LMNA, which make up 10-20% and 5.5% of cases, respectively.[3] This is drastically different from hypertrophic cardiomyopathy, the most common inherited cardiomyopathy, where variants in MYH7 and MYBPC3 represent 2-thirds of the variants identified.[24,25] The genetic heterogeneity in DCM has propagated a "final common pathway" hypothesis where different variants affect distinct processes to summate in a "final common phenotype."[26,27] Often a genetic variant will not be enough to cause a DCM phenotype unless there is an additional insult (i.e., hemodynamic, toxic, or stress), described as the "2 hit" hypothesis.[28] It is important to

Table 1
Common genetic variants associated with dilated cardiomyopathy

Inheritance pattern	Chromosome locus	Gene	Protein	Cardiac phenotype	Additional clinical features
Autosomal dominant	10q25.2	RBM20	RNA-binding motif protein 20	Aggressive DCM, malignant ventricular arrhythmias	
Autosomal dominant	10q26.11	BAG3	BAG cochaperone 3	DCM	Myofibrillar myopathy
Autosomal recessive	12p11.21	PKP2	Plakophillin-2	ARVC	
Autosomal dominant	14q12	MYH7	B-myosin heavy chain	HCM/DCM	
Autosomal dominant/recessive	18q12.1	DSG2	Desmoglein-2	ARVC, ventricular arrhythmia, sudden cardiac death	Wooly hair, keratoderma
Auotosomal dominant	18q12.1	DSC2	Desmocollin-2	ARVC	
Autosomal recessive	2q31.2	TTN	Titin	DCM	Girdle muscle weakness and myopathy
Autosomal dominant/recessive	2q35	DES	Desmin	ARVC, DCM	Skeletal myopathy
Autosomal dominant/recessive	3p22.2	SCN5A	Voltage-gated sodium channel	Long QT syndrome, atrial fibrillation, Brugada syndrome	
Autosomal dominant	3p25.1	TMEM43	Transmembrane protein 43	ARVC	
Autosomal dominant/recessive	6q22.31	PLN	Phospholamban	ARVC, ventricular tachycardia, atrial fibrillation, extrasystolic ventricular contraction	
Autosomal dominant/recessive	7q32.1	FLNC	Filamin C	Ventricular arrhythmias, sudden cardiac death	
X-linked	Xp21.2	DMD	Dystrophin	DCM early in the second decade of life	Duchenne muscular dystrophy, Berker muscular dystrophy, progressive skeletally weakness and atrophy
Autosomal dominant/recessive	1q21.2	LMNA	Lamin A/C	Cardiac conduction abnormalities, arrhythmic abnormalities	Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, contractures of the elbows, heels, and neck, progressive muscle weakness and atrophy
Autosomal recessive	6p24	DSP	Desmoplakin	ARVC, right bundle branch block, right and left ventricular arrhythmias, DCM	Carvajal syndrome, wooly hair, palmoplantar keratoderma
X-linked	Xq28	TAZ	Tafazzin	HCM, ventricular arrhythmia, sudden cardiac death, prolonged QT syndrome	Barth syndrome, skeletal myopathy particularly in proximal muscle groups, delayed motor milestones, growth delay, neutropenia
Mitochondrial	Maternal mDNA	Multiple gene variants	NADH dehydrogenase	Bundle branch blocks, atrioventricular block, cardiac arrest	Kearns-Sayre syndrome, progressive external ophthalmoplegia, ptosis, atypical pigment retinopathy,

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

recognize that many genetic variants associated with DCM have significant overlap with other cardiac conditions such as arrhythmogenic ventricular cardiomyopathy (AVC) and arrhythmogenic right ventricular cardiomyopathy (ARVC). This heterogeneity consequentially results in lower yield of genetic testing, previously reported to be 16% in patients with familial DCM.[29] However, with increased use of next generation sequencing, the diagnostic yield of genetic screening now ranges from 16 to 46%.[20,30,31]

It is helpful to classify the GDCM into nonsyndromic and syndromic etiologies. Nonsyndromic genetic causes include laminopathies, channelopathies, and desminopathies. The genetic syndromes associated with DCM include Emery-Dreifuss, limb girdle muscular dystrophy, and Barth syndrome.

Nonsyndromic

Lamins

Genetic variants that affect the nuclear lamina often result in DCM. Lamins are intermediate filament proteins that are important in the formation of the nuclear lamina. A-type lamins are encoded by the LMNA gene and play an important role in maintaining the nuclear architectural integrity and spatial organization of proteins in the inner nuclear membrane. Prior studies suggest that LMNA mutations are present in 2-4% of patients with DCM and are inherited in an autosomal dominant pattern with almost complete penetrance in individuals over the age of 70 years.[3,30,32–34] Mutations in LMNA usually cause DCM and is commonly associated with arrhythmias (both atrial and ventricular) and conduction abnormalities, like atrioventricular block.[35–37] Carriers of pathogenic LMNA variants often have electrocardiogram abnormalities that precede DCM diagnosis by a median of 7 years.[38] The genotype-phenotype relationship of LMNA with DCM and associated molecular mechanisms are still poorly understood. However, recent advancements in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) have shown that LMNA variants were associated with decreased pacing functionality along with prolonged action potential durations within the cardiomyocyte.[39] Additional hiPSC-CM studies have shown abnormal platelet-derived growth factor signaling, which stimulates proliferation of cardiac interstitial fibroblasts and eventual cardiac fibrosis.[36] This effect was further ameliorated by treatment with platelet-derived growth factor receptor inhibitors showing potential therapeutic approaches for certain variants of LMNA.[36]

SCN5A

Variants in the major cardiac sodium channel alpha subunit, encoded by the gene SCN5A, have been associated with a form of GDCM that is often preceded by cardiac conduction disorders such as long QT syndrome and atrial fibrillation.[26,40–42] Thus, patients with SCN5A-associated DCM present with similar clinical features to those with LMNA-associated DCM. However, individuals with SCN5A-associated DCM may be harder to identify since SCN5A has a considerable amount of variation in both penetrance and severity between individuals.[43]

PLN

Phospholamban, encoded by the gene PLN, is a key protein involved in regulation of calcium cycling in the sarcoplasmic reticulum. The R14del variant has a high prevalence in the Netherlands and strong correlation with DCM phenotype.[44] Individuals with PLN-associated DCM often present with an aggressive form of DCM, frequently accompanied by arrhythmic abnormalities such as extra systolic ventricular contractions, ventricular tachycardia, and atrial fibrillation.[45,46] Functional studies of PLN variants in transgenic mice and hiPSC-CM models have shown super-inhibition of the sarcoplasmic reticulum Ca^{2+}-ATPase, leading to disruption of natural calcium cycling, altered cardiomyocyte contractility, and ventricular dilation.[45,46]

Desmosome

Desmosomes are major intracellular adhesive junctions that provide mechanical strength in cardiac muscle. Genetic variants involved in the formation and function of the desmosome are predominantly associated with AVC, ARVC, and DCM. Recent studies have also shown that patients with desmosomal variants have a high propensity for sudden cardiac death and malignant ventricular arrhythmias, similar to those with LMNA variants.[31] Genetic variants of DSP, desmoglein-2, desmocollin-2, desmin, and plakophilin-2 and their protein products all fall within this intersection.[47–53]

Sarcomeric Proteins

TTN, the largest sarcomeric protein found in humans, is responsible for proper sarcomere assembly and plays a critical role in sensing mechanical stress and force generation.[54–56] TTN variants have been implicated in up to 25% of patients with familial DCM and idiopathic DCM.[23,30] Patients with TTN variant DCM have worse clinical outcomes, mainly in the form of ventricular arrhythmias, when exposed to external triggers.[57] Truncating mutations in TTN have been shown in hiPSC-CMs to affect proper sarcomere formation and functionality, which could explain the observed DCM phenotype.[58] Additional studies in mice with heterozygous TTN truncating variants exposed to cardiac stress demonstrated the development of marked LV dilation with impaired fractional shortening and diffuse myocardial fibrosis.[59] Patients with TTN variant DCM usually show a blunted hypertrophic response and a lower LV mass index in comparison to other patients with DCM.[60] However, this difference in LV mass is not significant enough to differentiate TTN variant DCM from other forms of DCM.[60]

Abnormalities in beta-myosin heavy chain, another sarcomeric protein encoded by MYH7 gene, account for up to 3% of DCM cases.[61] Variants in MYH7 have been extensively studied in the context of hypertrophic cardiomyopathy, but how these variants contribute to the progression of DCM is not well elucidated. Carriers of MYH7 variants typically exhibit symptoms around age 40 years with significant penetrance by age 60 years.[62]

FLNC

FLNC is a dimeric protein that is highly enriched in skeletal and cardiac muscle. It is found in the z-disc of the sarcomere where it anchors the actin thin filaments, playing a key role in the force generation of the sarcomere. FLNC variants have emerged as a common cause of various cardiomyopathies including GDCM. Specifically, truncating variants of FLNC have been associated with about 3 to 4% of DCM cases.[63–65] Like LMNA variant GDCM, FLNC variant GDCM has been associated with high rates of ventricular arrhythmias and sudden cardiac death irrespective of LVEF.[66–68] Mechanistic insights from hiPSC-CM have shown that haploinsufficiency of FLNC impairs sarcomere protein turnover leading to disruption of proteostasis.[69] This impaired proteostasis ultimately leads to cardiomyocyte dysfunction and dilation.[69]

RBM20

RNA-binding motif protein 20, encoded by the gene RBM20, is important in the splicing of titin sarcomeric protein. Variants in RBM20 are strongly associated with an aggressive form of DCM and can be found in up to 3% of patients with DCM.[70] It is hypothesized that variants in RBM20 cause abnormal splicing of titin resulting in defective protein that leads to sarcomere dysfunction.[71,72] Patients with RBM20 variant GDCM have a high preponderance of malignant ventricular arrhythmias. Recent studies in RBM20 knockout mice suggest that increased arrhythmia risk may be due to abnormal calcium handling by cardiomyocytes which causes abnormal electrical behavior of the cells.[73]

BAG3

BAG3 codes for the antiapoptotic protein located on the sarcomere Z-disc in cardiomyocytes. Variants of the BAG3 gene are typically associated with myofibrillar and skeletal myopathies with rapidly progressing

proximal muscle weakness.[74–76] BAG3 variants have also been associated with early-onset DCM leading to high rates of heart transplantation, ventricular assist devices, or heart failure-related death.[74,77,78] The protein product of BAG3 aids in sarcomere stability and mechanical stress response, and dysfunction of sarcomere stability can lead to cardiomyocyte injury.[79]

Syndromic

Syndromic DCM disorders, such as Duchenne, limb-girdle, and Emery-Dreifuss muscular dystrophies, experience a higher incidence of DCM at a significantly younger age (~90% by age 18 years) when compared to the general population.[80] Patients with these disorders are also at higher risk for malignant arrhythmias and advanced heart failure.[80]

Duchenne and Becker Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a neuromuscular disease characterized by progressive skeletal weakness and atrophy. DMD affects the heart, with most patients developing DCM by the second decade of life.[81] DMD is caused by dysfunctional dystrophin, which weakens striated myocytes and interferes with its ability to withstand the mechanical stress of contraction. Upon contraction, these cells experience membrane damage and subsequent injuries lead to a loss of membrane integrity and myocyte death.[81] Symptoms of DMD are characterized by a progressive weakening and atrophy of skeletal muscle throughout childhood accelerating to immobility.[81]

Becker muscular dystrophy is due to partial loss of functional dystrophin and presents with similar signs and symptoms, although less severe than DMD. When compared to DMD, patients with Becker muscular dystrophy may have a later age of onset and longer life expectancy. Cardiomyopathy symptoms often preclude skeletal ones.[81]

Emery-Dreifuss

Emery-Dreifuss muscular dystrophy is characterized by a triad of early contractures of the elbow, heels, and neck, progressive muscle weakness and atrophy, and cardiac abnormalities.[82] Contractures typically occur within the first decade of life and become more prominent during adolescence. Muscle weakness and atrophy typically emerges during the second or third decade of life.[83] Emery-Dreifuss muscular dystrophy can lead to DCM with severe arrhythmias, some of which may be caused by LMNA variants.[84–86]

Limb Girdle Muscular Dystrophy

Limb girdle muscular dystrophy describes a diverse group of muscular dystrophies that predominantly affect the proximal muscles of the shoulders and hips. Patients typically experience progressive weakening of these muscle groups with a high incidence of DCM, some of which are due to LMNA and other genetic variants (Table 1).[87,88]

Carvajal Syndrome

Carvajal syndrome is an autosomal recessive syndrome that is associated with wooly hair, palmoplantar keratoderma, and DCM. Variants in DSP have been associated with the DCM phenotype, which overlaps with genetic AVC and ARVC.[89–91]

Therapies

Current treatment of GDCM includes standard guideline-directed medical therapies aimed at preventing or slowing the progression of heart failure. These medications include the standard regimen of beta blockers, angiotensin receptor-neprolysin inhibitors, sodium-glucose contransporter-2 inhibitors, and mineralocorticoid receptor antagonists.[92] Recent guidelines utilize genetic variants such as LMNA, FLNC, and PLN to risk stratify patients for malignant arrhythmias and recommend primary prevention ICD above the typical LVEF threshold of 35%.[5,16,18]

New personalized therapies include small molecule inhibitors and myosin activators that target the underlying mechanism of disease. For example, it has been shown that the p38 MAPK pathway is upregulated in GDCM due to LMNA variants. This led to the development of ARRY-371797, an oral small molecule inhibitor of p38 MAPK pathway, which showed promising phase 2 clinical results with notable improvements in 6-minute walk test distance and decreases in BNPP.[93] However, the phase 3 Dilated Cardiomyopathy Due to Lamin A/C Gene Mutation (REALM-DCM) trial was halted after interim analysis showed that the trial would not meet its primary endpoint for the 6-minute walk test. Next, omecamtiv mercabil and danicamtiv are 2 myosin activators with in vitro studies demonstrating prolonged muscle contraction while preserving relaxation.[94–96] Thus far, omecamtiv mercabil has been evaluated in 2 trials, Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) and Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF). In the first trial, omecamtiv was shown to improve various echocardiographic parameters including LV systolic ejection time, stroke volume, and LV end-systolic diameter in patients with heart failure with reduced ejection fraction (HFrEF).[97] In the latter trial, omecamtiv mercabil showed a significant absolute risk reduction of 2.1% in the composite outcome of cardiovascular death or HF event with greater effects seen in subgroups with more LV dysfunction and hypotension.[98,99] Additionally, a phase 2a trial for danicamtiv has shown improvement in myocardial function through reduction in LV volumes, LV strain, and increases in left atrial function indices in patients with HFrEF.[96] Danicamtiv, like omecamtiv mercabil was well tolerated and improved LV systolic functions in these patients.[96] Overall, omecamtiv mecarbil and danicamtiv are promising therapeutics, but face significant challenges as studies are limited by small sample sizes and lack of long-term data.[96] In fact, the Food and Drug Administration advisory committee recently concluded that omecamtiv mercabil showed more risks than benefits for patients with HFrEF and voted against its approval.

Gene replacement therapies are challenging in genetic DCM due to vast genetic heterogeneity.[100] Current research is primarily targeted in the direction of muscular dystrophies that are highly associated with DCM such as DMD. Significant improvements in adeno-associated viral vectors and muscle-specific dystrophin gene cassettes have paved the way for 3 human clinical trials involving the delivery of adeno-associated viral vectors containing dystrophin in the United States.[101,102]

Future Directions

As promising therapies develop for genetic DCMs, refining clinical trial design and patient selection criteria will be critical to move the field toward precision medicine guided by genotyping. Ideally, therapies should be started early in the disease before irreversible damage has occurred. However, variable penetrance and expressivity make positive genotype by itself an unreliable predictor of disease and treatment benefit. Instead, discovery and validation of biomarkers that precede or predict the onset of clinical cardiac dysfunction, such as global longitudinal strain, may aid in patient selection and potentially serve as surrogate endpoints in rare disease clinical trials, which are often underpowered to detect mortality differences.[103] We are at a pivotal moment in cardiovascular genetics where the successful completion of these rare disease clinical trials will determine the utility of genotyping a DCM patient.

Conclusion

Over the past decades, there have been significant advancements in our understanding of what used to be largely classified as idiopathic DCM. Improvements in our ability to sequence and interrogate the human genome as well as advancements with in vitro cell culturing

techniques, like hiPSC-CMs, have strengthened genotype-phenotype relationships and aided in our understanding and interpretation of numerous VUS. However, significant challenges remain with regard to practical implications for genetic testing and ushering in personalized therapeutics.

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Funding

The authors have no funding to report.

Disclosure Statement

Eric Adler has equity interest in Rocket Pharmaceuticals and is the Chief Scientific Officer at Lexeo Therapeutics. Quan Bui is a Consultant for Lexeo Therpaeutics. Jeffrey Ding, and Kimberly Hong report no conflicts of interest.

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