Genetics of Complex Diseases

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Review

The genetics of cardiomyopathy, new technologies and the path to personalised medicine

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Abstract

Introduction

Cardiomyopathy is defined as the weakening of the heart muscle, which reduces the ability of the heart to pump blood. Inherited cardiomyopathies include hypertrophic, dilated, arrythmogenic right ventricular, restrictive and unclassified cardiomyopathies. The discovery of numerous disease-causing genes has demonstrated these cardiomyopathies have a substantial genetic aetiology. Molecular genetic diagnosis in individuals with cardiomyopathy facilitates medical interventions to prevent serious complications, such as heart failure and arrhythmia. In addition, it enables cascade testing to identify additional at-risk family members and the provision of informed counselling. Traditionally, issues of genetic heterogeneity, clinical variability and reduced penetrance have meant that molecular genetic screening was time consuming and costly. However, modern genomic technologies, in particular Next Generation Sequencing, support comprehensive and rapid molecular genetic screening for cardiomyopathy. The aim of this article is to provide an overview of the genetics and pathogenesis of cardiomyopathy. We will also discuss how new genetic technologies are being used to accelerate gene discovery and molecular genetic diagnosis and increase the potential for personalised medicine for individuals with cardiomyopathy.

Conclusion

Considerable progress in understanding of the biology of cardiomyopathy has been driven in part by gene identification, which has been accelerated dramatically by Next Generation Sequencing technology. Next Generation Sequencing coupled with increased understanding of disease biology is making personalised medicine a reality. Despite the advances in technology, limitations remain in data quality, analysis and interpretation. A portion of patients with cardiomyopathy still remain undiagnosed due in part to the difficulty in identifying casual variants among the many genetic variants identified by Next Generation Sequencing. This has highlighted the need to advance current databases and improve collaboration between the laboratory and clinic.

Introduction

Cardiomyopathies (CMs) are the main cause of cardiovascular morbidity and mortality in both children and adults. The overall incidence of CM in children <18 years of age in the United States is 1.13 cases per 100,000 population[1]. More than 24,000 deaths are caused annually by CM, which is second only to coronary artery disease as the most common direct cause of sudden death[1].

Primary CMs are a clinically heterogeneous group of disorders affecting the heart muscle, which can lead to compromised heart function. The classification of primary CMs has been an on-going debate, but in 2008 the European Society of Cardiology classified CM into several major categories based on morphology and function: hypertrophic (HCM), dilated (DCM), arrythmogenic right ventricular (ARVC), restrictive (RCM) and unclassified CM[2]. This review will focus on HCM and DCM, the two predominant types of CM. The other categories have been recently reviewed elsewhere[3–5], but for completeness the full list of known CM disease-associated genes is provided in Table 1.

Discussion

The discovery of disease-causing genes in individuals with CM has increased our knowledge of disease pathophysiology and improved patient treatment options. There are now over 50 genes known to be associated with CM (Table 1). Gene discovery enables molecular analysis to be performed, potentially resulting in early diagnosis and the provision of cascade testing within the family. Early diagnosis and identification of at-risk individuals is important as the clinical implications and outcomes vary depending on both the gene and mutation type. For example, within the HCM genes, mutations in myosin heavy chain beta (*MYH7*) and cardiac troponin T (*TNNT2*) are associated with poor prognosis including sudden death, whereas individuals with cardiac myosin-binding protein C (*MYBPC3*) mutations have a comparatively good outcome[6]. Recent studies have also illustrated that gene discovery can enable analysis of potential targets for therapeutic intervention in CM[7,8].

Major advances in the field of molecular genetics have led to a rapid

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Table 1 Genes associated with cardiomyopathy*

Gene	Protein	Cardiomyopathy classification			Protein localisation
		HCM	DCM	Other CM	
ABCC9	ATP-binding cassette, sub-family C, member 9	–	X	–	Sarcolemma
ACTC1	Actin, alpha cardiac muscle 1	X	X	X (RCM, UNC)	Sarcomere
ACTG1	Actin, gamma 1	–	X	–	Cytoskeleton
ACTN2	Actinin, alpha 2	X	X	–	Z-disk
ANKRD1	Ankyrin repeat domain 1	X	X	–	Z-disk
BAG3	BCL2-associated athanogene 3	X	X	X (RCM)	Z-disk
CASQ2	Calsequestrin 1	X	–	X (UNC)	Sarcoplasmic reticulum
CAV3	Caveolin 3	X	X	–	Sarcolemma
CRYAB	Crystallin, alpha B	–	X	–	Cytoskeleton
CSRP3	Cysteine and glycine-rich protein 3	X	X	–	Z-disk
CTF1	Cardiotrophin 1	–	X	–	Intra/extracellular—cytokine
DAG1	Dystroglycan 1	–	X	–	Dystrophin-associated protein complex
DES	Desmin	–	X	X (ARVC, RCM)	Cytoplasm—intermediate filament
DMD	Dystrophin	–	X	–	Cytoskeleton
DSC2	Desmocollin 2	–	X	X (ARVC)	Desmosome
DSG2	Desmoglein 2	–	X	X (ARVC)	Desmosome
DSP	Desmoplakin	–	X	X (ARVC)	Desmosome
DTNA	Dystrobrevin alpha	–	X	X (UNC)	Dystrophin-associated protein complex
EMD	Emerin	–	X	–	Nuclear membrane
EYA4	Eyes absent homolog 4	–	X	–	Nucleus—transcriptional activator
FHL2	Four and a half LIM domains 2	–	X	–	Z-disk
FKTN	Fukutin	–	X	–	Dystrophin-associated protein complex
FKRP	Fukutin-related protein	–	X	–	Dystrophin-associated protein complex
GATAD1	GATA zinc finger domain containing 1	–	X	–	Nucleus—histone modification
GLA	Galactosidase, alpha	X	–	–	Cytoplasm—lysosome
ILK	Integrin-linked kinase	–	X	–	Sarcolemma
JUP	Junction plakoglobin	–	–	X (ARVC)	Desmosome
JPH2	Junctophilin 2	X	–	–	Sarcoplasmic reticulum
LAMA4	Laminin, alpha 4	–	X	–	Basement membrane
LAMP2	Lysosomal-associated membrane protein 2	X	X	–	Cytoplasm—lysosome
LDB3	LIM domain binding 3	X	X	X (UNC)	Z-disk
LMNA	Lamin A/C	–	X	X (UNC)	Nuclear membrane
MYBPC3	Myosin-binding protein C, cardiac	X	X	X (UNC)	Sarcomere

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Table 1 Continued					
MYH6	Myosin, heavy polypeptide 6, cardiac muscle, alpha	X	X	–	Sarcomere
MYH7	Myosin, heavy chain 7, cardiac muscle, beta	X	X	X (RCM, UNC)	Sarcomere
MYL2	Myosin, light chain 2, regulatory, cardiac, slow	X	–	–	Sarcomere
MYL3	Myosin, light chain 3, alkali; ventricular, skeletal, slow	X	–	–	Sarcomere
MYLK2	Myosin light chain kinase 2	X	–	–	Sarcomere
MYOZ2	Myozenin 2	X	–	–	Z-disk
MYPN	Myopalladin	X	X	X (RCM)	Z-disc
NEBL	Nebulette	–	X	–	Z-disk
NEXN	Nexilin (F actin-binding protein)	X	X	–	Z-disk
PDLIM3	PDZ and LIM domain 3	–	X	–	Cytoskeleton
PKP2	Plakophilin 2	–	X	X (ARVC)	Desmosome
PLN	Phospholamban	X	X	–	Sarcoplasmic reticulum
PRKAG2	Protein kinase, AMP-activated, gamma 2 non-catalytic subunit	X	–	–	Intracellular—kinase
PSEN1	Presenilin 1	–	X	–	Transmembrane
PSEN2	Presenilin 2	–	X	–	Transmembrane
RBM20	RNA-binding motif protein 20	–	X	–	Nucleus
RYR2	Ryanodine receptor 2	X	–	X (ARVC)	Sarcoplasmic reticulum
SCN5A	Sodium channel, voltage-gated, type V, alpha subunit	–	X	–	Sarcolemma
SGCG	Sarcoglycan, gamma	–	X	–	Dystrophin-associated protein complex
SGCD	Sarcoglycan, delta	–	X	–	Dystrophin-associated protein complex
TAZ	Tafazzin	–	X	X (UNC)	Mitochondrial
TCAP	Titin cap	X	X	–	Z-disk
TMEM43	Transmembrane protein 43	–	–	X (ARVC)	Transmembrane
TMPO	Thymopoietin	–	X	–	Nuclear membrane
TNNC1	Troponin C type 1	X	X	–	Sarcomere
TNNI3	Troponin I type 3	X	X	X (RCM)	Sarcomere
TNNT2	Troponin T type 2	X	X	X (RCM, UNC)	Sarcomere
TPM1	Tropomyosin 1	X	X	–	Sarcomere
TTN	Titin	X	X	X (ARVC)	Sarcomere
TTR	Transthyretin	X	–	–	Cytoplasm—transport protein
VCL	Vinculin	X	X	X (UNC)	Z-disk

*Genes associated with the development of CM are listed, where the presence of an (X) indicates involvement of the gene in each specific cardiomyopathy classification. The localisation of the protein encoded by each disease gene is also described (where known).

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acceleration in the availability of genetic testing for patients with CM. Next Generation Sequencing (NGS)-based technologies, which include CM-specific targeted panels, whole exome and whole genome analysis, now allow comprehensive genetic screening in a fast and efficient manner. NGS technologies are making personalised medicine a reality; however, they also present complex clinical and ethical issues. Currently, the guidelines for clinical testing and management of CM do not adequately address the issues arising from availability of NGS in the diagnostic setting.

Hypertrophic cardiomyopathy

HCM is the most common hereditary disease of the heart with an estimated prevalence of 1 per 500 in the general population[9]. HCM is the most common cause of sudden cardiac death in young athletes[10]. It is characterised by left, or less commonly right, ventricular hypertrophy (excessive thickening of the myocardium) without an identifiable cause, such as hypertension[11]. The extent and localisation of wall thickening is highly variable, usually asymmetric and can involve the interventricular septum (Figure 1)[12].

HCM patients typically exhibit myocardial fibre disarray with cardiomyocyte thickening due to an increase in sarcomeric units[13]. Heart systolic function usually remains normal; however, fibrosis and hypertrophy generally result in diastolic dysfunction[14]. Left ventricular hypertrophy can also result in a narrowed left ventricular outflow tract causing outflow obstruction and left atrioventricular regurgitation[15]. Ventricular arrhythmia also can occur due to myocardial perturbations and impaired calcium handling[16].

The hypertrophy process, which is triggered by mutations in genes encoding sarcomeric proteins, remains incompletely understood. Several theories have been developed to explain how altered biophysical properties of individual sarcomeric proteins might result in hypertrophic remodelling. These include disruption of contractile function, altered energy homoeostasis, altered calcium cycling and sensitivity, an increase in myocardial fibrosis, impaired biomechanical stress sensing and microvascular dysfunction[16–18].

HCM is generally inherited in an autosomal dominant manner with hundreds of mutations affecting more than 27 genes identified to date (Table 1 and Figure 2)[13]. Mutations in genes encoding sarcomere contractile proteins, which result in compromised sarcomere function, represent the largest single class[19–21]. The proteins myosin heavy chain beta (MYH7), cardiac myosin-binding protein C (MYBPC3) and troponin T type 2 (TNNT2) are the most commonly affected proteins and mutations in the genes encoding these three proteins account for up to 55% of familial HCM cases[22]. Given the strong genetic basis of HCM, genetic testing is recommended as part of routine clinical care for individuals with CM and their families[23].

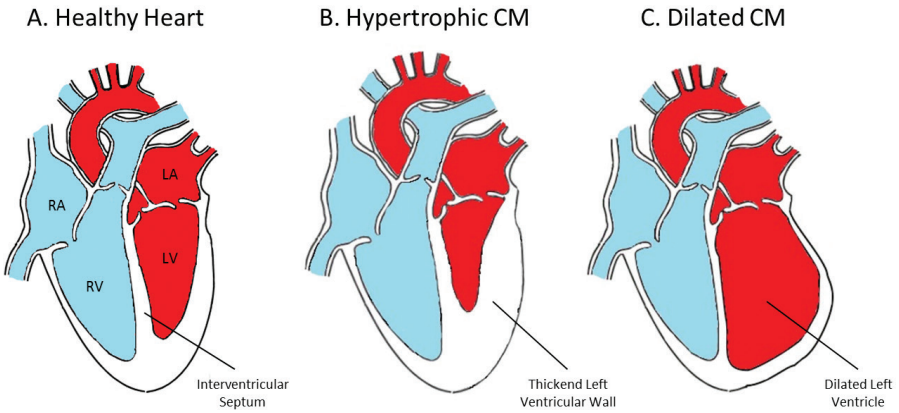

Figure 1: Patterns of cardiac remodelling in HCM and DCM. The anatomy of a healthy human heart (A) consists of right atrium (RA) and right ventricle (RV), which are separated from the left atrium (LA) and left ventricle (LV) by the interventricular septum. Cardiac remodelling occurring in asymmetric HCM (B) is characterised by hypertrophy (thickening) of the LV wall and can include the interventricular septum. Biventricular hypertrophy can also occur, however, this is rare and therefore not depicted in the illustration. In contrast, DCM (C) is characterised by left ventricular enlargement associated with thinning of the left ventricular wall. Atrial enlargement in DCM is occasionally observed as a secondary consequence of the expanded ventricle.

Dilated cardiomyopathy

DCM is characterised by dilation and impaired contraction of the left ventricle or both ventricles, resulting in systolic dysfunction without an identifiable external cause[12]. In the United States, DCM affects approximately one in 2500 individuals and is a leading cause of heart failure and arrhythmia; there is substantial morbidity and premature mortality associated with the disease[14,24].

DCM can be idiopathic or familial with previous studies suggesting that 35–48% of DCM is familial[25,26]. Familial DCM is heterogeneous; autosomal dominant, autosomal recessive, X-linked recessive and mitochondrial inheritance patterns have all been documented[27]. The pathogenesis of DCM is characterised by pronounced ventricular chamber dilation, often

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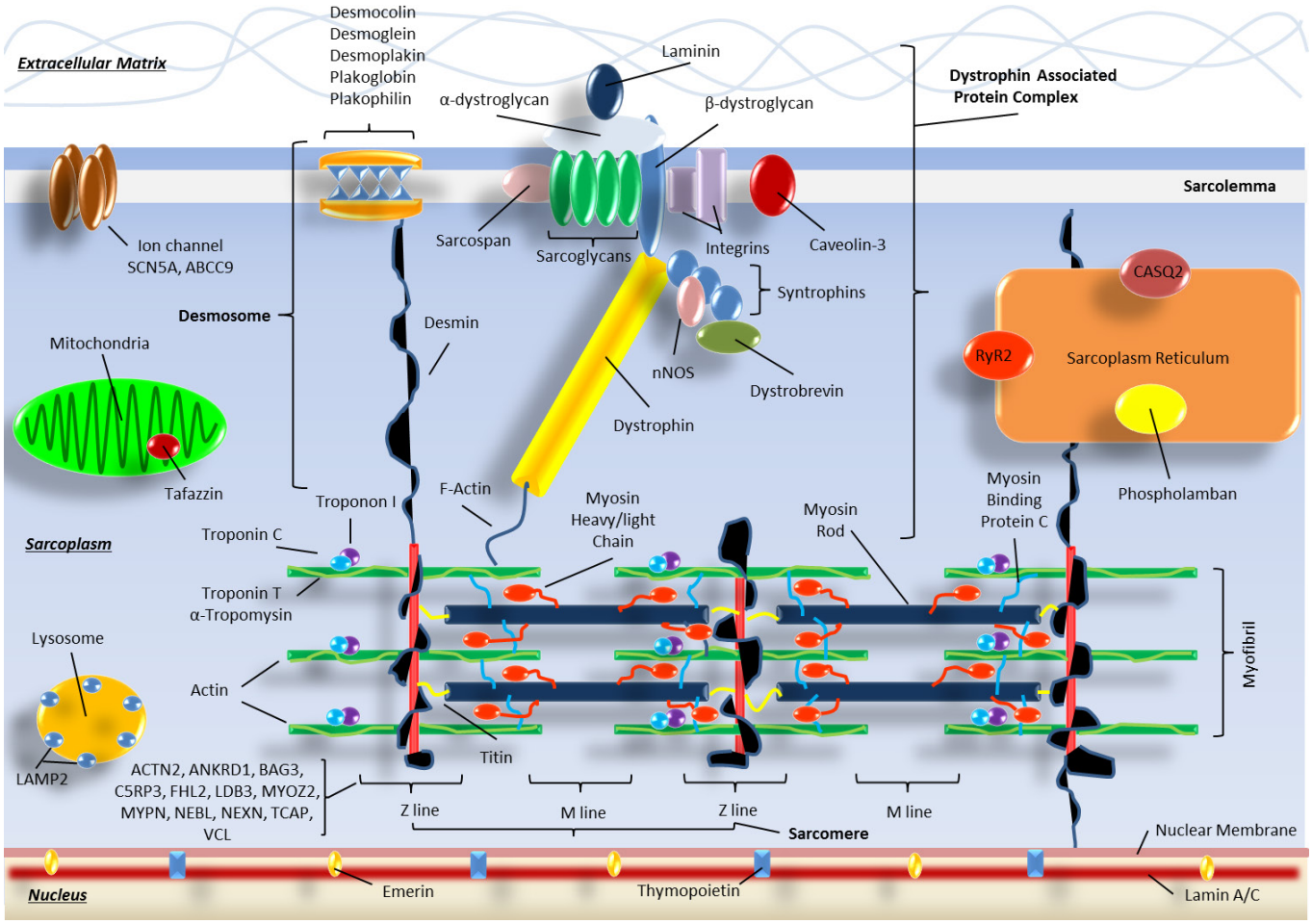

Figure 2: Cellular localisation of proteins encoded by CM genes. The cardiomyocyte cell membrane is known as the sarcolemma. A key component of the sarcolemma is the dystrophin-associated protein complex (DAPC), which has a structural role in linking the actin cytoskeleton to the extracellular matrix whilst stabilising the sarcolemma during repeated cycles of contraction and relaxation. The complex includes membrane proteins, such as the dystroglycans and sarcoglycans. Mutations in the genes encoding both protein families are associated with DCM. The dystroglycans mediate interactions with extracellular matrix (ECM) proteins, such as Laminin. Similarly, the DAPC cytoplasmic components syntrophin, dystrophin and dystrobrevin have an important role within the cell. For example, dystrophin links the complex to the cytoskeleton, by anchoring to the cytoskeletal protein F-actin. The DAPC has also been implicated in signal transduction. This is mediated through the DAPC integrins and interactions with neuronal nitric oxide synthase (nNOS). Additional sarcolemma elements affected in CMs include ion channels, caveolin proteins and the desmosome.

The desmosome has a key role in the transmission of force during muscle contraction. It is a protein complex that forms a junction between adjacent cardiomyocytes and connects to the cytoskeleton through the intermediate filament Desmin (DES). Proteins involved in desmosome structure and/or function include, Desmocolin-2 (DSC2), Desmoglein-2 (DSG2), Desmoplakin (DSP), Plakoglobin (JUP) and Plakophilin-2 (PKP2). With the exception of Plakoglobin (JUP), mutations in genes encoding these desmosomal proteins have all been associated with DCM and ARVC.

The majority of proteins associated with CM contribute to the structure or function of the sarcomere. The sarcomere is the basic structural unit of cardiomyocytes that enables contraction–relaxation of the cardiac muscle. Each sarcomere is composed of parallel alternating thin actin filaments and thick myosin rods that are contained within the Z-line (Z-disc). The Z-line forms the boundary between adjacent sarcomeres. The thin actin filaments anchored to the Z-line incorporate regulatory proteins Troponin I, Troponin C, Troponin T and α-Tropomysin. The actin filaments are linked to the myosin rods via the myosin-binding protein C. Similarly, the myosin rod is connected to the Z-line by the large protein Titin. The myosin filaments are composed of the myosin heavy and light chains. The central point of the filament is the M-line (M-band), where the myosin myofilaments crosslink to maintain alignment during muscle contraction–relaxation. Mutations in genes encoding all of the sarcomeric proteins mentioned have been associated with both HCM and DCM.

Another structure unique to muscle cells is the sarcoplasmic reticulum (SR). The SR functions to maintain the cardiomyocyte calcium store and actively pumps Ca^{2+} in/or out of the sarcoplasm during excitation–contraction coupling. Disruption of proteins involved in SR calcium handling, such as ryanodine receptor 2 (RyR2), calsequestrin 2 (CASQ2) and junctophilin 2 (JPN2) have been associated with HCM. Alterations to the SR calcium-handling protein phospholamban (PLN) have been implicated in both HCM and DCM.

To date, nuclear proteins have been associated with DCM but not with HCM. These include the nuclear membrane proteins Lamin A and C (LMNA), Emerin (EMD), Thymopoietin (TMPO) and the RNA-binding protein RBM20. Other organelles implicated in the development of CM include the mitochondria and lysosome, where causative mutations affecting the Tafazzin (TAZ) and lysosomal-associated membrane protein 2 (LAMP2) proteins, respectively, have been identified.

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atrial enlargement and a reduction in ventricular wall thickness (Figure 1)[28]. The histological changes associated with DCM include myocyte death, interstitial fibrosis and myocyte morphological alterations, which typically include nuclear hypertrophy and an empty appearance due to myofibril loss[28].

Due to the genetic heterogeneity and diversity of cellular processes affected in DCM patients, the pathophysiology is complex and incompletely understood[18]. DCM is predominantly caused by mutations in genes that encode for cytoskeleton and sarcomeric proteins. Mutations appear to cause disease by multiple mechanisms, including abnormal transmission of contractile force to the extracellular matrix, impaired activation of the normal transcriptional response to mechanical strain and diminished cell viability during periods of mechanical strain[17]. Mutations in other genes encoding cytoskeletal proteins have been suggested to cause DCM through more complex mechanisms including the accumulation of amyloid and resultant cytotoxicity[29]. In contrast to HCM-associated mutations, the pathogenesis of sarcomeric mutations in DCM appears to involve decreased motor function and the disruption of the sarcomere's response to calcium signalling[30,31]. Altered energetic and metabolic processes within the myocyte have also been shown to cause DCM in a small proportion of cases[32].

Mutations in *MYH7* gene that encodes the sarcomeric myosin heavy chain beta, are the most common cause of familial DCM accounting for approximately 6% of cases. In contrast, mutations in *DMD*, encoding cytoskeletal dystrophin, are the most common cause of sporadic DCM in Japanese patients[33]. Although DCM has a mixed aetiology and therefore lower genetic test sensitivity compared to HCM, there is substantial evidence supporting a genetic basis for DCM (Table 1 and Figure 2). Therefore, as with HCM, genetic testing is recommended as part of routine clinical care for affected individuals and their families[23].

Phenotype/genotype complexities associated with cardiomyopathy

CMs have traditionally been classified by clinical features including ventricular morphology and function[2]. However, it has become apparent that substantial genetic and phenotypic overlap exists between the distinct clinical classifications[34]. Accurate discrimination between the different CM classes and/or phenocopies is important to best inform inheritance pattern, disease course and potential therapeutic options[18]. For example, mutations in genes encoding sarcomeric proteins, which initially were associated with HCM, have recently been identified in patients with DCM, RCM and an unclassified LVNC CM[34]. This phenotypic overlap can even occur within families, for example, a single genetic mutation can cause LVNC and HCM within the same family[4].

Potential genotype/phenotype correlations are also limited in some cases due to the uncertainty of variant classification. Recent large-scale genotyping and sequencing projects, such as the 1000 genomes[56] and the Exome sequencing projects[57], have begun to delineate pathogenic mutations and rare benign variants. These large projects have illustrated errors in previous studies and databases due to poorly powered studies and lack of functional testing of described variants[34]. Limitations also arise because CM-causing mutations are often private (individual- or family-specific) and have incomplete penetrance, therefore, the genotype of a patient can have limited usefulness in clinical management (recently reviewed[18]). The phenotypic variability, reduced penetrance and limited genotype/phenotype correlation observed in CM may be accounted for by modifier genes, post transcriptional and epigenetic effects and/or environmental factors[18]. The development and application of new genomic technologies is allowing these complex issues to be systematically studied and tested.

New genomic technologies: research benefits and clinical role in cardiomyopathy

Recent advances in molecular genetic technologies have provided important tools for both molecular diagnosis and novel disease gene discovery in the field of cardiomyopathy[35]. The two main technologies underpinning these advances are high-density genotyping arrays and NGS.

High-density genotyping arrays allow simultaneous determination of genotypes of numerous single nucleotide polymorphisms (SNPs). Genotyping arrays have been shown to have several applications in the context of CM, including:

- Gene discovery in familial CM: Linkage analysis can be performed using genotyping array data to identify the disease loci in CM families[36,37].
- Direct identification of known CM disease loci: High-density genotyping arrays assay for SNPs and genomic deletions and duplications. Copy number variations (CNVs) in CM have not been extensively studied but have been shown in rare cases to cause CM[38,39].
- Identification of risk alleles/common variants associated with cardiomyopathy: Genome-wide association studies (GWASs) analyse many SNPs in large case–control cohorts to identify variants associated with a particular trait. Several recent GWASs have identified genes associated with cardiovascular disease. The validation of these studies is on-going and translation to clinical practice is currently limited[40,41]. However, as our understanding of the molecular basis of CM improves, there is likely to be increased utilisation of dense genotype data to calculate risk profiles and predict therapeutic treatment outcomes.

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NGS involving simultaneous sequencing of thousands of DNA fragments has revolutionised molecular genetic testing. The main advantages of NGS over traditional Sanger sequencing are throughput, scalability and quantity of data generated. Therefore, molecular diagnoses can be delivered in a comprehensive, rapid and cost-efficient manner[42]. The massively parallel approach of NGS technology allows the simultaneous sequencing of many genes; it is therefore an ideal technology for molecular genetic diagnosis of CM and other genetically heterogeneous disorders.

Targeted enrichment of known disease-causing genes from genomic DNA is one strategy that can be used to screen CM-associated genes using NGS technology[43] and is being successfully applied in the clinic[42,44,45]. Several commercial enrichment panels, such as 34-gene panel (Agilent Technologies), 46-gene panel (Illumina's Trusight) and 51-gene panel (Emory Genetics) have been designed specifically for genetic testing of CM. The advantages of this targeted approach are that the datasets generated are small enough for simple analysis and that great depth of sequencing is achievable. In addition, knowledge of the structure and function of proteins encoded by the targeted genes is generally available; therefore, interpretation of identified variants is simplified. The primary disadvantage of targeted panels is that only known genes are analysed and therefore novel disease-causing genes will not be identified.

An alternative approach to targeted gene sequencing is to use NGS in the context of whole exome sequencing (WES) or whole genome sequencing (WGS). The majority of mutations underlying CM are located within or very close to the coding regions (exons) of genes. Exons make up approximately 1% of the entire genome; therefore, WES essentially represents a large-scale version of a targeted panel[46]. The advantages of WES are that it interrogates the majority of genes within the genome; therefore, novel disease-causing genes may be identified. In addition, the datasets produced are relatively small and can be easily managed and analysed[46]. The disadvantages of WES include the variable depth of sequence achieved across the different genes targeted. The scale of WES means that bioinformatics support is necessary and comprehensive variant databases need to be available. In addition, many more variants are identified compared to the targeted panels. Not only does this mean variants of unknown significance (VUS) are identified, but the complex issue of the 'incidentalome' needs to be managed. The incidentalome refers to the vast amount of incidental data generated by NGS[47,48]. Currently, how these incidental findings are reported to patients is highly variable depending on the diagnostic centre and associated clinical service. However, recent guidelines have been developed to provide direction and standardise the practice for reporting NGS results[49,50].

The ultimate application of NGS technologies is WGS that involves the non-targeted sequencing of the majority of the approximately three billion DNA bases that make up the human genome. The advantage of WGS is that the entire genome is sequenced, which includes both coding and intronic regions not captured by WES. CNV analysis can also be performed due to the uniform depth of sequencing usually achieved. The primary disadvantages of WGS include the cost and the very large datasets that are generated. Data analysis requires dedicated bioinformatics support, is time consuming and identifies hundreds of thousands of variants. These need to be assessed by experts with appropriate bioinformatics and biological expertise.

NGS technologies are not limited to the genome; current areas of development in the context of CM and other disorders include transcriptomics (RNA-Seq: gene expression profiling), the epigenome (MeDIP-Seq: DNA methylation patterns) and the regulome (ChIP-Seq: transcription factor binding)[51,52].

WES/WGS is beginning to be applied in the clinic. For example, neonatal intensive care units have applied WGS to achieve a rapid (<50 hours) definitive diagnosis of genetic disorders. This dramatically has reduced diagnosis time and has offered new hope for personalised intervention and treatment[53,54]. WES has also been used to improve diagnosis and alter patient management in patients with neurological disorders[55]. However, personalised medicine for CM patients currently remains controversial, in part due to the complex phenotype–genotype correlations and lack of understanding of disease pathophysiology.

Conclusion

Molecular genetic screening for CM has until now been a cumbersome and expensive task due to the issues of genetic heterogeneity, clinical variability and reduced penetrance. Recent advances in genetic technologies, in particular NGS, have addressed these issues and provided important tools for molecular genetic diagnosis and accelerated novel disease gene discovery in CM. As these new genomic technologies have found application in the clinic settings, they have raised additional scientific, clinical and ethical issues that need to be considered. These include the interpretation and classification of variants of unknown significance and reporting of incidental findings. Appropriate clinical genomic guidelines need to be developed and implemented to address these issues and maximise benefits to the patient. Interestingly, the American College of Medical Genetics and Genomics (ACMG) recently announced recommendations for the reporting

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of incidental findings. The authors identified 57 genes where early intervention was considered likely to reduce or prevent morbidity or mortality, and 11 of these genes were associated with HCM. As the technology continues to improve, becoming more affordable and accessible, and with our increasing understanding of CM disease pathophysiology, personalised medicine for affected individuals and families is fast becoming a reality.

Abbreviations list

ACMG, American College of Medical Genetics and Genomics; ARVC, arrythmogenic right ventricular cardiomyopathy; CASQ2, calsequestrin 2; CM, cardiomyopathy; CNVs, copy number variations; DAPC, dystrophin-associated protein complex; DCM, dilated cardiomyopathy; DES, Desmin; DSC2, Desmocolin-2; DSG2, Desmoglein-2; DSP, Desmoplakin; EMD, Emerin; GWASs, Genome-wide association studies; HCM, hypertrophic cardiomyopathy; IRIISS, Independent Research Institutes Infrastructure Support Scheme; JPN2, junctophilin 2; JUP, Plakoglobin; A, left atrium; LAMP2, lysosomal-associated membrane protein-2; LMNA, Lamin A and C; LV, left ventricle; MYBPC3, cardiac myosin-binding protein C; MYH7, myosin heavy chain beta; NGS, Next Generation Sequencing; NHMRC, National Health and Medical Research Council; nNOS, neuronal nitric oxide synthase; PKP2, Plakophilin-2; PLN, phospholamban; RA, right atrium; RCM, restrictive cardiomyopathy; RV, right ventricle; RyR2, ryanodine receptor 2; SNP, single nucleotide polymorphism; SR, sarcoplasmic reticulum; TMPO, Thymopoietin; TNNT2, cardiac troponin T; TAZ, Tafazzin; VUS, variants of unknown significance; WES, whole exome sequencing; WGS, whole genome sequencing.

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