Review Article

Genotype-phenotype Correlations in Inherited Cardiomyopathies, their Role in Clinical Decision-making and Implications in Personalized Cardiac Medicine in Multi-omics as Well as Disease Modelling Eras

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ABSTRACT

Inherited cardiomyopathies are a diverse group of heart muscle diseases caused by genetic mutations that result in structural and functional abnormalities of the myocardium. Understanding genotype-phenotype correlations in these conditions is vital for personalized cardiac medicine, enabling targeted therapeutic strategies and predictive diagnostics. This review explores the major types of inherited cardiomyopathies: Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), Arrhythmogenic Cardiomyopathy (ACM) and Restrictive Cardiomyopathy (RCM) and provides detailed insights into how different genetic mutations manifest as clinical features. The integration of multi-omics approaches and advanced disease modelling techniques has enhanced our ability to dissect these correlations. The review also discusses the implications of these findings for personalized medicine, including tailored therapeutic strategies, predictive diagnostics, and future research directions.

Keywords: Cardiomyopathy; Multi-omics techniques; Personalized medicine; Genetic testing

INTRODUCTION

Inherited cardiomyopathies represent a heterogeneous group of heart muscle diseases characterized by structural and functional abnormalities of the myocardium [1]. These conditions are primarily caused by genetic mutations that lead to varying clinical phenotypes. Understanding the genotype-phenotype correlations in these diseases is crucial for advancing personalized cardiac medicine, as it allows for the development of targeted therapeutic strategies and predictive diagnostics [2]. The integration of multi-omics approaches and advanced disease modelling techniques has further enhanced our ability to dissect these correlations and tailor therapeutic interventions [3]. Cardiomyopathies were first described in the mid-20th century, with early classifications based on clinical and pathological findings. Over time, it became evident that many

cardiomyopathies had a genetic basis, leading to the identification of specific mutations associated with different forms of the disease. The major types of inherited cardiomyopathies include Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), Arrhythmogenic Cardiomyopathy (ACM), and Restrictive Cardiomyopathy (RCM) [4]. Genotype-phenotype correlations provide insights into how specific genetic mutations manifest as particular clinical features [2]. These correlations are essential for genetic counseling, risk stratification, and the development of personalized treatment plans.

LITERATURE REVIEW

Inherited cardiomyopathies

Inherited cardiomyopathies include Hypertrophic Cardiomyopathy (HCM) with thickened heart walls, Dilated Cardiomyopathy (DCM) with enlarged and weakened ventricles, Arrhythmogenic Cardiomyopathy (ACM) involving fibrofatty tissue in the heart, and Restrictive Cardiomyopathy (RCM) characterized by stiffened heart muscles, all leading to impaired cardiac function and increased risk of heart failure.

Hypertrophic Cardiomyopathy (HCM): HCM is the most common inherited cardiomyopathy, with a prevalence of 1 in 500 individuals. It is primarily caused by mutations in genes encoding sarcomeric proteins, such as *MYH7*, *MYBPC3*, and *TNNT2*. These mutations lead to abnormal sarcomeric function and myocardial hypertrophy [5]. Genotype-phenotype studies have shown that specific mutations are associated with varying degrees of hypertrophy, arrhythmias, and risk of sudden cardiac death [6]. For instance, mutations in the *MYH7* gene often result in more severe hypertrophy and a higher risk of sudden cardiac death, necessitating aggressive management and consideration for Implantable Cardioverter-Defibrillators (ICDs) [7]. On the other hand, mutations in the *MYBPC3* gene may present with milder hypertrophy but carry a higher risk of heart failure [8]. Recent clinical guidelines recommend genetic testing for all first-degree relatives of patients with HCM to identify those at risk and guide early intervention strategies [9]. Patients with *MYH7* mutations often exhibit severe hypertrophy and are at a higher risk of sudden cardiac death [10], while *MYBPC3* mutations are associated with a more diverse clinical presentation, ranging from mild to severe hypertrophy [8]. Clinical management may involve the use of ICDs for primary prevention in these patients. Additionally, beta-blockers and calcium channel blockers are recommended to manage symptoms and reduce arrhythmias [11].

Dilated Cardiomyopathy (DCM): DCM is characterized by left ventricular dilatation and systolic dysfunction [12]. It is caused by mutations in a diverse set of genes, including those encoding cytoskeletal, sarcomeric, and nuclear envelope proteins. Notable genes include *TTN*, *LMNA*, *FLNC*, *DES*, *TMEM43* and DSP [13]. Genotype-phenotype correlations in DCM are complex, with some mutations leading to severe dilatation and heart failure, while others result in milder phenotypes [14,15]. *TTN* truncating variants are among the most common mutations found in DCM and are associated with a wide spectrum of clinical outcomes, from asymptomatic carriers to severe heart failure requiring transplantation [16,17].

Mutations in the *LMNA* gene are particularly associated with early-onset heart failure, conduction system disease, and arrhythmias, often necessitating the early implantation of pacemakers or ICDs [18,19]. Clinical guidelines emphasize the importance of early

genetic testing in DCM patients to identify those with *LMNA* mutations and implement appropriate monitoring and preventive measures [20]. Therapies with DCM may vary by presciber, symptoms, and specific disease pathology. Angiotensin-converting enzyme inhibitors, Angiotensin II receptor blockers, β-blockers, mineralocorticoid receptor antagonists, ivabradine, and sodium-glucose contransporter-2 inhibitor showed a significant reduction of hospitalization and/or mortality. Other treatment options include pacemaker, ablation therapy, cardiac resynchronization therapy, and ICD therapy. Severe cases may require heart transplant, IV inotropes, durable ventricular assist device and extracorporeal membrane oxygenation [21].

Arrhythmogenic Cardiomyopathy (ACM): ACM or previously known as Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is characterized by fibrofatty replacement of the right ventricular myocardium and ventricular arrhythmias. It is commonly caused by mutations in desmosomal genes, such as *PKP2*, *DSP*, and *SG2*. These mutations disrupt cell-cell adhesion, leading to myocardial degeneration and arrhythmias [22]. Genotype-phenotype studies have shown that specific mutations are associated with varying degrees of ventricular dysfunction and arrhythmic risk [23]. *PKP2* mutations are often associated with more severe arrhythmic events and a higher risk of sudden cardiac death, necessitating aggressive arrhythmia management and consideration for ICD implantation [24]. *DSP* mutations may present with both right and left ventricular involvement, complicating the clinical picture and requiring comprehensive management strategies [25,26]. Current clinical guidelines recommend genetic testing for all first-degree relatives of ARVC patients to identify those at risk and guide surveillance and treatment plans [26,27]. Treating ARVC can be challenging due to progressive fibrosis, phenotypic variations, and differential diagnosis with other conditions. Patients with *PKP2* mutations often exhibit severe ventricular arrhythmias, and clinical guidelines recommend the use of ICDs for primary prevention of sudden cardiac death. Antiarrhythmic drugs and beta-blockers are also recommended to manage arrhythmias. Patients with *DSP* mutations may require more comprehensive management due to potential involvement of both ventricles. Clinical management may involve the regular monitoring of both right and left ventricular function and the use of ICDs for arrhythmia prevention [22,28].

Restrictive Cardiomyopathy (RCM): RCM is the least common form of inherited cardiomyopathy, characterized by diastolic dysfunction and restrictive filling of the ventricles (24). It can be caused by mutations in sarcomeric and nonsarcomeric genes, including *TNNI3*, *MYH7*, *FLNC*, and *DES* [15,29].

Genotype-phenotype correlations in RCM are less well-defined due to the rarity of the disease, but certain mutations are associated with severe diastolic dysfunction and poor prognosis [30,31]. *TNNI3* mutations can lead to severe restrictive physiology and early heart failure [32,33], while *MYH7* mutations may present with overlapping features of HCM and RCM, complicating the diagnosis and management [34]. Clinical guidelines recommend comprehensive genetic testing in RCM patients to identify causative mutations and tailor treatment strategies accordingly [35]. Patients with *TNNI3* mutations often present with severe diastolic dysfunction and may benefit from aggressive diuretic therapy to manage symptoms of heart failure [36]. Anticoagulation therapy may be recommended to prevent thromboembolic complications [37]. Due to the potential overlap with HCM [38], patients with *MYH7* mutations may require a combination of therapies used

for both HCM and RCM, including beta-blockers, calcium channel blockers, and diuretics. Regular monitoring for changes in phenotype and heart failure progression is crucial [39].

The layering of genotype and phenotype is complicated by overlaps amongst the major subtypes of inherited cardiomyopathies. Differential mutation detection in different types of cardiomyopathies can aid in differential diagnosis, prognostic stratification, and selection of treatment. For example, identifying a *TTN* mutation in a patient with DCM can indicate a potential for severe heart failure and guide decisions regarding early intervention with heart failure therapies or consideration for heart transplantation [40]. Similarly, detecting a *PKP2* mutation in a patient with ARVC can highlight the need for aggressive arrhythmia management and consideration of an ICD [41].

Multi-omics approaches in cardiomyopathies

The advent of multi-omics technologies has revolutionized the study of cardiomyopathies [42]. Multi-omics approaches integrate data from various omics layers, including genomics, transcriptomics, proteomics, and metabolomics, to provide a comprehensive view of the molecular mechanisms driving disease phenotypes [43].

Genomics: Genomic studies have identified numerous genetic mutations associated with inherited cardiomyopathies. Whole-Exome Sequencing (WES) and Whole-Genome Sequencing (WGS) have been particularly useful in identifying rare and novel variants [44]. These technologies have also facilitated the study of genetic modifiers that influence disease severity and penetrance [45].

Transcriptomics: Transcriptomic analyses, such as RNA sequencing, provide insights into gene expression changes associated with cardiomyopathies [46,47]. These studies have identified differentially expressed genes and pathways that contribute to disease pathogenesis [48].

For example, transcriptomic studies in HCM have revealed upregulation of hypertrophic signaling pathways and downregulation of energy metabolism genes [49].

Proteomics: Proteomic approaches, including mass spectrometry, have been used to study protein expression and post-translational modifications in cardiomyopathies [50,51]. These studies have identified altered protein networks and signaling pathways that contribute to disease phenotypes [52]. For instance, proteomic analyses in DCM have revealed dysregulation of cytoskeletal and mitochondrial proteins [53].

Metabolomics: Metabolomic studies provide insights into metabolic alterations associated with cardiomyopathies [50,54]. These studies have identified changes in metabolites and metabolic pathways that contribute to disease progression [55]. For example, metabolomics analyses in ARVC have revealed alterations in lipid metabolism and energy production [56].

Disease modeling in cardiomyopathies

Advanced disease modeling techniques, such as the use of induced Pluripotent Stem Cells (iPSCs) and animal models, have provided valuable platforms for studying cardiomyopathies. These models enable the investigation of disease mechanisms, the testing of therapeutic interventions, and the study of patient-specific disease phenotypes [57]. Indeed, these preclinical models can also help to clarify the genotype-phenotype associations and the pathophysiological mechanisms.

Induced Pluripotent Stem Cells (iPSCs): iPSCs are derived from patient-specific somatic cells and can be differentiated into cardiomyocytes [58]. While monolayer iPSC cultures exhibit considerable scalability, they yield a model that is inherently simplified and less intricate in comparison to the complexity observed in both 3D *in vitro* models and *in vivo* systems (Figure 1). Despite this, iPSC-derived cardiomyocytes can still recapitulate many aspects of the patient's disease phenotype, allowing for the study of disease mechanisms and drug testing in a patient-specific context. For example, iPSC models of HCM have been used to study the effects of *MYBPC3* mutations on sarcomere function and calcium handling [59]. Indeed, the technology of using iPSC-derived cardiomyocytes has been used to model numerous inherited cardiomyopathies, whether by producing patient-specific cells, editing the genome of healthy cells, or even overexpressing mutated ion channels.
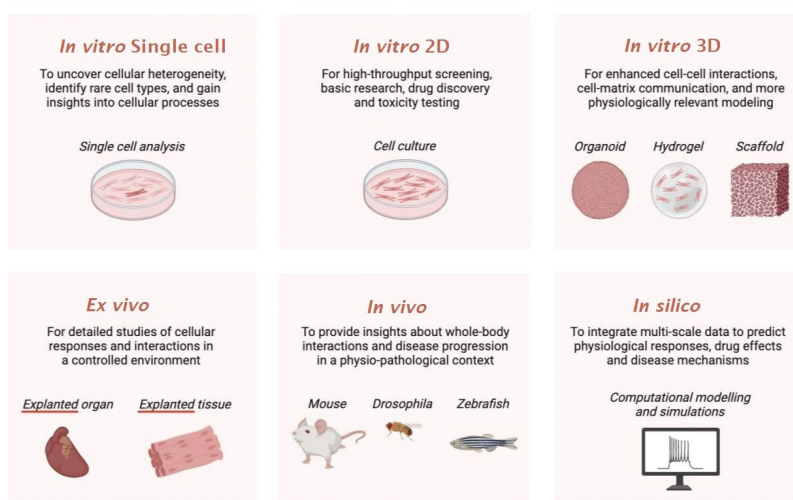
Figure 1: Summary of the available *in vitro, in vivo, ex vivo,* and *in silico* platforms that can model inherited cardiomyopathy.

Animal models: Animal models, including transgenic mice and zebrafish, have been widely used to study cardiomyopathies [60]. These models allow for the investigation of gene function and the study of disease progression in a whole-organism context [61]. For instance, transgenic mouse models of DCM have been used to study the effects of *TTN* mutations on cardiac function and remodeling [62].

DISCUSSION

Future impact of cardiac regenerative medicine in finding innovative treatment for cardiomyopathies

The field of cardiac regenerative medicine and the use of cardiac stem cells hold significant promise for developing innovative treatments for cardiomyopathies. Recent advancements in stem cell biology and regenerative medicine have paved the way for novel therapeutic approaches that aim to repair or replace damaged cardiac tissue, thereby improving cardiac function and patient outcomes [63].

Cardiac stem cells, including induced Pluripotent Stem Cells (iPSCs) and Mesenchymal Stem Cells (MSCs), have shown potential in regenerating damaged myocardium [64]. iPSCs can be generated from a patient's own somatic cells and differentiated into cardiomyocytes, which can then be used to replace damaged or dysfunctional heart tissue. This approach not only provides a personalized therapy option but also minimizes the risk of immune rejection [65,66]. Several studies have demonstrated the efficacy of iPSC-derived cardiomyocytes in improving cardiac function in animal models of cardiomyopathy [67].

In addition to iPSCs, MSCs have been explored for their regenerative potential in cardiac tissues. MSCs possess immunomodulatory properties and can promote tissue repair through paracrine signaling. They secrete a variety of growth factors, cytokines, and extracellular vesicles that can enhance angiogenesis, reduce fibrosis, and stimulate endogenous cardiac repair mechanisms [68]. Clinical trials investigating the use of MSCs in patients with cardiomyopathy have shown promising results, with improvements in cardiac function and reductions in adverse remodeling [69,70].

Another promising approach in cardiac regenerative medicine is the use of Extracellular Vesicles (EVs) derived from stem cells. EVs are small membrane-bound vesicles that contain bioactive molecules, such as proteins, lipids, and nucleic acids, which can modulate cellular processes and promote tissue repair. Studies have shown that EVs derived from stem cells can enhance cardiac regeneration by promoting cell survival, reducing inflammation, and stimulating angiogenesis [71]. The use of EVs as a therapeutic modality offers several advantages, including ease of administration, low immunogenicity, and the ability to cross biological barriers [72,73].

Tissue engineering and 3D bioprinting technologies are also being explored for their potential to create functional cardiac tissues for transplantation. These technologies involve the use of biomaterials, stem cells, and growth factors to construct three-dimensional cardiac tissues that can mimic the structure and function of native myocardium. Engineered cardiac tissues can be used to replace damaged heart tissue and restore cardiac function [74]. Recent advancements in 3D bioprinting have enabled the fabrication of complex cardiac structures with high precision, which can be tailored to individual patients' needs [75,76].

Despite the promising potential of cardiac regenerative medicine, several challenges remain to be addressed. These include the scalability and reproducibility of stem cell production, the risk of tumorigenicity, and the integration of transplanted cells with the host myocardium [77]. Additionally, the long-term safety and efficacy of these therapies need to be thoroughly evaluated in clinical trials [78].

Future research in cardiac regenerative medicine should focus on optimizing cell delivery methods, enhancing the survival and integration of transplanted cells, and developing strategies to modulate the cardiac microenvironment to support regeneration [79,80]. Collaborative efforts between researchers, clinicians, and industry partners will be essential to translate these innovative therapies from the bench to the bedside.

Implications for personalized medicine

Personalized medicine aims to tailor medical treatment to the individual characteristics of each patient [81]. In the context of cardiomyopathies, understanding genotype-phenotype correlations allows for the development of targeted therapies and predictive diagnostics [35].

Tailored therapeutic strategies: Personalized treatment plans based on genetic profiles have shown promise in improving outcomes for patients with cardiomyopathies [82,83]. For example, genotype-specific therapies, such as small-molecule inhibitors and gene therapies, are being developed for patients with specific mutations [84]. Additionally, personalized exercise and lifestyle recommendations can be made based on the patient's genetic risk factors [85].

Predictive diagnostics: Predictive diagnostics based on genotype-phenotype correlations can help identify individuals at high risk for developing cardiomyopathies and guide early intervention strategies [86,87]. For example, genetic testing can identify individuals with pathogenic mutations, allowing for close monitoring and preventive measures to reduce the risk of adverse outcomes [88].

Challenges and future directions: Despite the promise of personalized medicine, there are several challenges to its implementation. These include the complexity of genotype-phenotype correlations, the need for large-scale data integration, and the ethical considerations of genetic testing [81,89,90]. Future research should focus on addressing these challenges and further refining personalized treatment and diagnostic approaches.

Gaps in current research

Despite significant advancements, there are still gaps in our understanding of genotype-phenotype correlations in cardiomyopathies. Some genetic mutations have variable expressivity and incomplete penetrance, complicating the prediction of clinical outcomes [91]. Additionally, the integration of multi-omics data remains challenging due to the complexity and volume of data generated [92]. The lack of knowledge can be summarized into:

Unresolved correlations: Certain genotype-phenotype correlations remain unclear, with some mutations leading to highly variable clinical presentations. For example, mutations in the *LMNA* gene can cause a wide range of phenotypes, from mild dilatation to severe heart failure and arrhythmias [93]. Further research is needed to elucidate the factors that contribute to this variability.

Technological and methodological limitations: Current research methodologies have limitations that hinder the full understanding of genotype-phenotype correlations. For instance, WES and WGS may miss certain types of genetic variants, such as structural variants and deep intronic mutations [94]. Additionally, the integration of multi-omics data requires advanced computational tools and techniques, which are still in development [95].

Recommendations for future research: To address these gaps, future research should focus on improving genetic testing techniques, developing better data integration methods, and conducting large-scale studies to validate genotype-phenotype correlations. Collaborative efforts and the use of advanced technologies, such as machine learning, will be essential in advancing our understanding of inherited cardiomyopathies.

Future directions

Advances in multi-omics: Emerging technologies in multi-omics research, such as single-cell RNA sequencing and spatial transcriptomics, have the potential to provide deeper insights into the cellular and molecular mechanisms of cardiomyopathies [96]. These technologies can help identify novel therapeutic targets and biomarkers for personalized treatment [97].

Innovations in disease modelling: New approaches to disease modeling, such as the use of organ-on-a-chip technology and 3D bioprinting, can enhance our ability to study cardiomyopathies in a more physiologically relevant context [98]. These models can be used to test the efficacy and safety of new therapies and to study the interactions between different cell types in the heart [99].

Translational research and clinical applications: Bridging the gap between research and clinical practice is essential for translating scientific discoveries into effective treatments for patients with cardiomyopathies [100]. Collaborative efforts between researchers, clinicians, and industry partners will be important in developing and implementing personalized therapeutic strategies.

CONCLUSION

In summary, genotype-phenotype correlations play a pivotal role in the study and management of inherited cardiomyopathies. The integration of multi-omics approaches and advanced disease modeling techniques has significantly advanced our understanding of these complex diseases. However, further research is needed to fully elucidate the molecular mechanisms driving disease phenotypes and to translate these findings into effective personalized therapeutic strategies. Continued advancements in genetic testing, data integration, and disease modeling will be essential in improving outcomes for patients with inherited cardiomyopathies. Additionally, the emerging therapeutic strategies in cardiac regenerative medicine and the role of gene editing technologies such as CRISPR-Cas9 offer promising avenues for treatment. Advances in cardiac imaging, artificial intelligence, and the use of stem cell-derived extracellular vesicles may further enhance our ability to diagnose and treat these conditions. The integration of personalized medicine, novel biomarkers, and wearable technology into clinical practice will play an important role in managing cardiomyopathies. Future research should continue to focus on these innovative approaches to develop more effective treatments and improve patient outcomes.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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