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Heart Failure (W Tang, Section Editor)

Updates on the Genetic Paradigm in Heart Failure

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Abstract

Purpose of review The rapidly evolving field of cardiovascular genetics has already improved the care of patients with heart failure and families. The purpose of the current review is to describe the most and provide the most pertinent updates in the field of heart failure genetics.
Recent findings Recent advanced in heart failure genetics have begun to not only increase the yield of testing through improving technology and use of whole exome or whole genome screening, but also enabled the improving technology and increasing use of whole exome or whole genome screening, but also enabled an enhanced understanding of the implications of results of genetic testing. For instance, new data have described differential responses to heart failure therapies based on genetic testing. Additionally, variant analysis by locus in genetic cardiomyopathies has facilitated a much-improved prognostic understanding of phenotype. Recent years have seen advancements in the understanding of the genetics of rare disorders, including pediatric-onset cardiomyopathies, previously under-investigated; restrictive cardiomyopathies; and non-compaction cardiomyopathy.
Summary The last few years have heralded not only a broader understanding of the scope of the genetics of heart failure, but have also provided notable leaps in mechanistic and prognostic understanding, which will serve as the foundation for clinical investigation and future genetic variant assessment.

Introduction

The current burden of heart failure in the USA is massive with an approximate incidence of one million patients per year and with attributable costs around $30 billion per year [1, 2]. Given the scope of the disease, an understanding of the molecular etiology of cardiomyopathy and the variable response to treatment of heart failure including identification of reliable biomarkers that guide therapy should be of paramount importance. However, at present but with notable exceptions, an exhaustive evaluation of the pathophysiology of cardiomyopathy and an intense focus on the neurohormonal axis and its antagonism have been limited in its ability to stratify treatment modalities or distinguish clinical outcomes [3]. These limitations reflect on the lack of development of new paradigms for the treatment of both heart failure with reduced and preserved ejection fraction and the notable failure to substantially improve survival for these disease conditions over the past decade.

Nevertheless, one component of the workup that continues to generate important clinical implications is genetic testing. Genetic testing can provide evidence of pathogenic variants in the genome associated with clinical disease; however, testing is not performed routinely, even among those with dilated cardiomyopathy (DCM), as the yield of testing and clinical implications in some scenarios has been variable. With increased recognition, utilization of genetic testing in cases of familial DCM has increased, and newer estimates suggest the presence of identifiable pathogenic variants in 20–35% of cases [4–6].

In specific cardiomyopathies, with hypertrophic cardiomyopathy (HCM) providing the prototypical example, an identifiable pathogenic variant may be detected in greater than 50% of cases [7]. Data on underlying genetic underpinnings in HCM is well-developed due to the relative homogeneity of phenotype relative to DCM. HCM genetic testing is generally not performed for diagnosis but rather (a) risk stratification and prognosis as well as (b) facilitating family screening [8]. The absence of genetic markers in first-degree relatives of a proband with HCM with a pathogenic variant can provide reassurance about the absence of future phenotypic expression, which can then inform second-degree relatives (so-called cascade screening). Although the same logical inference can be made in DCM cases, the yield of testing in sporadic DCM is variable and lower than familial DCM.

Genetic variants implicated in restrictive cardiomyopathies (RCM) and left-ventricular non-compaction/non-compaction cardiomyopathies (NCCM) are less well described and in large part due to relatively low prevalence of the former heterogeneous nature of the latter. Although RCM has a greater tendency to have a familial inheritance pattern than DCM [9], genetic underpinnings are poorly understood. Although the phenotype of NCCM is defined by the presence of sufficient non-compacted to compacted myocardium, the actual phenotype may overlap other disease processes or represent a separate phenotypic expression of certain genetic mutations, thereby making the ascertainment of pathogenesis due to genetic variants more challenging [10, 11].

In general, well-described pathogenic variants in cardiomyopathies can be categorized into genes encoding nuclear envelope, sarcomeric, myofibrillar (or intermediate filament), desmosomal, and ion channel proteins. Other culprit genetic variants have been identified as well. Additionally, cardiomyopathies may be involved in a systemic syndrome and genetic variants in these cases may be better described, such as those of muscular dystrophies or those involved in the mitochondrial myopathies. Advances in the identification of causative genetic variants and in the understanding of pathogenesis have resulted in an important new classification scheme in an attempt to improve phenotyping of patients. This system is termed the MOGE(S) classification (M-morphology, O-organ(s) involvement, G-genetic inheritance pattern, E-etiology, and S-functional status) thus facilitating a consistent, granular, and comprehensive terminology for the description of cardiomyopathies [12, 13].

However, genetic testing is a complex endeavor, as patients need to be counseled and there is variability in insurance coverage, cardiomyopathy gene panels, and interpretation of results depending on the laboratory performing testing and the genetic locus. Genetic variants are classified into benign, likely benign, variant of unknown significance (VUS), likely pathogenic, and pathogenic [14]. Additionally, the classification and interpretation of these genetic markers can change over time as new information becomes available based on familial segregation studies and functional validation of genetic variants, resulting in significant differences in up to 18% of genetic results [15]. Therefore, careful

consideration and a thoughtful approach to decision-making surrounding genetic testing must be utilized.

In the present review, we focus on recent updates in the field of genetics of heart failure in the context of literature within the last year and provide a perspective on the development in the paradigm of genetic and genomics testing in heart failure. A flow-chart describing the current state of evidence and a perspective on the future of the paradigm of genomics in heart failure is shown in Fig. 1.

Characterization of pathogenic variants and novel genetic loci of disease

Characterization of poorly defined previously described pathogenic variants and novel genetic variant identification have both occurred in the preceding year, contributing significantly to the understanding of the genetics of heart failure. A summary of the novel insights gained from selected recent manuscripts is shown in Table 1.

Clinical presentation of *BAG3* variants

In the largest description of DCM secondary to BLC2-associated athanogene 3 (*BAG3*) genetic variation, the European Genetic Cardiomyopathies Initiative investigators provided comprehensive clinical and prognostic data to previously limited literature on variation in the *BAG3* gene [16]. Investigators found that patients with pathogenic *BAG3* variants presented on average in the 4th decade

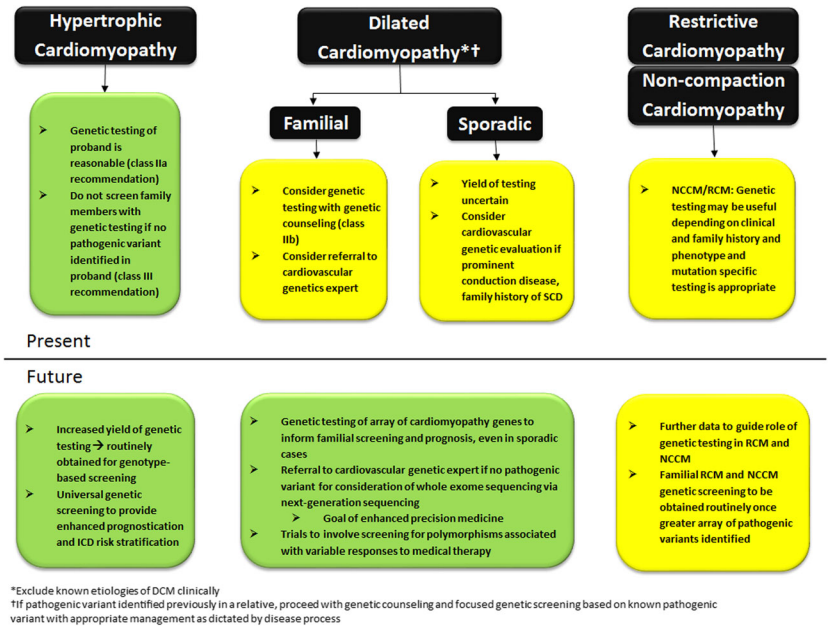

Fig. 1. Guideline-based recommendations and future consideration for genetic testing by cardiomyopathy. Flow chart indicates appropriate guideline-based approach to genetic testing. Colors of recommendation roughly correspond to strength of evidence as indicated by certainty of recommendation by guideline committee. Future segment of chart corresponds to expected levels of evidence over time.

Table 1. Selected highlights of recent literature on genetics in heart failure by gene and disease process

Gene	Novel insight
BAG3	Presentation: On average in the 4th decade, majority asymptomatic Outcome: 20% with VA or HF event. If DCM, 5% events/year ↑↑ risk LVAD/cardiac transplant, ↑ risk SCD
LMNA	High phenotype heterogeneity. Some loci, ↑ risk DCM progression, VA; ↑ risk if variant before nuclear localization signal or truncating mutation
FHOD3	Up to 1–2% of HCM cases; HCM presentation similar but ↑ risk low LVEF and hypertrabeculation
FLNC	Novel variant in DCM and RCM; In DCM ↑ risk SCD, VA. Pathogenesis ➔ Z-disc disarray, ↓cell adhesion
CAP2	Novel variant in DCM identified
TJP1	Novel variant in ARVC identified
JPH2	Novel variant in HCM identified; ↑ risk conduction defects
TNNI3K	Novel variant in DCM identified; ↑ risk conduction defects
PLN	Novel variant in DCM with AR inheritance
RBM20	Novel variant in NCCM identified
NRAP2	Novel variant in DCM identified
Disease process	Novel insight
NCCM	Large cohort analyses ➔ primary culprit mutations in *MYH7*, *MYBPC3*, *TTN*, and *LMNA*. If pathogenic variant ➔ ↑ risk systolic dysfunction, worse CV outcome
Pediatric DCM	Two large series ➔ several novel variants (*NRAP*, *PPA2*, *NEK8*, *RBM20*, *LMNA*, *TNNT2*, *TBX20*, *TAB2*, *JPH2*, *CALM1*, *PRDM1*, *RRACG*, *ALMS1*, and *TAF1A*)
Adult DCM	LV reverse remodeling ➔ ↑ in TTN, ↓ in LMNA and "any pathogenic variant" cohorts

VA ventricular arrhythmia, *HF* heart failure, *LVAD* left ventricular assist device, *SCD* sudden cardiac death, *CV* cardiovascular

of life and the majority were asymptomatic at diagnosis. Nevertheless, in the entire cohort, 20% experienced an arrhythmia- or heart failure-related event (with an event rate of 5% per year in the DCM cohort). Moreover, in the cohort with DCM ($n = 78$), 22 patients required heart transplant, LVAD, or died of sudden cardiac arrest.

Genetic variants in NCCM

In the preceding year, researchers have attempted to clarify the complex genetics of NCCM. One group recently attempted to characterize a large cohort of NCCM and relate clinical features and outcomes to genetic causes. These researchers found that variation in sarcomeric genes, *MYH7* and *MYBPC3* and structural *TTN*, were culprits in the majority of NCCM cases with a genetic cause, but a pathogenic variant was found only in 30% of total cases. In those with a pathogenic variant, risk of LV systolic dysfunction was increased and predictive of major cardiovascular outcomes raising the possibility that LVNC is more an associated phenomenon of genetic dilated cardiomyopathies than a separate entity in itself [17•]. A similar analysis was conducted in another large cohort of NCCM patients, in which investigators found culprit gene variants in 38% of the NCCM cohort, including *TTN*, *MYBPC3*, and additionally *LMNA* [18•]. This group also found genetic variants in *RBM20*, a novel finding in

NCCM. As compared with a control DCM cohort, the overall NCCM cohort experienced a higher risk of cardiovascular events confirming findings of the prior study.

New insights into the variable expressivity of culprit genetic variants

Even among single pathogenic genetic variants associated with a clinical phenotype, significant heterogeneity of phenotype and prognosis has been identified. One of the genes associated with significant variability is the *LMNA* gene, which creates challenges with regard to prognostication [19]. Recent data has identified novel *LMNA* variants associated with high risk of progression and ventricular arrhythmias [20]. However, another group of investigators who evaluated natural history stratified by location of the genetic variants found in general, only those that were upstream of the "nuclear localization signal" locus within the gene (Fig. 2) were associated with worse phenotype compared with variants located elsewhere within the gene [21•]. Another group analyzed *LMNA* variants by the presence of truncation or missense variants and found the former to be associated with increased risk of conduction tissue disease and low ejection fraction [22]. These insights allow for perhaps improved accuracy in prognostication if after genetic testing in patients reveals *LMNA* pathogenic variants. Variable expressivity has been demonstrated in most genes with pathogenic mutations, but researchers have recently added *RBM20*, previously thought to be associated with a universally severe phenotype, to the list of genes with significant variability in phenotypic expression [23].

Novel genetic variants in pediatric dilated cardiomyopathies

A recent collaborative group sought to evaluate genetic causes of childhood cardiomyopathies with a severe phenotype requiring advanced heart failure

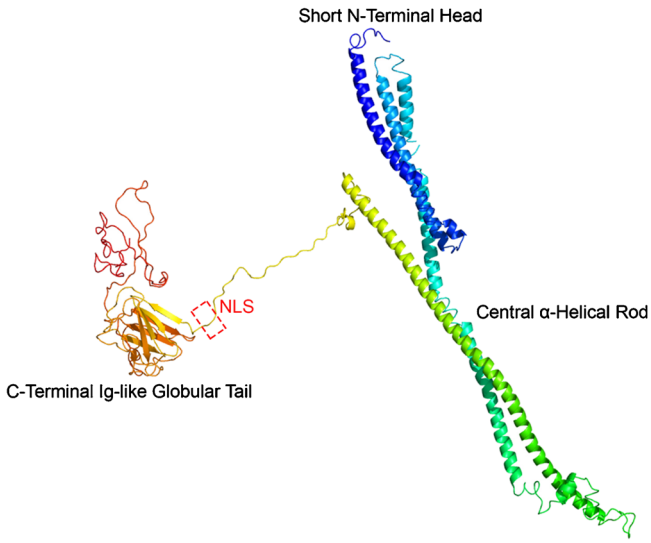

Fig. 2. Schematic of the tertiary structure of the lamin A protein. The diagram highlights the "nuclear localization signal" of the protein, which facilitates intracellular trafficking to the nucleus. Variants within this portion of the gene are associated with more severe presentation. "Three-dimensional model of wild-type lamin A" by Captur et al. (doi:https://doi.org/10.1136/openhrt-2018-000915): Open access, licensed under CC BY 4.0 (no changes made).

therapies. Due to the severity of disease and a median age of onset at 4 months, this cohort was likely to have an underlying de novo pathogenic genetic variants, possibly novel of which less severe or non-truncating forms could hypothetically result in an adult-onset cardiomyopathy [24••]. Indeed, the investigators discovered several novel pathogenic variants in 39% of the patient cohort, with a large proportion being de novo (46%) and autosomal recessive (34%). Genes involved in metabolic (e.g., PRKAG2), MAPK (e.g., HRAS), development (e.g., NEK8), calcium signaling (e.g., CALM1), and sarcomeric contraction pathways (e.g., TNNC1) were implicated. A related analysis was conducted in a general pediatric DCM cohort, which demonstrated the value of WES, which had a diagnostic yield of 50% and included de novo variants in *RBM20*, *LMNA*, *TNNT2*, and *PRDM1* as well as *TNNT2*, *RRACG*, *ALMS1*, and *TAF1A* [25].

Novel genetic variants in HCM

One of the most important novel variants identified in the preceding year in adults involved the formin homology 2 domain containing 3 (*FHOD3*) gene, found to be implicated in HCM and possibly responsible for 1–2% of HCM cases. Clinical presentation was similar to other pathogenic variant HCM cohorts with the exception of a higher prevalence of low LVEF (14%) and hypertrabeculation (16%) [26]. Additionally, junctophilin-2 (*JPH2*), encoding a structural protein that links L-type calcium channels and type 2 ryanodine receptors, was recently found to harbor pathogenic variants for HCM with high penetrance and with associated conduction tissue abnormalities [27].

Novel genetic variants in DCM and arrythmogenic cardiomyopathy

Case series and family cohorts have identified other new pathogenic variants in a broad array of cardiomyopathies. In one report, a variant in the cyclase-associated actin cytoskeleton regulatory protein 2 (*CAP2*) gene was identified as pathogenic in DCM in a consanguineous family, with dysfunction related to actin polymerization regulation, demonstrated in patient-derived skin fibroblasts obtained from the proband [28]. In arrhythmogenic cardiomyopathy (ACM), WES resulted in the identification of a variant in the tight junction protein 1 (*TJP1*), previously unreported, although the role of TJP1 in the pathogenesis of the cardiomyopathy is unknown [29]. Lastly, a novel variant in *TNNI3K* was discovered in a familial DCM case with conduction system disease [30].

Most pathogenic variants discovered thus far, including those above, follow an autosomal dominant inheritance pattern, but this may be due to a selection bias based on inheritance patterns [31]. Nevertheless, a recent study found an autosomal recessive pathogenic nonsense variant in the *PLN* gene encoding phospholamban [32].

Genetic controversy

An area of some controversy involves the filamin C (*FLNC* gene), which was initially described to be associated with HCM in 2014, but was recently called into question by a group, who found a higher than expected prevalence of these *FLNC* variants in the healthy controls and lack of an association of *FLNC* variants with outcomes in the HCM

population [33]. However, the importance of *FLNC* was highlighted when a frameshift variant in the gene was found to be associated with DCM in a GWAS study, although it was not as penetrant for a severe phenotype as compared to a missense variant in the *NKX2-5* gene that was also found to be associated with DCM [34]. In addition, novel pathogenic variants in *FLNC* have been found to be associated with RCM [35]. Most convincingly, however, recent data has shown that truncating mutations within *FLNC* were shown to be present in 2.2% of familial ACM cases in a multinational collaborative study. A structural analysis showed Z-disk disarray and decreased desmoplakin within the myocardium, highlighting its possible role in pathogenesis [36].

Common genomic and epigenomic variation and its role in cardiomyopathies

Common genetic variants identified in GWAS, typically single-nucleotide polymorphisms (SNPs), have been increasingly used as prognostic markers. Although perhaps not directly contributing to the pathogenesis of cases given that these are common variants and if pathogenic the prevalence of cardiomyopathy would be far higher, these SNPs may modify disease course or predispose individuals to disease.

In an important study of mechanism, *BAG3*-associated genetic variants (SNPs) identified in a cohort of African American patients was shown to be of important prognostic significance as variants were associated with a two-fold higher risk of cardiac events compared to controls. The authors also demonstrated pathogenesis by transfecting ventricular cardiomyocytes with *BAG3*-mutated plasmids and showed enhanced apoptosis of these cells relative to cells transfected with transfected with wild-type *BAG-3* plasmids under physiologic stress [37•]. In a separate GWAS study to identify genes associated with DCM, genetic variation in *ZBTB17*, *TTN*, *SLC39A8*, *MLIP*, *FLNC*, *ALPK3*, and *FHOD3* was identified to be significantly associated with sporadic DCM [38].

Insights regarding response to neurohormonal blockade therapy in heart failure have been an area of significant investigation, and one recent contribution to the literature showed that a particular SNP (c.Arg16Gly) within the β2-adrenergic receptor (*ADRB2* gene) was associated with worse outcomes but the Gly16 allele cohort had a greater response to β-blockade therapy than the homozygotes for Arg16; these results were replicated in a separate cohort [39]. This extends the current body of literature regarding the role of β-adrenergic receptor polymorphisms and response to β-blocker therapy [40–42].

In the first epigenome-wide association study in cardiomyopathies, a recent study not only refined methods of high-quality DNA and RNA extraction from tissue, but also identified that DNA methylation may play a significant role in regulatory changes associated with the development of a DCM phenotype [43•]. These authors found three novel loci of methylation, which met statistical criteria for genome-wide significance for association with DCM phenotype, suggesting that epigenetic regulation of transcription may play a critical role in development of DCM.

Evolution in the framework of known genetic cardiomyopathies—beyond diagnosis

A study evaluating the determinants of left ventricular reverse remodeling in a cohort of patients with DCM found that in addition to clinical features that predicted response to medical therapy and reverse remodeling, pathogenic variants in cardiomyopathy genes in general and *LMNA* in particular were associated with reduced likelihood of reverse remodeling; conversely, *TTN* mutations were associated with an improved likelihood of reverse remodeling [44••]. This investigation provides new insights into the potential prognostic significance of genetic testing in DCM.

Recent data from the SHaRe Registry (Sarcomeric Human Cardiomyopathy Registry) highlight the importance of genetic testing in HCM, as these patients with likely pathogenic sarcomeric genetic variants were twice as likely to experience adverse events, including mortality, heart failure, and SCD and ICD firing. In addition, the authors identified an increased risk among patients with sarcomere VUS relative to patients with negative genetic testing [45•].

Several important contributions to the literature recently do not involve primary data. In a scientific statement from the Working Group of Myocardial Function of the European Society of Cardiology, the coalition sought to develop a framework for genetics in cardiomyopathy not as an isolated genetic defect, but as a spectrum of disease, partly determined by the penetrance of the gene variant and partly a result of environmental exposures, which can increase the expressivity of the phenotype [46]. Two important reviews sought to frame discussions of heritable cardiomyopathy. In the first, the authors attempted to describe the current state of cardiomyopathies in hereditary skeletal muscle disorders in order to argue that characterization of cardiac phenotype is critical as the cardiomyopathy or associated rhythm disorder may be of greatest prognostic significance [47]. In the second review, authors provide a comprehensive overview of genetic causes of DCM with arrhythmic association. This perspective highlights one of the important implications of genetic testing, which is the alteration in management by the identification of elevated risk of sudden cardiac death. The authors of this review also highlight meaningful phenotypic variation of a number of traditional "DCM mutations" or "Arrhythmic or ARVC-related mutations." [48•]

Conclusion

In the current era, the recognition of novel pathogenic variants within genes involved in myocardial structure and function as well as the understanding of the molecular pathogenic mechanism of heart failure continues to expand at an ever-growing rate. The recent contributions to the literature described in this update highlight the potential for not only identifying genetic underpinning of cardiomyopathies but an enhanced understanding of the natural history and prognosis. At present, there is sufficient evidence to warrant genetic workup in most familial cases of cardiomyopathy, and an enhanced sensitivity of testing and more complete understanding of the implications of identification of pathogenic

variants may ultimately facilitate the inclusion of genetic testing in the routine workup of new-onset cardiomyopathy as well as improving prognostication of the disease.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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