Clinical genetics of dilated cardiomyopathy: on the way to personalized medicine?

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This editorial refers to ‘Atlas of the clinical genetics of human dilated cardiomyopathy’¹, by J. Haas et al., on page 1123.

In their multicentre and multinational study, Haas and co-authors investigated 639 samples of clinically excellently characterized patients with sporadic dilated cardiomyopathy (DCM) and proven familial DCM from eight different cardiology centres in Europe by targeted next-generation sequencing (NGS).¹ All known coding exons of 84 relevant genes in human DCM were covered using an optimized custom target-enriched assay based on in-solution hybridization targeting. In total, 8269 unique genetic variants were identified, denoting 359 669 variants across the investigated target region for 639 included patients. After exclusion of variants observed in large non-DCM controls in 46% of all patients, a previously described cardiomyopathy mutation was identified. Interestingly, when excluding mutations described for other cardiomyopathies such as hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC), only in 16% of all patients were known mutations detected. When searching for rare or private mutations not yet annotated in databases, 117 highly likely pathogenic variants such as frameshift insertions/deletions, stop-gain/-loss variants, and splice mutations were detected in 26 genes in 23% of the patients. By searching for potential disease mutations, 154 rare variants in 350 patients were detected, mostly affecting the TTN and LMNA gene. Finally, 12.8% of the patients carried at least two known disease mutations. With regard to genotype–phenotype associations, an exploratory association analysis was performed, showing that mutations detected in certain genes are associated with left ventricular ejection fraction (LVEF), having received a heart transplant or implantable cardioverter defibrillator (ICD), left ventricular end-diastolic diameter (LVEDD), or age of diagnosis. Novel DCM disease genes, for example SMYD1 and alpha-crystallin B, were detected. The composition of the study group and consequentially of the study patients contributed to a comparison of the distribution of cardiomyopathy-relevant variants throughout Europe, with Germany showing the lowest and the UK showing the highest rate. Nevertheless, a more or less homogenous mutation frequency of DCM genes was described.

The most important benefit of this excellent investigation is based on different prerequisites. In particular the clinical definition of sporadic and familial DCM patients, the standardized collection of clinical data and samples within the different centres in Europe, and the use of NGS for this large cohort of patients reflect at least 30 years of effort in the field of genetics in cardiomyopathies.

History of genetics in cardiomyopathies

The first data on the identification of a gene responsible for familial cardiomyopathy were published in 1989² by performing genetic linkage analyses with polymorphic DNA loci dispersed throughout the entire genome. The locus which was inherited with HCM in 108 members of a large family, 44 of whom presented with clinical HCM including 24 sudden cardiac deaths, was located on chromosome 14. This was the starting point for rapid advances in the knowledge of the molecular defects responsible for HCM,³,⁴ which have supported the understanding of the disorder and have suggested new approaches to clinical and genetic assessment of prognosis⁵,⁶ (Figure 1).

Dilated cardiomyopathy affects 1 in 2500 individuals and is the major cause of heart transplantation and death from non-ischaemic heart failure in adolescents and young adults. As one of the most common heart muscle diseases in high-income as well as in low- and middle-income countries with the clinical picture of systolic impairment and LV dilatation in the absence of previous myocardial infarction, a wide spectrum of clinical phenotypes can accompany the disease.⁷ For that reason, the term DCM was used commonly, often depicting quite different phenotypes. Inherited DCM at that time was thought to account only for a small percentage of cases. When family screening was undertaken, it was shown that ~20% of DCM patients had family members with echocardiographic
evidence of DCM. In consequence, a common protocol with defined diagnostic criteria and simple but sufficiently sensitive and specific methods for familial DCM was developed. This originated from the need to define a common base to undergo clinical and molecular genetic studies in familial DCM. In parallel, there was growing evidence of a genetic aetiology in more than a third of sporadic DCM cases, reflecting the importance of genetics in the aetiology of inherited and sporadic forms of DCM compared with other aetiologies such as inflammation, infection, or autoimmune processes. Candidate gene approaches and genome-wide genotyping, linkage analyses, and gene mapping were used for DCM-associated gene discovery, showing a broad genetic heterogeneity with reduced or age-dependent penetrance based on different clinical features, different patterns of genetic transmission, combinatorial effects of relevant variants, and possible environmental triggers. In summary, clinical phenotypes and outcome in patients with DCM often vary according to the disease gene, penetrance, age, and type of mutation.

**Definitions and position statements**

One of the most important milestones in solving the inaccuracy in definition of patients with cardiomyopathies was the update of the classification system for cardiomyopathies within a position statement of the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases (Table 1). Grouping of cardiomyopathies into specific morphological and functional phenotypes with a subsequent division into familial and non-familial forms was designed first to raise awareness of a genetic disease as a cause of heart muscle dysfunction. The second aim was to provide a logical framework to ensure its continued utility in everyday clinical practice on which further investigations should be based. With an additional position paper of the same group, advances in molecular genetics were reflected in the development of new and specific treatment options in inherited cardiomyopathies with new risk stratification models.

**Table 1 Requirements for diagnosis and treatment of inherited cardiomyopathies**

(a) Requirements to achieve the diagnosis of inherited cardiomyopathy

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<td>Exact phenotyping of patients using a standardized classification system for cardiomyopathies in everyday clinical practice</td>
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<td>Defined diagnostic criteria for familial cardiomyopathies</td>
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<td>Standardized genetic counselling, family screening, and genetic testing for all patients with cardiomyopathies</td>
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<td>High-quality targeted next-generation sequencing with standardized quality controlled assays and transparent classification algorithms</td>
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<td>Standardized nomenclature for description of cardiomyopathies associated with mutations in different genes</td>
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(b) Further needs for specific care and treatment in families with cardiomyopathy

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<td>Establishment of prospective databases including follow-up investigations across Europe (to prove new variants and genes as disease causing, to establish new models with regard to risk stratification, and to add information on prognosis)</td>
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<td>Understanding of the pathophysiological consequences of the underlying disease-causing mutation in order to be able to develop specific therapies</td>
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genetics were recognized, presenting new opportunities and challenges for cardiologists who manage patients and families with cardiomyopathies. The paper reviewed general issues related to genetic counselling, family screening, and genetic testing in families with a cardiomyopathy. The key message was that genetic counselling is recommended for any patients with a cardiomyopathy, unless an acquired cause of the cardiomyopathy is demonstrated. Genetic counselling is also appropriate in the families of those patients and should take place in the context of multidisciplinary management.

An important advance of the investigation by Haas et al. is the involvement of several members of the INHERITANCE consortium sharing common clinical, scientific, and ethical standards regarding patient care and family screening. In either case, individual expertise in the clinical management and molecular genetics of inherited cardiomyopathies is based on scientific and clinical experience over years. To date, knowledge derived from basic research was not being subsequently translated into clinical practice, and the study of Haas et al. describes for the first time a systematic investigation for all clinically relevant DCM genes in a large European cohort of clinically well-defined DCM patients including clinical data, familial history, and clinical follow-up data generated within a standardized study protocol. This important prerequisite with regard to patient samples and data was combined with high-quality targeted NGS, reaching a very high 50-fold target coverage of 99.1% over all genes. Interestingly, quite comparable results using NGS with a panel covering 46 DCM genes in a smaller cohort of 149 patients were demonstrated by Pugh et al. High and reproducible sequence coverage to identify relevant mutations can be achieved if standardized quality-controlled assays and transparent classification algorithms are used.

Future perspectives

The current sequence approaches and probably future commercial clinical molecular genetic testing will lead to the identification of higher numbers of rare, private, or unique variants of partly unknown significance. This requires large efforts with regard to interpretation of clinical importance, conservation, segregation within a diseased family, and probability of the variant inducing DCM. In this context, a subsequent clinical follow-up of thoroughly phenotyped index patients and all family members is required, to establish phenotype—genotype correlations and to provide new prognostic information. This should be done using national or international prospective, multicentre, observational registries of patients presenting to referral centres in European countries such as, for example, the ESC Cardiomyopathy and Myocarditis Registry. The ESC registry is planned to determine the proportion of patients with potentially inheritable heart muscle disorders as well as to include the genetic profile and genotype—phenotype correlations of patients with identified genetic mutations. A prospective and consecutive data collection should be planned for the future.

Finally, genetic data obtained in each patient require a nomenclature for description of cardiomyopathies associated with mutations in different genes. Morphofunctional trait and organ system involvement with a familial inheritance pattern, identified genetic defect, or other aetiologies should arise from this nomenclature. The MOGE(S) system published in 2013 proposes a nosology that addresses five attributes of cardiomyopathies, including morphofunctional characteristic (M), organ involvement (O), genetic or familial inheritance pattern (G), and an explicit aetiological annotation (E) with details of the genetic defect or underlying disease/case, allowing complete description of the disease and precise communication among physicians.

Taking this together, the most important prerequisites needed to confirm a definite diagnosis in patients with cardiomyopathies and their family members including geno- and phenotyping are already established. Future efforts have to focus on the introduction of prospective databases to be able finally to first prove new variants and genes as disease causing. The understanding of the molecular defect and its consequence on cell function may lead to the development of new and specific treatment options in inherited cardiomyopathies as it is discussed for small molecules interrupting the pathological cascade within the heart muscle cell. Secondly, new models with regard to risk stratification in a particular family, in addition to information on the prognosis, will emerge from the data which arise.

Conflict of interest: none declared

References


A 28-year-old woman underwent bioprosthetic tricuspid valve replacement (TVR) and mitral valve repair for congenital tricuspid valve dysplasia. Two months later she developed *Staphylococcus aureus* endocarditis and underwent mitral valve replacement and redo-TVR, with a complicated postoperative course.

Prosthetic tricuspid valve leaflet thickening with failure of coaptation and torrential regurgitation was noted at 2 year follow-up. There was also marked thickening of the mitral valve prosthetic cusps with failure of leaflet opening (⁎), resulting in moderate stenosis (Panels A–C, Supplementary material online, Video 1) and mild regurgitation. Inflammatory markers and multiple blood cultures were negative. Her risk for re-operation was felt to be prohibitive and consideration of cardiac transplantation was recommended.

We opted instead for a dual approach: warfarin anticoagulation for suspected mitral prosthetic valve thrombosis, followed by valve-in-valve implantation for degenerated tricuspid bioprosthesis. Transoesophageal echocardiography performed after 6 weeks anticoagulation demonstrated a marked resolution of mitral bioprosthesis thrombosis with normal mobility of all cusps, and a normal gradient (Panels D–F, Supplementary material online, Video 2). A Melody valve was implanted percutaneously to address the tricuspid regurgitation (Panels G–I, Supplementary material online, Video 3).

This case demonstrates the unique challenges in diagnosis and management of dual pathology with mitral bioprosthetic thrombosis and tricuspid bioprosthetic degeneration. While bioprosthetic valve thrombosis is a rare complication typically occurring early after implantation, it may occur late after surgical implantation and mimic recurrent endocarditis. A high index of suspicion for prosthetic valve thrombosis is necessary to avoid inappropriate therapy including antibiotics and re-do surgery. Early identification and management of such patients with anticoagulation can result in excellent outcomes.

Supplementary material is available at European Heart Journal online.