Genetic determinants of heart failure: facts and numbers

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Abstract

The relevance of gene mutations leading to heart diseases and hence heart failure has become evident. The risk for and the course of heart failure depends on genomic variants and mutations underlying the so-called genetic predisposition. Genetic contribution to heart failure is highly heterogenous and complex. For any patient with a likely inherited heart failure syndrome, genetic counselling is recommended and important. In the last few years, novel sequencing technologies (named next-generation sequencing – NGS) have dramatically improved the availability of molecular testing, the efficiency of genetic analyses, and moreover reduced the cost for genetic testing. Due to this development, genetic testing has become increasingly accessible and NGS-based sequencing is now applied in clinical routine diagnostics. One of the most common reasons of heart failure are cardiomyopathies such as the dilated or the hypertrophic cardiomyopathy. Nearly 100 disease-associated genes have been identified for cardiomyopathies. The knowledge of a pathogenic mutation can be used for genetic counselling, risk and prognosis determination, therapy guidance and hence for a more effective treatment. Besides, family cascade screening for a known familial, pathogenic mutation can lead to an early diagnosis in affected individuals. At that timepoint, a preventative intervention could be used to avoid or delay disease onset or delay disease progression. Understanding the cellular basis of genetic heart failure syndromes in more detail may provide new insights into the molecular biology of physiological and impaired cardiac (cell) function. As our understanding of the molecular and genetic pathophysiology of heart failure will increase, this might help to identify novel therapeutic targets and may lead to the development of new and specific treatment options in patients with heart failure.

Keywords cardiomyopathy; DCM; HCM; heart failure; cardiogenetics

Received: 15 December 2017; Accepted: 22 December 2017

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Introduction

Heart failure is a continuously growing public health problem. Presently, almost 40 million people are affected by heart failure worldwide.¹⁻³ In developed countries, the prevalence of heart failure is approximately 1–2% of the adult population.⁴⁻⁵ Because of the ageing of our population in general, it is increasing in prevalence.⁶ Despite substantial improvements in medical treatments that delay onset and prolong life with heart failure, morbidity and mortality for this disease remain extremely high. Heart failure is associated with cognitive impairment, reduced exercise tolerance, and multiorgan impairment, which all reduce quality of life tremendously, particularly in the multimorbid older population. Besides, healthcare costs for heart failure are enormous as it is one of the main reasons leading to hospitalization among adults.

Heart failure is a clinical syndrome characterized by typical patient symptoms and physical examination findings caused by impaired ventricular function. Its treatment can be challenging as the term encompasses diverse underlying aetiologies. A broad range of cardiac diseases, inherited disorders, and systematic diseases can result in heart failure.³ The situation is even more complex, as heart failure can have mixed aetiologies, which mutually do not exclude each other. Heart failure itself represents a final common pathway in response to genetic and/or environmental influences.
Prevention of heart failure by identifying and treating risk factors and subclinical precursors currently represents a big challenge. Increasing evidence suggests that risk and course of heart failure depend on genetic predisposition. Recently, the involvement of mutations in various genes leading to heart diseases and hence heart failure has become clearer. Accurate and comprehensive genetic testing strategies might be a powerful tool to identify patients at risk and to treat heart failure in these patients more effectively. With genetic testing, patients at risk for heart failure could be identified before overt disease is present. At that timepoint, a preventative intervention could be used to avoid or delay disease onset or progression.

Genetic contribution to heart failure is heterogeneous and sometimes complex. At one end of the disease spectrum, there are familial monogenic heart failure syndromes with monogenic causative gene mutations with high penetrance. Mainly, they are inherited in an autosomal-dominant way, less commonly in a recessive, mitochondrial, or X-linked inheritance pattern. At the other end, heart failure susceptibility might be influenced by more common, but less penetrant, genetic variants. In that case, the cumulative effect of common variants interacts with environmental factors and determines heart failure susceptibility, and heart failure should be considered as a multifactorial disease.

**Familial (genetic) predisposition for heart failure**

Susceptibility to heart failure often has a genetic and therefore heritable component. In the Framingham Offspring Study, parental heart failure was associated with asymptomatic left ventricular dysfunction and an increased risk for overt heart failure in the offspring. This study clearly demonstrated the importance of familial (genetic) factors as determinants of heart failure. In another large nationwide Swedish population study, the relevance of genetic factors as independent risk factors for heart failure was also shown: The risk for heart failure even increased in individuals having more than one sibling affected with heart failure. Moreover, this situation was associated with early onset of heart failure.

In children with heart failure, a familial origin is frequently identified. In unselected adult heart failure populations, prevalence of heart failure caused by (monogenic) cardiomyopathies is probably lower compared with that in paediatric populations.

**A definition of (genetic) cardiomyopathies**

One of the most common causes of heart failure are cardiomyopathies. In 2006, the American Heart Association described cardiomyopathies as a heterogeneous group of myocardial diseases that are predominantly genetic and associated with mechanical and/or electrical dysfunction. Two years later, the European Society of Cardiology provided their own classification of cardiomyopathies and defined them as ‘a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality’. Based on specific morphological and functional phenotypes, cardiomyopathies can be clinically divided into five groups: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathies such as the left ventricular non-compaction cardiomyopathy (Figure 1). These five entities can be further subdivided into familial (genetic) and non-familial (non-genetic) cardiomyopathies.

**Figure 1** Classification of cardiomyopathies. Cardiomyopathies can be classified into five groups according to different morphological and functional criteria. Figure adapted from Elliot et al.12

![Cardiomyopathies](image-url)
non-familial (non-genetic) forms. In 2013, the World Heart Federation concluded that ‘a substantial increase in the knowledge of the genetic basis of cardiomyopathy called for a standardized, universally acceptable classification/nosology system that integrates phenotype description as well as genetic information’. Therefore, the so-called MOGE(S) nosology system was proposed, which describes cardiomyopathies not only according to the morphofunctional phenotype (M) but also according to organ involvement (O), genetic inheritance pattern (G), aetiological annotation (E) including genetic defect or underlying disease/substrate, and functional status (S) of the disease. This classification system offers a better flexibility in categorizing overlapping genetic and phenotypic syndromes.

Genetic diagnostics and genetic terminology in heart failure

A clear distinction between acquired and inherited heart failure syndromes remains challenging. Examination of heart failure patients should include an inquiry of the occurrence of sudden cardiac death and other heart failure symptoms among their family members. This should help to determine potential genetic causes of the disease and to identify other persons in the family being at risk for heart failure. Genetic counselling is strongly recommended for any patient with a cardiomyopathy, unless an acquired cause of the cardiomyopathy is clearly demonstrated. In the case of a potential genetic component, genetic testing should be considered for these individuals. In the current heart failure guidelines of the European Society of Cardiology, genetic testing is recommended when the prevalence of detectable mutations is sufficiently high and consistent to justify routine targeted genetic screening. Cardiogenetic counselling should be exclusively performed by someone with enough knowledge and expertise of the specific psychological, social, and medical implications of a cardiogenetic diagnosis.

In the last years, next-generation sequencing (NGS) has dramatically improved and revolutionized genetic testing, leading to a high efficiency, and has reduced the cost of genetic analyses. Because of this technological development, genetic testing has become increasingly accessible and is nowadays applied in clinical routine diagnostics.

NGS-based genetic testing of all disease-associated genes can produce different results. First of all, a pathogenic mutation can be identified in a given gene, and the causative nature of the mutation can be determined by human geneticists in accordance with interpretation guidelines. Sometimes, identified variants can only be described as ‘variants of uncertain significance’. These are often sequence changes that are not commonly detected in the population, but for which there exist only few supporting cues that these variants might be pathogenic. In addition, genetic testing might show only so-called benign polymorphisms, which are relatively frequent variants (frequencies >0.1–1% are not likely to cause a disease) and are not considered as being disease causing. Many of the identified disease-causing mutations are rare and frequently ‘private’, that is, specific to an individual (and his or her family). Detailed clinical phenotyping of patients and their families is crucial, as it allows uncovering of familial segregations, family members at risk, reduced penetrance of specific mutations, or de novo occurrence of dominant mutations.

Different inheritance patterns are described for heart failure syndromes. Autosomal-dominant inheritance is the predominant form of transmission. However, autosomal-recessive, X-linked, or mitochondrial inheritance are also found. In addition, dominant mutations can also occur de novo in patients having a risk of 50% to be inherited to their offspring.

Each cardiomyopathy phenotype can be caused by mutations in one of the numerous different genes described (i.e. genetic heterogeneity). However, even mutations in the same disease-associated gene can cause a distinct quantitative variability in the expression of the cardiomyopathy phenotype (i.e. phenotypic heterogeneity). Interestingly, different mutations within a specific gene might cause different functional effects and thereby produce different phenotypes. Variable expressivity and penetrance imply that factors beyond the single pathogenic mutations (i.e. genetic, epigenetic, or environmental modifiers) might influence the phenotype.

In addition, it is suggested that patients with inherited heart failure might also carry more than one pathogenic mutation. Cardiomyopathies attributable to compound heterozygosity (two mutations in the same gene, autosomal-recessive inheritance) or digenic inheritance (two mutations in different genes) are found in heart failure patients, particularly in diseases known to be associated with a low penetrance. Oligogenic inheritance might be one explanation for the, sometimes observed, tremendous variations in disease penetrance in individual families but has not yet been genetically proven. Even in monogenic disease, multiple other loci are likely to act as modifiers of the disease phenotype.

Genetic cardiomyopathies and their associated genes

In the last decades, nearly 100 genes whose mutations cause different forms of cardiomyopathies have been identified. Most of these genes are associated with DCM and HCM, fewer with RCM and ARVC. Selected common genes whose mutations can cause cardiomyopathies are also shown in Table 1.
**Table 1** Selected genes associated with cardiomyopathies

| Cardiomyopathy form       | Gene  | Chromosome | Protein name           |
|---------------------------|-------|------------|------------------------|
| Dilated cardiomyopathy    | LMNA  | 1          | Lamin A/C              |
|                           | MYH7  | 14         | Beta myosin heavy chain|
|                           | TTN   | 2          | Titin                  |
|                           | TNNT2 | 1          | Troponin T             |
| Hypertrophic cardiomyopathy| MYBPC3| 11         | Cardiac myosin binding protein C |
|                           | MYH7  | 14         | Beta myosin heavy chain|
|                           | TNN1  | 19         | Troponin I             |
|                           | TNNT2 | 1          | Troponin T             |
|                           | TPM1  | 15         | Alpha-tropomyosin       |
|                           | MYL3  | 3          | Myosin light chain 3   |
| Restrictive cardiomyopathy| DES   | 2          | Desmin                 |
|                           | MYH7  | 14         | Beta myosin heavy chain|
|                           | TNN1  | 19         | Troponin I             |
| Arrhythmogenic right ventricular cardiomyopathy| DSC2  | 18         | Desmocollin            |
|                           | DSG2  | 18         | Desmoglein 2           |
|                           | DSP   | 6          | Desmoplakin            |
|                           | JUP   | 17         | Plakoglobin            |
|                           | PKP2  | 12         | Plakophilin 2          |

DCM is characterized by the presence of a left ventricular or biventricular dilatation and systolic impairment in the absence of abnormal loading conditions. It is the second most common aetiology for heart failure with reduced ejection fraction. DCM is a complex disorder with different genetic variants and environmental factors that determine disease onset and course. The familial form (due to single-gene mutations) of DCM has an estimated prevalence of approximately 1:2500, although this might be underestimated. DCM is most often autosomal-dominantly inherited, and it is genetically highly heterogeneous. Genes associated with DCM primarily encode for structural proteins in the cardiomyocyte sarcomere, cytoskeleton, and nuclear envelope and also for membrane ion channels and desmosomes. Of note, mutations in the genes MYH7 encoding beta myosin heavy chain, TNNT2 encoding troponin T, TTN encoding titin, and LMNA encoding a nuclear envelope protein are frequent causes of familial DCM. TTN is the gene with the most exons in the human genome, and mutations are suggested to be most frequent with approximately 25%, but it has to be taken into consideration that many of the described disease-causing mutations in TTN might just be variants of unclear significance.

HCM is characterized by an abnormal left ventricular wall thickening and mass. It is the most common hereditary cardiac disease with a prevalence of 1:500. HCM is a frequent cause of sudden cardiac death in young and asymptomatic individuals. Most HCM cases are inherited in an autosomal-dominant manner with variable expressivity and age-related penetrance. By now, in more than 60% of all HCM patients, the specific genetic cause of the disease can be identified by NGS-based sequencing strategies. Nearly 70% of all HCM mutations can be found in the sarcomere genes MYH7 and MYBPC3 (encoding for cardiac myosin binding protein C). Further common mutations are localized in TNNT2 and in the genes for troponin I (TNN1), alpha-tropomyosin (TPM1), or myosin light chain 3 (MYL3).

RCM is characterized by a rigid ventricular wall. The resulting impaired cardiac muscle relaxation leads to a decreased ventricular filling. Diagnosis of RCM is really difficult, as the heart seems more or less morphologically normal. Overall, prognosis of RCM is very bad. RCM is one of the most seldom cardiac diseases. Familial forms are caused by gene mutations affecting sarcomeric and cytoskeletal proteins as well as intermediate filaments. The inheritance pattern is normally autosomal dominant, but most RCM cases are based on a de novo mutation. Among others, mutations in TNN1, in MYH7, and in the gene for desmin (DES) are described.

ARVC is a progressive heart muscle disorder associated with structural and functional abnormalities mainly of the right ventricle, as its cardiomyocytes are replaced by fatty tissue and fibrosis. Besides, a biventricular and left-dominated form also exist. ARVC is a frequent cause of sudden cardiac death in young adults and athletes. It is inherited in most cases in an autosomal-dominant pattern and has a prevalence of 1:2000–1:5000. In approximately 50% of all cases, ARVC is caused by mutations in genes encoding for desmosomal proteins. Especially, mutations in the plakophilin 2 (PKP2) gene are frequent. Besides, common mutations can be found in the genes for desmplakin (DSP), plakoglobin (JUP), desmoglein 2 (DSG2), and desmocollin (DSC2).

Other inherited cardiomyopathy forms triggering heart failure can be due to metabolic or mitochondrial diseases. Mutations in proteins involved in fat or carbohydrate metabolism or mitochondrial biogenesis cause these diseases. Most of them are associated with an unexplained left ventricular hypertrophy imitating a phenotype reminding of HCM, DCM, or RCM. However, the genetic cause of these diseases cannot be found in the genes described for cardiomyopathies. They are so-called phenocopies with totally different pathophysiological, extracardiac manifestations, and therapies. An example of such a phenocopy is Fabry disease, a lysosomal storage disease caused by a mutation in the gene GLA encoding for α-galactosidase A.

**Clinical consequences of genetic findings in heart failure patients**

Identification of a pathogenic mutation has important and different implications. The information can be used for accurate genetic counselling, for therapy guidance, and for family...
cascade screening and thus early diagnosis in affected individuals. Therefore, genetic findings in patients with heart failure are recommended and have concrete clinical aspects and consequences.

A couple of mutations in specific genes are associated with a poor prognosis and an increased risk for sudden cardiac death. If such a mutation is discovered in a patient, the threshold for recommending an implantable cardiac defibrillator to a patient should be decreased. LMNA mutation carriers have an increased occurrence of malignant (potentially life-threatening) ventricular arrhythmias and sudden cardiac death. Other examples are TNNT2 and DES mutation carriers, who also present with a high arrhythmia risk. In these patients, decisions regarding the primary prophylactic implantation of an implantable cardiac defibrillator should take genetic aspects into account.

Genetic cascade screening of asymptomatic family members in inherited heart failure can also have direct medical implications. Many patients have a long preclinical phase with few or even no symptoms. Before clear clinical heart failure symptoms are apparent, patients can present with asymptomatic structural or functional cardiac abnormalities. These might be potential precursors of heart failure syndromes. After identification of a pathogenic mutation in asymptomatic family members, these so-called genotype-positive phenotype-negative patients should undergo early risk stratification. Depending on the mutation, preventative measures, such as avoidance of competitive sport, or an early start of cardioprotective medication can positively influence the disease course, thereby delaying cardiac decompensation or remodelling and preventing sudden cardiac death.

Finally, understanding the cellular basis of genetic heart failure in more detail may provide new insights into the biology of normal and impaired cardiac (cell) functions. This might help to identify novel therapeutic targets for heart failure and may lead to the development of new and specific treatment options in inherited cardiomyopathies.

**Conclusions**

Prevention and treatment of heart failure by identifying its genetic (and environmental) determinants is of high importance. On the one hand, heart failure can be caused by mutations in different disease-associated genes. On the other hand, a complex interaction between genetic and environmental factors can also trigger heart failure. A clear genetic diagnosis can positively influence patient treatment and, thereby, improve prognosis. Furthermore, comprehensive genetic testing facilitates early identification of additional family members at risk for heart failure. Besides, understanding the pathogenesis of genetically induced heart failure at its molecular level may lead to the development of specific individual heart failure therapies in the future.

**Conflict of interest**

None declared.

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