Editorial

Dilated cardiomyopathy: more genes means more phenotypes

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This editorial refers to 'Mutation screening in dilated cardiomyopathy: prominent role of the beta myosin heavy chain gene'† by E. Villard et al., on page 794

Dilated cardiomyopathy (DCM) is the third most common cause of heart failure after coronary artery disease and hypertension. DCM is the most frequent form of primary myocardial disease. Clinically, DCM is characterized by a progressive course of ventricular dilatation and systolic dysfunction. The different stages of DCM are reflected by the presentation of asymptomatic patients with left ventricular dilatation or impaired systolic function, patients with exercise-induced symptoms of heart failure, or overt congestive heart failure. The life expectancy is limited and varies according to the underlying aetiology. Myocarditis, immunological abnormalities, toxic myocardial damage, and genetic factors are all assumed to be causes. The familial occurrence of DCM, mostly as an autosomal dominant trait, is more common than generally believed. As a matter of fact, 20–30% of all cases of DCM are caused by genetic mutations.

In the past decade, major progress has been achieved by investigating families with inherited DCM. The analysis of candidate genes led to the discovery of cardiac α-actin, the first DCM-causing gene. Additional candidate gene screening and linkage analyses in large families were successful in identifying 19 additional disease-causing genes (Figure 1, Table 1).

The interesting report by Villard et al.4 sheds new light on the frequency of mutations in the β-myosin heavy chain (MYH7) and cardiac troponin T (TNNT2) genes. The group examined 96 patients with DCM and most of their first-degree relatives. This important study design feature enabled the investigators to differentiate between sporadic and familial cases. Villard et al.4 identified 54 patients with inherited DCM. This proportion of inherited cases in a cohort of patients with ‘idiopathic’ DCM is higher than in previous reports and may be related to the function of the Pitie-Salpetriere hospital as a tertiary referral centre. In contrast, the investigators in most other studies did not differentiate between genetic and sporadic DCM patients or they reported solely on selected patients with idiopathic DCM. Because of the unknown number of inherited cases, the mutation frequency observed in many studies is prone to referral bias and must therefore be interpreted with caution.

Villard et al.4 found seven missense mutations in the MYH7 gene and two mutations in the TNNT2 gene. They found no mutations in cardiac α-actin, desmin, δ-sarcoglycan, phospholamban, or the metavinculin gene in this group of patients or in a similar population of DCM patients.5,6 The screening methods employed have a sensitivity of ~80–90% in mutation detection. Bearing this fact in mind, these genes and probably many other DCM disease genes are rare causes of familial or sporadic DCM cases. Some mutations, the so-called private mutations, may be so rare as to be regarded a characteristic of only a single family.

In the first report on MYH7 mutations as cause of familial DCM, two different missense mutations were identified in 2 out of 21 families with heritable pure DCM without other organ manifestations.7 This report was followed by two additional studies identifying two novel mutations in 46 unrelated German DCM patients and one novel mutation in one of the 52 Finnish DCM patients.8,9 In addition, several groups have described patients who exhibit a conversion from a hypertrophic cardiomyopathy (HCM) to a DCM phenotype. In such instances, mutations of the MYH7 gene seem to be...
rather common (2 of 11 cases). Considering the frequencies reported by Villard et al. and those of other investigators, 9% (7/75) of patients with familial DCM have mutations in the MYH7 gene. However, only 4% (5/140) of patients with sporadic ‘idiopathic’ DCM have mutations in this gene. Therefore, mutations in the MYH7 gene are not only a major cause of familial HCM, but also of familial and sporadic DCM forms. The large number of patients examined by Villard et al. has substantially facilitated our understanding of MYH7 and its role in this process.

Similarly to HCM, Villard et al. observed a lower cardiac TNNT2 mutation frequency in their familial and sporadic DCM patients. When adding available reports, ∼3% (7/238) of all familial DCM patients, but <1% (2/273) of patients with sporadic DCM, actually have mutations in cardiac TNNT2.

Although the number of genotyped DCM families is small in their study, genotype-phenotype correlations are necessary to obtain a better insight into the clinical characteristics of the genotyped patients. Interpretation is even more difficult because often only few affected individuals of the same family are available for examination and longitudinal follow-up has not yet been possible. The report by Villard et al. comprised the largest number of DCM patients screened for four disease genes. The investigators found that MYH7 mutation carriers usually become symptomatic after the age of 30. DCM was diagnosed in the patients at a mean age of 48 years and two-thirds of patients...
reached an age ≥65 years. Other investigators reported an onset of DCM caused by MYH7 mutations as early as at birth and as late as 57 years of age.7

In contrast, the mean age at diagnosis was lower in the four patients with TNNT2 mutations. TNNT2 mutations can probably lead to an onset of disease as early as 1 month and as late as the fifth decade.7,12 The reason for this wide variation in disease onset, even within the same family, is still unknown; however, the cause may reside in different modifying genetic factors. Mutations in TNNT2 seem to lead to complete penetrance and a high proportion of patients die suddenly at younger ages whereas patients with mutations in MYH7 may have a more benign disease course. Because of large variations in onset and also in the course of the disease, particular care must be applied when generalizing results on the basis of the limited number of genotyped patients and families. Nevertheless, such studies are very valuable but need to be confirmed in larger cohorts of genotyped DCM patients.

When considering the contribution of all known DCM genes, we estimate that mutations in known disease genes are the cause of inherited DCM in ≤20% of cases. This low proportion reflects a more complicated genetic aetiology than previously assumed. Our perception of DCM becomes even more complex when we focus not only on isolated DCM but also on DCM associated with conduction defects, early atrial fibrillation, or skeletal muscular dystrophy (Figure 2). Specific mutations in many of the known DCM disease genes can also cause other cardiac disorders such as left ventricular non-compaction, restrictive cardiomyopathy, long QT syndrome, Brugada syndrome, or atrioventricular block. In addition, there is a wide overlap between disease-causing HCM and DCM genes (Figure 2). An example is the muscle LIM protein (MLP). MLP gene-disrupted mice showed predominantly DCM,13 whereas mutations in humans were described in patients with DCM14 as well as in patients with HCM.15

The many different mutations within the wide array of disease genes make a unifying hypothesis regarding the pathogenesis of DCM difficult indeed. The multitude of genetic causes is similar to the many acquired cardiac injuries leading to DCM. Therefore, DCM can be regarded as the final common pathway of inborn or acquired abnormalities, which impair myocellular systolic function.
function. The initial defect may reside within the sarcomere or cytoskeleton with respect to force generation and transmission, in the calcium cycling leading to inefficient force activation, or within the mitochondria leading to deficient energy generation.

Identifying the responsible mutations is only the first step towards a better understanding of this disease. The new genetics-based knowledge helped pose new hypotheses on the pathogenesis of DCM, which in turn triggers further experimental research. Genetic heterogeneity of familial DCM will increase over the following years. However, there has been remarkable progress in genetic methods and techniques, which facilitates genetic screening. In the future, microarrays and chip technology will offer interesting possibilities for faster resequencing and mutation detection.

More studies like the one by Villard et al.4 are needed for a better understanding of known mutations and their influence on disease onset, severity, and clinical course. Clearly, there is a strong demand for cooperation and specialization on a national and international level. Hopefully, centres for genetics in cardiomyopathy will arise that offer counselling and genetic analyses to the practising physicians. Well-coordinated networks of basic researchers and clinicians (for instance, the German network on heart failure and other similar bodies, www.knhi.de) will be the basis to provide access to genetic and clinical data for patients and professionals. We are convinced that only such combined effort will finally translate into better diagnostic and therapeutic options of this devastating disease.

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References


