Outcome of clinical versus genetic family screening in hypertrophic cardiomyopathy with focus on cardiac beta-myosin gene mutations:
Prediction of clinical status—is molecular genetics a new tool for the management of hypertrophic cardiomyopathy in clinical practice?

C. Hengstenberg a,*, J. Erdmann a, P. Charron b

aDepartment of Internal Medicine, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
bDepartment of Genetics, and Department of Cardiology, Hôpital Pitié-Salpêtrière, Paris, France

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See article by Havndrup et al. [1] (pages 347–357) in this issue.

1. Introduction

During the last decade, there was a major breakthrough in the molecular genetics of hypertrophic cardiomyopathy (HCM) and a total of nine genes could be identified to cause HCM (for review see [2]). Since all of these genes code for sarcomeric proteins, it has been hypothesised that HCM is a disease of the sarcomere [3]. The abnormal function of the sarcomere is, thus, the primary and hypertrophy of the myocardium the secondary abnormality [4,5].

However, HCM exposes phenotypic heterogeneity which means that with a certain gene mutation (e.g. a mutation in the β-MHC gene), there is a wide range of clinical features, such as a variable degree of LV hypertrophy, a variable age of onset, and a variable degree of risk for sudden cardiac death (SCD) [6]. Furthermore, the risk for SCD is probably not directly related to the extent or the severity of LV hypertrophy [7]. Interestingly, accumulating data support the role of the genetic heterogeneity (different genes, different mutations) to explain, at least in part, the phenotypic heterogeneity of the disease. Some mutations have been associated with particularly high incidence of SCD (in the MYH7 (β myosin heavy chain gene) and in the TNNT2 (cardiac troponin T gene)) whereas others appear to have a more ‘benign’ course [8,9].

Therefore, for both the patient and the doctor, there is a clear need to have a tool in hand: (1) to estimate the patient’s risk for SCD and with it the patient’s prognosis; (2) to evaluate HCM relatives pre-symptomatically; and (3) to examine molecular testing as diagnostic (or even prenatal) tool. In these respects, several conventional cardiological methods (such as ECG, stress ECG, Holter monitoring, invasive electrophysiological examination, etc.) have been examined and proven to be of limited value [7,10].

In this issue, Havndrup et al. report on the role of molecular genetics as a medical tool in clinical practice. The authors support this new tool for a better diagnosis and for an improved management of both, HCM patients and their families [1]. Sixty-eight index cases with HCM were investigated and of the MYH7 gene the exons 3–23 (where almost all mutations are located) were screened for mutations. Eight different mutations were found in nine index cases (13% of all 68 HCM patients), and the mutations were associated with an adverse prognosis. A total of 327 relatives of index patients were then investigated using both, conventional cardiological tools and molecular genetic testing. A comparison of the clinical and the genetic examinations was performed. Conventional cardiological examination was characterised by both, a low positive and a low negative predictive value. In contrast, the authors found that molecular screening correctly identified genetically affected relatives (17%) and genetically unaffected relatives (83%).

*Corresponding author. Tel.: +49-941-944-7211; fax: +49-941-944-7235.
E-mail address: christian.hengstenberg@klinik.uni-regensburg.de
(C. Hengstenberg).
2. Implications for the clinician

2.1. Genetic testing as prognostic tool in HCM patients

The main question for a clinician is: Could molecular genetic testing allow to better stratify the prognosis of a given HCM patient? Can it identify a subgroup of patients with a particularly high risk for SCD which might subsequently benefit from invasive therapeutic (and prophylactic) strategies, such as an implantable cardioverter defibrillator? The presence of several different disease genes, like β myosin heavy chain gene (MYH7), cardiac myosin binding protein C (MYBPC3), cardiac troponin T gene (TNNT2), and others, may result in a different natural history of the disease. In families related to the MYH7 gene, the phenotype varies considerably according to the mutation. Some mutations were associated with a more malignant prognosis with up to 50% mortality by the age of 40 years (R403Q, R403L, R453C, G716R, R719W and R723G), whereas others have a more benign prognosis (G256E, F513C, V606M, L908V) [2,8,11,12]. In families related to the TNNT2 gene, the phenotype appears to be similar for the different mutations, and characterised by an incomplete penetrance (75%), a relatively mild and sometimes subclinical hypertrophy (mean 17±5 mm) but a high incidence of sudden death before 30 years-of-age [13]. In families related to the MYBPC3 gene, the phenotype appears also similar for the different mutations and characterised by both, a low penetrance (41%), a low degree of hypertrophy before 30 years-of-age (mean 12±4 mm), a delayed age at onset of symptoms, and a favourable prognosis before 30 years-of-age [11,12,14]. All of these results could be particularly useful for the purpose of risk stratification in HCM patients and for leading to a better clinical management. However, caution is required and further studies based on large populations are needed to confirm these data since available studies were performed in small populations, data were usually retrospective, and some exceptions to these correlations have been reported [15].

2.2. Pre-symptomatic genetic testing in relatives of HCM patients

When a disease causing mutation was identified in the index patient of the family, the genetic testing in family members is very efficient as compared to a cardiological screening. This has also been shown in the present paper by Havndrup et al. [1]. However, what is the potential benefit of the procedure? At present, for mutation carriers there is no therapy available which could reverse or prevent the development of the disease. Moreover, identification of a mutation through a pre-symptomatic screening may result in an adverse psychological effect (to be certain to be at risk for major complications) and may additionally have also adverse outcomes (social, occupational, and insurance matters) [16].

Moreover, the right of the subject not to know his/her genetic status should absolutely be respected. Therefore, in our opinion, a genetic counselling should provide detailed information about the disease and the current medical knowledge in order to clarify both, the potential benefits and limitations of the genetic testing.

In most cases, genetic testing in apparently healthy relatives will indicate the absence of a mutation, and thus, subjects will be reassured. In addition, in these negatively tested relatives regular cardiological visits with ECG and echocardiography can be stopped, which will result in cost reductions for the society. In contrast, in relatives with a mutation, a strict medical follow-up will be required. This will allow to detect the onset of the disease very early and this will probably lead to improved management. Since sudden death is often the first symptom of the disease, the early diagnosis of the disease expression in the heart, even before the occurrence of the symptoms, will lead to a refined cardiac examination and risk stratification including exercise test and Holter monitoring. This will allow to estimate the individual’s (and family’s) risk and gives the opportunity to discuss the therapeutic strategy according to the risk stratification (for example, implantation of a cardioverter defibrillator [17]).

In addition, pre-symptomatic diagnosis might result in additional benefit in selected cases. In teenagers planning to become an athlete or individuals with high physical activity in their profession, genetic testing may help them to decide for their future professional activity. If a mutation could be identified and LV hypertrophy (cardiac expression of the disease) is present, physical activity restriction will be anticipated. In the case of mutation detection and absence of LV hypertrophy, it remains subject to discussion as to whether physical activity restriction should be advised (in case of numerous premature cardiac deaths in the family, this advise appears reasonable [16]).

2.3. Genetic testing as a diagnostic tool

In a patient with LV hypertrophy, it is sometimes difficult to diagnose correctly HCM as the cause of LV hypertrophy (especially when hypertrophy is symmetric, and when the familial context of a cardiac disease is absent). In these cases, it may be useful to characterise the molecular cause, so that the therapeutic strategy could be better defined. Indeed, specific therapeutics are required in other rare causes of LV hypertrophy, such as Fabry disease or cardiac amyloidosis. Moreover, in a patient with an apparently sporadic form of HCM, it may be useful to determine the genetic origin of the disease, in order to determine the risk of transmitting the disease to offspring.

2.4. Genetic testing as a prenatal diagnosis

Sometimes, prenatal diagnosis is requested by parents who have a high incidence of SCD in one of their families,
and who carry, therefore, a high psychosocial burden. To perform such a prenatal procedure implies that the couple wants to draw practical conclusions from the testing, i.e., to possibly perform a pregnancy termination if the foetus has the mutation. This prenatal testing is, however, dependent on the knowledge of the mutation in this family. If the mutation is not known, the prenatal testing will be probably be ineffective, because currently the speed to detect an unknown mutation is slower than necessary to terminate a ‘carrier’ pregnancy. Therefore, at present and from a medical point of view, the prenatal testing procedure can not be recommended in most cases due to the variable and mostly benign prognosis of the disease [16]. In selected cases, however, the prenatal testing can be discussed, especially when the family history is characterised by numerous premature cardiac deaths [18].

3. Implications for the molecular biologist

The molecular screening of several HCM causing genes is feasible. Since there is both, locus (different genes make the same disease) and allelic (different mutations in one gene) heterogeneity, the screening is very time and cost-consuming. In the study by Havndrup et al. [1], in only 13% of HCM index cases a mutation in the MYH7 gene could be identified. For this low identification rate there are some possible explanations: (1) the MYH7 gene accounts for the genetic cause of ~30–50% of all HCM families (MyBPC3 ~30–50% and all other genes ~10%) and Havndrup et al. screened only exons 3–23 of the MYH7 gene; (2) the sensitivity of the screening method (single strand conformation polymorphism, SSCP) is usually only about 70 to 90% (performed with two temperatures at 4 and 20 °C), thus, some mutations might have been missed; and (3) sporadic and familial forms of HCM were mixed and sporadic HCM cases are possibly less related to a genetic cause. In addition, double mutations (double heterozygous subjects) were found in the paper of Havndrup et al. [1], although the pathogenic role of the MYBPC3 variant was not certain. This finding, and previous ones [19,20], support a systematic screening of the entire gene and also additional genes in a given subject with HCM, even when a (first) mutation is identified.

4. Conclusions

Until recently, molecular genetic testing was confined to research laboratories and fundamental studies for augmentation of basic knowledge. This is now a turning point. Molecular genetics becomes a medical tool which can be used in clinical practice. The findings of Havndrup et al. support this notion. However, we have to take into account the complex medical and psychological implications of this new approach.

Phenotype-genotype correlations have to be confirmed and expanded before to be applied and recommended in clinical practice. In order to see clear differences in clinical expression (e.g. LV hypertrophy, survival, SCD) between the different mutations in the different genes, the power of the statistics is critical and therefore large numbers need to be included. At present, however, it is not possible to clinically examine a HCM patient (or a HCM family) and to deduce the disease gene from the phenotype (in the present paper, in only 13% of all HCM patients a mutation in the MYH7 gene was found). In this respect, it may be imaginable to enter and to follow-up members of HCM families in a large database, possibly worldwide. Such an effort has been achieved in part for cataloguing all HCM mutations (http://morgan.angis.su.oz.au/Databases/Heart/heartbreak.html). Furthermore, detailed and prospective analyses of large HCM cohorts will be necessary to unravel the presence and importance of genes that modify the phenotype (so-called modifier genes).

Concerning the medical counselling of the patients, it will be wise to install a specific and multidisciplinary approach to ensure good medical practice [16]. This counselling should include a cardiologist, a geneticist and a psychologist, and should meet the following requirements: (1) the subject or the family should be counselled in advance for the potential benefit and the limitations of the test; (2) the genetic counselling should always precede the blood sampling, which results solely from the decision by the applicant; and (3) confidentiality of the procedure must be granted. If these practices can be accepted, we can be confident and hope that molecular genetics will result in an improvement of the quality of life of HCM patients and their families. In the next few years, fast and less expensive mutation detection techniques, like chip-based sequencing, are on the horizon. These techniques will allow a fast and cost-effective mutation detection in the clinical routine.

References


