Familial screening and genetic counselling in hypertrophic cardiomyopathy: the Rotterdam experience

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Hypertrophic cardiomyopathy (HCM) is a disease characterised by unexplained left ventricular hypertrophy (LVH) (i.e. LVH in the absence of another cardiac or systemic disease that could produce a similar degree of hypertrophy), electrical instability and sudden death (SD).

Germline mutations in genes encoding for sarcomere proteins are found in more than half of the cases of unexplained LVH. The autosomal dominant inherited forms of HCM are characterised by incomplete penetrance and variability in clinical and echocardiographic features, prognosis and therapeutic modalities. The identification of the genetic defect in one of the HCM genes allows accurate presymptomatic detection of mutation carriers in a family. Cardiac evaluation of at-risk relatives enables early diagnosis and identification of those patients at high risk for SD, which can be the first manifestation of the disease in asymptomatic persons.

In this article we present our experience with genetic testing and cardiac screening in our HCM population and give an overview of the current literature available on this subject. (*Neth Heart J* 2007;15:184-9.)

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The prevalence of unexplained left ventricular hypertrophy (LVH) in the general population is estimated to be 1 in 500.^{1,2} Hypertrophic cardiomyopathy (HCM) caused by genetic defects in sarcomere genes may account for up to 60% of cases of LVH. This makes HCM the most common genetic cardiovascular disorder.^{3,4} The first HCM gene was identified in 1990;⁵ since then more than 11 HCM genes, mostly encoding for one of the sarcomere proteins, have been identified.

HCM is the most common cause of sudden death (SD) in the young and a major cause of morbidity and mortality in the elderly.⁶ SD may be the first manifestation of the disease in an asymptomatic individual. Many studies in HCM have shown extensive variability in expression, prognosis and therapy, even within families. Identification of disease-causing genetic defects in familial HCM allows reliable identification of at-risk relatives. Cardiac evaluation of at-risk relatives enables early diagnosis and identification of those patients at high risk for SD.

Genetic studies in HCM

At present, more than 400 disease-causing mutations in 11 genes, mostly encoding one of the myocardial contractile proteins (table 1), have been identified in familial HCM. In approximately 60% of HCM families a sarcomere mutation is identified.^{3,7,8} Disease-causing mutations are identified in 60% (142/236) of the HCM families currently being followed and completely genotyped for eight HCM genes in Rotterdam.

At the cardiogenetics clinic of the Erasmus Medical Centre in Rotterdam, the molecular analysis of HCM involves initial screening for the three Dutch founder mutations in the MYBPC3 gene. In the absence of the founder mutations, subsequently the MYBPC3 and the MYH7, cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), regulatory and essential myosin light chain, α -actin, α -tropomyosin are sequenced. DNA sequencing is time consuming and expensive, molecular analysis of all HCM genes will take about six months.

Table 1. Genes identified in familial hypertrophic cardiomyopathy (modified from Ho et al).¹⁷

Gene	Encoding protein	Locus
MyBPC3	Myosin binding protein C	11p11.2
MYH7	β -myosin heavy chain	14q12
TNNT2	Troponin T	1q32
TNNI3	Troponin I	19q13.4
TPM1	α -tropomyosin	15q22.1
MYL2	Regulatory myosin light chain	12q23-q24.3
MYL3	Essential myosin light chain	3p21.3-p21.2
ACTC	α -actin	15q11-q14
TTN	Titin	2q24.3
MYH6	α -myosin heavy chain	14q12
PRKAG2	Protein kinase A (γ -subunit)	7q36

Generally, mutations in the MYBPC3 are the most common genetic defect in HCM with a prevalence ranging from 20 to 42%.^{3,9} In the Netherlands this percentage is higher because of the existence of three founder mutations in MyBPC3.¹⁰ In the Rotterdam HCM population, 70% (100/142) of the HCM families with an identified mutation had an MYBPC3 mutation. Of these families, 65% (65/100) had one of the three founder mutations in MyBPC3; we identified 39 families with the 2373insG mutation, 15 families with the R943X mutation and 11 families with the 2864delCT mutation.

Mutations in the MYH7 gene have been reported frequently, accounting for up to 40% of cases.³ In the Rotterdam HCM families the contribution of MYH7 mutations was 18% (25/142).

Other HCM genes involved in the Rotterdam population are TNNT2, TNNI3, regulatory myosin light chain and α -tropomyosin; mutations in these genes are found in 2 to 3% of HCM families.

Given the high prevalence of HCM in the general population it is not surprising to encounter compound heterozygosity, especially in patients with severe, early onset of symptoms. Since it has been demonstrated that occurrence of multiple HCM gene mutations in a single patient is associated with a more severe phenotype, we pursue molecular analysis of HCM genes in patients with severe phenotype after the identification of a single mutation.^{7,11}

Genotype/phenotype correlation in HCM

HCM is the final common pathway of several different sarcomere defects. There is a continuing debate over the prognostic significance of HCM-causing mutations.^{12,13} Several highly penetrant genetic defects have been identified for Mendelian inherited forms of HCM. However, the clinical variability of HCM observed even within families suggests that the disease is at least partially the result of the additive or synergetic effect of risk factors, thus precluding the use of the genotype

as the main clinical and prognostic tool for individual patients, at least until the mechanisms underlying the clinical variability are elucidated.

Genetic counselling, presymptomatic testing and screening of at-risk relatives

After the clinical diagnosis of HCM is established at our HCM outpatient clinic, the cardiologist discusses the importance of molecular confirmation, also in patients with no family history of HCM or SD, with the patient (figure 1). Supported by the new classification of cardiomyopathies as proposed by Maron et al. we think that part of the diagnosis of HCM should be molecular classification.¹⁴ After informed consent, blood samples are drawn for DNA analysis of the proband.

Subsequently, patients are referred to the department of clinical genetics to ascertain the family history, allowing the identification of relatives at increased risk for HCM. Initially, we intend to inform first- and second-degree relatives about the occurrence of HCM in the family and invite them for genetic counselling by a clinical geneticist and/or a genetic nurse. Expanding the family history allows the identification of more at-risk relatives who are subsequently invited for genetic counselling (figure 1).

The results of the DNA analysis are conveyed at the department of clinical genetics, where the consequences of these results for the patient and their relatives are discussed. In HCM families in which we were able to identify a mutation in one of the HCM genes, presymptomatic DNA testing is offered to adults at risk. The results of presymptomatic testing of at-risk relatives are received within six weeks. No further cardiac screening is indicated for relatives without the disease-causing mutation. The mutation carriers are referred for cardiac screening by medical history, clinical examination, echocardiography, exercise-ECG and 24-hour Holter monitoring. In 2006, 45 asymptomatic mutation carriers were screened, which led to the

Figure 1. Flowchart used at the cardiogenetics department in the Erasmus Medical Centre showing the multidisciplinary approach by the cardiologist (dashed boxes) and clinical genetic nurses and medical doctors (un-dashed boxes). X-ECG=exercise test, 24 H Holter=24-hour Holter monitoring).

Table 2. Risk factors for sudden death in hypertrophic cardiomyopathy (modified from Elliot et al).³⁸

Nonsustained ventricular tachycardia on ambulatory electrocardiography
 Syncope
 Blood pressure rise <25 mmHg during exercise in patients < 40 years
 Family history of sudden death
 Left ventricular wall thickness >30 mm

diagnosis of HCM in 16 (36%) of the referred subjects. Subjects carrying a mutation in MYH7 were affected at a significantly younger age than subjects carrying a mutation in MyBPC3. The diagnosis led to lifestyle changes, leading to cessation of competitive sports in seven (16%) subjects and in three (7%) subjects medical therapy was started. According to the established risk factors for SD (table 2) 44 (98%) of referred subjects had a low risk for SD.

Relatives who decline presymptomatic DNA testing and at-risk relatives from families where we were not able to detect a disease-causing mutation are referred for cardiac screening by medical history, clinical examination, electrocardiography and echocardiography. In 1997 McKenna et al. proposed new diagnostic criteria for HCM in adult members of affected families based on echocardiographic and electrocardiographic findings (table 3). The diagnosis would be fulfilled in the presence of one major criterion; two minor echocardiograph criteria; or one minor echocardiographic plus two minor electrocardiographic criteria.¹⁵ In relatives meeting the diagnostic criteria for HCM we continue with an exercise-ECG and 24-hours Holter monitoring for risk stratification.

In mutation carriers and in relatives in whom the genotype is not known, the cardiac screening is re-

peated according to the results, and therapy is initiated when necessary. In adult persons repeated screening is indicated after three to five years when all tests are normal (figure 1).^{16,17}

The goal for the next three years is to further develop our cardiogenetic outpatient clinic and to identify all affected at-risk relatives of the HCM patients in the Rijnmond region.

Screening for HCM in children

Cardiac screening by medical history, physical examination, ECG and echocardiogram in children from HCM families is performed after the age of 10. Cardiac screening of younger children will be done when there is suspicion of HCM symptoms in the child, when the family history includes early-onset HCM or SD, upon parental request or if the child with suspicion of HCM enrolls in a competitive sport.

Presymptomatic genetic testing in children remains controversial, since the medical benefit of presymptomatic diagnosis in HCM in childhood has not been established. Some clinicians have emphasised the potential benefit of testing in HCM,¹⁸ however, the only medical implication is a regular follow-up in mutation carriers, which will allow the detection of clinical expression of the disease very early. Others consider presymptomatic testing in children more deleterious than beneficial, because of the lack of efficient treatment

Table 3. Diagnostic criteria for hypertrophic cardiomyopathy in adult members of affected families (modified from McKenna et al).¹⁵

Major criteria	Minor criteria
Echocardiography	
Anterior septum or posterior wall ≥ 13 mm	Anterior septum or posterior wall 12 mm
Posterior septum or free wall ≥ 15 mm	Posterior septum or free wall 14 mm
Severe SAM (septal-leaflet contact)	Moderate SAM (no septal-leaflet contact)
	Redundant MV leaflets
Electrocardiography	
LVH + repolarisation changes	Complete BBB (or (minor) interventricular conduction defect (in LV leads)
T-wave inversion in leads I and aVL (≥ 3 mm), V_3 - V_6 (≥ 3 mm) or II, III, aVF (≥ 5 mm)	Minor repolarisation changes in LV leads
Abnormal Q (>40 ms or >25% R wave) in at least 2 leads from II, III, aVF, V_1 - V_4 ; or I, aVL, V_5 - V_6	Deep S in V_2 (>25 mm)

SAM=systolic anterior motion, LVH=left ventricular hypertrophy, MV=mitral valve, BBB=bundle branch block.

to prevent clinical expression in children bearing a mutation, combined with possible adverse psychological effects.¹⁹

If HCM is diagnosed by echocardiography, the diagnosis may be confirmed by screening for the familial mutation. Presymptomatic genotyping of children is, as in other mostly late adult-onset diseases, only done in exceptional cases.²⁰

Genetic counselling and prenatal diagnosis

In autosomal dominantly inherited HCM, there is a risk of 50% of transmitting the genetic defect to a child. In families where the disease-causing mutations have been identified, there is a possibility for prenatal diagnosis of HCM with chorionic villus sampling as early as at ten weeks of gestation, or by amniocentesis in the 16th week of the pregnancy. However, prenatal diagnosis of HCM is almost never indicated because of the variability in expression of the disease and the small risk of cardiac disease at young age. Although early expression of HCM is extremely rare, pregnant women are offered a structural sonography in the 18th to 20th week of pregnancy.

Recommendations for follow-up of mutation carriers and at-risk relatives

The variability in age at onset of HCM and lack of cardiac pathology in a proportion of known HCM mutation carriers and at-risk relatives mandates long-term follow-up, even when they are asymptomatic at cardiac screening. In the Netherlands these mutation carriers are invited to participate in the Escape study, which is supported by the ICIN and focuses on the prognostic factors of these individuals.

Cardiac follow-up

Age at presentation varies in HCM, even in families carrying the same HCM mutation.²¹⁻²³ In a long-term follow-up study of patients with a mutation in MyBPC3 disease penetrance was 100% in patients aged >50 years.²¹ Follow-up at regular intervals, including echocardiography, exercise testing and 24-hour Holter monitoring, is therefore mandatory. During echocardiography in these patients we focus on subtle abnormalities and perform tissue Doppler imaging (TDI), since low systolic and diastolic velocities can be a predictor of the development of hypertrophy.²⁴

In asymptomatic carriers and at-risk relatives repeated clinical screening is advised, every two years between the age of 10 to 22 years, and every five years in older mutation carriers.¹⁷

Sport participation

According to the guidelines, all patients with a probable or unequivocal clinical diagnosis of HCM should be excluded from most competitive sports. Some moderate- and low-intensity level recreational sports such as swimming, brisk walking, biking and skating are permitted.²⁵ For asymptomatic mutation carriers

and at-risk relatives there are no compelling data available to prohibit competitive sports, particularly in the absence of cardiac symptoms or a family history of SD. Athletes with preclinical HCM should be carefully examined every 12 to 18 months with electrocardiogram, echocardiography, exercise testing and ambulatory Holter electrocardiogram.^{26,27}

Socioeconomic consequences of presymptomatic testing for HCM

In an unselected patient population HCM is a benign disease with an incidence of cardiac death of less than 1% per year.²⁸ However, these studies on prognosis did not include mutation carriers whose prognosis is suspected to be at least similar and most likely better. Until follow-up studies of mutation carriers are available insurance companies will work with the available studies, which will mean higher insurance premium for life insurance, disability, critical illness, and long-term care insurance.²⁹ Especially in young patients this can be a reason to postpone presymptomatic testing.

Future perspective in the delay of onset or prevention of HCM

There are promising results from animal studies using calcium channel blockers³⁰ and statins³¹ showing delay in onset of HCM. In patients with nonobstructive HCM, treatment with angiotensin II blockade³² seems to be beneficial. Studies from our institution have shown that alterations of hypertrophy in HCM patients are influenced by polymorphisms in the renin-angiotensin-aldosterone system genes; these results support the use of agents that influence this system in HCM patients.³³⁻³⁵

Treatment of patients with clinical diagnosis of HCM

The HCM patients are treated according to the guidelines.³⁶ Medical treatment is first-line therapy, traditionally with either β -blockers or nondihydropyridine calcium channel blockers to facilitate diastolic filling and to reduce intracavitary gradients. The negative inotropic effect of disopyramide also may be beneficial in reducing obstructive physiology.³⁷ Significant (>50 mmHg at rest or >100 mmHg at provocation) intracavitary obstruction with refractory symptoms can be addressed by surgical myectomy or by ethanol septal ablation. It is important to assess the risk of sudden death (SD) in these patients, because the prophylactic implantation of a cardioverter-defibrillator can be defended in some cases. In a study by Elliot et al. several risk factors were identified demonstrating that patients with ≥ 2 risk factors (table 2) had a 4 to 5% estimated annual SD risk, whereas in the absence of risk factors this risk was <1%.³⁸ A recent study from the same group showed that left ventricular outflow tract obstruction in asymptomatic patients with no other SD risk markers was not related to increased mortality and did not warrant aggressive interventions.³⁹ Prophylactic pharmacological therapy with β -blockers or calcium channel

antagonists has frequently been used, but efficacy in SD prevention has not been established. Empiric use of amiodarone has been reported to be associated with improved survival in one observational study with historical controls.⁴⁰ Supported by other data we believe that implantation of a cardioverter-defibrillator is the preferred therapy for primary prevention in high-risk patients and for secondary prevention in patients who survived life-threatening arrhythmias.^{41,42}

Conclusions

The identification of autosomal dominantly inherited genetic defects in an HCM gene provides new opportunities for accurate identification of at-risk relatives and effective screening of the relatives of HCM patients. The variability in age at onset of symptoms of HCM demands repeated cardiac screening of adults at risk for HCM, whether carriers of known mutations or relatives of families where no genetic defect has been identified. ■

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