Hypertrophic cardiomyopathy: towards an optimal strategy
Christiaans, I.

Citation for published version (APA):
Christiaans, I. (2010). Hypertrophic cardiomyopathy: towards an optimal strategy

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Introduction and outline of this thesis

1.1 Hypertrophic cardiomyopathy

Based on:

Preface
Hypertrophic cardiomyopathy (HCM) has been described in medical literature for several centuries. The resurgence of anatomy in the Renaissance allowed further study of disease and dissections of victims of sudden death revealed bulky hearts. Nowadays, HCM is still a major cause of sudden cardiac death (SCD) in the young, and the most common hereditary heart disease. This chapter discusses not only the epidemiology, diagnosis, pathophysiology and therapy of HCM but also deals with topics specific for cardiogenetic diseases like the genetic background, risk stratification for SCD, and the screening strategies in HCM families. It is intended to better understand the research described in this thesis and to be of help for all involved in the care for HCM patients and their families.

Prevalence and diagnosis
Hypertrophic cardiomyopathy is a relatively common autosomal dominant disease affecting at least 1 in 500 persons in the general population worldwide. The clinical diagnosis is made when there is a hypertrophied (often asymmetric), nondilated left ventricle on echocardiography (left ventricle wall thickness ≥ 15 mm) in the absence of other cardiac or systemic diseases that may cause cardiac hypertrophy, such as aortic valve stenosis and arterial hypertension. Because of the hereditary nature of the disease, relatives of a patient can also be affected. In a patient’s relative the diagnosis can be made if certain ECG abnormalities and/or a left ventricle wall thickness ≥ 13 mm are present.

Considering the prevalence of clinical diagnosed HCM is at least 1 in 500, in the Netherlands with a population of 16.4 million at least 32,800 people must have HCM and many more may be at risk of developing HCM, particularly mutation carrying relatives who have not developed left ventricular hypertrophy yet. In a country like China the number of individuals with HCM would be more than 2.6 million. Many of these HCM patients are unaware of their disease and/or unaware of its hereditary nature. It is estimated that in the Netherlands only 10-20% of HCM mutation carriers have been identified.

Pathophysiology and natural history
The British pathologist Robert Donald Teare is assumed to be the first to describe hypertrophic cardiomyopathy in 1958. Although bulky hearts and hypertrophy in sudden death victims have been described centuries earlier and subaortic stenosis (a former name for hypertrophic cardiomyopathy) was described earlier in literature, Teare was the first to describe the asymmetrical appearance of hypertrophy together with its familial nature. He also described a disordered arrangement of muscle fibres at microscopic examination of the hearts of his cases, now known as myocyte disarray (Figure 1). With electron microscopy one can also notice a disordered arrangement of the myofilaments as well. Myocardial disarray is not confined to the thickened parts of the left ventricle; left ventricular regions with normal thickness can also be disorganised. Fibrosis is another feature of HCM visualised by microscopy or MRI. Both fibrosis and myocyte disarray are thought to be related to ventricular arrhythmias. Besides hypertrophy, fibrosis, and disarray, abnormalities in the intramyocardial small vessels are a pathological finding in HCM. Vessels may show a thickening of the vessel wall and a decrease in luminal size.

The diagnosis of HCM is most often made in adulthood, but HCM can present at any age. HCM is clinically heterogeneous; patients are often asymptomatic and diagnosed in routine screening, but HCM can also emerge as a disabling disease giving rise to dyspnoea,
Hypertrophic cardiomyopathy

exertional angina, palpitations and (pre)syncope. The anatomic changes in HCM can be a substrate for arrhythmias, which may lead to palpitations, syncope and even sudden cardiac death.

Early pathogenesis in HCM starts in the functional unit of contraction within the cardiomyocytes. The sarcomere is a protein complex divided into thick and thin myofilaments and proteins involved in the cyto-architecture of the sarcomeres, like proteins in the Z-disc connecting the thin myofilaments of the sarcomere (Figure 2). In response to electrical depolarisation of the cardiomyocyte intracellular levels of calcium rise. Calcium binds to the troponin complex of the thin filament and releases the inhibition of interactions between the thick filament (myosin) and thin filament (actin) by troponin I. The myosin head can then bind to actin and when ATP binds to myosin the myosin head moves along the thin filament. ATP hydrolysis occurs and force is generated. During relaxation, calcium is removed from the cytosol. Calcium is not only a key molecule regulating both cardiac contraction and relaxation but also seems to play an important role in the early pathogenesis of HCM. It is hypothesised that the genetic defect in a gene encoding a sarcomeric protein disrupts normal contraction and relaxation of the sarcomere and calcium accumulates within the sarcomere. This leads to a reduction of calcium re-uptake and eventually to reduced stores in the sarcoplasmic reticulum and increased calcium sensitivity. Myocytes in mice with HCM also display an inefficient use of ATP. This in combination with the increased calcium sensitivity triggers a remodelling process moderated by several transcription factors resulting in hypertrophy of cardiomyocytes. The increased mass of cardiomyocytes and inefficient use of ATP lead to an increased energy demand. When this energy demand cannot be met ischemia can result in premature myocyte death and replacement fibrosis.

The hallmark of HCM, left ventricular hypertrophy (LVH), can appear at virtually any age and increases or decreases dynamically throughout life. Studies suggest that extreme LVH occurs more frequently in the young, i.e. in puberty or early adulthood. A modestly decreasing magnitude of LVH with increasing age has also been found, however, this inverse relation was largely gender-specific for women. These studies suggest that LVH is a dynamic feature of HCM, although all studies were cross-sectional in design.

There might be two possible explanations for the observation that left ventricular wall thickness is generally milder in patients of more advanced age than in the young. Firstly, young patients with marked LVH have a higher rate of premature cardiac death. This means that patients with extreme LVH are underrepresented in the subgroup of older patients (the so called healthy survivor phenomenon). Secondly, progression to 'end-stage' HCM may account in part for this. About 5–10% of HCM patients progress to this end-stage, burn-out phase, which is characterised by systolic dysfunction, dilatation of the left ventricle and wall thinning, resembling the features of dilated cardiomyopathy. Patients with this so called dilated-hypokinetic evolution are younger at first evaluation, and more often have a family history of HCM or SCD than patients who do not develop these features. Most of the reported patients with a dilated-hypokinetic evolution of HCM were 60 years or older.

The most common location for LVH is the anterior part of the interventricular septum, giving rise to an asymmetrical appearance of hypertrophy. The asymmetrical septal hypertrophy can be divided into two subtypes: the sigmoid subtype with an ovoid LV cavity and a pronounced basal septal bulge and the reverse curvature subtype with a crescent shaped LV cavity and midseptal hypertrophy. Other forms of hypertrophy, for example concentric or neutral hypertrophy and apical hypertrophy can also be found in HCM (Figure
Introduction and outline of this thesis

Figure 1. A: Normal heart and heart with hypertrophic cardiomyopathy. B: Heart muscle on microscopy with structured fiber pattern in the normal heart and myocardial disarray in the heart with hypertrophic cardiomyopathy.


Figure 2. Main sarcomeric proteins (courtesy of Ackerman et al. Mayo Clinic).
Hypertrophic cardiomyopathy

3). The latter form seems to occur more frequently in East Asian patients.32, 33

Not only can HCM present at any age, the clinical course is also variable. Patients can remain asymptomatic throughout life, but the disease can also give rise to heart failure and other adverse advents like sudden unexpected death and embolic stroke. First symptoms are often exertional dyspnea, disability (often associated with chest pain), dizziness and (pre) syncope. These symptoms are primarily caused by diastolic dysfunction with impaired filling of the left ventricle due to abnormal relaxation and increased stiffness of the myocardial wall, leading in turn to elevated left atrial and left ventricular end-diastolic pressures, pulmonary congestion and impaired exercise performance.34, 35 Systolic function is often spared, but systolic dysfunction can arise in patients with the so called ‘end stage’ form of HCM. Symptoms may become more disabling in the presence of other associated pathophysiological mechanisms, like myocardial ischemia, left ventricular outflow tract obstruction (LVOTO) and atrial fibrillation.

In the early descriptions of HCM, patients almost always had left ventricular outflow tract obstruction and the disease was also called HOCM (hypertrophic obstructive cardiomyopathy). Nowadays obstruction is still a frequent finding, but only a minority (20-30%) of HCM patients have LVOTO, which is in HCM often caused by systolic anterior motion (SAM) of the mitral valve leaflets (Figure 4).31, 36-39 In general LVOTO is defined as a peak gradient of 30 mmHg or more identified by Doppler echocardiography under basal (resting) conditions,31, 36-39 but the degree of LVOTO can vary in time and some patients only have provocabile obstruction. The presence of LVOTO is a strong predictor of disease progression; symptoms of heart failure and death due to heart failure and stroke.38

Atrial fibrillation is another frequent symptom in HCM (about 20% of patients). It
Introduction and outline of this thesis

is associated with advanced age, congestive symptoms, and an increased left atrial size at diagnosis. HCM patients with atrial fibrillation have an increased risk of heart failure related death, besides the risk of cerebrovascular accidents.

Disease penetrance

HCM has long been regarded as a disease that mainly affects young people. It was thought that penetrance, i.e. the presence of left ventricular hypertrophy, was complete at approximately 20 years of age. Nowadays it is more and more recognised that not only symptoms but also hypertrophy can develop at any point in life. Looking at symptoms of the disease, in an unselected patient group 65% of patients aged 75 years or older had no or only mild symptoms. In this study the probability of survival for 5, 10 and 15 years for patients diagnosed with HCM after the age of 50 did not differ significantly from the (matched) general population. These data show that patients can have normal survival and that the disease may not give symptoms until late in life, or even may give no symptoms at all.

Although the abovementioned study is performed in an unselected population of HCM patients and based on the presence of symptoms, disease penetrance is not based on the presence of symptoms but on the presence of hypertrophy and is best investigated in a population with proven mutation carriers. Studies in mutation carriers show that disease penetrance is incomplete in adult life, but reaches 95-100% after the age of 50 years. The relationship between disease penetrance and the genotype (defined as the mutated gene or a specific mutation within a gene) is still not completely resolved. Studies including a large number of mutation carriers show no difference in disease penetrance between carriers of different mutated genes.

Therapy

Management in HCM patients is directed towards control of symptoms, risk stratification for and prevention of SCD (see SCD and risk stratification) and screening of relatives (see Screening of relatives: genetic counselling and testing). Symptoms of dyspnoea, angina, syncope and fatigue are appraised and treated (Figure 5). Prophylactic pharmacological treatment in
asymptomatic patients has not been proved to be effective in preventing progression of the disease. Drugs are often the only available treatment modality for symptomatic patients without LVOTO. Negative inotropic agents like beta-blockers and calcium antagonists have been shown to relieve symptoms. Beta-blockers decrease the heart rate which results in a prolongation of the diastole and relaxation phase of the heart and an increase in passive ventricular filling. Besides, beta-blockers decrease left ventricular contractibility and myocardial oxygen demand and can possibly reduce ischemia in myocardial microvessels. Verapamil, a calcium antagonist, also has favourable effects on symptoms by improving ventricular relaxation and filling. In patients with progressive heart failure symptoms with LVOTO, disopyramide, a negative inotropic and type I-A antiarrhythmic drug, can be used. It can decrease systolic anterior movement of the mitral valve, LVOTO, and mitral regurgitation. In end stage HCM load reducing drugs (ACE inhibitors, angiotensin-II receptor blockers, diuretics, digitalis, beta-blockers or spironolactone) can be used to alleviate symptoms from systolic failure.34

For HCM patients with LVOTO other treatment modalities are available if pharmacological treatment cannot alleviate symptoms. Ventricular septal myectomy (Morrow operation) is the next preferable treatment.47 Septal myectomy has been associated with a considerable risk of mortality and morbidity. Nowadays, isolated myectomy has low operative mortality and brings effective long lasting improvement of symptoms.48 An alternative more recently developed treatment modality for symptomatic LVOTO is percutaneous alcohol septal ablation. The introduction of alcohol in the septal perforator branch of the left anterior descending coronary artery mimics septal myectomy.49 Although both percutaneous alcohol septal ablation and septal myectomy can alleviate symptoms, the latter therapy is considered the gold standard because of a lower rate of procedural complications and more available knowledge on the long term outcomes.48, 50

Indirect evidence suggests an association between exercise and sudden cardiac death. Intense physical activity (e.g. sprinting) or systematic isometric exercise (e.g. heavy lifting) should be discouraged. (Young) HCM patients should be advised to avoid intense competitive sports and professional athletic careers. Bacterial endocarditis prophylaxis is recommended in HCM patients with LVOTO in resting or exercise conditions.34

Sudden cardiac death and risk stratification
One of the most used definitions of sudden cardiac death is: ‘Natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms; pre-existing heart diseases may have been known to be present, but the time and mode of death are unexpected’.51 In the past HCM was seen as a disease with an ominous prognosis, because of severe symptoms and high rates of SCD (3-6% per year).26, 51-56 These data, however, came from highly selected patient populations of severely affected patients treated in tertiary referral centres. These populations underrepresented clinically stable and asymptomatic patients.57, 58 Recent reports with less referral bias indicate overall annual mortality rates from HCM of 1 to 2% (SCD and heart failure related death). Annual mortality from SCD alone in HCM patients is 0.4 to 1%.59-65

Although the overall risk of SCD for HCM patients is small in absolute terms, a small subset of patients is at much higher risk of SCD. Much would be gained in terms of treatment benefits and avoidance of diagnostic and treatment burden if this subset could be detected at an early stage. The ACC/ESC Consensus Document suggests that for this purpose all HCM
Introduction and outline of this thesis

patients should be identified and undergo cardiological diagnostics, to evaluate clinical signs of HCM and to estimate the risk of SCD. Currently, six major risk factors for SCD have been identified which are mainly based on the outcome of various cardiological diagnostic tests: (1) prior cardiac arrest (ventricular fibrillation) or spontaneous sustained ventricular tachycardia, (2) a family history of premature sudden death, (3) unexplained syncope, (4) left ventricular wall thickness ≥ 30 mm, (5) abnormal exercise blood pressure and (6) nonsustained ventricular tachycardia. Possible minor risk factors for SCD include: (1) atrial fibrillation, (2) myocardial ischemia, (3) left ventricular outflow tract obstruction, (4) a high-risk mutation and (5) intense (competitive) physical exertion. Recently, myocardial fibrosis assessed by magnetic resonance imaging is being evaluated as a possible risk factor for SCD. Associations with nonsustained ventricular tachycardia and other risk factors have been found, but a prognostic study evaluating fibrosis as an independent predictor for SCD is still lacking.

HCM patients, particularly those under the age of 60 years, should undergo a yearly clinical assessment including risk stratification based on the presence of the six major risk factors for SCD: careful personal and family history, 12-lead ECG, echocardiography, Holter recording and exercise test. The presence of two major risk factors is associated with an estimated annual risk of SCD of 4 to 5%. According to international guidelines this risk is regarded sufficiently high to justify primary prevention of SCD by means of an implantable...
cardioverter defibrillator (ICD). In patients with a prior cardiac arrest or spontaneous sustained ventricular tachycardia an ICD should be implanted for secondary prevention. Recent guidelines on arrhythmia and the prevention of SCD also support ICD implantation in HCM patients with only one of the six major risk factors who are considered to be at high risk for SCD by their physician. At present the implantable cardioverter defibrillator (ICD) appears to be an effective prophylactic treatment modality. However, due to the low positive predictive value of the major risk factors, the decision to implant an ICD in HCM patients with only one major risk factor for SCD remains controversial in general terms, and a difficult one in terms of patient care.

**Genetics of HCM**

HCM is inherited as an autosomal dominant trait. In more than half of the HCM patients the disease causing mutation can be identified currently. Mutations can be located in many genes, but are most often found in the genes encoding sarcomeric proteins (Table 1, Figure 2). Sarcomeric genes can be divided in genes encoding for myofilament proteins and genes encoding for Z-disc proteins. Most HCM patients are heterozygous for the mutation, but in 3-5% of cases, patients carry two mutations in the same gene (different alleles –compound heterozygous or homozygous—) or in different genes (digenic). This is generally associated with a more severe phenotype with younger age of onset (often < 10 years) and more adverse events suggesting a gene-dosage effect. The two most frequently mutated genes are MYBPC3 and MYH7, encoding the sarcomeric proteins cardiac myosin-binding protein C and beta myosin heavy chain, respectively (Table 1). Both proteins are major components of the sarcomeric thick filament. In contrast to MYH7 and most of the other genes associated with HCM, 70% of MYBPC3 gene mutations are nonsense or frameshift and should result in truncated proteins, suggesting haploinsufficiency. In the other genes missense mutations are most frequent which create a mutant protein that interferes with normal function (dominant negative effect).

Since the discovery of the first genes for HCM, many papers on genotype-phenotype correlations have been written. At first specific mutations, mainly in the MYH7 gene, were described that were associated with a ‘malignant’ phenotype (decreased survival). So called ‘benign’ mutations were reported in families with normal longevity, as well. These suggested ‘malignant’ and ‘benign’ mutations have been contradicted in many subsequent studies. Nowadays it is believed that, possibly apart from rare exceptions, there are no clear genotype-phenotype relations with respect to magnitude of left ventricular hypertrophy and incidence of sudden cardiac death. Moreover, genetic studies have revealed that not all mutation carriers are clinically affected, using standard echocardiography. This suggests the existence of modifier genes, which modulate the phenotypic expression of the disease. Associations have been found with polymorphisms in genes for the angiotensin II type 1 and type 2 receptors and in the promotor region of the calmodulin III gene. Non-sarcomeric genes have been associated with specific phenotypes which include besides HCM almost always a distinct non-cardiac syndromic phenotype, like the PTPN11 gene in Noonan syndrome and the LAMP2 gene in Danon disease. However, mutations in the GLA gene, associated with Fabry disease, can give rise to HCM without further symptoms of Fabry disease, especially in women. PRKAG2 is the other non-sarcomeric gene which presents with an exclusively cardiac phenotype. The cardiac phenotype is distinct and includes besides

---

**Table 1**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation Type</th>
<th>Phenotype Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYBPC3</td>
<td>Nonsense or Frameshift</td>
<td>Severe phenotype with younger age of onset</td>
</tr>
<tr>
<td>MYH7</td>
<td></td>
<td>Normal phenotype</td>
</tr>
<tr>
<td>PTPN11</td>
<td></td>
<td>Noonan syndrome</td>
</tr>
<tr>
<td>LAMP2</td>
<td></td>
<td>Danon disease</td>
</tr>
<tr>
<td>GLA</td>
<td></td>
<td>Fabry disease</td>
</tr>
</tbody>
</table>

---

**Figure 2**

The schematic representation of the sarcomeric thick filament showing the location of the sarcomeric proteins MYBPC3 and MYH7.
HCM electrical pre-excitation (Table 1).\textsuperscript{113}

De novo mutations and germline mosaicism occur very rarely in HCM.\textsuperscript{114-118} Because most mutations are private, many of the identified mutations are novel. In certain countries/populations, however, founder mutations have been identified, in which haplotype analysis suggests a common ancestor. These founder mutations often comprise a large part (10-25\%) of the detected mutations in these countries. Founder mutations have been found in the Netherlands,\textsuperscript{119, 120} South Africa,\textsuperscript{121} Finland,\textsuperscript{122} Italy,\textsuperscript{123} Japan,\textsuperscript{124} and in the Amish population of the United States.\textsuperscript{125}

Like in other genetic diseases, identified mutations in HCM patients can be pathogenic (disease causing), silent polymorphisms, or unclassified variants of which the pathogenic

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>Detection rate</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcomeric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYBP C3</td>
<td>Myosin-binding protein C</td>
<td>13-32%</td>
<td></td>
</tr>
<tr>
<td>MYH7</td>
<td>Beta myosin heavy chain</td>
<td>4-25%</td>
<td></td>
</tr>
<tr>
<td>TNNT2</td>
<td>Troponin T2</td>
<td>0.5-7%</td>
<td></td>
</tr>
<tr>
<td>TNNI3</td>
<td>Cardiac troponin 1</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>MYL2</td>
<td>Myosin light chain 2</td>
<td>&lt;3%</td>
<td></td>
</tr>
<tr>
<td>MYL3</td>
<td>Myosin light chain 3</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>TPM1</td>
<td>Alpha tropomyosin</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>ACTC</td>
<td>Alpha actin</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>TNNC1</td>
<td>Troponin C</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Z-disc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTN2</td>
<td>Alpha-2 actinin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSRP3</td>
<td>Cysteine- and glycine-rich protein 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBD3 (or ZASP)</td>
<td>Lim domain-binding 3</td>
<td>4-5%</td>
<td></td>
</tr>
<tr>
<td>TCAP</td>
<td>Titin-cap (Telethonin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCL</td>
<td>Vinculin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYOZ2</td>
<td>Myozenin 2</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Non-sarcomeric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRKAG2</td>
<td>AMP-activated protein kinase gamma 2</td>
<td></td>
<td>LVH / pre-excitation (Wolf-Parkinson-White syndrome)</td>
</tr>
<tr>
<td>LAMP2</td>
<td>Lysoseme-associated membrane protein 2</td>
<td></td>
<td>/ conduction disturbances</td>
</tr>
<tr>
<td>GLA</td>
<td>Alpha galactosidase</td>
<td></td>
<td>Fabry disease</td>
</tr>
<tr>
<td>PTPN11</td>
<td>Protein-tyrosine phosphatase non-receptor-type 11</td>
<td>Noonan, Leopard, CFC syndrome</td>
<td></td>
</tr>
<tr>
<td>KRAS2</td>
<td>Kirsten rat sarcoma viral oncogen homolog</td>
<td>Noonan, Leopard, CFC syndrome</td>
<td></td>
</tr>
<tr>
<td>SOS1</td>
<td>Son of sevenless homolog 1</td>
<td>Noonan syndrome</td>
<td></td>
</tr>
<tr>
<td>BRAF1</td>
<td>V-RAF murine sarcoma viral oncogen homolog</td>
<td>CFC syndrome</td>
<td></td>
</tr>
<tr>
<td>MAP2K1</td>
<td>Mitogen-activated protein kinase gamma 1</td>
<td>CFC syndrome</td>
<td></td>
</tr>
<tr>
<td>MAP2K2</td>
<td>Mitogen-activated protein kinase gamma 2</td>
<td>CFC syndrome</td>
<td></td>
</tr>
<tr>
<td>HRAS</td>
<td>Harvey rat sarcoma viral oncogen homolog</td>
<td>Costello syndrome</td>
<td></td>
</tr>
<tr>
<td>GAA</td>
<td>Glucosidase alpha acid</td>
<td>Pompe disease</td>
<td></td>
</tr>
<tr>
<td>GDE</td>
<td>Glycogen debrancher enzyme</td>
<td>Glycogen storage disorder III</td>
<td></td>
</tr>
<tr>
<td>FXN</td>
<td>Frataxin</td>
<td>Friedreich ataxia</td>
<td></td>
</tr>
<tr>
<td>TTR</td>
<td>Transthyretin</td>
<td>Amyloidosis I</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial DNA</td>
<td></td>
<td>LHV “plus”</td>
<td></td>
</tr>
</tbody>
</table>

* Because of specific phenotype mutation detection rate is not provided.

Table 1. Genes associated with HCM and their detection rate.\textsuperscript{74,75,78-80,85-90}
effect is still unclear. Nonsense or frameshift mutations are most often pathogenic because they are predicted to result in a C-terminal truncated protein that is likely to be non-functional. Moreover, due to the presence of two quality controls, the nonsense-mediated mRNA decay degrading nonsense (truncated) mRNAs\textsuperscript{126} and the ubiquitin-proteasome degrading aberrant proteins,\textsuperscript{127} truncating mutations most often do not result in the formation of protein at all and therefore lead to haploinsufficiency of the protein encoded by the mutated allele in the cells. Missense mutations create a mutant protein that either interferes with normal function (dominant negative effect) or assumes a new function. Sometimes however it remains unclear if a missense mutation results in a protein with no or abnormal function. The amino acid substitution in missense mutations can give some indications for pathogenicity. Missense mutations at codons conserved between species and/or isoforms are more likely to be pathogenic than mutations at poorly conserved regions. Different in silico methods have been developed to assess not only conservation, but also changes in protein structure, chemical and biophysical characteristics and interactions. These in silico methods to define pathogenicity have to be validated by comparison to a gold standard. Gold standards can be functional assays, frequently found mutations (e.g. founder mutations) or segregation with the phenotype. All of these potential standards, however, have their own strengths and weaknesses.\textsuperscript{128, 129} Unclassified variants and even polymorphisms in HCM associated genes and other genes (e.g. polymorphisms in the renin-angiotensin-aldosterone system\textsuperscript{130, 131}) may exhibit phenotype modifying effects. In most countries analysis of uncertain variants and modifiers in HCM patients is currently performed in research setting only and not used in clinical decision making.

**Screening of relatives: genetic counselling and testing**

Consensus documents on HCM encourage screening of relatives because of the risk of HCM associated sudden cardiac death.\textsuperscript{14} Identification of a disease causing mutation in a HCM patient (the proband) implies the opportunity of screening in relatives by means of predictive DNA testing. DNA testing for HCM, and especially predictive DNA testing in relatives, is not common practice in most countries, because health insurance does not cover the costs of DNA testing, and/or because genetic counselling is unavailable. DNA testing is therefore often only available in a research setting. Instead, most of these countries use clinical modalities such as echocardiography and ECG to screen relatives on the presence of disease. In the Netherlands diagnostic DNA testing is covered by standard health insurance and DNA testing for HCM has been increasing since 1996 with specialised multidisciplinary cardiogenetics outpatient clinics now present in all eight university hospitals. Most mutations (80%) in the Netherlands are found in the MYBPC3 gene, mainly because of three founder mutations (c.2373_2374insG, c.2827C>T and c.2864_2865delCT).

In the Netherlands there is much experience with family screening for HCM and other cardiogenetic diseases as specialised outpatient clinics have been developed in the early stages of DNA testing. Here, systematic screening of relatives in families with a disease causing mutation, so called cascade screening, starts with the proband. Probands in whom a disease causing mutation is detected, receive a family letter to inform their direct relatives about the possibilities of DNA testing and its pros and cons. Predictive DNA testing in relatives >10 years can only be performed after genetic counselling. A genetic counselling session involves one session with a genetic counsellor (clinical geneticist or genetic consulent) and a cardiologist and takes on average between 30 and 45 minutes. An additional session with a psychologist...
Introduction and outline of this thesis

or social worker is offered to all counselees but is only mandatory before DNA testing when children are involved. The DNA test result can be communicated to the counselee face to face at the outpatient clinic, by telephone, or by mail, according to the counselee’s preference. All counselees receive a letter with their DNA test result and its implications for the counselee and his or her relatives.¹³²

Relatives without the familial HCM mutation can be discharged from cardiological follow-up. Relatives who carry the familial HCM mutation are, according to international guidelines, like affected HCM patients with or without identified mutation, advised to undergo regular cardiological evaluation to evaluate the presence of left ventricular hypertrophy and risk factors for SCD.³⁴ During follow-up left ventricular hypertrophy (manifest disease) can present at any age. The presence of risk factors for SCD in mutation carriers is associated with an increased risk of SCD if HCM is manifest (i.e. if left ventricular hypertrophy is present). In mutation carrying relatives (still) without manifest HCM, risk stratification is advised; yet it is unclear if the major risk factors established for clinically diagnosed HCM patients are also valid for mutation carrying relatives without manifest disease and if the presence of these risk factors is associated with an increased risk of SCD.

If no mutation can be detected in a proband with HCM, (first degree) relatives still have a risk to develop hypertrophic cardiomyopathy. DNA testing in these relatives is impossible; they are all advised to undergo regular cardiological evaluations (annual between 12-18 years and once every five years >18 years) assessing the presence of hypertrophy or ECG abnormalities directing towards HCM.³⁴

To prevent HCM associated SCD it is important to identify all relatives at risk of developing HCM. In families with a known disease causing mutation, the cascade screening method is used to identify as many mutation carrying relatives as possible. However, the effectiveness of this method mainly depends on family communication. From a public health point of view uptake of genetic counselling and testing and consecutive cardiological evaluations should be as high as possible to prevent SCD. On the other hand it has not been proven yet that risk stratification for SCD in mutation carrying relatives can prevent SCD and if this screening approach is desirable from a psychosocial perspective.
References

27. Elliott PM, Gimeno Blanes JR, Mahon NG, et al. Relation between severity of left-ventricular hypertrophy and...


51. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of
Hypertrophic cardiomyopathy


100. Marian AJ, Roberts R. Molecular genetic basis of hypertrophic cardiomyopathy: genetic markers for sudden


125. 25
Introduction and outline of this thesis