

Hypertrophic Cardiomyopathy

Guidance for clinical genetics

Background

Hypertrophic cardiomyopathy is a common, autosomal dominant disorder of heart muscle. It affects around 1/500 people¹⁻³, and carries an annual cardiovascular mortality rate of between 0.7 and 1.4%^{4,5}. The clinical features are very variable, with symptoms occurring at any age^{5,6}. Some individuals with positive ECG or echocardiographic findings may never have symptoms^{5,7}. Cardiac failure and arrhythmia (which may cause sudden death) are the principle causes of morbidity and mortality, although around one third of patients die from other vascular disorders such as stroke⁵. Symptoms may resemble other cardiac disorders, and a careful family history to prompt appropriate clinical investigation will aid diagnosis. Correct diagnosis of early symptoms, and presymptomatic diagnosis allows appropriate clinical surveillance and preventative intervention such as early anti-arrhythmic therapy. Lifestyle factors such as inappropriate exercise may contribute to the risk of sudden death^{5,8}. Clinical management of an affected patient requires the specialist expertise of a cardiologist, but clinical genetics has an important role in diagnosis and coordination of care for relatives. Presymptomatic diagnosis may have adverse psychological, social or financial consequences and suitable pre-test counselling is essential^{9,10}. DNA based diagnosis is problematic because of genetic heterogeneity: there are at least 13 loci (table), and multiple mutations occur in the identified genes, most of which encode sarcomere components¹. Most mutations are unique, but there are some hotspots such as codon 403 in MYH7. Mutation here tends to be associated with a severe phenotype. Mutations in TNNT2 may be non-penetrant, or associated with mild hypertrophy yet a high incidence of sudden death, while mutations in MYBPC3 tend to have a good prognosis¹. Where there is good clinical information about the effects of particular mutations, genotyping may be useful in clinical risk assessment. The risk of developing hypertrophy may be affected by modifier loci such as polymorphisms in the angiotensin 1 converting enzyme. Family history is often the only guide, although some cases arise de novo¹¹, and genotyping is not currently available outside the research environment.

The Guidelines

1 *Diagnosis in an index case*

HCM may occur as a single system disorder, or it may occur as part of a syndrome such as Noonan's syndrome, Neurofibromatosis, Friedreich's ataxia, and Anderson Fabry disease. The different inheritance patterns and clinical courses of these disorders may be revealed by the family history. Cardiac hypertrophy may also occur on a background of hypertension, valvular disease or an athletic lifestyle. In cases diagnosed for the first time at post-mortem, expert histological review may be helpful.

- **Confirm the diagnosis in the index case**

2 *Ascertainment and verification of the family history*

Compiling detailed information about the family history will assist in confirming the underlying diagnosis and will identify relatives at risk who might benefit from counselling, testing, clinical surveillance and cardiological intervention. Verification of the reported family medical history ensures accurate genetic counselling and appropriate surveillance and intervention.

- **Compile a detailed family history**
- **Verify diagnosis in relatives**

Verification of diagnosis may require clinical assessment or review of medical records with appropriate consent. This requires recording of name, date of birth/death, age of onset and/or diagnosis of illness, and hospital or GP details for relevant family members.

3 *At risk relatives*

Information about at risk relatives may be given by different family members (consultands) who attend a clinic. Contact with relatives, to offer an appointment to discuss implications and further management, should be made with the consent, and usually with the assistance of the consultand.

- **Advise consultands to inform at risk relatives about the family diagnosis and to encourage them to make contact with the clinic to arrange an appointment.**

4 *Clinical discussion and management of at risk relatives*

HCM has health, lifestyle and financial implications for affected individuals and their families.

- **Discussion with affected individuals and at risk relatives should include information about the nature of HCM, its inheritance, management and personal implications.**
- **Support group information should be offered.**

Early identification of affected individuals allows appropriate intervention to reduce the risk of sudden death. The condition may present at any time from childhood to old age. Usually, it is difficult to determine prognosis in a particular family, although family history, genotype information, and cardiology findings may be helpful. At present, genotyping is undertaken only in research laboratories.

- **At risk relatives should be offered screening by echocardiography and ECG.**
- **Screening should be considered from childhood, and surveillance may need to continue throughout adult life.**

Different mutations in several different genes may cause HCM. Mutation testing in an individual family is therefore difficult at present. If a mutation can be identified in an affected individual, now or through future research, pre-symptomatic genetic testing will then be possible for relatives. Pre-symptomatic testing requires appropriate counselling and support.

- **DNA from affected individuals should be banked, with appropriate consent.**
- **Where possible, pre-symptomatic testing should be offered to at risk relatives.**

5 *Affected Relatives*

Affected relatives may be diagnosed through family screening or may be already attending a follow-up clinic.

- **Refer to cardiology for appropriate surveillance and clinical management.**
- **DNA from affected individuals should be banked, with appropriate consent (see above).**

6 *Follow-up of individuals and families*

Because of the variable natural history of HCM, the age of onset in an individual is difficult to predict, highlighting the importance of continuing clinical surveillance in those at risk.

- **Clear designation of arrangements for follow-up of individuals should be documented.**

Future research may allow mutation detection and pre-symptomatic testing in specific families. Because of its inherited nature, HCM may affect present or future offspring of affected individuals. These at risk descendants should be offered counselling, screening and testing at an appropriate age. In some centres, a genetic register may help fulfil this function, although in others, different arrangements may pertain¹².

- **The arrangements for recontact with relatives and descendants of affected individuals should be explicit and documented.**

References

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TABLE Genes mutated in Hypertrophic Cardiomyopathy

Gene	Locus	Protein
MYH7	14q11.2-q12	β -myosin heavy chain
TNNT2	1q3	Cardiac troponin T
MYBPC3	11p11.2	Myosin binding protein C
TPM1	15q22	α -tropomyosin
TNNI3	19p13.2-q13.2	Cardiac troponin I
MYL3	3p21.2-p21.3	Ventricular myosin essential light chain
MYL2	12q23-q24.3	Ventricular myosin regulatory light chain
ACTC	11q	Cardiac α actin
TTN	2q24	Titin
KCNQ4	1p34	Voltage gated K channel
MYH6	14q	α myosin heavy chain
MTTI	mitochondria	Isoleucine tRNA, glycine tRNA
?	7q3	unknown