HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a relatively common condition affecting the heart muscle that can present at any age. HCM is usually detected by echocardiogram and/or electrocardiogram. Symptoms range from mild shortness of breath on exertion to sudden cardiac death, often in young athletes. Early identification of HCM provides the best opportunity to implement clinical and lifestyle management strategies, potentially reducing mortality. HCM should be considered in cases of sudden death in young people. Since HCM is usually inherited in a dominant manner, at-risk first degree relatives should be referred for cardiac assessment by a specialist familiar with HCM and to a genetics clinic for assessment, counselling, and review of genetic testing opportunities. A growing number of genes are known to be associated with isolated HCM and testing is available in most provinces. In addition, there are genetic syndromes in which HCM may be a feature (e.g. Noonan syndrome, Fabry disease).

HCM is an important heart condition for which there is growing availability of genetic testing. Any individual with clinical features or family history of HCM should be referred for cardiac and genetic assessment.

WHAT IS HYPERTROPHIC CARDIOMYOPATHY?

Hypertrophic cardiomyopathy (HCM) is a condition in which the myocardium is thickened and the myocytes fibrotic and disorganized, leading to increased risk for heart failure and arrhythmia. Symptoms include dyspnea, chest pain, palpitations, syncope and, in some cases, sudden death. Syncope with exercise is a warning symptom of HCM and other potentially heritable heart problems in young athletes and should be thoroughly investigated.[1]

HCM can present from infancy to late adulthood with a prevalence of 1 in 500.[2] It may be isolated or related to a broad spectrum of causes such as inborn errors of metabolism, various syndromes, and neuromuscular disorders. Individuals presenting before the age of one year have the most diverse etiologies and poorest outcomes.[3] Hypertrophy can be septal, apical, or concentric; asymmetrical ventricular hypertrophy is most common. Obstructive HCM occurs when ventricular outflow is compromised. HCM can be associated with sudden cardiac death, even in the absence of marked hypertrophy.

Treatment options, dependent on symptoms, include medical management of heart failure and atrial fibrillation, implantable cardioverter defibrillators, surgery, medications that decrease afterload, and avoidance of triggers such as burst activity. Individuals with HCM are usually advised against participation in competitive sport.[4] HCM can develop secondary to other factors such as longstanding hypertension and significant physical training (athlete's heart).

Numerous genes are associated with the predisposition to isolated HCM. Many are dominantly-inherited genes encoding sarcomeric proteins such as the 5 listed below, which account for the majority of cases. Typically, an individual with HCM has a mutation in just one gene; however, some individuals may have two or even three contributing gene mutations.[5]

- *MYH7* Beta-myosin heavy chain
- *MYBPC3* Myosin-binding protein C
- *TNNT2* Cardiac troponin T
- *TNNI3* Cardiac troponin I
- *TPM1* Alpha-tropomyosin

Other genetic syndromes, caused by mutations in the following genes, can include HCM as part of syndromic presentation:

- *PRKAG2* AMP-activated protein kinase subunit: HCM and Wolff-Parkinson-White syndrome (autosomal dominant)
- *GLA* alpha-galactosidase: Fabry disease (X-linked)
- *LAMP2* lysosome-associated membrane protein 2: Danon disease (X-linked)
- *PTPN11, RAF1, SOS1* and other genes of the RasMAPK pathway: Noonan syndrome (autosomal dominant)

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

Most tests are panel-based, testing multiple genes concurrently. Testing can often be arranged via your local genetics centre and is most usefully initiated in an individual known to have HCM.[6]

- Consider referral for genetic consultation for individuals with HCM or with a family history of HCM[7]

WHAT DOES THE GENETIC TEST RESULT MEAN?

Test sensitivity for HCM is currently approximately 60%[8], which means that 40% of individuals tested will not receive an informative result.
Test results fall into three categories:

- **Positive**: causative gene mutation(s) detected. Diagnosis is confirmed and genetic testing of at-risk relatives becomes available.
- **Negative**: no causative gene mutation detected. Diagnosis is neither confirmed nor ruled out. There is no genetic test available to determine risk status of relatives.
- **Variant of unknown significance**: alteration(s) in HCM-related gene(s) are detected, but there is insufficient evidence to determine if they are truly associated with disease. Clinically, these results are usually treated as "negative" and the test is not useful for at-risk relatives.

A man or woman with dominant HCM due to one contributing gene has a 50% chance of passing the predisposition to HCM to each child (autosomal dominant).

Both males and females with HCM-associated gene mutations are at risk to develop HCM at any point in life (not just into early adulthood, as previously believed) and should be followed with regular echocardiographic and electrocardiographic surveillance. At the present time, genotype-phenotype correlations are not well established (knowing the gene mutation does not predict disease course or response to treatment).

All first-degree relatives of an affected person should have regular cardiac exams, echocardiograms and electrocardiograms, unless they test negative for a known disease-causing familial mutation.[9]

With regards to competitive sport restriction for (asymptomatic) mutation carriers, there are conflicting recommendations from U.S. and European cardiology societies as there are no firm clinical or experimental data to support either position. Thus recommendations are generally made on a case by case basis by the individual's cardiologist.[10]

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

Genetic testing for HCM can help with:

- Clarification of HCM status for individuals with borderline clinical investigations.
- Assistance with life planning (e.g., decisions about careers, participation in competitive sports).
- Providing relief, to those who test negative for a known family mutation, from worry that they are at greater risk of developing the disease in the future, and knowledge that their children are not at risk of inheriting the predisposition to HCM.

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

Genetic testing can result in:

- Adverse psychological reaction, particularly due to potential for risk of sudden cardiac death.
- Uncertainty due to a genetic variant of unknown significance.

For recent review articles on cardiomyopathy see Gersh BJ *et al*., ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force of Practice Guidelines. *Circulation* 2011; 124:2761–96.

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Other HCM resource: The Canadian Sudden Arrhythmia Death Syndromes (SADS) Foundation website http://www.sads.ca/

Authors: C Honeywell MSc CCGC, JC Carroll MD CCFP, S Morrison MS CGC, JE Allanson MD FRCPC

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GenetiKit team: Principal Investigators: Carroll JC, Allanson J, Wilson BJ, Co-Investigators: Blaine S, Cremin C, Dorman H, Gibbons C, Graham GE, Graham I, Grimshaw J, Honeywell C, Meschino WS, Permaul J, Wilson BJ.