Familial Hypertrophic Cardiomyopathy

Subjects: Genetics & Heredity
Contributor: Nicole Yin

Familial hypertrophic cardiomyopathy is a heart condition characterized by thickening (hypertrophy) of the heart (cardiac) muscle. Thickening usually occurs in the interventricular septum, which is the muscular wall that separates the lower left chamber of the heart (the left ventricle) from the lower right chamber (the right ventricle).

Keywords: genetic conditions

1. Introduction

In some people, thickening of the interventricular septum impedes the flow of oxygen-rich blood from the heart, which may lead to an abnormal heart sound during a heartbeat (heart murmur) and other signs and symptoms of the condition. Other affected individuals do not have physical obstruction of blood flow, but the pumping of blood is less efficient, which can also lead to symptoms of the condition. Cardiac hypertrophy often begins in adolescence or young adulthood, although it can develop at any time throughout life.

The symptoms of familial hypertrophic cardiomyopathy are variable, even within the same family. Many affected individuals have no symptoms. Other people with familial hypertrophic cardiomyopathy may experience chest pain; shortness of breath, especially with physical exertion; a sensation of fluttering or pounding in the chest (palpitations); lightheadedness; dizziness; and fainting.

While most people with familial hypertrophic cardiomyopathy are symptom-free or have only mild symptoms, this condition can have serious consequences. It can cause abnormal heart rhythms (arrhythmias) that may be life threatening. People with familial hypertrophic cardiomyopathy have an increased risk of sudden death, even if they have no other symptoms of the condition. A small number of affected individuals develop potentially fatal heart failure, which may require heart transplantation.

2. Frequency

Familial hypertrophic cardiomyopathy affects an estimated 1 in 500 people worldwide. It is the most common genetic heart disease in the United States.

3. Causes

Mutations in one of several genes can cause familial hypertrophic cardiomyopathy; the most commonly involved genes are *MYH7*, *MYBPC3*, *TNNT2*, and *TNNI3*. Other genes, including some that have not been identified, may also be involved in this condition.

The proteins produced from the genes associated with familial hypertrophic cardiomyopathy play important roles in contraction of the heart muscle by forming muscle cell structures called sarcomeres. Sarcomeres, which are the basic units of muscle contraction, are made up of thick and thin protein filaments. The overlapping thick and thin filaments attach to each other and release, which allows the filaments to move relative to one another so that muscles can contract. In the heart, regular contractions of cardiac muscle pump blood to the rest of the body.

The protein produced from the *MYH7* gene, called cardiac beta (β)-myosin heavy chain, is the major component of the thick filament in sarcomeres. The protein produced from the *MYBPC3* gene, cardiac myosin binding protein C, associates with the thick filament, providing structural support and helping to regulate muscle contractions.

The *TNNT2* and *TNNI3* genes provide instructions for making cardiac troponin T and cardiac troponin I, respectively, which are two of the three proteins that make up the troponin protein complex found in cardiac muscle cells. The troponin complex associates with the thin filament of sarcomeres. It controls muscle contraction and relaxation by regulating the

interaction of the thick and thin filaments.

It is unknown how mutations in sarcomere-related genes lead to hypertrophy of the heart muscle and problems with heart rhythm. The mutations may result in an altered sarcomere protein or reduce the amount of the protein. An abnormality in or shortage of any one of these proteins may impair the function of the sarcomere, disrupting normal cardiac muscle contraction. Research shows that, in affected individuals, contraction and relaxation of the heart muscle is abnormal, even before hypertrophy develops. However, it is not clear how these contraction problems are related to hypertrophy or the symptoms of familial hypertrophic cardiomyopathy.

3.1. The Genes Associated with Familial Hypertrophic Cardiomyopathy

- MYBPC3
- MYH7
- PRKAG2
- TNNI3
- TNNT2
- TTN

4. Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Rarely, both copies of the gene are altered, leading to more severe signs and symptoms.

In most cases, an affected person has one parent with the condition.

5. Other Names for This Condition

- familial asymmetric septal hypertrophy
- HCM
- hereditary ventricular hypertrophy
- heritable hypertrophic cardiomyopathy
- idiopathic hypertrophic subaortic stenosis

References

1. Bashyam MD, Savithri GR, Kumar MS, Narasimhan C, Nallari P. Molecular geneticsof familial hypertrophic cardiomyop athy (FHC). J Hum Genet. 2003;48(2):55-64.Review.
2. Frey N, Luedde M, Katus HA. Mechanisms of disease: hypertrophiccardiomyopathy. Nat Rev Cardiol. 2011 Oct 25;9 (2):91-100. doi:10.1038/nrcardio.2011.159. Review.
3. Ho CY. New Paradigms in Hypertrophic Cardiomyopathy: Insights from Genetics.Prog Pediatr Cardiol. 2011 May;31(2): 93-98.
4. Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the geneticdeterminants of clinical disease expression. Nat Clin Pract Cardiovasc Med. 2008 Mar;5(3):158-68. doi: 10.1038/ncpcardio1110.in: Nat Clin Pract Cardiovasc Med. 2008 Nov;5(11):747.
5. Kimura A. Molecular genetics and pathogenesis of cardiomyopathy. J Hum Genet. 2016 Jan;61(1):41-50. doi: 10.1038/j hg.2015.83.
6. Marston S, Copeland O, Gehmlich K, Schlossarek S, Carrier L. How do MYBPC3mutations cause hypertrophic cardio myopathy? J Muscle Res Cell Motil. 2012May;33(1):75-80. doi: 10.1007/s10974-011-9268-3.in: J Muscle Res Cell Moti l. 2012 May;33(1):81. Carrrier, Lucie [corrected toCarrier, Lucie].
7. Rodríguez JE, McCudden CR, Willis MS. Familial hypertrophic cardiomyopathy:basic concepts and future molecular di agnostics. Clin Biochem. 2009Jun;42(9):755-65. doi: 10.1016/j.clinbiochem.2009.01.020.Review.