

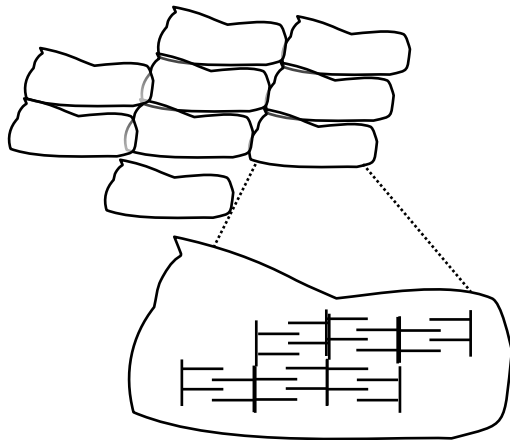
HYPERTROPHIC CARDIOMYOPATHY (HCM) IN SOUTH AFRICAN PATIENTS AND THEIR FAMILIES

WHAT IS HYPERTROPHIC CARDIOMYOPATHY AND WHAT CAUSES IT?

Hypertrophic cardiomyopathy (HCM) is a common disease of the heart which may be inherited in a family, the name means “overgrowth of heart muscle”.

To understand how HCM comes about, we need to know a little more about the heart. The heart is an organ that pumps blood around the body, taking oxygen and food to every part of the body. The heart is made up of four chambers, the walls of these chambers are made out of muscle. This muscle, in turn, is made out of cells called myocytes that are arranged in a very orderly way, like bricks in a wall. Inside each cell are many smaller, linked-together structures, called sarcomeres.

Orderly arranged myocyte “wall”



Linked sarcomeres inside a myocyte, showing
the thick and thin rods inside the sarcomere

These sarcomeres are the contractile units of muscle, they are the things that allow muscle to contract or relax. On the one side of a sarcomere there are a number of thin rods, and on the other side, a number of thick rods. These sets of rods move over each other each time muscle contracts, much like pistons in an engine. The movement is possible because the thick rods have “hands” which grab hold of the thin rods and move the thick rods over them by pulling in a hand-over-hand motion. When muscle relaxes, the hands let go and the thick and thin rods return to their starting position.

In HCM, a small fault (or mutation) in the inherited material (DNA) causes a protein in these rods to become defective. Because of this, the “piston-like” movement of the rods during muscle contraction is damaged, and the orderly array of “bricks” in the heart muscle becomes disordered and, because of this, the pump-action of the heart is affected. In most people with HCM, this also leads to a thickening of the muscle walls of the heart. Because the heart muscle is thicker than it should be, a person then often suffers from fainting, palpitations and chest pain. A person with HCM, is also at an increased risk of dying early, and suddenly, even if he/she has not previously had any visible symptoms of the condition and even if their heart muscle wall is not noticeably thickened.

Although many people with HCM display a thickened heart muscle on sonar (echocardiogram) examination, natural variation in heart muscle wall-thickness and the amount of symptoms displayed may result in the disease diagnosis being missed in persons who are actually affected. This may be especially serious as the first sign of disease may be sudden death and, as this disease may “run in the family”, other relatives may unknowingly be at risk, too.

WHY ARE WE STUDYING HCM AND WHAT HAS BEEN FOUND?

A person with HCM has a small fault (*mutation*) in their inherited “blue-print” (*DNA*) that can be passed

on to his/her children, who are then at risk of developing the disease. Scientists know that many different faults in at least thirteen different DNA factors (*genes*) trigger HCM, and that there are other, still unknown DNA factors (*modifiers*) that cause some people with HCM to be more severely affected than others.

What is a mutation?

The body is made up out of millions and millions of cells, each of which contains DNA, the inherited material that is the blue-print for life. This DNA can be likened to a set of do-it-yourself manuals, containing instructions for how to make the proteins and enzymes that the body needs in order to function normally. These instructions, which we call genes, are “sentences” made up of three letter words. We can think of a gene as saying: “put the cat on a mat”.

A genetic defect, or mutation, can be thought of as a spelling mistake in the sentence. For instance, now the sentence may read: “put the cat on a hat”. This instruction is very different from the original, and following it will lead to a very different outcome than was originally intended.

Similarly, if a gene becomes mutated, the enzyme that is made from it functions differently to the way it should, and so messes up the function of the cell in which it is made. This, in turn, causes the organ that is made up out of those cells to malfunction, and this causes a person to have a disease that affects that organ.

We would like to find out which particular DNA faults cause HCM in South African patients and their families and use this information to help us to understand more about this disease. This knowledge will also help us to more easily identify genetically affected individuals, especially those who have no visible symptoms or in whom the echocardiogram does not clearly indicate disease. This will mean that those who are affected can be treated more effectively or make lifestyle changes to avoid situations that may trigger sudden death.

Already, more than 100 different South African HCM-affected families have joined our study and the HCM-causing gene and its associated fault has been found in more than 50% of these families.

The most important finding, so far, is that many families carry the same genetic fault (*a founder mutation*), which is believed to have been introduced into the blood-line by a common forefather. Three such founder mutations have been found in the South African population, which account for 25%, 15% and 5% of HCM cases in the Western and Eastern Cape. The frequency of these common faults in South Africa means that it is easier for us to find the fault in many affected families. The search in other families, however, can be hard and long, as the genetic fault may be different in each family with the disease.

In those cases where we have already now found the genetic fault that causes the disease, we are looking for combinations of other naturally occurring variations in genes in the heart that may cause some people to experience more severe heart muscle thickening and others less.

HOW CAN YOU HELP?

The eventual success of our HCM study is dependent on gathering as much information as possible on all relatives in an affected family. Blood samples and a clinical history, with special reference to all possibly relevant symptoms, are needed from both affected and unaffected individuals of all available generations. This helps us to pinpoint which of the thirteen possible genes should be searched first in our laboratory in order to find the causative fault.

Taking part in this study is voluntary but we believe that the willing participation of all family members may, in time, benefit many people, including yourself and your family. Your taking part in the study will be confidential. Only the investigating doctor and his immediate colleagues involved in this research will have access to any of the information that you supply or that is found in the laboratory.

HOW IS THIS RESEARCH DONE?

If you are willing to participate, you will be asked to give a blood sample (about 6 teaspoons), from which DNA (the genetic material) is extracted in the laboratory. The DNA extracts are first tested by a series of molecular methods for the presence of the common 'founder mutation'. If this is not present, the search for the causative fault continues, although it is more difficult and time-consuming. In such a case, it may be a long time before we can give your doctor a definitive result. We will also treat a part of your blood sample (to make a cell line) so that it can serve as a longer-term source of DNA, in case the search for the particular cause in your case is a long and hard one.

If you have not been clinically examined before, and we do find the genetic fault in your DNA, we will ask you to be clinically examined by a cardiologist, at no cost to yourself. We collect this clinical information to form a better picture of how serious the consequences of the different genetic faults are.

WHY IS THE RESEARCH IMPORTANT?

Finding the specific disease-causing faults in South African families affected by HCM will allow us to design simple blood-tests to identify others who are at risk from HCM. This is especially important for people who do not have symptoms or where clinical diagnosis is not clear-cut. This will help your doctor to give relevant counselling and clinical management for affected persons, which may include lifestyle changes to avoid situations that could trigger sudden death. It will also reassure those that are not at risk of the consequences of the disease.

In addition, the large number of South African families with the same 'founder mutation' will help scientists find why not everyone with HCM becomes equally sick. It is thought that finding these factors which cause people to be affected differently will

eventually lead to the development of treatment that is specific for the needs of every affected individual.

We have presented our findings and their implications for South African HCM-affected persons and their families, while maintaining the anonymity of all these individuals, to cardiologists both in here in South Africa and overseas and have become the referral centre for molecular investigations into HCM in South Africa.

This information was prepared by:

US/MRC Centre for Molecular and Cellular Biology and Department of Internal Medicine, Faculty of Health Sciences, University of Stellenbosch, Tygerberg.

Information on HCM is provided for the public on our Sudden Death Website:

http://www.sun.ac.za/medbiochem/sudden_death/home/html

Contact: Sr Althea Goosen

Tel: 021-938 9484

Fax: 021-931-1188

Email: ag3@sun.ac.za