Genetic breakthrough to target care for deadly heart condition

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New genetic faults discovered in people with a heart condition that is sometimes inherited in families could transform the diagnosis and treatment of the hidden disease, according to research funded by the British Heart Foundation (BHF) and published in *Nature Genetics*.

Researchers have found a new type of genetic change in the DNA of people with hypertrophic cardiomyopathy (HCM)—a silent killer amongst families that can cause sudden death in young people due to the thickening of the heart muscle.

This ground-breaking discovery, which may be the biggest advance in our knowledge of the genetic basis of the disease in 25 years, will help doctors better predict which family members need to be monitored for the condition and which can be ruled out from further tests or treatment.

For over 25 years, scientists have known that HCM is caused by 'rare' genetic faults in the machinery responsible for helping the heart muscle to contract and pump blood around the body. However, researchers and cardiologists have never been able to explain why the condition is so varied amongst family members who have the same rare mutation and why some people without these mutations still go on to develop HCM.

Now, BHF Professor Hugh Watkins and his team at the Radcliffe Department of Medicine at the University of Oxford have discovered that the inheritance of a different type of genetic fault—called 'common variants'—not involved in the contractile machinery, form the missing piece to this long-awaited puzzle.

By comparing the DNA of 2,780 people with HCM and 47,486 people

without HCM, the team found that the number of these common variants, in combination with the rare mutations, determine whether a person is protected or more susceptible to the disease. Another important consequence is that people who have HCM due to the common variants alone are unlikely to pass the disease onto their children.

HCM affects around 1 in 500 people in the UK, but most people who have it have few, if any, symptoms. If it's left undetected and untreated it can cause sudden cardiac death, even in young people under 35 years of age.

BHF Professor Hugh Watkins, Radcliffe Professor of Medicine and Director of the BHF Centre of Research Excellence, University of Oxford, said:

"It's now time we think differently about the way this hidden heart condition is detected and treated.

"We now have a new genetic tool that we believe will better predict which members of affected families will have a bad form of the disease, identifying those who need early intervention. It will also take away the worry for many families as it enables us to identify those who are unlikely to pass faulty genes onto their children. This will reduce the need for unnecessary genetic testing and regular follow-ups."

Professor Sir Nilesh Samani, Medical Director of the BHF and cardiologist, said:

"This research is a major step forward in our understanding of the genetics that underpin hypertrophic cardiomyopathy. It will revolutionize the way we screen people who have family members with this silent killer.

"HCM is one of the most common inherited cardiac conditions, affecting thousands of families across the UK. These discoveries will bring long-awaited answers to many families, and free many individuals from the need for regular clinical checks and the worry of whether they have also inherited the disease."

The impact of this research is wide-ranging. It also revealed that lowering blood pressure in people with HCM due to these 'common' genetic faults could help to prevent the disease from developing.

More information: Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity, *Nature Genetics* (2021). DOI: 10.1038/s41588-020-00764-0 , www.nature.com/articles/s41588-020-00764-0

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