New study reveals titin gene mutations affect heart function in healthy individuals

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A new multinational study by researchers from Singapore, the UK and Germany has discovered that gene mutations in a protein called titin affect the heart function in healthy individuals. It was previously thought that the mutations affect only patients with dilated cardiomyopathy, one of the most common forms of inherited heart disease.

The finding may help scientists to understand a paradox: namely that around one per cent of the world's population carry this genetic mutation with no apparent effect. The key, the team now believes, is that the hearts of such people may be "primed to fail" if they suffer a second hit, whether genetic or environmental. This could mean that there are about 35 million people in this position globally. The research paper is published in leading medical journal, *Nature Genetics* today, 21 November 2016.

Titin is the largest protein in the human body that causes dilated cardiomyopathy, a condition in which the heart muscle becomes weakened, enlarged and cannot pump blood efficiently. Dilated cardiomyopathy is a type of inherited cardiac condition and affects about 1 in 250 people worldwide.

The researchers studied the effects of titin gene mutations in 2,495 patients with dilated cardiomyopathy. They also generated two rat models to understand the impact of these mutations on the molecular level and heart function. In addition, cardiac gene sequencing tests were performed in 1,409 healthy volunteers, coupled with 2D and 3D cardiac magnetic resonance imaging (MRI) that gave high resolution information on the heart size and shape of the study subjects. The data collected gave major new insights on multiple levels, allowing researchers to better understand the variants that represent the commonest genetic cause of dilated cardiomyopathy, yet are prevalent in the general population. The study was led by the National Heart Centre Singapore in collaboration with Duke-NUS Medical School, Medical Research Council Clinical Sciences Centre, Imperial College London and Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC).

Assistant Professor Sebastian Schäfer, Senior Research Fellow at the National Heart Centre Singapore who is the first author of the paper explained: "We could directly show the impact of the mutations on the titin protein production which has an impact on the heart. Even though the heart appears healthy initially, it reacts to this genetic stress on many levels such as changes to its gene expression and energy source. The heart can compensate and its cardiac function remains fine until an additional stressor occurs. That's when the heart fails, as it no longer has the capacity to react the same way a healthy heart does."

Professor Stuart Cook, Tanoto Foundation Professor of Cardiovascular Medicine at the SingHealth Duke-NUS Academic Medical Centre and co-senior author, elaborated: "We now know that the heart of a healthy individual with titin gene mutation lives in a compensated state and that the main heart pumping chamber is slightly bigger. Our next step is to find out the specific genetic factors or environmental triggers, such as alcohol or viral infection that may put certain people with titin mutations at risk of heart failure."

Dr Antonio de Marvao, Clinical Lecturer at Imperial College London and the MRC Clinical Sciences Centre, said: "Our previous work showed that mutations in the titin gene are very common in people diagnosed with heart failure. Around 1% of the general population also carry these mutations, but until now it wasn't known if these are 'silent' gene changes or changes that can adversely affect the heart. Using state-of-the-art cardiac MRI, we created extremely detailed 3D "virtual hearts" from the scans of 1,409 healthy adults. We found that those with mutations have an enlarged heart, and

in a pattern similar to that seen in heart failure patients. This may impact as many as 35 million people around the world. In future work we will investigate if the heart function of our volunteers is indeed impaired, by MRI scanning them as they exercise on a bike."

Dr James Ware, Clinical Senior Lecturer in Genomic Medicine at Imperial College London and the MRC Clinical Sciences Centre, added: "For patients with dilated cardiomyopathy, this study has improved our understanding of the disease, revealed possible new targets for drugs and other new therapies, and importantly has improved our ability to diagnose the condition confidently with genetic tests. This work required a very collaborative approach, with many institutions involved in assembling genetic data from tens of thousands of individuals. The finding that titin mutations are affecting the hearts of so many otherwise apparently healthy people worldwide, and potentially increasing their risk of heart failure, poses even pressing questions, such as why some people with these mutations seem to do well in the long term, while others do not. Fortunately, we are in a strong position to tackle these questions from lots of different angles, by analysing aggregated genetic and clinical data from a network of collaborating units around the world."

Professor Norbert Hübner, Professor of Cardiovascular and Metabolic Sciences at the MDC and co-senior author, detailed: "By using a variety of genomic approaches we showed that the RNA that is produced from the actual titin allele which carries the mutation, is degraded in the cells of the heart. This led to important insights on how these titin mutations operate."

Currently for patients with inherited cardiac conditions, they can undergo a cardiac genetic test that will screen them of 174 genes in 17 such conditions to diagnose the exact condition and gene, to prescribe effective treatment.

More information: Titin-truncating variants affect heart function in disease cohorts and the general population, *Nature Genetics*, DOI: 10.1038/ng.3719

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