Scientists find 'missing link' between heart failure and environment

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(PhysOrg.com) -- Scientists have found what they believe is the "missing link" between heart failure, our genes and our environment. The study could open up completely new ways of managing and treating heart disease.

The Cambridge team compared heart tissue from two groups - patients with end-stage heart failure and those with healthy hearts. The diseased tissue came from men who had undergone heart transplants at Papworth Hospital, Cambridge, and the healthy hearts from age-matched victims of road traffic accidents.

They found that specific regions of the DNA in the diseased hearts contained "marks" known as DNA methylation, whereas the healthy hearts did not. This is the first study linking DNA methylation with human heart failure.

DNA methylation is already known to play a key part in development of most cancers, and its role in other complex diseases such as schizophrenia and diabetes is being investigated.

This study, funded by the British Heart Foundation, suggests the process also underlies development of different types of heart disease.

According to lead author Dr Roger Foo of the University of Cambridge: "DNA methylation leaves 'marks' on the genome, and there is already good evidence that these marks are strongly influenced by environment

and diet. We found that this process is different in diseased and normal hearts. Linking all these things together suggests this may be the 'missing link' between environmental factors and heart failure."

The findings deepen our understanding of the genetic changes that can lead to heart disease, and how these can be caused by diet and the environment. As a result, Foo's findings should open up new ways of managing and treating heart disease.

"The next stage of our research is to find hotspots in the genome. This should help us identify people at risk of heart disease, and pinpoint patients whose disease will progress fastest. This would radically alter how we manage patients with heart disease, allowing us to target treatments and tailor monitoring," Foo explains.

The DNA that makes up our genes comprises four "bases" or nucleotides - cytosine, guanine, adenine and thymine, commonly abbreviated to C, G, A and T. DNA methylation is the addition of a methyl group (CH3) to cytosine.

When bound to cytosine, the methyl group sticks out. This means it looks different and is recognised differently by proteins. As a result, methylation alters how genes are expressed, ie which are turned on and off.

Foo likens DNA methlyation to a fifth nucleotide: "We often think of DNA as being composed of four nucleotides. Now, we are beginning to think there is a fifth - the methylated C."

DNA methylation is a crucial part of normal development, allowing different cells to become different tissues despite having the same genes. As well as happening during development, DNA methlyation continues throughout our lives in response to environmental changes and can lead

to disease.

According to the study's first author, Dr Mehregan Movassagh of the University of Cambridge: "DNA methylation is a mechanism by which the environment and diet alters the expression of certain human genes, and has been the explanation for why, for instance, identical twins may have differing features and differ in their susceptibility to disease, despite having an identical set of genes."

It is also a very widespread process, occurring in plants and insects as well as vertebrates. In honey bees, for example, it is the reduction in DNA methylation that occurs as a result of feeding royal jelly which causes genetically identical larvae to develop into a queen, rather than a worker.

Epigenetic factors, such as DNA methylation, are currently the focus of much medical research because they offer further insight into disease than simply looking at our genes.

"We already know that several genes play an important role in heart failure. Researchers have looked at mutations in these genes and sometimes don't see any, so it could be methylation, not mutation, which is responsible for the altered expression that leads to disease. This opens a new window on the link between genome and disease," Movassagh says.

Professor Jeremy Pearson, Associate Medical Director at the British Heart Foundation (BHF), which funded the research, said: "By detecting these molecular changes in failing hearts, this research suggests that previously unsuspected mechanisms contribute to the development of heart failure. The findings open up the possibility of identifying new ways to treat this debilitating condition, which affects more than 700,000 people in the UK. We're supporting these researchers and others

around the country to help us turn these vital discoveries into treatments for patients."

The research is published today in *PLoS ONE*.

More information: Mehregan Movassagh et al, 'Differential DNA methylation correlates with differential expression of angiogenic factors in human heart failure' is published in *PLoS ONE* on 13 January 2010.

Provided by University of Cambridge