Genes for common heart condition and kidney problem identified

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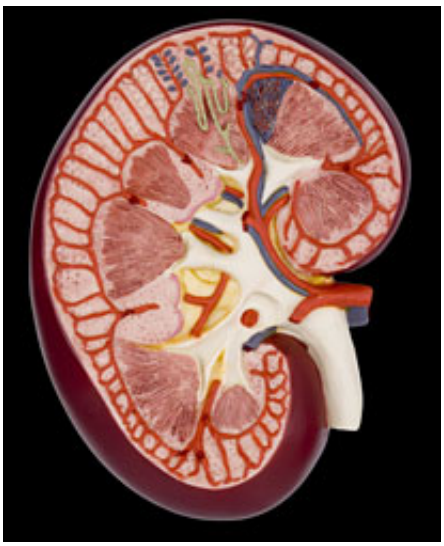

The discovery of the Jund gene could offer a route for tackling the destruction of kidney tissue which can occur in lupus patients, causing renal failure.

A gene that can cause the heart to become enlarged, greatly increasing the risk of heart attacks and heart failure, is identified today in a new study. A gene that can cause the kidney to become inflamed, which can lead to kidney failure, is also revealed in a parallel discovery.

The heart research, published in the journal *Nature Genetics*, reveals how a gene called osteoglycin (Ogn), which had not previously been linked with heart function, plays a key role in regulating heart growth. The study suggests that the gene can behave abnormally in some people, and

that this can lead to the heart becoming abnormally enlarged.

The researchers hope that through understanding how enlarged hearts are linked to the workings of genes like Ogn, they will be able to develop new treatments for the condition, which affects a large proportion of those with high blood pressure, obesity and diabetes.

Scientists believe that enlarged hearts are caused by a combination of genetic factors and external stimuli such as high blood pressure and obesity. However, the role played by genes has remained largely unknown.

The researchers, from Imperial College London, the Medical Research Council (MRC), and other international institutions, hope that their findings will provide new avenues for treating people who either have an enlarged heart or are at risk of developing one. At present enlarged hearts can only be treated by lowering blood pressure.

The study shows that Ogn regulates the growth of the heart's main pumping chamber, its left ventricle. If the left ventricle thickens, this creates a condition known as elevated Left Ventricular Mass (LVM), a major contributing factor for common heart diseases. When the heart is enlarged it needs more oxygen and becomes stiff. This can cause shortness of breath or lead to a heart attack.

The researchers found that higher than normal levels of Ogn were associated with the heart becoming enlarged in rats and mice and in humans. Dr Stuart Cook, one of the corresponding authors of the study from the MRC Clinical Sciences Centre and the National Heart and Lung Institute at Imperial College London, said:

"Enlarged hearts are very common. A person whose heart is enlarged is more likely to suffer a heart attack or heart failure than someone whose

heart is a normal size. We can't currently treat the condition directly, so lowering a patient's blood pressure is the only option we have. Now that we are unravelling how genes control heart growth, we can gain a better understanding of common forms of heart disease. This should lead to new and more effective ways of treating people."

The study was primarily funded by the British Heart Foundation and the UK Department of Health.

The researchers first linked the Ogn gene with elevated LVM by looking at rat models and analysing how LVM related to the genetic makeup of rats with both elevated and normal LVM.

They then carried out the same analyses on samples from the human heart, volunteered by patients who had undergone cardiac surgery at Hammersmith Hospital, part of Imperial College Healthcare NHS Trust, and from a second group of patients from the Netherlands. These analyses showed that out of 22,000 possible genes, Ogn was the gene most strongly correlated with elevated LVM in humans.

Professor Tim Aitman, also a corresponding author of the study from the MRC Clinical Sciences Centre and Imperial College London, added: "This study shows how we can use the wealth of new genome technologies for analysing people's genes to gain a much greater understanding of common human disorders. We already knew that enlarged hearts were linked with conditions such as high blood pressure and obesity but figuring out the genetic causes as well could be key to working out how to treat the condition."

In a parallel development today, Professor Aitman, working with colleagues including Professor Terry Cook from Imperial College London, has identified a gene which controls the activity of a group of cells thought to be responsible for potentially severe inflammation of the

kidney. The gene, also revealed in a study in Nature Genetics, is known as Jund and it could offer a route for tackling the auto-immune destruction of kidney tissue which can occur in lupus patients, causing renal failure.

Jund regulates the activity of macrophages, cells which help us fight infection by eating up cellular debris and pathogens, and stimulating immune cells. The new research showed that when these cells are overactive, they can destroy healthy kidney tissue.

Professor Aitman, who led the Medical Research Council team, said: "We are hoping that this discovery will allow us to find a new and effective way of treating this potentially fatal form of kidney failure. By reducing the activity of the Jund gene, we were able to reduce activity of inflammatory cells that can become overactive in certain diseases of the kidney. Such a therapy would be of obvious benefit to patients suffering from auto-immune diseases such as lupus. This would allow them to avoid dialysis and maintain their quality of life."

Source: Imperial College London