

## Twin Studies Reveal Genetic Components Leading to Cardiac and Kidney Disease

*Studies may point to new drug targets for heritable conditions*

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Daniel O'Connor, M.D., Professor of Medicine and Pharmacology at the University of California, San Diego (UCSD) School of Medicine has studied about 265 twin pairs over the past few years, which has led him to some surprising discoveries.

"By studying many traits and genes, we have started to put together unexpected stories," he said.

Studying genetic variations in twins provides scientists with data on traits that are heritable, or passed down through human DNA, versus those determined by the environment, age or how a person cares for his or her health, factors such as medical care or diet and exercise. In a series of studies published in the American Heart Association journals *Circulation* and *Hypertension*, O'Connor has identified particular genes that influence human health in unexpected ways.

"Factors linked to cardiac or kidney disease - such as hypertension, a tendency toward obesity or diabetes, elevated blood glucose and lipids - were just amorphous risk factors before," said O'Connor. "Now we know that they run in families, not only because of a shared environment, but because they are determined in part by particular genes.

"Behavioral studies with twins have been conducted for decades, but in the post-genomic era, we can now factor in genotypes and determine the effect of specific genes on traits," O'Connor said. By studying both monozygotic (MZ, or genetically identical) and dizygotic (DZ, or fraternal, who share half of their genetic information) twin pairs, researchers can more readily pinpoint specific genes in people who are the same age. A formula measuring the difference in the frequency of traits between the siblings in each MZ and DZ twin pair establishes what is called the index of heritability.

The human genome has three billion base pairs and about 30,000 genes. O'Connor and his research team have looked at about 900 of these 30,000 genes.

"We're just scratching the surface," he said. The researchers hope to more densely and systematically evaluate genotypes by studying blood samples from more twin pairs, in order to more extensively map genetic components that lead to increased risk of disease.

### CRP and Heart Disease

For example, by studying twins, O'Connor's team has identified three genes that are correlated with systemic inflammation. This study indicates a strong effect of heredity in the occurrence of C-reactive protein or CRP, a blood protein that serves as a marker for inflammation. Its presence indicates a heightened state of inflammation in the body and can indicate cardiovascular risk.

CRP is associated with increased blood pressure, body mass index, and insulin resistance, among other factors. In twin subjects with elevated CRP, multiple, common genetic variants were found along a pathway associated with the adrenergic system. Adrenergic stimulation is what is involved in the 'flight or fight' response, and results in an increased heart rate, sweating, and increased blood pressure. Evidence emerging from the twin studies uncovered links between the adrenergic system and inflammation, suggesting new strategies to probe the role and actions of this pathway in inflammation. This study was published in the February 2007 issue of the *Journal of Hypertension*.

#### Genes and Vascular Disease

In a study on line in advance of publication in the May 1 edition of *Circulation* the UCSD team reports findings regarding the effect of genetics on the endothelium, the single-cell lining of blood vessels. Endothelial function, or dysfunction, is the basis of every common vascular disease, such as heart attack or stroke.

"When blood vessels stop contracting and relaxing properly, it is the first indication of vascular dysfunction," said O'Connor

The endothelium secretes several hormones that are markers of how well it is functioning. Release of one of these markers, called endothelin (ET-1), is triggered by a gene that regulates catecholamines, chemical compounds produced in the adrenal gland that are released in reaction to stress. The study measured the plasma concentration of ET-1 in about 300 twins. The results establish and verify a previously unsuspected link between catecholamines and the endothelial system, showing that this link is due to a genetic variation and therefore runs in families. Heredity and Kidney Disease

The same twin pool study revealed the influence of heredity on renal protein (albumin) excretion. Excretion of the protein albumin in urine is one sign of kidney disease, which can be a complication of diabetes.

"Normally kidneys filter the blood to rid the body of accumulated toxins. In healthy kidneys, more than a million little 'baskets' or 'sieves' filter out the bad chemicals without leaking 'good' cells or proteins," said O'Connor, adding that how well these filters work appears to be a heritable factor.

Albumin leaks are an indication that the permeability of these filters has increased, allowing leakage of good molecules with the bad. This trait is linked to a heightened risk of cardiovascular disease and premature death. The study shows that both elevated blood pressure and changes to the kidney's filters are caused by genetic variation at multiple points along the adrenergic pathway. Links between adrenergic activity and renal injury could lead to novel approaches to predicting, preventing, diagnosing and treating kidney disease. These findings are published in the May 1, 2007 issue of *Hypertension*.

Others at UCSD involved in the twin pair research are Fangwen Rao, M.D., Jennifer Wessel, Ph.D., Guillermo Moratorio, M.S., Elizabeth O. Lillie, Ph.D., Maple Fung, M.D., Yuqing Chen, M.D., Ph.D., Rany M. Salem, Ph.D., Kuixing Zhang, M.D., Ph.D., Brinda K. Rana, Ph.D., Douglas W. Smith, Ph.D., Brenda Thomas, L.V.N., Srikrishna Khandrika, Ph.D., Manjula Mahata, Ph.D., Sushil K. Mahata, Ph.D., Laurent Taupenot, Ph.D., Michael G. Ziegler, M.D., Bruce A. Hamilton, Ph.D., Geert W. Schmid-Schoenbein, Ph.D., and Nicholas J. Schork, Ph.D.

For more information on how twins can sign up to participate in these and other health-related studies at UCSD, call 858-552-8585, extension 6178.

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