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Kidney function discovery sheds light on genetic complexity of disease

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To find a cure for cancer, haemophilia and other diseases, researchers need to be looking for complex, interacting genetic factors, according to the authors of a new study.

A new study, published in the *Journal of Clinical Investigation* by researchers at the Centenary Institute, Royal Prince Alfred Hospital (RPA) and The Australian National University (ANU), has exposed a greater level of genetic complexity for diseases than was originally thought.

The researchers looked at two disorders of kidney function - iminoglycinuria and hyperglycinuria. These disorders, first described 50 years ago, are conditions where large amounts of individual amino acids (the building blocks of proteins in our body) are wasted by the kidney.

Professor John Rasko, Head, Gene and Stem Cell Therapy program at Centenary Institute and Cell and Molecular Therapies at RPA, says although up to one in every thousand babies has this disorder at birth, it usually resolves in the first year of life. For those individuals in whom it continues to occur, it is generally thought not to cause medical problems but previous cases have been linked to high blood pressure, kidney stones, deafness and problems in the brain.

"Iminoglycinuria was observed to occur in families and the pattern of inheritance suggested that the cause might be due to an inherited abnormality of a specific pump on the surface of kidney cells,"

Professor Rasko explains.

The teams from Centenary Institute, RPA and ANU have now unravelled the genetic explanation by showing that not one, but up to four different pumps present in the kidney determine whether or not this particular abnormality occurs.

"The study demonstrates that in some cases mutations occur only in one gene, while in other cases mutations in two or even three different genes are observed, and that the disorders can arise due to mutations in a group of genes carrying out related functions," says Professor Stefan Broer, School of Biochemistry and Molecular Biology at ANU.

"From the point of view of understanding complex diseases in humans, it suggests we need to integrate much greater levels of complex genetic information to reach a clear understanding."

Professor Rasko says that these findings provide a foundation to improve our understanding of common human diseases, and greater potential to develop effective gene therapies to reduce the impact of diseases on patients.

"Gene therapies, whereby cells can be modified and then re-introduced into the body without the genetic mutations that cause illness, provide enormous potential to help cure diseases including haemophilia, cancer and cardiovascular disease," Professor Rasko explains.

"A crucial ingredient of successfully developing gene therapies is a thorough understanding of all the genetic factors at play in disease. This discovery takes us one step closer to understanding the complex factors at work in these serious diseases."

Source: Research Australia