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Sweeping genetic analysis of rare disease yields common mechanism of hypertension

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Analyzing all the genes of dozens of people suffering from a rare form of hypertension, Yale University researchers have discovered a new mechanism that regulates the blood pressure of all humans.

The findings by an international research team headed by Yale scientists, published online Jan. 22 in the journal *Nature*, may help explain what goes wrong in the one billion people who suffer from high blood pressure. The study also demonstrates the power of new DNA sequencing methods to find previously unknown disease-causing genes.

The team used a technique called whole exome sequencing — an analysis of the makeup of all the genes — to study a rare inherited form of hypertension characterized by excess levels of potassium in the blood. They found mutations in either of two genes that caused the disease in affected members of 41 families suffering from the condition.

The two genes interact with one another in a complex that targets other proteins for degradation, and they orchestrate the balance between salt reabsorption and potassium secretion in the kidney.

"These genes were not previously suspected to play a role in blood pressure regulation, but if they are lost, the kidney can't put the brakes on salt reabsorption, resulting in hypertension," said Richard Lifton, Sterling Professor and chair of the Department of Genetics at Yale and senior author of the paper.

The mutations had previously been difficult to find because there were very few affected members in each family, so traditional methods to map the genes' locations had been ineffective.

"The mutations in one gene were almost all new mutations found in affected patients but not their parents, while mutations in the other gene could be either dominant or recessive. The exome sequencing technology was ideally suited to cutting through these complexities," said Lynn Boyden of Yale, the first author of the paper.

The next step is to establish how these new components are involved in regulating sodium reabsorption in the kidney, in hopes of finding new ways intervene in hypertension, a major global health problem.

"We are finding all the individual parts to a complicated machine, and we need to understand how they are all put together to make the machine work," said Lifton, who is also an investigator of the Howard Hughes Medical Institute.

Provided by Yale University