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Sodium channel gene key to high blood pressure of Liddle's syndrome

High blood pressure is a malady some Americans acquire as a consequence of many factors, including genetics, diet and age. The broad range of components involved have made it extremely difficult for scientists to pinpoint which faulty genes might cause blood pressure to inch skyward.

So it is particularly instructive when researchers stumble across a family in which high blood pressure is an inherited trait. In 1963, Grant Liddle, a physician at Vanderbilt University, found a Tennessee family in which several of the members had extremely high blood pressure and low potassium levels.

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— **Richard P. Lifton**

Liddle's work suggested that people in this family could not maintain the proper balance of salt and water in the body. Their chemical imbalance created the alarmingly high blood pressure that is the cardinal feature of what came to be called Liddle's syndrome.

Thirty-one years after Liddle's seminal observations, researchers with the Howard Hughes Medical Institute at Yale University led a team that found the genetic cause at the heart of Liddle's syndrome. The group reported in the November 4, 1994 issue of *Cell* that an abnormal sodium channel gene in the kidney causes the body to retain excessive amounts of salt and water, which leads to high blood pressure.

"These findings are useful to families with this rare disorder," said Richard Lifton, an HHMI investigator at Yale. "Moreover, this work raises the possibility that more subtle mutations in this same gene may contribute to more common forms of high blood pressure. Finally, these mutations reveal the presence of a novel mechanism regulating sodium reabsorption."

Since the early 1960s, Liddle's syndrome has remained an interesting sideline in the field of hypertension research. The rarity of the disorder had precluded

scientists from obtaining enough blood samples for serious molecular study of the syndrome. Lifton tried to track down members of the family Liddle used in his original study; however, "it was as if the family had vanished," he said.

In 1991 his luck began to change. A chance encounter with David Warnock, a kidney specialist at the University of Alabama, Birmingham (UAB), led to the news that one of the members of the family in Liddle's original study had developed renal failure and had just undergone a kidney transplant at UAB. "That this family just resurfaced after 28 years was incredible luck," Lifton said.

Lifton and Warnock agreed that genetic approaches might finally pin down a cause of the high blood pressure. They were pointed in the right direction by a scientific paper by Drs. Cecilia Canessa and Bernard Rossier of the University of Lausanne in Switzerland, who reported cloning genes responsible for sodium reabsorption in the kidneys of rodents.

Lifton's group surmised that mutations in the corresponding genes in humans might be the cause of Liddle's syndrome. Richard Shimkets, a Ph.D. candidate at Yale whose graduate work is supported by HHMI, tested that hypothesis and found a mutation in the same part of the sodium channel in every clinically affected member of the family Liddle had originally studied.

Further studies of four more affected families confirmed similar mutations in all of these patients. "It's as if the flood gates to a dam have been left open and can't be closed," Lifton said. "These patients are always retaining too much salt and water."

The new findings provide the basis for a genetic test which permits people with this disorder to be identified earlier and then treated with the proper medications. Lifton is hopeful that the work will shed light on the more common causes of high blood pressure, a disease that affects 50 million Americans and kills about 200,000 annually.