SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS LINK GENE WITH KIDNEY STONES, BONE LOSS IN PATIENTS WHO ABSORB TOO MUCH CALCIUM

DALLAS – April 11, 2002 – A team of researchers at UT Southwestern Medical Center has identified a set of genetic abnormalities that increase risk for kidney stones and could indicate increased risk for osteoporosis.

The research team's findings, published in today's edition of the *Journal of Clinical Endocrinology and Metabolism*, associate six base substitutions – deviations from a particular gene's normal structure – with absorptive hypercalciuria (AH), a condition that makes the intestine absorb too much calcium and causes about 45 percent of all kidney stones.

The presence of at least one of the six base substitutions identified in the study translates into a 2.2- to 3.5-fold increase in the risk of having AH. The presence of more than one of the base substitutions increases risk even more; people who carry any five of the base substitutions are 11.5 times as likely to have AH as those with normal structure in the gene in question, an adenylate cyclase gene.

Dr. Berenice Reed-Gitomer, associate professor of internal medicine and the principal investigator of the study, said there is much to be learned about the molecular mechanism that ties the genetic abnormalities to the resulting disorders, but simply connecting specific genetic abnormalities with AH was an important step. She said it has long been known that kidney-stone formation runs in families, but identifying a genetic connection was elusive.

"We started about 10 years ago looking for a genetic cause," Gitomer said. "We picked out several individual genes that we thought could be involved, but we hit a blank. It would have been like winning the lottery to find it that way."

Gitomer and her team changed their approach. They turned to families with AH and looked for genetic similarities. That comparison pointed to a particular location in the human genome. Through study of the genes from this region, the team focused on a new gene that was similar to a recently described rat gene (with function unrelated to calcium metabolism) and subsequently identified the six base substitutions in this gene that occurred far more frequently in AH patients.

Dr. Charles Y.C. Pak, senior author of the study and director of UT Southwestern's Center for Mineral Metabolism and Clinical Research, described the study as a landmark.

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"It represents the molecular elucidation of a clinical syndrome," Pak said. "It is the result of 30 years of work on a clinical syndrome and its molecular explanation."

The study involved 212 participants: 80 unrelated AH patients and 132 "normal" volunteers. The AH patients were diagnosed at the Center for Mineral Metabolism and Clinical Research's kidney stone clinic. In the control group, volunteers with any personal or family history of stone disease, osteoporosis, history of abnormal serum parathyroid hormone (which helps control calcium and phosphate balance in the body), or abnormal calcium were excluded from the study.

The study provides a definite marker for kidney-stone risk, but it also could lead to early-stage identification and treatment for bone loss and osteoporosis, Gitomer said. As part of the study, patients' bone mineral density in the lower spine was measured, and the presence of one or more of the six base changes was associated with lower vertebral bone density in the lumbar region.

"If you look at the population, if people ever form a stone, they're probably at greater risk of bone loss or osteoporosis," Gitomer said.

Pak, who led the development of Citracal, an over-the-counter calcium citrate supplement, said the findings could help identify people at high risk for bone loss before the bone loss becomes evident. While osteoporosis is most frequent in postmenopausal women, in whom estrogen loss is the primary cause, some children, pre-menopausal women and younger men suffer from idiopathic osteoporosis, or osteoporosis of unknown cause.

"I think many (idiopathic osteoporosis patients) carry this genetic defect," Pak said. "And if a woman is postmenopausal and has the genetic defect, she's even more likely to get bone loss."

Other UT Southwestern researchers who contributed to the study were: Dr. William L. Gitomer, assistant professor of internal medicine; Dr. Howard J. Heller, assistant professor of internal medicine; Ming Chue Hsu and Martha Lemke, research associates in the Center for Mineral Metabolism and Clinical Research; and Paulette Padalino, research scientist in the Center for Mineral Metabolism and Clinical Research.

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