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Malfunctioning gene is a cause of gout (w/Video)

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Having partnered last year with an international team that surveyed the genomes of 12,000 individuals to find a genetic cause for gout, Johns Hopkins scientists now have shown that the malfunctioning gene they helped uncover can lead to high concentrations of blood urate that forms crystals in joint tissue, causing inflammation and pain — the hallmark of this disease.

The ABCG2 gene, they found, makes a protein that normally transports urate out of the kidney and into urine before the waste product does any harm. In studies using frog egg cells genetically engineered with human DNA, the Hopkins researchers established the role of the ABCG2 gene as a cause of gout, lending credence to suspicions that metabolic deficiencies, in addition to too much rich food and alcohol, are mostly to blame for this painful type of arthritis that affects 3 million Americans. The gene, they believe, may be responsible for some 10 percent of gout in Caucasians.

A report on the research, funded by the National Institutes of Health, was published June 8 in the online Early Edition *PNAS*.

The research began with a "genome-wide association study" that involved participants of the Artherosclerosis Risk in Communities Study, originally initiated two decades ago to examine the roots of heart disease. Over the course of that research, blood was collected from the study participants and analyzed for a variety of chemical elements, including uric acid. Subjects also reported whether they had ever been

diagnosed with gout, enabling researchers to link information from DNA, uric acid levels and gout.

By analyzing associations between blood uric acid levels and genotypes, the researchers identified the gene known as ABCG2 and specifically a certain mutation as a candidate for causing the joint inflammation and pain that are symptoms of gout. Because animal models for gout are not representative of humans — all mammals except for higher primates have an enzyme that efficiently breaks down uric acid — the researchers turned to genetic engineering to figure out just how the human ABCG2 gene might work to regulate uric acid levels, and how its mutation may lead to gout.

First, the team injected both normal and the mutant versions of the human ABCG2 gene into frog eggs which served as the live "factories" for producing the protein made by the gene. A couple of days later, after the egg cells produced lots of ABCG2 protein, the researchers bathed them in a radioactive-tagged uric acid bath.

Using the tag to identify and measure how much urate accumulated in the cells, the investigators then measured how quickly the urate left the cell. Comparing these so-called "efflux rates" to rates in control cells injected with the normal ABCG2, the scientists found that the cells with the mutant ABCG2 protein excreted uric acid at a rate just half of normal.

"We were able to show for what we believe is the first time that the ABCG2 protein is vital for transporting urate out of cells,"says Owen Woodward, Ph.D., a postdoctoral fellow in physiology in the Johns Hopkins University School of Medicine.

The researchers further showed that the ABCG2 protein is located in the kidney at a location where urate exretion takes place. They suggest that a

lack of efficiency in removing urate from the blood leads to its increased concentration and crystallization. In humans, these crystals get caught in joint tissues, leading to painful inflammation.

"As the first major gene identified to cause gout, we believe that ABCG2 also represents an attractive new drug target," says Michael Kottgen, M.D., a biological chemistry research associate in the Johns Hopkins University School of Medicine.

One strategy is to identify a drug that makes excretion faster and more efficient by activating the "urate transporter" protein.

"Instead of trying to limit urate production — the major current approach to gout treatment — newer treatments could focus on getting urate out of the bloodstream," Kottgen says. "We anticipate that activation of ABCG2 with a drug may help to promote excretion of urate."

"It's exciting that a finding from genome-wide association studies has been directly translated into better understanding physiology and perhaps will help us find better clinical therapies", says Anna Kottgen, M.D., M.P.H., an epidemiologist in the Johns Hopkins University Bloomberg School of Public Health.

Source: Johns Hopkins Medical Institutions

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