Genetic discovery could lead to early detection, treatment for osteoarthritis

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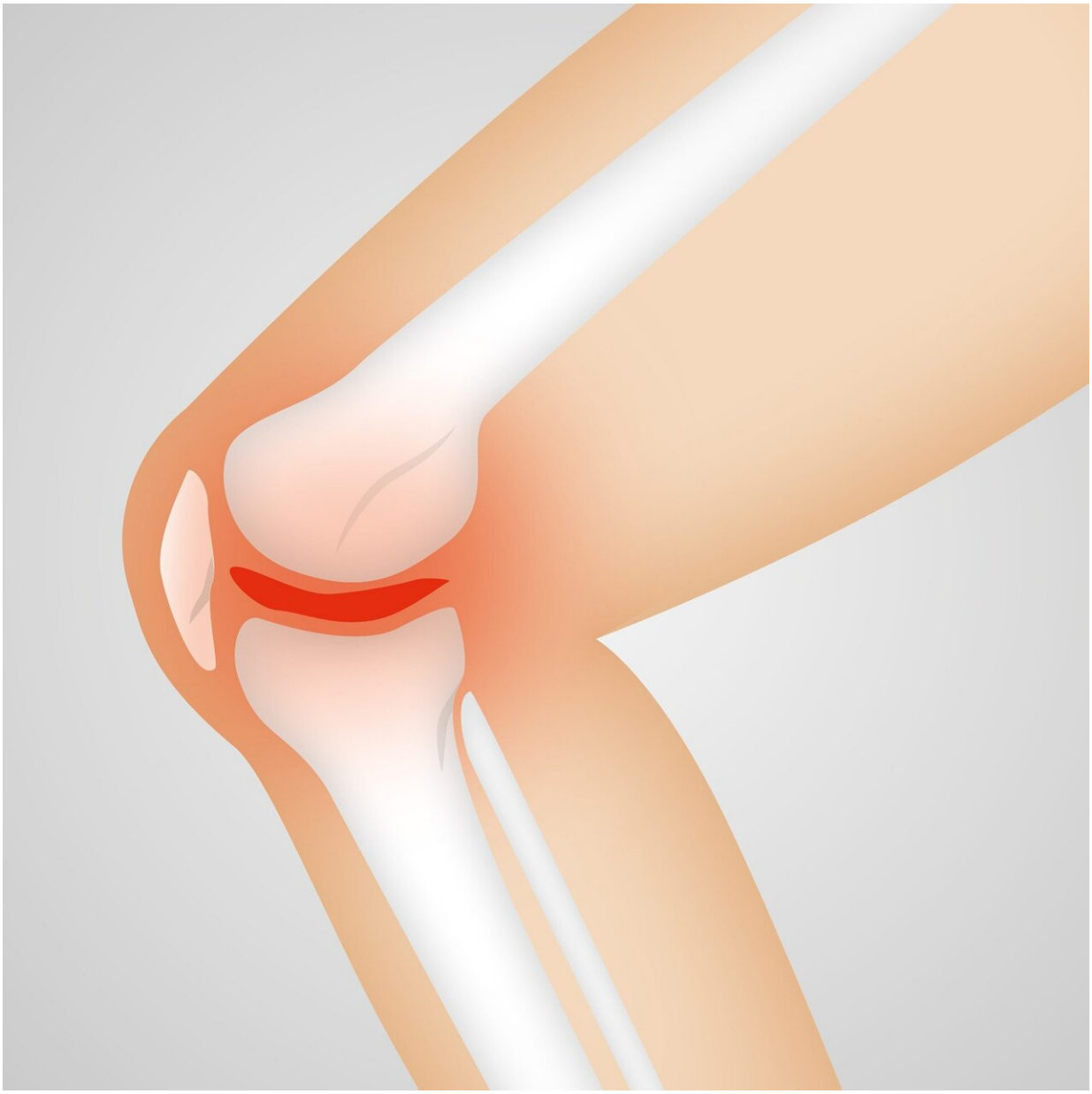

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A newly detected flaw in a genetic signaling pathway that leads to a hyper-active inflammatory response could help explain why some people are more prone to develop severe osteoarthritis than others, according to University of Utah Health scientists. They say the discovery could eventually lead to ways of detecting early onset of the disease—even before symptoms occur—and the development of new treatments for it.

The finding, among the first to suggest that a heightened inflammatory response is a major risk factor in osteoarthritis, appears in *Annals of the Rheumatic Diseases*. It is based on mouse studies and analysis of family information derived from the Utah Population Database.

"Researchers have long known that inflammation is a part of osteoarthritis, but no one had definitely shown that changing the inflammatory process is an initiating factor in the onset of the disease," says Michael Jurynec, Ph.D., lead author of the study and a research assistant professor in the Departments of Orthopedics and Human Genetics at U of U Health.

"But that's exactly what our study suggests. Learning as much as we can about this process could allow us to predict who might be susceptible to osteoarthritis and screen for drugs that would inhibit this molecular pathway."

Osteoarthritis is the most common form of arthritis, affecting more than 32 million Americans, according to the Centers for Disease Control and Prevention (CDC). The disease disrupts the normal function of the joint, occurring most frequently in the hands, hips, and knees. As the disease progresses, the cartilage within a joint begins to break down and the

underlying bone begins to change. As a result, it causes pain, stiffness, and swelling.

Its risk factors include age, obesity, and genetics. For now, there is no cure for osteoarthritis, but exercise, physical therapy, pain medications, and weight loss can help relieve its symptoms.

Previously, Jurynec and his colleagues discovered a mutation in a gene that regulates inflammation, called RIPK2, that was associated with osteoarthritis in the big toe in several generations of a family in the Utah Population Database.

In this new study, the researchers analyzed the genomes of 150 families in the database that had a pattern of inherited osteoarthritis affecting several joints. In all, they found six genetic variants affecting proteins in the NOD/RIPK2 signaling pathway. Normally, this pathway, which is found throughout the body, helps the immune system fend off bacterial infections. When it is activated, it temporarily causes inflammation near or around an infection or injury.

Building on this finding, Jurynec and colleagues theorized that genetic mutations in this pathway could amplify or prolong the NOD/RIPK2 pathway's inflammatory response to joint damage and contribute to the development of osteoarthritis.

"Just discovering the genes in these families doesn't necessarily prove that they are causative of osteoarthritis," Jurynec says. "That's why we chose to do animal studies so that we can begin to understand how the dysregulation of this pathway can increase susceptibility to the disease."

To determine if the mutation in RIPK2 is sufficient to cause susceptibility to osteoarthritis, the researchers used CRISPR/Cas9 gene-editing technology to introduce the flawed human amino acid in

laboratory mice. They next injured the knee to induce osteoarthritis. Mice are a good model of this process, Jurynec says, because they essentially have the same joint structure as humans.

After eight weeks, knee joints of mice with the human RIPK2 mutation showed a significant increase in the extent and severity of cartilage compared with rodents in the control group. The experimental mice with the human mutation also displayed greater activity in the NOD/RIPK2 pathway than the control group, suggesting that it had a prime role in the early signs of osteoarthritis the researchers detected in their knee joints

Although the study focused on rare mutations found in a select number of families, Jurynec says its findings could have broad implications for those at risk for more common forms of osteoarthritis.

"There are likely many ways in which the genes in this pathway can be altered by aging, obesity, and other disease states," Jurynec says. "Those alterations could predispose an individual to osteoarthritis. With that in mind, we could possibly start to consider how we identify biomarkers of this pathway that would allow us to identify people who have the disease before the onset of symptoms and find earlier and better treatments."

More information: Michael J Jurynec et al, NOD/RIPK2 signalling pathway contributes to osteoarthritis susceptibility, *Annals of the Rheumatic Diseases* (2022). DOI: 10.1136/annrheumdis-2022-222497

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