# Disjointed: Cell differences may explain why rheumatoid arthritis varies by location

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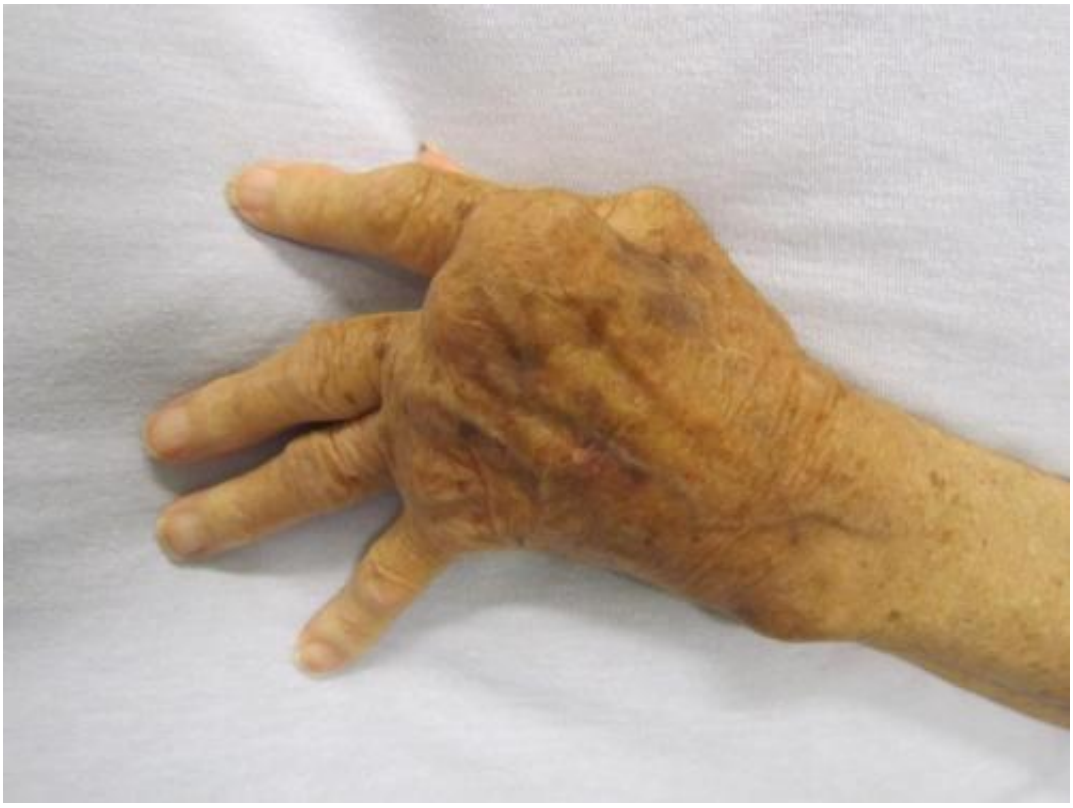

A hand affected by rheumatoid arthritis. Credit: James Heilman, MD/Wikipedia

Researchers at the University of California San Diego School of Medicine, with colleagues in Pennsylvania and China, report that not only are there distinct differences in key cellular processes and molecular signatures between rheumatoid arthritis (RA) and osteoarthritis (OA) but, more surprisingly, there are joint-specific

differences in RA. The findings help explain, in part, why drugs treating RA vary in effect—why, for example, a treatment that might work in arthritic knees isn't effective in an arthritic hip - and provide a potential new template for precisely targeting treatment for each and every ailing joint.

The results are published in the June 10 online issue of *Nature Communications* and represent a collaborative project that combined the power of computational science with modern biology and a deep understanding of the causes of arthritis.

At least 50 million adults and 300,000 children in the United States have some type of arthritis, which includes more than 100 different diseases, according to the Centers for Disease Control. Osteoarthritis is the most common type and involves damage to and ultimately the loss of cartilage—the cushion inside joints that permits them to move smoothly and painlessly. Rheumatoid arthritis is the most common chronic inflammatory arthritis and also affects joints. It can rapidly damage joints and, in the days before effective therapy, routinely put patients in a wheelchair after a few years.

While OA tends to localize in weight-bearing joints where cartilage is specifically worn away, RA is distributed more symmetrically—both hands may be affected equally, for example—and often evolves from the small joints of the hands and wrists to the larger weight-bearing joints. Why some joints are affected early, some late and some not at all has remained unknown.

In their new study, co-corresponding authors Wei Wang, PhD, professor in the departments of Chemistry and Biochemistry and Cellular and Molecular Medicine, and Gary S. Firestein, MD, professor in the Department of Medicine, investigated epigenetic patterns in fibroblast-like synoviocytes (FLS)—a specialized type of cell that lines the inside

of joints.

"We hypothesized that changes in epigenetic modifications and gene expression between FLS in different joints might potentially contribute to differences in synovial inflammation and responses to clinical treatment," said Wang.

The researchers discovered that DNA methylation—a fundamental, life-long process in which a methyl group is added or removed from the cytosine molecule in DNA to promote or suppress gene activity and expression—does in fact vary between FLS from the knees and hips of RA patients.

"We showed that the epigenetic marks vary from joint to joint in diseases like rheumatoid arthritis," said Firestein. "Even more importantly, the differences involved key genes and pathways that are designed to be blocked by new RA treatments. This might provide an explanation as to why some joints improve while others do not, even though they are exposed to the same drug."

Firestein, who is also director of the Clinical and Translational Research Institute at UC San Diego, said the work "opens up the potential for precision medicine approaches that allow us to target all of the joints, not just a subset. It has broad implications for how we evaluate new drugs in clinical trials as well."

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