

Juvenile arthritis: why genetic risk is not in the genes

July 31 2015, by Ellen Goldbaum

Scientists have been finding that genetic risk for many diseases lies primarily in noncoding parts of the genome, which used to be called "junk DNA," and not in the genes themselves. But that finding naturally begs more questions about what these noncoding regions do to cause a disease and how.

Now, University at Buffalo medical researchers who study [juvenile idiopathic arthritis](#) (also called juvenile rheumatoid arthritis) have figured out some important answers.

The paper, was published in June, online before print, in *Arthritis & Rheumatology*.

"Juvenile arthritis is often thought of as an autoimmune disease," said James N. Jarvis, MD, professor in the Department of Pediatrics in the UB School of Medicine and Biomedical Sciences. "That would mean a disease that emerges because the immune system gets mixed up in its ability to distinguish from itself what's foreign, for example, a bacteria or a virus. The trouble is, no one could ever figure out why so many areas of the genome that seemed to convey genetic risk for juvenile arthritis weren't located in [genes](#) that control that process."

The new data suggest a more nuanced paradigm, involving human neutrophils, the white blood cells that fight infections and which are part of the innate immune system, which instantly responds to an injury or infection. Jarvis is one of the few researchers who has been studying

their role in JIA.

"Neutrophils are actually the most abundant cell in the inflamed joints of children with juvenile arthritis," explained Jarvis, who also sees patients through UBMD Pediatrics.

Jarvis and his colleagues sequenced ribonucleic acid (RNA) from the neutrophils of 16 children with a form of JIA. In addition, they looked at gene control switches in both neutrophils and CD4+ T cells, which also fight infections, from healthy adults.

"Different cell types have slightly different 'control switches,' located in and around the DNA, to regulate and coordinate the turning on and off of specific genes," Jarvis said. "We show that there are important 'control switches' in neutrophils that lie right in the middle of the regions where other investigators have identified genetic risk for this disease."

He explained that finding that neutrophils play a key role in [juvenile arthritis](#) demonstrates that the disease involves the innate immune system, which operates almost instantly when someone experiences an injury or infection.

"It's the innate immune system that causes, for example, the redness and swelling that you get around a cut or a bruise," Jarvis explained. "People have assumed that because JIA is a chronic disease, that innate immunity must not be very important. We have shown that it is. The new paper reinforces some of our previous findings showing that genetic risk for JIA resides in neutrophils, some of the most important elements in the innate [immune system](#)."

These regions also happen to be strongly affected by epigenetic changes, DNA changes that don't alter DNA sequencing, but which are influenced by factors in both the genomic environment and the individual's

environment, including lifestyle, behavior, exposure to pollutants and many other factors.

"Our paper shows that genetic risk and epigenetic risk are closely linked in JIA, as most of the genetic risk occurs in regions of the genome where epigenetic influences also are operating," he said.

UB co-authors with Jarvis are Kaiya Jiang, research scientist in pediatrics; Lisha Zhu, PhD, post-doctoral associate in biochemistry; Michael J. Buck, PhD, assistant professor in biochemistry; Yanmin Chen, research technician in pediatrics; Bradley Carrier, a medical student; and Tao Liu, PhD, assistant professor of biochemistry.

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