Genomic study: Why children in remission from rheumatoid arthritis experience recurrences

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More children with juvenile rheumatoid arthritis are experiencing remission of their symptoms, thanks to new biological therapies, but the remission is not well-understood. A new study published today in *Arthritis Research & Therapy* provides the first genomic characterization of remission in juvenile rheumatoid arthritis patients.

"It turns out that even though these children in remission appear to be perfectly normal and symptom-free, their immune systems are still perturbed," says James N. Jarvis, MD, clinical professor of pediatrics in the University at Buffalo School of Medicine and Biomedical Sciences and the study's lead author.

The study notes that 35-50 percent of children with juvenile rheumatoid arthritis achieve remission while being treated with the standard treatments, methotrexate or methotrexate in combination with biopharmaceuticals.

"Our study provides some insight into why so many children in remission experience disease flares even when their disease has been stable for weeks or months, and why 50 percent of children who try to come off medication experience disease flares within two to six months," Jarvis says.

The research was conducted at the University of Oklahoma Health

Sciences Center by Jarvis and co-authors, and was supported by the National Institutes of Health, the Oklahoma Center for the Advancement of Science and Technology and the Arthritis Foundation, which continues to fund Jarvis' research in this area. Some members of the team, including Jarvis, now work at UB's Clinical and Translational Research Center (CTRC).

The study compared gene expression profiles from two independent cohorts of 14 patients each, all in remission from juvenile rheumatoid arthritis, to those of 15 healthy controls. The patients were on two different medication regimens. Patients were followed every two to three months for at least a year.

"Remission, of course, is our goal," says Jarvis. "I like to say it's hard to get somewhere when you don't know where 'somewhere' is. My lab is trying to build a 'genomic roadmap' for what remission is and exactly how we get there. That way, we can find a way to get these children into remission more quickly and for longer periods."

The new study confirms preliminary research by Jarvis, suggesting that remission experienced by patients with juvenile rheumatoid arthritis on medication is not a "return to normal" but is, instead, a distinct biologic state. The study finds that this distinct biologic state results from pro-inflammatory responses being counter-balanced by anti-inflammatory responses caused by gene expression changes that medication induces.

A key finding is that remission in these patients depends on HNF4a, a transcription factor that binds to DNA, acting as an "on" or "off" switch for gene expression. Until now, Jarvis says, HNF4a was seen only as a regulator of metabolism in liver and pancreatic cells.

"Our research suggests that HNF4a is one of what we suspect is a group of master switches that regulate therapeutic response," explains Jarvis.

The study found that more than 200 genes in white blood cells were expressed differently in children taking a combination treatment of methotrexate and a biological drug called etanercept compared to healthy controls. Some of those differentially expressed genes have been shown to bind to HNF4a.

Jarvis notes that the findings will make possible future studies that will identify specific biomarkers involved in how individual patients respond to specific therapies.

"This is a first step toward the goal of identifying biomarkers that will ultimately allow clinicians to personalize treatment by predicting which patients will respond best to which therapies," he says.

He adds that this kind of research will depend on longitudinal studies that monitor gene expression before, during and after treatment. Jarvis currently is principal investigator on a $1.2 million NIH grant to study microarray-based biomarkers in juvenile idiopathic arthritis. He also is studying the role of epigenetics in juvenile rheumatoid arthritis supported by several foundation grants.

Provided by University at Buffalo

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