Gene expression findings a step toward better classification and treatment of juvenile arthritis

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Scientists have discovered gene expression differences that could lead to better ways to classify, predict outcome, and treat juvenile idiopathic arthritis (JIA). Eventually such findings could enable doctors to target more aggressive treatment to children at risk of more severe arthritis, while those likely to have milder disease could be spared the stronger treatments that carry a greater risk of side effects. The researchers were supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the National Institutes of Health.

JIA is an inflammatory and sometimes disabling joint disease that affects an estimated 294,000 children in the United States. At present, making a diagnosis of JIA is imprecise and based largely on the presence of joint inflammation persisting for at least six weeks, for which no other cause can be determined, says Robert A. Colbert, M.D., Ph.D., chief of the NIAMS Pediatric Translational Research Branch. Based on the number of joints involved and other clinical features (fever and rash, for example), doctors classify patients into one of four or five major subtypes of JIA, which helps them predict a patient's most likely outcome and guide appropriate treatments. "But, recent research suggests there is more variability in JIA than the four or five major subtypes we currently recognize," Dr. Colbert says.

In the first of two such NIAMS-supported studies to be published in the July issue of *Arthritis & Rheumatism*, scientists led by Michael Barnes,

Ph.D., of Cincinnati Children's Hospital Medical Center used a large data set to compare a number of children newly diagnosed with one of four major subtypes of JIA - persistent oligoarthritis (affecting four or fewer joints), polyarthritis (affecting five or more joints), systemic arthritis (with fever and rash and inflammation throughout the body) and enthesitis-related arthritis (affecting the junctions between tendons and bones). Using gene expression technology - a method by which scientists can determine the relative levels of expression of thousands of different genes at the same time and compare a pattern from one subject with another - the researchers looked for differences in the children's blood samples that corresponded with the different forms of JIA.

"We analyzed gene expression patterns in blood cells and found that we could indeed distinguish the major subtypes of JIA," says Dr. Colbert, who was a leader of this research program at Cincinnati Children's Hospital Medical Center before coming to NIAMS. "Many of the genes whose expression is altered function in the immune system. This means that not only is there immune activation, but it differs depending on the subtype of JIA that is present."

In the second study, led by Thomas Griffin, M.D., Ph.D., also at Cincinnati Children's Hospital Medical Center, scientists looked more closely at patients from the study with one particular subtype of the disease - polyarticular JIA - to determine if that form was more complicated, or if there were more subgroups than originally thought. They included children with rheumatoid factor (RF) positive JIA, meaning their blood tested positive for an antibody commonly seen in adults with rheumatoid arthritis (RA). Surprisingly, the scientists found patterns of gene expression that indicated at least three subgroups of polyarthritis.

There was an older subgroup (average age 11) that included both RF positive and negative children with an inflammatory gene expression

signature bearing some resemblance to adult RA. A second older subgroup (RF negative) had less severe arthritis and an anti-inflammatory gene expression signature. A third subgroup was comprised mostly of younger patients (average age 7) who had no clearly defined gene expression signature and did have antinuclear antibodies (ANA). This third subgroup may be more similar to oligoarthritis patients, who frequently have a positive ANA, than to the other subgroups of polyarticular JIA.

Dr. Colbert says the new findings take pediatric rheumatologists a step closer to more precisely classifying JIA, and eventually developing individually tailored treatments that maximize the benefits, while minimizing the risks. "In pediatric rheumatology, we are at the early stages of improving our classification system for JIA. We expect that complementary studies designed to uncover the genetic differences that contribute to susceptibility will confirm the presence of several JIA subtypes, and add important information about what causes this group of diseases," he said. "We look forward to the day when we can use a combination of genetic and gene expression tests in the clinic to help us better diagnose and treat childhood arthritis."

More information:

Barnes M, Grom A, Thompson S, et al. Subtype-specific peripheral blood gene expression profiles in recent-onset juvenile idiopathic arthritis. Arthritis Rheum 2009;60(7):2102. DOI 10.1002/art.24601.

Griffin T, Barnes M, Ilowite N, et al. Gene expression signatures in polyarticular juvenile idiopathic arthritis demonstrate disease heterogeneity and offer a molecular classification of disease subsets. Arthritis Rheum 2009;60(7):2113. DOI 10.1002/art.24534.

Source: NIH/National Institute of Arthritis and Musculoskeletal and Skin

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