How can identical twins be genetically different?

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They sleep together, eat together, and most people find it impossible to tell them apart. Identical twins who grow up together share just about everything, including their genes. But sometimes only one twin will have health problems when genetics predicts both of them should.

Scientists at the University of Michigan Medical School are just beginning to understand how two people who are so similar biologically can be so different when it comes to the development of diseases like rheumatoid arthritis.

U-M researchers have discovered three genes that are over-expressed in rheumatoid arthritis, or RA, that were not known to be associated with the disease before. They also found that non-genetic factors influenced the expression of these genes and that the expression patterns varied between identical twins where only one twin had RA. Results of the U-M study were published in the July issue of Arthritis and Rheumatism.

RA is a chronic inflammatory disease that damages joints. RA causes pain, loss of movement, and bone deformities. It affects 2.1 million Americans. There are many genetic factors that put people at a high-risk for developing RA, yet only 15 percent of identical twins will both develop it.

Scientists compared gene expression patterns of 11 pairs of monozygotic twins, who shared the same egg and were genetically identical, but only one of them had RA. They found three new genes that were significantly

over-expressed in the twin with RA compared to the one without the disease. This is the first report for RA that examines gene expression patterns in monozygotic twins.

“This is the crux of the issue we are trying to address in RA -- how two patients can have the same genes but different disease outcomes. Identical twins represent the best experimental system to address this question,” says Joseph Holoshitz, M.D., an associate professor of internal medicine at U-M Medical School and co-author of the study.

The advantage of studying twins is that they start out with the exact same genetic information. Therefore, differences in gene expression are attributable to different environmental factors rather than genetics. Such factors could cause a random genetic mutation or affects how DNA is packaged.

“There’s a lot of variability in the severity of the disease, symptoms, and the response a patient will have to treatment. Differences in the expression of genes caused by environmental factors that modify DNA have a lot to do with this variability,” says Holoshitz.

The most significantly over-expressed of the three genes codes for a protein called laeverin. This is an enzyme that destroys certain types of proteins. Scientists hypothesize that laeverin promotes the tissue damage of the joint found in RA by degrading cartilage and bone.

Another previously unidentified gene codes for a protein called 11β-HSD2 that helps deactivate the hormone cortisol. This hormone is involved in the response to stress and also has anti-inflammatory effects. The discovery that 11β-HSD2 is over-expressed in patients may explain a common characteristic of RA patients.

“It has been known for a long time that there is a deficiency of cortisol

in RA patients," says Holoshitz.

The third gene U-M scientists discovered codes for Cyr61, which plays a role in angiogenesis, a process that recruits new blood vessels to an area.

In the early stages of RA, the tissue in the joint begins to grow and divide similarly to a benign tumor. The growing mass, which secretes proteins that degrade tissue, uses angiogenesis to recruit new blood vessels to supply it with nutrients. The angiogenic factor Cyr61 could be involved with this process.

"This paper describes only a glimpse of what this approach might reveal. There are many other categories of genes where expression varies between twins. We are just beginning to understand how RA is able to affect people in different ways. The newly discovered genes provide important insights into the nature of the disease and facilitate the design of novel treatment strategies for RA," says Holoshitz.

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