Children's genes affect their mothers' risk of rheumatoid arthritis

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A child's genetic makeup may contribute to his or her mother's risk of rheumatoid arthritis, possibly explaining why women are at higher risk of developing the disease than men. This research will be presented Tuesday, October 21, at the American Society of Human Genetics (ASHG) 2014 Annual Meeting in San Diego.

Rheumatoid arthritis, a painful inflammatory condition that primarily affects the joints, has been tied to a variety of genetic and environmental factors, including lifestyle factors and previous infections. Women are three times more likely to develop rheumatoid arthritis than men, with peak rates among women in their 40s and 50s. Certain versions of the immune system gene HLA-DRB1, known collectively as the shared epitope alleles, are associated with the condition. HLA genes are best known for their involvement in the immune system's response to infection and in transplant medicine for differentiating between one's own cells and those that are foreign.

The female predilection of rheumatoid arthritis strongly suggests that factors involved in pregnancy are involved, said Giovanna Cruz, MS, graduate student at the University of California, Berkeley, and first author on the new study.

"During pregnancy, you'll find a small number of fetal cells circulating around the mother's body, and it seems that in some women, they persist as long as several decades. Women with rheumatoid arthritis are more likely to have this persistence of fetal cells, known as fetal microchimerism, than women without the condition, suggesting that it is a potential risk factor for the development of rheumatoid arthritis," Ms. Cruz said. "Why it happens, we don't know, but we suspect HLA genes and their activity may be involved," she explained.

The researchers analyzed the genes of women with and without the shared epitope or other forms of HLA genes associated with risk of rheumatoid arthritis, and their children. They found that having children with these high-risk alleles – inherited from the children's father – increased the women's risk of rheumatoid arthritis, even after accounting for differences among the mothers' genes. These results showed that beyond a woman's own genetic risk of rheumatoid arthritis, there is additional risk conferred by carrying and bearing children with certain high-risk alleles.

"We don't yet understand how the shared epitope and other HLA alleles influence rheumatoid arthritis risk, but one possibility is that interactions between the proteins these genes encode may stimulate the autoimmune symptoms of the disease," Ms. Cruz said. In other words, a woman's immune system may detect proteins produced by the fetus and mistakenly tag lingering fetal cells as a threat, causing an immune reaction and symptoms of rheumatoid arthritis.

In addition to explaining why women are at increased risk of rheumatoid arthritis, the findings may lead to new ways of assessing a woman's risk of disease depending on whether her children or partner carries high-risk versions of genes, an area of research that Ms. Cruz and her colleagues are planning to explore. Other future research includes genetically analyzing multiple generations of rheumatoid arthritis cases, including mothers of people with the disease, and further exploring the role of HLA-encoded proteins and microchimerism.

More information: abstracts.ashg.org/cgi-bin/201… l.pl?absno=140121028

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