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Gene variants found associated with human immune system, autoimmune disease

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Numerous studies have reported that certain diseases are inherited. But genetics also plays a role in immune response, affecting our ability to stave off disease, according to a team of international researchers. The new findings, from the SardiNIA Study of Aging, supported in part by the National Institute on Aging (NIA) at the National Institutes of Health, are published in the Sept. 26, 2013 issue of *Cell*.

The SardiNIA researchers found 89 independent gene variants on the genome associated with regulating production of immune system cells. Five of these sites for the gene variants coincide with known genetic contributors to autoimmune diseases, and extend previous knowledge to identify the particular cell types that are affected by these genes.

"We know that certain diseases run in families. From this study, we wanted to know the extent to which relative immune resistance or susceptibility to disease is inherited in families," said David Schlessinger, Ph.D., chief of NIA's Laboratory of Genetics. "If your mother is rarely sick, for example, does that mean you don't have to worry about the bug that's going around? Is immunity in the genes? According to our findings, the answer is yes, at least in part."

The study team, led by Francesco Cucca, M.D., director of the National Research Council's Institute of Genetic and Biomedical Research in Italy, discovered that variants in particular genes had very significant effects on the levels of one or more particular types of immune system cells. A number of these genes are also implicated in risk for various

autoimmune diseases, including ulcerative colitis, multiple sclerosis, rheumatoid arthritis, and celiac disease.

Understanding the genes affecting immune system cells and risk for autoimmune disease is the first step in developing therapies that are personalized according to an individual's needs, although more research is needed to further characterize the role genetics plays in the complex dynamics of the immune system, the researchers pointed out.

The human immune system is a complex network of cells, tissues, and organs working together to fight disease and keep us at optimal health and function. Our first line of defense, the innate immune system, includes barriers, like skin and mucus as well as specific cells and molecules providing a prompt but nonspecific response to harmful germs—pathogens—preventing them from entering the body or eliminating them rapidly after infection. The second line of defense, the adaptive immune system, engages the body to produce, store, and transport cells and molecules providing more specific responses to combat pathogens. The immune system has evolved to reject pathogens and even some cancers, but high levels of immune function can also make the body prone to autoimmune disease. Autoimmune diseases occur when the body uses the immune system against itself, attacking normal, healthy cells.

The number of adaptive immune system cells available to attack a pathogen or, in the case of autoimmune disease, attack healthy cells, is what appears to be regulated by genetics. The SardiNIA research team tested the heritability of this immune response using a genome-wide association study, looking at approximately 8.2 million variants in blood samples taken from 1,629 Sardinians.

Small, single-letter variations in genes naturally occur throughout the DNA code and are generally without effect on any specific trait.

However, in some instances, scientists find that a particular variant is more common among people with a trait or disease.

In the analyses, researchers identified 89 independent variants and 53 sites associated with immune cell characteristics. Most of these associations were previously undiscovered. Some had been identified before in other studies, but without firm statistical significance. The researchers compared their findings with data in public repositories, and in some cases, found that these genes had already been associated with autoimmune disease.

This finding is the most recent of several discoveries made by the SardiNIA study itself and in conjunction with other groups in international consortia. Previous findings identified gene associations with height, fasting blood sugar, cholesterol and other fats in the blood, beta-thalassemia (a blood disorder), and uric acid levels, which can contribute to gout and risk of heart and kidney disease.

One of the unique features of the investigation is its study population—the Sardinians. "The lineage of most Sardinians goes back approximately 20,000 years, to the Mediterranean island's original settler population—and an ideal group for this type of research," said Cucca. "We have learned that in case after case, findings in Sardinia have been applicable world-wide."

Researchers note that understanding the genetics behind immune system response and autoimmune disease may have future implications on therapeutic targets, especially in the treatment of autoimmune disease.

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