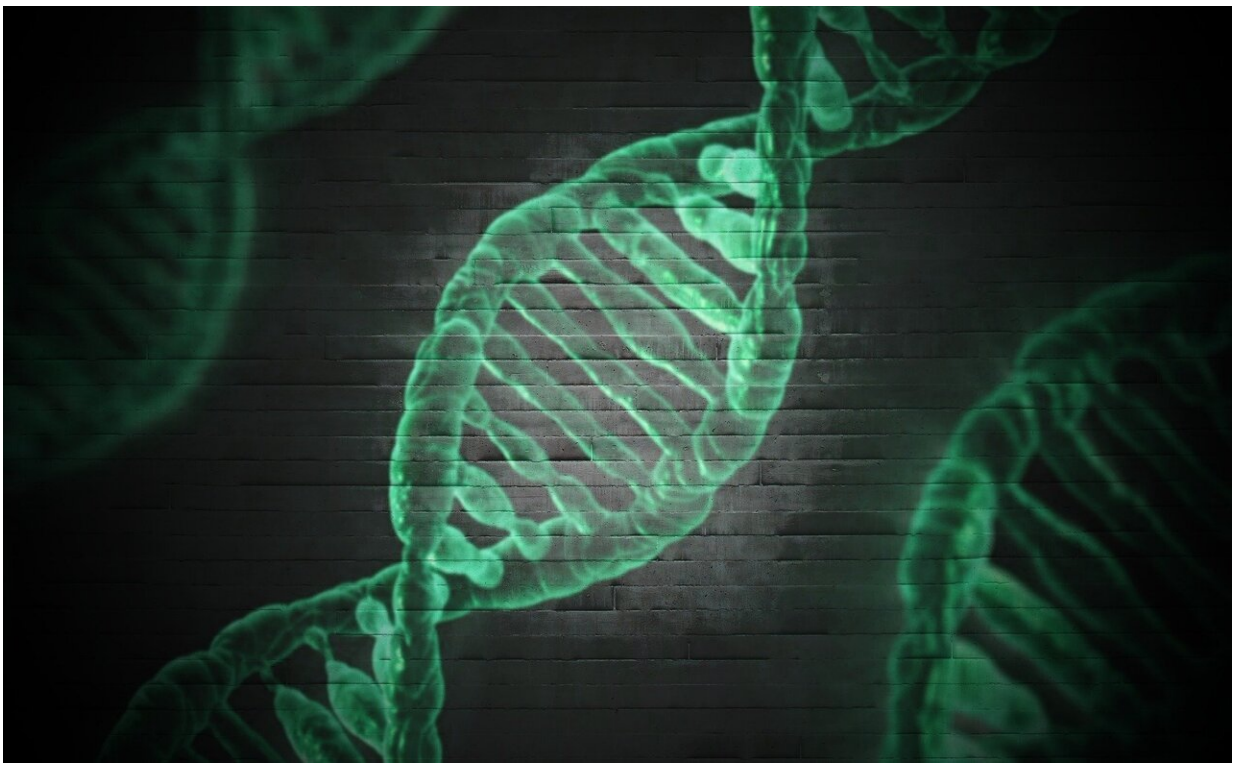
# Immunosuppressants linked to severe reactions in people with common genetic profile

November 23 2021, by Erin Digitale



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A Stanford Medicine-led research team has identified a common genetic profile that predicts severe, potentially fatal reactions to four powerful immune-suppressing drugs. The genetic profile is found in about 20% of

the general population.

The drug reactions, reported in a study published online Nov. 17 in *Annals of the Rheumatic Diseases*, were identified in patients with a rare condition called Still's disease. The drugs are prescribed for a variety of conditions, and two of the medications have been given for severe COVID-19, raising concern that a large number of patients are at risk.

"We need caution with the use of these drugs," said Vivian Saper, MD, a pediatric rheumatologist and allergist at the Stanford University School of Medicine and a lead author of the study. The medications tamp down inflammation and can help reverse a cytokine storm, in which an overabundance of immune signals causes severe inflammation. "These drugs are amazing, except when they're not," Saper said, adding that the research team hopes the FDA will add warning on the label requiring pre-prescription screening for the risky genes.

Saper shares lead authorship of the study with Michael Ombrello, MD, of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The study's senior authors are Elizabeth Mellins, MD, professor of pediatrics at Stanford Medicine, who initiated the project, and Jill Hollenbach, Ph.D., of the University of California-San Francisco.

The drugs in question are anakinra, canakinumab and rilonacept, which block the inflammation-provoking immune molecule interleukin-1 (IL-1); and tocilizumab, which blocks the pro-inflammatory immune signal called interleukin-6 (IL-6).

Most doctors do not know the risks these drugs carry, Saper said, adding that a widely available blood test can reveal the risky genetic signature. Identifying at-risk patients is a matter of knowing which lab test to order.

## Mysterious new lung problems

When the drugs that block IL-1 and IL-6 were introduced in the early 2010s, they revolutionized treatment for several autoinflammatory conditions, including Still's disease, which is characterized by high fevers and severe joint inflammation. (In children, the disease is also called systemic juvenile idiopathic arthritis.) For many patients, the drugs eliminate their symptoms and reduce or even prevent flare-ups.

However, in 2013, a scientific article reported mysterious, life-threatening new lung problems in some Still's patients. The Stanford researchers hypothesized that lung infections could be responsible, or that some Still's patients might have a genetic profile that caused the lung problems.

For their study, the researchers acquired lung biopsy results and lung CT scans from patients around the world. The team's pathologists noted features of an uncommon lung pathology called alveolar proteinosis, in which air spaces in the organ become filled with a protein that normally forms the lung surfactant. (In a healthy lung, a thin layer of surfactant coats the air sacs to help them stay open.) The team's radiologists also pointed out that a subset of patients had lung CT scans showing an odd combination of tissue abnormalities and unusual-appearing lymph nodes.

Mellins and Saper looked into the history of patients with both the pathologic and lung CT features and found that they were all taking IL-1 or IL-6 blockers; patients without this combination were not taking the medications. "We said, "Wow, we think it's the drugs,'" Saper said.

Meanwhile, Mellins extracted human leucocyte antigen (HLA) profiles from the genetic data of 20 lung disease patients and found that more than half shared the same genetic signature. HLAs are the proteins on cell surfaces that distinguish "self" from "nonself" tissues.

## Evidence points to drug reaction

"I picked up the phone and called Jill Hollenbach, an immunogeneticist at UCSF, and she said, "This is remarkable,'" Mellins said. Hollenbach thought that the results indicated a severe drug reaction rather than a genetically linked feature of Still's disease.

The researchers realized that patients with the lung problems met criteria for drug reaction with eosinophilia and systemic symptoms, or DRESS, a type of severe, delayed medication reaction. Although features of DRESS, easily missed with Still's disease, began soon after the drug was started, on average it took 14 months on the drugs for patients' severe lung disease to become apparent.

The researchers compared 66 Still's disease patients who had DRESS with 65 patients who did well on the drugs. Among other problems, three-quarters of the patients with DRESS, with or without lung disease, had liver enzyme levels indicating serious liver dysfunction, and 64% developed a cytokine storm.

The reactions were not always recognized by the patients' physicians. Patients who were taken off and kept off the drugs did well. Tragically, of 33 patients who kept taking the medications after their reactions began, nine died.

"This [drug reaction] is a very, very complicated signal, and it's hard for clinicians to realize that stopping the drug is what you do, especially if there is organ involvement, such as lung or liver dysfunction," Saper said.

The genetic signature that confers higher risk is found in 20% of the population at large and in 80% of patients in the study who had DRESS. Blood testing for HLA markers is available in clinical labs. Since the

gene test did not predict all who reacted, this study indicates that physicians should watch carefully for DRESS reactions to inhibitors of IL-1 and IL-6.

## COVID-19 concern

Two of the immune-blocking medications, tocilizumab and anakinra, have recently been used in patients experiencing cytokine storms due to severe COVID-19.

This worries the research team because the risky HLA markers are quite common. A recent scientific report on 24 very ill COVID-19 patients treated with tocilizumab noted that six patients died. The Stanford researchers suggest caution in using this drug for COVID-19.

"There's all this circumstantial evidence in COVID patients, but it requires more investigation," Saper said.

Meanwhile, the researchers hope the findings will quickly prompt HLA testing of Still's patients.

"One imperative we have is, "The right drug, for the right person, at the right time,'" Saper said. "In Still's disease, for most people these drugs are exactly right. But we've been able to identify a simple genetic test that could tell if this is not the right drug for you."

**More information:** Vivian E Saper et al, Severe delayed hypersensitivity reactions to IL-1 and IL-6 inhibitors link to common HLA-DRB1*15 alleles, *Annals of the Rheumatic Diseases* (2021). DOI: 10.1136/annrheumdis-2021-220578