Medical Xpress

Genetic link discovered in life-threatening reaction to common antibiotic

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A gene has been found by researchers to increase the risk for a severe and potentially life-threatening reaction to a commonly prescribed antibiotic—vancomycin.

Studies led by Murdoch University and Vanderbilt University scientist

Professor Elizabeth Phillips have also led to the development of a rapid and inexpensive test to identify the gene responsible.

Routine testing for this gene could improve patient safety and reduce unnecessary avoidance of other antibiotics, researchers reported in the *Journal of Allergy and Clinical Immunology* and the *Journal of Molecular Diagnosis*.

Professor Phillips, who led both studies, is director of the Centre for Clinical Pharmacology and Infectious Diseases at the Institute for Immunology and Infectious Diseases at Murdoch University and is the John A. Oates Chair in Clinical Research and Professor of Medicine and Pharmacology at Vanderbilt University.

An internationally known expert on severe adverse drug reactions, Professor Phillips said the test would be important in the clinical care of patients starting vancomycin and will prevent death and short- and long-term complications.

Vancomycin is commonly given in the hospital or as home intravenous therapy for several weeks in combination with other powerful antibiotics to treat serious and potentially life-threatening bacterial infections.

Dangerous reactions to antibiotics

Within two to eight weeks of starting antibiotic therapy, however, some patients develop a severe reaction known as DRESS—Drug Rash with Eosinophilia and Systemic Symptoms—characterised by fever, widespread skin rash and internal organ damage caused by an aberrant T-cell mediated immune response to the drug.

When DRESS develops, all treatment is stopped. The mortality rate that results, often from a combination of organ damage, the need for strong

immunosuppressants such as steroids and compromised treatment options for the underlying infection, approaches 10 percent.

"While the true incidence of DRESS is not known, every year in the United States hundreds of thousands of patients are at risk," said Professor Phillips.

"For several years, vancomycin has been known to be a common antibiotic trigger for DRESS, however the genetic risk factors predisposing specific patients were not known."

Zeroing in on a genetic link

This new finding shows that vancomycin-associated DRESS occurs in patients who carry specific variations in human leukocyte antigen (HLA) genes. HLA genes encode proteins that present foreign peptides (antigens) to T cells (a kind of white blood cell) to stimulate an immune response.

To better understand the HLA-DRESS connection, the researchers searched Vanderbilt University Medical Center (VUMC)'s biobank, BioVU, which contains nearly 250,000 unique, research-ready DNA samples linked to de-identified patient records.

Through a detailed search mechanism and review of the records, they were able to identify that patients in the databank who developed DRESS while taking vancomycin had an over-representation of the genetic variant HLA-A*32:01.

The researchers confirmed their findings in a prospective cohort of patients from Australia and VUMC who had been diagnosed with DRESS.

Since many patients who develop DRESS are often exposed to multiple antibiotics and other drugs simultaneously, the researchers used a specific diagnostic test developed in their laboratories called gamma-interferon ELISpot, which exposed patients' white blood cells to vancomycin and other concurrently administered antibiotics.

This test enabled them to determine which drug was most likely causing DRESS.

Investigating the vancomycin connection

Combining the BioVU and prospective data, the researchers found that 86 percent of patients who developed probable vancomycin-associated DRESS carried HLA-A*32:01, compared to none of the matched control patients who received vancomycin for several weeks and did not develop a reaction to it.

By conducting a survival analysis of the Vanderbilt BioVU patients with HLA-A*32:01 versus controls who did not carry the risk gene, the researchers determined that approximately 20 percent of patients who started vancomycin and who carried the HLA variant developed DRESS within four weeks.

To facilitate translation into clinical practice, Professor Phillips and her group have developed a simple and inexpensive diagnostic test for HLA-A*32:01 that can be set up in routine diagnostic laboratories.

More information: Munir Pirmohamed. HLA- and immune-mediated adverse drug reactions: Another hit with vancomycin, *Journal of Allergy and Clinical Immunology* (2019). DOI: 10.1016/j.jaci.2019.04.009