Genetic test can diagnose certain immune system disorders

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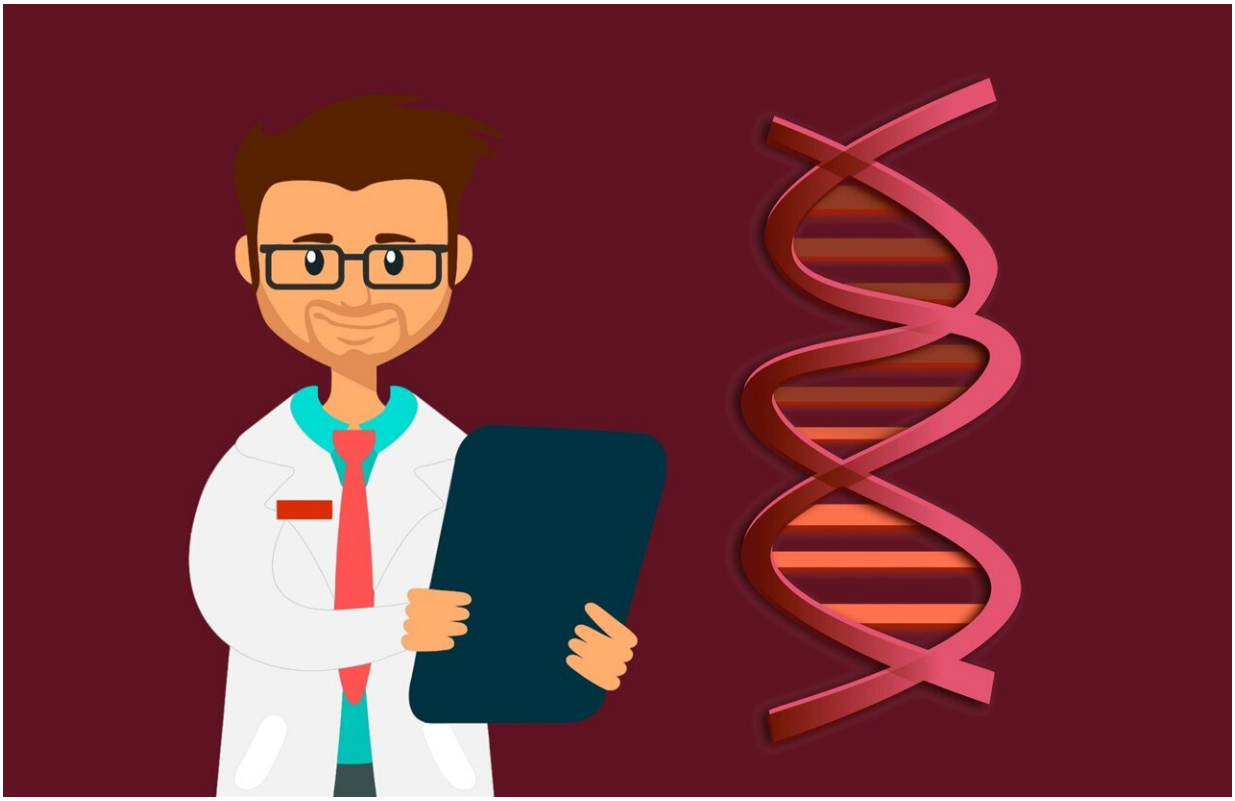

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Primary immunodeficiency disorders (PID) can result in chronic and sometimes life-threatening infections. More than 450 PIDs have been described, but timely and accurate diagnoses remain a challenge. In a new study in *The Journal of Molecular Diagnostics*, investigators used

next-generation sequencing technology to test a DNA panel of 130 different immune system genes from 22 study participants. They found that many patients had inherited a genetic defect that caused a disorder in their immune system. These findings will facilitate better treatment options and earlier diagnosis in family members who may have inherited the same genetic abnormality.

"Genetic testing was costly to perform and was mostly targeted to DNA sequencing of a single or very small number of genes. Therefore, a genetic diagnosis was limited for many patients with PIDs," explained lead investigator Lloyd J. D'Orsogna, MBBS, Ph.D., School of Medicine, the University of Western Australia; and Department of Clinical Immunology at PathWest Laboratory Medicine, Fiona Stanley Hospital, Perth, Western Australia.

"Recent advances in genetic technology allow affordable testing of multiple genes from the same individual. We can therefore identify a specific gene that may lead to frequent infections in patients. An earlier and more accurate diagnosis may improve the patient outcome and prevent complications," said Dr. D'Orsogna.

Twenty-two unrelated patients with common variable immunodeficiency (CVID), a common type of PID, and a previously unknown genetic diagnosis, were recruited for the study. DNA samples were tested and processed with a next-generation sequencing panel containing 120 different immune genes. One-hundred and thirty genetic variants were identified for analysis. The pathogenicity of the novel variants not previously associated with CVID were assessed through literature review, functional assays, and family studies.

The investigators identified likely pathogenetic variants in six of the 22 patients (27%). In an additional four patients, variants of unknown significance (VOUS) were identified. VOUS are genetic variants whose

clinical significance is not clear at this stage but might cause the disease. Overall, the investigators were able to identify genetic abnormalities in nearly half of the patients. All detected variants were confirmed with conventional Sanger sequencing.

Among the notable findings of the study was a patient with a novel variant in the AICDA gene that had not previously been reported. Her son also had a confirmed diagnosis of CVID and has also inherited the same mutation. Another patient had a novel pathogenic variant of the ICOS gene, which is implicated in immunodeficiency and immune response. In another CVID patient, a genetic variant was also detected in the BAFF-R gene, which enhances B cell survival; however, it was confirmed as pathogenic by flow cytometry analysis.

Such genetic diagnoses can inform decisions on targeted therapeutic options for patients. They can also provide earlier intervention for family members of patients with confirmed CVID. For example, the son of the patient with the novel AICDA variant was referred for genetic counseling before starting a family.

"I hope the new age of genetic medicine enables earlier and more accurate diagnosis, likely leading to better treatment and outcomes for all," said Dr. D'Orsogna.

More information: William Kermode et al, A Novel Targeted Amplicon Next-Generation Sequencing Gene Panel for the Diagnosis of Common Variable Immunodeficiency Has a High Diagnostic Yield, *The Journal of Molecular Diagnostics* (2022). DOI: 10.1016/j.jmoldx.2022.02.007

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