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For puzzling childhood immune disorder, gene research opens door to first diagnostic test

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A new genomics study, led by the Center for Applied Genomics at The Children's Hospital of Philadelphia, sets the stage for the first predictive diagnostic test in a serious immunodeficiency disease in children. If the disorder, common variable immunodeficiency disease (CVID), can be diagnosed early, children may receive life-saving treatments before the disease can progress.

"Currently, there may be a delay of up to nine years from the first time a child becomes sick from this very complex disease until he or she is diagnosed," said Jordan S. Orange, M.D., Ph.D., a pediatric immunologist at The Children's Hospital of Philadelphia and co-lead author of the study. "During this delay, a child may suffer repeated infections and life-shortening organ damage. Identifying CVID at an early stage may allow physicians to intervene earlier with appropriate treatment."

At Children's Hospital, Orange directs the Jeffrey Modell Diagnostic Center and cares for children with primary immunodeficiency diseases. Orange collaborated with Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia, Charlotte Cunningham Rundles, M.D., of Mt. Sinai School of Medicine, New York City, and researchers from several other institutions.

The research, the first genome-wide population-based study of CVID, appeared online April 15 in the Journal of Allergy and Clinical Immunology.

In CVID, a child has a low level of antibodies (specifically immunoglobulins), reducing the body's ability to fight disease, and leaving the child vulnerable to recurrent infections. CVID can first occur early or later in life, and the symptoms are highly variable. Frequent respiratory infections may lead to permanent lung damage. Patients may also suffer joint inflammation, stomach and bowel disorders, and a higher risk of cancers.

The great variability of the disease, coupled with the lack of a clear-cut diagnostic test, often causes CVID to go undiagnosed for years before doctors can initiate treatment. The complexity of the disease has also frustrated attempts to identify causes.

In the current study, the research team conducted a genome-wide association study (GWAS) to search for both common and rare genetic variants that might allow physicians to identify genetic patterns found in children with CVID but not in healthy children.

Using highly automated genotyping equipment at Children's Hospital's Center for Applied Genomics, the study team performed a GWAS in a sample of 363 patients with CVID, compared to 3,031 healthy controls. They searched for single-nucleotide polymorphisms (SNPs) as well as for rarer copy number variations (CNVs). SNPs are changes in a single base of DNA, while CNVs are deleted or repeated sequences in a stretch of DNA.

The GWAS detected a strong association with genes in the major histocompatibility complex (MHC) region, an area known to play an important role in immune-related conditions, and previously linked to

CVID. The researchers also found SNPs in an area that codes for a family of proteins involved in immune responses.

In its CNV research the study team also found more than a dozen novel genes with direct or potential relevance to the immune system. The gene discoveries provided clues to the largely unknown biology of how CVID develops, shedding light on the biological mechanisms underlying the disease. "These findings provide insight into the pathogenesis of CVID and its various subtypes, and may lead to future treatments," said Orange.

The GWAS findings confirmed the genetic complexity of CVID, but more importantly for clinical application, the researchers were able to use their discoveries to develop a predictive algorithm. When they tested that algorithm on cohorts of CVID cases and controls, they were able to distinguish CVID from healthy controls with 99 percent accuracy.

The investigators are now working to refine the algorithm into a standardized diagnostic test for CVID. Orange added, "This is very exciting. It suggests that we may be able to use a patient's genetic profile at an early stage to predict whether he or she will develop CVID. Since earlier treatment may greatly improve a child's ability to live with CVID, this research may represent an important advance in managing a complex, puzzling disease."

More information: "Genome-wide association identifies diverse causes of common variable immunodeficiency," Journal of Allergy and Clinical Immunology, published online April 15, 2011; to appear in June 2011 print edition. doi: 10.1016/j.jaci.2011.02.039

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