Missing genetic link found in a challenging immune disease

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In the largest genetic study to date of a challenging immunodeficiency disorder, scientists have identified a gene that may be a "missing link" between overactive and underactive immune activity. The gene candidate also plays a key role in autoimmune diseases such as type 1 diabetes, rheumatoid arthritis and allergies.

The researchers analyzed common variable immunodeficiency disorder (CVID), in which weak antibody responses lead to recurrent, often severe bacterial respiratory tract infections.

"Although this finding does not lead to immediate clinical applications, it raises new opportunities for understanding underlying causes of different immune disorders, and eventually developing more effective

diagnostic tests and therapies," said co-study leader, Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia (CHOP).

Hakonarson is the corresponding author of the study published online April 20 in *Nature Communications*. His co-study leaders were Lennart Hammarstrom of Karolinska Hospital, Stockholm; Eva Ellinghaus, of Christian-Albrechts-University in Kiel, Germany; and Tom Hemming Karlsen of Oslo University Hospital, Norway.

CVID occurs in roughly one in 25,000 individuals, both children and adults, in European populations. Defective B cells in the immune system cause a low level of antibodies, leaving patients vulnerable to recurrent infections. Some infections may cause permanent lung damage.

At least 25 percent of patients with CVID have various autoimmune disorders, in which the body mounts overactive immune responses. These include rheumatoid arthritis, stomach and bowel disorders, and autoimmune thrombocytopenia, a bleeding disorder. B-cell defects may also raise the risk of a type of lymphoma. Thus many CVID patients may develop symptoms resulting from an admixture of both insufficient and overactive immune components of immune dysfunction.

In the current study, the scientists searched for genetic differences between 778 patients with CVID and 11,000 control patients, all from the U.S., the U.K., Germany, Sweden and Norway. They used the Immunochip, a genotyping tool customized to detect hundreds of thousands of single-nucleotide polymorphisms (SNPs) already associated with 12 immune-related diseases.

Hakonarson and CHOP colleagues had discovered in 2011 that CVID was linked to the HLA-related gene region on chromosome 6p21; the current study confirmed that association. That gene region codes for the

HLA (human leukocyte antigen) complex, a well-known group of proteins that helps recognize invading microorganisms.

In this current study, the investigators additionally found a robust, novel candidate for a risk gene in CVID: the CLEC16A gene region on chromosome 16p13.13. "This is the first risk susceptibility gene for CVID identified by a genome-wide association study that does not code for the HLA complex," said Hakonarson.

He added that the CLEC16A gene region offers a very compelling target for understanding CVID. In the current study, the international research team showed that mice with reduced activity in the corresponding animal gene had lower levels of B cells, the immune cells that are depleted in the human disease. In addition, previous genetic studies by Hakonarson and other researchers found that changes in CLEC16A raised the risk of type 1 diabetes, inflammatory bowel disease and other autoimmune disorders.

"The biological mechanisms that cause disease symptoms in CVID are still unclear," added Hakonarson, "but this study may suggest that altered function in CLEC16A and its associated proteins may represent a 'missing link' between immunodeficiency and autoimmunity in CVID. This may offer new opportunities for eventually designing more effective treatments."

More information: Jin Li et al, "Association of CLEC16A with common variable immunodeficiency disorder and role in murine B cells," *Nature Communications*, published online April 20, 2015. doi.org/10.1038/ncomms7804

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