Team pinpoints amino acid variation in immune response gene linked with ulcerative colitis

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The association between the inflammatory bowel disease ulcerative colitis and a gene that makes certain cell surface proteins has been pinpointed to a variant amino acid in a crucial binding site that profoundly influences immune response to antigens, including gut bacteria, reports a team of researchers at the University of Pittsburgh, Cleveland Clinic, Carnegie Mellon University and Harvard Medical School. They published the findings today in the online version of *Genes & Immunity*.

Variations in genes that regulate immune responses in a region of chromosome 6 have long been linked with susceptibility for many infectious and chronic inflammatory conditions, including ulcerative colitis, said Richard H. Duerr, M.D., professor of medicine, Pitt School of Medicine, co-director and scientific director, UPMC Inflammatory Bowel Disease Center, and the corresponding author of the study. Ulcerative colitis is characterized by recurrent inflammation of the large intestine that results in diarrhea mixed with blood and abdominal pain.

"We tested more than 10,000 points, called single nucleotide polymorphisms, or SNPs, in the gene sequence in this chromosomal region, and we also tested amino acid variations in human leukocyte antigen (HLA) proteins that were deduced from the SNPs to identify those most important for ulcerative colitis," Dr. Duerr said. "Refining the gene association signals in this region enabled us to better understand

the underlying mechanisms of the disease."

Using sophisticated association techniques, the authors confirmed that an HLA gene called DRB1, which codes for a protein that is involved in the immune response and routinely tested in tissue matching for organ transplantation, was uniquely related to ulcerative colitis. Variation, or polymorphism, in that gene altered which amino acid was selected for the 11th position in the DRB1 protein – a key location because it is in a pocket of the so-called binding cleft where other proteins, such as antigens or markers of foreign cells, attach.

"This particular position probably plays a significant role in determining the human immune response to extracellular antigens," Dr. Duerr said. "It ties into theories that ulcerative colitis might result from an abnormal immune response to gastrointestinal bacterial antigens or might be an autoimmune disorder caused by an abnormal immune response to a self-antigen."

The researchers also looked for a similar relationship between that amino acid position and Crohn's disease, another chronic inflammatory bowel condition, but did not find a strong association. Still, variants in immune response genes on chromosome 6 likely contribute not only to ulcerative colitis and Crohn's disease, but also to other immune-mediated diseases such as rheumatoid arthritis and multiple sclerosis, added Jean-Paul Achkar, M.D., Department of Gastroenterology & Hepatology, Cleveland Clinic Digestive Disease Institute, an alum of the gastroenterology and hepatology training program at UPMC, and first author of the study.

Provided by University of Pittsburgh Schools of the Health Sciences

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