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Researchers Discover Mutations in Two Genes that Cause Early-Onset Inflammatory Bowel Disease

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Discovery of the genetic mutations allowed the researchers to successfully treat one of the study patients with a bone marrow transplant. The patient, who had not responded to other therapies, showed dramatic improvement following the bone marrow transplant and has remained in remission from IBD for more than a year.

The collaborative study included researchers from the National Center for Biotechnology Information (NCBI) at the National Institutes of Health, Hannover Medical School in Germany, University College London (UCL) in the United Kingdom, and several other institutions.

"This is an excellent example of how discovery of causative genes and mutations can enable clinicians to go from bench to bedside for an informed treatment of patients," said Professor Christoph Klein,

Medical School of Hannover, Germany, who led the diagnosis and treatment effort. Professor Klein and his team recently created the "Care for Rare Foundation" (www.care-for-rare.org) to support treatment of children with rare immunological disorders and to speed their treatment based on new discoveries such as genetic mutations.

The IBD research will be published in the Nov. 19, 2009 edition of *The* New England Journal of Medicine.

The successful treatment of the patient in this study built upon a well established treatment approach: that bone marrow transplants can be curative in genetic disorders where the affected gene is normally active in cells derived from the bone marrow. Because of the risks associated with bone marrow transplants, they are used only in cases of severe diseases, where the potential benefits outweigh the risks. Patients with the IBD caused by the genetic mutations identified in this research have very severe disease that meets this general criterion, though each case must be evaluated individually. In order to perform a bone marrow transplant a matched donor is needed. The study patient's matched donor was a healthy sibling, which is the preferred approach, but bone marrow transplants also can be done using more distantly related or unrelated matched donors.

The study is the first to show that a single genetic mutation is sufficient to cause IBD. Other research groups focusing primarily on adult-onset IBD have identified dozens of genes and variants that affect the risk for IBD, but none that singly can cause the disease.

The mutated genes identified in the study encode the proteins IL10R1 and IL10R2, which act together to receive signals from the cytokine IL10. IL10 (interleukin 10) plays a crucial role in keeping the body's inflammatory responses in check. The human body is continuously generating local inflammatory responses to control microbial infections

and repair damage from other toxins, but if that inflammatory response is not properly controlled tissues may be excessively damaged. When either IL10R1 or IL10R2 is mutated, the signals from IL10 cannot be received, and the resulting inflammation causes tissue damage, especially in the gastrointestinal system.

"This discovery is a milestone in research on inflammatory bowel disease, and will enable us to gain further insights into the physiology and immunity of the intestine," said Erik Glocker, UCL, who found the first mutation in IL10R2 identified in the study. Analysis of additional patients with early-onset IBD revealed mutations in IL10R1.

The gene identification effort was led by Professor Bodo Grimbacher, UCL Medical School (Royal Free Campus Hampstead), and head of the Marie-Curie Excellence Research Group, who said: "This discovery will lead to future therapeutic options not only in children, but potentially also in adult patients with IL10 signalling problems."

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