Rare gene variants linked to inflammatory bowel disease

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(Medical Xpress) -- An international team of scientists, including researchers from Karolinska Institutet, have identified several rare gene variants that predispose to IBD (Inflammatory Bowel Disease). The study provides new insights into disease pathogenesis, and suggests next-generation sequencing may speed hoped-for personalized treatment of common complex disorders.

Common chronic diseases such as coronary heart disease, hypertension, obesity, diabetes, asthma, rheumatoid arthritis, inflammatory bowel disease and many others show genetic predisposition, and hundreds of susceptibility genes have been recently identified. DNA variants associated with modestly increased risk can be frequently found in the general population, but the pathogenetic relevance of rare genetic changes is often unknown in these complex disorders.

Accurate sequencing of the entire human genome has become feasible with the recent advent of next-generation sequencing, and a large International team of scientists, including researchers from Karolinska Institutet, have now used this approach to seek for rare DNA variants in 56 genes known to predispose to Crohn's disease (CD), one of the two major forms of IBD together with ulcerative colitis. In their study, the genomic regions containing these genes have been re-sequenced in 350 Crohn's disease patients and 350 healthy controls, and several newly identified rare variants further tested for their risk effects in 16054 Crohn's disease patients, 12153 ulcerative colitis patients and 17575 controls from different countries.

"The results suggest that, even in the same gene, rare and common DNA variants are both important in determining one's risk to inflammatory bowel disease, with rare variants possibly more deleterious", says Associate Professor Mauro D'Amato at the Department of Biosciences and Nutrition, Karolinska Institutet, who led the Swedish part of the investigation. "This observation, should it become commonplace in complex diseases, may mean additional variants are to be routinely searched for in individual patients. With the cost of human genome sequencing rapidly decreasing, we should be well equipped for future clinical applications and improved diagnostics."

Crohn's disease and ulcerative colitis manifest as chronic inflammation of the gastrointestinal tract, with life-long symptoms including abdominal pain, diarrhea, rectal bleeding, ulcers, weight loss and debility. More than 1% of the general population is affected, there is currently no cure and surgery is often necessary in the most severe cases.

The study was published in the top-ranking journal *Nature Genetics*, and stems from an International collaboration of several laboratories in Europe and USA, and the contribution of the International IBD Genetic Consortium (IIBDGC). Corresponding authors are Dr Manuel Rivas and Associate Professor Mark Daly from the Broad Institute of Harvard and MIT in the US.

More information: Rivas MA, Beaudoin M, Gardet A, et al., *Nature Genetics* (2011) online 9 October.

Provided by Karolinska Institutet