RNA sequencing used to discover novel genes and pathways in celiac disease

April 18 2019

Credit: CC0 Public Domain

Researchers at the Mucosal Immunology and Biology Research Center at MassGeneral Hospital for Children (MGHfC) have discovered novel genes and pathways related to early stages in the development of celiac disease and the ongoing inflammation and comorbidities associated with the condition. The findings, published in *PLOS One*, include analyses of RNA sequences in duodenal biopsies from individuals with and without celiac disease and are consistent with many previously described pathways in the development of celiac disease.

In collaboration with Regeneron Pharmaceuticals, Inc. - a biopharmaceutical company based in Tarrytown, New York—researchers performed whole-transcriptome shotgun sequencing of 12 patients with active celiac disease, 15 celiac patients in remission with no intestinal damage, and 15 individuals without celiac disease. By analyzing participants' transcriptome—the total sum of transcribed RNA sequences—researchers discovered which genes were expressed and which genes were not expressed to determine genetic signatures linked to celiac disease.

"We know that celiac disease is a multifactorial disease with about 57 genes associated with this autoimmune condition. By performing RNA sequencing, we have uncovered additional genetic 'signatures' and moved closer to identifying targets for future therapeutic agents—in celiac disease and possibly other autoimmune conditions," says Maureen Leonard, MD, clinical director of the Center for Celiac Research and Treatment at MGHfC, an instructor in Pediatrics at Harvard Medical School and first author of the study.

The results showed clear differences in gene expressions among the

three groups. Researchers found significant differences in the expression of 945 genes between people with active celiac disease and non-celiac controls; 290 genes between people with celiac disease in remission and the non-celiac group; and 538 genes between the active celiac group and the celiac disease in remission group.

"The identified genes activated three major pathways: innate immunity, gut permeability and differentiation in cell maturation," says Alessio Fasano, MD, director of the Center for Celiac Research and Treatment at MGHfC, a professor of Pediatrics at Harvard Medical School and senior author of the *PLOS One* report. "We can confirm that these functions are instrumental when you develop celiac disease." Expression of some of the genes returned to normal when patients were placed on a gluten-free diet, he notes, and some did not. Fasano notes that this finding could provide some insight into why some people have persistent intestinal damage even after following a strict gluten-free diet.

From the enormous array of data generated, researchers chose to focus on functional pathways that were significantly different between the active celiac group and those in remission. Two of the three top perturbed pathways in the active celiac group involved signaling by cytokines and chemokines, which are known as the immune system's "first responders" and markers of inflammation in innate immunity in the early stages of disease development. The researchers also found evidence to suggest that the risk of co-morbid autoimmune disorder may be high in active celiac disease, as pathways for type 1 diabetes, lupus and autoimmune thyroid disease also were upregulated.

Identifying potential targets for therapeutic intervention in celiac disease and other autoimmune conditions is a long-term goal of the research group. "This study is only the beginning. Our findings provide the framework for future validation studies to investigate the early steps in celiac disease pathogenesis and to examine the remission state," says

Leonard. Research is underway at other centers for the use of the transcriptome in targeted therapy in Inflammatory Bowel Disease, and Leonard and Fasano hope to see this replicated for celiac disease.

More information: *PLOS One* (2019). DOI: 10.1371/journal.pone.0215132