Study reveals complication predictors in children with Crohn's disease

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Subra Kugathasan, M.D., Emory University principal investigator and lead author of the paper, is shown with Evelyn Whitaker, who was eight years old when the photo was taken. Credit: Children's Healthcare of Atlanta

Researchers have successfully identified biological signatures in

pediatric patients with newly diagnosed Crohn's disease (CD) capable of predicting whether a child will develop disease-related complications requiring major surgery within three to five years. The results of this research, "Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study," have been published in the journal, *The Lancet*.

This groundbreaking work is the result of the Crohn's & Colitis Foundation's "RISK Stratification" study, the largest new-onset study completed on pediatric Crohn's disease patients. It is a multicenter research initiative that consists of 25 U.S. institutions and three from Canada and a cohort of 1,112 CD children enrolled at diagnosis, of which 913 were included in the published study. Of the 28 research sites, four are located in Atlanta—Emory University, Georgia Institute of Technology, Children's Healthcare of Atlanta, and the Children's Center for Digestive Health Care. The goal of this research was to identify measurable indicators of the two most common complications in pediatric Crohn's disease that require surgery—stricturing and penetrating disease.

Stricturing, also referred to as fibrostenosis, is characterized by a build-up of fibrotic scar tissue which leads to thickening of the intestinal wall and narrowing of the intestinal passage. Penetrating disease is the result of sustained inflammation that spreads beyond the intestinal wall resulting in the creation of fistulas, abnormal connections between the intestine and other organs. Penetrating complications can also lead to the formation of abscesses at the sites of fistulas.

"Twenty five percent of patients with Crohn's disease account for 80 percent of complications, hospitalizations, surgery and health care costs. The aim of RISK is to preemptively identify those 25 percent of patients at diagnosis," Subra Kugathasan, M.D., Emory University, principal investigator and lead author of the paper. "Through the study of baseline

[gene expression](#), immune reactivity, and intestinal bacteria, we have identified distinct biological signatures capable of predicting stricturing and penetrating disease, at diagnosis. After analyzing millions of biological and clinical data points, RISK has generated a composite [risk stratification](#) model."

"Stricturing and penetrating disease account for substantial morbidity in both pediatric and adult patients with Crohn's disease, but there are no validated models to predict risk and the effect of treatment," said Caren Heller, M.D., chief scientific officer of the Foundation.

RISK study researchers looked at intestinal gene expression levels to identify risk factor genes whose levels are altered (increased or decreased) at enrollment, and identified distinct biological gene expression signatures at baseline that could distinguish children who will develop strictures form those who develop fistulas or abscesses, without the confounding effects of treatment on gene expression. Therefore, these genetic signatures together with other biological and clinical variables they evaluated could be used as predictors of complications and treatment outcomes at diagnosis.

"Importantly, the functional nature of these genetic signatures is consistent with the clinical presentation of the complications," said Ted Denson, M.D., Cincinnati Children's Hospital, co-principal investigator and lead author of the paper. "This means that while patients who develop fibrostenosis exhibit, at diagnosis, increased levels of several genes involved in the fibrosis process, patients who develop penetrating disease have increased levels of genes involved in the inflammatory response."

In addition to providing predictive biological signatures for development of complications, the RISK study also found that patients who receive early anti-TNFa biologic treatment, within three months of diagnosis,

were less likely to develop penetrating complications. However, patients with stricturing complications were poorly responsive to early intervention with biologics. These data support the utility of risk stratification of pediatric Crohn's disease patients at diagnosis, and may guide early tailored use of anti-TNFa therapy. The data also highlight the unmet medical need to find new treatment options for children likely to develop strictures.

"These discoveries are great steps toward precision medicine in the treatment of pediatric Crohn's disease," said Andrés Hurtado-Lorenzo, Ph.D., Director of Translational Research of the Foundation. "In the coming years, we plan to translate these findings into a risk diagnostic tool that could use these biological signatures as biomarkers to predict risk of complications and to help clinicians make therapeutic decisions at diagnosis."

The Foundation has made significant investments in support of pediatric IBD research through the PRO-KIIDS network, an umbrella for clinics participating in pediatric IBD research. Although many projects are expected to arise from this network the Risk Stratification has been the flagship study.

"Pediatric patients are the fastest growing group of the IBD population. Under the auspices of the PRO-KIIDS network, every major pediatric IBD center in the country is touched by our work or funding," said Michael Osso, President and CEO of the Foundation. "Through the network, and the results of the RISK study, we are furthering research that will significantly lower the treatment burden on kids, and help minimize side effects on the quality of life surrounding the most vulnerable of patients."

As part of the study, Georgia Tech postdoctoral researcher Urko Marigorta analyzed RNAseq gene expression data from biopsies

provided by Cincinnati Children's Hospital. The work identified dozens of pathways that are differentially expressed in complicated disease, and showed that immune activity is more disrupted in penetrating disease while extracellular matrix is more involved in stricturing disease. Inclusion of these profiles in a statistical model with the serological and classical markers improved the predictive accuracy of the model significantly.

"We performed statistical and bioinformatic analyses of the genomic data which led to enhanced discrimination of which patients are likely to progress to complicated disease," said Greg Gibson, a professor in the Georgia Tech School of Biological Sciences and one of the paper's co-authors. "The involvement of TNF-alpha signaling in progression to stricturing disease is consistent with the overall finding that these are the patients who respond to TNF-alpha therapy."

More information: Subra Kugathasan et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study, *The Lancet* (2017). DOI: 10.1016/S0140-6736(17)30317-3

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