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First multi-whole-genome study of IBD in African Americans

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In African Americans, the genetic risk landscape for inflammatory bowel disease (IBD) is very different from that of people with European ancestry, according to results of the first whole-genome study of IBD in African Americans. The authors say that future clinical research on IBD needs to take ancestry into account.

Findings of the multi-center study, which analyzed the whole genomes of more than 1,700 affected individuals with Crohn's disease and ulcerative colitis and more than 1,600 controls, were published on February 17 in the *American Journal of Human Genetics*.

As part of their analysis, the researchers developed an algorithm that corrects for ancestry when calculating an IBD polygenic risk score. Polygenic risk scores are tools for calculating gene-based risk for a disease, which are used for IBD as well as other complex conditions such as coronary artery disease.

"Even though the disease destination looks the same, the populations look very different, in terms of what specific genes contribute to risk for IBD," says lead author Subra Kugathasan, MD. "It shows that you can't develop a polygenic risk score based on one population and apply it to another."

Kugathasan is scientific director of the pediatric IBD program and director of the Children's Center for Transplantation and Immune-mediated Disorders at Children's Healthcare of Atlanta,as well as

Marcus professor of pediatrics and human genetics at Emory University School of Medicine.

The first author of the paper is geneticist Hari Somineni, Ph.D., who earned his doctorate working with Kugathasan at Emory, and is now working at Goldfinch Bio in Massachusetts.

The primary sites to recruit study participants were Emory, Cedars-Sinai and Rutgers, along with Johns Hopkins and Washington University at Saint Louis. Along with Kugathasan, the co-senior authors and co-organizers of the study were Steven Brant, MD from Rutgers and Dermot McGovern, MD, Ph.D. from Cedars-Sinai.

"One of our goals in treating IBD is to move toward a more personalized approach," says McGovern, the Joshua L. and Lisa Z. Greer Chair in Inflammatory Bowel Disease Genetics at Cedars-Sinai. "Deciphering the genetic architecture is an important part of this effort. Studies such as this one are vital to ensure that diverse populations, including African-Americans, benefit from the tremendous advances promised by genomic medicine."

Having a first-degree relative with a form of IBD confers a greater risk than any known environmental factor. African-Americans are conventionally thought to be less at risk for IBD, but Kugathasan says that view may reflect disparities in diagnosis and access to healthcare.

The study showed that the most important genetic risk locus for IBD in African Americans—PTGER4—is relatively minor in European ancestry populations, Kugathasan says. In contrast, two gene loci that are major in Europeans—NOD2 and IL23R—play smaller roles in African Americans.

There is some overlap in genetic risk factors based on the African-

American population historically having about 20 percent European genetic background, with known IBD risk factors such as IL23R coming from the European side.

In 2016, the research team published the first genome-wide association study of IBD in African Americans, identifying regions of the genome associated with ulcerative colitis only in people of African descent.

Future clinical studies of IBD treatments need to take the genetic background of specific populations into account, Kugathasan says. Several therapies are being developed for IBD targeting the IL23 receptor pathway, partly because IL23R is a major genetic risk factor, with little focus on PTGER4. That needs to change, he says.

The current study also identified rare genetic variants conferring IBD risk that are specific to African Americans, which had not been observed in previous studies. The variants are connected to the gene encoding calbindin 2 (CALB2), a protein involved in nervous system signaling.

What the study did not find—disappointing the researchers—were a host of rare genetic variants that explain the "missing heritability" in IBD among African-Americans. In genome-wide association studies, missing heritability refers to disease risk that is not accounted for by common gene variants.

For the future of the IBD field, Kugathasan says studies of gene-environment interactions—examining factors such as diet, microbiome, or toxic exposures—may yield insights that genome-wide association studies have not.

More information: Hari K. Somineni et al, Whole-genome sequencing of African Americans implicates differential genetic architecture in

inflammatory bowel disease, *The American Journal of Human Genetics* (2021). DOI: 10.1016/j.ajhg.2021.02.001