Published in final edited form as:

Gastroenterology. 2015 November ; 149(6): 1323–1326. doi:10.1053/j.gastro.2015.09.029.

Deciphering the genetic code of gastrointestinal diseases among African Americans

Adeyinka O. Laiyemo, MD, MPH¹ and Maria T. Abreu, MD²

¹Division of Gastroenterology, Department of Medicine, Howard University College of Medicine, Washington DC

²Division of Gastroenterology, Department of Medicine, Miller School of Medicine, University of Miami, FL

The susceptibility of individuals to diseases is influenced by a complex interplay of their genetic makeup and interaction with the environment. Although we cannot change our genes, lifestyle modification and appropriate disease-specific medical interventions including screening may significantly minimize its risk or alter the course of disease. To prevent disease or treat it optimally, a thorough understanding of its pathogenesis is required. For many common diseases, ancestral events such as exposure to specific pathogens have shaped genetic susceptibility. Malaria and sickle cell trait are classic examples of this phenomenon. African Americans represent a distinct and critical population for whom common diseases can have disproportionately negative outcomes. For a variety of reasons, African Americans remain relatively understudied with respect to the genetic basis of diseases and remain underrepresented in clinical trials. These challenges face us in the gastroenterology office as we strive to deliver the best, targeted care to all of our patients. For example, African Americans have poorer response to interferon-based strategies for hepatitis C. It was not until the identification of polymorphisms in interleukin (IL)-28B that we recognized the mechanistic basis for this observation.¹ Now here is genomics more important than in oncology, wherein an understanding of genetic mutations in a tumor or inherited germ-line mutations has an enormous impact on the response rate to chemotherapy and surveillance. For example, treatment with 5-fluorouracil-based regimens has been the standard chemotherapy for colorectal cancer (CRC), but studies demonstrated that patients with stage II and stage III CRC did not derive much benefit from this chemotherapy if their tumors exhibited high microsatellite instability.^{2,3} Similarly, treatment with monoclonal antibodies panitumumab and cetuximab which target the epidermal growth factor receptor did not benefit patients with metastatic CRC if they have mutant K-ras in their malignancies.⁴ Thus, the future precision medical care delivery requires knowledge of the

Contact information of authors: **Adeyinka O. Laiyemo, MD, MPH, FACP**. Division of Gastroenterology, Department of Medicine, Howard University College of Medicine, 2041 Georgia Avenue, NW, Washington DC 20060. Phone: (202) 865 – 7186; Fax: (202) 865 – 4607; adeyinka.laiyemo@howard.edu

Maria T. Abreu, M.D. Chief, Division of Gastroenterology, Martin Kalser Chair in Gastroenterology, Professor of Medicine and Professor of Microbiology and Immunology, Director, Crohn's & Colitis Center, Department of Medicine, University of Miami, FL, Academic office (305) 243-6404; Fax (305) 243-6125; Mabreu1@med.miami.edu

Conflict of interest: None.

biological risk of the individual. Evaluating the risk of diseases using information based on genetic susceptibilities is an example of such a process.

Unfortunately, the genetic basis of diseases has not been well-studied among African Americans. This may be related to less participation of African American patients in biomedical research, lack of minority investigators to reach out in a culturally acceptable manner to African Americans, or lack of optimal access to cutting edge technology among institutions that serve African Americans.⁵ Tehranifar et al⁶ reported that, as invasive cancers become more amenable to treatment, disparities widen for African Americans. This suggests that improvement in medical practice leads to further widening of disparities because underserved populations are less likely to have early access to the technological advancement. Therefore, studies evaluating the genetic basis of diseases among African Americans are needed to improve our understanding of biological susceptibility to chronic diseases among African Americans in preparation for precision medicine. In this issue of *Gastroenterology*, 2 articles improve our understanding of the genetic basis of inflammatory bowel disease (IBD)⁷ and mutation spectrum and risk of CRC associated with the Lynch syndrome⁸ among African Americans.

IBD is common and a lot has been learned about the genetics of IBD in patients of European descent.⁹ On the basis of a metaanalysis of ImmunoChip data, 163 distinct loci have been replicated as contributing susceptibility to IBD. These studies have provided fertile ground to pursue novel pathogenetic pathways. For example, the Jostins et al⁹ study used a systems biology approach and found that patients with IBD had polymorphisms in the pathways related to control of mycobacterial infections. Unfortunately, very few studies have explored IBD genetic risk in non-Caucasian populations. Studying non-Caucasians may identify new pathways, especially those involved in pathogen recognition, that are associated with IBD. It may also confirm whether a particular single nucleotide polymorphism (SNP) truly lies in the gene that is contributing to IBD pathogenesis or is merely “nearby.”

In the first article, Huang et al⁷ characterized the genetic loci that affect susceptibility to IBD among African Americans. The investigators should be commended at the collaborative effort of almost 30 institutions to study 1,511 African Americans with IBD (1,088 with Crohn's disease, 361 with ulcerative colitis, and 62 with IBD type-unknown). Importantly, the investigators also included 1,797 African American controls so that they could account for differences that are attributable to baseline genetic variation. In particular, African Americans represent a classic admixed population that is approximately 80% from West Africa and 20% European—although the degree of admixture varies across the country; thus, a large, well-matched control group was essential for this study. The investigators used a powerful technique termed “admixture linkage disequilibrium” to take into account differences in allele frequencies of potentially causal variants between populations. Association and admixture loci were mapped primarily by replicating previously known associations using the Immunochip, which evaluates previously established IBD-related loci. A total of 130,241 autosomal SNPs were analyzed for these subjects. Of the 163 susceptibility loci that have been identified among Caucasians, 152 passed quality control for this study. The authors found that the associations related to these 152 SNPs were comparable with those reported among Caucasians and that the relationship in allelic

frequency (ie, higher or lower compared with the baseline population) was similar to Caucasians. Five important SNPs were replicated using their criteria for replication ($P < .05/163$; ie, $P < 3.1^{-4}$). The authors confirmed that in African Americans NOD2 polymorphisms were present as were polymorphisms in the IL-23 receptor pathway. Other polymorphisms that were significantly different in African American patients with IBD compared with African American controls and similar to Caucasians with IBD included polymorphisms in a receptor for immunoglobulin (Ig)G involved in autoimmune diseases (the Fc fragment of IgG, low-affinity Ila, receptor [CD32] FCGR2A gene), a SNP in a gene desert that regulates expression of the prostaglandin receptor EP4, *PTGER4*, gene (<http://dx.doi.org/10.1371/journal.pgen.0030058>) and a SNP near IKZF3, a gene that encodes a member of the Ikaros family of hematopoietic-specific transcription factors. The potential function of these genes in IBD pathogenesis has not been established. In addition, they also reported that 2 of the replicated loci (5p13.1 and IL23R) had additional SNPs with suggestive association with Crohn's disease and should be examined in future studies in African Americans. In general, the European ancestry increased the risk of IBD whereas the West African ancestry protected against IBD.

However, there were some notable differences in infectious disease pathways between African Americans and Caucasians. Using KEGG pathway mapping to analyze the genome-wide association studies data, the top 3 pathways found in African Americans that are altered in IBD were cytokines, Jak-STAT signaling, and chemokines. Whereas Caucasians had polymorphisms in pathways involved in control of *Leishmania* infection, the African American patients harbored polymorphisms in the measles pathway and the African trypanosomiasis pathway. These were not observed in Caucasians. These findings highlight the hope of studying other non-European populations because they identify other potential triggers that underpin development of IBD. Overall, the study by Huang et al⁷ lends credence to the model that genetic susceptibility in IBD reflects the interaction, and likely protection, of the host against pathogens. It also demonstrates the not-unexpected finding that African Americans share similar major pathways as Caucasians, but have subtle other differences that may eventually demonstrate differences in response to medications or identify specific targets that can be used in this patient population.¹⁰ Not only do these studies permit the future deployment of targeted therapies based on genotype, they edify pathogenetic microbial pathways that are extant in these complex immunologic diseases.

It is well-known that African Americans suffer the highest burden from CRC of all race-ethnicities in the United States.¹¹ However, familial risk of CRC has not been well-studied among African Americans. In the second article, Guindalini et al⁸ characterized the mutation spectrum and CRC risk among 51 African American families with the Lynch syndrome. The authors reported that among African Americans, the predominant phenotype was MLH1 (61%) followed by MSH2 (21%), whereas among Caucasians with the Lynch syndrome in the literature, the predominant phenotype is MSH2 followed by MLH1.¹² Of note, in academic institutions and the Colon Cancer Family Registry, from where the 51 African American families in this study were identified, MLH1 mutation phenotype was 29.5% among Caucasians. The authors also found 11 mutations that have not been previously reported. Among probands, CRC was diagnosed among 42 (82%) with predominance of proximal cancers and Lynch syndrome-related cancers were diagnosed among 16 (31%).

Among the included 920 members of the African American families with the Lynch syndrome, 123 (13.4%) were diagnosed with CRC. The estimated risk of CRC at age 80 years was 36% for males and 30% for females. If confirmed in larger studies, the predominance of mutations in MLH1 among African Americans with the Lynch syndrome raises the possibility of developing cost-effective targeted panel that may be used in low-resource settings.

There are notable limitations of these 2 studies. Although they are the largest on their respective topics among African Americans to date, it is noteworthy that they are both limited by sample size. This precluded genome-wide association analysis in the study by Huang et al⁷ and only 51 African American families were included in the study by Guindalini et al.⁸ There was also a significant amount of missing data including colon cancer screening and surveillance practice information. Furthermore, Huang et al⁷ used the Immunochip. The bias of using this strategy is that unique African genetic pathways may be missed because the chip is based on European–Caucasian populations. In chip-based studies, the tagging SNPs may not represent the causal variant. In the Huang study, polymorphisms in STAT5A/STAT3 were found in African Americans, but the risk is conferred by the Caucasian genetic contribution. As a result of this observation in African Americans, it makes it very likely that these are causal variants in Caucasians and African Americans. Thus, studying the genetics of African Americans not only is helpful in African Americans, but more broadly. Chip-based strategies will need to be updated to incorporate the latest discoveries and improved inclusion of genetic variation found in non-Caucasian populations.¹³

Nonetheless, these 2 studies focus on important hereditary gastrointestinal diseases with substantial health care burden. They demonstrate the need to understand the biologic basis of susceptibility of hereditary diseases among African Americans and other minority groups. Figure 1 shows the conceptual framework of interventions to improve patient outcomes among African Americans from hereditary diseases. It is apparent that both studies were conducted among institutions, registries, and consortia that serve few African Americans. Thus, this raises a possibility that the included African Americans may not truly represent the overall African American population in the United States. It is well-established that the majority of African Americans receive their care in minority serving institutions and these are not well-represented among the collaborating institutions for these studies. Ideally, investments should be directed at providing the resources to minority serving institutions so that a more representative group of African Americans can be included in registries and consortia. This will go a long way toward reducing health care disparities and getting minorities participating in precision medicine. There is also a need for public education and outreach to African Americans to improve health literacy and promote family discussions about disease susceptibility. In particular, culturally sensitive education about the value of genetic testing and clinical trials must occur to guide therapy and research in minority populations, especially African Americans. The interaction between health care providers and the community can foster meaningful engagement and can lead to the development of meaningful, targeted interventions that will be acceptable and easily adopted by the underserved populations.

Despite their limitations, these studies by Huang et al⁷ and Guindalini et al⁸ are very important, because they increase our understanding that major genetic susceptibility to gastrointestinal diseases in African Americans is similar but not the same as it is in Caucasians. Differences in patient outcomes may be related to the gene–environment interplay and is likely to be distinct in minority populations. To achieve the goal of precision medicine, we must include and understand all of our patients at genetic, environmental, and cultural levels so that we improve patient outcomes.

Acknowledgments

Grant support: Dr Laiyemo is supported by grant awards from the National Center for Advancing Translational Science, (Grant: KL2TR000102-04 and UL1RT000101), from the National Institute for Diabetes, Digestive Diseases and Kidney (Grant: R21DK100875), National Institutes of Health and from Charles and Mary Latham Funds.

Dr Abreu is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (2R01DK099076-07A1), the Crohn's and Colitis Foundation of America (Senior Research Award #3786), Broad Medical Foundation – CCFA (IBD-0389) and Department of Defense – US Army (PR121364). Additional funding was provided by The Micky & Madeleine Arison Family Foundation Crohn's & Colitis Discovery Laboratory.

References

1. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009 Oct 8; 461(7265):798–801. [PubMed: 19759533]
2. Carethers JM, Smith EJ, Behling CA, et al. Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. *Gastroenterology*. 2004 Feb; 126(2):394–401. [PubMed: 14762775]
3. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med*. 2003 Jul 17; 349(3):247–57. [PubMed: 12867608]
4. Siena S, Sartore-Bianchi A, Di Nicolantonio F, et al. Biomarkers predicting clinical outcome of epidermal growth factor receptor-targeted therapy in metastatic colorectal cancer. *J Natl Cancer Inst*. 2009 Oct 7; 101(19):1308–24. [PubMed: 19738166]
5. Laiyemo AO. In search of a perfect solution to ensure that “no colon is left behind”. *Dig Dis Sci*. 2012 Feb; 57(2):263–5. [PubMed: 22183821]
6. Tehranifar P, Neugut AI, Phelan JC, et al. Medical advances and racial/ethnic disparities in cancer survival. *Cancer Epidemiol Biomarkers Prev*. 2009 Oct; 18(10):2701–8. [PubMed: 19789367]
7. Huang C, Haritunians C, Okou DT, et al. Characterization of Genetic Loci That Affect Susceptibility to Inflammatory Bowel Diseases in African Americans. *Gastroenterology*. 2015 xxxx.
8. Guindalini RS, Win AK, Gulden C, et al. Mutation spectrum and risk of colorectal cancer in African American families with Lynch Syndrome. *Gastroenterology*. 2015 xxxx.
9. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012 Nov 1; 491(7422):119–24. [PubMed: 23128233]
10. Yamazaki K, Umeno J, Takahashi A, et al. A genome-wide association study identifies susceptibility Loci for Crohn's disease in a Japanese population. *Gastroenterology*. 2013 Apr; 144(4):781–8. [PubMed: 23266558]
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015 Jan-Feb;65(1):5–29. [PubMed: 25559415]
12. Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. *Gastroenterology*. 2009 Nov; 137(5):1621–7. [PubMed: 19622357]

13. Parkes M, Cortes A, van Heel DA, et al. Genetic insights into common pathways and complex relationships among immune-mediated diseases. *Nat Rev Genet.* 2013 Sep; 14(9):661–73. [PubMed: 23917628]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1. Proposed interventions to improve patient outcomes in familial diseases among African Americans