

Spotlight

Ethnicity-Influenced
Microbiota: A Future
Healthcare Perspective

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Global research is focused on understanding the factors affecting human gut microbiota vis-à-vis health. Brooks *et al.* [*PLoS Biol.* (2018) 16, e2006842] has reported a group of microbial taxa that vary across ethnicity in the USA (AGP and HMP data sets). Ethnicity-specific microbial signatures will aid in developing therapeutics for targeted microbiota modulation.

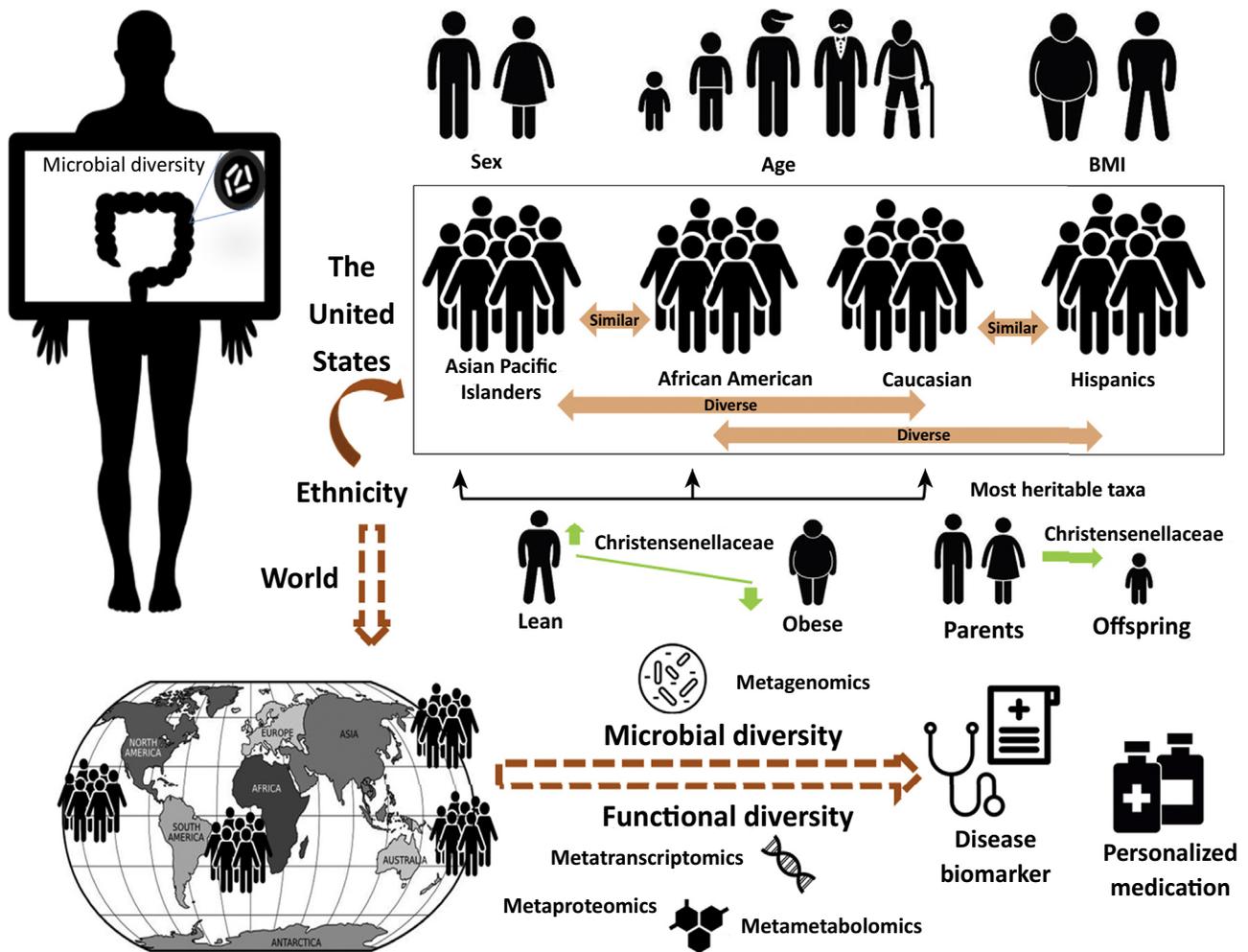
Microbes have coevolved with their hosts over millions of years of adaptation in changing environments. The human gut microbiota, comprising around 1000 species, has been a focus of this century due to its influence on host physiology and health. Knowledge of the integral association of the microbiota with the host, and its role in health and disease, has been expanding rapidly in this decade. Understanding the factors that affect the composition of the gut microbiota, as well as the functions of the gut microbial ecosystem, is crucial to the development of any therapeutic approach for targeted modulation. Global research on the gut microbiota indicates dominant roles for diet, lifestyle, genetics, and geography in determining the microbial composition of the gut. As human ethnic groups are formed by migration, isolation, and adaptation over a long period of time – and as individuals of a given ethnic group share such factors in a relatively homogeneous manner – it follows that a consideration of ethnicity would be ideal to draw a baseline on the composition of the healthy gut

microbiota in order to define a dysbiotic state associated with disease.

Brooks *et al.* [1] have recently reported a group of gut bacteria that reproducibly vary across four ethnicities – Asian Pacific Islanders, Caucasians, African Americans, and Hispanics – in the USA. 16S rDNA-based microbiome data sets of 1673 individuals from the American Gut Project (AGP) and the Human Microbiome Project (HMP) belonging to the four ethnic groups were analyzed using multiple statistical tools to detect probable links between the composition of their microbiota and various factors, including ethnicity, sex, age, and body mass index (BMI) (Figure 1). Though there was a data set-specific disparity in microbial diversity, the microbiota was subtly demarcated by ethnicity among the factors in both the data sets. Among the ethnic groups, both microbial richness and evenness were highest in Hispanics, followed by Caucasians and Asian Pacific Islanders in both study groups. Lower beta diversity between individuals of the same ethnicity (intraethnic) than between ethnicity (interethnic) in both data sets indicated the influence of ethnicity on the composition of the gut microbiota. Hispanics had the lowest intraethnic beta diversity as they shared the most common operational taxonomic units (OTUs) or microbial taxa across individuals, indicating bacterial stability in Hispanics (though low abundance but high ubiquity). The authors have also reported that among the ethnic groups, Asian Pacific Islanders and Caucasians had a major effect on gut microbial distinguishability. Pairwise combination of beta diversity metrics showed strong distinguishability between (i) African Americans and Hispanics, and (ii) Asian Pacific Islanders and Caucasians.

A significant finding in this study was the abundance of 12 bacterial taxa under

(i) the genera *Veillonella*, *Odoribacter*, and unclassified Coriobacteriaceae, and (ii) the families Peptococcaceae, Dehalobacteriaceae, Christensenellaceae, Verrucomicrobiaceae, Victivallaceae, Odoribacteriaceae, Rikenellaceae, and unclassified Clostridiales and RF39 that recurrently varied among the ethnic groups. A majority of these taxa have previously been shown to be heritable, and out of the 12 taxa, a co-occurring group of 11 taxa were earlier reported to be members of the ‘Christensenellaceae Consortium’ associated with genetic variations in the human formate oxidation gene and aldehyde dehydrogenase 1 family member 1 (*ALDH1L1*), known to be a genetic risk factor for stroke [2]. The family Odoribacteriaceae and the genus *Odoribacter* were significantly less abundant in Asian Pacific Islanders compared to Caucasians and Hispanics in both data sets. The family Odoribacteriaceae is known to be the primary butyrate producer in the gut; members of this family are reduced during ulcerative colitis and Crohn’s disease [3,4]. The severity of ulcerative colitis upon hospital admission has previously been shown to be significantly higher in Asian Americans [5]. Interestingly, the authors in this study have reported ethnicity-dependent abundance of the family Christensenellaceae; this was previously found to be a highly heritable taxon associated with human genetic variations [6]. As reported earlier [7], an association of Christensenellaceae with lower BMI was also observed in this study across the ethnic groups, except Hispanics. In Asian Americans, mortality due to gastrointestinal cancer is more than that due to heart disease. It has been hypothesized that, as over 70% of Asian Americans were born overseas and adopted a Western lifestyle after immigration, a shift in the traditionally harbored microbiota could be the cause of the increase in gastrointestinal and colon cancer [8].



Trends in Microbiology

Figure 1. Schematic Representation of the Study by Brooks *et al.* [1] and Its Future Perspectives. 16S rDNA-based microbiome data sets from the American Gut Project (AGP) and the Human Microbiome Project (HMP) belonging to four ethnic groups in the USA – Asian Pacific Islanders, Caucasians, African Americans and Hispanics – were analyzed using multiple statistical tools to detect probable links between the composition of the microbiota and various factors, including ethnicity, sex, age, and body mass index (BMI). A group of bacteria associated with ethnicity were identified, including the heritable family Christensenellaceae, known to have a link with BMI. The results warrant further research involving metatranscriptomics, metaproteomics, and metametabolomics on functional redundancy of ethnicity-influenced gut microbiota for development of personalized medication.

In a previous study with six ethnic groups (Dutch, Ghanaians, Moroccans, Turks, African Surinamese, and South Asian Surinamese) in The Netherlands, ethnicity was found to be the determining factor in the composition of the gut microbiota [9]. Another study on 15 ethnic groups from four geographies in India indicated a cumulative effect of ethnicity and geography on gut microbiota [10]. However, the study failed to differentiate the roles of

ethnicity and geography, which could be due to the small sample size.

The study by Brooks *et al.* [1] has substantially added to our knowledge of the influence of ethnicity on gut microbiota. Acknowledging the enormous global diversity of ethnicities, this study urges examination of the gut microbiota of worldwide ethnicities for the 12 bacterial taxa and their co-occurring groups, and/

or other ethnicity-specific signatures, as well as their links with health disparities. Furthermore, such metagenomic DNA-based bacterial diversity studies may not reflect the true nature of microbial interactions in the gut ecological landscape. Future research should also address the functional redundancy of the gut microbiota to see how the abundance of these ethnicity-influenced bacterial taxa relates to gut ecological

functions. Such studies should necessarily integrate data of metatranscriptomics, metaproteomics, and metametabolomics to understand functional redundancy in the gut microbiota of various ethnicities. Nevertheless, functionalities should also include studies on stability, resistance, and resilience under perturbations, such as those associated with lifestyle changes in the era of global migrations and assimilations. Finally, a global database on ethnicity-specific gut microbiota and health disparities will pave the way towards developing personalized medication for targeted modulation.

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References

- Brooks, A.W. *et al.* (2018) Gut microbiota diversity across ethnicities in the United States. *PLoS Biol.* 16, e2006842
- Williams, D.R. *et al.* (2016) Understanding associations among race, socioeconomic status, and health: patterns and prospects. *Health Psychol.* 35, 407–411
- Morgan, X.C. *et al.* (2012) Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol.* 13, R79
- Goker, M. *et al.* (2011) Complete genome sequence of *Odoribacter splanchnicus* type strain (1651/6). *Stand Genomic Sci.* 4, 200–209
- Castaneda, G. *et al.* (2017) Race/ethnicity-specific disparities in the severity of disease at presentation in adults with ulcerative colitis: a cross-sectional study. *Dig. Dis. Sci.* 62, 2876–2881
- Goodrich, J.K. *et al.* (2014) Human genetics shape the gut microbiome. *Cell* 159, 789–799
- Fu, J. *et al.* (2015) The gut microbiome contributes to a substantial proportion of the variation in blood lipids. *Cir. Res.* 117, 817–824
- Pourhoseingholi, M.A. *et al.* (2015) Burden of gastrointestinal cancer in Asia; an overview. *Gastroenterol. Hepatol. Bed Bench* 8, 19–27
- Deschasaux, M. *et al.* (2018) Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography. *Nat. Med.* 24, 1526–1531
- Dehingia, M. *et al.* (2015) Gut bacterial diversity of the tribes of India and comparison with the worldwide data. *Sci. Rep.* 5, 18563

Forum

An Evolutionary Perspective on Ethylene Sensing in Microorganisms

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Ethylene is a gas and a plant hormone with wide ranging effects and a well defined signaling pathway. The recent identification of ethylene receptors in various microorganisms provides new insights into the early propagation of the ethylene signaling pathway in the course of evolution.

The Roles of Ethylene: In a Historical Way, a Plant Story

Ethylene is a gas naturally produced by plants, algae, fungi, and bacteria [1]. The role of ethylene was first documented in plants where it acts primarily as a hormone that regulates many aspects of development such as seed germination, leaf senescence, and fruit ripening. It also orchestrates plant defenses against microorganisms and animals, the establishment of symbiosis, and responses to abiotic stresses such as high salt, drought, flooding, and pollutants. The effects of ethylene on nonplant species is less studied, and the data on this issue remain more fragmentary [2].

Ethylene Signaling in Plants and *Synechocystis*

Ethylene is produced by many microbes and is also abiotically generated from incomplete combustion and from light interacting with dissolved organics [1]. Thus, it is likely that ethylene was broadly present on ancient earth, leading to the idea that this simple gas was co-opted as a signaling molecule by

early organisms. However, most studies on ethylene signaling focus on plants, and the first ethylene receptor (ETR) was discovered in the model plant *Arabidopsis thaliana* [3]. ETRs of higher plants are related to the histidine kinase superfamily (Figure 1A). Histidine kinases are relatively rare in eukaryotes, and autophosphorylation of plant ETRs and phosphotransfer to other effectors are not critical for ethylene signaling. Upon binding to the dimerized ETR, ethylene negatively regulates a cell signaling pathway involving downstream mediators, including the raf-like protein kinase constitutive triple response 1 (CTR1), the endoplasmic reticulum-localized protein ethylene-insensitive 2 (EIN2), and the EIN3 and EIN3-like (EIL) transcription factors [4]. This land plant-type ethylene signaling pathway likely occurs in the green lineage from unicellular algae since ETR homologs are detected in some chlorophyte genomes (e.g., *Coelastrella* and *Coccomyxa* sp.).

It has long been supposed that the above-described canonical ETR-mediated signaling pathways were restricted to terrestrial plants [5], although a putative ETR, slr1212, was identified almost 20 years ago in the cyanobacterium *Synechocystis* sp. [6]. This led to the idea that plants acquired ETRs from the cyanobacterium that gave rise to chloroplasts and subsequent gene transfer to the host cell. However, it was only recently that this protein was shown to be a bona fide ETR, as well as photoreceptor, that governs various processes underlying cell motility [7,8] (Figure 1B).

From a structural point of view, it is important to highlight that ethylene sensing through ETRs occurs by the interaction of the gaseous molecule with the ethylene-binding domain (EtBD) located at the N terminus of