

Indian human microbiome initiative: Indian-ness through the magnifying glass

The quest for the molecular basis of genetic inheritance began with Griffith's experiments in 1928, and by 1944 it was unequivocally established that DNA is the molecule which carries the genetic information. The initial techniques for DNA sequencing developed by Maxam, Gilbert and Sanger were revolutionary and yielded useful information. However, these were not suitable to obtain whole genome sequences. The sequence of its DNA is the key to understanding the genetic make-up of an organism. Touted famously therefore as the first step towards understanding ourselves, the complete sequencing of the human genome was announced about 15 years ago. Completion of the human genome project was indeed a significant achievement in understanding human biology and disease – the effort often being compared to the first successful mission of sending man to the moon, or achieving the first nuclear fission reaction. However, it was rightly pointed out then that without understanding the synergy between humans and their surrounding living world, mostly microbes, this effort would remain incomplete.

The human body is host to a rich and diverse microbial community, which is predominantly bacterial and referred to as the 'Human Microbiome'. Body parts which show a rich diversity of microbial species include, gut, oral cavity, skin and vagina. According to current estimates, a typical adult human is composed of $\sim 10^{13}$ cells, whereas the human body is inhabited by $\sim 10^{13}$ – 10^{14} microbial cells. Moreover, the number of genes contributed by the commensal microbial community is more than 300 times contributed by human genes. The resident commensal microbial community on these body parts influences almost every aspect of human life that includes development, physiology, nutrition, behaviour and even lifespan. The evolutionary selection on interactions between humans and the symbiotic bacteria has therefore been such that any imbalance in the population of these microbial species is detrimental to human health.

There is an increasing body of evidence that shows association between dysbiosis of gut microbiota and diseases such as diabetes, atherosclerosis, obesity, intestinal and even psychological disorders. Recognizing the importance of human microbiome in human health, many consortia have been formed around the world, such as the

'The Human Microbiome Project' (HMP), which was pioneered by the United States National Institutes of Health (NIH) in 2007 (<https://commonfund.nih.gov/hmp/index>) and Metagenome of Human Intestinal Tract (MetaHIT), a project financed by the European Commission (<http://www.metahit.eu>). These mega projects are very large collaborative efforts among life scientists, reminiscent of the mega collaborative projects among physicists. These collaborations have led to the creation of reference databases and are beginning to define the boundaries of normal microbiome variation in humans. More recently, several other countries have followed suit and initiated projects, e.g. Australian Gut Project, American Gut Project, British Gut Project, Initiative in Skin and Oral Microbiome (iMicroCare, China), Canadian Microbiome Initiative, Human MetaGenome Consortium Japan (HMGJ), EU-funded MyNewGut Project, and International Human Microbiome Consortia (IHMC, 12 countries). In USA alone, large amount of resources are being spent by the federal government on microbiome research. Considering the potential of health benefits of microbiome-based therapies, recently a National Microbiome Initiative (NMI) with the commitment of US\$ 121 million has been launched with the involvement of various federal agencies like NIH, Department of Energy, NASA, National Science Foundation and the US Department of Agriculture. Moreover, many charitable and private organizations such as the Bill and Melinda Gates Foundation, One Codex, etc. have committed to invest generously in human microbiome research in the next five years. Thus, a deeper understanding of human–microbe interactions and their relationship to various diseases appears to be entering an exciting era.

Interestingly, considering the immense potential of microbiome research on human health, the area has seen a shift from that of pure academic pursuit to the one where many start-ups are being founded upon. Moreover, many leading pharmaceutical companies have invested in the potential medical applications of microbiome research. The total investment by the top 25 entrepreneurial ventures within countries like the US, France, Belgium, UK, The Netherlands, and Japan crosses billion US dollars. The recent acquisition of Vedanta, a Boston-based start-up by Janssen Biotech, a Johnson & Johnson

company, for US\$ 241 million, is an indication of the commercial potential of this area.

Recent trends in microbiome research indicate a move towards the development of microbial consortia and applications in the affected individuals, which would be potent in terms of modifying diseases or symptoms. Once considered to be 'last resort therapy' by medical professionals due to its unusual nature and invasiveness compared with antibiotics, fecal transplant therapy (also termed as 'bacteriotherapy') is now being explored for the treatment of *Clostridium difficile* infection. Additionally, orally administered mixture of bacterial spores has been successful to mimic a healthy gut community for bacterial vaginosis and recurrent urinary tract infections. For cardiovascular diseases, the focus appears to be on designing small-molecule inhibitor of bacterial trimethylamine synthesis without any bioavailability. Additionally, for gastrointestinal disorders, searches are being carried out for designing small-molecule antagonist against bacterial adhesion. Thus, interventions targeted towards the microbiome, and not the host cells, are attracting attention for future therapies.

With this backdrop, we would like to argue that the time is ripe for initiating large-scale microbiome studies on the Indian population which harbours tremendous genetic and cultural diversity. It consists of ~6000 communities and an estimated ~40,000 endogamous groups. Most of the modern populations around the world have mixed genetic make-up due to migrations and genetic admixture, contrary to the Indian communities, which appear to have remained largely endogamous due to cultural reasons. The high genetic diversity in Indians presents a challenge for defining a core microbiome, but at the same time uniqueness of the population may provide answers to many interesting questions. For example, the co-evolution of microbial communities with human host is driven by the diet, which in turn is influenced by geographical conditions. India has a combination of both, and this has resulted in enormous dietary diversity. The diet varies based on geographical region, ethnicity, socio-economic status and even season. This diversity is not seen anywhere else in the world. Moreover, India is host to a large number of autochthonous tribal populations that are largely unaffected by the 'modern' diet and lifestyle, and would probably reflect 'virgin' gut microbial communities. India is also known for the use of spices, and some recent reports indicate definitive role for the spices in shaping gut microbial communities and in turn host physiology. Thus, there is uniqueness in the Indian population and possibly the microbiome that it hosts, which is in need of exploration.

Emerging epidemiological evidence suggests that there is increasing incidence of a variety of lifestyle-associated disorders in the Indian population. These include Inflammatory bowel disease, irritable bowel syndrome, coronary heart disease, diabetes, celiac disease and many more. This rise is concomitant with the adoption of a 'Western' lifestyle that includes consumption of junk

food, change in social habits, indiscriminate use of antibiotics, or even increased caesarian deliveries against vaginal ones. All the lifestyle-associated disorders are likely to be significantly influenced by the host microbiome. Thus, taken together, the Indian population is an ideal cohort to answer many interesting questions on host-microbiome interactions. Yet, till date there have been few studies on gut microbiome of the Indian population.

Considering these unique features of the Indian population and potential health benefits that are likely to be offered by microbiome research, there is a need to undertake a nationwide study with robust sampling design accounting for genetic, cultural and biogeographic diversity. Nationwide study on human microbiome is a challenging task, especially considering the tremendous variation in the Indian population. Arriving at a 'representative' and statistically significant sample size could be a daunting task. Also, accessing the tribal areas and educating the tribals to participate in such studies is another problem that needs to be resolved. Despite these challenges, initiation of the Indian microbiome project is an urgent need for the potential benefits that it offers to the healthcare system.

The rewards of microbiome research in India would exceed by many orders of magnitude the expenses incurred on such a project. According to the Global Report on Urban Health released by the World Health Organization (WHO), the healthcare expenditure in India in 2015 was US\$ 61.86 billion. The UN analysis indicates that heart ailments, cancer, diabetes and other lifestyle-associated diseases will cost India US\$ 6.2 trillion by 2030, which is almost thrice the current GDP (US\$ 2.2 trillion, nominal). The regimens for personalized medicine and preventive health based on the outcomes of the proposed initiative are expected to lower the incidence of lifestyle-associated disorders, thus improving the health of the population and lowering the burden on the Indian economy. There is sufficient evidence to suggest that genetic as well as microbial composition of the Indian population is distinct, and hence the results from other populations may not be applicable to Indians. A project of such dimensions requires multi-disciplinary expertise and strong financial support. The outcome of the project has far reaching implications in different areas like basic sciences, health, pharmaceuticals, and even commerce and industry. Considering this, a separate funding mechanism can be devised to support such an effort. This needs to be done at the earliest, given the rate of migration and change in food habits and other lifestyle factors in India. Otherwise, it will be yet another opportunity lost.

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