Published in final edited form as:

Trends Microbiol. 2012 January ; 20(1): 1–4. doi:10.1016/j.tim.2011.10.004.

The Human Microbiome Project: lessons from human genomics

Cecil M. Lewis Jr., Alexandra Obregón-Tito, Raul Y. Tito, Morris W. Foster, and Paul G. Spicer

Department of Anthropology, University of Oklahoma, Norman, Oklahoma, USA

Abstract

The Human Microbiome Project (HMP) is following in the footsteps of the Human Genome Project (HGP), which will include exciting discoveries, but also potential disappointment and resentment over the lack of medical applications. There is a wiser path for the HMP. This path includes a greater attention to rare variation, an early commitment to an ethical inclusion of indigenous communities, and a recruitment strategy in which medical benefits are de-emphasized.

The accomplishments of the HGP include advances in technology, basic science and ethics; however, at the time of the completion of the first draft of the human genome a major source of optimism was the anticipation of a revolution in medicine [1]. Although statistical associations between genes and disease dominate high-impact academic journals, these associations have resulted in few practical applications [2], raising the question of whether the HGP legacy will fail to produce anticipated medical benefits as quickly or directly as had been anticipated by project leaders.

The HMP [3] may share a similar trajectory. The HMP includes National Institutes of Health (NIH) initiatives that aim to characterize the microbial communities typical of human body sites. HMP initiatives include the development of scientific tools and repositories and exploration of ethical, legal and social implications. Similar to the HGP, the HMP is providing intriguing health-related associations. But HGP has taught us that the discovery of associations very rarely translates to direct interventions.

Green and Guyer [2] reviewed the accomplishments of the HGP and provided a schematic of the progress of genomic medicine. They hypothesized that significant improvements in the effectiveness of healthcare will begin sometime after 2020. In Figure 1 we adapt this concept for the HMP. As with the HGP, the HMP will impact upon basic biological science and technology. Even so, with respect to genomic medicine the HMP is still at an initial stage, largely focused on the discovery of disease associations. The degree to which these associations result in practical applications will depend on how the HMP handles challenges that are analogous to those faced by human genomics.

One challenge for the HMP is the magnitude of the need for genomic sequencing infrastructure. Innovative genome-sequencing technologies provided the groundwork for metagenomics, but further advances will be necessary considering that the size of a human microbiome dwarfs a human genome. A gut microbiome can harbor over 100 times the number of protein-coding genes that a human genome has [3]. Generation of these enormous datasets is possible, but the infrastructure to store and access these data is insufficient.

Managing DNA sequence data is only one part of the challenge. There is unlikely to be momentum in medical applications while there are still many gaps in our understanding of human microbial ecologies. A better integration with other ‘omic’ sciences (proteomic, metabolomic, and others) will be needed for higher-resolution assessments of functional potential. Moreover, individual microbes within these ecologies may have a disproportionate impact upon function and health, but for microbiomes such as the human gut roughly 80% of the phylotypes represent uncultured bacteria [4]. Consequently, microbiomes represent a collection of organisms that we know very little about individually. Greater attention to isolating and culturing of individual microbes is warranted.

Determining how the microbiome diversity influences disease will be more challenging if rare variants within the ecology have a large functional impact. A classic topic in genetics and medicine is the common disease–common variant (CD–CV) hypothesis [5], which attributes complex diseases to the additive effects of common alleles. If true, this facilitates the discovery of broadly applicable interventions. Generating data for common variants is easier than for rare variants. Moreover, common variation is less ethically challenging because it is unlikely to single out individuals or communities. If CD–CV is false, interventions will need to be highly individualized and will have the potential to be more stigmatizing.

After hundreds of genome-wide association studies (GWAS) it appears that characterizing common variations is insufficient for an understanding of most complex diseases. In part, this can be attributed to the challenge of understanding gene–gene and gene–environment interactions. More worrisome is the hypothesis that the current GWAS produce ‘synthetic associations’ that are attributed to rare variants [6]; if true, then GWAS studies may never contribute significantly to medicine.

The HMP could face an analogous challenge with rare variants. Figure 2 provides three distinct concepts of rare disease variants in human genetics that may have human microbiome analogs. The HMP focuses on core variations shared by most humans; early studies suggest that there are three common species-driven gut enterotypes that are neither continent- nor nation-specific [7]. Enterotype distributions are similar to the general distribution of human genetic variation: an allele common to one population is typically common worldwide. For human genetics, this is attributed to the sequential series of founder effects of our species [8]; for enterotypes, the mechanism is unclear. Because enterotypes provide a broad view of microbiome diversity, they are unlikely to provide a useful scale of analysis for predicting disease risk.

Future HMP research may be challenged by an ascertainment bias similar to that faced by human genetic studies [9]. The first extensive sampling within dbGaP [10], accession phv00158794, is dominated by Euro-Americans (~80%) living in Houston, Texas and St. Louis, Missouri. Speculatively, if a microbiome-related predisposition for disease is more common to one community or ethnic group than others, then the science may be much more prepared to develop interventions with Euro-Americans of middle to upper socio-economic status than with others.

The HMP supports a wide range of demonstration projects that may help to reduce sample bias, but if we consider the HMP as an analog to the HGP, we should emphasize exploration of the range of human diversity in early program initiatives. During the HGP, population-based studies became crucial, leading to projects such as HapMap (www.hapmap.org). Microbiomes may harbor even more rare and localized variants than human genes because microbiome variation is a complex product of biological processes, environmental factors and socio-cultural practices.

The study of indigenous populations can provide insights into human behaviors that define human microbiome variation, such as non-industrialized subsistence and the functional potential of microbiomes before the potentially damaging effects of antibiotics [11]. Human microbiomes from countries harboring traditional communities can be more diverse than those from countries strictly harboring cosmopolitan communities. As noted by Filippo and associates in their study of European and rural African gut microbiomes: 'Reduction in microbial richness is possibly one of the undesirable effects of globalization and of eating generic, nutrient-rich, uncontaminated foods' [12].

The early inclusion of indigenous communities and an emphasis on rare variants will expose the HMP to more challenging and immediate ethical issues. It has already been demonstrated that skin microbiomes can be individualized and are applicable in forensics [13]. The move toward rare variation might further single out individuals and pose greater risks for members of vulnerable communities. Fortunately, many of the established procedures for protecting participants, including historically disadvantaged communities [14], apply here as well.

But perhaps the most important consideration is how the HMP is promoted, particularly to vulnerable populations who may have high hopes for therapeutic benefits. The HGP provided a difficult lesson to learn in this area. As a result, our approach to engaging indigenous communities in the HMP is guided by our suspicion of a lack of direct clinical benefit in the foreseeable future. Instead, we emphasize building relationships through an 'ethics of care' framework [15]. The ethics of care focuses attention on the relationship between researchers and vulnerable communities, where questions of the sincerity of concern about their predicaments are often fundamental.

Even when there is no direct prospect of therapeutic benefit, the HMP can support ancillary (infrastructure) outcomes designed to benefit research participants. For low-risk research, the provision of education-related materials, health and science fairs, or additional investment in the community through employment are among the strategies that can allow researchers to leave vulnerable communities in a better state than when they were initially engaged. Clinical improvements are, of course, an important part of any research setting. Although researchers alone cannot build a healthcare system, screening, brief intervention, and referral can be provided in the context of most studies, as can work with local healthcare authorities to develop approaches to indicated health problems, even if they are not related directly to the HMP. Equally important in this framework is attention to the possibility of commercial exploitation, which can also undermine the dynamics of trust in research relationships with underserved communities.

In the final analysis, the HGP has taught us that greater attention to rare variations and early commitment to ethical inclusion of indigenous communities are important objectives in genomic medicine. A decade of experience with the HGP should emphasize to all of us that momentum in medical advances is likely to be slow. Thus, the mutual benefits of research are much better discussed in terms of ancillary outcomes rather than the more remote prospect of medical advances. Moving forward, we argue for a much more explicit recognition of ancillary benefits for vulnerable communities, where they can be seen as important investments in long-term relationships of mutual benefit and concern.

Acknowledgments

Support for this research is from the NIH (grants R01 HG005172-01 and R01 GM089886-01A1) and the National Science Foundation (NSF#0845314).

References

1. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. *JAMA*. 2001; 285:540–544. [PubMed: 11176855]
2. Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. *Nature*. 2011; 470:204–213. [PubMed: 21307933]
3. Turnbaugh PJ, et al. The human microbiome project. *Nature*. 2007; 449:804–810. [PubMed: 17943116]
4. Hattori M, Taylor TD. The human intestinal microbiome: a new frontier of human biology. *DNA Res*. 2009; 16:1–12. [PubMed: 19147530]
5. Reich DE, Lander ES. On the allelic spectrum of human disease. *Trends Genet*. 2001; 17:502–510. [PubMed: 11525833]
6. Dickson SP, et al. Rare variants create synthetic genome-wide associations. *PLoS Biol*. 2010; 8:e1000294. [PubMed: 20126254]
7. Arumugam M, et al. Enterotypes of the human gut microbiome. *Nature*. 2011; 473:174–180. [PubMed: 21508958]
8. Ramachandran S, et al. Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa. *Proc Natl Acad Sci U S A*. 2005; 102:15942–15947. [PubMed: 16243969]
9. Rogers AR, Jorde LB. Ascertainment bias in estimates of average heterozygosity. *Am J Hum Genet*. 1996; 58:1033–1041. [PubMed: 8651264]
10. Mailman MD, et al. The NCBI dbGaP database of genotypes and phenotypes. *Nat Genet*. 2007; 39:1181–1186. [PubMed: 17898773]
11. Blaser M. Antibiotic overuse: stop the killing of beneficial bacteria. *Nature*. 2011; 476:393–394. [PubMed: 21866137]
12. De Filippo C, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A*. 2010; 107:14691–14696. [PubMed: 20679230]
13. Fierera N, et al. Forensic identification using skin bacterial communities. *Proc Natl Acad Sci U S A*. 2010; 107:6477–6481. [PubMed: 20231444]
14. Sharp RR, Foster MW. Grappling with groups: protecting collective interests in biomedical research. *J Med Philos*. 2007; 32:321–337. [PubMed: 17712706]
15. Held, V. *The Ethics of Care: Personal, Political, and Global*. Oxford University Press; 2005.

Figure 1.

Schematic representation of the stage of the HMP with respect to the progress of the human genome research depicted as a heat map. Red reflects a higher density of contributions for a particular timeframe; adapted from Green and Guyer [2].

Figure 2.

Three concepts for rare variants and their impact upon disease. (a) Variation is rare within families and populations. (b) Variation is common within a family but rare between families. (c) Variation is common among families within a population but rare between populations.