

Human Microbiome, the Neglected Organ

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Microbiome as an organ

- An organ – “structural part of a system of the body that is composed of tissues and cells that enable it to perform a particular function” - Mosby's Medical Dictionary
- The microbiome - “signify the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease” - Joshua Lederberg 2001
- “Differentiation” – By co adaptation and evolution to form the healthy microbiome
- Studying an organ – Anatomy, physiology, biochemistry, pathology and diagnostics, treatment and prevention

The study of human microbiome

- Humans harbour $\approx 10^{14}$ bacteria
- Leeuwenhoek – microscopic examinations in late 1600
- Studies up mid 1990s documented basic characteristics and functions of normal flora
- Initial studies mostly focused on individual sites and dependent on culture/ microscopy based methods

Human Fecal Flora: The Normal Flora of 20 Japanese-Hawaiians

W. E. C. MOORE AND LILLIAN V. HOLDEMAN

Anaerobe Laboratory, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received for publication 21 January 1974

Quantitative and qualitative examination of the fecal flora of 20 clinically healthy Japanese-Hawaiian males was carried out by using anaerobic tube culture techniques. Cultural counts were 93% of the microscopic clump counts. Isolated colonies were selected in a randomized manner to give an unbiased sampling of the viable bacterial types. Each isolate was characterized for species identification. From a total of 1,147 isolates, 113 distinct types of organisms were observed. Statistical estimates indicate that these types account for 94% of the viable cells in the feces. The quantitative composition of the flora of this group of people, together with differential characteristics of previously unreported species, is presented for those kinds of bacteria which each represented at least 0.05% of the flora.

Structure of the human microbiome

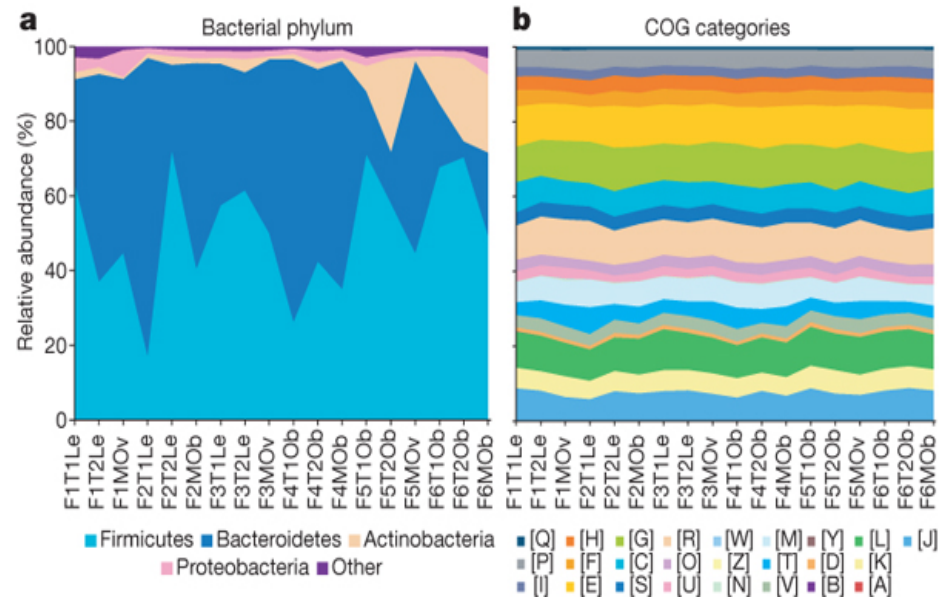
- 242 adults –4788 samples taken from 18 (female) or 15 (male) body sites
- Analysis by 16sRNA based sequencing and Whole Genome Sequencing (WGS)
- Repeated sampling in a select group
- Prevalence and abundance of different taxa and metabolic pathways at each site studied
- β diversity - same site, different subjects
- α diversity – within subject diversity

Features of the healthy human microbiome

- α and β diversity differs from site to site
- Patterns of variation in community structure followed the major body habitat groups
- Within-subject variation over time was consistently lower than between-subject variation
- Near absence of pathogens with exceptions and high prevalence of potential pathogens
- Community composition at a given site depends on the physical, biochemical and immunological properties of the site and inter-microbial interactions
- Ethnic differences in the microbial compositions

Features of the healthy human microbiome cnt

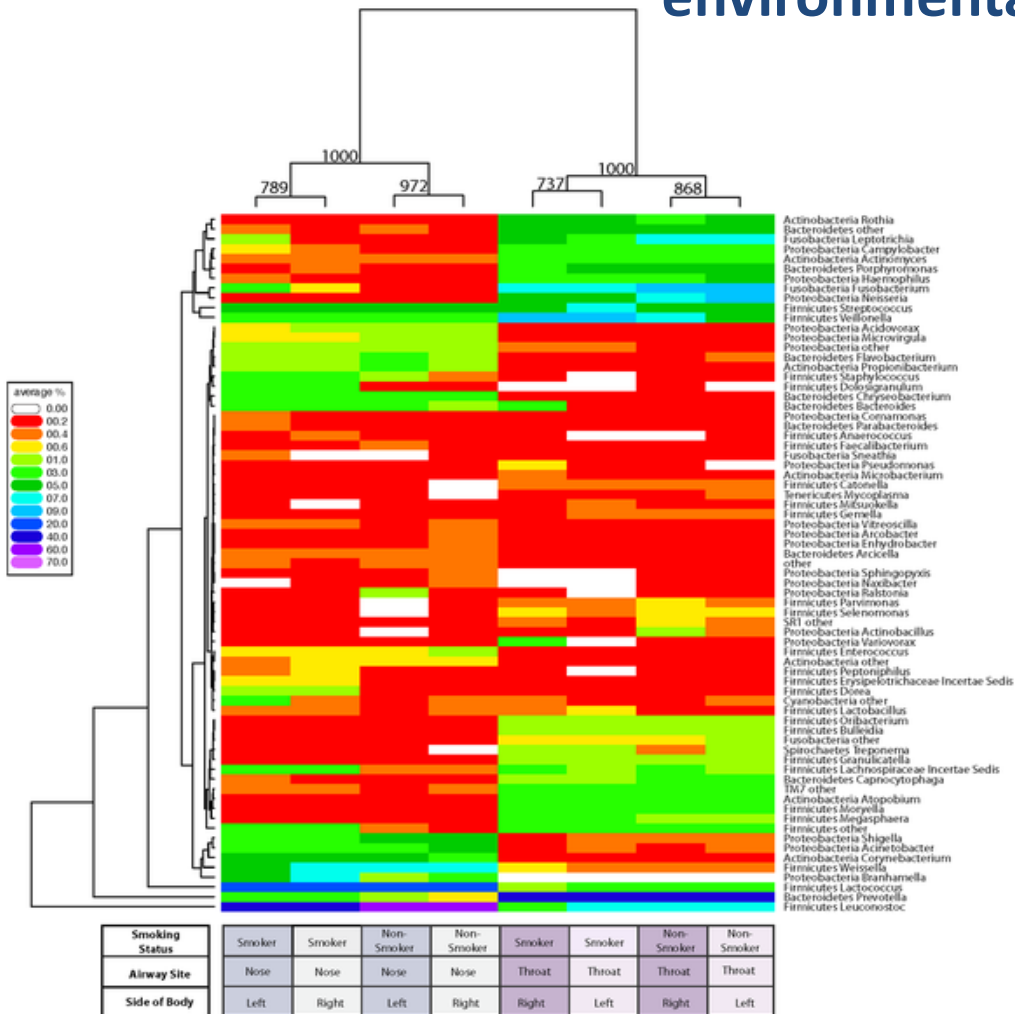
- Transcriptome studies
- WGS
- Identification of metabolic and functional pathways



PJ Turnbaugh *et al.* *Nature* **000**, 1-5 (2008) doi:10.1038/nature07540

Gosalbes MJ, Durbañ A, Pignatelli M, Abellan JJ, Jiméñez-Hernández N, et al. (2011) Metatranscriptomic Approach to Analyze the Functional Human Gut Microbiota. *PLoS ONE* 6(3): e17447. doi:10.1371/journal.pone.0017447

Variations in human microbiome due to physiological and environmental factors



Microbiota of smokers more diverse
 Clustered separately
 Enrichment of anaerobic lineages
 implicated in periodontal disease

Charlson ES, Chen J, Custers-Allen R, Bittinger K, et al. (2010) Disordered Microbial Communities in the Upper Respiratory Tract of Cigarette Smokers. PLoS ONE 5(12): e15216. doi:10.1371/journal.pone.0015216
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0015216>

Human microbiome and disease

- Traditional thinking – normal flora – different site/ breach in host defense – disease
- Microbiome - closely linked to or influences diseases that are traditionally thought as non communicable diseases

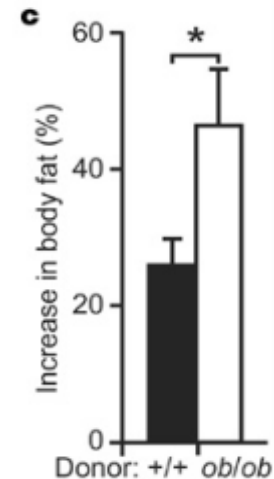
Associations of human conditions with normal flora

Disease	Relevant finding	Refs
Psoriasis	Increased ratio of Firmicutes to Actinobacteria	88
Reflux oesophagitis	Oesophageal microbiota dominated by gram-negative anaerobes; gastric microbiota with low or absent <i>Helicobacter pylori</i>	75,133
Obesity	Reduced ratio of Bacteroidetes to Firmicutes	17,31
Childhood-onset asthma	Absent gastric <i>H. pylori</i> (especially the cytotoxin-associated gene A (<i>cagA</i>) genotype)	96,134
Inflammatory bowel disease (colitis)	Larger populations of Enterobacteriaceae	113
Functional bowel diseases	Larger populations of <i>Veillonella</i> and <i>Lactobacillus</i>	135
Colorectal carcinoma	Larger populations of <i>Fusobacterium spp.</i>	101,102
Cardiovascular disease	Gut-microbiota-dependent metabolism of phosphatidylcholine	136

[The human microbiome: at the interface of health and disease](#). Ilseung Cho & Martin J. Blaser. *Nature Reviews Genetics* 13, 260-270 (April 2012)

Obesity and gut microbiome

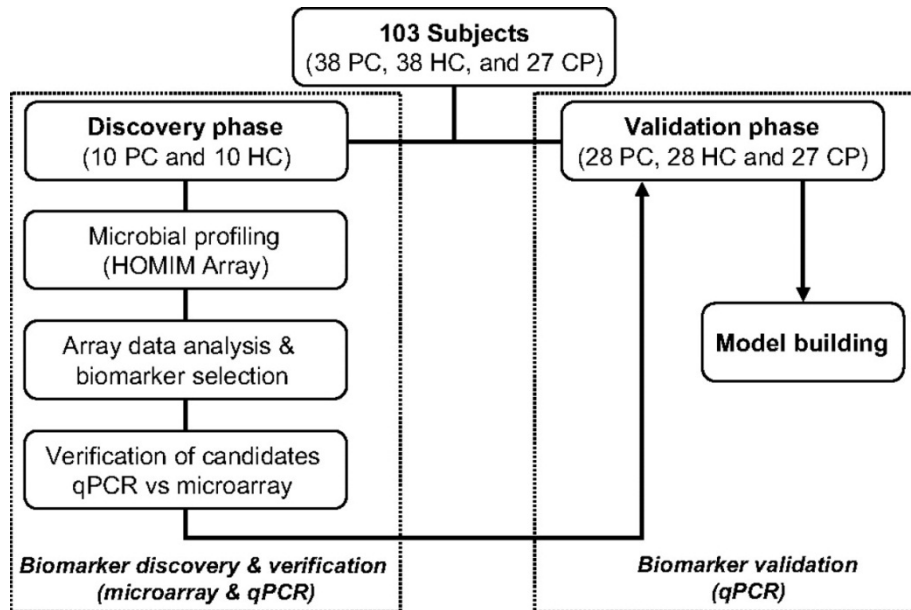
- Differences in the microbiome both in taxonomic based abundance and metabolic pathways differ in lean vs obese individuals
- In vivo study with microbiome transplantation to germ free mice identified the influence of microbiota on body fat composition



- Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006 Dec 21;444(7122):1027-31.
- Sharon Greenblum, Peter J. Turnbaugh, and Elhanan Borenstein Metagenomic systems biology of the human gut microbiome reveals topological shifts associated with obesity and inflammatory bowel disease *PNAS* 2012 109 (2) 594-599; published ahead of print December 19, 2011,

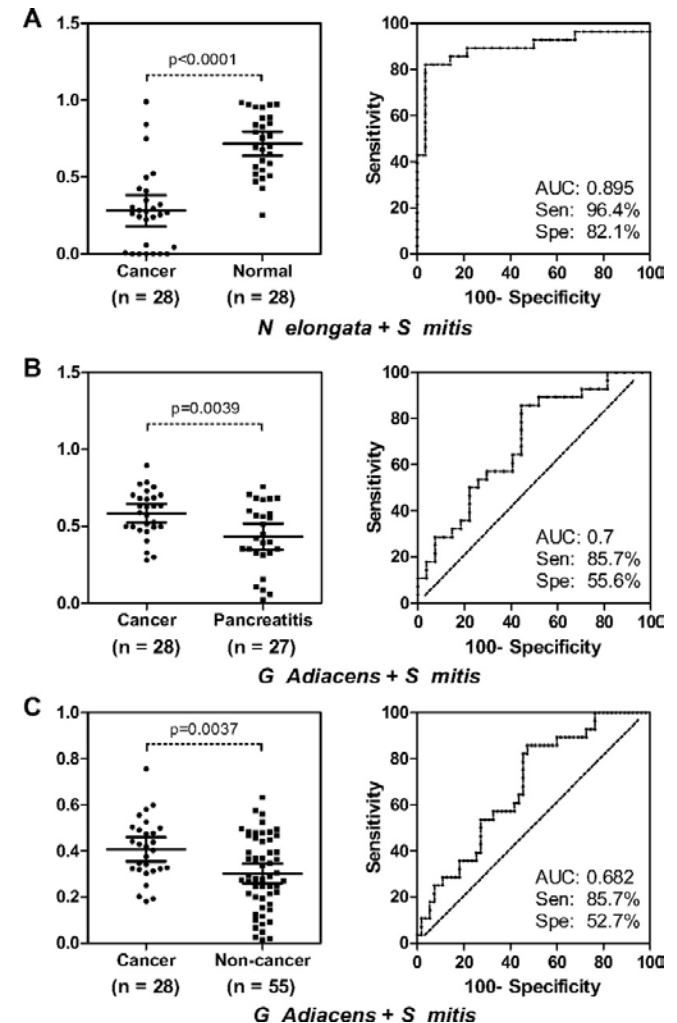
Diagnostics

- Disease specific signatures of microbiome



The combination of *N elongata* and *S mitis* – ROC 0.90 (95% CI 0.78 to 0.96, $p < 0.0001$) with a 96.4% sensitivity and 82.1% specificity in distinguishing patients with pancreatic cancer from healthy subjects

Farrell J J et al. Gut 2012;61:582-588



Therapeutics

- Currently in practice
 - Probiotics and prebiotics
 - Transplants
- Prospects
 - Drug delivery using microbiota
 - Using microbiota as drugs
 - Assessing the effect of relevant microbial profiles in drug development

Effect of relevant microbial profiles on drug metabolism

- Pre-dose and timed post dose urine metabolite profiles - by spectroscopy - healthy individuals given acetaminophen
- Acetaminophen sulfonation ability of a person can be significantly reduced by competitive *p*-cresol sulfonation; a product formed from protein-derived tyrosine in reactions involving gut bacteria.
- May be applicable for other drugs that need sulfonation

Future

- More studies on defining the variations in the normal healthy microbiome is needed at both structural and functional levels
- Evaluation of causal relationships with human disease

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**“Microbes maketh man. People are not just people.
They are an awful lot of microbes, too”**

The Economist

18/08/2012



Jon Berkeley/SPL

Thank you!

<http://www.economist.com/node/21560559>