Composition, Taxonomy And Functional Diversity Of The Oropharynx Microbiome In Individuals With Schizophrenia And Controls

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Abstract

- The role of the human microbiome in schizophrenia remains largely unexplored. The microbiome has been shown to alter brain development and modulate behavior and cognition in animals through gut-brain connections, and research in humans suggests that it may be a modulating factor in many disorders. This study reports findings from a shotgun metagenomic analysis of the oropharyngeal microbiome in 16 individuals with schizophrenia and 16 controls.
- High-level differences were evident at both the phylum and genus levels, with Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria dominating both schizophrenia patients and controls, and Ascomycota being more abundant in schizophrenia patients than controls.
- Controls were richer in species but less even in their distributions, i.e., dominated by fewer species, as opposed to schizophrenia patients.
- Lactic acid bacteria were relatively more abundant in schizophrenia, including species of Lactobacilli and Bifidobacterium, which have been shown to modulate chronic inflammation. We also found *Eubacterium halii*, a lactate-utilizing species.
- Functionally, the microbiomes of schizophrenia patients were characterized by an increased number of metabolic pathways related to metabolite transport systems including siderophores, glutamate, and vitamin B12. In contrast, carbohydrate and lipid pathways and energy metabolism were abundant in controls.
- These findings suggest that the oropharyngeal microbiome in individuals with schizophrenia is significantly different compared to controls, and that particular microbial species and metabolic pathways differentiate both groups.
- Confirmation of these findings in larger and more diverse samples, e.g., gut microbiome, will contribute to elucidating potential links between schizophrenia and the human microbiota.

Methods

- Participants were individuals with schizophrenia and non-psychiatric controls from the Stanley Research Program at Sheppard Pratt Hospital
- Sequencing libraries were matched one case and one control per lane and anonymized until analysis
- Sequences were generated using the Illumina HiSeq 2000 platform producing approximately 58-million single-end reads of 100 nucleotides in length per sample
- All sequencing data were deposited in the Sequence Read Archive (SRA) and are available under the BioProject PRJNA255439
- PRINSEQ, PathoScope, Bowtie2, HMP reference DB/Human genome (hg19), ggplot2, Phyloseq, DESeq2, STAMP, MaASLin, LEfSe

Results

Study Sample groups do not differ on any demographic variable but smoking

The study sample consisted of 16 schizophrenia patients and 16 controls. Cases were more likely to be cigarette smokers than controls ($\chi 2 = 18.6$; p value < 0.0001; 62.5% and 0%, respectively); groups did not differ significantly on any other demographic variable (Table).

	Entire Sample (N=32)	Schizophrenia Cases (N=16)	Controls (N=16)
Age	34.5 ± 7.8	34.7 ± 4.8	34.3 ± 10.1
Male gender	18/32 (56.3%)	9/16 (56.3%)	9/16 (56.3%)
White race	12/20 (37.5%)	7/16 (43.8%)	5/16 (31.3%)
Mother's education	13.6 ± 2.9	13.1 ± 2.97	14.1 ± 3.0
Cigarette smoker	10/32 (31.3%)	10/16 (62.5%)	0/16 (0%)

Microbial communities in the oropharynx of schizophrenia patients are significantly different than in controls

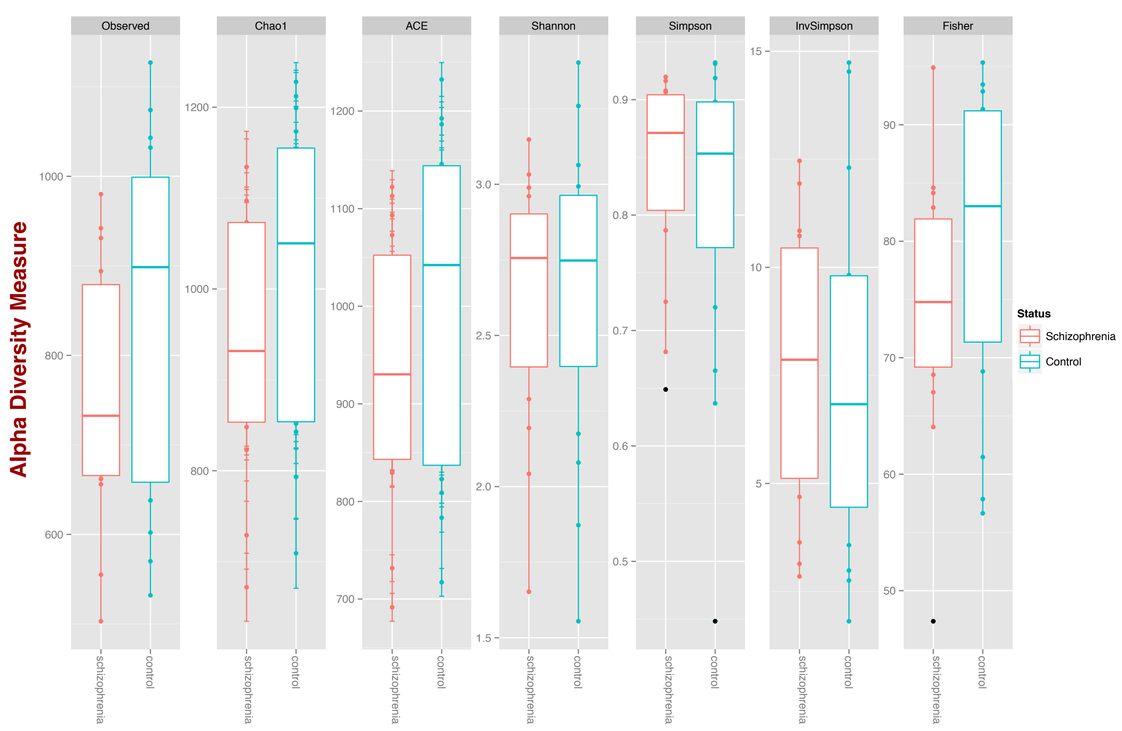

Figure 1: Schizophrenia samples are less rich in species than controls (Observed, Chao1, ACE indices) but are more homogeneously distributed (Shannon, Simpson, Inverse Simpson indices)

Figure 2: Oropharyngeal microbial composition at phylum and species levels exhibits different patterns for schizophrenia and control samples. The stacked bar chart shows the most prevalent species present in schizophrenia and controls color-coded by phylum. Green = Actinobacteria; Orange = Bacteroidetes; Blue = Firmicutes; Green = Proteobacteria.

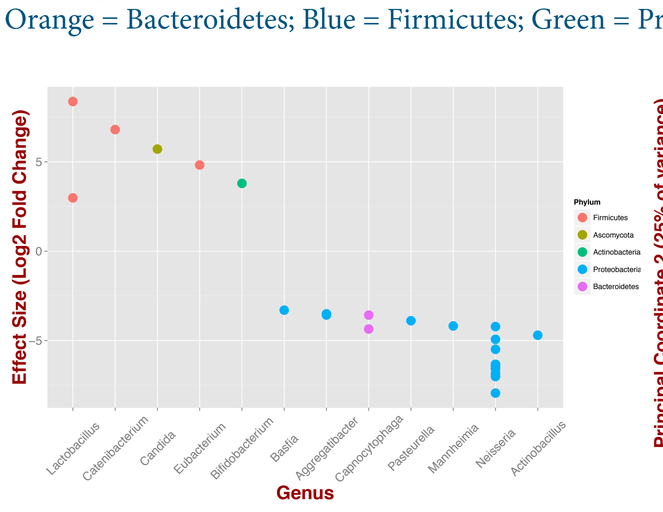

Figure 3: Species that are differentially abundant in schizophrenia and controls as shown by genus and color-coded by phylum. Dots represent species and y-axis is in Log2 scale

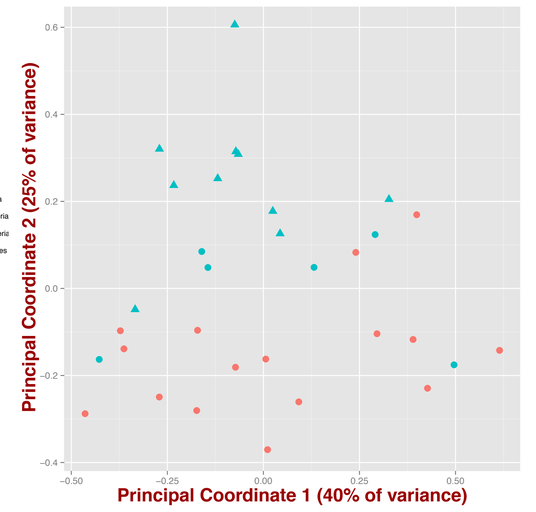

Figure 4: Covariation of community structure shows that diversity patterns of samples correlate with disease status, i.e., schizophrenia and controls. Points represent principal coordinate analysis (PCoA loadings) on Jensen-Shannon Diversity distances.

Metabolic pathways in schizophrenia patients are associated to environmental information processing and nucleotide and amino acid metabolism

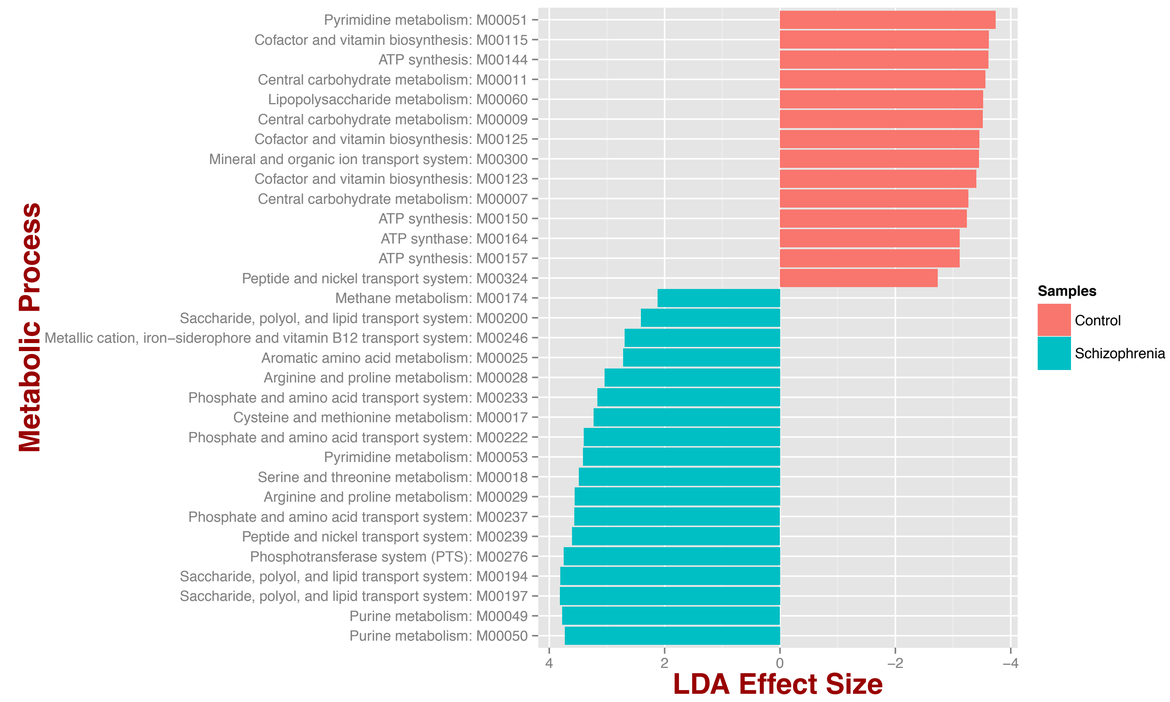

Figure 5: Microbial metabolic pathways with significantly altered abundances in the schizophrenia oropharyngeal microbiome. MXXXXX codes correspond to KEGG modules, i.e., a collection of manually defined functional units (genes). LDA = linear discriminant analysis.