Relationships between frailty, age, and the microbiome in an assisted-care facility

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Abstract

Background: An individual's frailty can be expressed as a relative proportion of accumulated health deficits. Frailty is a known risk factor for many negative outcomes including poor response to therapy and surgery, institutionalization, and death. Inhabitants of assisted-care facilities are among the most frail and vulnerable, and frailty assessment is a key component in maximizing their quality of life. Given previously observed associations between the microbiome and chronic conditions, it may be the case that there is an overall microbial signature of frailty, or that specific microbial taxa or functions are associated with frailty.

Methods: Ethical approval was obtained from XXX. We collected up to five weekly fecal samples from a cohort of 46 subjects in an assisted-care facility in Halifax, Nova Scotia, Canada, and profiled microbial diversity using both marker-gene taxonomic surrogates and metagenomic analysis. The taxonomic and functional diversity of subjects was compared with subject attributes including age, frailty, medication use, and specific medical conditions.

Results: We observed substantial variation in the microbiome of our study subjects despite their shared residence. The majority of individuals showed remarkable stability over a month of sampling, although we did observe dramatic shifts in the dominant microbiota in a small number of cases. Contrary to previously published studies, we found no significant relationship between frailty, age, and overall microbiome diversity; however, a small set of bacterial groups associated with frailty, and a larger set with age. Metagenomic analysis suggested large variation in the number of types of resistance genes present in different individuals, and *drug-metabolism /VF analysis?*

Conclusions: Our results suggest that there is no association between overall microbial diversity and age or frailty; however, certain taxa and functions may associate with specific aspects of frailty (*medication*)? From a diagnostic point of view, however, microbiome profiling can provide clear evidence for pathogen presence and risks associated with virulence and antimicrobial resistance. Given its minimal invasiveness and cost, "microbial frailty" can serve as a valuable complement to traditional frailty assessments.

Keywords: Frailty, microbial diversity, time series, antimicrobial resistance

Background

On average, health declines with age, but not everyone of the same age has the same risk, even at advanced ages [1]. People at greater risk due to the accumulation of health related deficits and the consequent, multiply determined decrease in the ability to respond to stress are said to be frail [**???**]. Frailty is an important clinical and public health problem, so that many lines of research are now directed to the determinants of frailty. [FINISH THIS PARAGRAPH WITH MORE STUFF ABOUT FRAILTY]

[LITERATURE REVIEW #1 - WHY MIGHT WE EXPECT CONNECTIONS BETWEEN FRAILTY AND THE MICROBIOME?]

[LITERATURE REVIEW #2 - WHAT HAVE PEOPLE FOUND? WHY HAVE SOME RESULTS BEEN INCONSISTENT?] A recent report extends an initial observation that frailty was associated with reduced gut microbiota diversity [Eldermet] in showing associations with specific taxa. (etc.)

(Jackson M, Jeffery IB, Beaumont M, Bell JT, Clark AG, Ley RE, O'Toole PW, Spector TD, Steves CJ. Signatures of early frailty in the gut microbiota. Genome Med. 2016 Jan 29;8(1):8. doi: 10.1186/s13073-016-0262-7. PMID: 26822992 Notes: that used an FI based on our criteria; replicated the Eldermet

sequences and analytics, more or less, in the Twins UK cohort (age range 42-86) – so low FIs. We will have higher / older.. Plus, have you seen this – couldn't get it.)

[HYPOTHESIS PARAGRAPH!!] Frailty is intended to give a holistic view of health, independent of any specific condition. Individuals in assisted-care facilities show a high degree of variation in age and frailty, which might suggest a high degree of variability in the microbiome. However, sharing a common residence and eating similar meals may tend to reduce the amount of variation exhibited by the microbiome. Here we assess the microbiome in a set of 46 study subjects from an assisted-care facility. The majority of individuals exhibit similar patterns of diversity and a high degree of stability over the five-week study period, but the overlap in microbiota among study subjects is surprisingly low. We also find stronger associations of both taxonomy and function with age than with frailty, and identify connected sets of co-occurring groups of microorganisms.

Background

Study Design

Ethical approval

Frailty Index CalculationA

The FI was constructed with 54 variables chosen from the CGA (Appendix). A total of 58 variables were considered but 4 were excluded due to either a 100% deficit prevalence or because the variable was missing in more than 20% of the sample. Co-morbidities were entered to a maximum of 18, so if someone had more than 18 co-morbidities listed on the CGA, only 18 was added to the calculation of the FI. The FI score of each person was calculated by dividing the number of deficits by the total number of variables that each person had. For people who had data on all 54 variables, the FI was the number of deficits divided by 54 but if someone was missing 3 variables then the FI was the number of deficits divided by 51.

Sample collection and DNA Extraction

Fecal samples were collected from forty-seven individuals as shown in figure X at different time points. Feces were collected with EasySampler Stool Collection Kit as manufacturer's instruction in most cases. Under circumstance where samples couldn't be collected with standard procedure, collection hat was used. Samples were stored at -80°C until processed further. Total genomic DNA from each fecal sample was extracted using the MoBio PowerFecal DNA isolation kit according to the manufacturer's instructions. Isolated DNA was quantified using UV-spectrophotometer and stored at -80°C until use. Additionally, we collected the diet intake for each subject throughout the sample collection period and drug administration records.

DNA sequencing

We used two independent approaches to decipher the taxonomic and functional composition of microbial community. First, a region of approximately 435bp, in the 16S rRNA gene covering the V6-V8 variable region, was amplified from each samples using gene specific primers to construct a sequencing library and sequenced using an Illumina MiSeq. We incorporated Illumina indices and sequencing region on amplification primers as reported earlier (Ref). Second, we choose third or later collected sample for each subject to perform shotgun metagenome sequencing on an Illumina NextSeq 500. Paired-end metagenomic library of 150bp were prepared using Nextera XT DNA Library Preparation Kit as per manufacturer's instruction. Sequencing was performed at an in-house sequencing facility IMR-CGEB (Integrated Microbiome Resource - Centre for Comparative Genomics

and Evolutionary Bioinformatics, Dalhousie University, Halifax, NS, Canada) on Illumina MiSeq generating 300-bp paired-end reads for 16S metagenomics and on NextSeq 500 generating 150bp paired-end reads for shotgun metagenomics. This produced *** of high quality reads, with *** (mean) and *** reads, with ***(mean± sd) on Miseq and NextSeq, respectively.

Data analysis

16S

PICRUSt

Metagenomics

Metabolomics

Everything together with metadata

Results

References

1. **Frailty in the Honolulu-Asia Aging Study: Deficit Accumulation in a Male Cohort Followed to 90% Mortality**
   J. J. Armstrong, A. Mitnitski, L. J. Launer, L. R. White, K. Rockwood
   The Journals of Gerontology Series A: Biological Sciences and Medical Sciences (2014-06-27)
   https://doi.org/f64b26
   DOI: 10.1093/gerona/glu089 · PMID: 24973228 · PMCID: PMC4296165