Perturbed Gut Viral Ecology in Inflammatory Bowel Disease: a Multi-cohort Study

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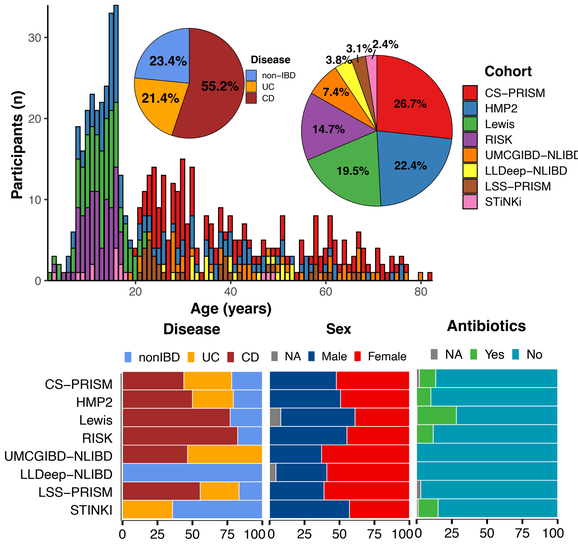
Background

- The burden of inflammatory bowel disease (IBD) is rising globally.
- While prior studies have uncovered the critical role of gut dysbiosis in IBD and its subtypes, Crohn's disease (CD) and ulcerative colitis (UC), most have focused on its bacterial determinants and few have explored gut viral ecology.

Study population and analysis design

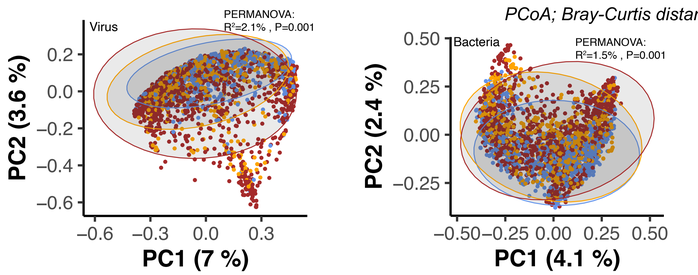


We uniformly processed and harmonized 2,574 IBD shotgun metagenomes

- 580 individuals (320 CD, 124 UC, 136 non-IBD controls)
- Eight independent international cohorts from the Human Microbiome Bioactives Resource

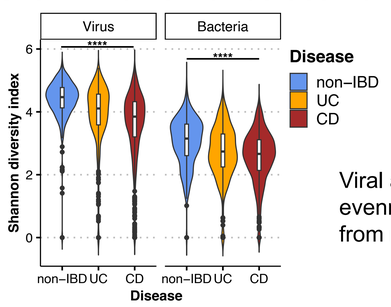
In total, we detected 5,391 unique viral genome bins (VGBs, akin to bacterial species-level clades).

Gut virome more associated with IBD



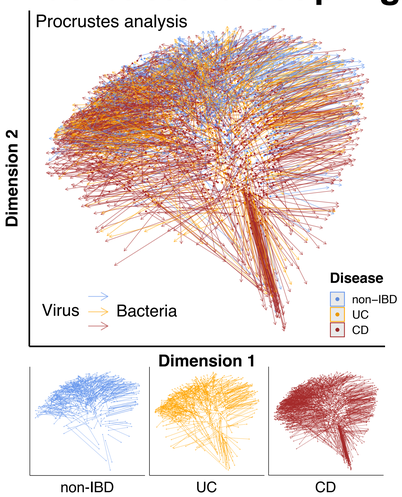
- The gut virome was 1.5x more associated with disease status (i.e., IBD vs. control) than gut bacteria (R^2=2.1%, p=0.001).
- Using a RF machine learner, we found comparable accuracy in classifying IBD vs. non-IBD when using viral features compared to bacteria (AUC>0.95).

Loss of viral and bacterial diversity in IBD



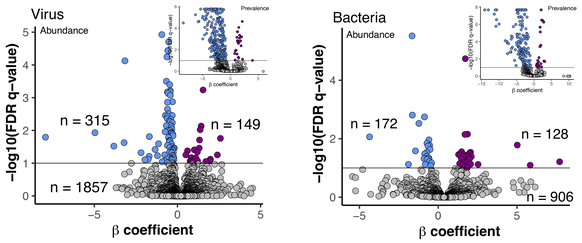
Viral and bacterial richness and evenness decreased monotonically from non-IBD to UC to CD.

Virus-bacteria coupling may be disrupted in IBD



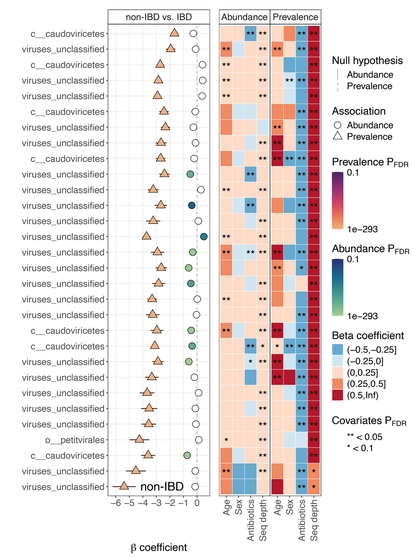
- Procrustes analysis showed that virome and bacteriome were significantly coupled and exhibited similar clustering patterns (Procrustes correlation = 0.89, p=0.001).
- While virome and bacteriome are globally correlated, compared with non-IBD, the discrepancy was significantly larger in CD, followed by UC, as evidenced by the longer lines connecting multi-kingdom profiles (pFDR≤0.01).

Gut viral ecology is perturbed in IBD



Using generalized multivariable linear models (MaAsLin3), we identified 343 differentially abundant VGBs in IBD compared to non-IBD.

- This represents 15.6% of all detected VGBs.
- This is 69% greater than the count for differentially abundant bacteria.

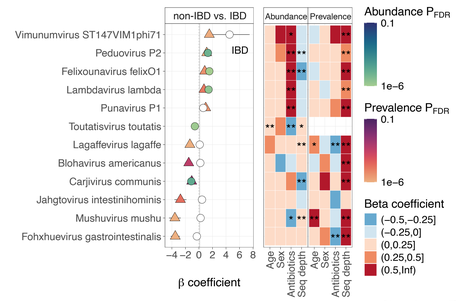


*Top 30 significant viruses associated with IBD vs. non-IBD as ranked by pFDR.

Novel viruses may be a critical yet underexplored factor in IBD

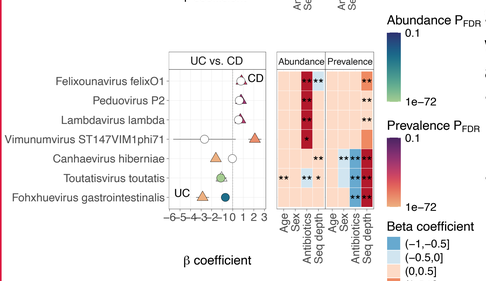
- Most of these significantly altered viruses were unclassified (75%).
- Among the 5,391 unique VGBs detected, the majority were unclassified viral "dark matter."
  - 78% were completely unclassified across all taxonomic levels.
  - This represents a relative overrepresentation of novel viruses in the IBD gut when compared to the 7% unclassified background of our reference database.

Some classified viruses are putative phage of IBD-associated bacteria



Five classified viruses were significantly enriched in IBD. All are bacteriophage.

- *Peduovirus P2, Lambdavirus lambda, and Punavirus P1* infect *E. coli*
- *Vimunumvirus ST147VIM1phi71* infects *Klebsiella pneumoniae*
- *Felixounavirus felixO1* primarily targets *Salmonella* species

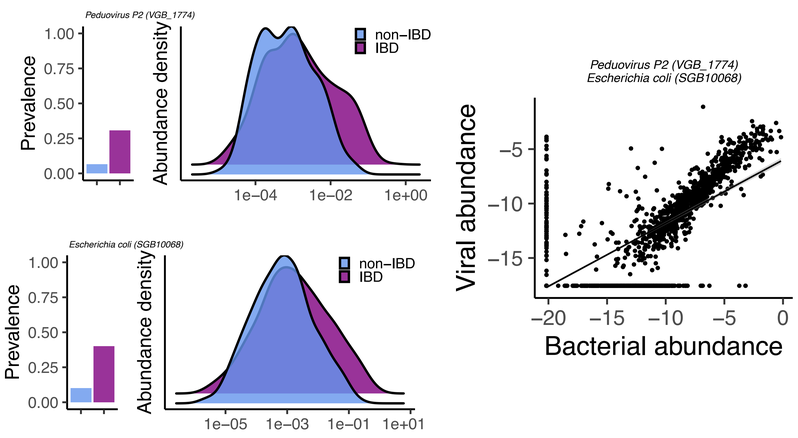


*ICTV-resolved viral species significantly associated with IBD vs. non-IBD and CD vs. UC.

Seven classified bacteriophage were differentially abundant/prevalent in CD vs. UC.

- *Felixounavirus felixO1* infects *Salmonella* species including *Salmonella enterica*
- *Fohxhuevirus gastrointestinalis* and *Canhaevirus hiberniae* possibly target Bacteroidaceae family
- *Toutatisvirus toutatis* infects *Faecalibacterium prausnitzii*

Explore phage-host relationships via correlation



Given accurate virome profiles from the same underlying metagenomics across many samples, we can now explore phage-host relationships via correlation. Here using *Peduovirus P2* & its bacterial host *E. coli* as an example, we show that they are both co-prevalent and co-abundant in gut.

Acknowledgments & Contact

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