Precision medicine approach identifies unique microbial strains associated with the IL-23/IL-17 axis in IBD

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SECOND GENOME

Background

Studies of the microbiome typically focus on comparisons between diseased patients and healthy controls. While this is a useful strategy, it lacks precision in heterogenous diseases such as Inflammatory Bowel Disease (IBD). **We hypothesized that segmenting patients based on IBD-relevant molecular gene signatures may help identify bacteria associated with specific pathologies.** This approach divides patients into groups based on gene expression profiles rather than clinical classifications, which will allow targeted investigation of microbial contributors to specific IBD-related immune processes, such as the clinically relevant IL-23/IL-17 axis**. This approach represents an opportunity to develop a targeted method to subset patients at the molecular level based on specific pathology.**

Methods

Four IBD clinical cohorts were used, each containing the following paired data for patients.

- Host-RNAseq gene expression from intestinal biopsy
- Microbial abundance from intestinal biopsy (16S NGS)

All cohorts included IBD patients and healthy controls. Cohorts 1-3 contain multiple sample pairs for some patients.

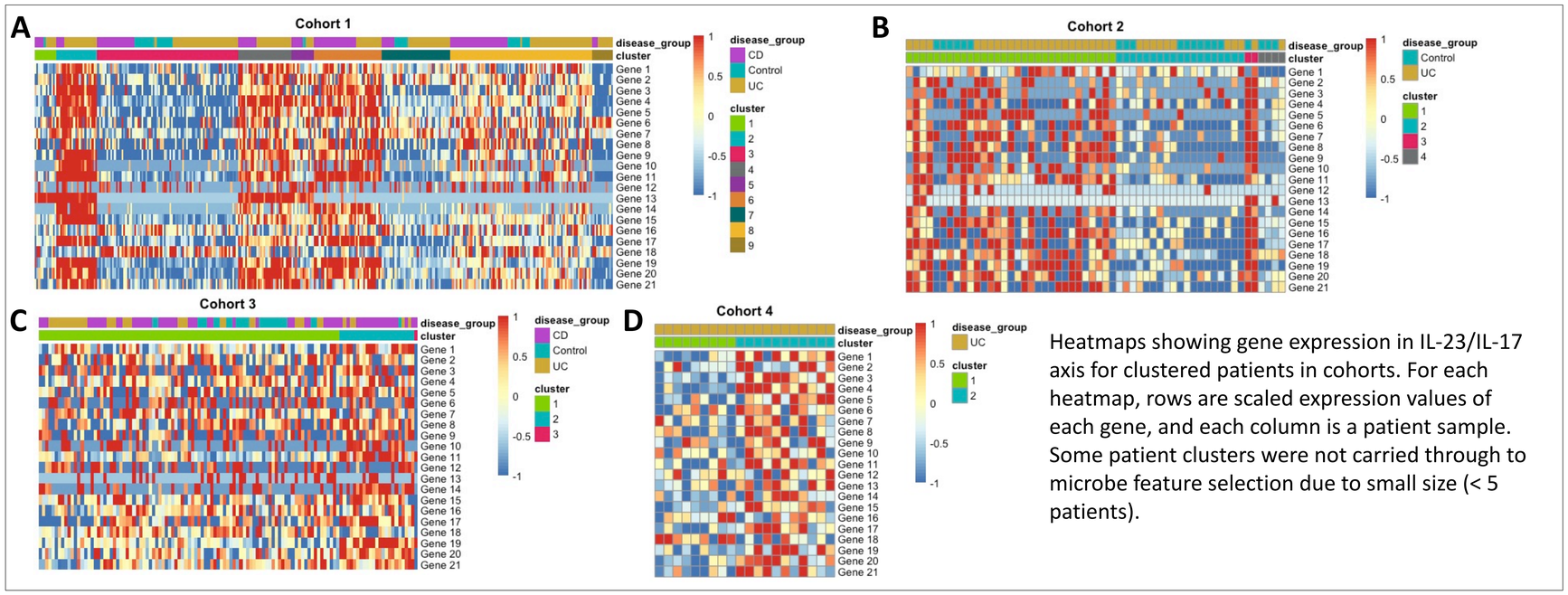
Cohort	Host data	16S NGS V4	16S NGS V3-V4	16S PhyloChip
Cohort 1 (N = 336)	X	X	X	X
Cohort 2 (N = 60)	X	X		X
Cohort 3 (N = 122)	X	X		
Cohort 4 (N = 26)	X	X		

We clustered patients by each cohort using a small set of genes to investigate the activation of IL-17 secreting cells via IL-23 signaling, a validated mechanism targeted by IBD therapeutics.
For each cohort, we separately normalized and clustered the biopsies by the expression levels in the host gene set to identify those with decreased or elevated inflammation signatures. We then compared the microbial communities embedded in the biopsies to identify bacterial strains associated with decreased inflammation. We performed a cross-cohort meta-analysis using a random effects model to integrate results from different cohorts.

Conclusions & future work

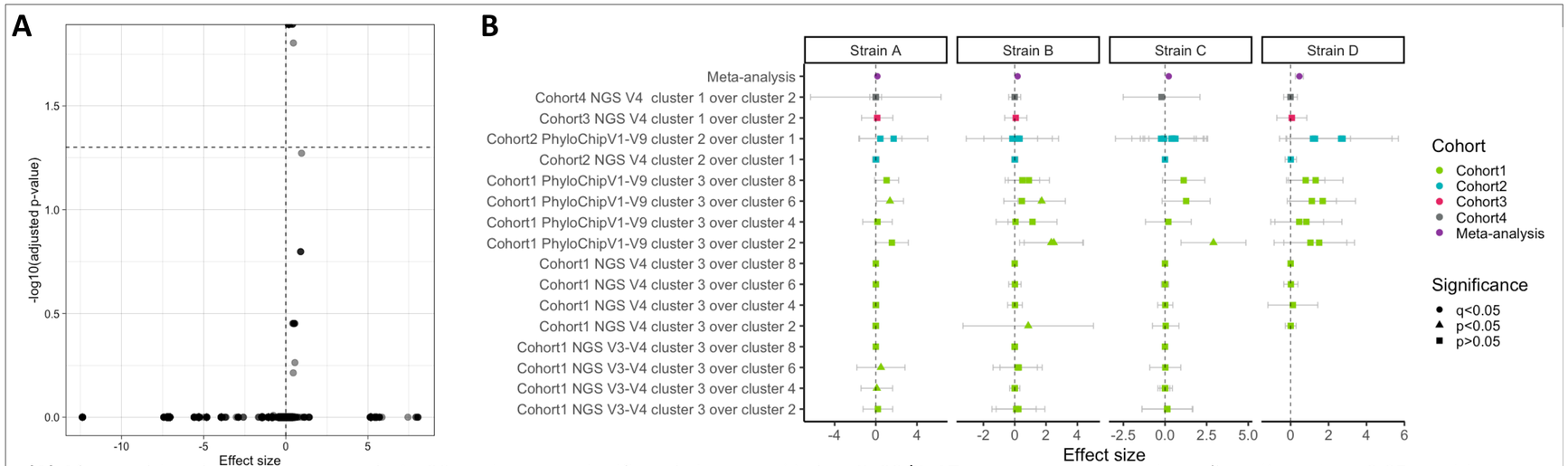
- Patients were able to be segmented by IL-23/IL-17 axis for all four cohorts.
- We demonstrated that multi-technology meta-analysis could identify strains associated with low IL-23/IL-17 axis gene expression across cohorts.
- **Our work demonstrates that specific bacteria associated with distinct pathological features of IBD, providing a novel avenue to segment patients based on the integration of microbial and host molecular signatures.**

Clustering patients by host-gene expression enables segmentation of patients based on expression of IL-23/IL-17 axis



Heatmaps showing gene expression in IL-23/IL-17 axis for clustered patients in cohorts. For each heatmap, rows are scaled expression values of each gene, and each column is a patient sample. Some patient clusters were not carried through to microbe feature selection due to small size (< 5 patients).

Multi-technology meta-analysis identifies strains associated with low IL-23/IL-17 axis gene expression across cohorts



(A) After multi-technology meta-analysis, 28 strains were significantly increased in low IL-23/IL-17 gene expression patients (by adjusted p < 0.05, positive effect size). Dotted lines represent effect size = 0, and padjust = 0.05. **(B)** Multi-technology meta-analysis and individual study results for 4 of the 28 significant strains. Purple points are the meta-analysis effect sizes, while other points show results for individual microbiome datasets and contrasts. Some cohorts had multiple microbiome data types used for comparison. Multi-technology meta-analysis found significant strains not reported significant in individual studies. For **(A)** and **(B)** All contrasts are low expression cluster over higher expression cluster.