Enhanced Gut Microbiome Capacity for Amino Acid Metabolism is Associated with Peanut Oral Immunotherapy Failure

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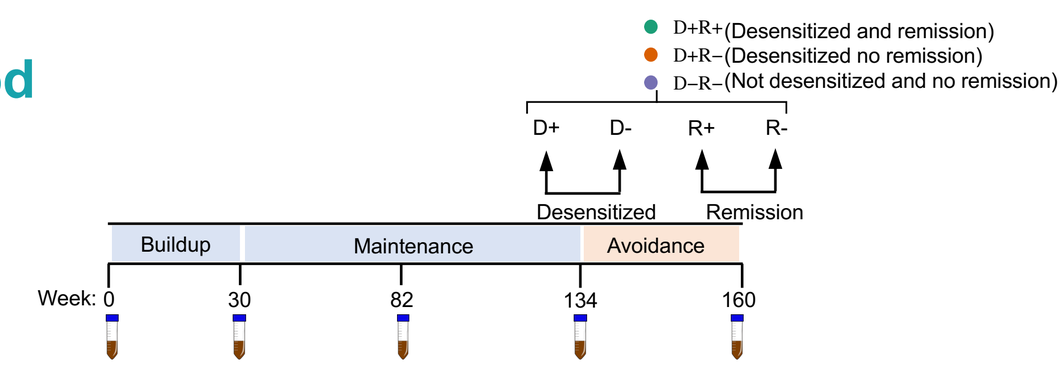
Background

- Peanut allergy affects approximately 4.6 million people in the US.
- Peanut Oral Immunotherapy (POIT) holds promise for remission of peanut allergy, though treatment is successful in only a subset of patients.
- What drives interindividual response to POIT is unknown.

Objective

- Investigate if the gut microbiome composition and/or it's metabolic activity of peanut allergic patients associate with POIT outcomes.

Method



	Baseline (Base)	End of Buildup (EoB)	Mid Maintenance (MM)	End of Treatment (EoT)	End of Avoidance (EoA)	Total Patient	Total Stool Samples
# of patients	140	61	60	61	59	144	381
16S rRNA Seq	96	47	50	53	51	116	297
Metagenome Seq	75			54	55	80	184
Metabolomics	59			59	59	59	177

Stool samples were collected at baseline at the end of treatment and avoidance periods from children undergoing POIT in a first double-blind, placebo-controlled, multicenter IMPACT clinical trial. Microbiota profiling using 16S rRNA sequencing, shotgun metagenomics and untargeted metabolomics of fecal samples was performed.

Results

Gut microbiota composition associates with POIT outcomes

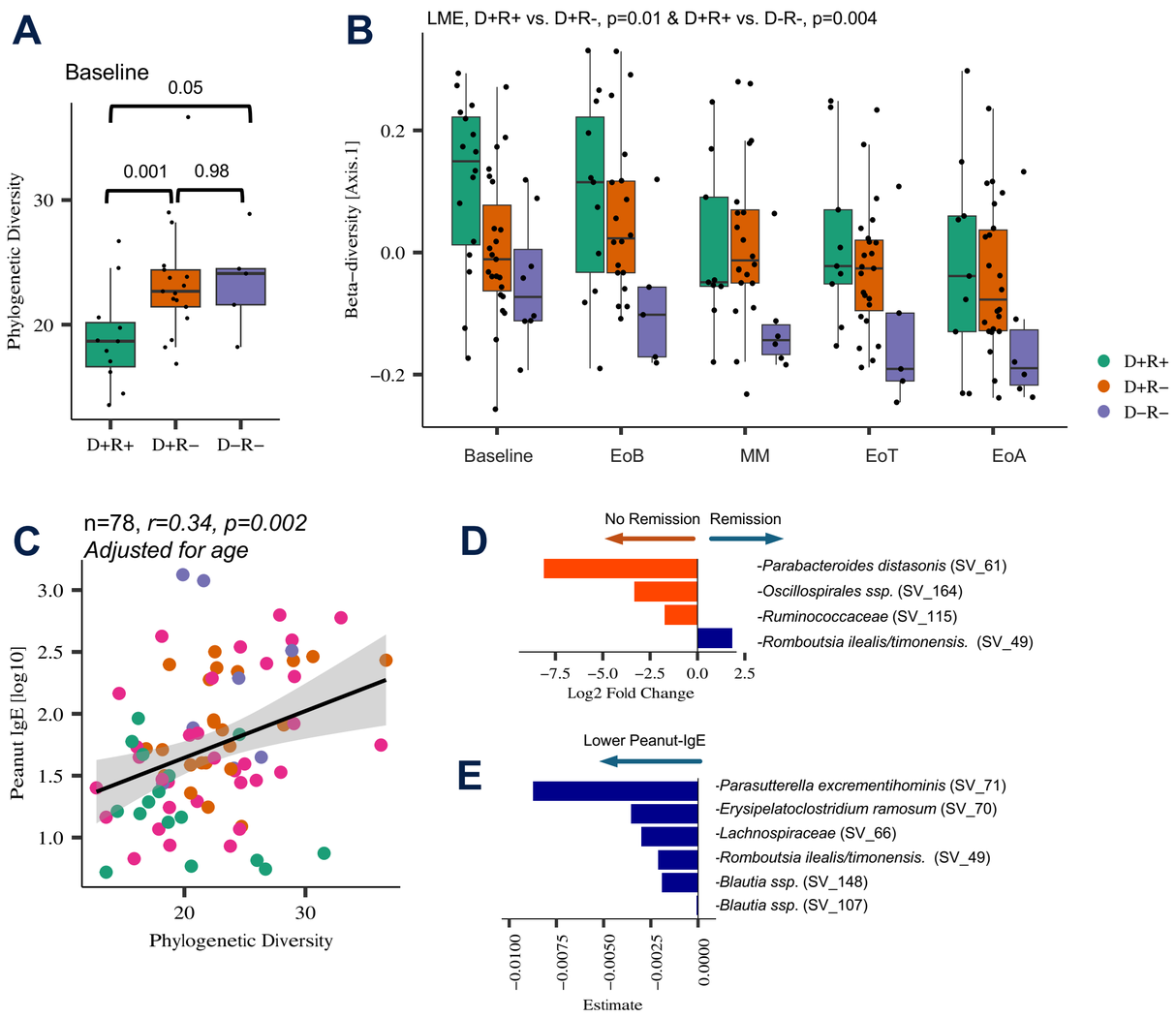


Figure 1. a, At baseline, prior to POIT initiation, the D+R+ group exhibit significantly lower phylogenetic diversity (α-diversity) compared to either the D+R- and D-R- groups. Wilcoxon signed-rank test, n=16 (D+R+), 23 (D+R), and 8 (D-R-). **b,** The D+R+ group exhibit a significantly distinct gut microbiota composition compared with either the D+R- or D-R- groups throughout the IMPACT trial. Linear Mixed Effect Model (*P<0.05*, not significant when adjusted for age). **c,** Baseline gut bacterial phylogenetic diversity positively correlates with baseline peanut-specific IgE, level. Pearson correlation, adjusted for age at screening. **d,** Baseline differentially abundant bacterial taxa between children who achieved remission versus no remission. Generalized Mixed Model (*P.FDR<0.05,* adjusted for age). **e,** Baseline Peanut-IgE associated bacterial taxa. Generalized Mixed Model (*P.FDR<0.05*).

Acknowledgements

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Baseline bile acid profile associates with POIT efficacy

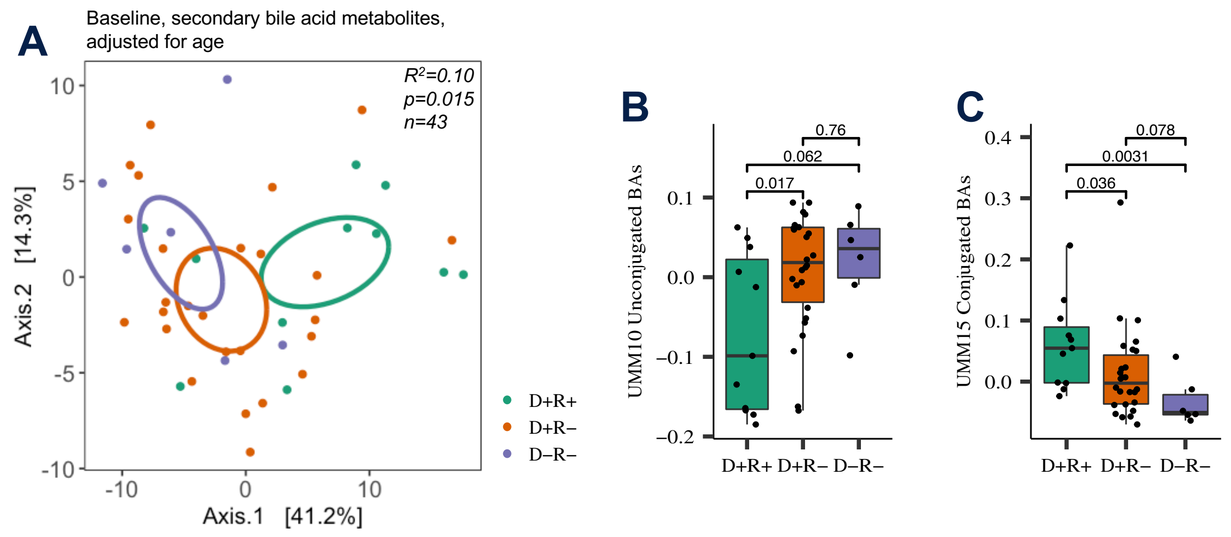

Figure 2. a, Ordination of baseline secondary bile acid metabolites (n=43, $R^2 = 0.10$; $P < 0.015$, adjusted for age), *PERMANOVA* analyses based on Euclidian dissimilarity metrics. **c,** Difference in baseline Module Eigengenes (ME), which were determined based on WGCNA analyses and represents a measure of the joint abundance profile of a specific module, of **b,** UMM10 Unconjugated BAs module, and **c,** UMM15 Conjugated BAs module between POIT-outcome groups (Wilcoxon signed-rank test).

The baseline abundance of five bile acid metabolites have a moderate POIT outcome predictive ability

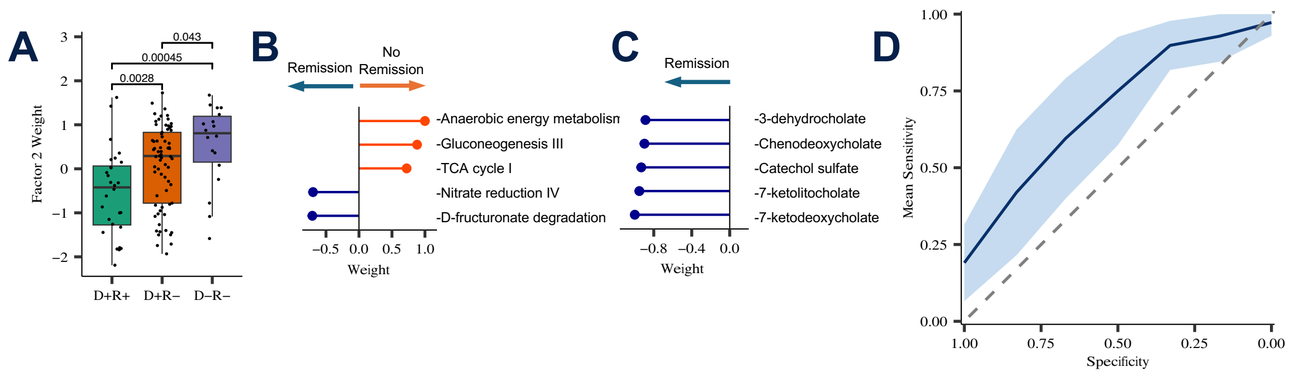

Figure 3. a, Factor 2 from MOFA analyses is the most significantly differential Factor between POIT response groups and weighted significantly higher in no remission groups compared to D+R+ group (*P<0.05*, Wilcoxon signed-rank test). **b,** Top 5 microbial pathways contributing the Factor 2 weight contains Gluconeogenesis and anaerobic energy metabolism pathways. **c,** Top 5 metabolites contributing the Factor 2 weight contains bile acid metabolites. **d,** The model's predictive ability expressed as the AUC computed from 100 times repeated five-fold cross-validation. Blue line shows the average across the 100 times repeated five-fold cross-validations with the shaded area representing the 95% CI (mean AUC ± standard deviation). The dashed diagonal line represents random chance.

Enhanced microbiome amino acid metabolism associates with failure to induce remission

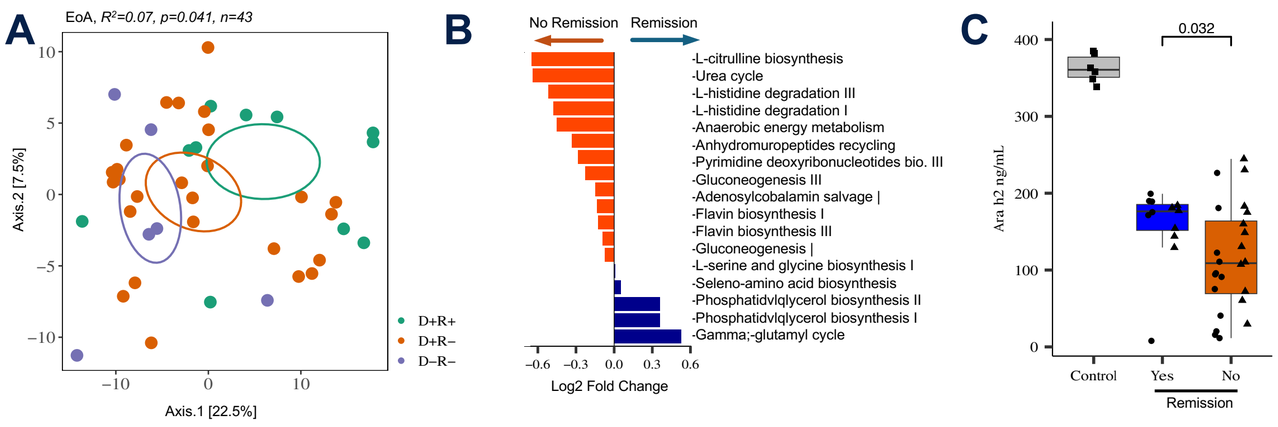

Figure 4. a, Fecal amino acid metabolite composition is distinct between POIT outcome groups at the end of avoidance (*n=43, $R^2 = 0.07$; $P = 0.039$*). The colors representing the POIT outcome groups are as follows: green for D+R+, orange for D+R-, blue for D-R-. **b,** Gut microbial pathways enriched in microbiome of children who developed remission (blue bars) versus no remission (orange bars). Generalized Mixed Models (*P<0.05, P.FDR>0.05*). **c,** Fecal microbiome of children who did not achieve POIT-induced remission have a higher capacity to metabolize peanut proteins compared to children who achieved POIT-induced remission (Wilcoxon signed-rank test). Data presented in this plot is the average of two independent experiment. Control group refers to BHI medium supplemented with peanut extract and incubated 48 h with other samples without the microbiome inoculation. Error bars represent standard deviation.

Conclusion

- Children who developed POIT-induced remission exhibited a distinct gut microbiome composition throughout the course of the trial.
- Children who did not develop POIT-induced remission showed a higher abundance of fecal unconjugated bile acids.
- Increased gut microbial amino acid and peanut protein metabolism are associated with POIT failure.

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