Fecal microbiota composition and activity of patients with propionic acidemia

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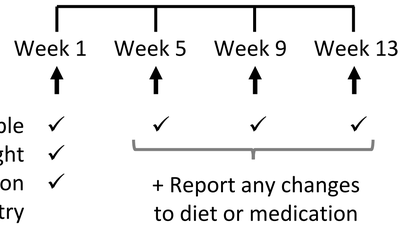
Background and Aim

- Despite intensive dietary and pharma treatment, long-term outcomes of patients with propionic acidemia (PA) remain unsatisfactory[1].
- Bacterial fermentation in the gut is an important source of propionic acid[2] and subsequently propionyl-CoA.
- The **gut microbiota** represents a **relevant**, potentially **modifiable**, **therapeutic target**[3]. However, microbiota **composition and activity in patients with PA is unknown**.
- **Study aim:** To **characterize the gut microbiota of patients with PA** (using fecal samples) and **compare gut microbial diversity** and **microbial metabolite production** between patients and their healthy parent or sibling.

Methods

Study Design



Microbiota characterization (based on stool samples)

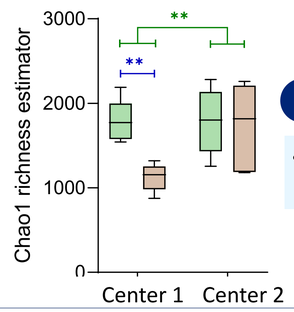
1. Physiological parameter measurements to assess **gut microbiota metabolic activity**: pH, short chain fatty acids (including acetate, propionate & butyrate), ammonia, lactate, and calprotectin.
2. 16S rRNA gene amplicon sequencing for **gut microbiota community profiling**.

Results

1 *Patients' characteristics*

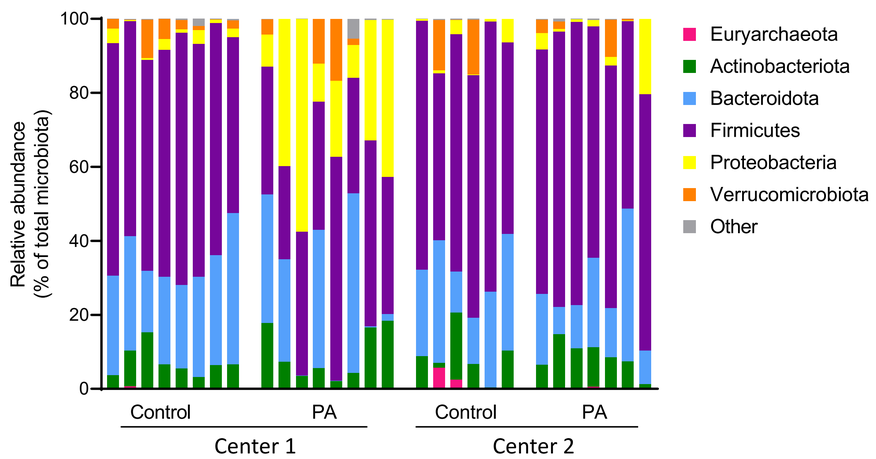
	Center 1 Birmingham	Center 2 Innsbruck
Gender (n ♂/♀)	4 / 4	4 / 3
Age (years)	**7.5 ± 3.7**	**22.1 ± 8.7**
Affected gene (n)	4 *PCCA* / 3 *PCCB*	3 *PCCA* / 4 *PCCB*
Diet (g/kg/d)		
Natural protein	1.11 ± 0.2	0.69 ± 0.27
PE protein substitute	**0**	0.16 ± 0.1
Tube feeding (n yes)	8	2 (1 partial)
Medication		
L-carnitine (mg/kg/d)	89 ± 6	24 ± 10
Antibiotics (n yes)	5	**0**
Laxatives (n yes)	6	**0**
Healthy controls	6 siblings 2 fathers	1 sibling 5 mothers

- **15 patients** & 14 controls included.
- 2 **heterogeneous** cohorts of patients from **Center 1: Birmingham** & **Center 2: Innsbruck**.



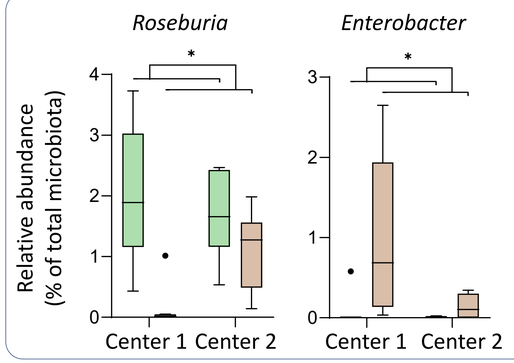
2 *Bacterial α-diversity*

- **Reduced α-diversity** for **patients from Center 1**.



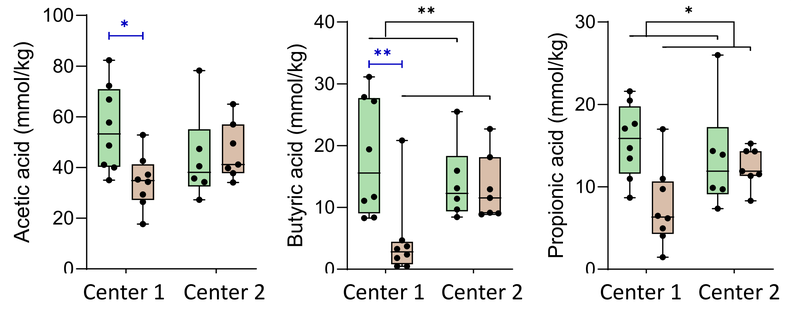
3 *Gut microbiota composition at high level (phylum)*

- **Increase of Proteobacteria in patients** with PA (especially Center 1).



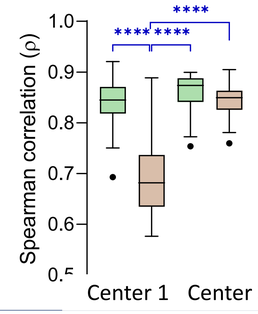
4 *Gut microbiota composition at genus level*

- **28 genera significantly different** between patients and controls (after correcting for Center effect). 2 examples shown (on the left).
- Several **microbial genera depleted in patients** (especially Center 1), e.g., *Roseburia* and *Faecalibacterium*, which harbor many **butyrate producing bacteria**.



5 *Fecal short chain fatty acid levels*

- Most measured **microbial metabolites were lower in patients** and especially butyrate was depleted in patients from Center 1.



6 *Microbiota profile stability (genus level)*

- **Lowest stability** over 3 months for **patients from Center 1**.

Conclusion

- ✓ **Gut (fecal) microbiota of patients with PA characterized for the 1st time**.
- ✓ **Differences in gut microbiota composition & activity** were found **between patients with PA and controls**, especially in Center 1, where patients' microbiota profile showed the lowest diversity and stability.

References: [1]Forny et al. Journal of inherited metabolic disease. 2021; [2]Thompson et al. European Journal of Pediatrics. 1990; [3]Burlina et al. Expert Opinion on Orphan Drugs. 2018