

## Genome-microbiome interactions in human health and complex diseases

Sanna<sup>1,2</sup>, Lopera-Maya<sup>2</sup>, Kurilshikov<sup>2</sup>, van der Graaf<sup>2</sup>, Hu<sup>2</sup>, Andreu-Sánchez<sup>2,3</sup>, Chen<sup>2,4</sup>, Vich Vila<sup>2,3</sup>, Gacesa<sup>2,3</sup>, Sinha<sup>3</sup>, Collij<sup>2,3</sup>, Klaassen<sup>2,3</sup>, Bolte<sup>2,3</sup>, Brandao Gois<sup>2</sup>, Neerincx<sup>2,5</sup>, Swertz<sup>2,5</sup>, LifeLines Cohort Study\*, Harmsen<sup>6</sup>, Wijmenga<sup>2</sup>, Fu<sup>2,4</sup>, Weersma<sup>3</sup>, Zhernakova<sup>2</sup>

<sup>1</sup> Institute for Genetic and Biomedical Research (IRGB), National Research Council (CNR), Cagliari,

<sup>2</sup> Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

<sup>3</sup> Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

<sup>4</sup> Department of Pediatrics, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

<sup>5</sup> University of Groningen, University Medical Center Groningen, Genomics Coordination Center, Groningen, the Netherlands.

### Background:

The gut microbiome is known to be similar among family members, yet is unclear how much this is due to shared genetic or to shared environment, and which genetic variants are involved. Identification of genetic effects on microbiome is essential in the prospective of using microbiome as alternative personalized therapy.

### Methods and Results:

To robustly characterize these effects, we performed the largest genetic study of human gut microbiome from a single population and using metagenomic sequencing. We identified two study-wide significant association signals near the *LCT* and *ABO* genes, highlighting novel associations with species and bacterial pathways. In silico analyses and functional studies in-vitro suggested that these genes contribute to the set-up of a favorable environment in the gut for the associated bacteria. We estimated that tens of thousands of samples are necessary to detect novel genome-microbiome interactions, but statistical power could be enhanced with different study approaches.

### Conclusions and Significance:

We performed the largest genetic associated study of microbiota and validated associations using in silico and in vitro experiments. Our studies have elucidated directions for future studies on gut microbiome aiming to understand interactions with the host genome.

### Keywords:

Gut microbiome, genetics, host-microbiome interaction

## References:

Gacesa R, Kurilshikov A, Vich Vila A, Sinha T, Klaassen MAY, Bolte LA, Andreu-Sánchez S, Chen L, Collij V, Hu S, Dekens JAM, Lenters VC, Björk JR, Swarte JC, Swertz MA, Jansen BH, Gelderloos-Arends J, Jankipersadsing S, Hofker M, Vermeulen RCH, Sanna S, Harmsen HJM, Wijmenga C, Fu J, Zhernakova A, Weersma RK. *Environmental factors shaping the gut microbiome in a Dutch population*. 2022 Nature. 604(7907):732-739

Lopera-Maya, Kurilshikov, van der Graaf, Hu , Andreu-Sánchez, Chen, Vich Vila, Gacesa, Sinha, Collij, Klaassen, Bolte, Brandao Gois, Neerincx, Swertz, LifeLines Cohort Study\*, Harmsen, Wijmenga, Fu, Weersma, Zhernakova and Sanna S. *Effect of host genetics on the gut microbiome in 7,738 participants of the Dutch Microbiome Project*. 2022, Nature Genetics, 54(2):143-151

Sanna S, Kurilshikov A, van der Graaf A, Fu J, Zhernakova A. *Challenges and future directions for studying effects of host genetics on the gut microbiome*. 2022, Nat Genetics, 54(2):100-106.

Sanna S, van Zuydam NR, Mahajan A, Kurilshikov A, Vich Vila A, Vösa U, Mujagic Z, Masclee AAM, Jonkers DMAE, Oosting M, Joosten LAB, Netea MG, Franke L, Zhernakova A, Fu J, Wijmenga C, McCarthy MI. *Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases*. 2019 Nat Genetics, 51(4):600-605

## Thematic Area:

- Frontiers in Microbiome Research
- ⊖ ~~Microbiome: from Research to Clinics~~

## Infrastructures:

N.A.