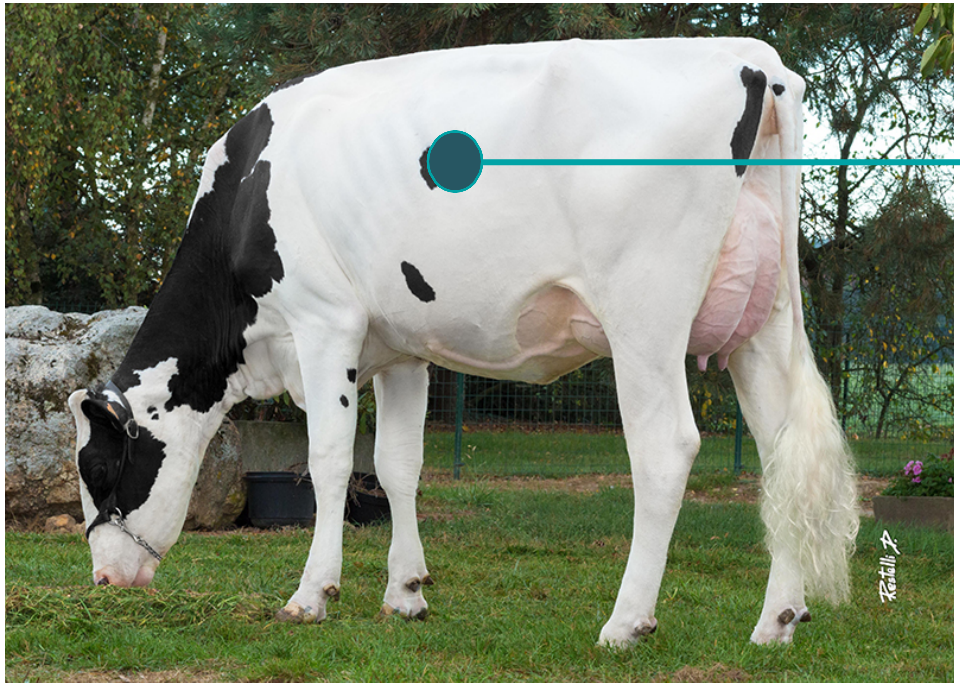
Host genetics affects the composition of the lower gut microbiota in dairy cows

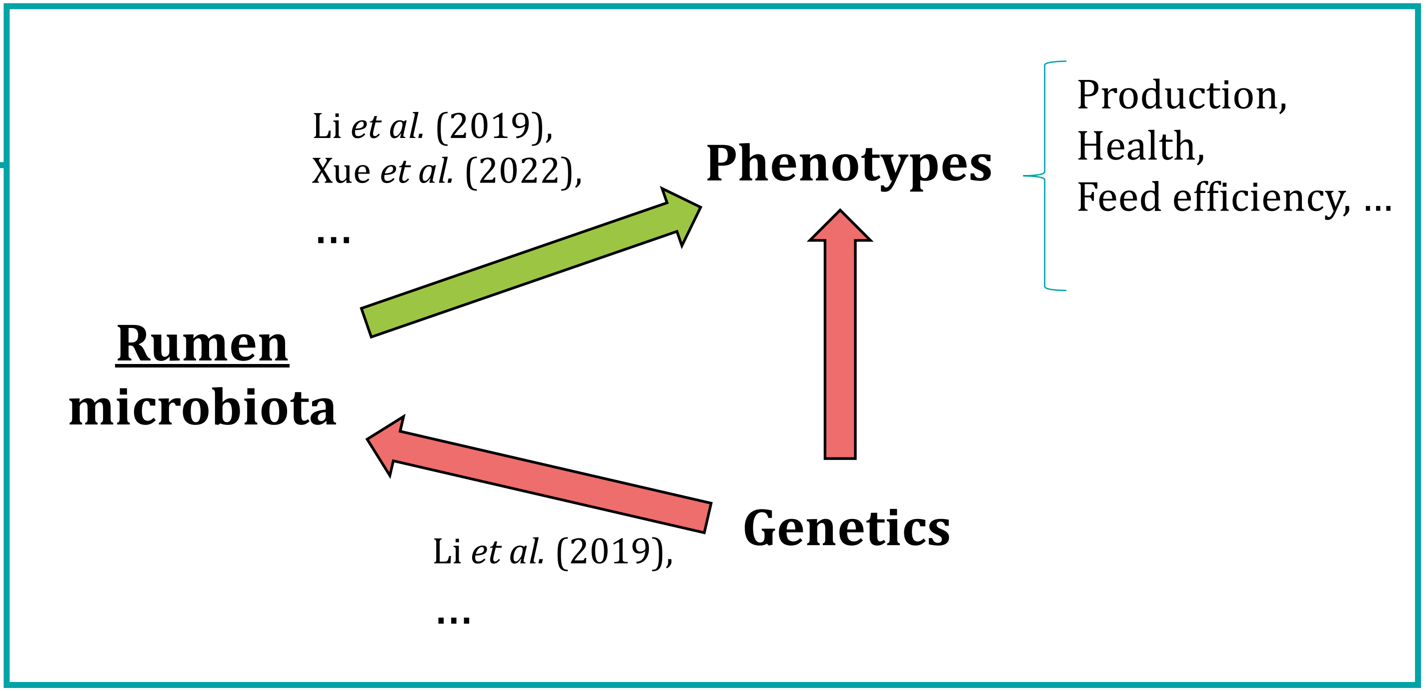
Brulin L.[1,2]*, Ducrocq S.[1], Estellé J.[2], Even G.[1], Martel S.[1],
Audebert C.[1], Croiseau P.[2], Sanchez M.P.[2]

1 GDBiotech / Gènes Diffusion, 59501 Douai Cedex, France
2 Université Paris-Saclay, INRAE, AgroParisTech, GABI, 78350 Jouy-en-Josas, France

* Correspondence: l.brulin@genesdiffusion.com

Introduction





Li *et al.* (2019),
Xue *et al.* (2022),
…

Phenotypes

Production,
Health,
Feed efficiency, …

Rumen microbiota

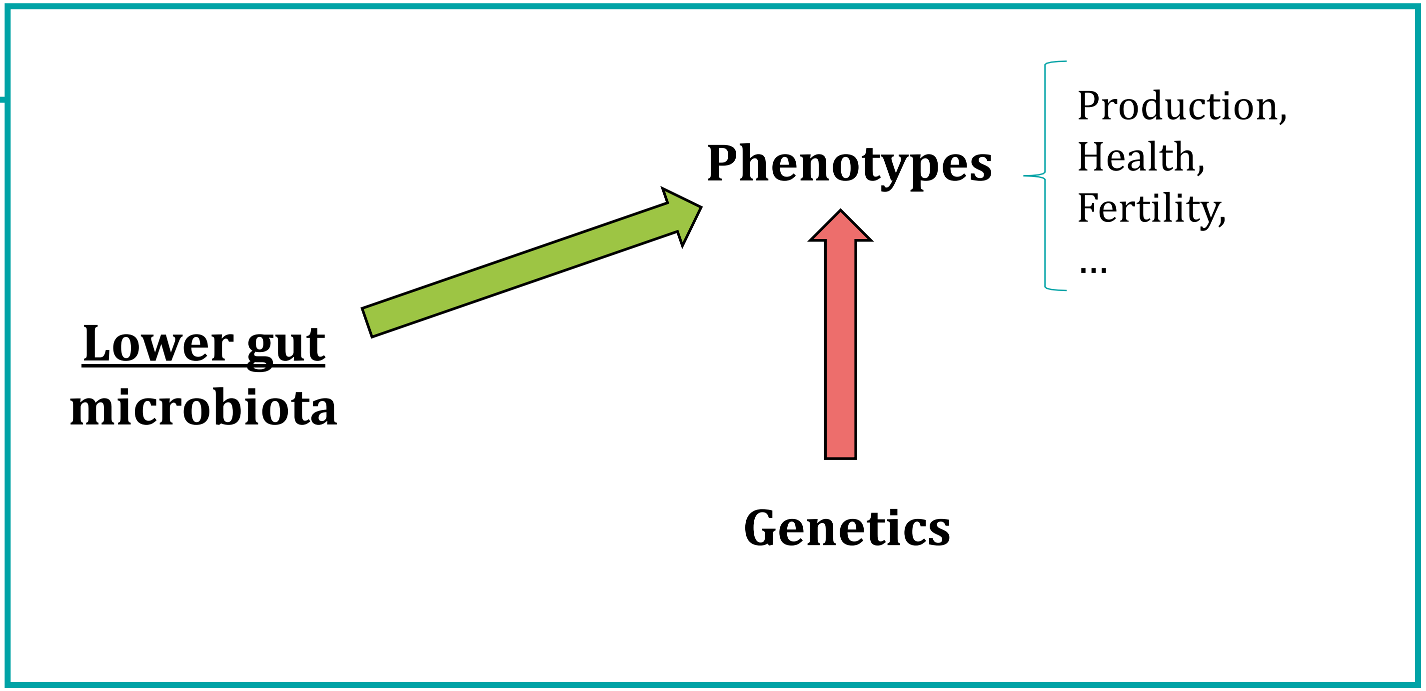
Genetics

Li *et al.* (2019),
…

But rumen sampling requires **complex** and **intrusive** manipulations…

→ Difficult to carry on a **large** population

Introduction



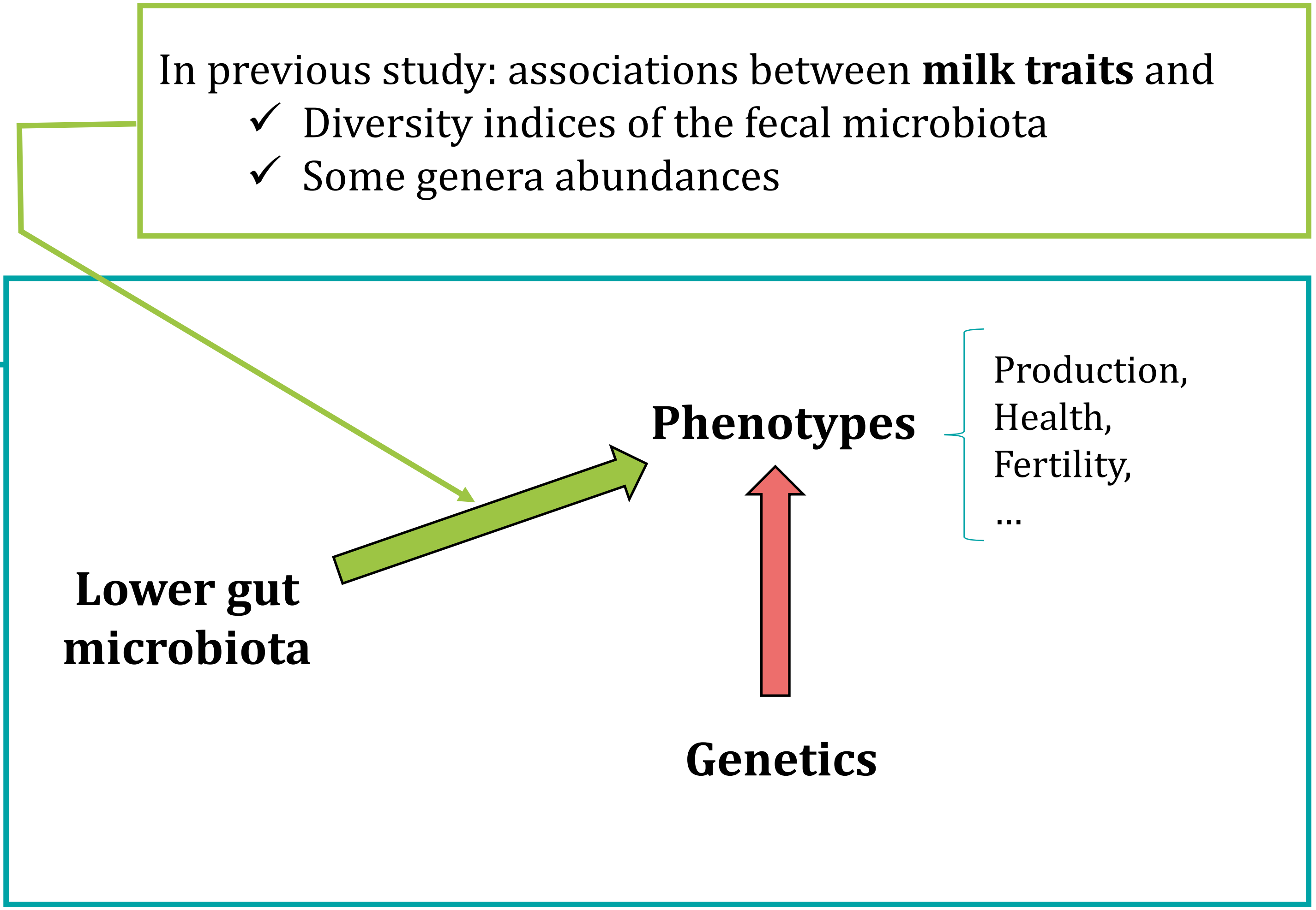
Lower gut microbiota

Phenotypes

Production,
Health,
Fertility,
…

Genetics

Introduction



In previous study: associations between **milk traits** and
- ✓ Diversity indices of the fecal microbiota
- ✓ Some genera abundances

Lower gut microbiota

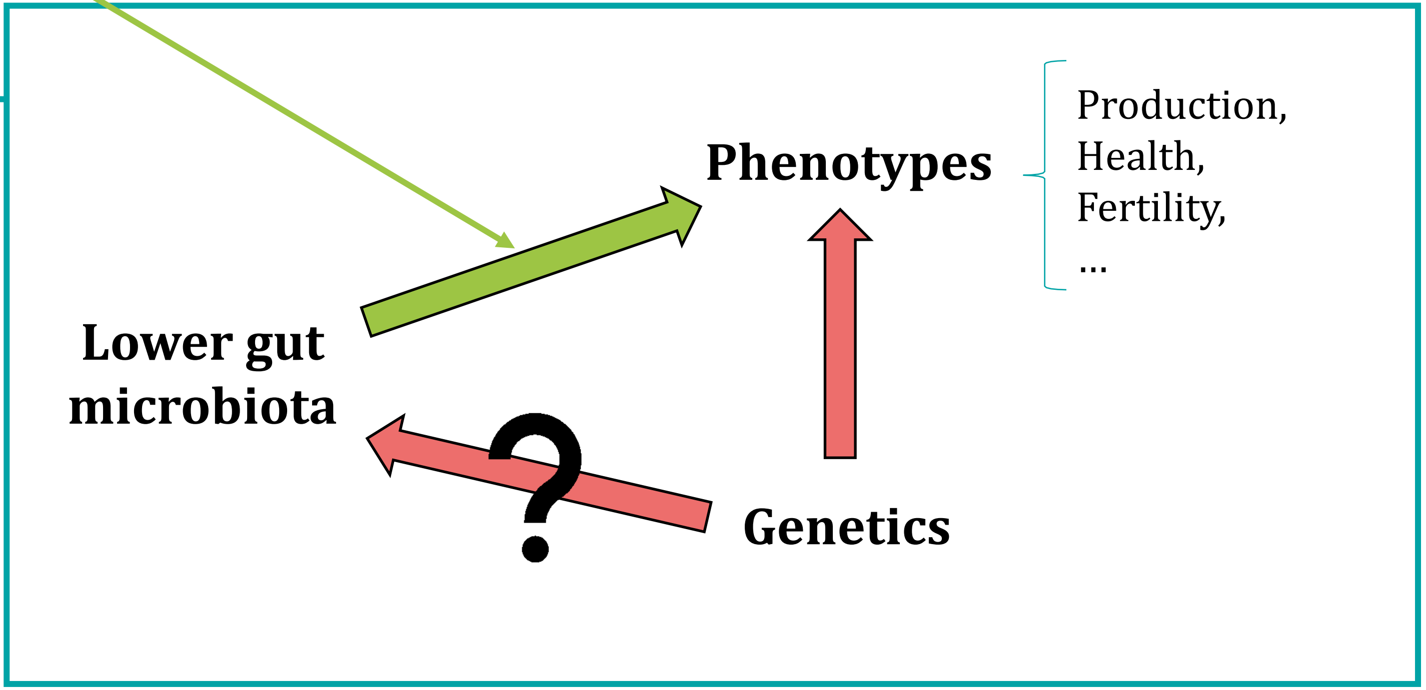
Phenotypes

Production,
Health,
Fertility,
…

Genetics

Introduction

In previous study: associations between **milk traits** and
- ✓ **Diversity indices**
- ✓ Some **genera abundances**


Lower gut microbiota

Phenotypes

Production,
Health,
Fertility,
…

Genetics

Is the lower gut microbiota under the control of the host genome in dairy cows?

Material and Methods

1860 Holstein cows

140 herds

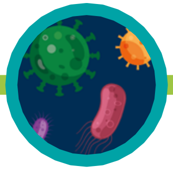
2020 – 2022

4 parities

30 lactation stages

Material and Methods

1860 Holstein cows
140 herds
2020 – 2022
4 parities
30 lactation stages



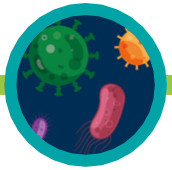
Lower gut sampling

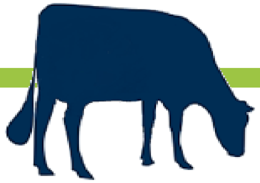
16S rRNA sequencing and grouping into **ASVs** (DADA2)

- **Abundance**
  - Centered log-ratios abundances of 90 genera

Material and Methods

1860 Holstein cows
140 herds
2020 – 2022
4 parities
30 lactation stages





Lower gut sampling

16S rRNA sequencing and grouping into **ASVs** (DADA2)

- **Abundance**
  - Centered log-ratios abundances of 90 genera

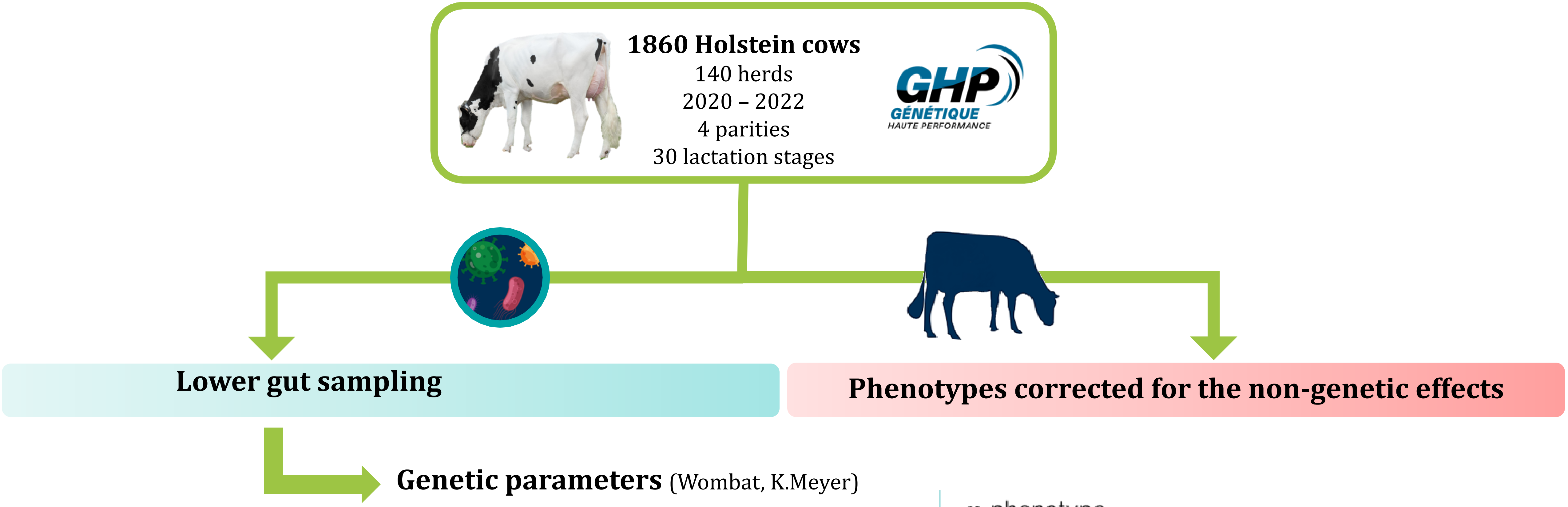
Phenotypes corrected for the non-genetic effects

Production
- Milk, Fat and Protein yields (MY, FY and PY)
- Fat and Protein contents (FC and PC)

Fertility
- Calving – First AI interval (CAIf)
- AI1 – AIf interval (IFL)
- Fertility (FERC)

Health
- Somatic cell counts (CEL)
- Production corrected-longevity (LGF)

Genetic parameters



1860 Holstein cows
140 herds
2020 – 2022
4 parities
30 lactation stages

Lower gut sampling

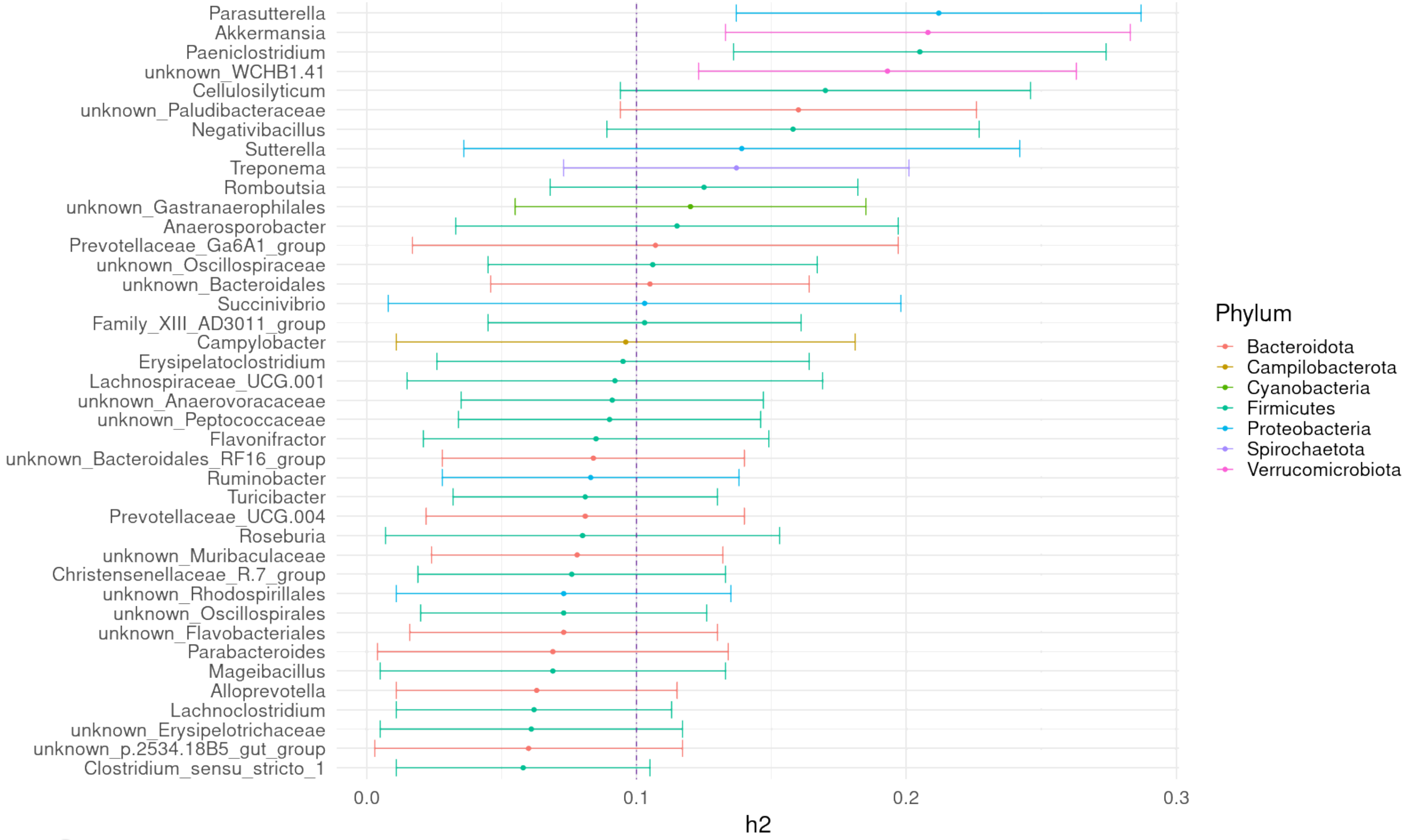
Phenotypes corrected for the non-genetic effects

Genetic parameters (Wombat, K.Meyer)

$$\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{Z\alpha} + \boldsymbol{e}$$

$\boldsymbol{y}$: phenotype ;
$\boldsymbol{\beta}$: fixed effects (herd-season-lab batch, parity, lactation stages);
$\boldsymbol{\alpha}$: additive genetic effects ;
$\boldsymbol{X}$ and $\boldsymbol{Z}$: incidence matrices ;
$\boldsymbol{e}$: residuals

Heritabilities

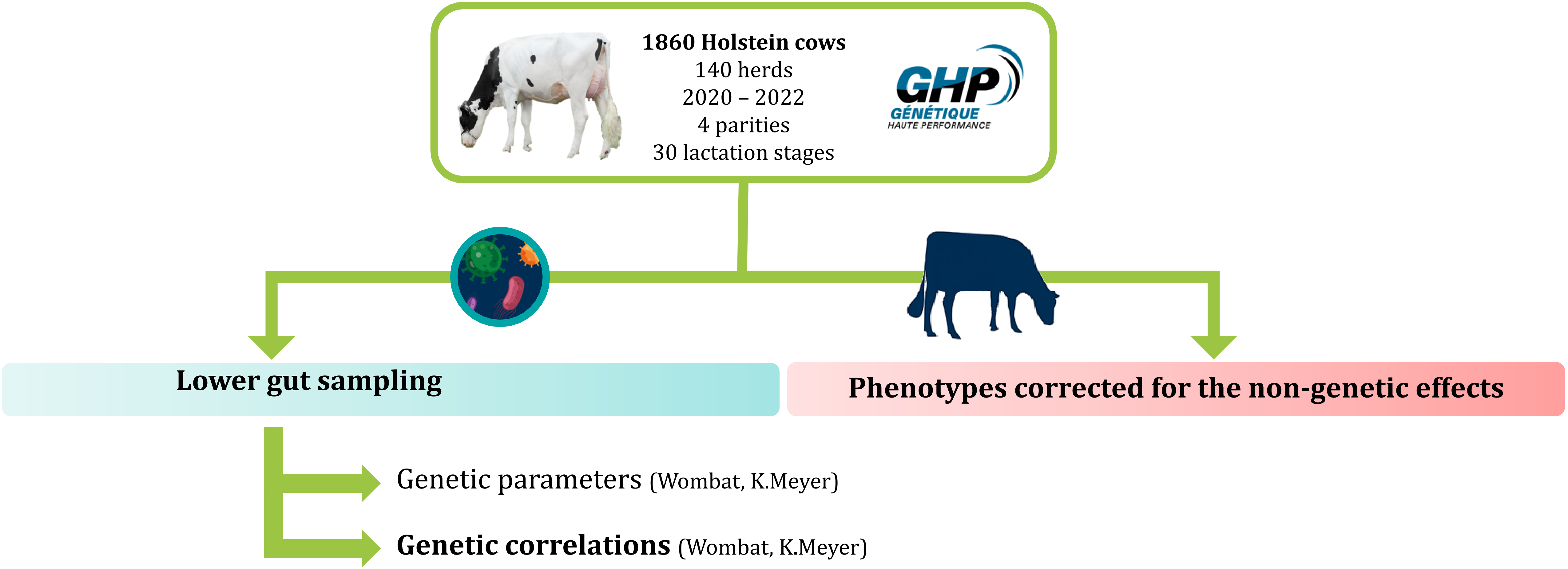


40/90 heritable genera

Range: 0.06 – 0.22

17 genera with $h^2 \geq 0.10$

Genetic correlations



1860 Holstein cows
140 herds
2020 – 2022
4 parities
30 lactation stages

Lower gut sampling

Phenotypes corrected for the non-genetic effects

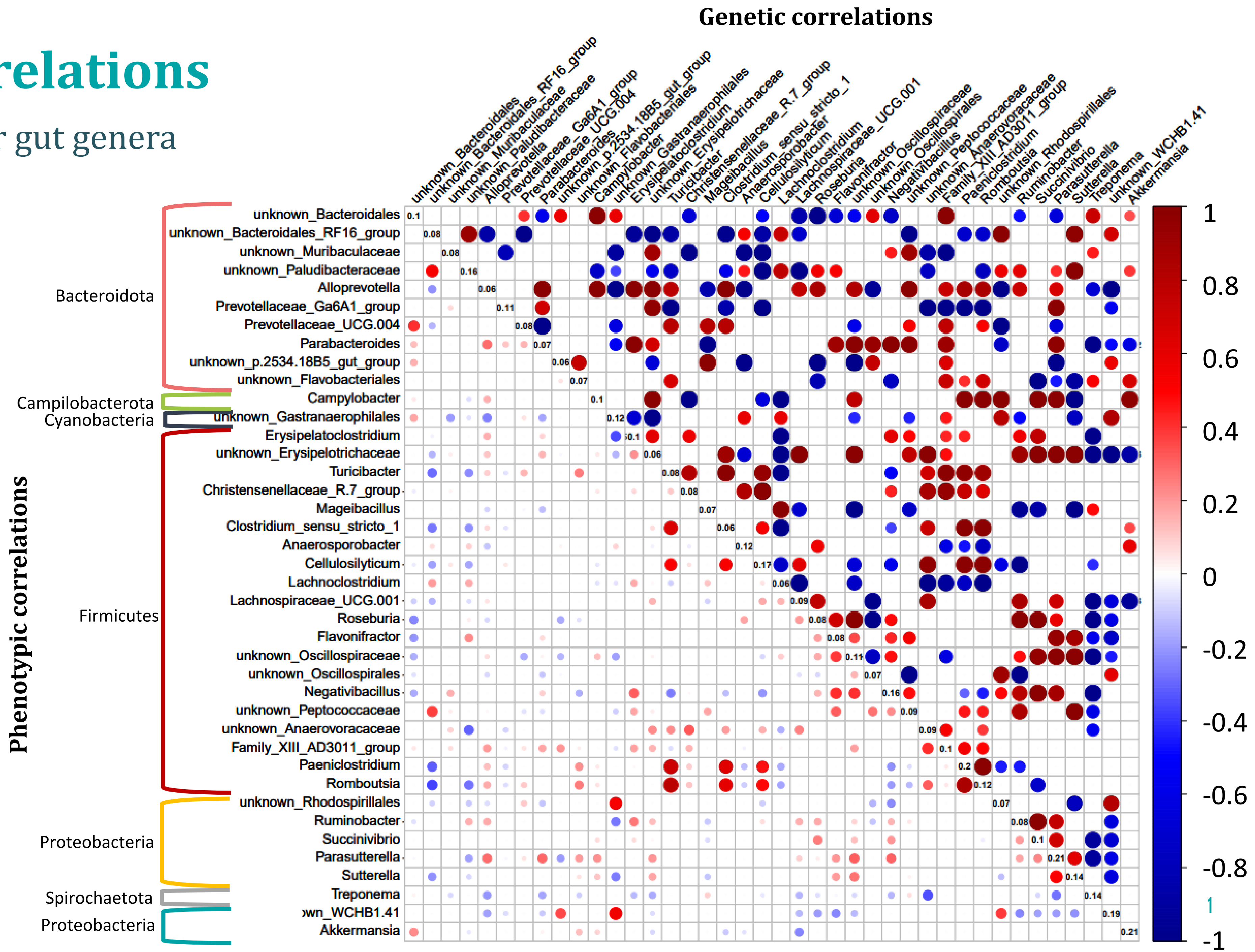
- Genetic parameters (Wombat, K.Meyer)
- **Genetic correlations** (Wombat, K.Meyer)

$$\begin{cases} y_1 = X_1\beta_1 + Z_1\alpha_1 + e \\ y_2 = X_2\beta_2 + Z_2\alpha_2 + e \end{cases}$$

y_i: phenotype of trait ***i*** ; β_i: fixed effects of trait ***i*** ; α_i: additive genetic effects of trait ***i*** ; X_i and Z_i : incidence matrices of trait ***i***; ***e*** : residuals

Genetic correlations

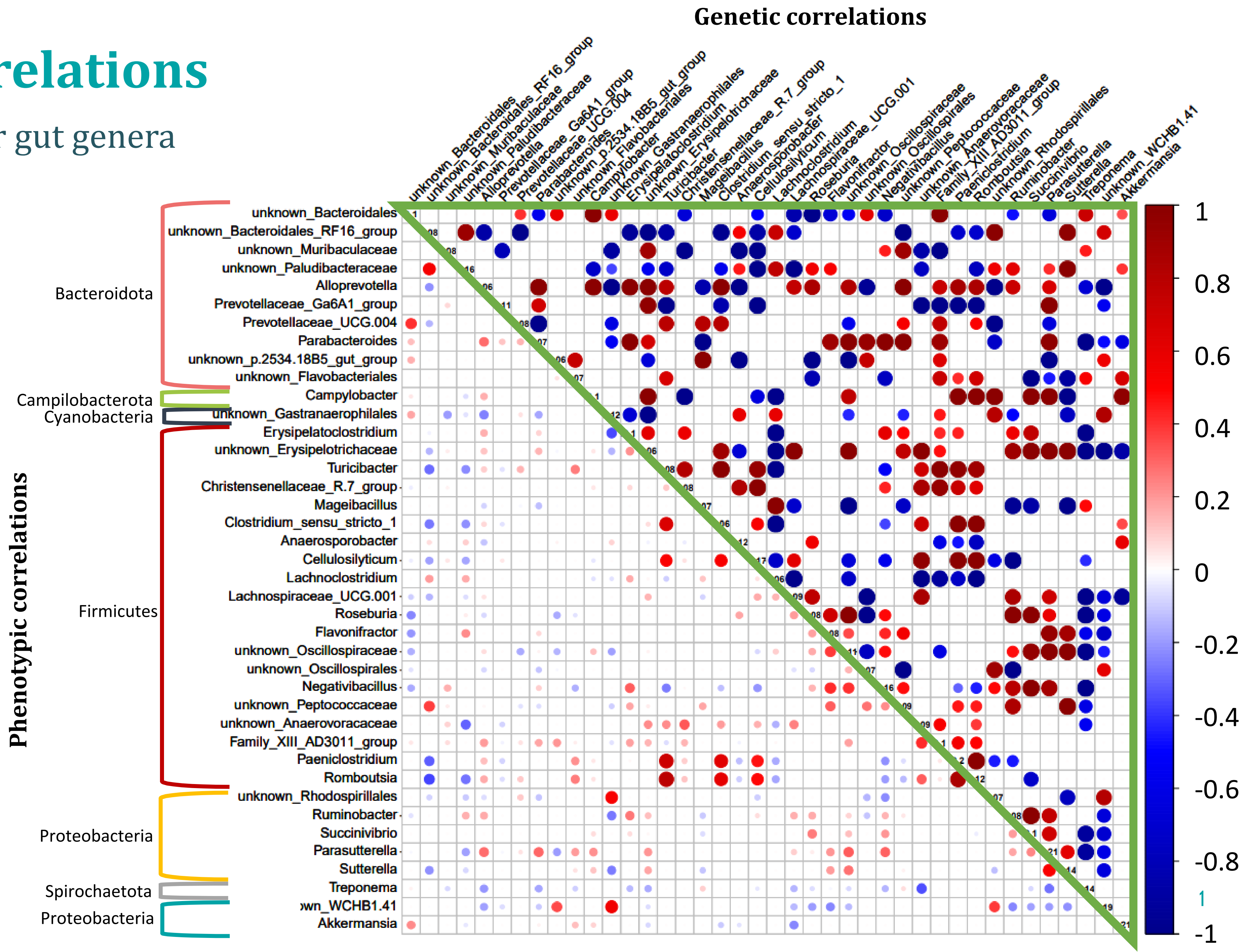
Correlations between lower gut genera



Genetic correlations

Correlations between lower gut genera

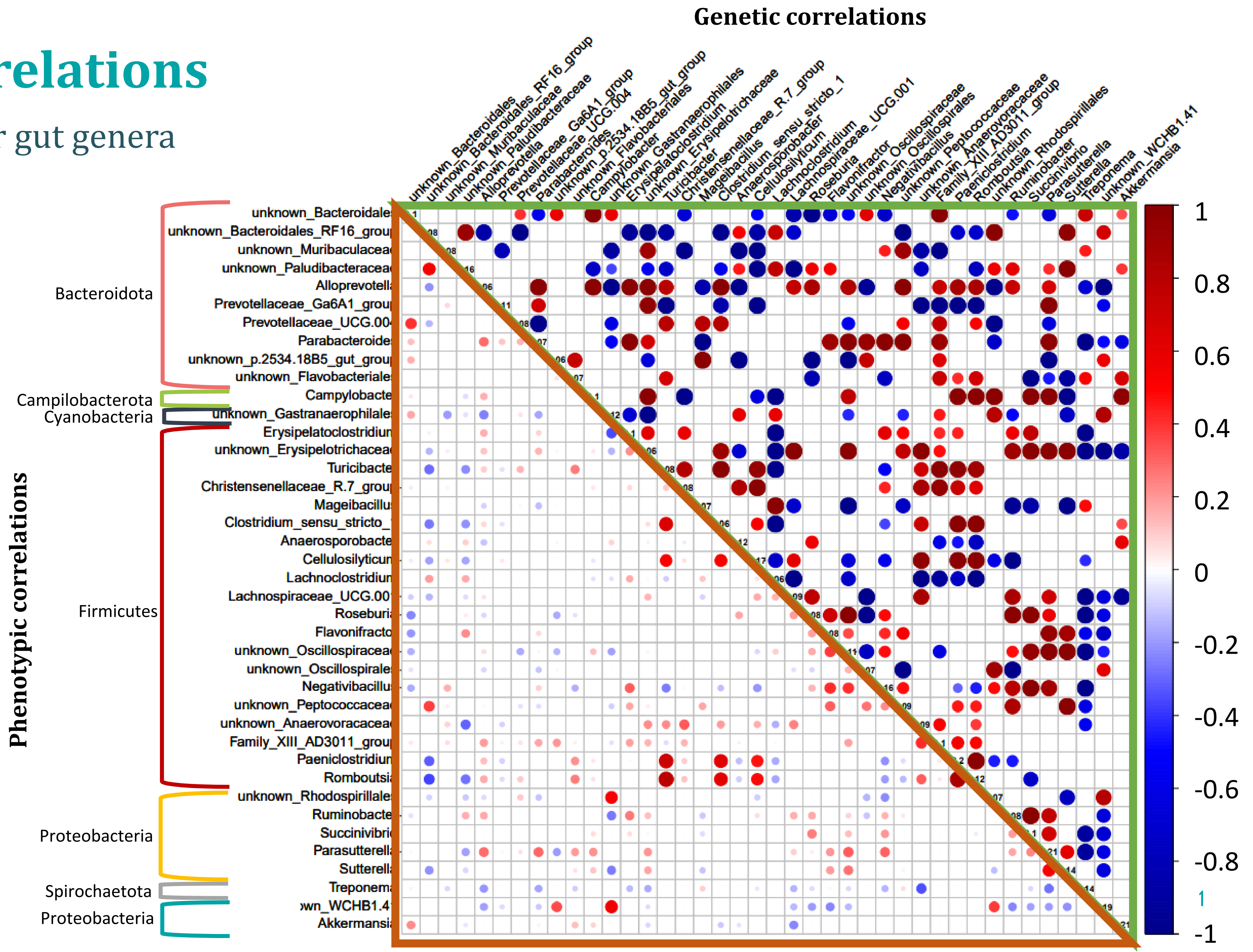
Genetic correlations



Genetic correlations

Correlations between lower gut genera

Genetic correlations >>
Phenotypic correlations



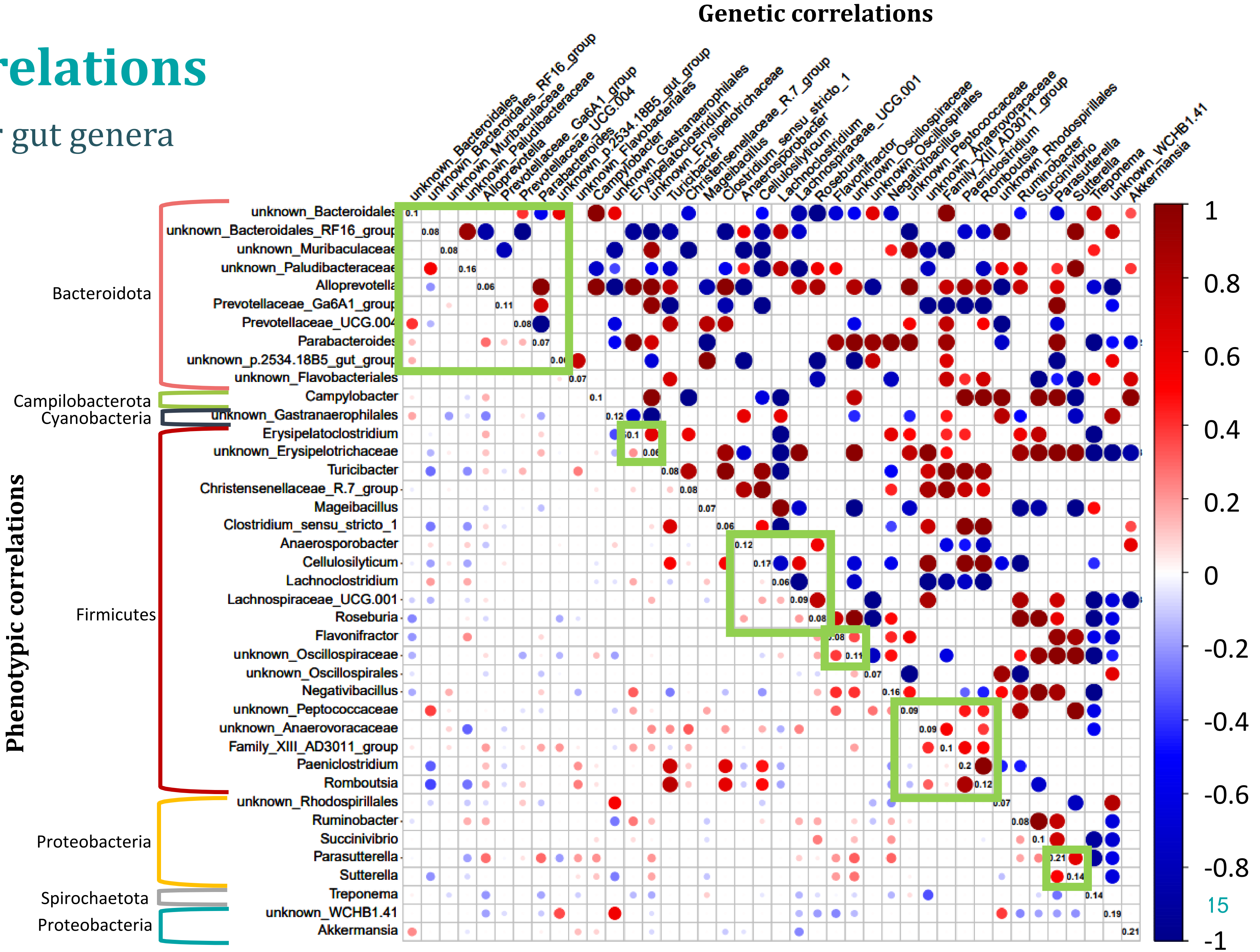
Genetic correlations

Correlations between lower gut genera

Genetic correlations >> Phenotypic correlations

Genetically close taxa are often genetically correlated …

BUT NOT ONLY!



Genetic correlations

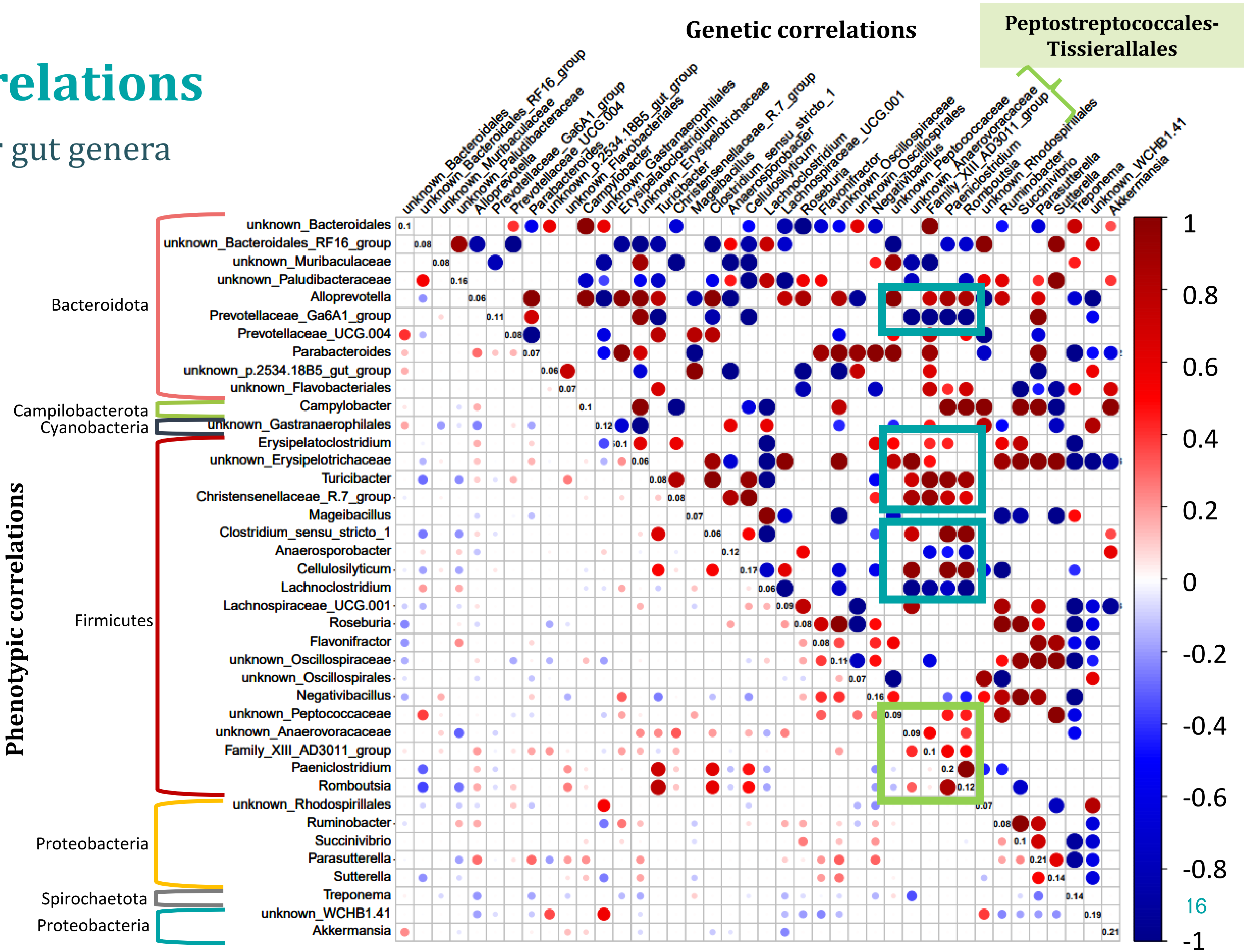
Correlations between lower gut genera

Genetic correlations >> Phenotypic correlations

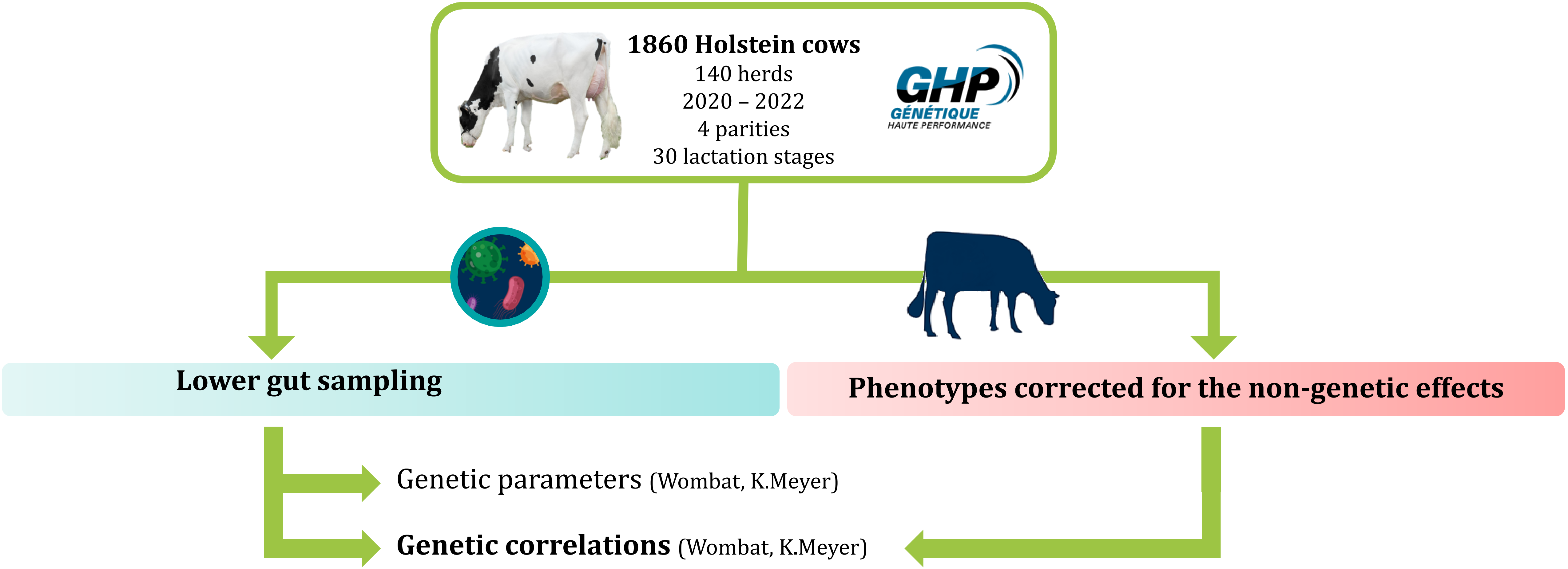
Genetically close taxa are often genetically correlated ...

BUT NOT ONLY!

Correlations with different taxa are similar for genera of the same family/order...



Genetic correlations



1860 Holstein cows
140 herds
2020 – 2022
4 parities
30 lactation stages

Lower gut sampling

Phenotypes corrected for the non-genetic effects

Genetic parameters (Wombat, K.Meyer)

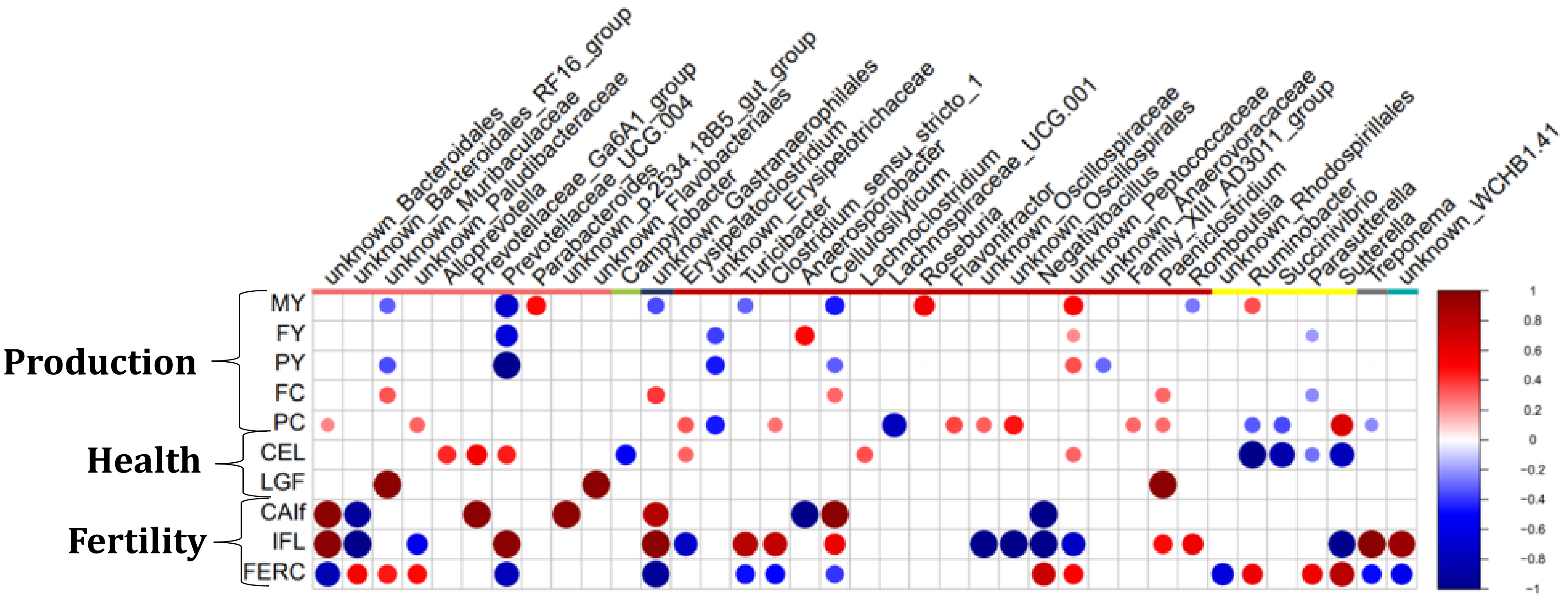
Genetic correlations (Wombat, K.Meyer)

$$\begin{cases} y_1 = X_1\beta_1 + Z_1\alpha_1 + e \\ y_2 = X_2\beta_2 + Z_2\alpha_2 + e \end{cases}$$

$\boldsymbol{y_i}$: phenotype of trait $\boldsymbol{i}$; $\boldsymbol{\beta_i}$: fixed effects of trait $\boldsymbol{i}$; $\boldsymbol{\alpha_i}$: additive genetic effects of trait $\boldsymbol{i}$; $\boldsymbol{X_i}$ and $\boldsymbol{Z_i}$: incidence matrices of trait $\boldsymbol{i}$; $\boldsymbol{e}$: residuals

Genetic correlations

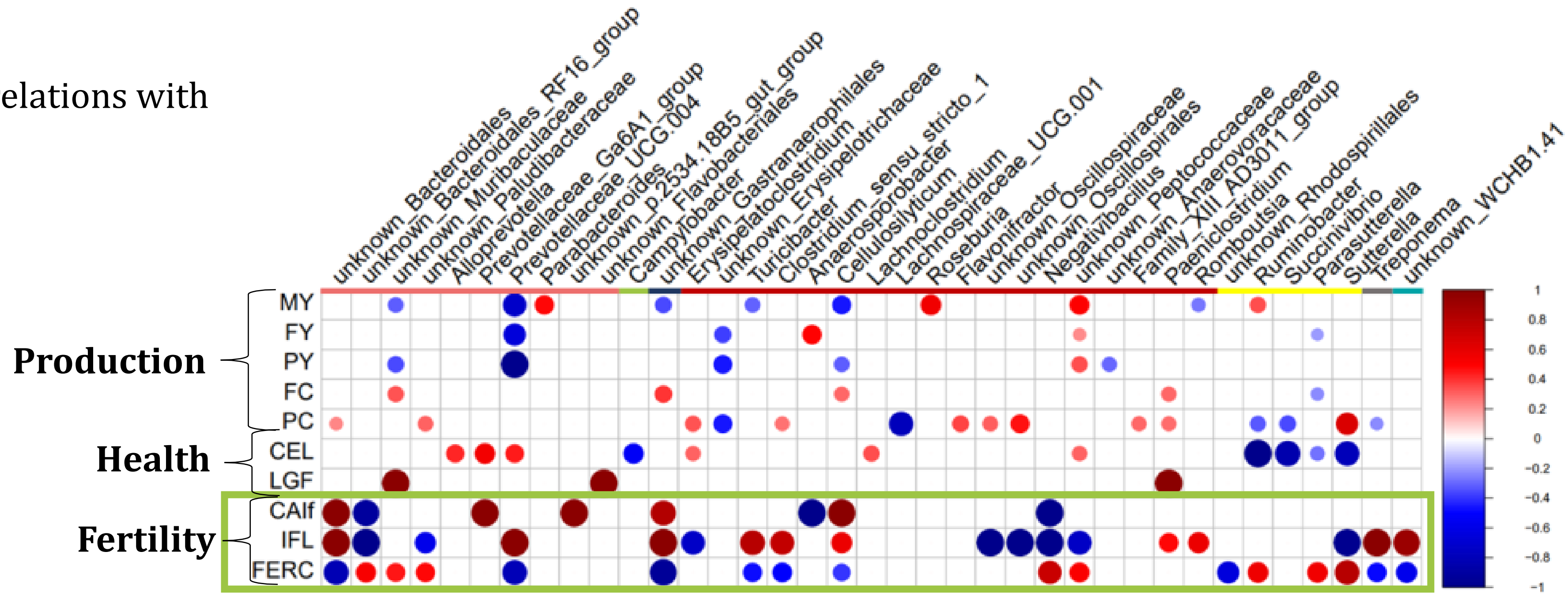
Genetic correlations between lower gut genera and phenotypes



Genetic correlations

Genetic correlations between lower gut genera and phenotypes

Fertility traits had strong genetic correlations with genera (*i.e.* AI1 – AIf interval)



Genetic correlations

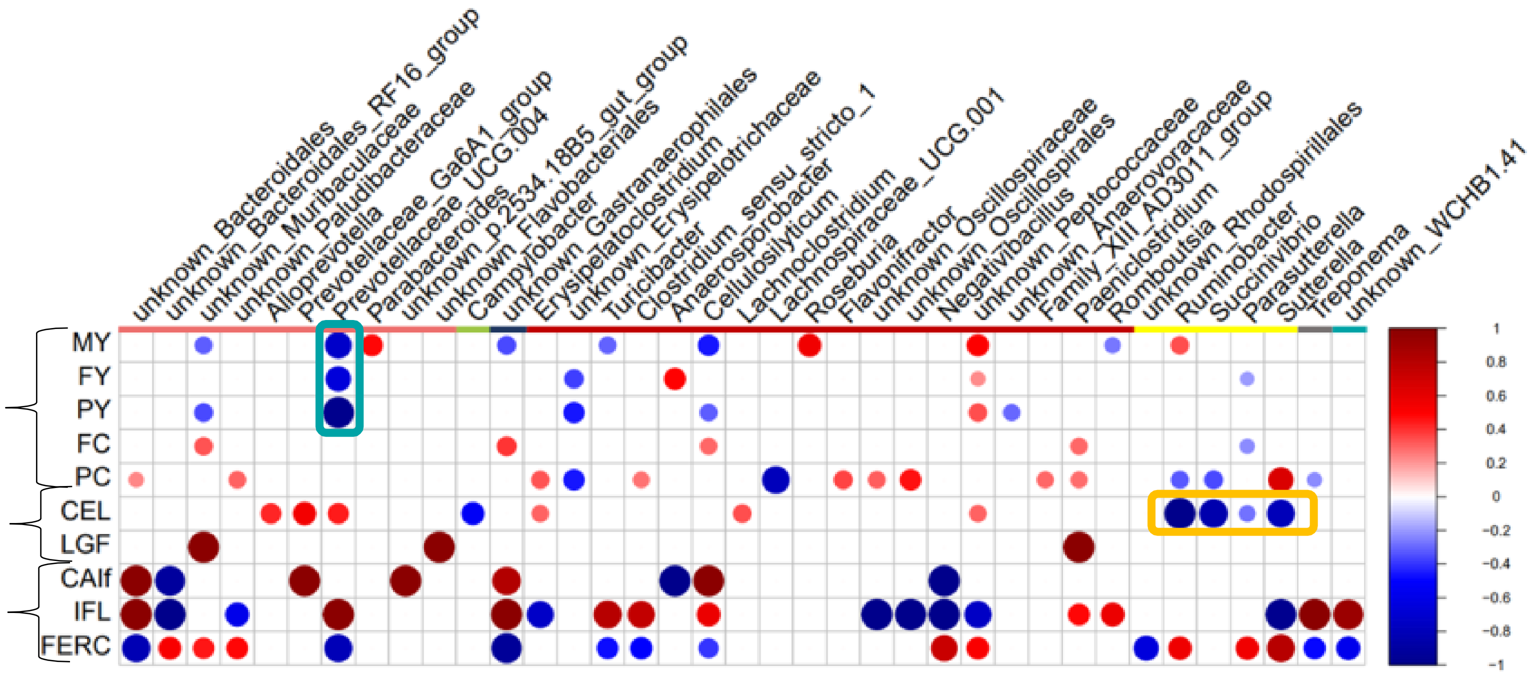
Genetic correlations between lower gut genera and phenotypes

Fertility traits had strong genetic correlations with genera (*i.e.* AI1 – AIf interval)

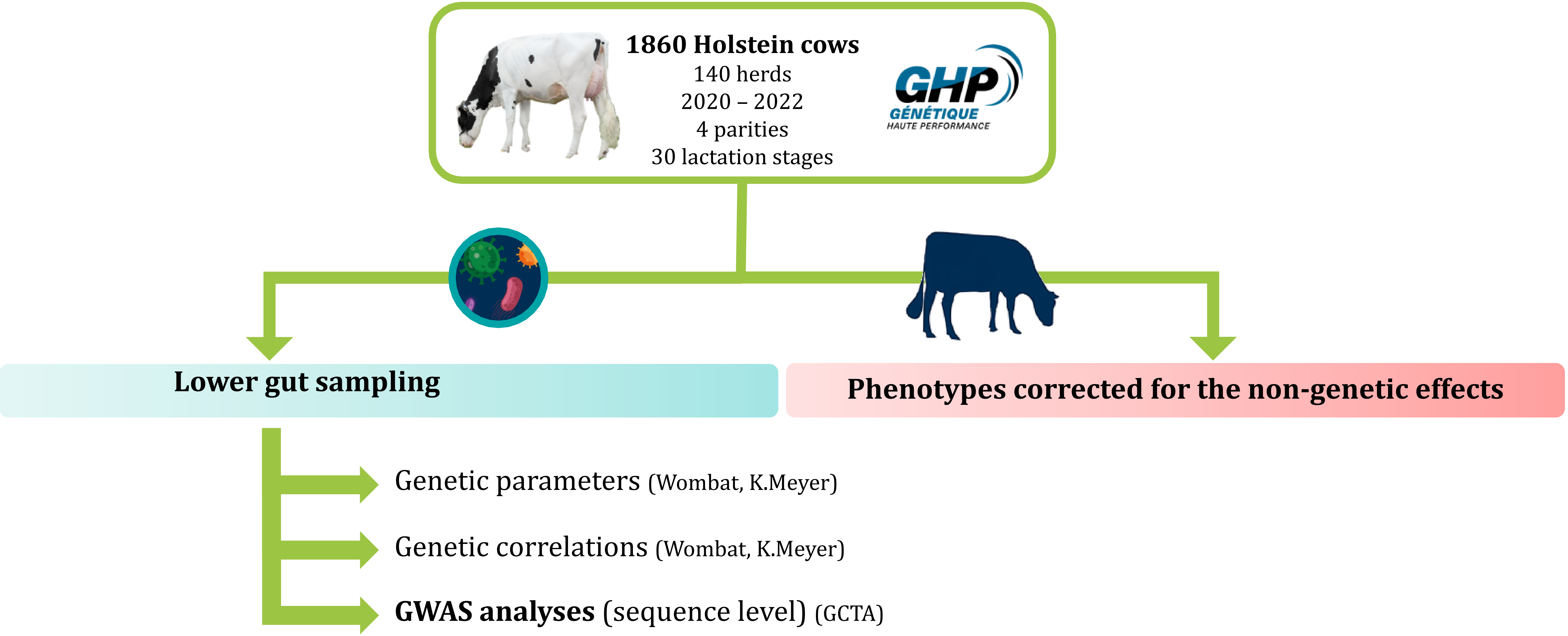
Prevotellaceae UCG.004 negatively correlated with **yield-traits** as Prevotellaceae family (Zhang *et al.*, 2022)

Genetically close genera tended to present similar correlations :

- Somatic cell counts **negatively** correlated with Gammaproteobacteria order
- Succinivibrionaceae family and Proteobacteria phylum enriched in cows **with low amounts of somatic cells** (Zhong *et al.*, 2018)



GWAS



1860 Holstein cows
140 herds
2020 – 2022
4 parities
30 lactation stages

Lower gut sampling

Phenotypes corrected for the non-genetic effects

- Genetic parameters (Wombat, K.Meyer)
- Genetic correlations (Wombat, K.Meyer)
- **GWAS analyses** (sequence level) (GCTA)

$$y_i = \mu + bg_i + u_i + e_i$$

y: corrected phenotype ; μ: mean ; b: incidence matrix for the tested variant ; g: variant effect ; u, genetic values ; e: residuals

GWAS

General method

Sequence-level imputations in two steps for 29 chromosomes

Use of 1000 bovine genomes project (3414 animals including 1414 Holstein individuals)

→

GWAS on the sequences (~13M variants) of 55 genera

Increased detection power and better resolution

→

Detection of QTLs using $p < 1x10^{-6}$ as a significant threshold

54 QTLs detected

GWAS

General results

Sequence-level imputations in two steps for 29 chromosomes

Use of 1000 bovine genomes project (3414 animals including 1414 Holstein individuals)

→

GWAS on the sequences (~13M variants) of 55 genera

Increased detection power and better resolution

→

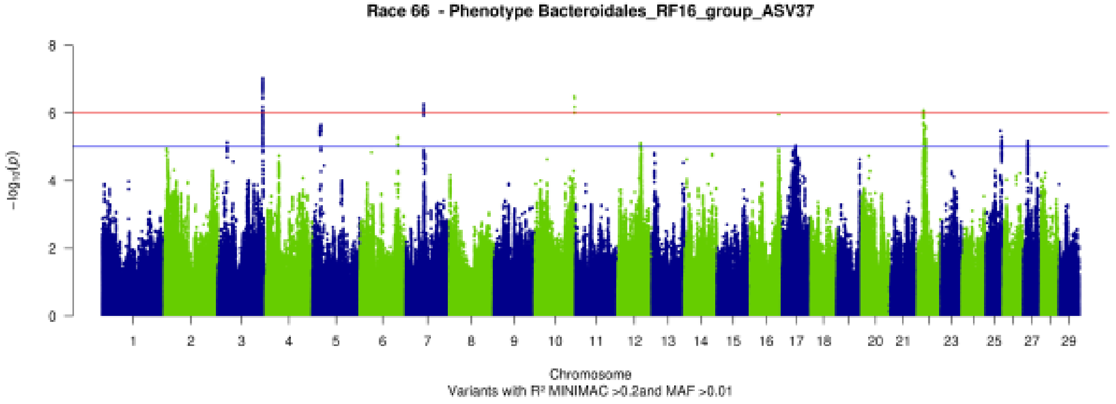
Detection of QTLs using $p < 1x10^{-6}$ as a significant threshold

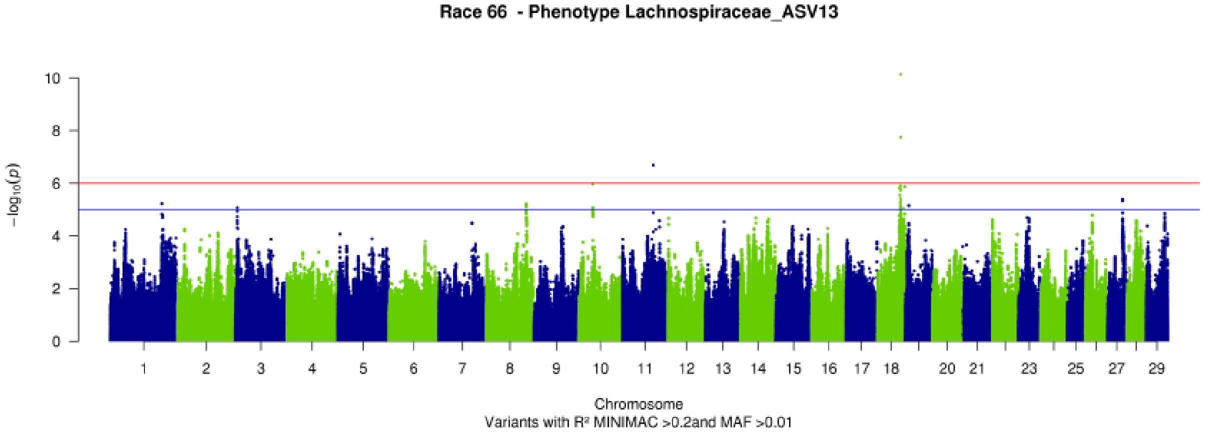
54 QTLs detected

	Minimum	**Mean**	**Maximum**	**SD**
Number QTL/chromosome	0	~2	5	1.4
Number QTL/taxa	0	~1	4	1.0
Significativity of the variants ($-\log10(p) \geq 6$)	6.0	6.6	10.1	0.5

GWAS

General results

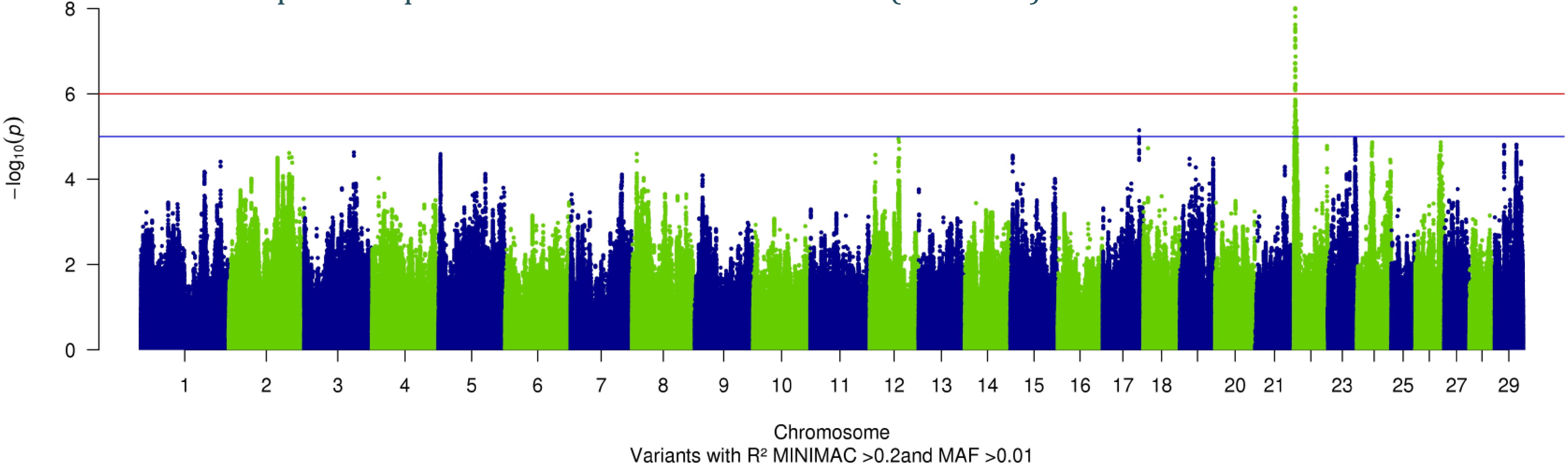

Race 66 - Phenotype Bacteroidales_RF16_group_ASV37


Race 66 - Phenotype Lachnospiraceae_ASV13

	Minimum	Mean	Maximum	SD
Number QTL/chromosome	0	~2	5	1.4
Number QTL/taxa	0	~1	4	1.0
Significativity of the variants ($-\log10(p) \geq 6$)	6.0	6.6	10.1	0.5

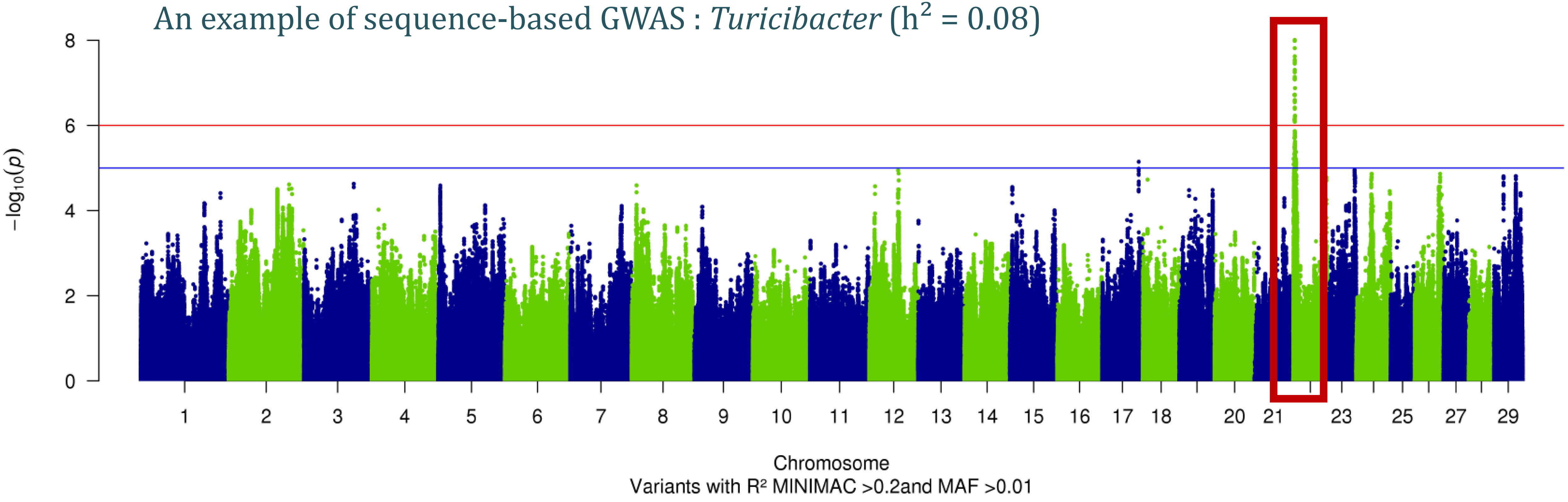
GWAS

An example of sequence-based GWAS : *Turicibacter* ($h^2 = 0.08$)



- Commonly found in mammalian gut
- Associated with lipid metabolism (Lynch *et al.*, 2023)

GWAS

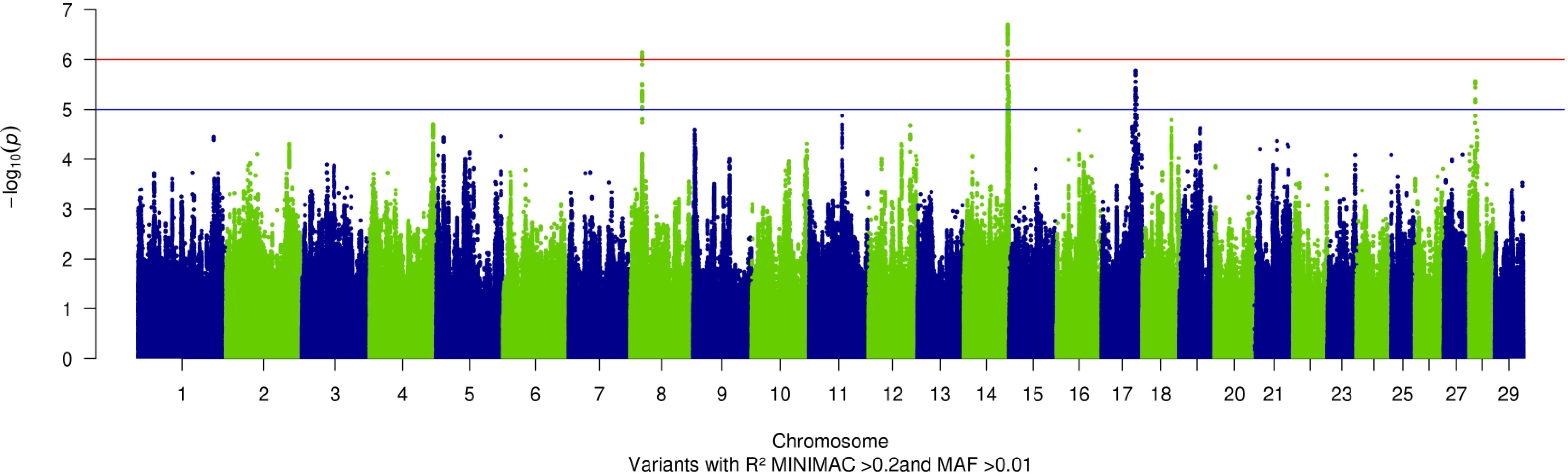


An example of sequence-based GWAS : *Turicibacter* ($h^2 = 0.08$)

- 1 major QTL on BTA22:
  - *EOMES* gene: differenciation of CD8+ T-cells which alter gut microbiota (Labarta-Bajo *et al.*, 2020)
  - *CMC1* gene: feed efficiency (Hardie *et al.*, 2017)

GWAS

An example of sequence-based GWAS : *Cellulosilyticum* ($h^2 = 0.17$)

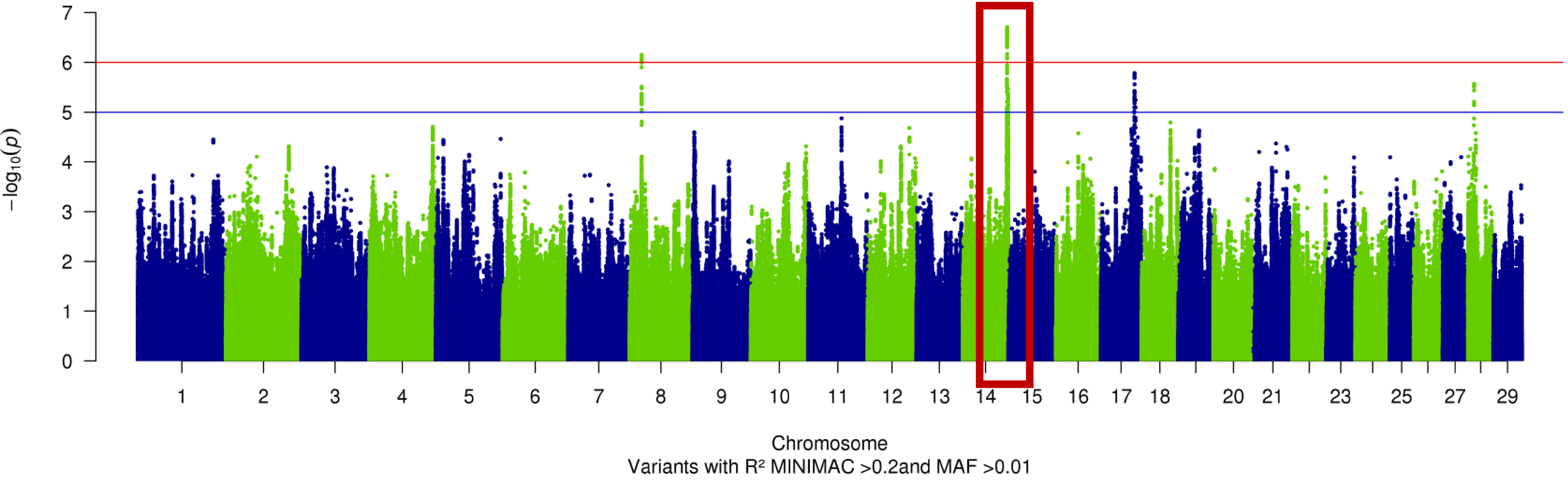


Variants with R² MINIMAC >0.2and MAF >0.01

- Cellulose-degrading genus
- Associated with older animals (Zhang *et al.*, 2019)

GWAS

An example of sequence-based GWAS : *Cellulosilyticum* ($h^2 = 0.17$)

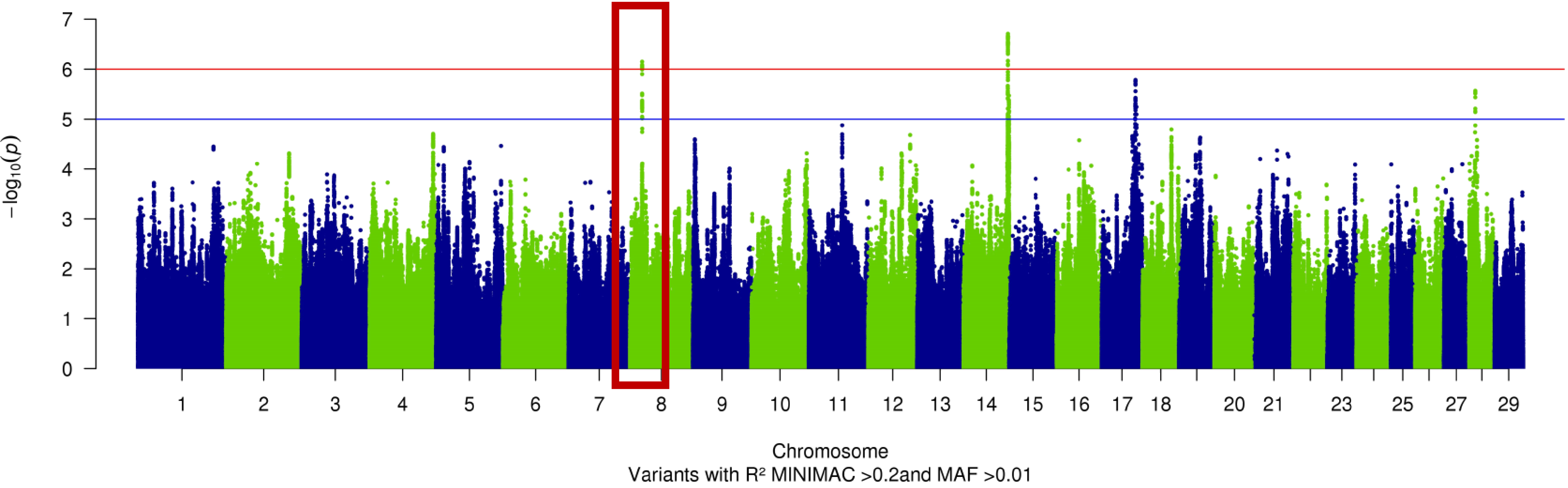


Potential QTL on BTA14:

- Presence of **Copy Number Variants** (CNVs) in the significant region? (Liu *et al.,* 2010; Mesbah *et al.*, 2017)

GWAS

An example of sequence-based GWAS : *Cellulosilyticum* ($h^2 = 0.17$)



On BTA8:

- Presence of **Copy Number Variants** (CNVs) in the significant region? (Boussaha *et al.*, 2016; Mesbah *et al.*, 2017)
- *DMRT1* gene: associated with body weight and change in gut microbiota in chicken (Ji *et al.*, 2020)

Take home messages

- ✓ The abondance of some genera is associated with the **host's genetics**.
- ✓ The **genetic correlations** between taxa help visualising associations inside the lower gut microbiota.
- ✓ Some taxa are genetically correlated with **traits of interest.**
- ✓ GWAS analyses highlight **QTLs and candidate genes** that are associated with some taxa abundance


Han Hopman

GENES DIFFUSION
PERFORMANCE PARTAGÉE

GD Biotech
AGRI-AGRO SOLUTIONS

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INRAE

Ecole Doctorale ABIES

AgroParisTech

université PARIS-SACLAY

Cifre Conventions

ANRT
ASSOCIATION NATIONALE RECHERCHE TECHNOLOGIE

Thank you for your attention!

Host genetics affects the composition of the lower gut microbiota in dairy cows

Brulin L.[1,2]*, Ducrocq S.[1], Estellé, J.[2], Even G.[1], Martel S.[1],
Audebert C.[1], Croiseau P.[2], Sanchez M.P.[2]

1 GDBiotech / Gènes Diffusion, 59501 Douai Cedex, France
2 Université Paris-Saclay, INRAE, AgroParisTech, GABI, 78350 Jouy-en-Josas, France

* Correspondence: l.brulin@genesdiffusion.com