Beyond the Host Genome: Host Genetics and Gut Microbiome Determinism in Livestock

Catherine Larzul[a] & **Jordi Estellé**[b]

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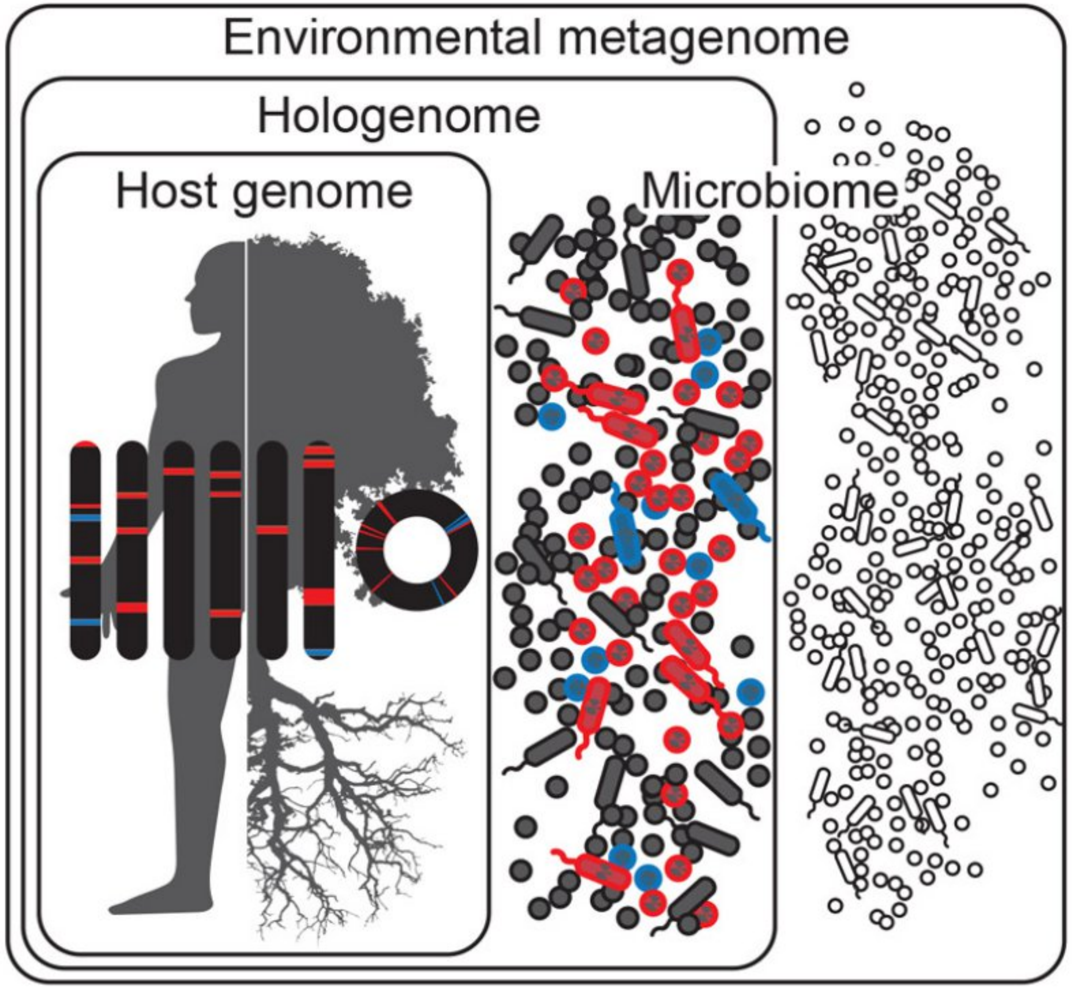
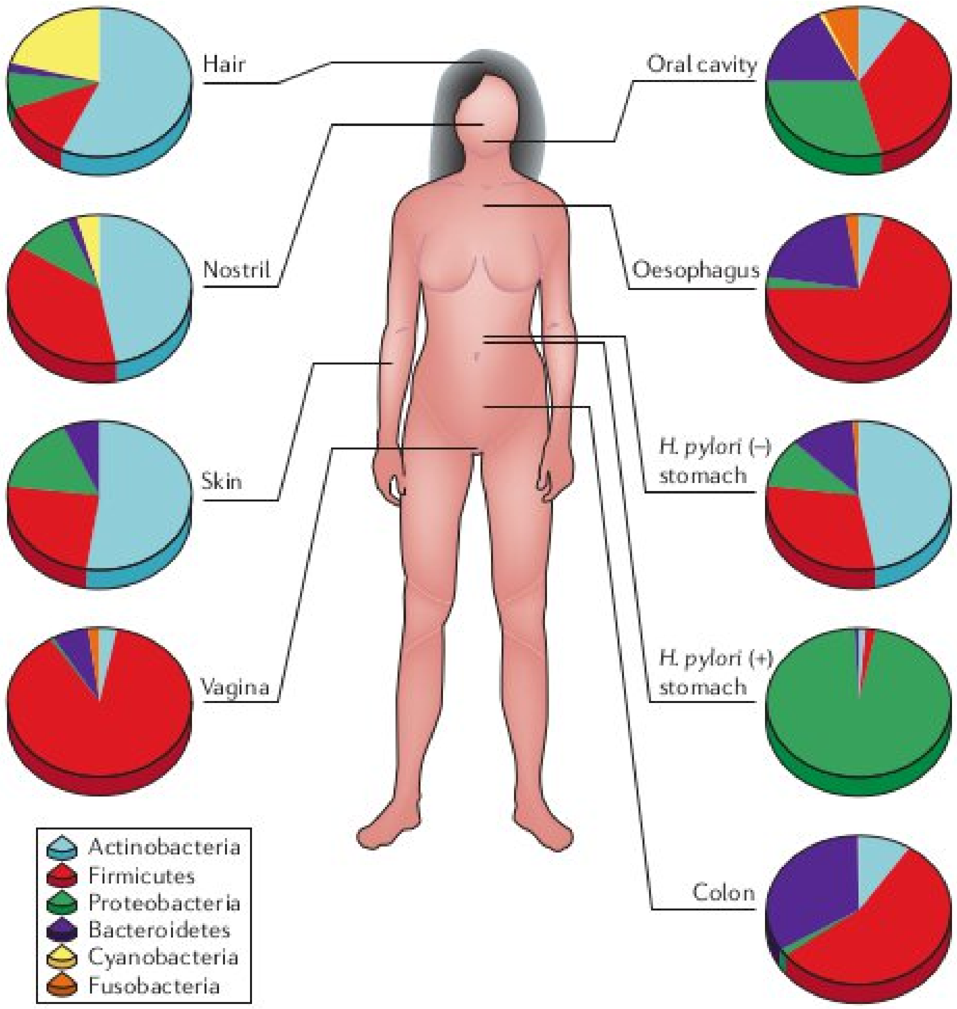
Holobionts !

Nature microbiome special

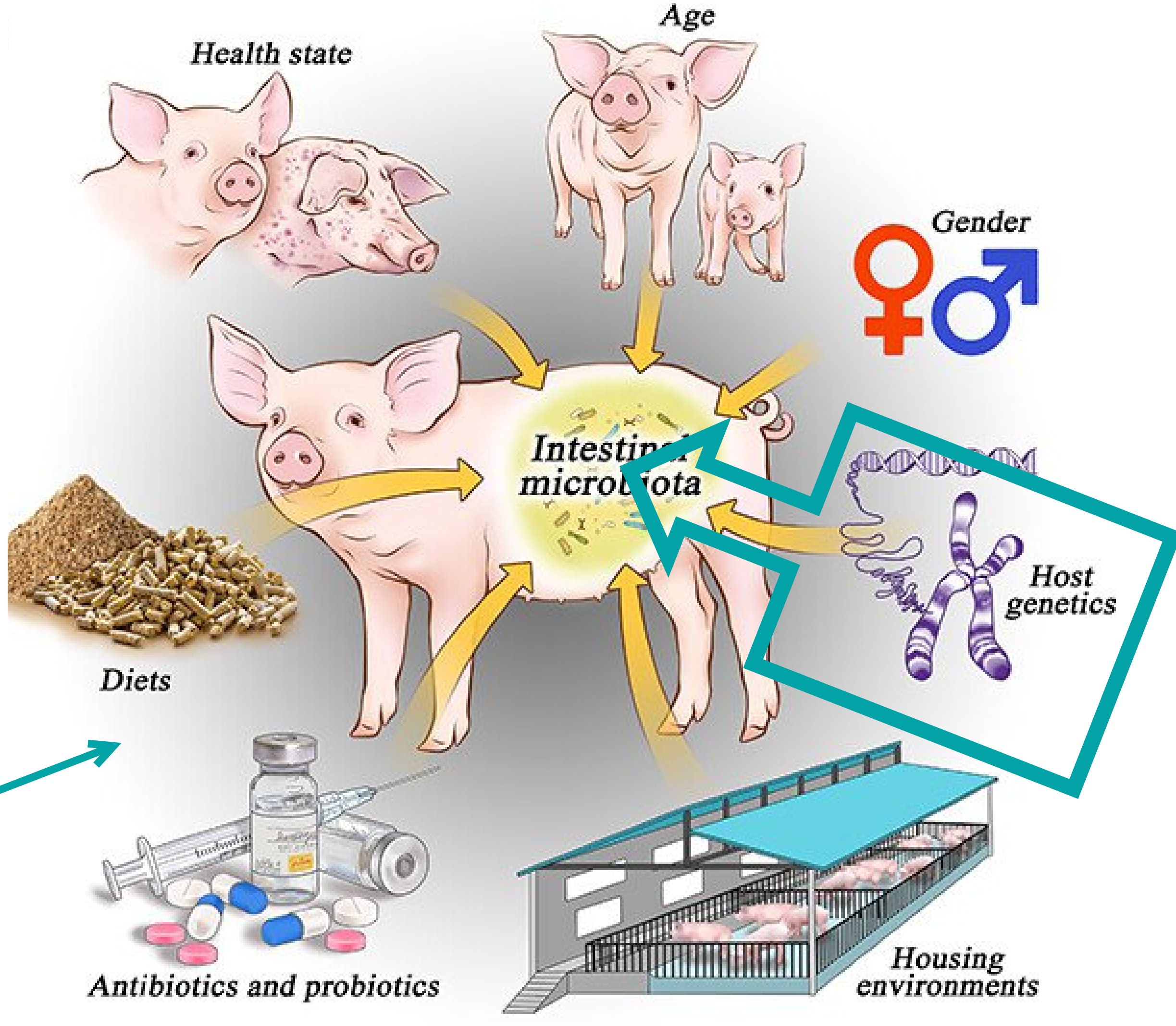


Theis et al. 2016 mSystems

Diversity and determinants of animal microbiomes



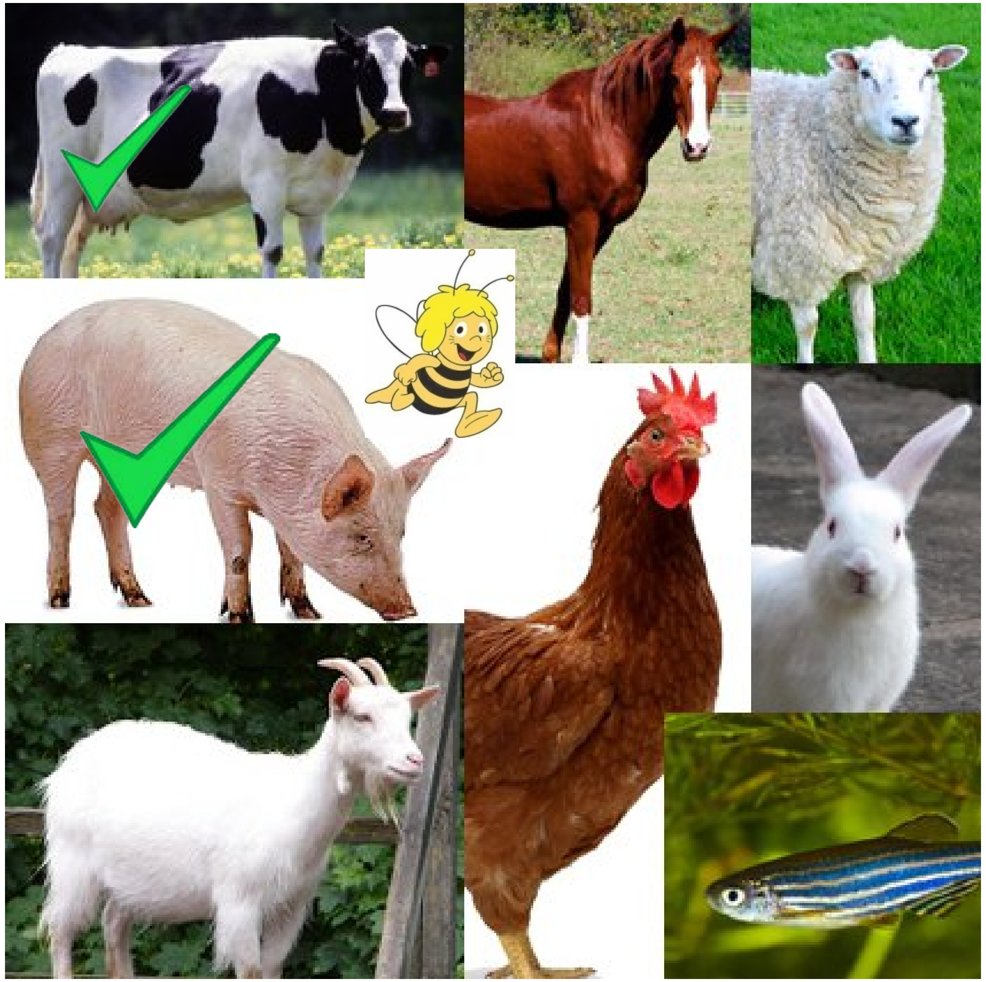
Cho & Blaser 2012 Nature Rev Genet



Huang & Chen 2023 Gut Microbes

Interest of microbiota studies in livestock production

- **Digestive microbiota**
  - **Associated with phenotypes of interest for livestock production**:
    - Feed efficiency, health, robusness, GHG, growth, welfare, …
  - Significant **impact of host genetics** on composition and diversity :
    - Heritability estimates & GWAS
    - Causal mutations !



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  - Significant **impact of host genetics** on composition and diversity :
    - Heritability estimates & GWAS
    - Causal mutations !
  - The **pig faecal microbial ecosystem** is organised into **two major enterotypes**
    - **Enterotype PM :** characterised by *Prevotella* & *Mitsuokella* abundance
    - **Enterotype RT** : characterised by *Ruminococcus* & *Treponema* abundance

The ISME Journal (2016), 1–5
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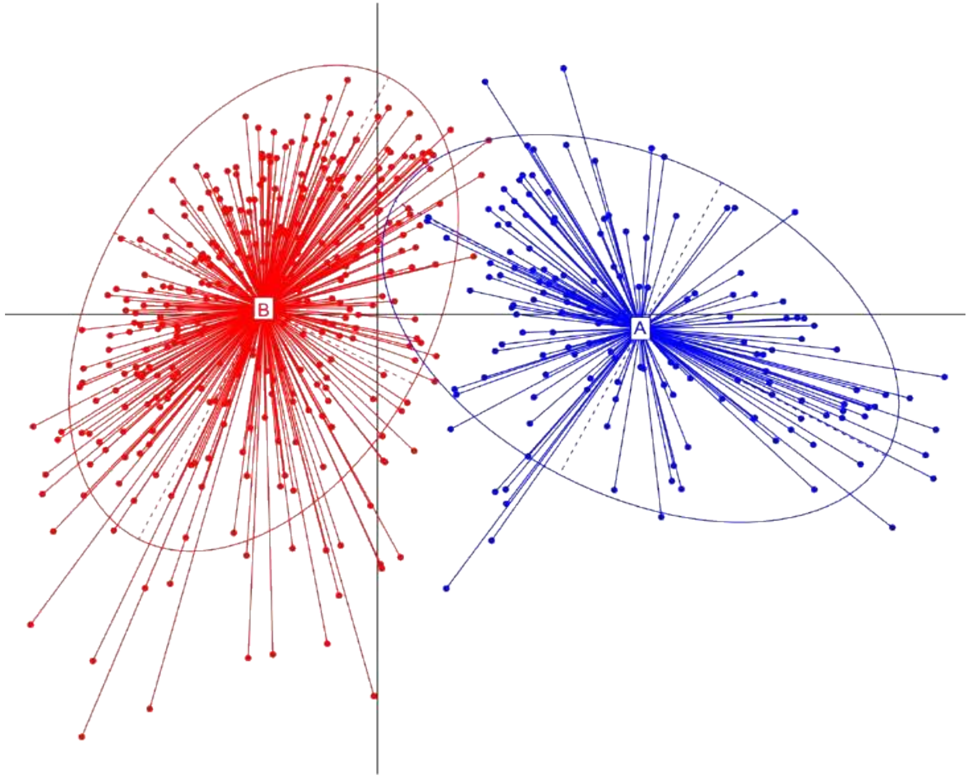
www.nature.com/ismej

SHORT COMMUNICATION

Phylogenetic network analysis applied to pig gut microbiota identifies an ecosystem structure linked with growth traits

Yuliaxis Ramayo-Caldas[1], Nuria Mach[1], Patricia Lepage[2,3], Florence Levenez[2,3], Catherine Denis[1], Gaetan Lemonnier[1], Jean-Jacques Leplat[1,4], Yvon Billon[5], Mustapha Berri[6], Jöel Doré[2,3], Claire Rogel-Gaillard[1] and Jordi Estellé[1]



>500 piglets at 60 days-of-age

Enterotypes : enteric ecotypes based on microbiota composition

- Ecotype = a group of organisms that is adapted to a specific environment.

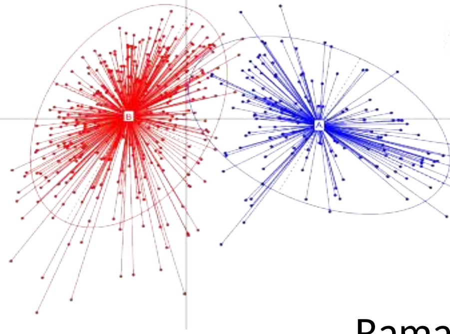
Ecotype A

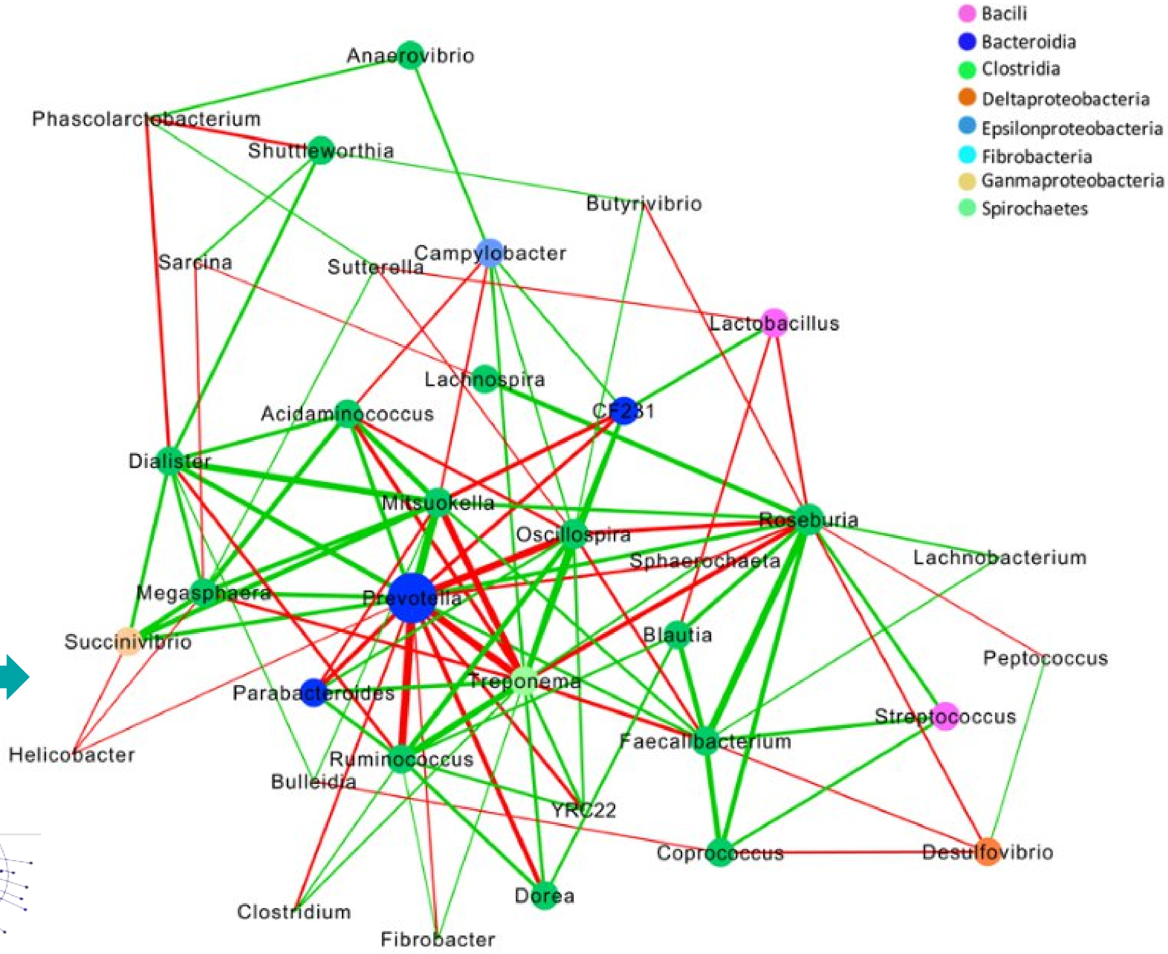
Ecotype B

Given host genome impact on microbiomes…

It is possible to use host genetic selection to influence faecal microbiota composition?

Key driving taxa from network interactions?

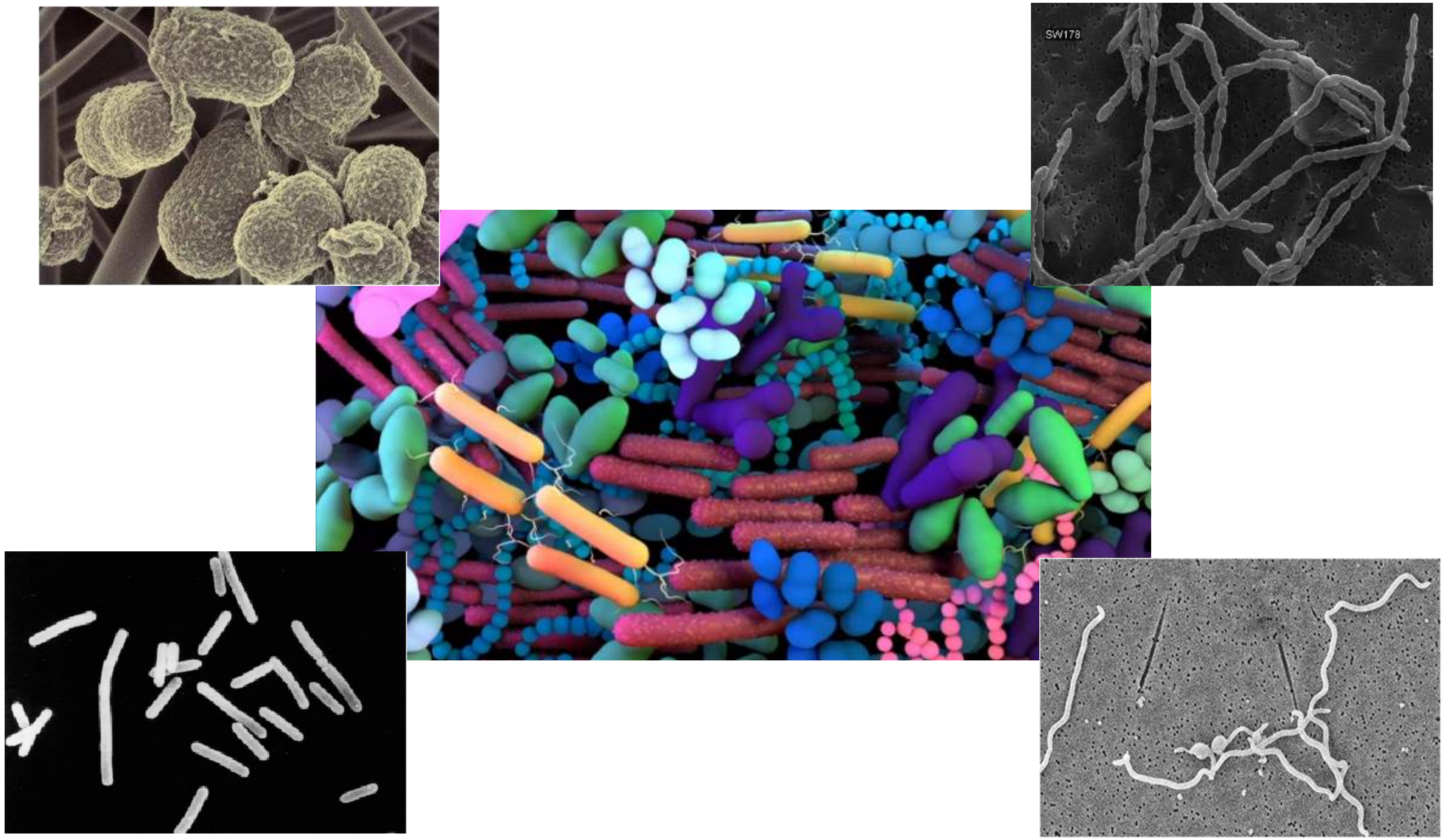




Ramayo-Caldas et al. 2016. ISME Journal

From complexity to simplicity

Prevotella

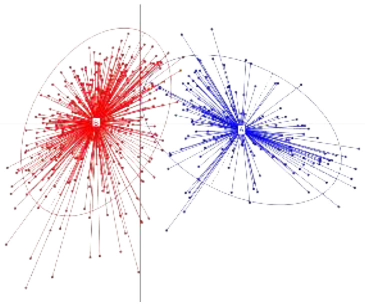


Ruminococcus

Mitsuokella

Treponema

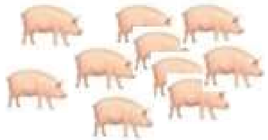
A divergent selection experiment for pig enterotypes



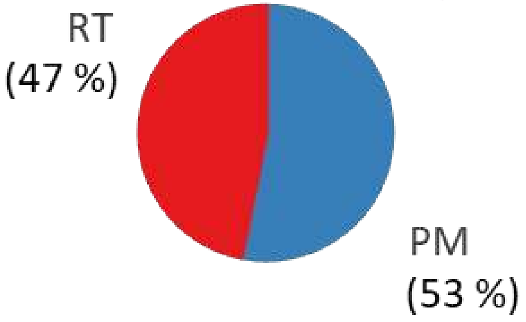
♂ x ♀

N = 30 N = 30

Generation G0



316 piglets from 30 litters



Pigs with enterotype PM

♂ x ♀

N = 6 N = 30

Pigs with enterotype RT

♂ x ♀

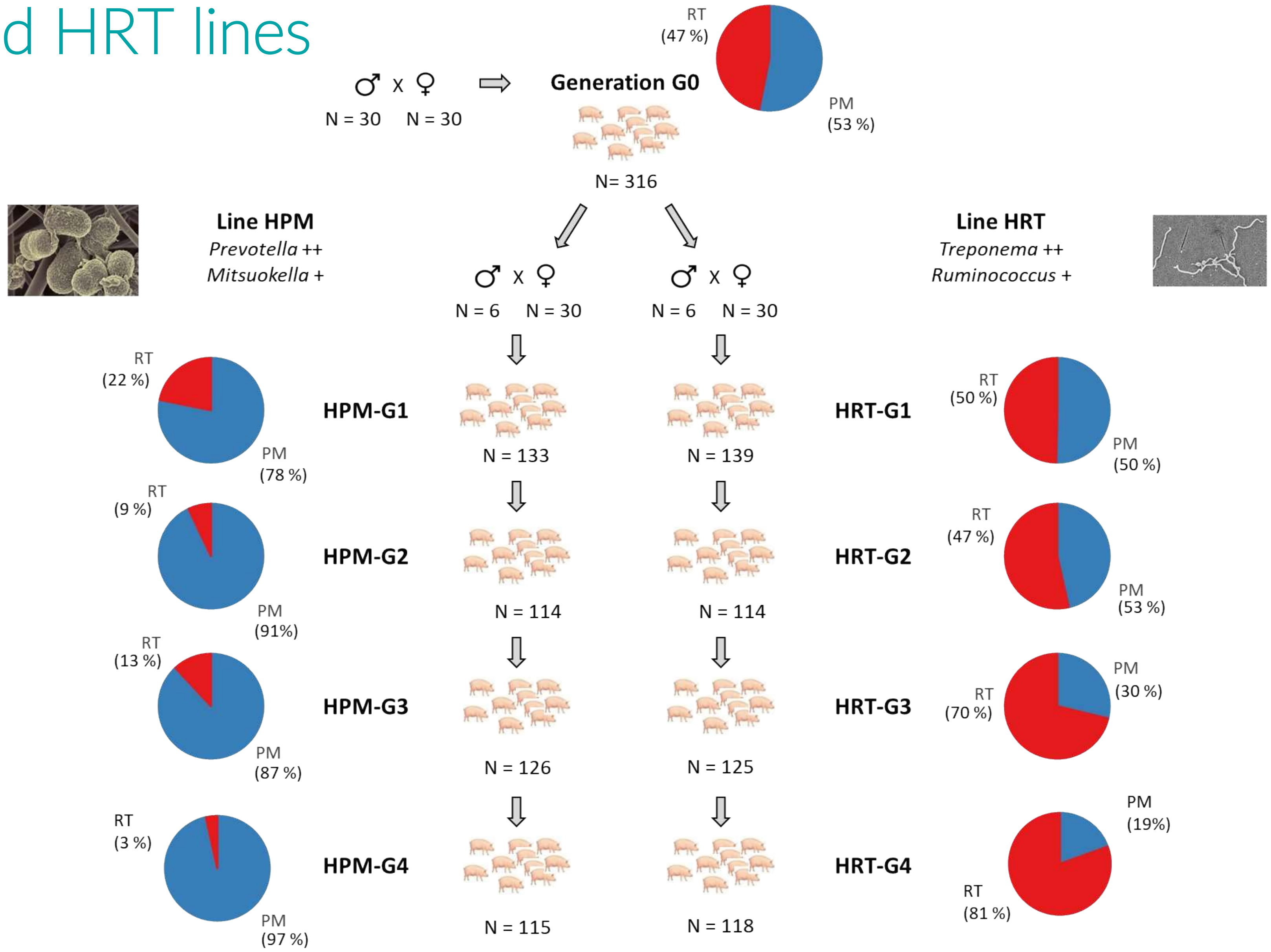
N = 6 N = 30

Line HPM
direct selection on *Prevotella* and *Mitsuokella* at D60

Line HRT
direct selection on *Treponema* (and *Ruminococcus*) at D60

Selection of HPM and HRT lines

Prevotella = ***Prevotella_9*** + *Prevotella_7* + *Prevotella*
Ruminococcus = ***Ruminococcus*** +
Ruminococcus_gnavus_group +
Ruminococcus_torques_group +
Ruminococcus_gauvreauii_group



♂ x ♀
N = 30 N = 30

Generation G0
N= 316

RT (47 %)
PM (53 %)

Line HPM
Prevotella ++
Mitsuokella +

♂ x ♀
N = 6 N = 30

Line HRT
Treponema ++
Ruminococcus +

♂ x ♀
N = 6 N = 30

HPM-G1
N = 133
RT (22 %)
PM (78 %)

HRT-G1
N = 139
RT (50 %)
PM (50 %)

HPM-G2
N = 114
RT (9 %)
PM (91%)

HRT-G2
N = 114
RT (47 %)
PM (53 %)

HPM-G3
N = 126
RT (13 %)
PM (87 %)

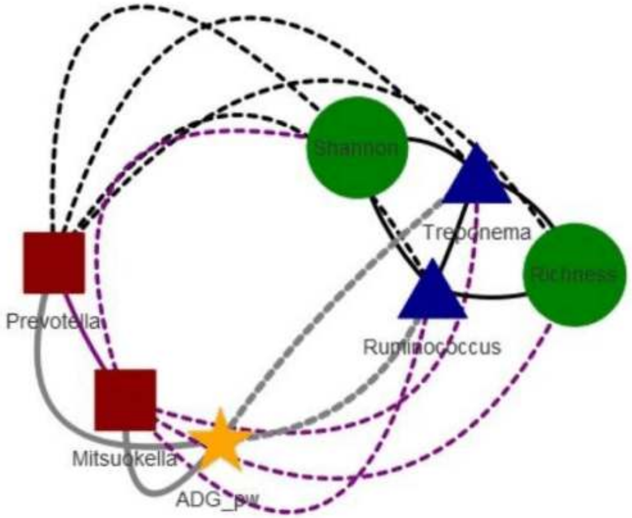
HRT-G3
N = 125
RT (70 %)
PM (30 %)

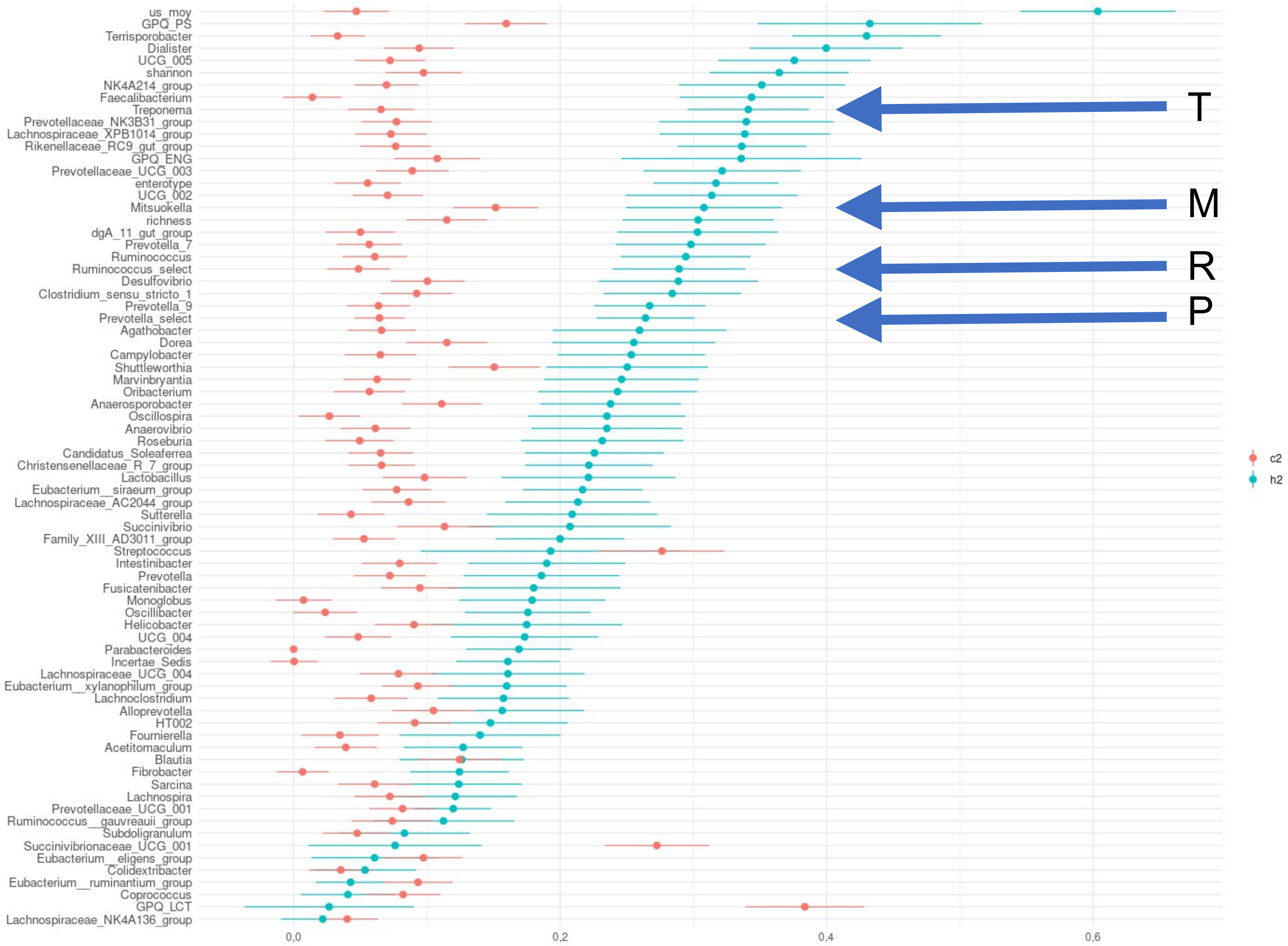
HPM-G4
N = 115
RT (3 %)
PM (97 %)

HRT-G4
N = 118
RT (81 %)
PM (19%)

Genetic parameters

- Significant heritability values
- Limited litter effect
- Genetic correlation
  - PM favorable to post-weaning growth

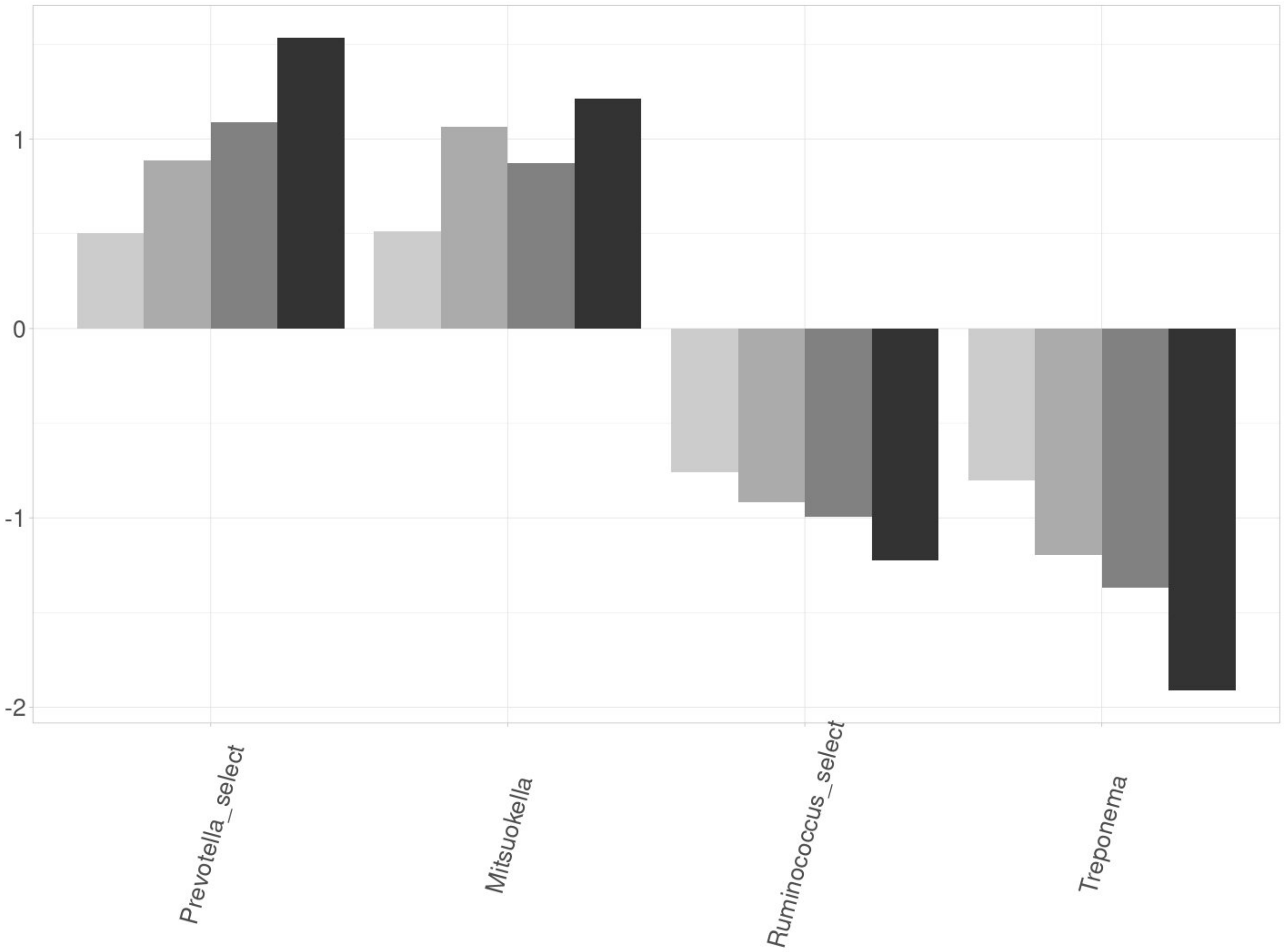


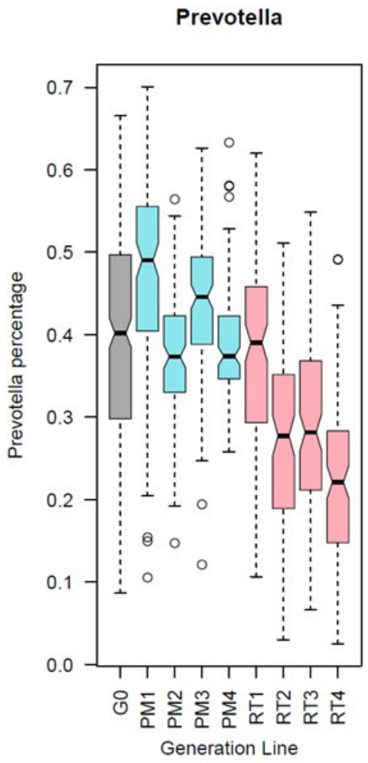


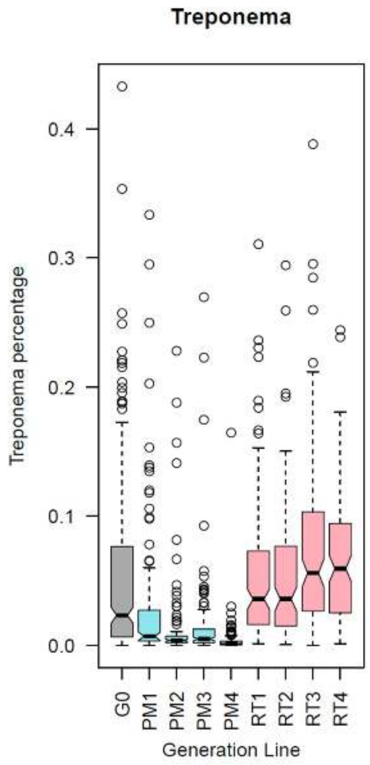
Heritability values in litterature

Samples	Interval h²	The most heritable	Reference
Feces	**0,32 – 0,57**	Uncultured *Succinivibrionaceae*	Camarinha-Silva et al., 2017
Feces	**0,15 – 0,33**	Shannon index	Lu et al., 2018
Colon	**0,025 – 0,55**	*Peptostreptococcaceae* OTU	Bergamaschi et al., 2020
Feces	**0 – 0,50**	*Clostridium_sensu_stricto_I*	Aliakbari et al., 2021
Colon	**0 – 0,39**	*Anaerovibrio*	Déru et al., 2022
Feces	**0,14 – 0,40**	*Terrisporobacter*	Larzul et al., 2024
Feces	**0,30**	Enterotypes	Larzul et al., 2024
Feces	**0,31 – 0,42**	Enterosignature *Treponema*	Vourlaki et al. 2024

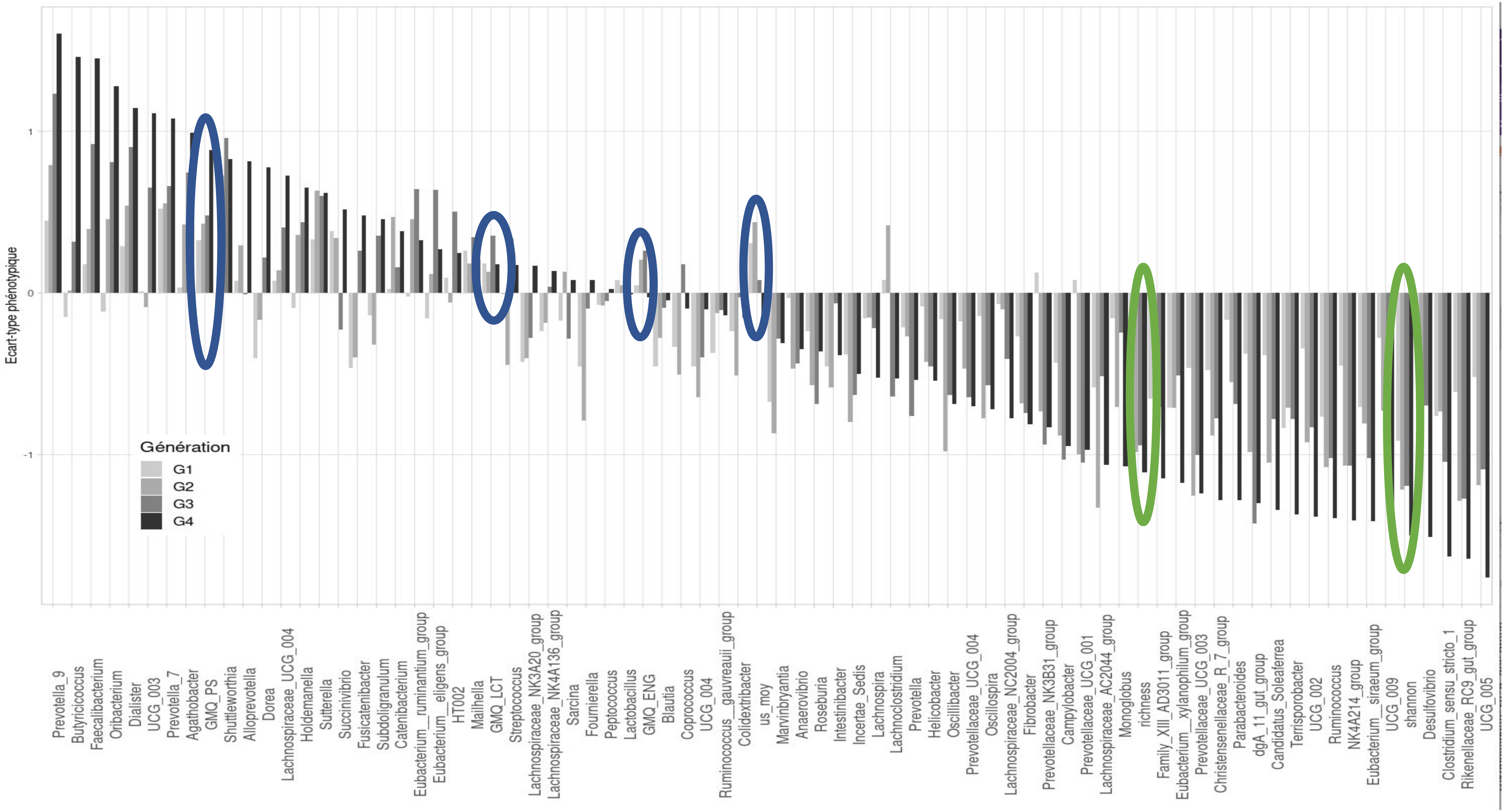
Response to selection: genera under direct selection







Indirect responses to selection

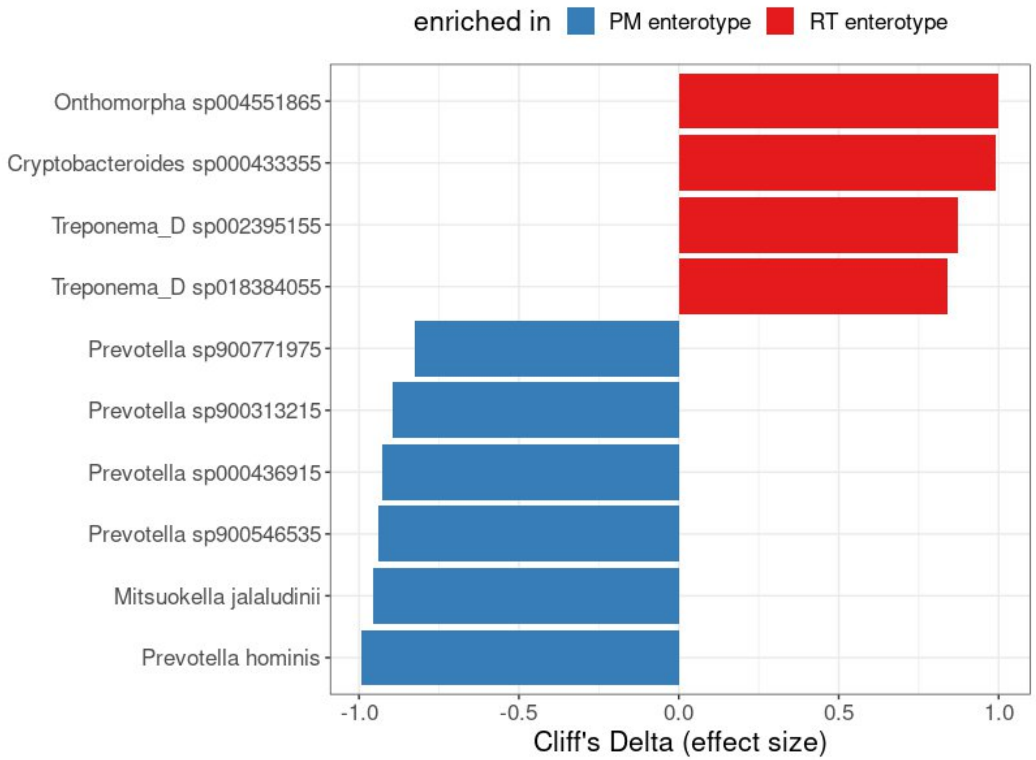


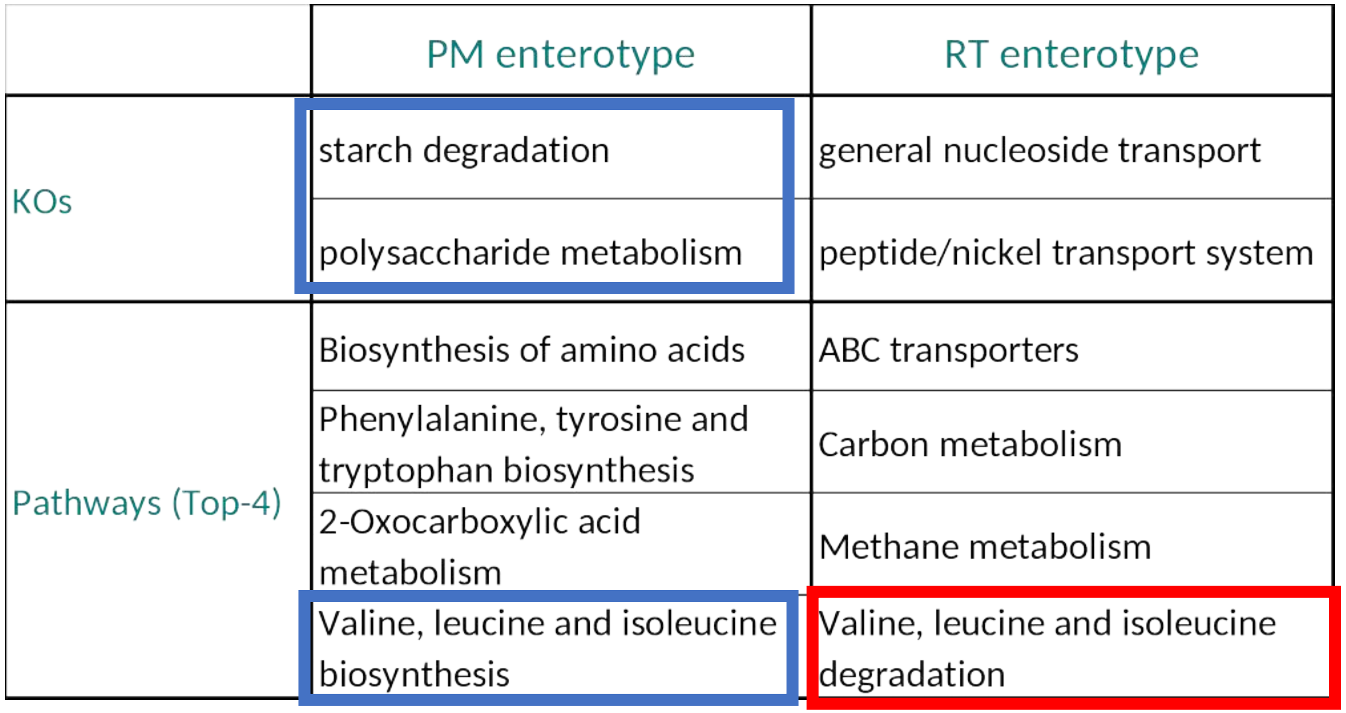
HPM vs HRT lines

- Whole metagenome sequencing on G0 (n= 15 *vs.* 15) : who are they and what are they doing ?

Metagenomic species :

KEGG Ortologs :





	PM enterotype	RT enterotype
KOs	starch degradation	general nucleoside transport
	polysaccharide metabolism	peptide/nickel transport system
Pathways (Top-4)	Biosynthesis of amino acids	ABC transporters
	Phenylalanine, tyrosine and tryptophan biosynthesis	Carbon metabolism
	2-Oxocarboxylic acid metabolism	Methane metabolism
	Valine, leucine and isoleucine biosynthesis	Valine, leucine and isoleucine degradation

HPM animals have better growth (ADG) at 60 days of age !

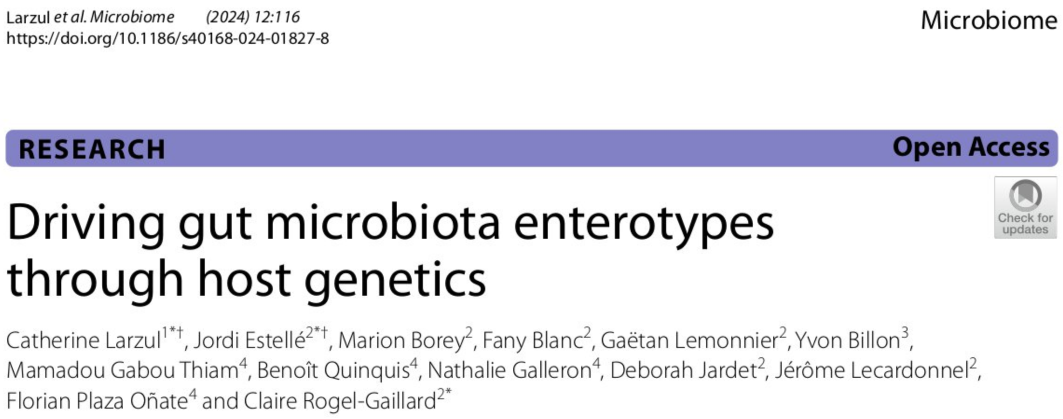
Our research questions :

It is possible to use host genetic selection to influence faecal microbiota composition?

YES

Would this selection have an impact on other ecosystems and also on host traits? →

https://youtu.be/PyKiDfq_Vfg



Larzul *et al. Microbiome* (2024) 12:116
https://doi.org/10.1186/s40168-024-01827-8

Microbiome

RESEARCH **Open Access**

Driving gut microbiota enterotypes through host genetics

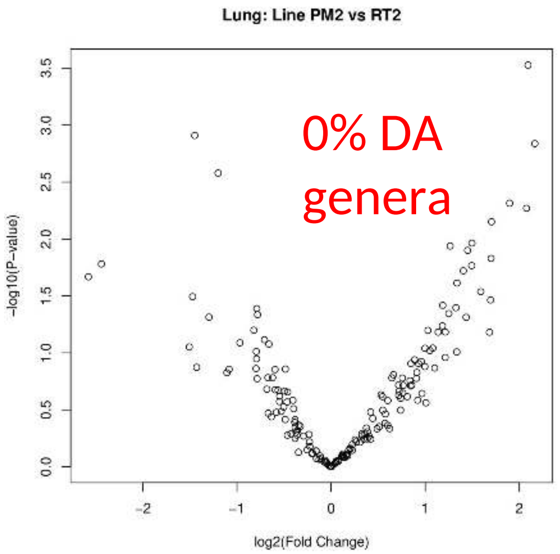
Catherine Larzul[1*†], Jordi Estellé[2*†], Marion Borey[2], Fany Blanc[2], Gaëtan Lemonnier[2], Yvon Billon[3], Mamadou Gabou Thiam[4], Benoît Quinquis[4], Nathalie Galleron[4], Deborah Jardet[2], Jérôme Lecardonnel[2], Florian Plaza Oñate[4] and Claire Rogel-Gaillard[2*]

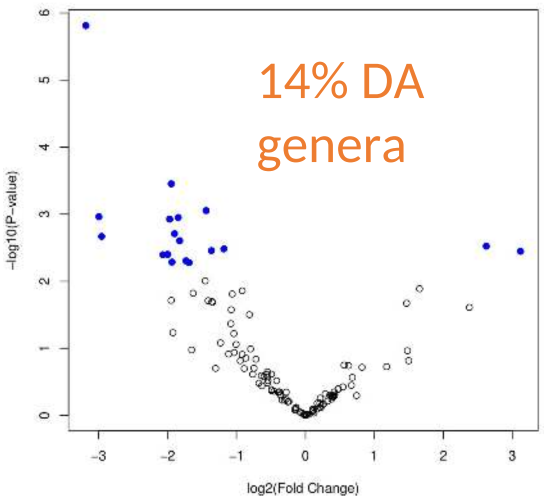
ADG → YES

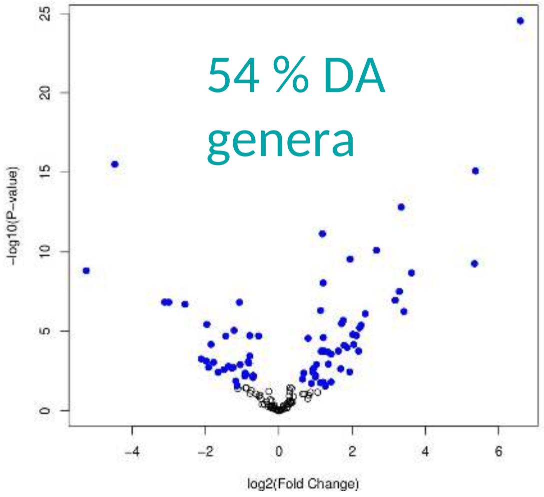
Other microbiota?

Other traits?

At G3 : differences HPM vs. HRT in gut and respiratory microbiota ?



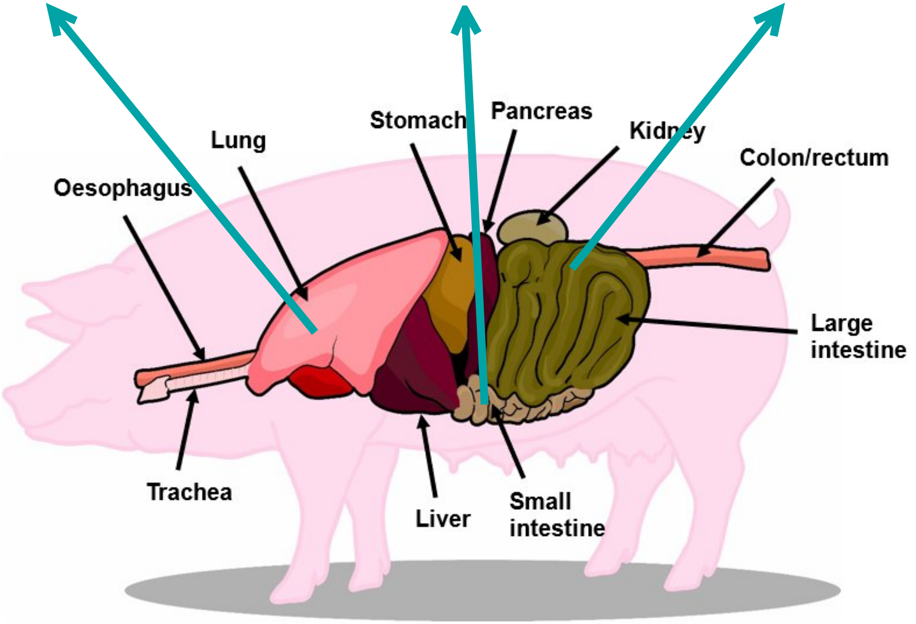




16S sequencing

DADA2 + SILVA

LinDA DA analysis



- Strong microbiota differences between lines at colon
  - Differences in the expected direction as HPM vs. HRT
- Signal less strong but present in small intestine
- No differences found in respiratory microbiota!

N = 40 HPM vs. 40 HRT

Blanc et al. 2024 EAAP

Our research questions :

It is possible to use host genetic selection to influence faecal microbiota composition? YES

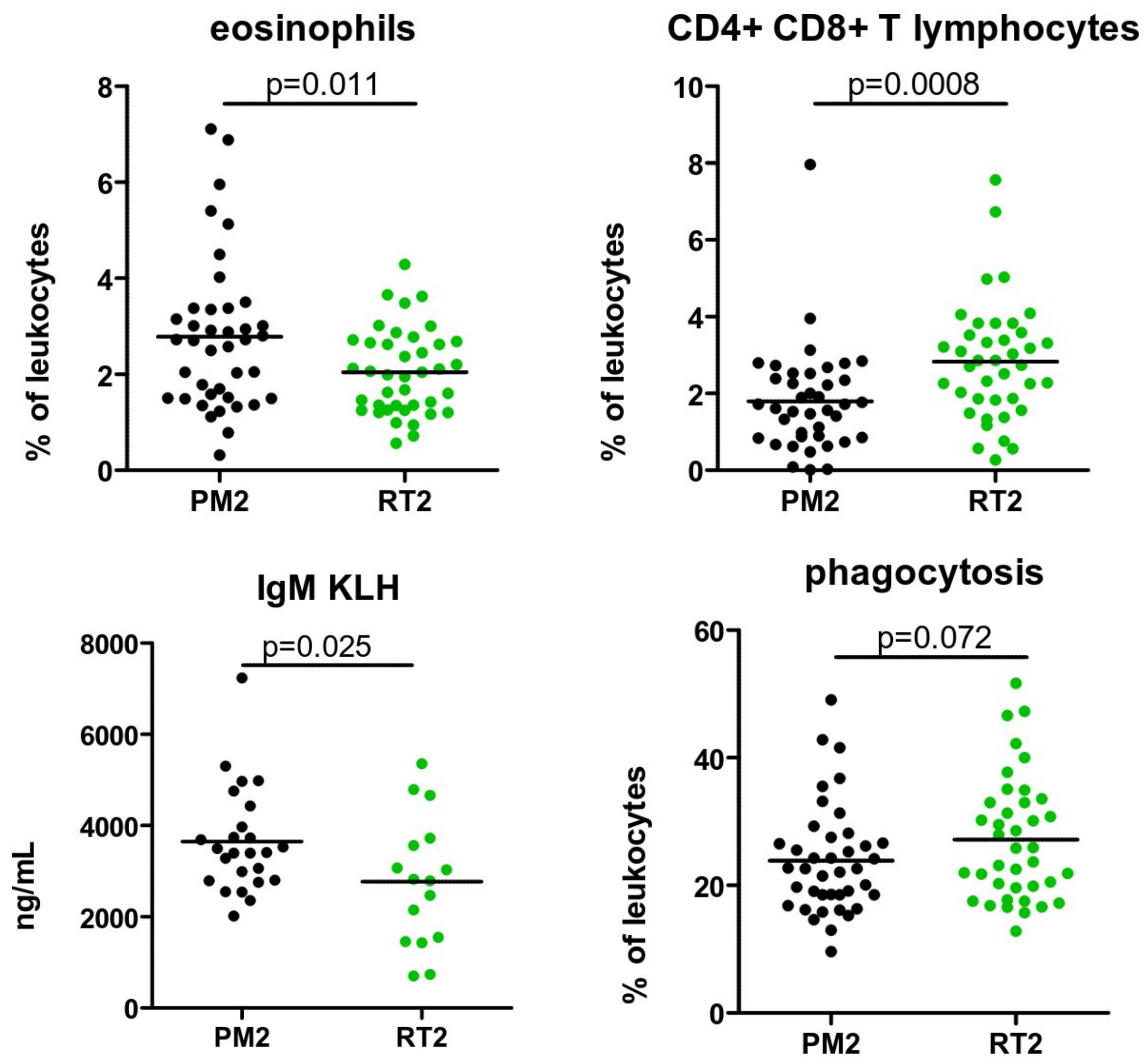
Would this selection have an impact on other ecosystems and also on host traits? →

ADG → YES

Other **digestive** microbiotas YES

Other traits?

At G3 : differences in blood immune response traits ?



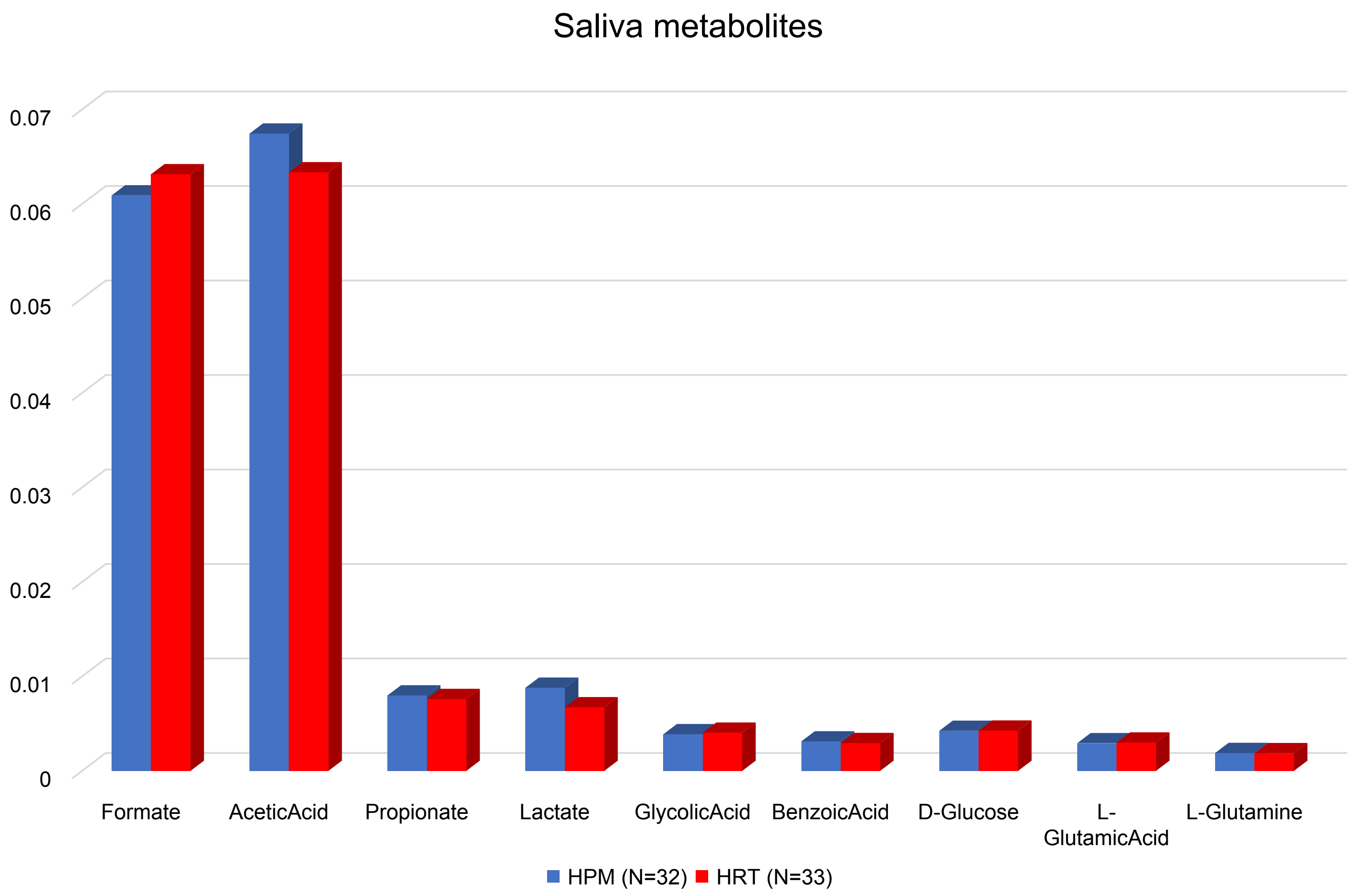
- Blood cell subpopulations by flow cytometry
- Plasma coloration
- Total IgG, IgA and IgM
- Natural antibodies
- Phagocytosis

N = 40 HPM vs. 40 HRT

Blanc et al. 2024 EVIW

Differences in saliva metabolites ?

125 metabolites detected
~No differences between lines



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Other **digestive** microbiotas YES

Health traits YES

APP DGA
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AGROÉCOLOGIE ET NUMÉRIQUE

anr

SOA18 (007-A1)

EUP AH&W
European Partnership on Animal Health and Welfare

Genetic selection for pig faecal enterotypes

THANKS!

- GABI, équipe Génétique Microbiote Santé : J Estellé, G Lemonnier, M Borey, N Bruneau, F Blanc, C Rogel-Gaillard, **et al.**
- GABI, Plateforme @BRIDGe : D Jardet, B Houel, K Alexis-Alphonse, J Lecardonnel, MN Rossignol
- GenPhySE, équipe ModGen : C Larzul
- MGP, équipe InfoBIoStat : F Plaza-Onate et al.
- UE GenESI, équipe Porcs : C Niort, Y Billon, **et al.**

Interest of microbiota studies in livestock production

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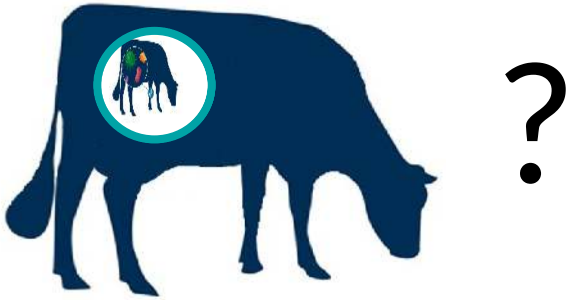
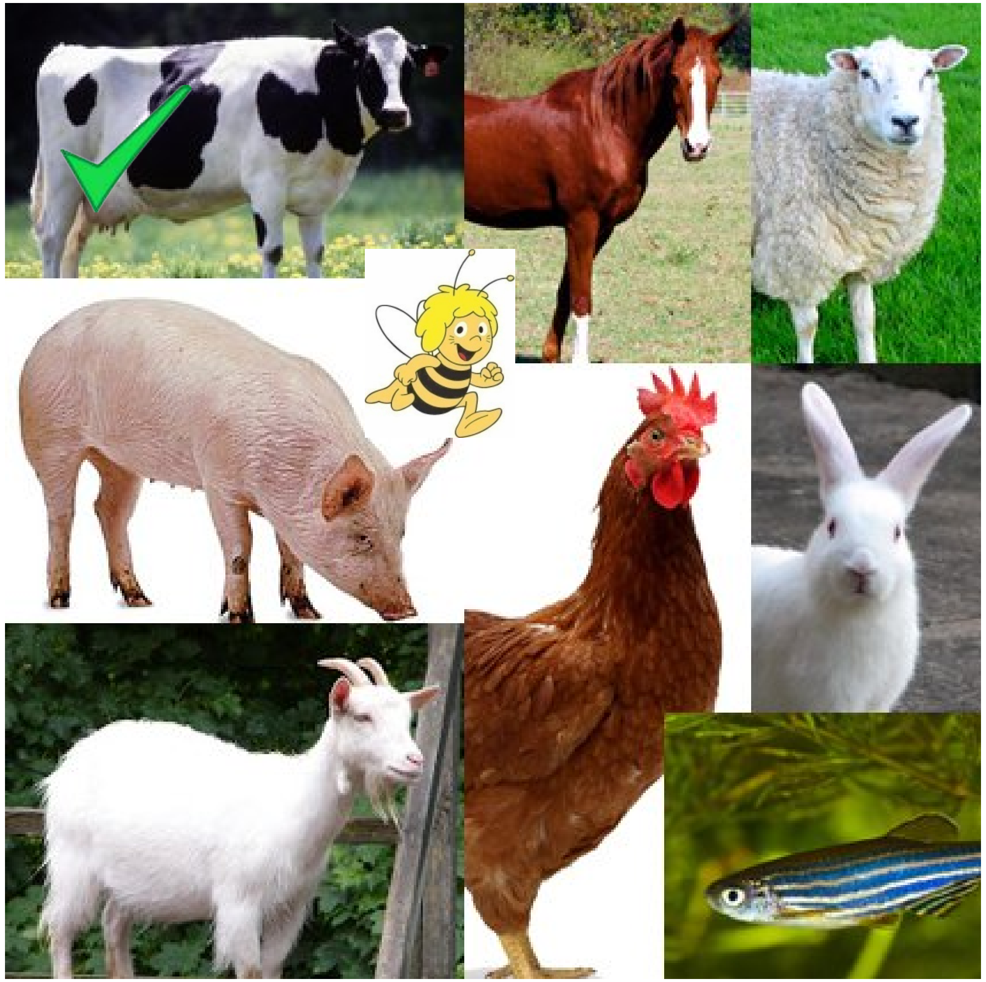
    - Heritability estimates & GWAS
    - Causal mutations
    - **Response to host selection!!**





Dairy cow fecal microbiome

GENES DIFFUSION
PERFORMANCE PARTAGÉE

GD Biotech
AGRI-AGRO SOLUTIONS

INRAE

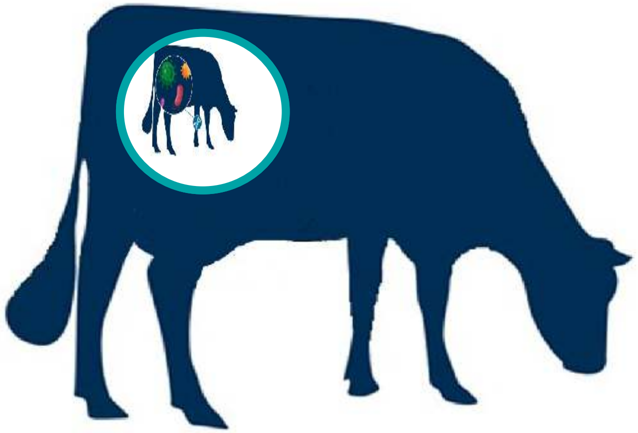
Cifre
Conventions

ANRT
ASSOCIATION NATIONALE
RECHERCHE TECHNOLOGIE

Louise Brulin

1860 Holstein cows
140 herds
2020 – 2022

16S secuencing
& host genotypes



Animal 18 (2024) 101243

Contents lists available at ScienceDirect

Animal
The international journal of animal biosciences

ELSEVIER

Short communication: *Bifidobacterium* abundance in the faecal microbiota is strongly associated with milk traits in dairy cattle

L. Brulin[a,b,*], S. Ducrocq[a,c], G. Even[a,c], M.P. Sanchez[b], S. Martel[a,c], S. Merlin[a,c], C. Audebert[a,c], P. Croiseau[b], J. Estellé[b]

J. Dairy Sci. 107:11254–11268
https://doi.org/10.3168/jds.2024-25003
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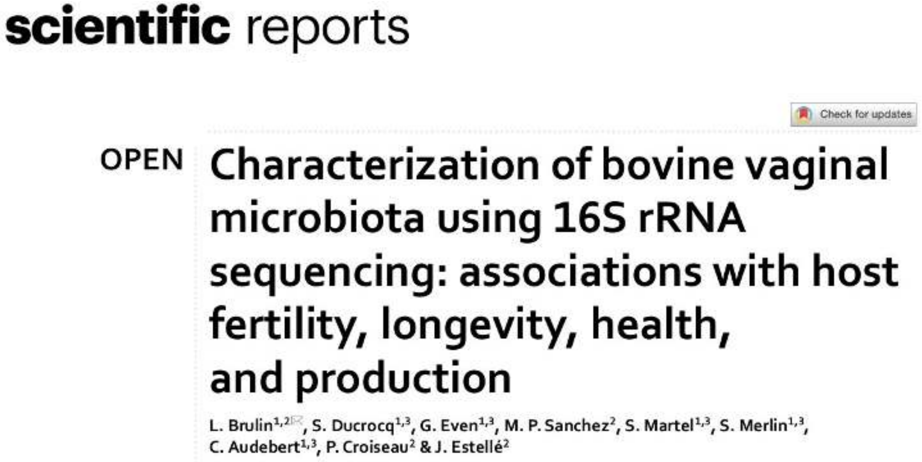
The fecal microbiota of Holstein cows is heritable and genetically correlated to dairy performances

L. Brulin,[1,2*] S. Ducrocq,[1,3] J. Estellé,[2] G. Even,[1,3] S. Martel,[1,3] S. Merlin,[1,3] C. Audebert,[1,3] P. Croiseau,[2] and M.-P. Sanchez[2]



scientific reports

Check for updates

OPEN

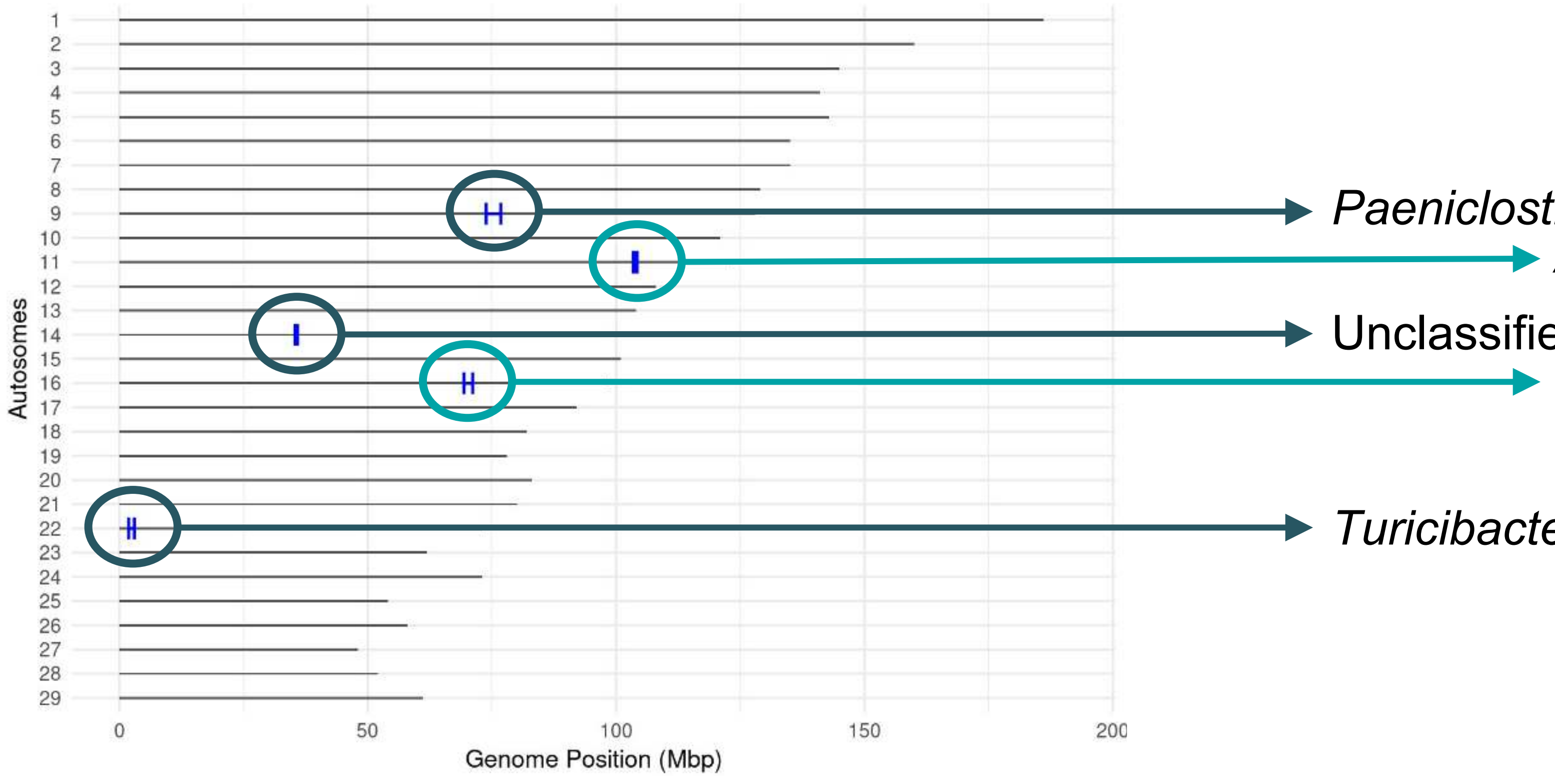
Characterization of bovine vaginal microbiota using 16S rRNA sequencing: associations with host fertility, longevity, health, and production

L. Brulin[1,2], S. Ducrocq[1,3], G. Even[1,3], M. P. Sanchez[2], S. Martel[1,3], S. Merlin[1,3], C. Audebert[1,3], P. Croiseau[2] & J. Estellé[2]

Sequence-based GWAS for cow fecal microbiome

- Significance at –log10(P) of 7,3 (Sahana et al., 2022)

Louise Brulin



Paeniclostridium (4,38%)

***Akkermansia* (2.26%)**

Unclassified Paludibacteraceae (2,51%)

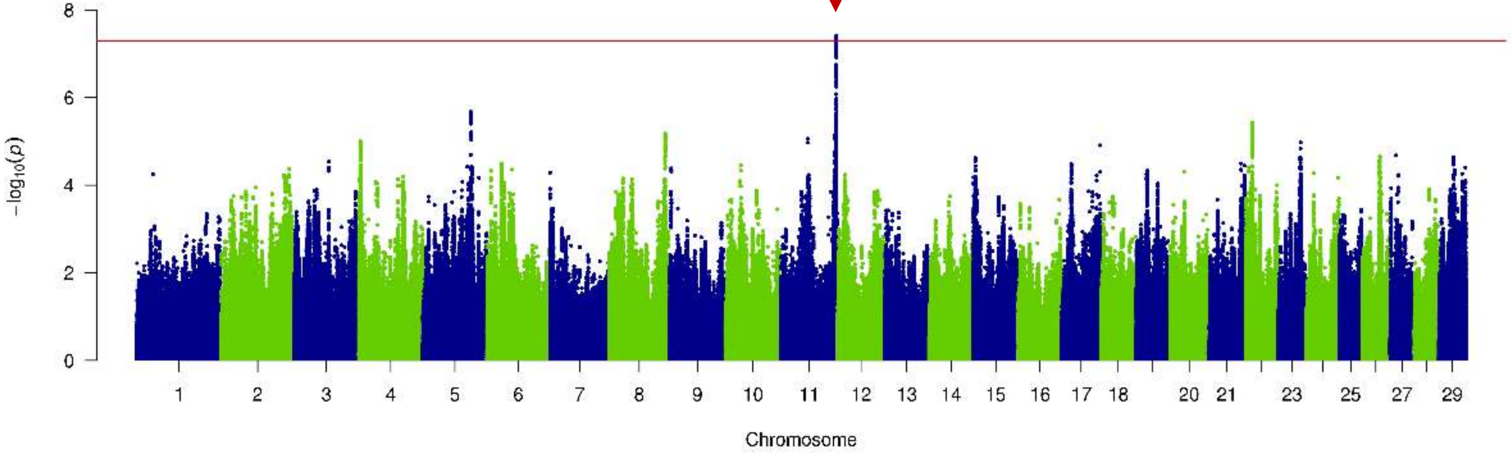
Sutterella (25,49%)

Turicibacter (2,02%)

Brulin et al. (submitted)

Sequence-based GWAS for cow fecal microbiome

- ***Akkermansia*** !



Louise Brulin

Bovine **ABO** gene

~~Erysipelotrichaceae~~ family :

Article

ABO genotype alters the gut microbiota by regulating GalNAc levels in pigs

https://doi.org/10.1038/s41586-022-04769-z

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Published online: 27 April 2022

Hui Yang[1,3], Jinyuan Wu[1,3], Xiaochang Huang[1], Yunyan Zhou[1], Yifeng Zhang[1], Min Liu[1], Qin Liu[1], Shanlin Ke[1], Maozhang He[1], Hao Fu[1], Shaoming Fang[1], Xinwei Xiong[1], Hui Jiang[1], Zhe Chen[1], Zhongzi Wu[1], Huanfa Gong[1], Xinkai Tong[1], Yizhong Huang[1], Junwu Ma[1], Jun Gao[1], Carole Charlier[1,2], Wouter Coppieters[2], Lev Shagam[2], Zhiyan Zhang[1], Huashui Ai[1], Bin Yang[1], Michel Georges[1,2,4]✉, Congying Chen[1,4]✉ & Lusheng Huang[1,4]✉

Brulin et al. (submitted)

Conclusions & Perspectives

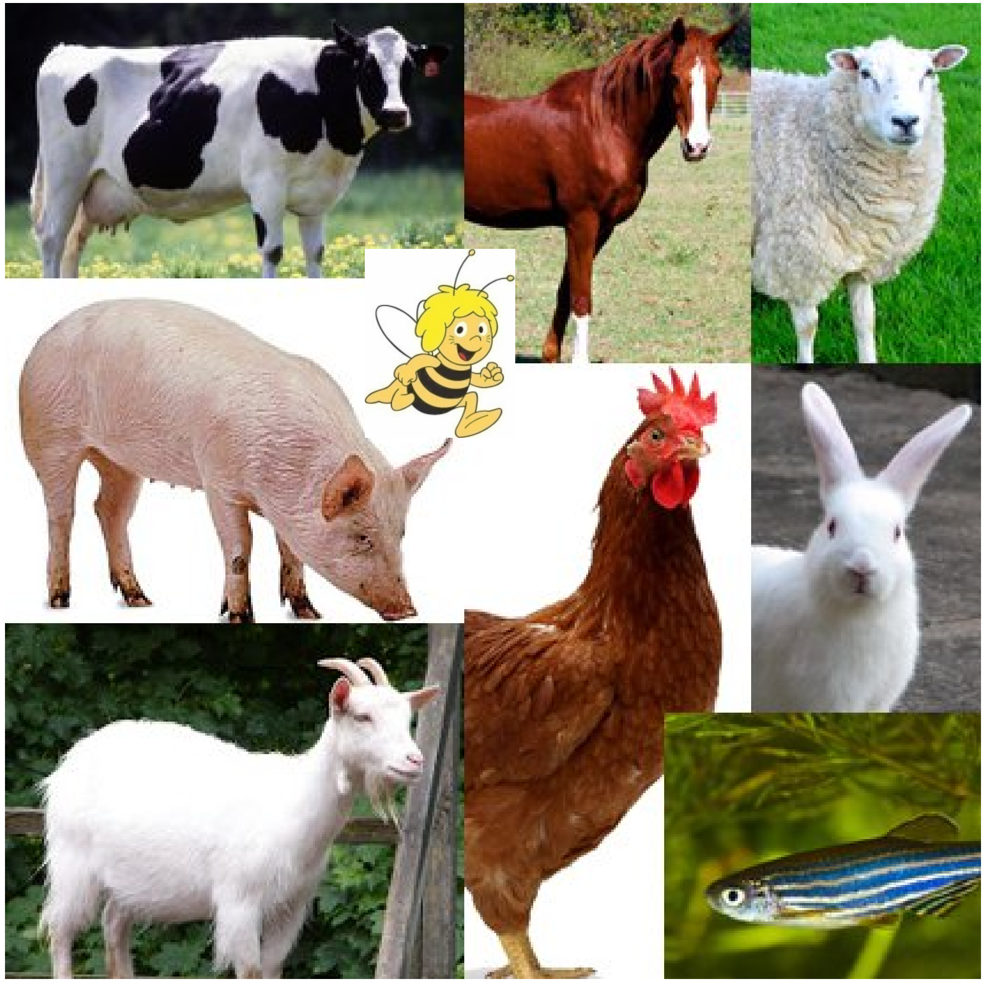
It is possible to use host genetic selection to influence faecal microbiota composition?

YES

Does this impact other ecosystems and host traits?

YES

Is it useful?

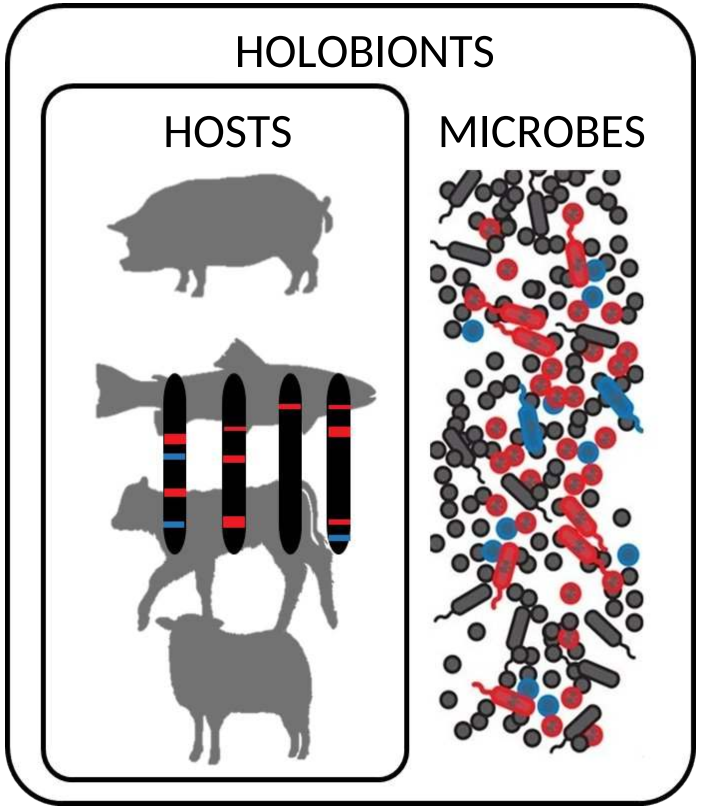


Conclusions & Perspectives

- Hosts or microbes? **Holobionts !** →

$$P = G + M + E \quad (+\,€)$$

- **Upcoming (shared!) challenges :**
  - Define cost-effectiveness of microbiome-informed breeding and selection
  - Update statistical and modeling approaches
  - **Biology…**
    - Which microbiomes? When?
    - What are microbes doing ?
      - Metatranscriptomes
      - Metaproteomics
    - **Useful for all host traits?**



https://www.isag.us/2025/

- Microbiomes session !

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[a] Université de Toulouse, INRAE, ENVT, GenPhySE, Castanet Tolosan, 31326, France

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