

Multi-cohort analysis identifies robust host genetic effects on the rat gut microbiome



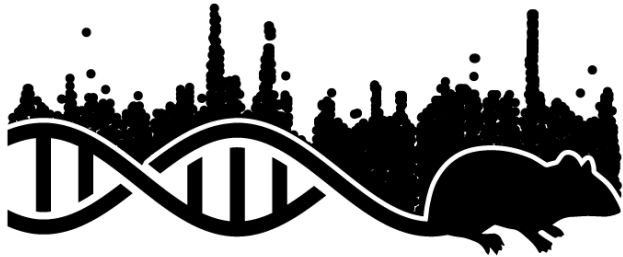
Amelie Baud

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Why study host – microbiome interactions *in outbred laboratory rats?*

- associations (correlations) in humans: **causal effects of confounding?**
- extreme lab interventions: the gut microbiome can impact host health, but **does it, in normal conditions?**
- **HS rat study: the best of both worlds**
 - avoid/limit confounding with a well-designed, laboratory study
 - study variation arising from natural variants
 - rats with a normal microbiome (non germ-free, no antibiotics...)
 - leverage host genetic effects to determine causality

Four cohorts of HS rats (total N = 4,154 rats)



Genes and Addiction

NIDA Center for GWAS in Outbred Rats

Microbiome data from rats studied in first P50 (2014 - 2019)

Oksana Polesskaya, Abraham A Palmer, Leah Solberg Woods, Paul J Meyer, Terry E. Robinson, Shelly Flagel, Hao Chen, Keita Ishiwari, Jerry B. Richards and many group members: **thank you!!**



Rob Knight lab @ UCSD

Differences between the four cohorts

Differences between the four cohorts



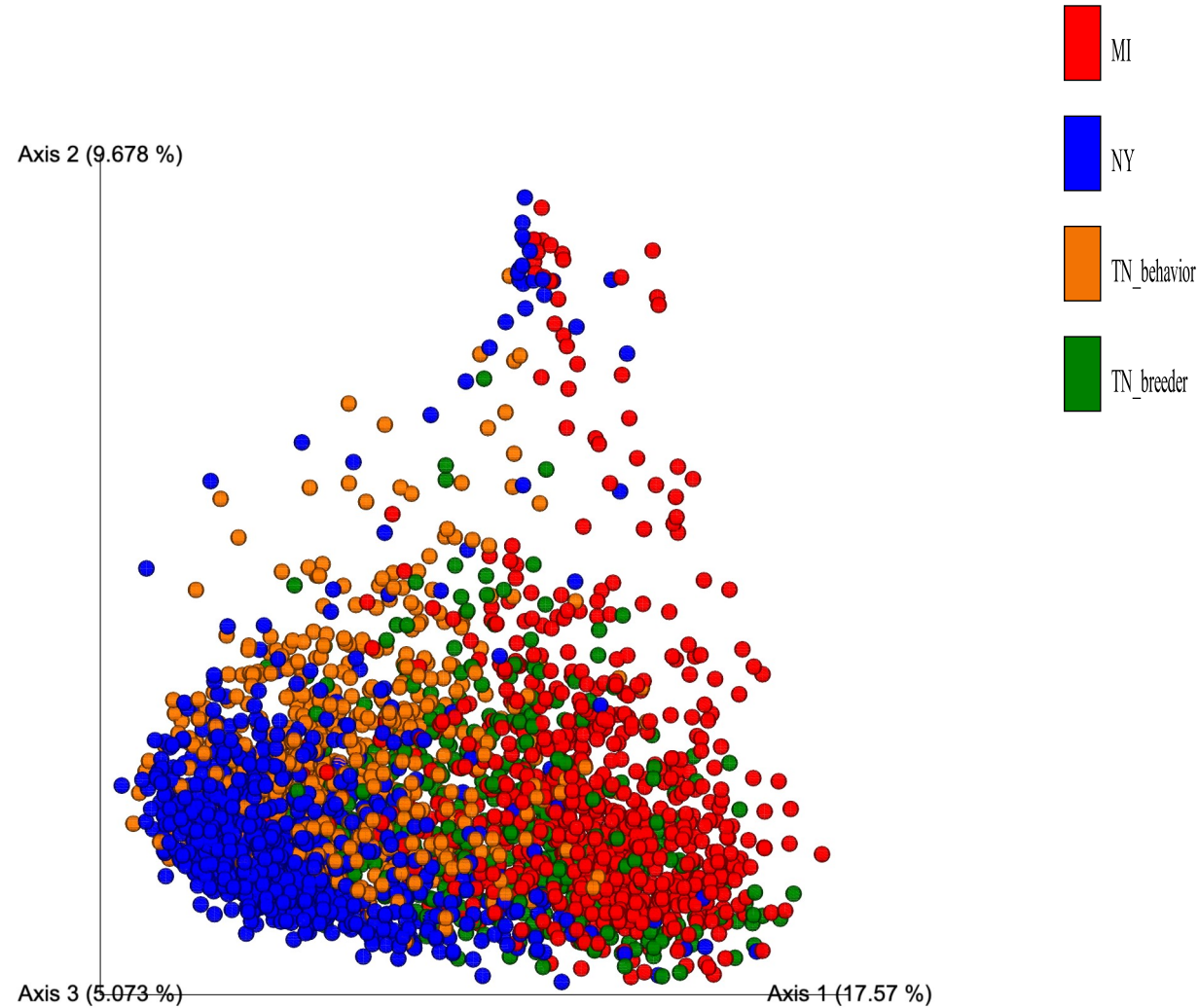
Differences between the four cohorts



Differences between the four cohorts



Microbiome differences between the four cohorts



Four cohorts analysed separately

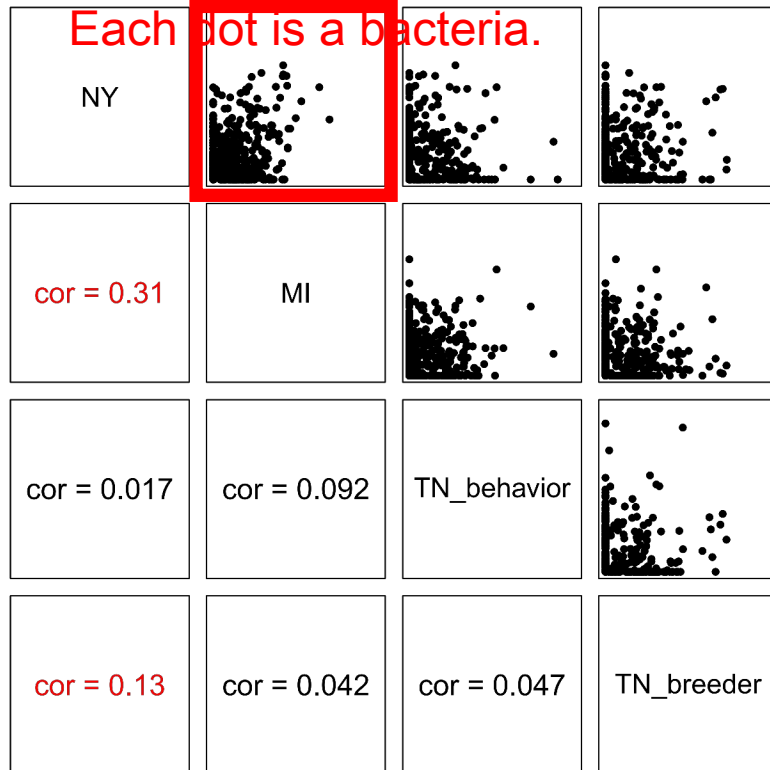
- 1) To what extent do host genetic effects depend on the environment?
- 2) Can we identify robust (replicated) host genetic effects ?

Four cohorts analysed separately

1) To what extent do host genetic effects depend on the environment?

Heritability in NY (y-axis)
vs heritability in MI (x-axis).

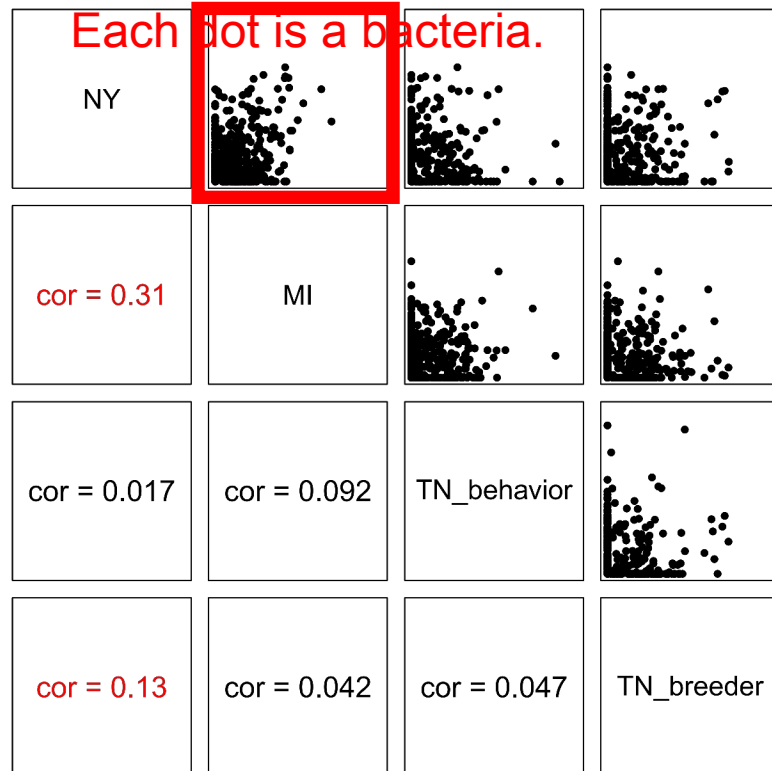
Each dot is a bacteria.



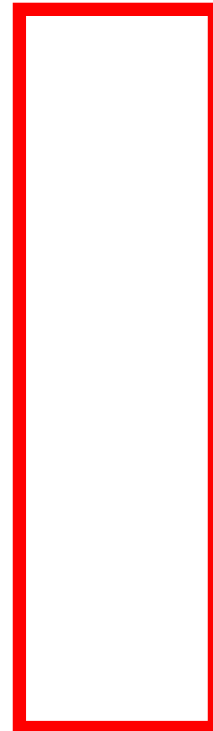
Four cohorts analysed separately

1) To what extent do host genetic effects depend on the environment?

Heritability in NY (y-axis)
vs heritability in MI (x-axis).



Genetic correlation (y-axis)
between abundance of bacteria in MI
and abundance of same bacteria in
NY.



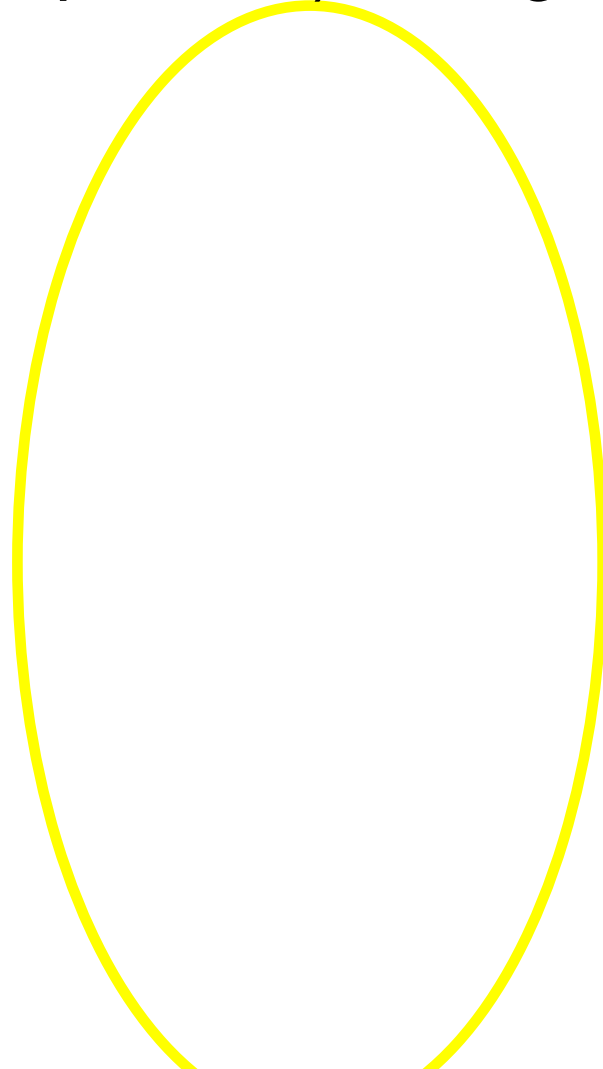
Four cohorts analysed separately

2) Can we identify robust (replicated) host genetic effects ?

*Compare to: only one
locus strictly replicated
in humans (LCT)*

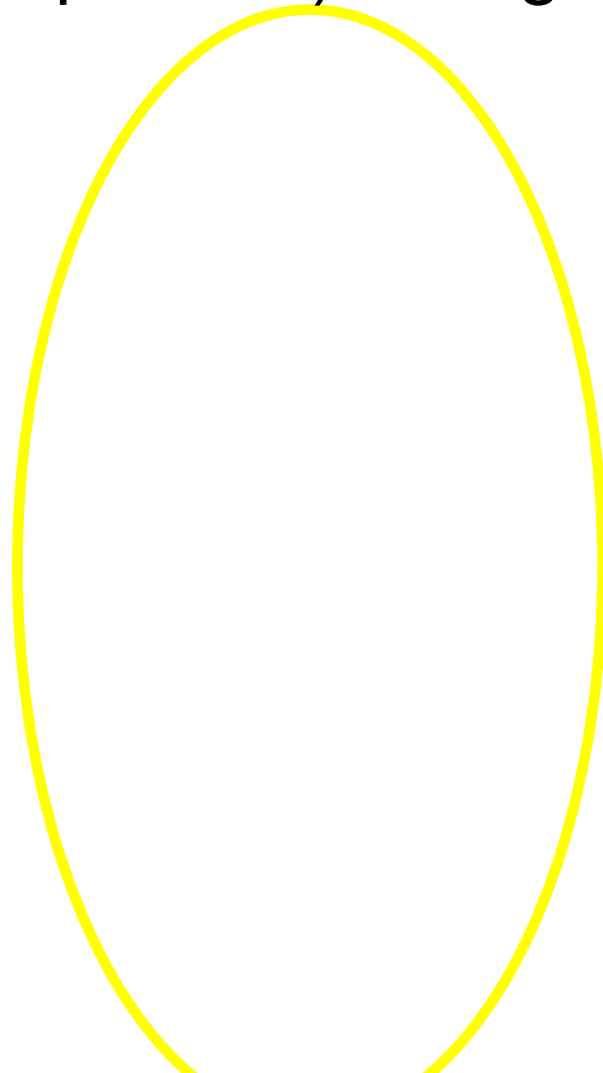
Four cohorts analysed separately

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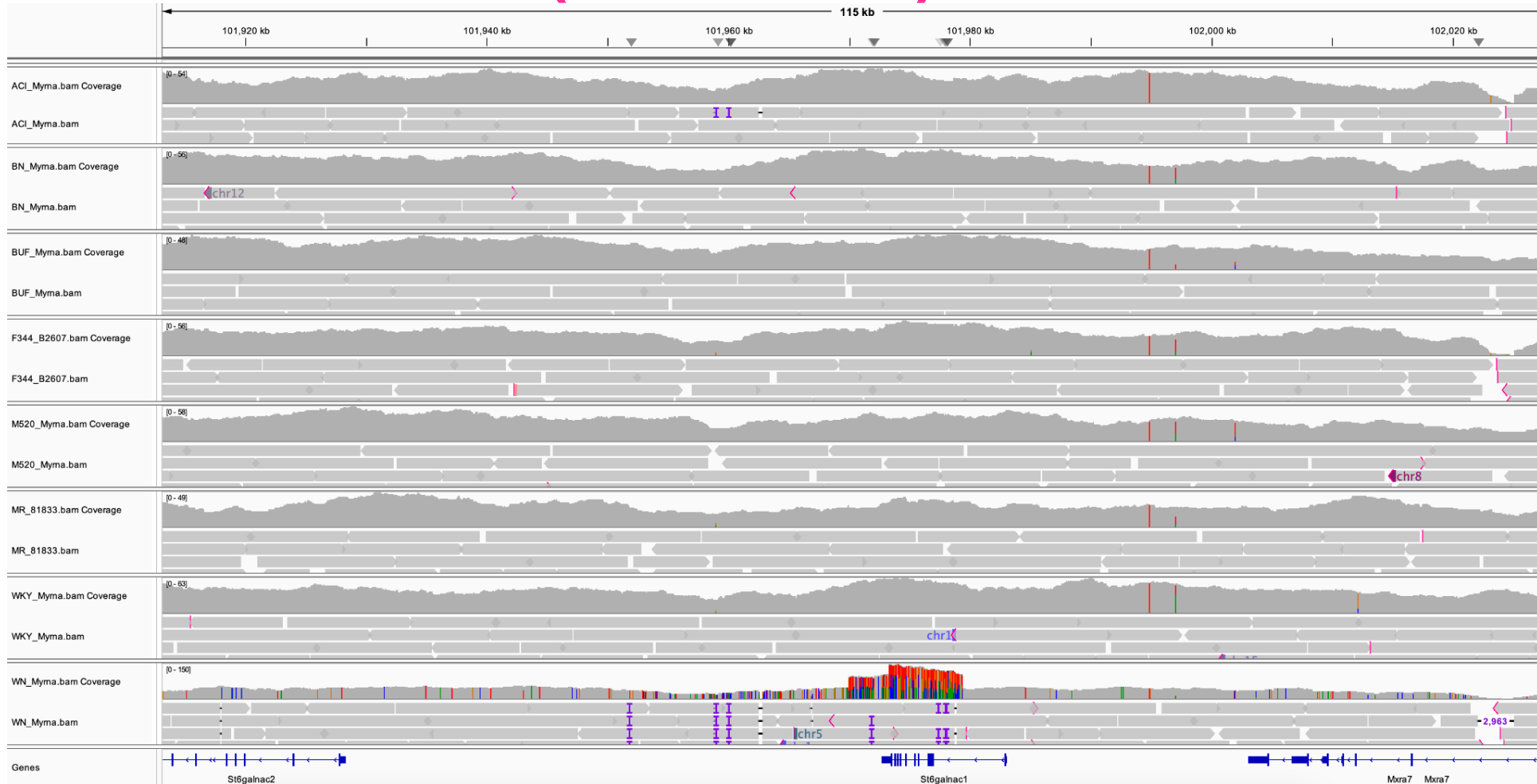
2) Can we identify robust (replicated) host genetic effects ?



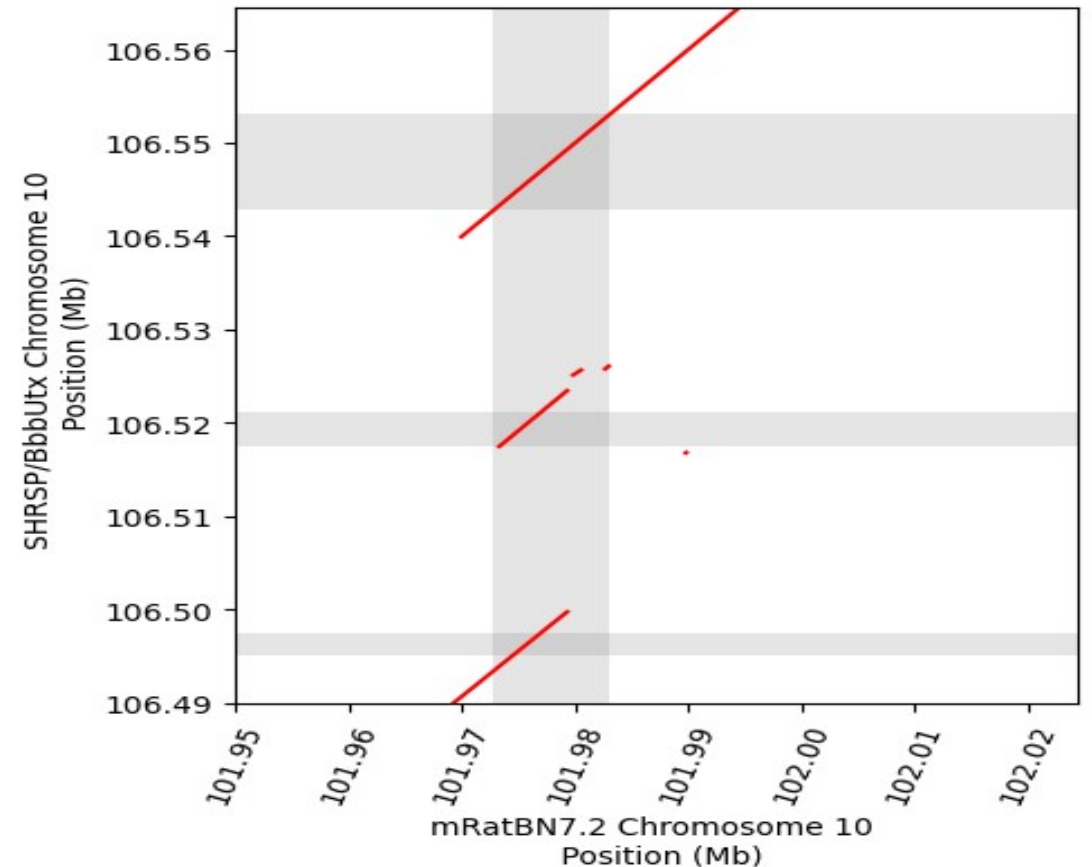
- causal variant(s)?
- causal gene(s)?
- mechanism(s)?

Partial duplication/triplication of *St6galnac1* in WN/N

Evidence 1: PacBio of HS founders, analysed by **Denghui Chen**
(Palmer lab)

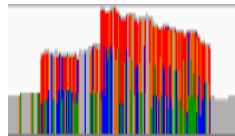
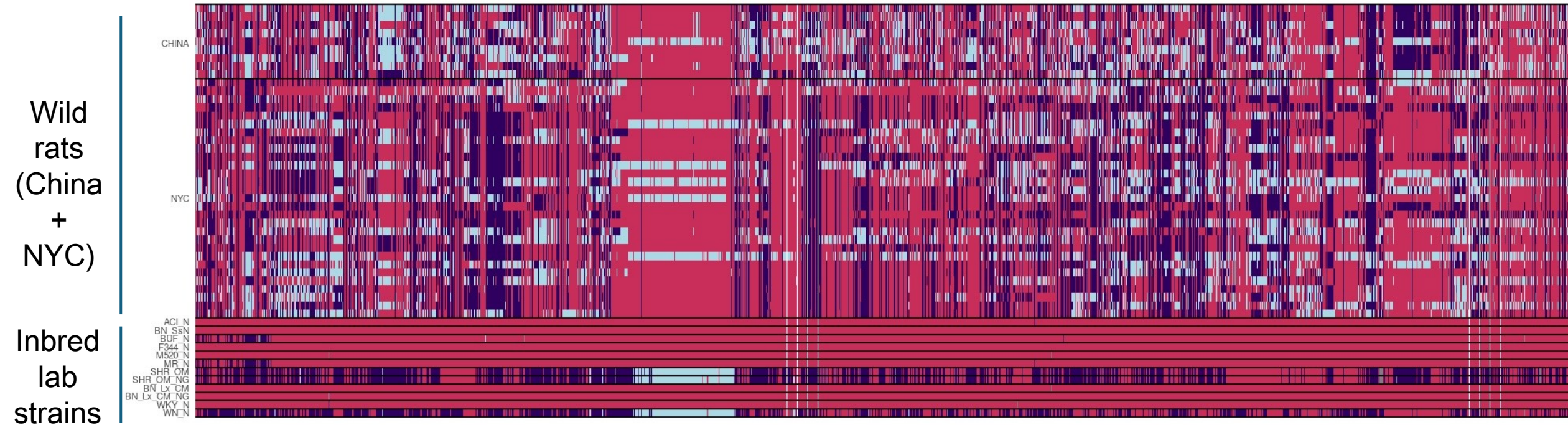


Evidence 2: SHRSP genome assembly (from P. Doris and colleagues)



Partial triplication of *St6galnac1* and signature of selection

Genotype  HOM REF  HET  HOM ALT



 *St6galnac1*

Similar *St6galnac1* copy number variant in mice

Thus, BXSB, NZW, 129, NZB and SB/Le have all three regions; B10, SM/J, SJL, C57BL/KsJ, MRL, B6 and AKR have both regions 1 and 2 while BALB/c, CBA, A/WySnJ, DBA and C3H have just region 1.

Long-term balancing selection?

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Long-term balancing selection?

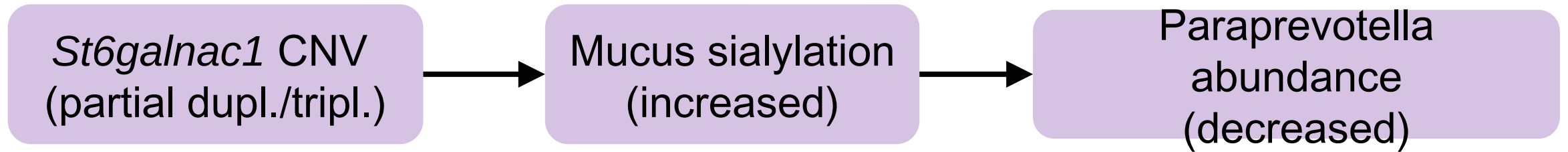
St6galnac1 → Akkermansia → mucin sialylation

Yao et al. Mucus sialylation determines intestinal host-commensal homeostasis, Cell (2022)

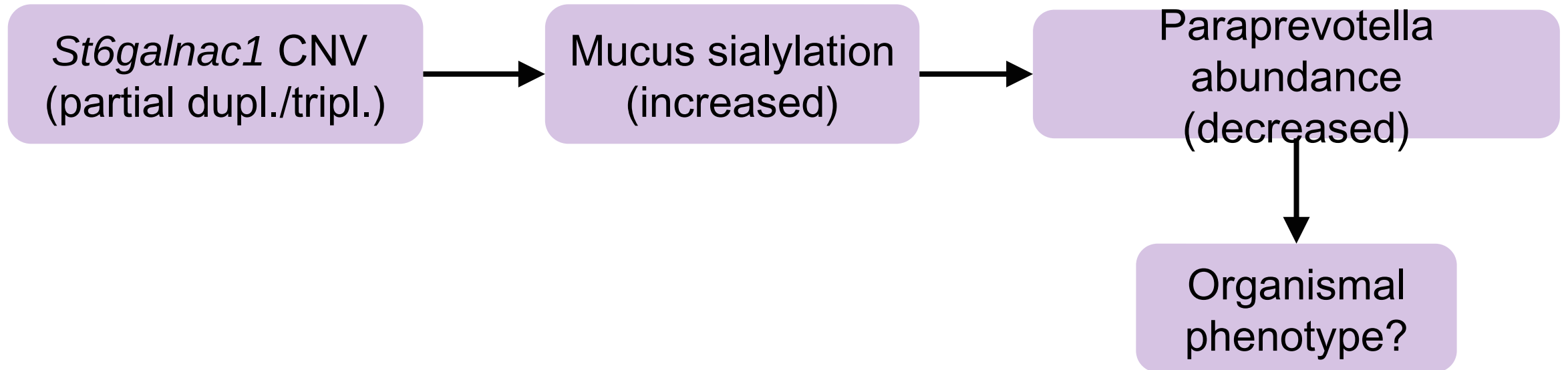
- using human cell lines and human St6galnac1 KO mutation put into mice -

In HS rats: partial duplication/triplication of St6galnac1 results in increased mucus sialylation and decreased Akkermansia & Paraprevotella abundances.

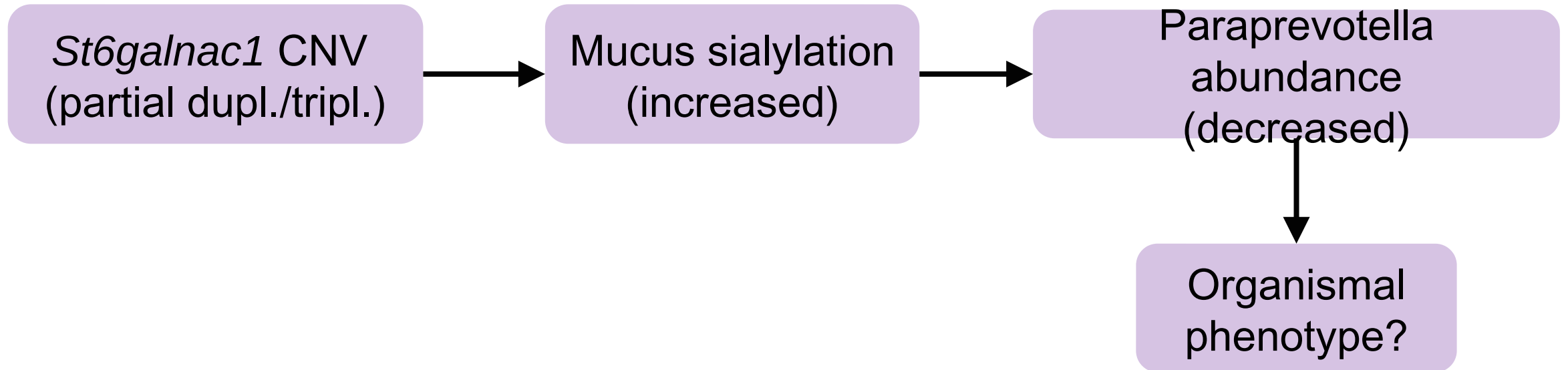
Phenotypic consequences of the association between the *St6galnac1* locus and *Paraprevotella*



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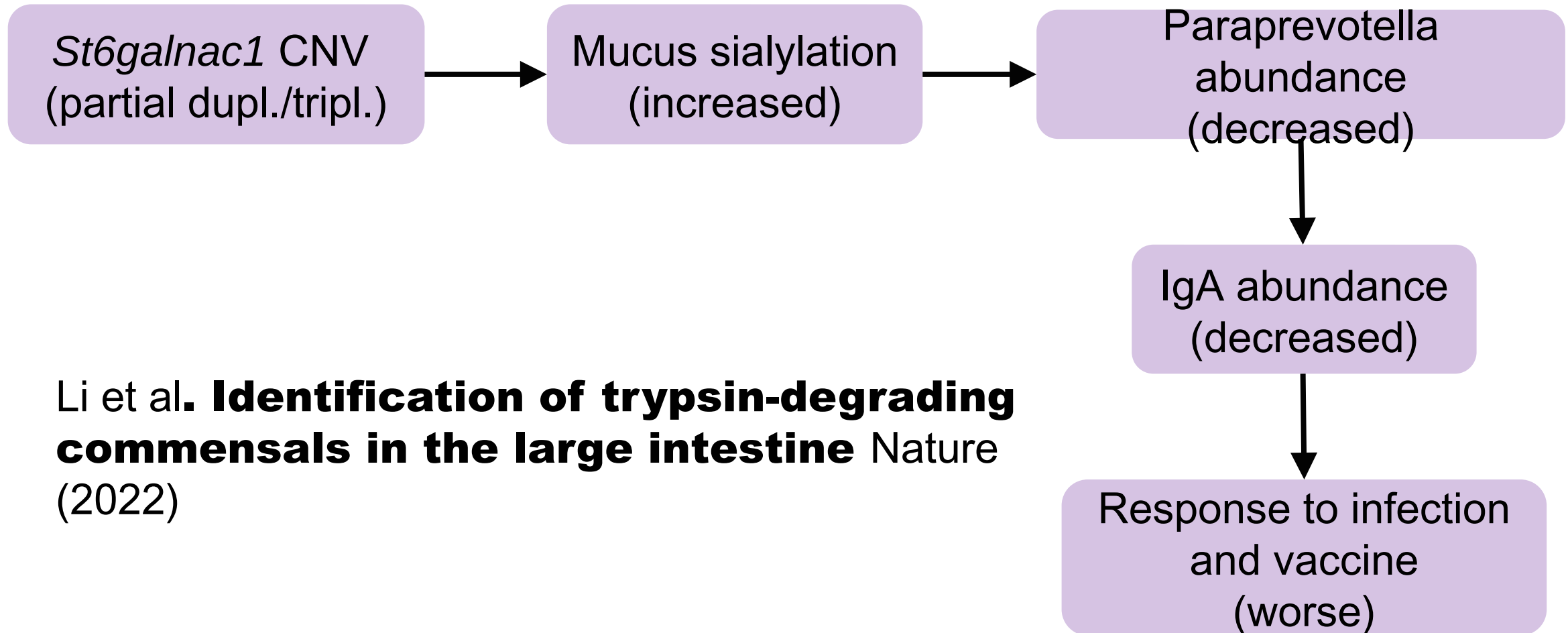


Phenotypic consequences of the association between the *St6galnac1* locus and *Paraprevotella*



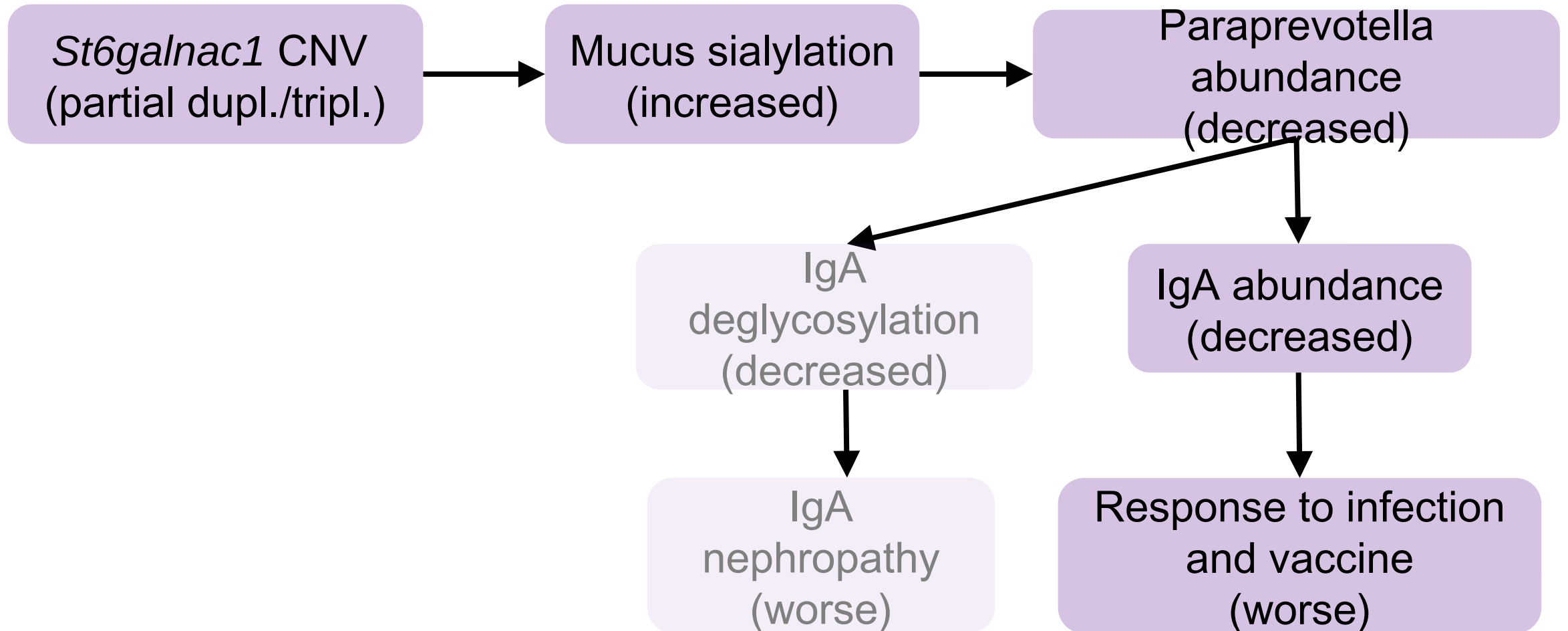
None of the phenotypes measured in HS rats is affected by the *St6galnac1* CNV (PheWAS by **Thiago Sanches, Palmer lab**).

Phenotypic consequences of the association between the *St6galnac1* locus and *Paraprevotella*

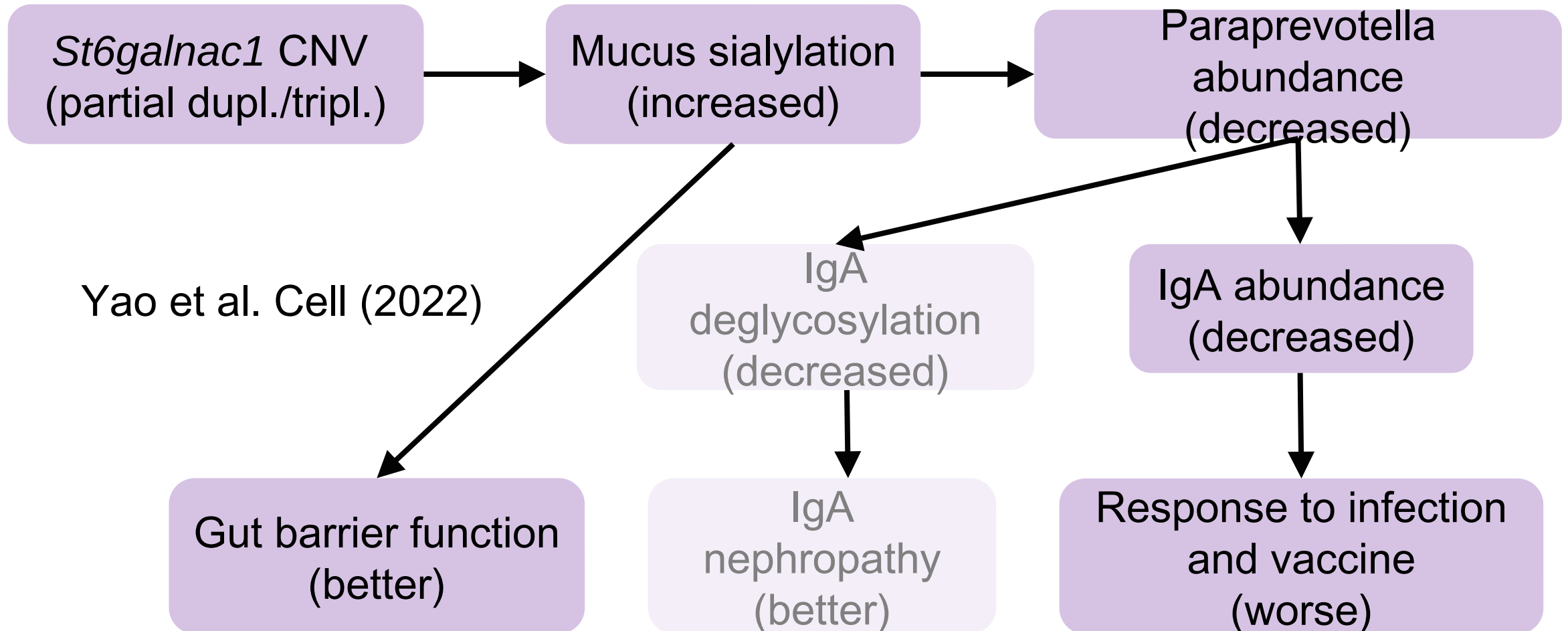


Li et al. **Identification of trypsin-degrading commensals in the large intestine** Nature (2022)

Phenotypic consequences of the association between the *St6galnac1* locus and *Paraprevotella*



Phenotypic consequences of the association between the *St6galnac1* locus and *Paraprevotella*



Allo-coprophagy, microbiome transmission and indirect (social) genetic effects on the microbiome

Rat microbiome projects in the lab

- test association between St6galnac1 and Paraprevotella in 30 **BxH / HxB** strains from Michal Pravenec
- comparison of 16S and **shallow shotgun sequencing** for detecting host genetic effects
- **catalogue of metagenome-assembled genomes**
- rerun microbiome GWAS using **deep shotgun sequencing**
- analysis of **microbiome transmission** based on strain-level profiling
- **gut microbial functions** ↔ **gut metabolome** (LC-MS-MS, collaboration with Dorrestein lab @ UCSD)
 - *paper on metabolome GWAS by Joel Leal-Gutierrez coming soon*

HS rats

Open to collaborations on the microbiome!

**Please consider saving cecal/fecal samples from
your rats**

Acknowledgements



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Centre for Genomic regulation

Felipe Morillo

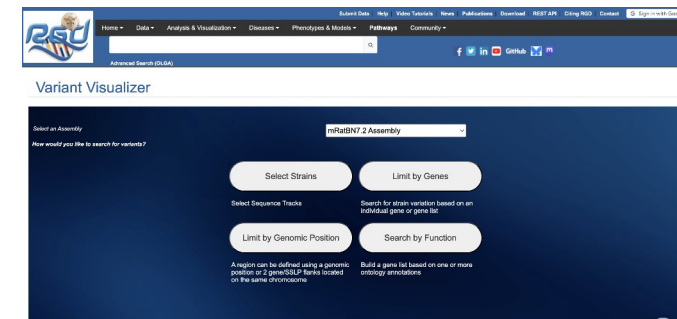
Helene Tonnele



UC San Diego

Abraham Palmer & lab

Rob Knight & lab



RGD Team

Institute for Evolutionary Biology

Jorge Garcia Calleja

