A Microbe Associated with Sleep Revealed by a Novel Systems Genetic Analysis of the Microbiome in Collaborative Cross Mice
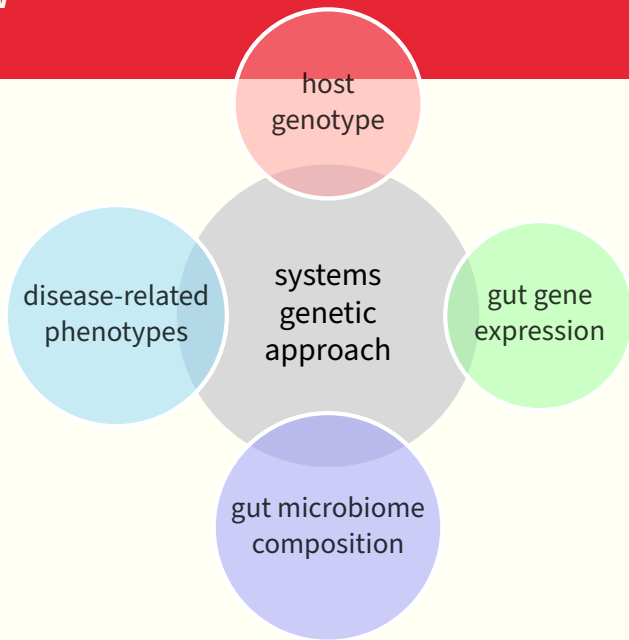
by

Jason A. Bubier et al.

host genotype
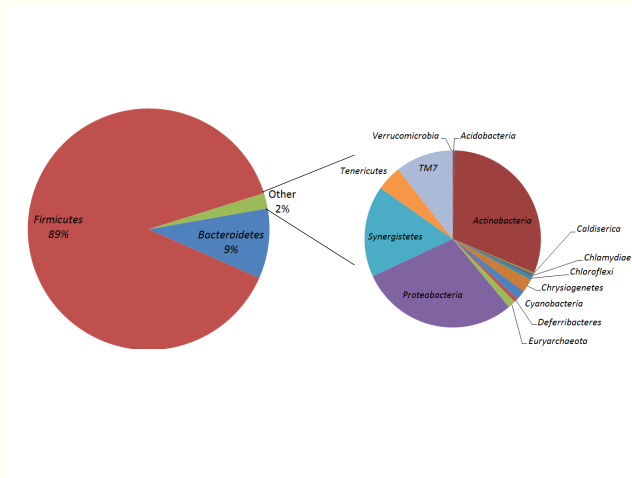
systems genetic approach

gut gene expression

disease-related phenotypes

gut microbiome composition

Results

Microbial community composition of incepient CC mice

Cecal microbial profile across mouse samples

Microbial abundance QTL

- 18 significant microbial abundance QTL
- 1.5 LOD C.I.: 2-24Mb, average of 7.5 Mb

eQTL in the CC cecum

- Used microarrays for estimates of transcript abundances
- QTL analysis to identify host genomic regions harboring allelic variants that influence the abundance of each probe
- 1641 significant QTL for probes, corresponding to 1513 genes
- 950 loci were *cis*-eQTL, which contain polymorphisms that are proximal to transcript-coding regions
  $\rightarrow$ useful for identifying expression regulatory mechanisms

Genetic correlation of microbial abundance to disease-related traits reveals a microbe associated with sleep

- 122 disease-related behavioral and physiological phenotypes tested
- 45 trait-microbe correlations, 26 exceeded the multiple testing FDR threshold
- 41 contained sleep phenotypes with 10 different microbes, 22 ($q < 0.05$)
- OTU 273 *Odoribacter* correlated with 21 phenotypes comparison-wise and 13 family-wise adjusted

Genetic regulation of the abundance of *Odoribacter*

- *Micab7*: NZO allele associated with increased abundance *Odoribacter*, is obese and prone to diabetes
- Previous studies: diabetic *db/db* mice and abnormal sleep pattern

Hypothesis

Odoribacter, *Lepr* and sleep are connected through a common mechanism.

We expect an overlap between one or more of the QTL positional candidates and the *Lepr* pathway, and that perturbations of the gut microbiota of *db/db* mice should affect sleep patterns.

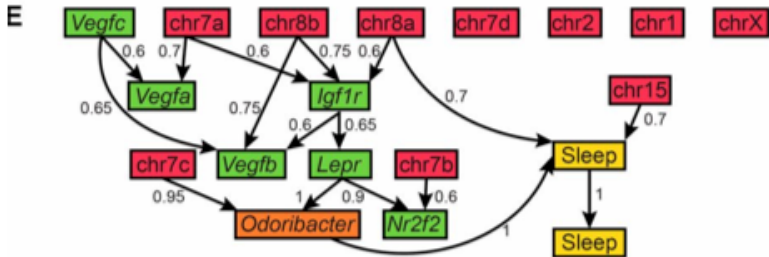# Genetic regulation of the abundance of *Odoribacter*

Ingenuity Pathway Analysis

42 positional candidates with Lepr: *Nr2f2* and *Igf1r* as most likely
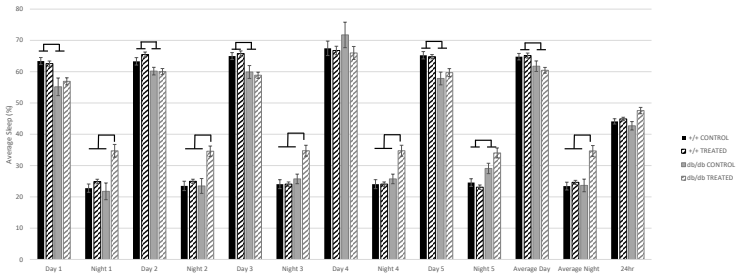
Causal graphical models G-P

Infer the direct and the indirect associations among results of the IPA, the leptin pathway, and sleep

Inferred network

Broad-spectrum antibiotic treatment alters sleep patterns in Lepr[db]Lepr[db] mice

Mice treated with antibiotics from conception. This showed a genotype-specific effect on sleep architecture.

Broad-spectrum antibiotic treatment alters sleep patterns in Lepr^db Lepr^db mice
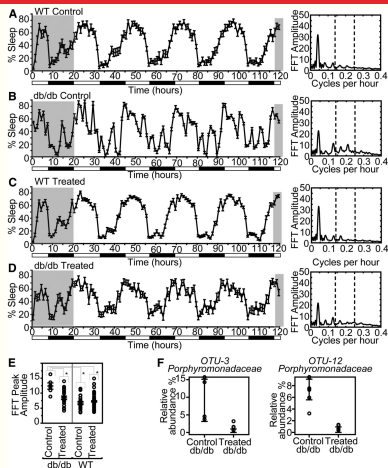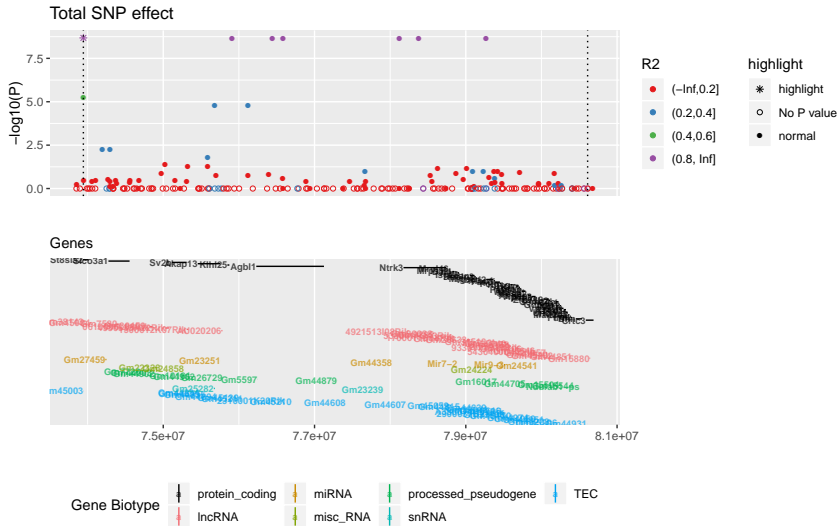

Mean and SE for the percentage sleep time over a 5-day test, with cyclic patterns characterized on the right by an FFT of the mean sleep percentage time series.
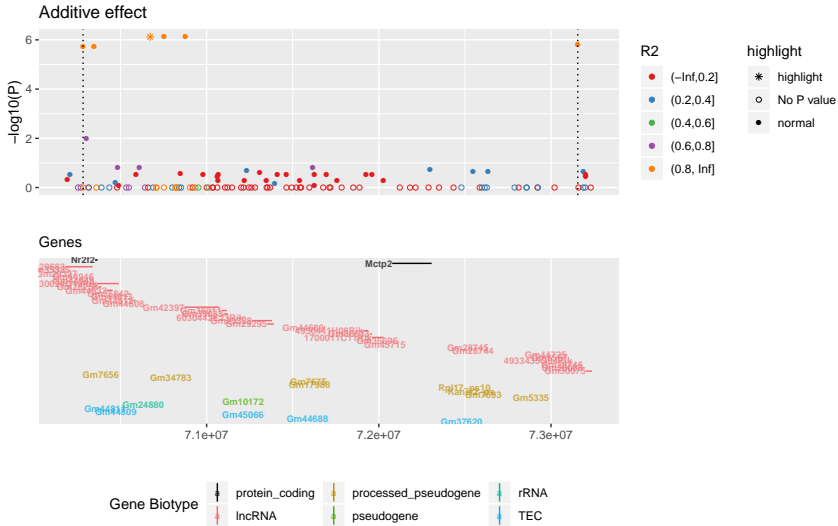
Conclusion

Conclusion

- They show for the first time a relationship between abundance of a specific microbe and sleep
    - OTU273 *Odoribacter* abundance is associated with *Micab7* QTL and was correlated with multiple sleep phenotype measures
    - Genomic network analyses revealed that the primary candidate gene for the QTL is *Igf1r*
    - Perturbation of this pathway in the db/db Lepr mutant mouse is associated with abnormal phenotype and an elevated abundance of *Odoribacter* (among other microbes)
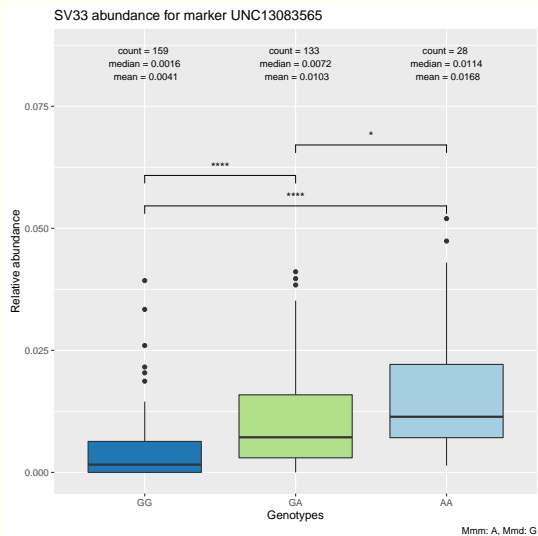   - Both of these phenomena can be restored by antibiotic treatment

- They have not yet demonstrated that *Igf1r* variation is i=the specific causal regulator
- whether the locus is associated with abnormal Odoribacter abundance
- whether inoculation of *Lepr* or *Igf1r* mice with *Odoribacter* and its metabolites influences sleep

SV35

Total SNP effect

Genes

R2
- (−Inf,0.2]
- (0.2,0.4]
- (0.4,0.6]
- (0.8, Inf]

highlight
- highlight
- No P value
- normal

Gene Biotype
- protein_coding
- lncRNA
- miRNA
- misc_RNA
- processed_pseudogene
- snRNA
- TEC

Data source: https://uswest.ensembl.org:443/biomart/martservice?redirect=no + Data set: mmusculus_gene_ensembl

SV33 abundance for marker UNC13083565

Genus Paraprevotella

G_Paraprevotella abundance for marker UNC13034282