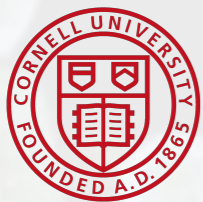


The role of *host genetics* in determining gut microbiome composition

Emily R. Davenport

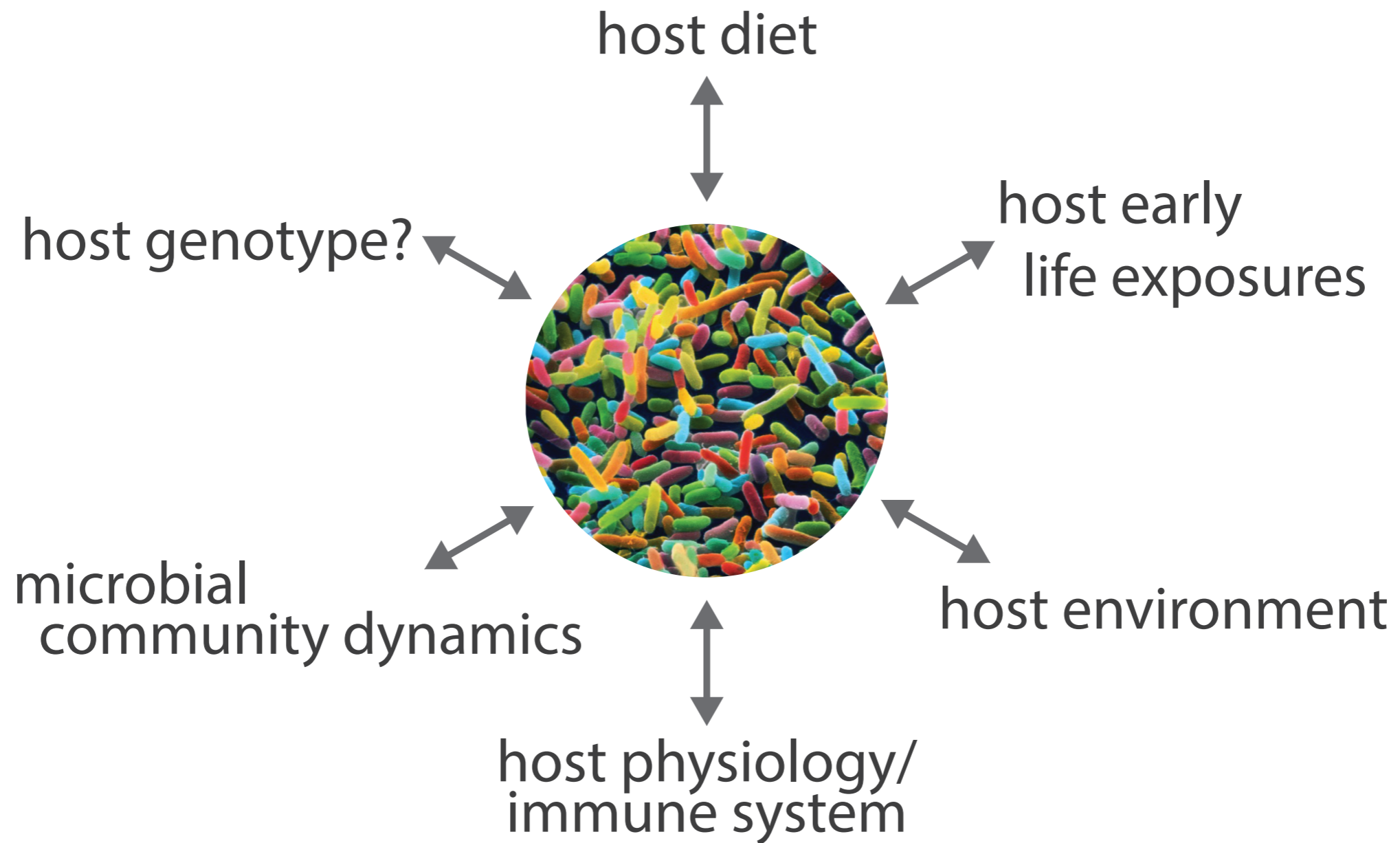


Postdoctoral Fellow - Clark Lab
Cornell University

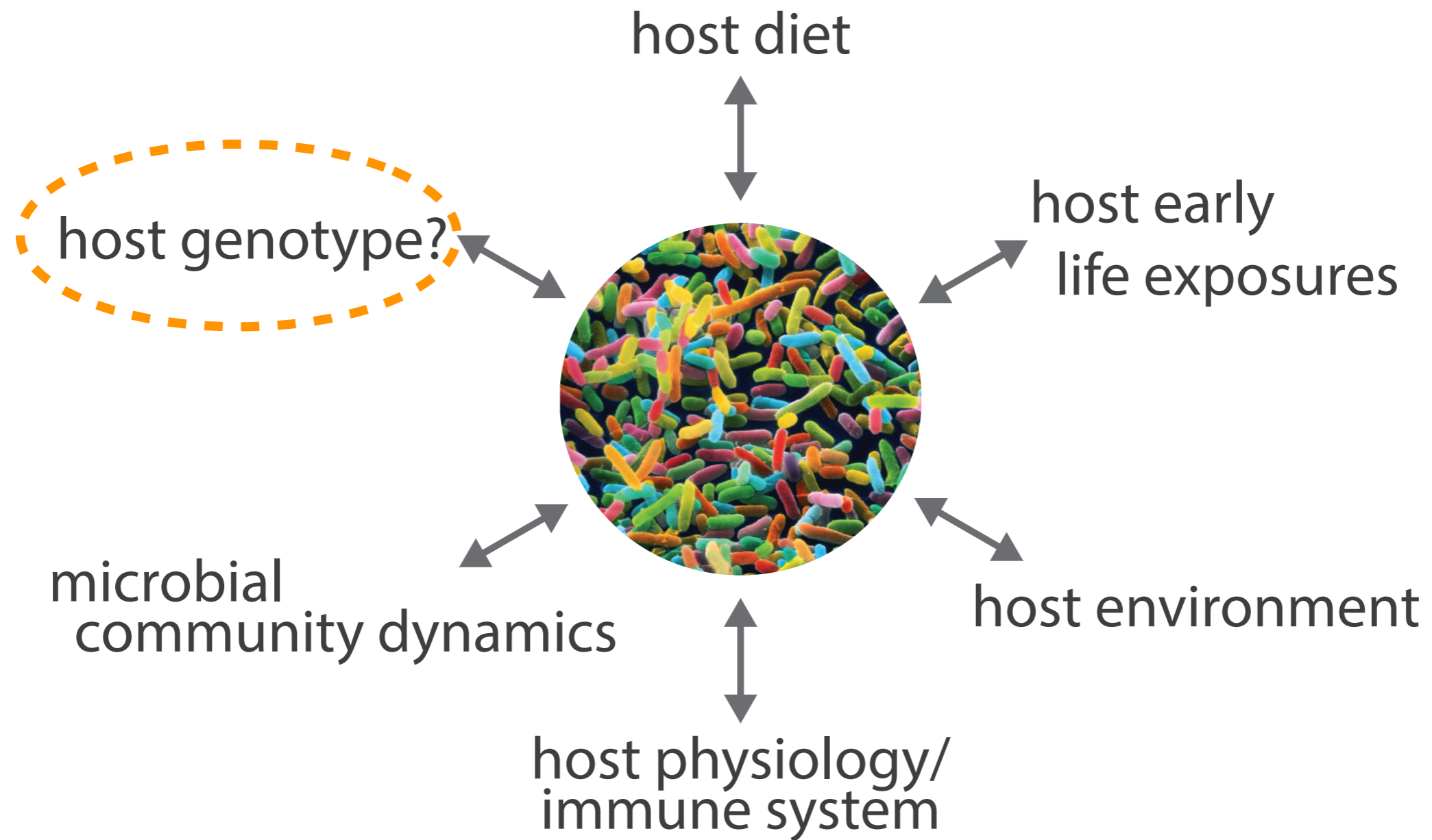


@emo_davenport

What determines microbiome *composition*?



What determines microbiome *composition*?



Open *questions*:

Open questions:

Is the microbiome *heritable*?

Open questions:

Is the microbiome *heritable*?

If so, can we identify *variants* in the human genome associated with microbial abundance?

Outline

1. Genome-wide association studies of the human gut microbiota

the Hutterites



2. Genetic determinants of the gut microbiome in UK twins

the TwinsUK



Outline

1. Genome-wide association studies of the human gut microbiota
the Hutterites



Davenport ER, Cusanovich DA, Michelini K, Barreiro LB, Ober C, and Gilad Y. *Genome-wide association studies of the human gut microbiota*. PLoS One. 2015;10(11):e0140301 (epub 2015 Nov 3)

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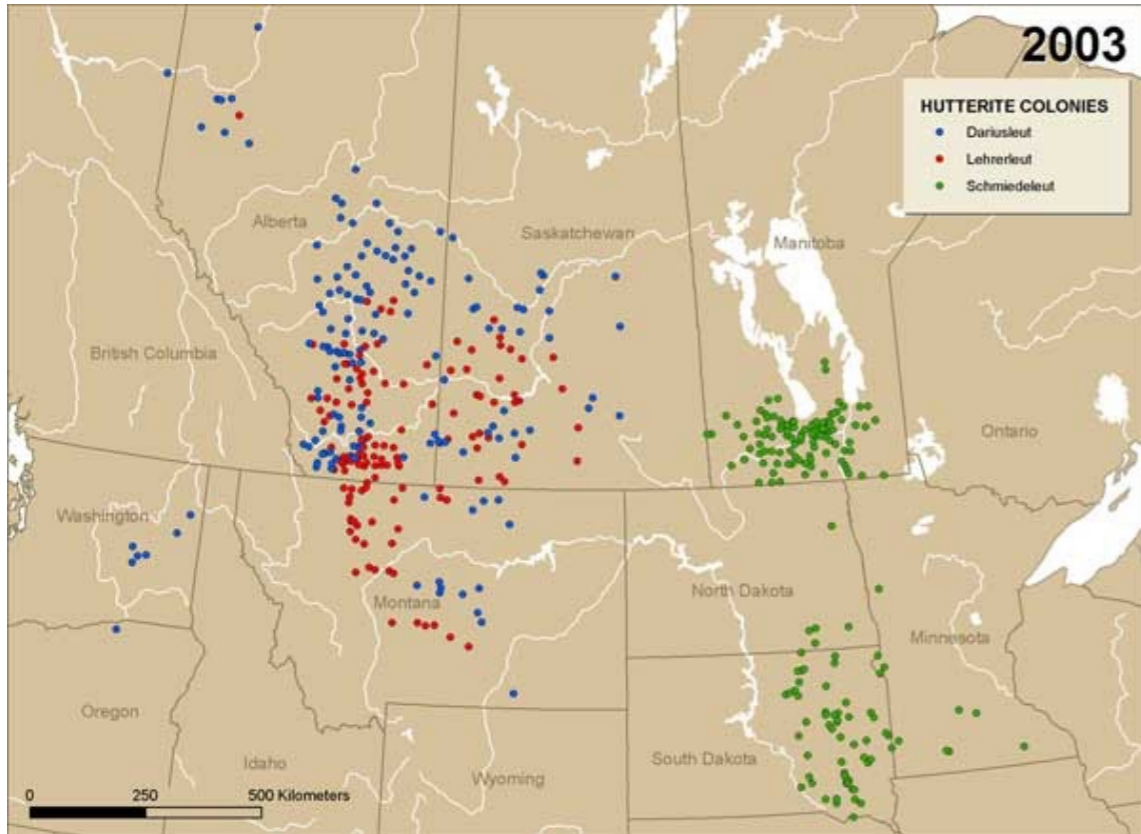
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2. Which *variants* in the human genome are associated with bacterial abundance?

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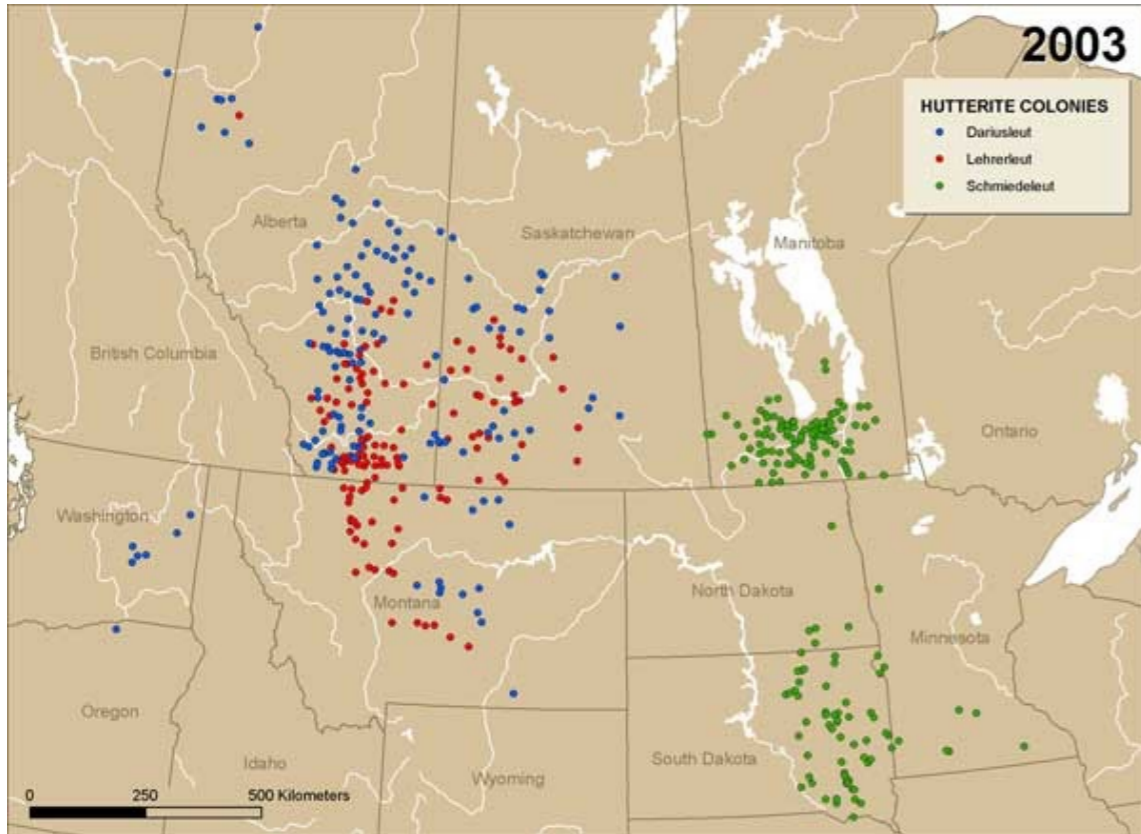
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Study design: *the Hutterites*



Study design: *the Hutterites*

Hutterites eat *communally*

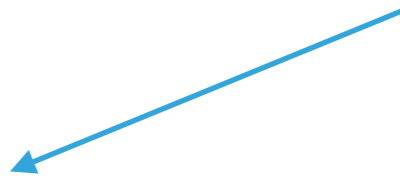


Study design: *sample collection*



127 individuals

microbiome data



Study design: *sample collection*



127 individuals

microbiome data

genetic data

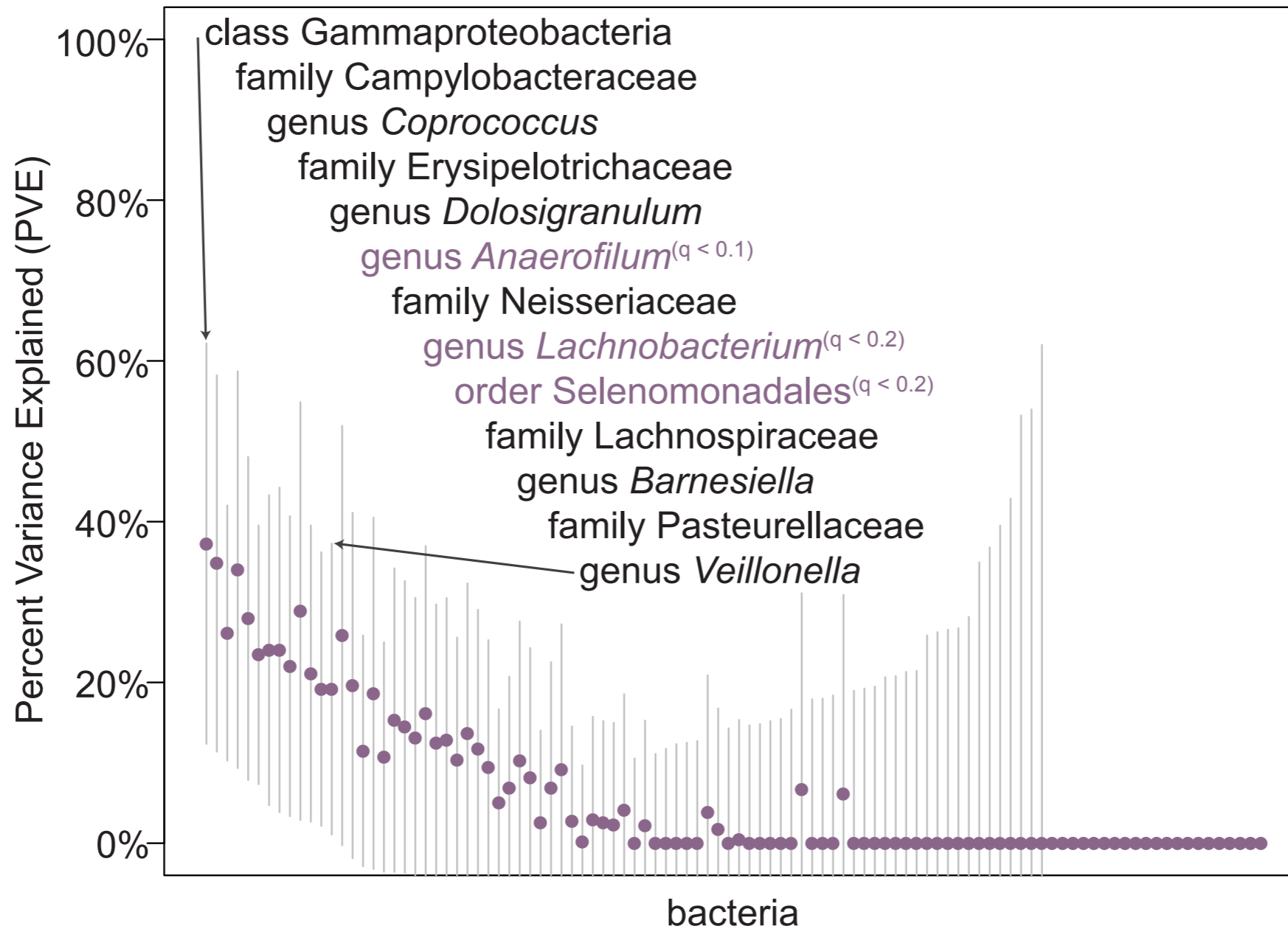


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Several taxa show “chip” heritability

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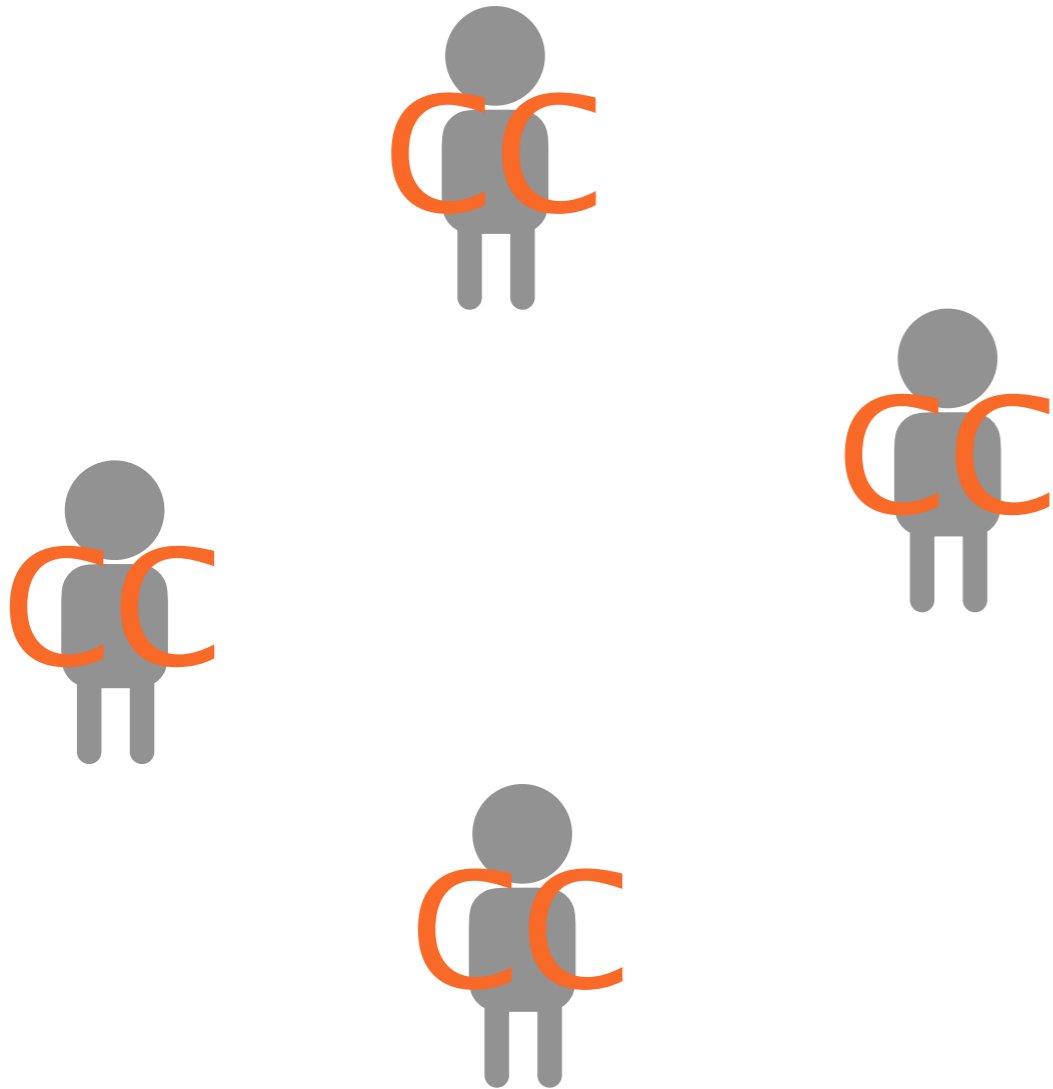
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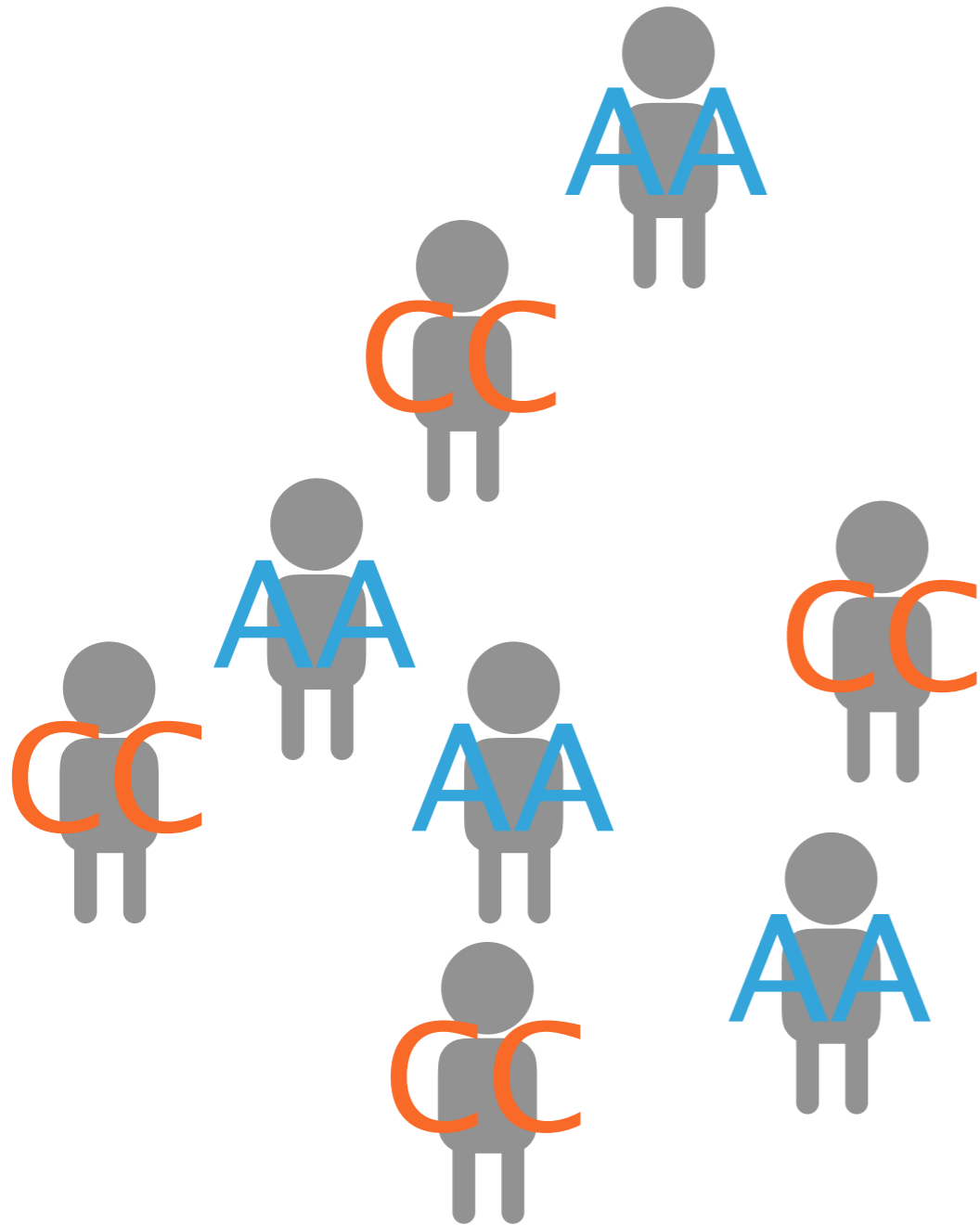
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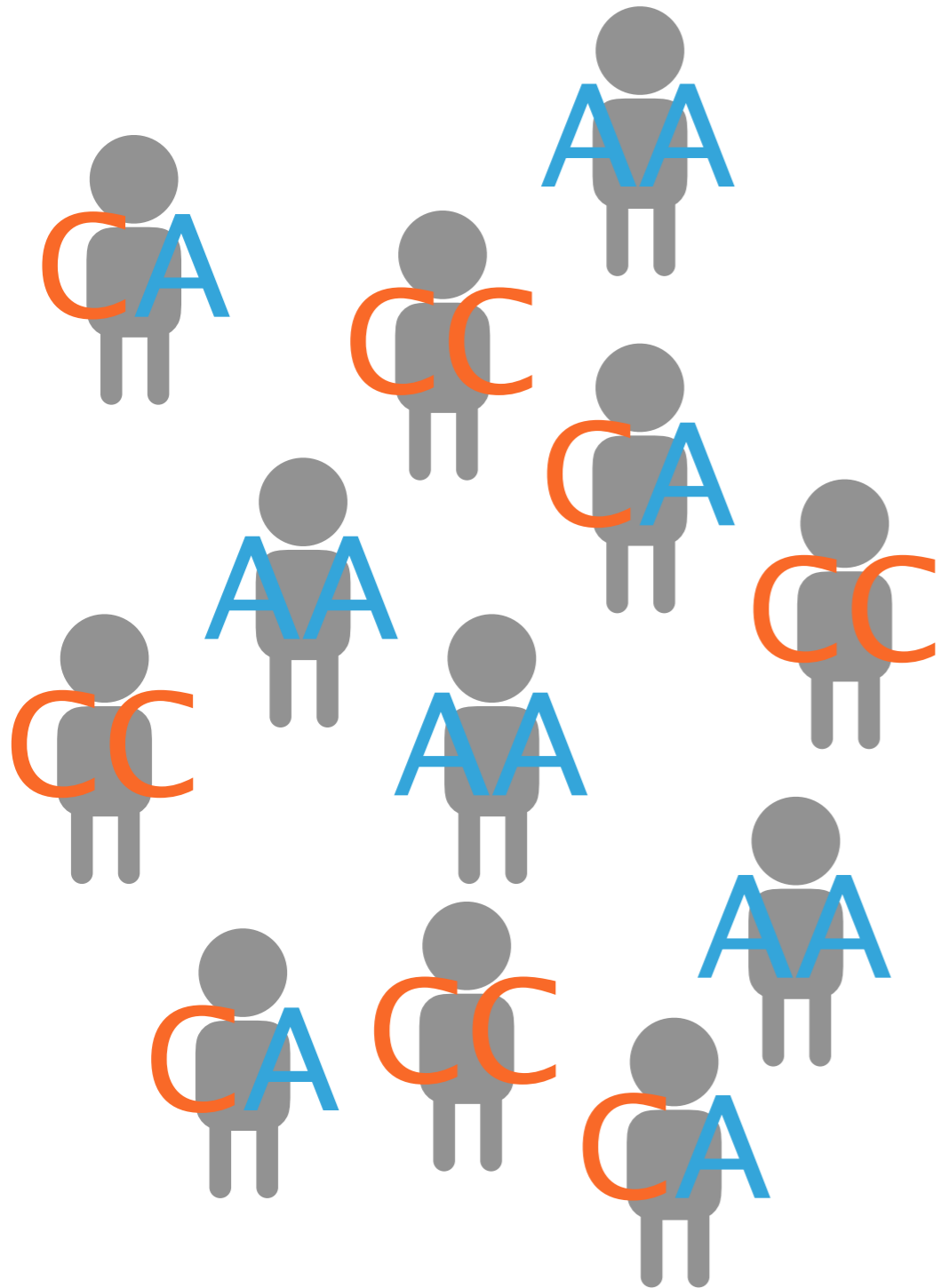
GWAS identifies *variants* associated with *phenotypes*



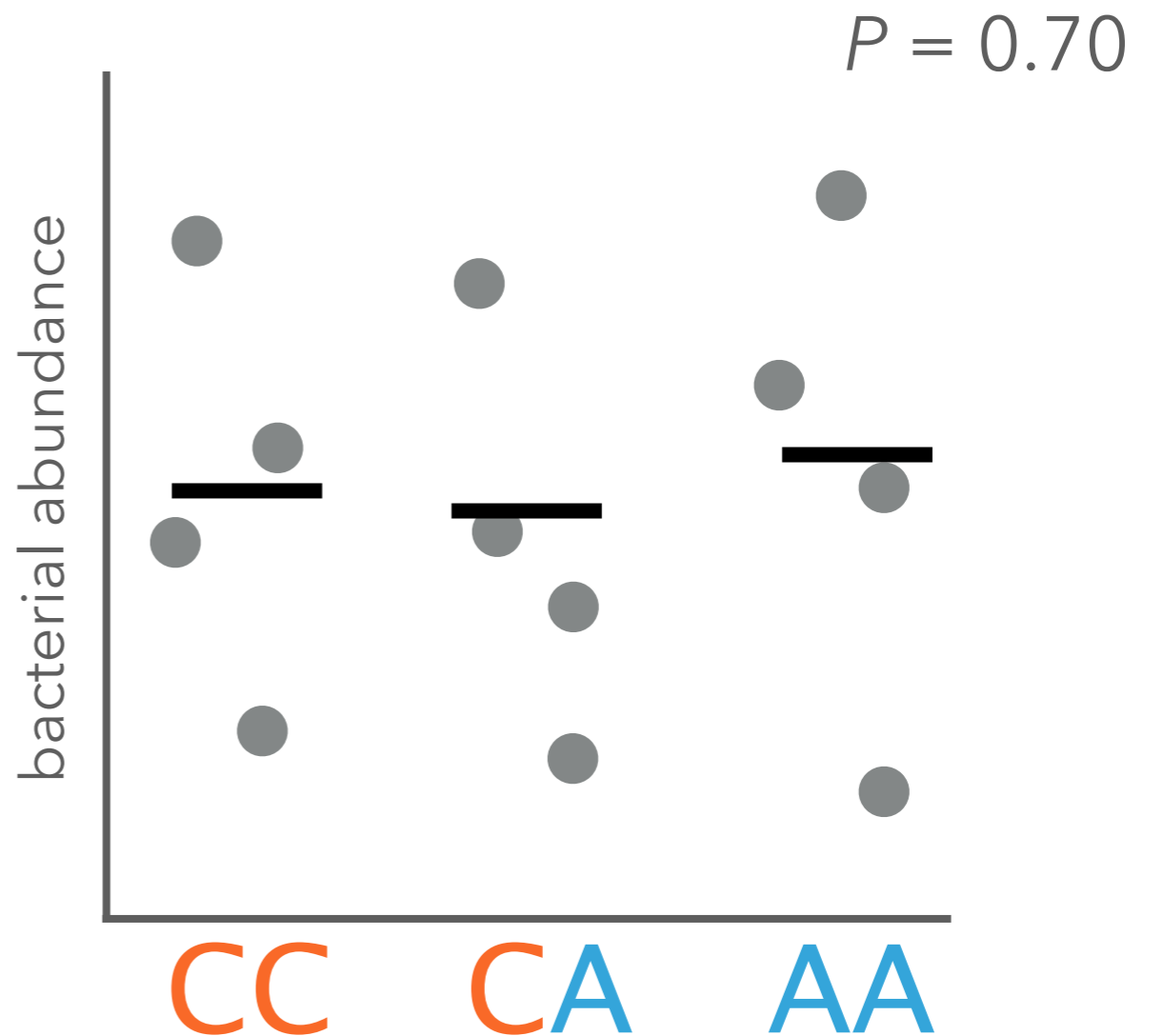
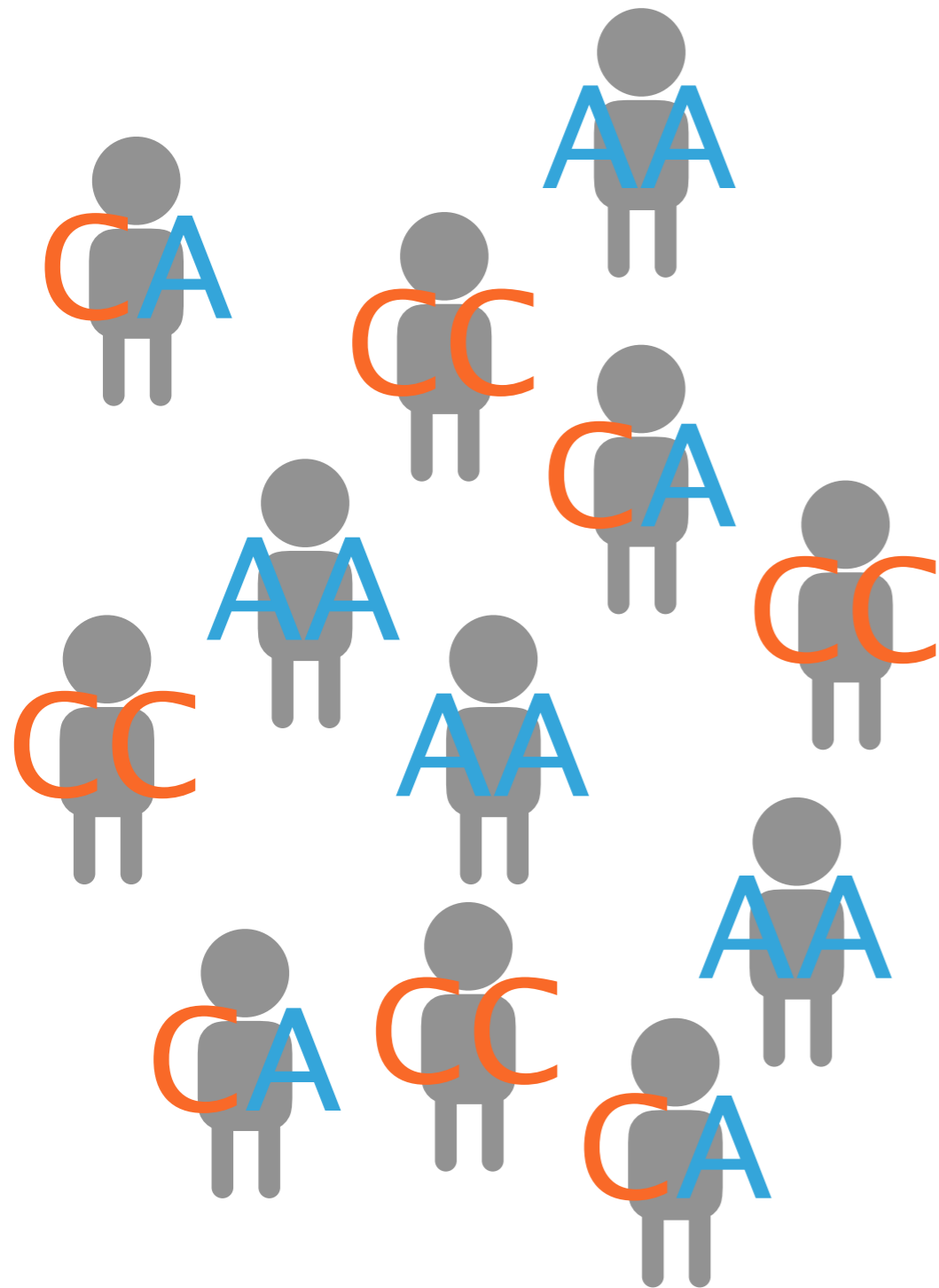
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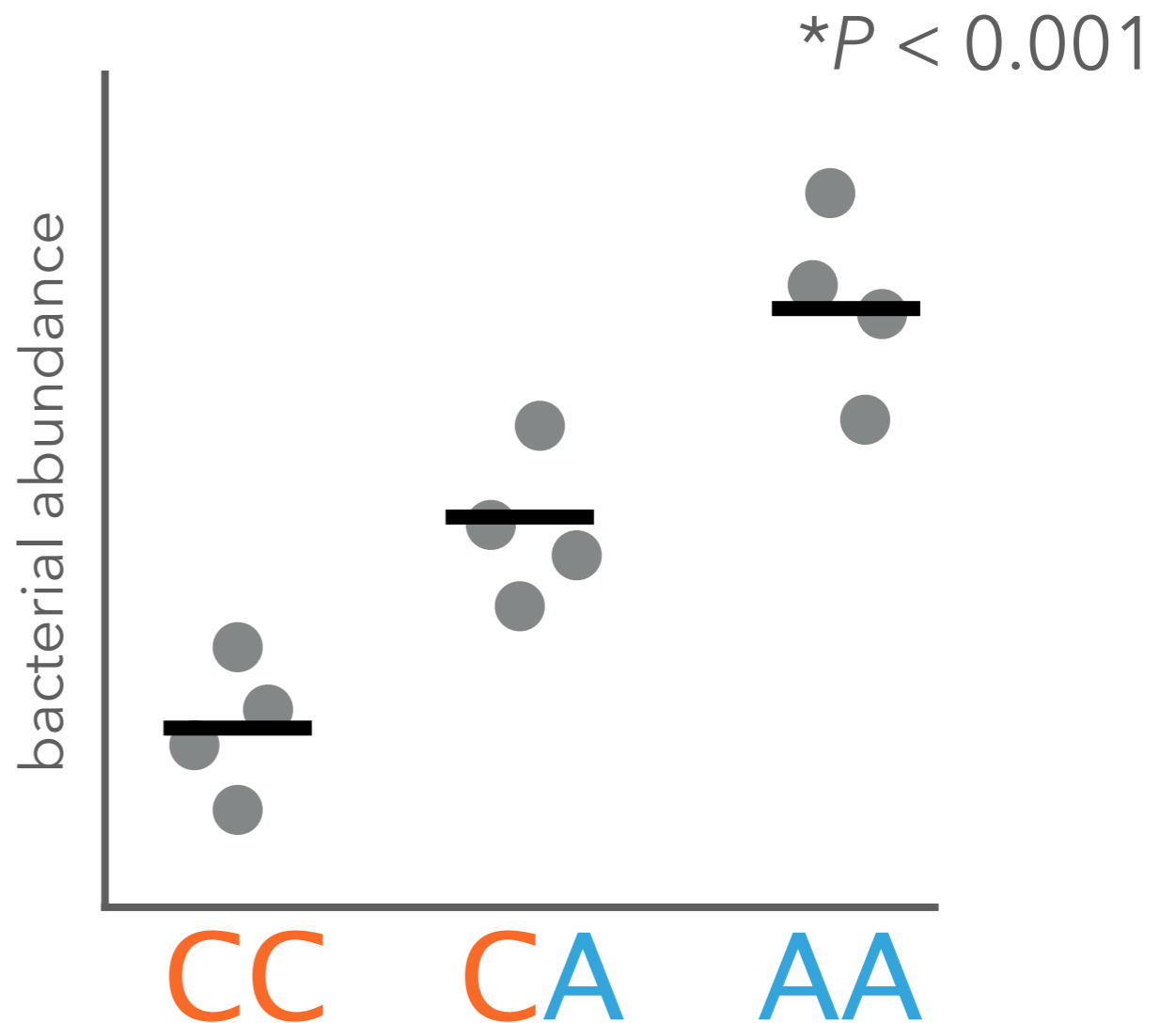
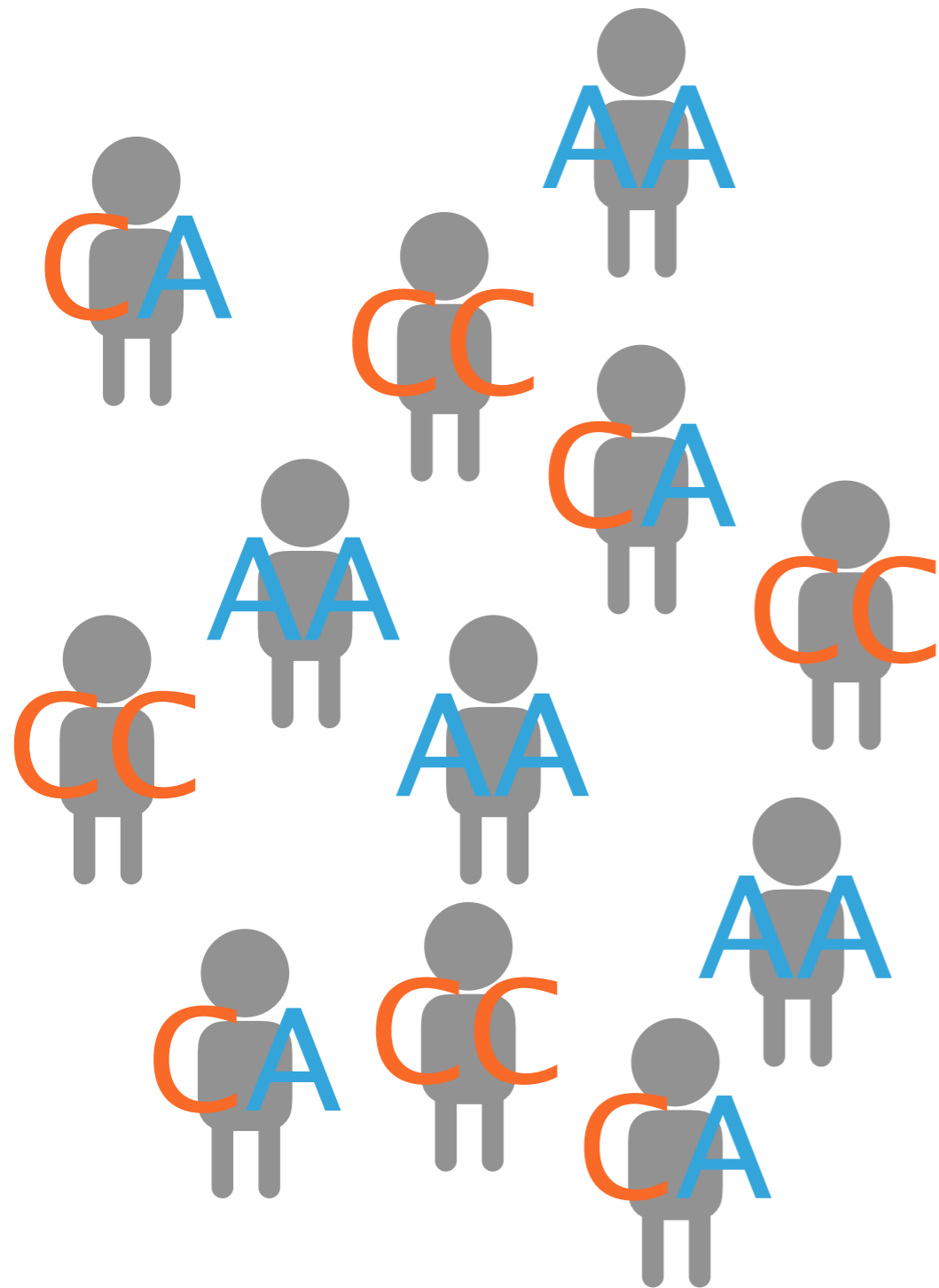
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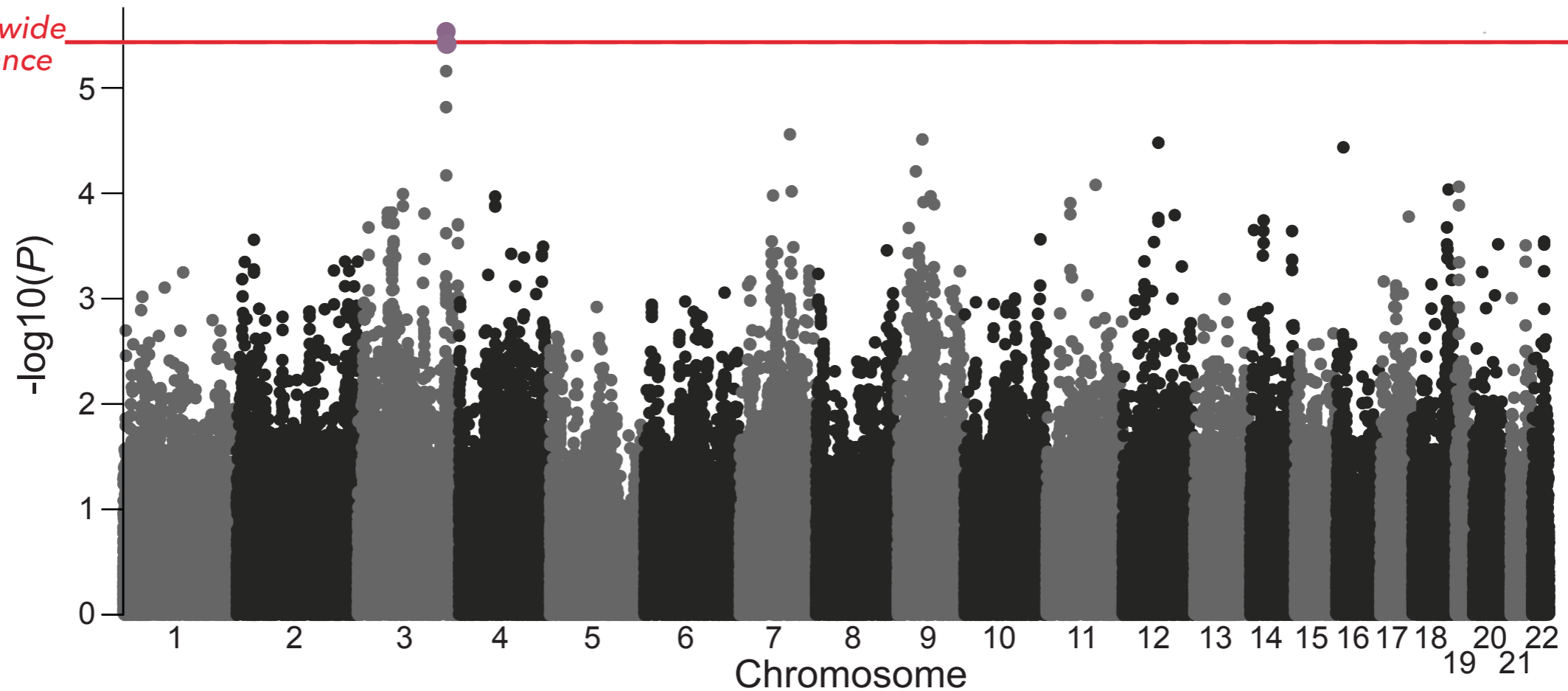
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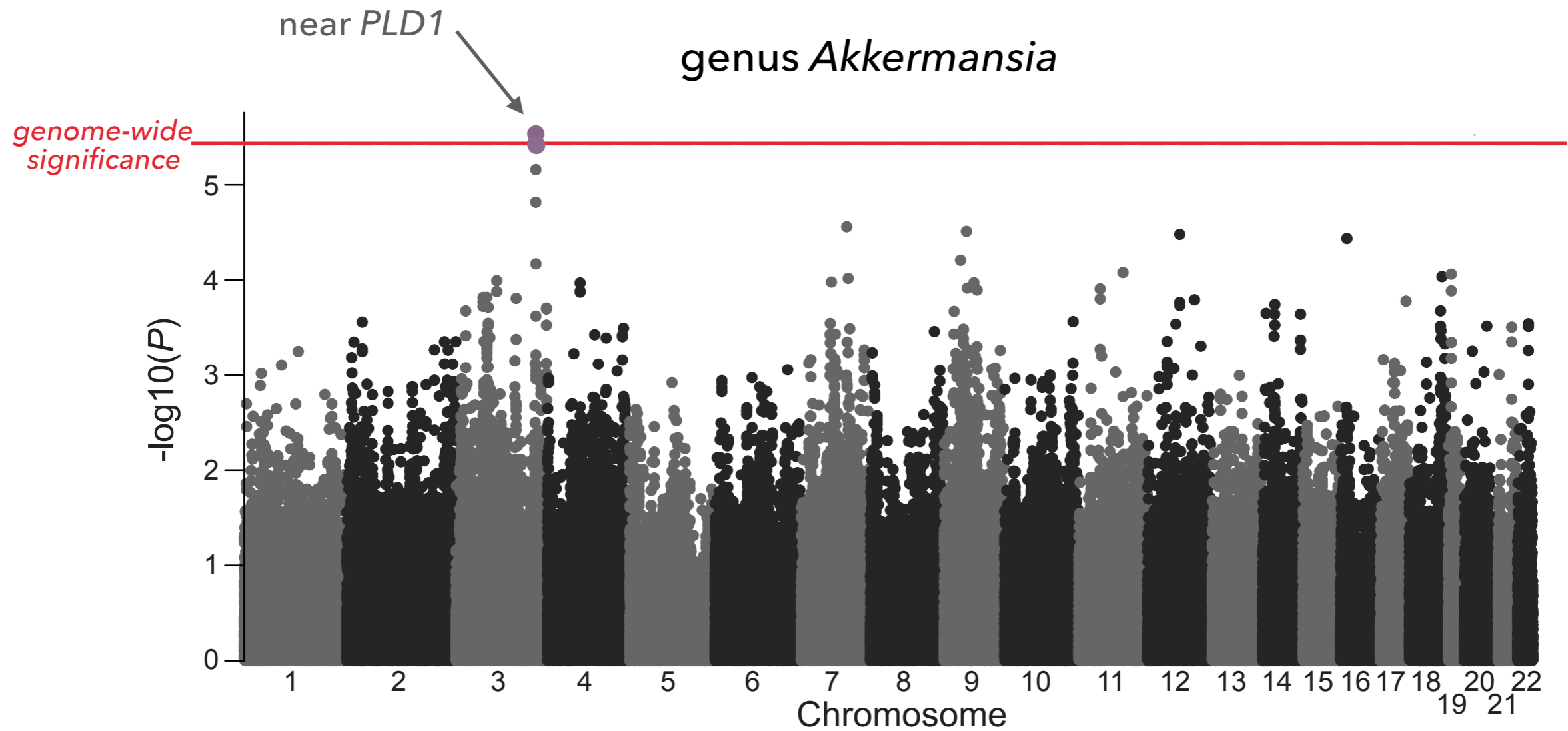
Variants associated with *Akkermansia* lie near a gene implicated in obesity

genus *Akkermansia*

genome-wide
significance

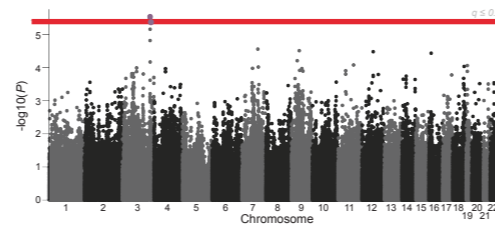


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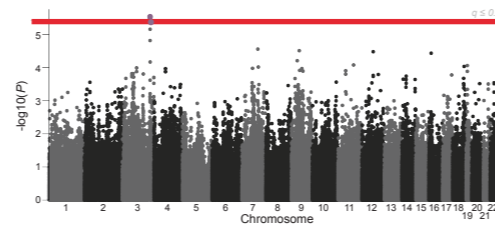
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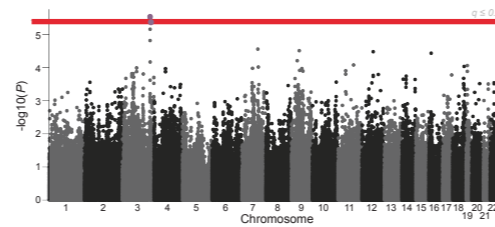
PLD1 associated with *BMI* in African Americans

Genome-Wide Association of BMI in African Americans

Maggie C.Y. Ng^{1,2}, Jessica M. Hester^{1,2,3}, Maria R. Wing^{1,2,3}, Jiang Li^{1,2}, Jianzhao Xu^{1,2}, Pamela J. Hicks^{1,2,4}, Bong H. Roh^{1,2,4}, Lingyi Lu⁵, Jasmin Divers⁵, Carl D. Langefeld⁵, Barry I. Freedman⁶, Nichole D. Palmer^{1,2,4}, and Donald W. Bowden^{1,2,4,6}

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Akkermansia protects against *obesity*

Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

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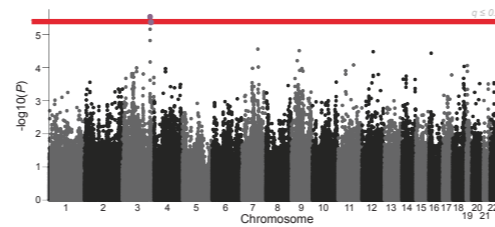
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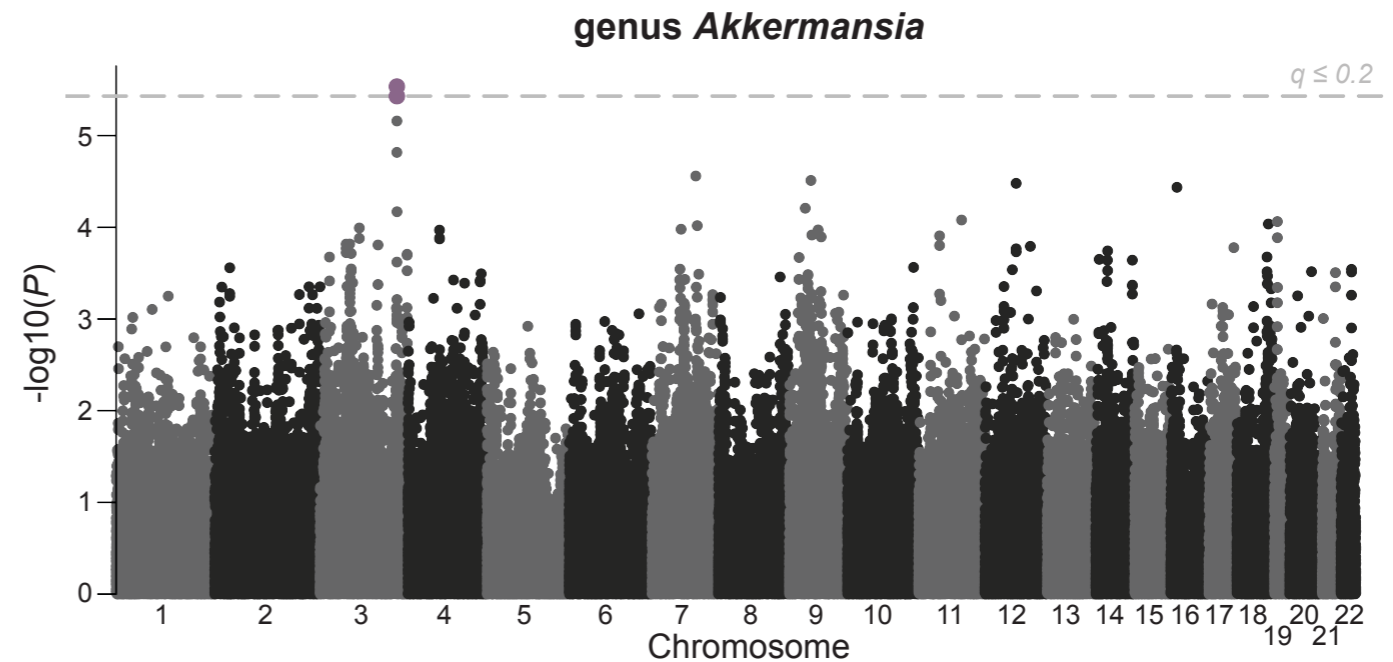
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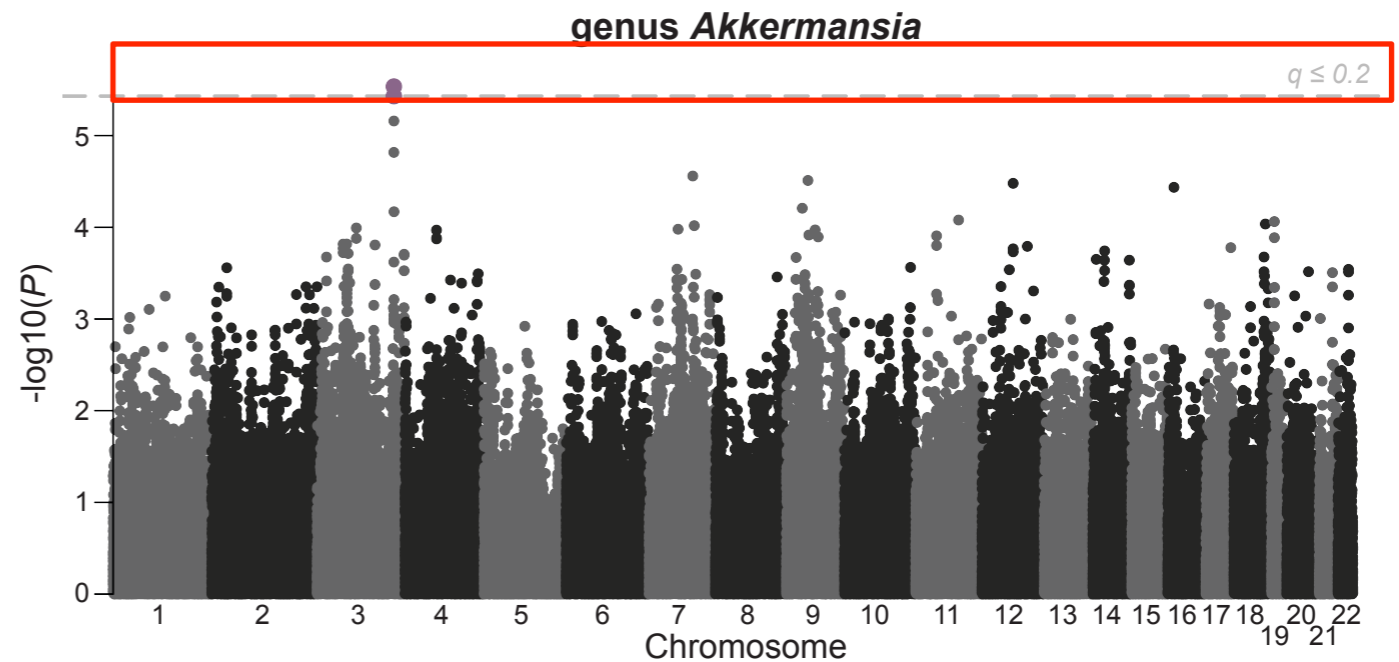
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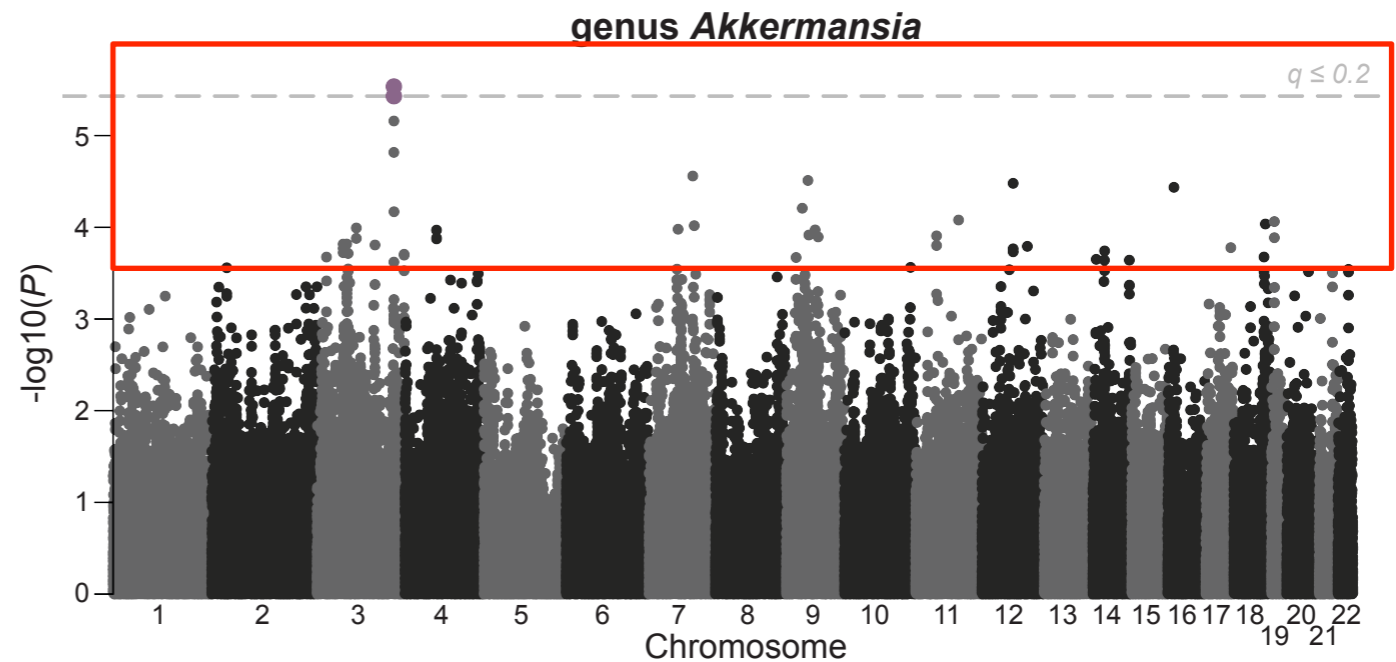
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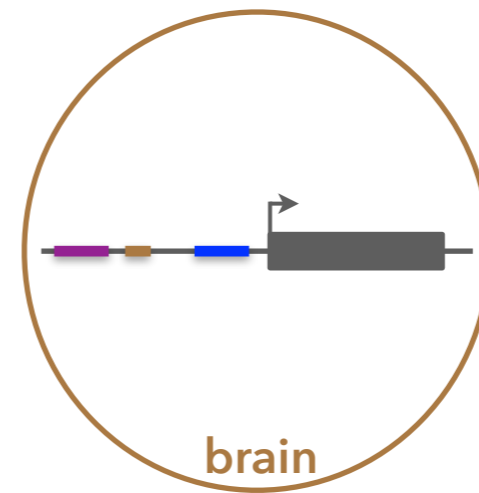
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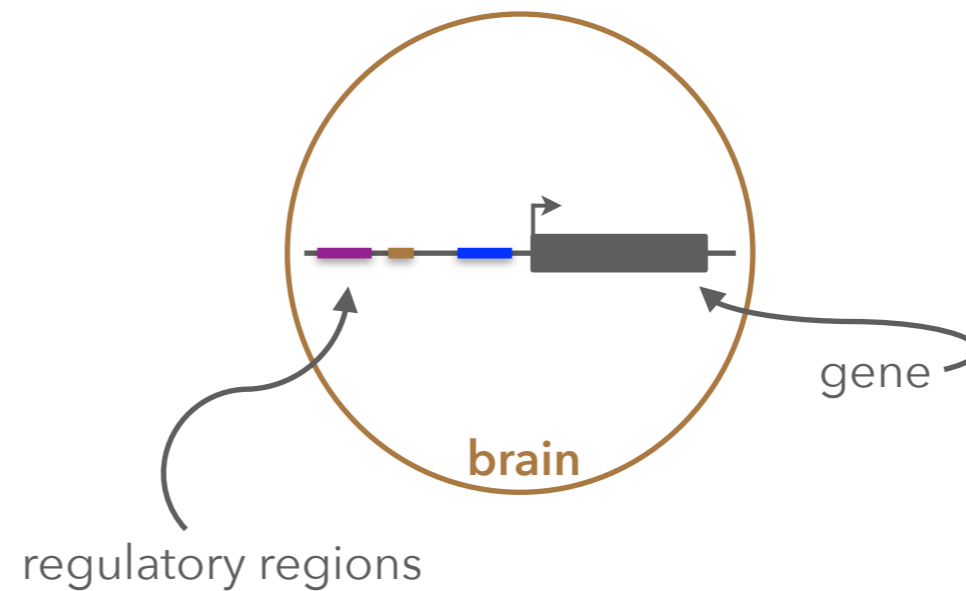
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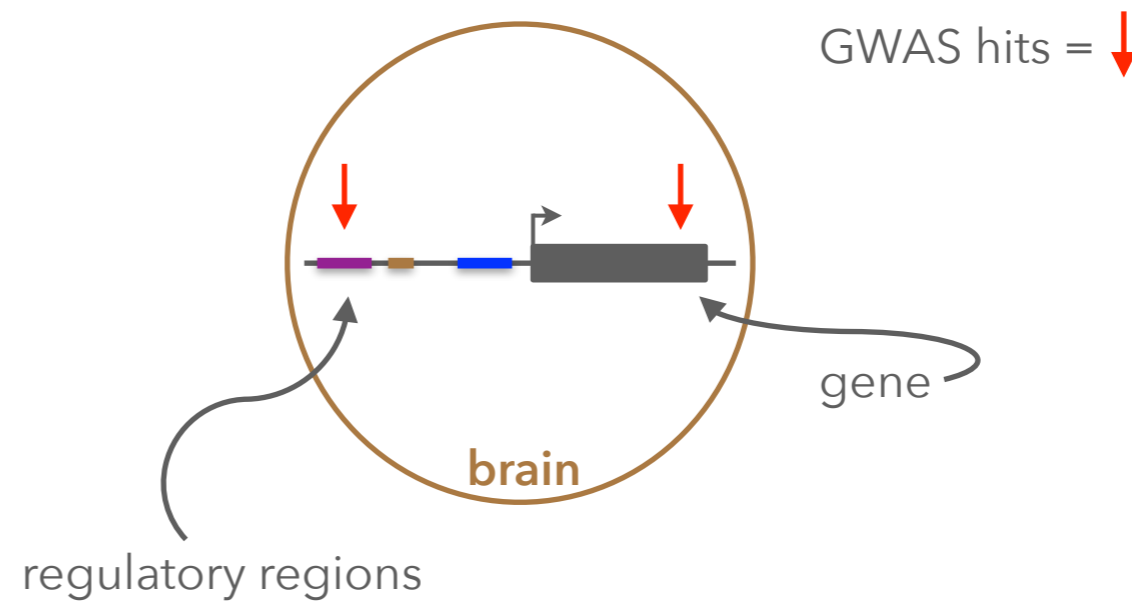
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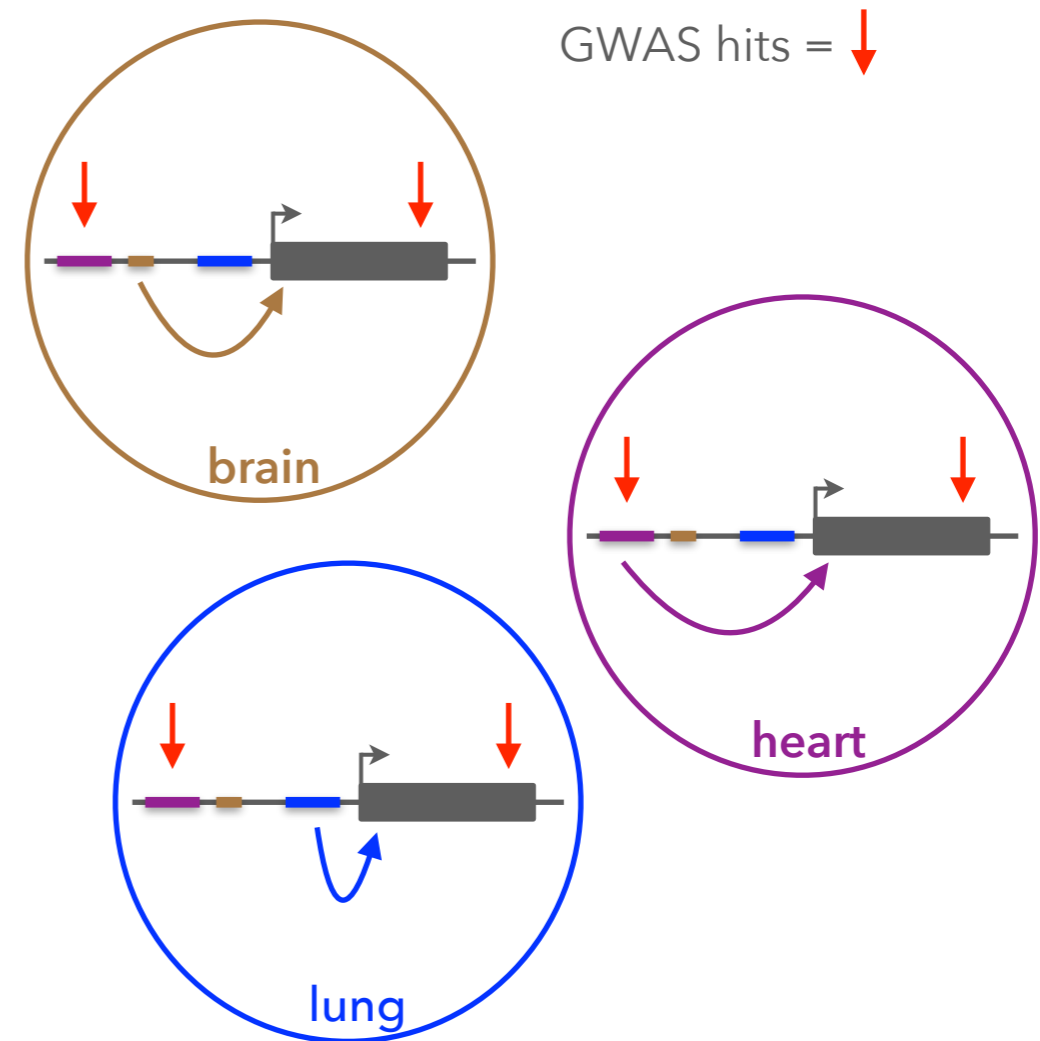
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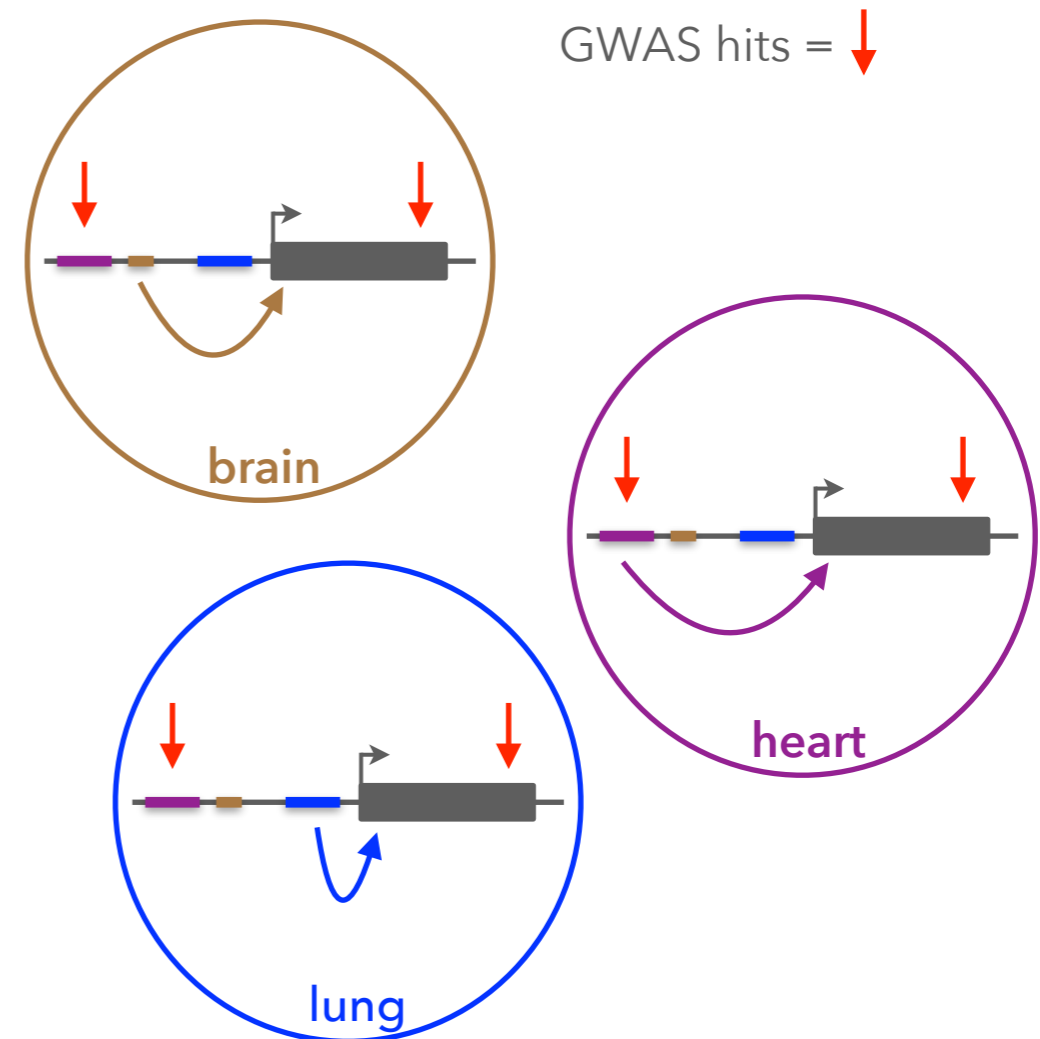
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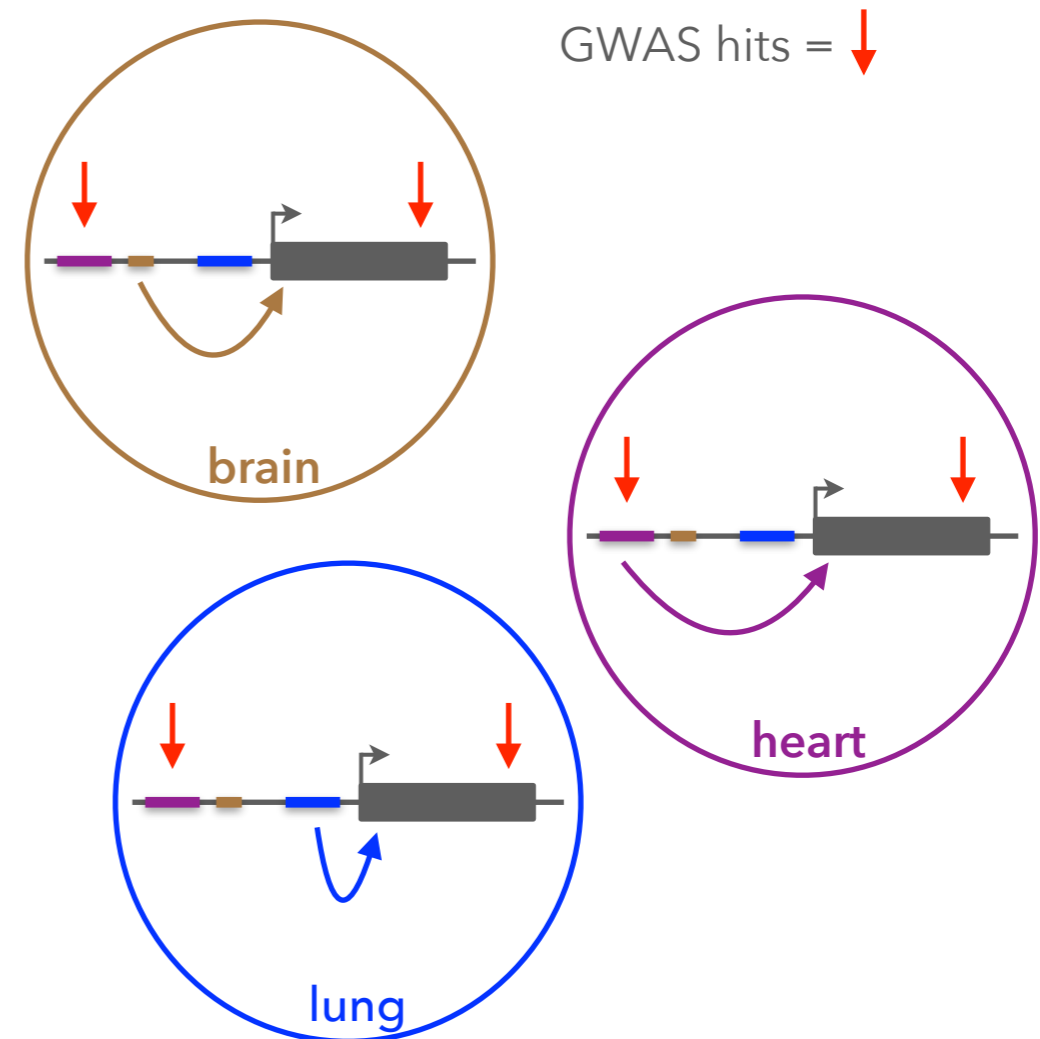
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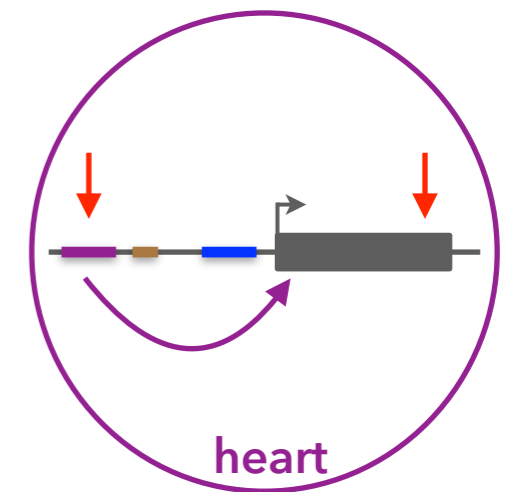
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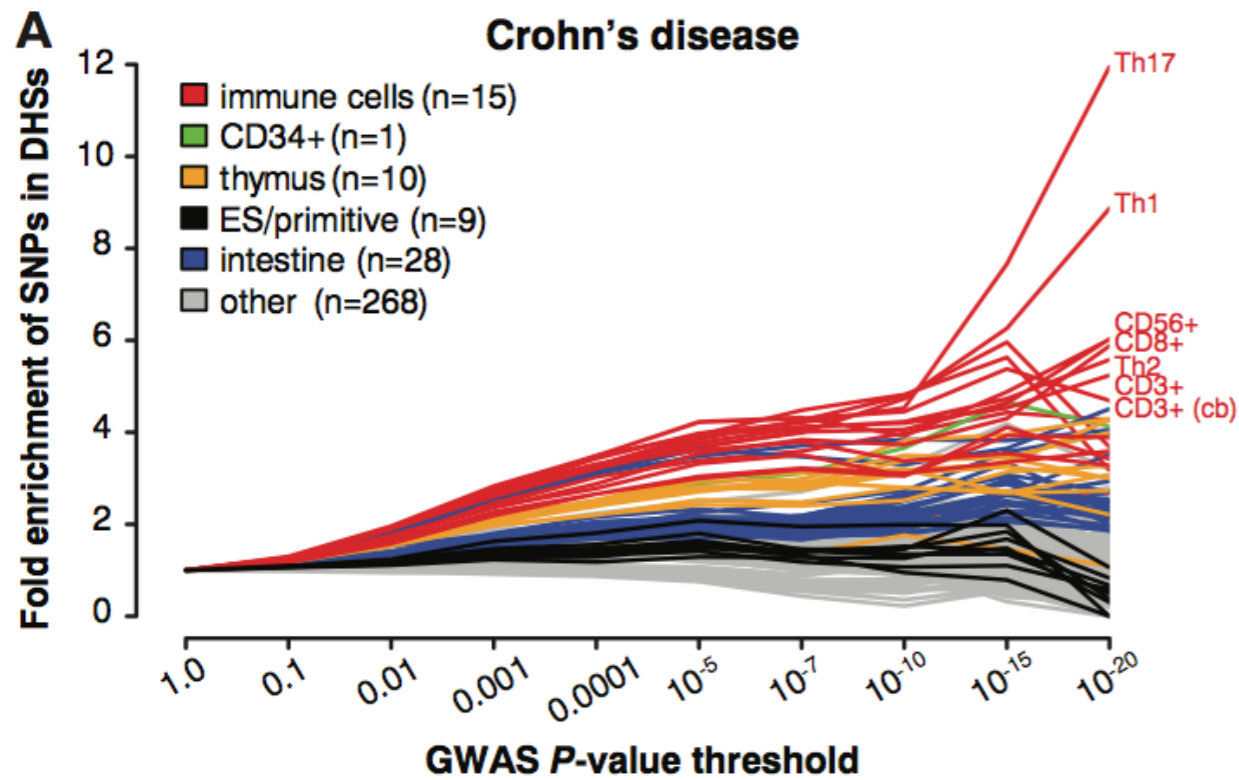
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GWAS hits = ↓

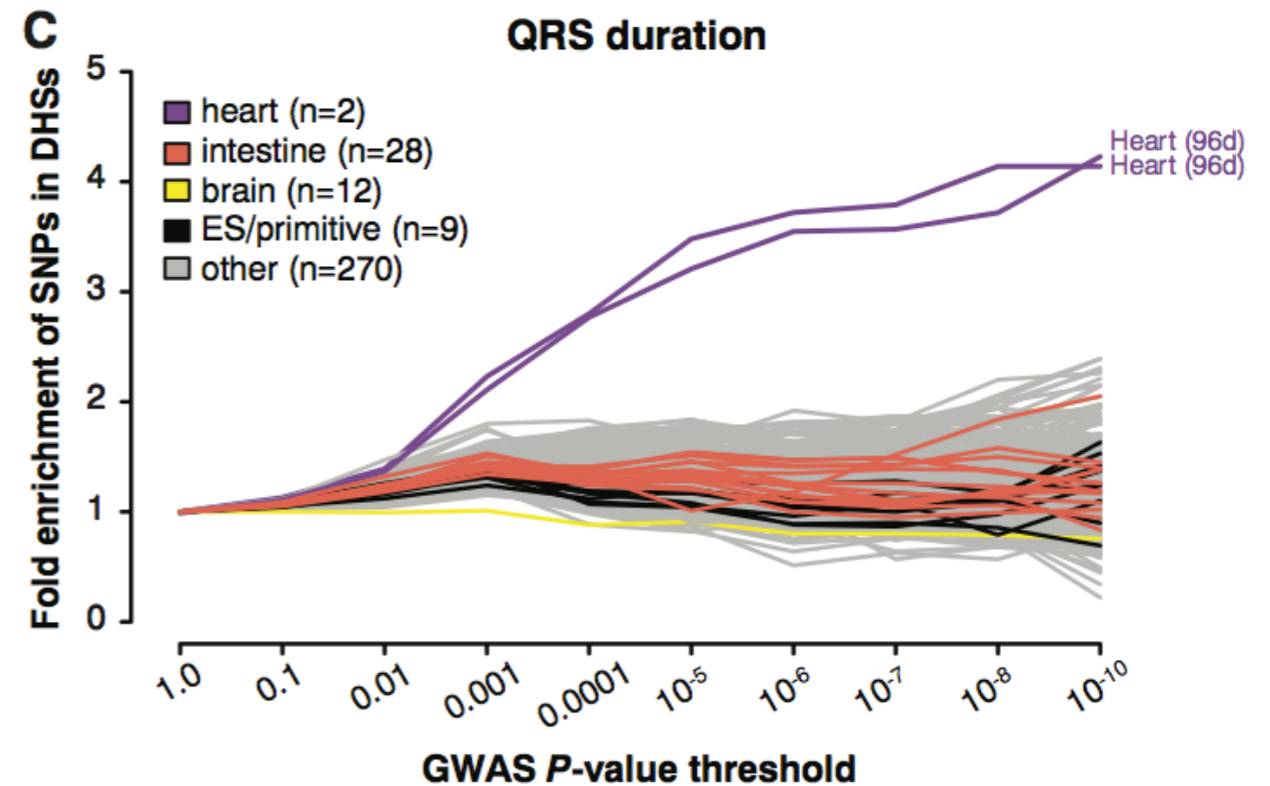
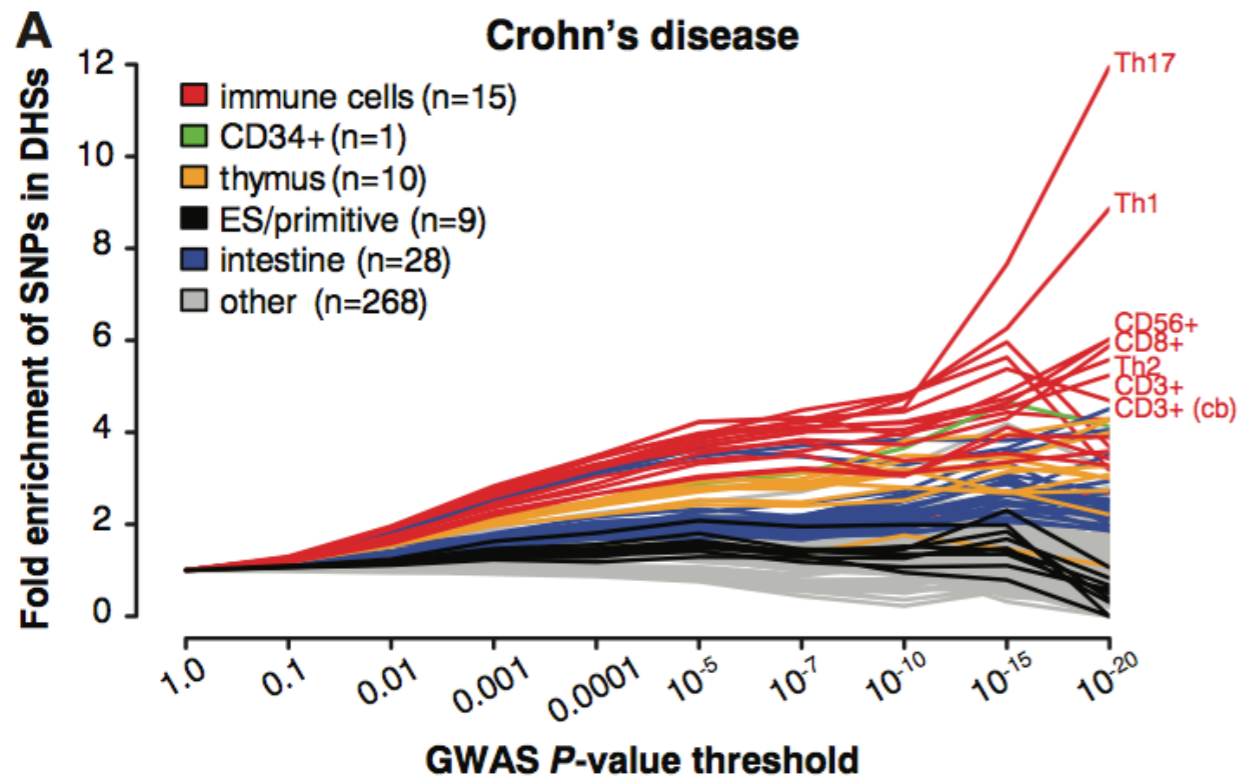


Use DNase hypersensitivity sites (DHS) to identify pathogenic tissues

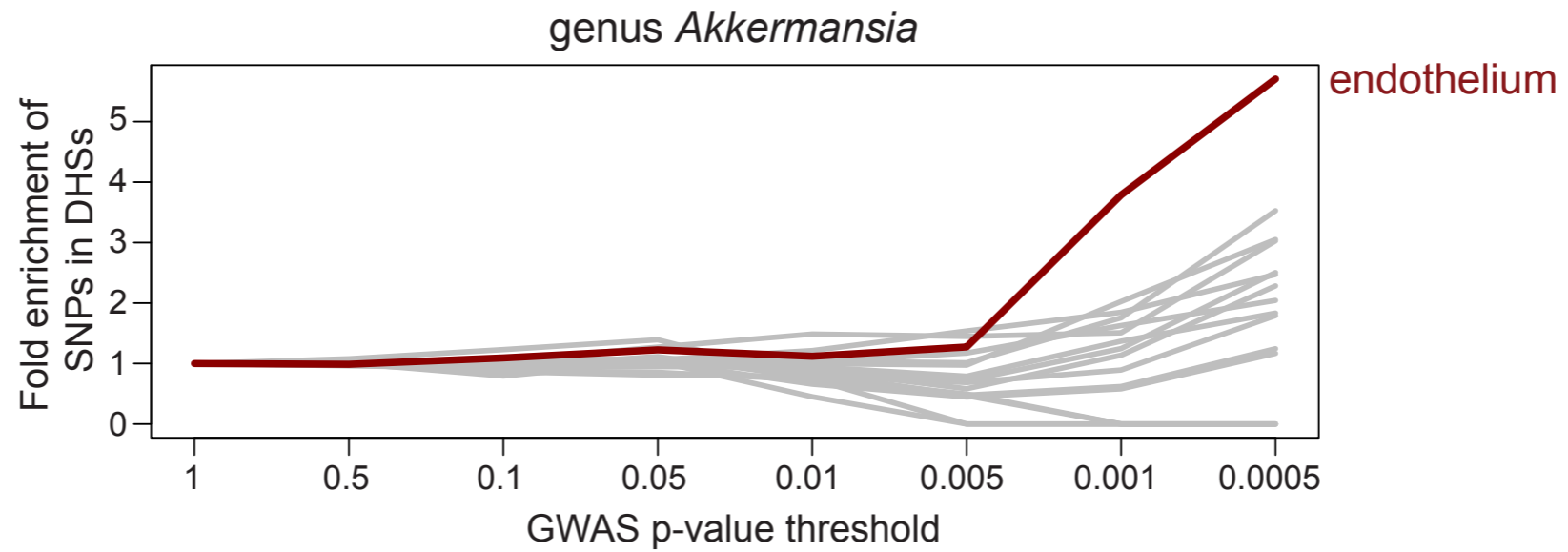
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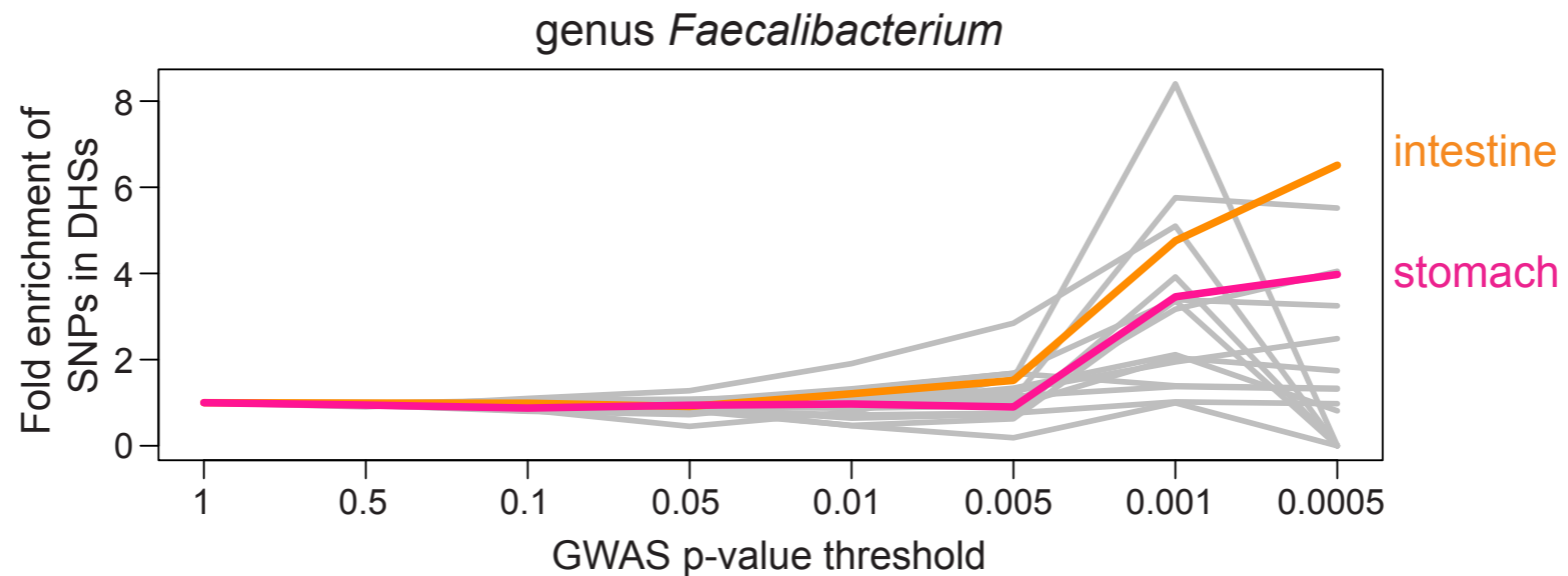
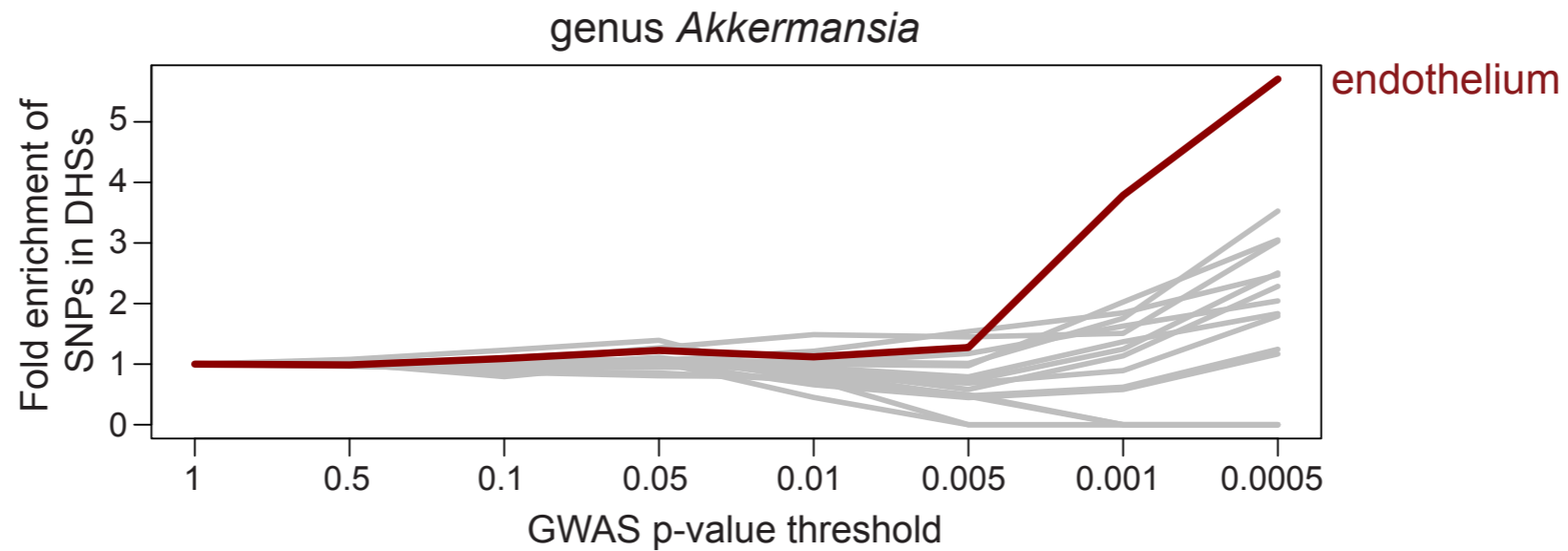
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Endothelial, stomach, and intestine tissues implicated in DHS analysis



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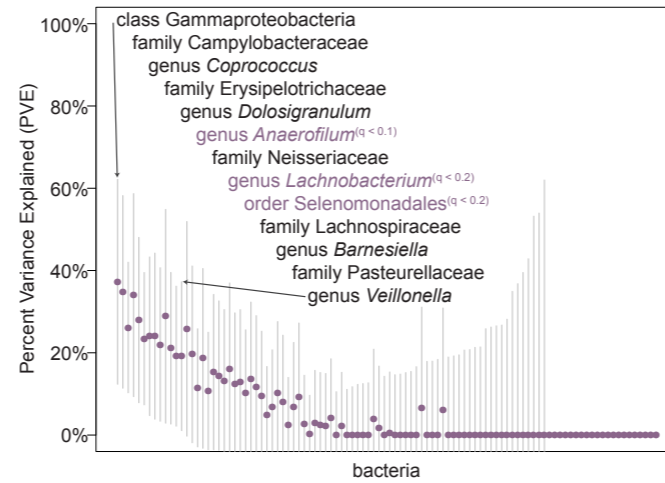
- endothelium, stomach, and intestine

Conclusions

Conclusions

1

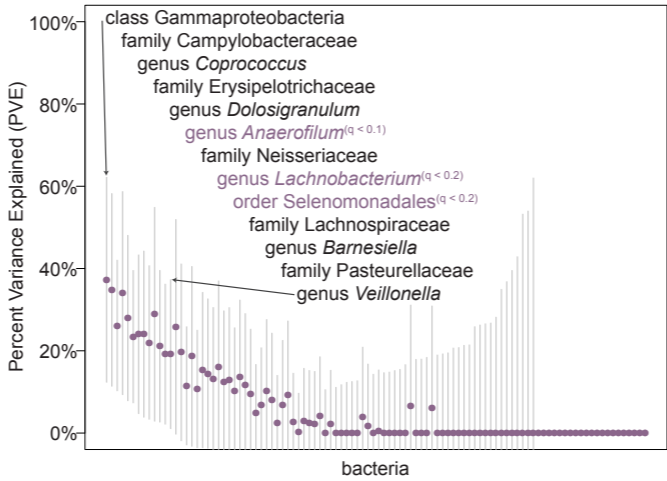
Identified bacteria
whose abundances
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Conclusions

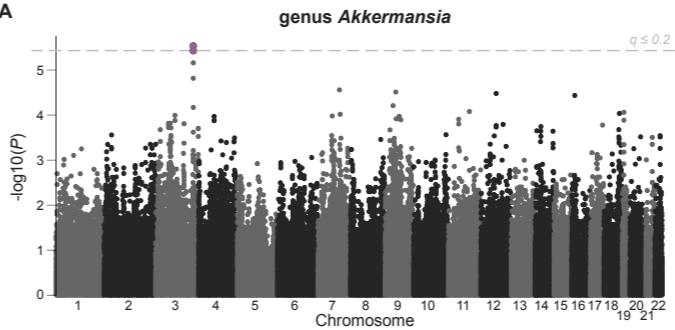
1

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2

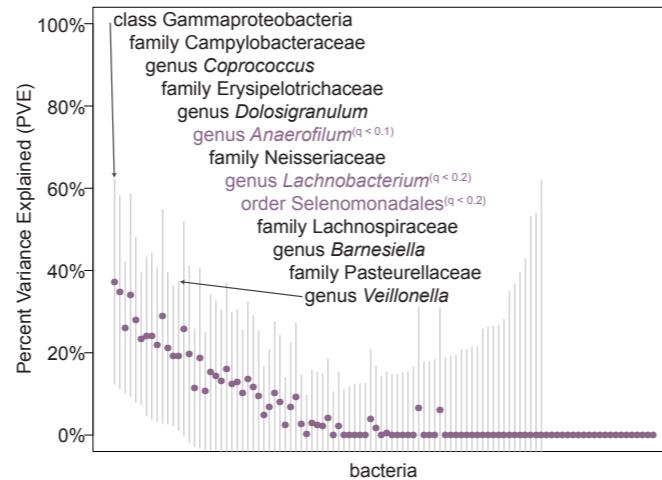
Identified *variants* in the genome associated with microbial abundance



Conclusions

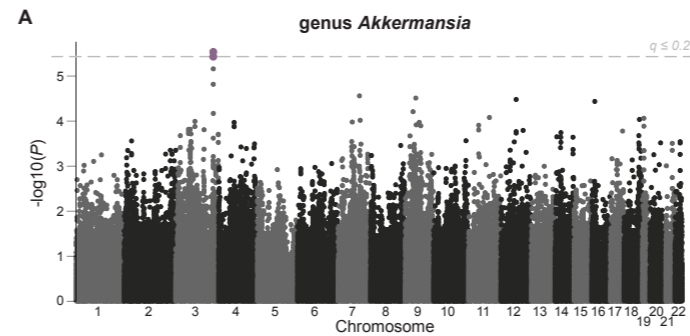
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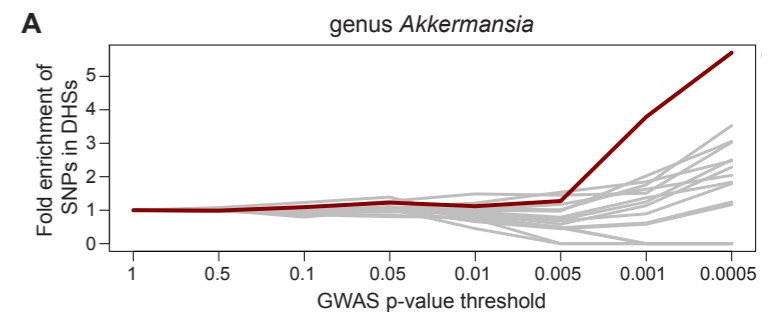
2

Identified *variants* in the genome associated with microbial abundance



3

Identified *tissues* where these variants may act



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Goodrich JK, Davenport ER, Beaumont M, Jackson MA, Knight R, Ober C, Spector TD, Bell JT, Clark AG, Ley RE. *Genetic determinants of the gut microbiome in UK twins*. Cell Host & Microbe. 2016;19(5)

Study design: *TwinsUK* microbiome GWAS

Twin Registry (*TwinsUK*) ~ 6000 genotyped twins



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led by
Julia Goodrich



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486 DZ twin-pairs

637 MZ twin-pairs

>3,000 stool samples



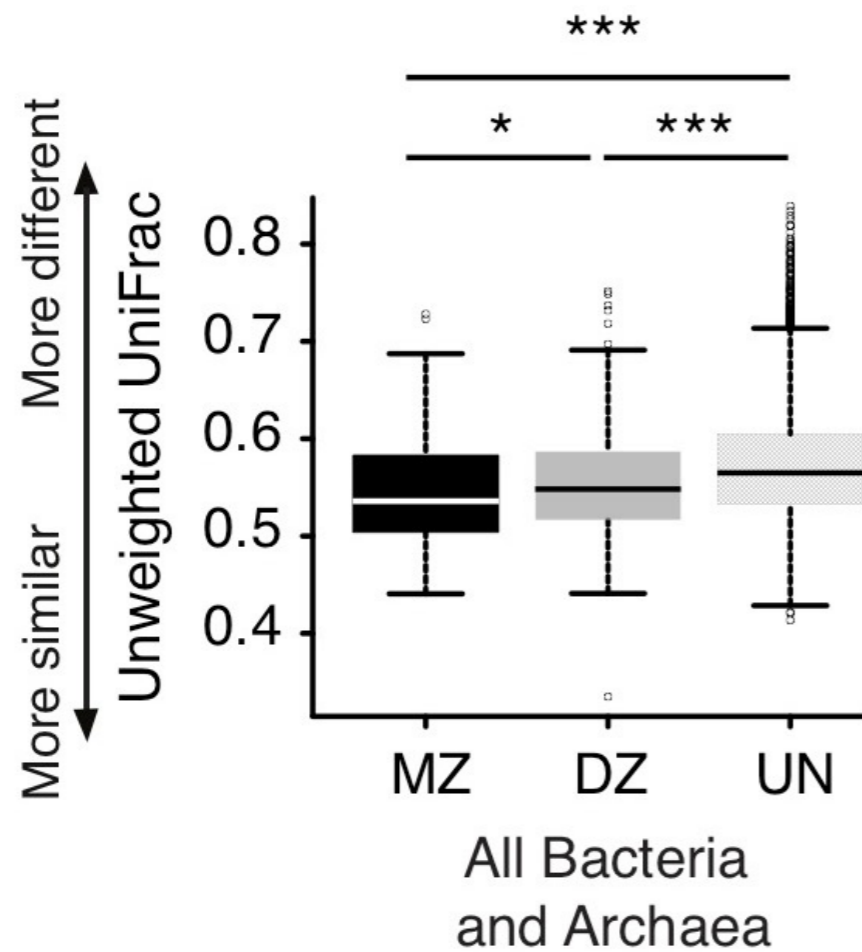
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TwinsUK microbiome project reveals *heritable* microbes



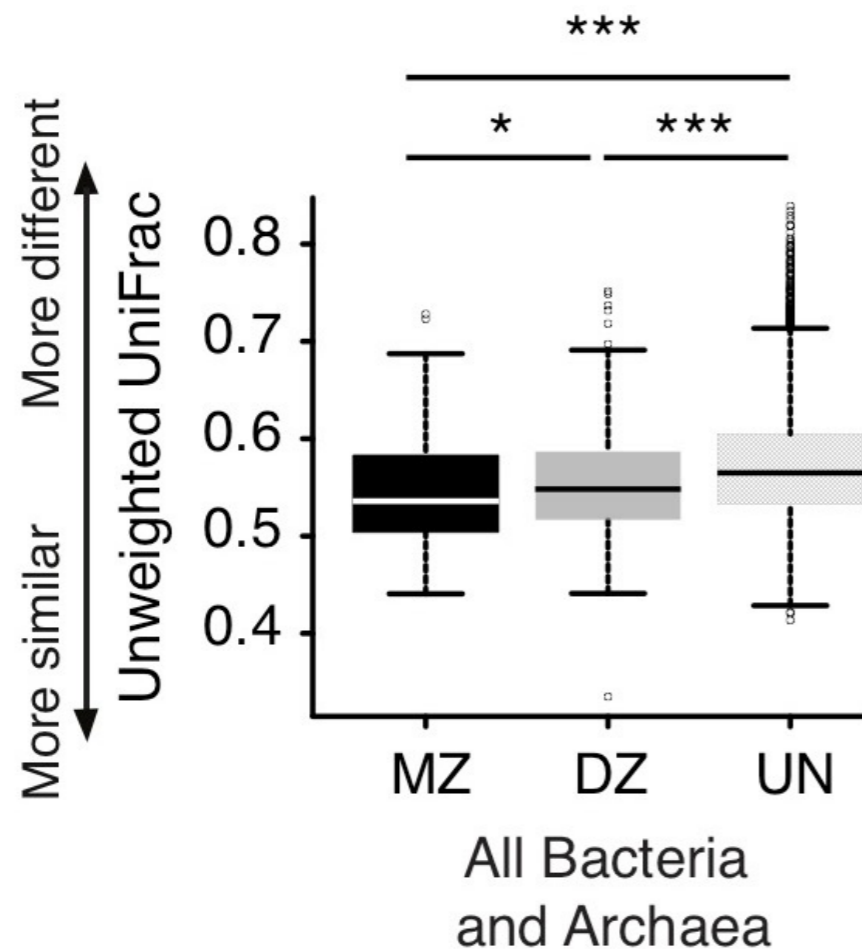
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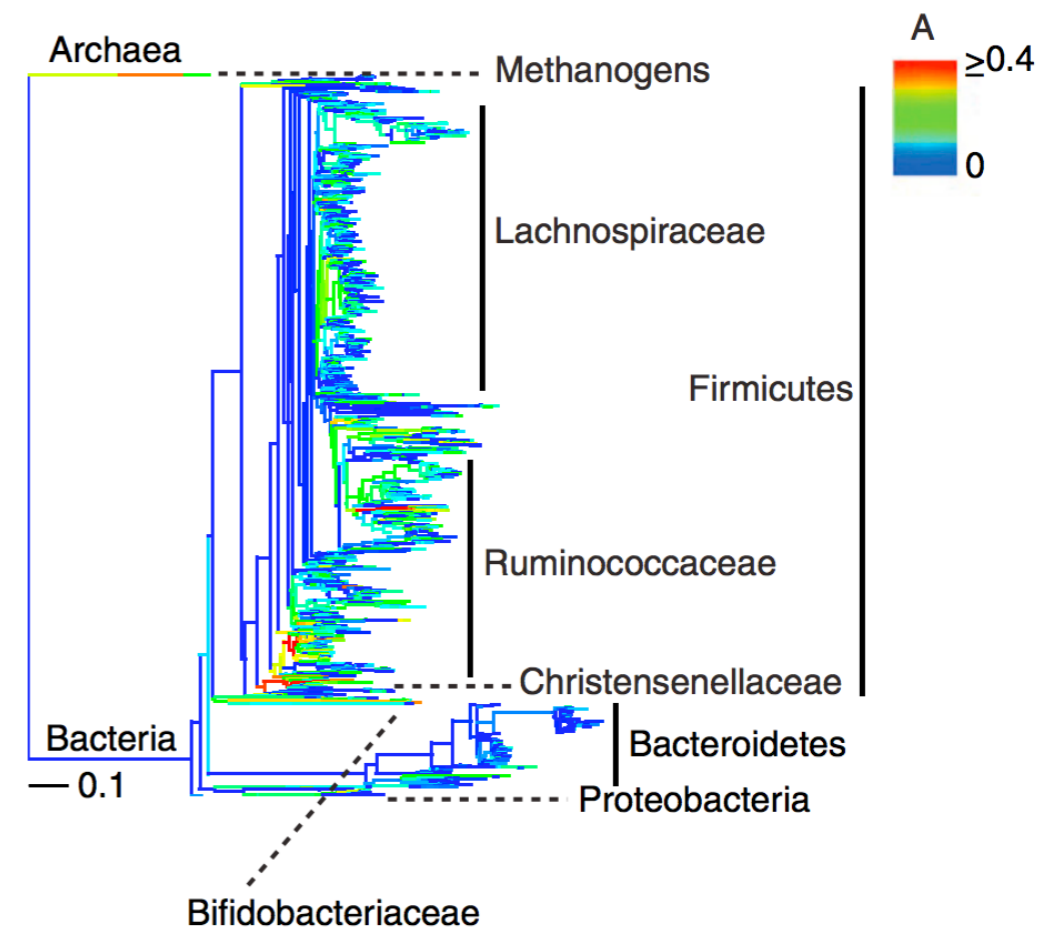
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microbiome composition is *heritable*...



...but only *select microbes* are driving this



Open questions:

1. Do we see *replication* of microbiome GWAS results across populations?

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Does the *Bifidobacteria* - LCT association replicate across populations?

Blekhman *et al.* *Genome Biology* (2015) 16:191
DOI 10.1186/s13059-015-0759-1



RESEARCH

Open Access

Host genetic variation impacts microbiome composition across human body sites



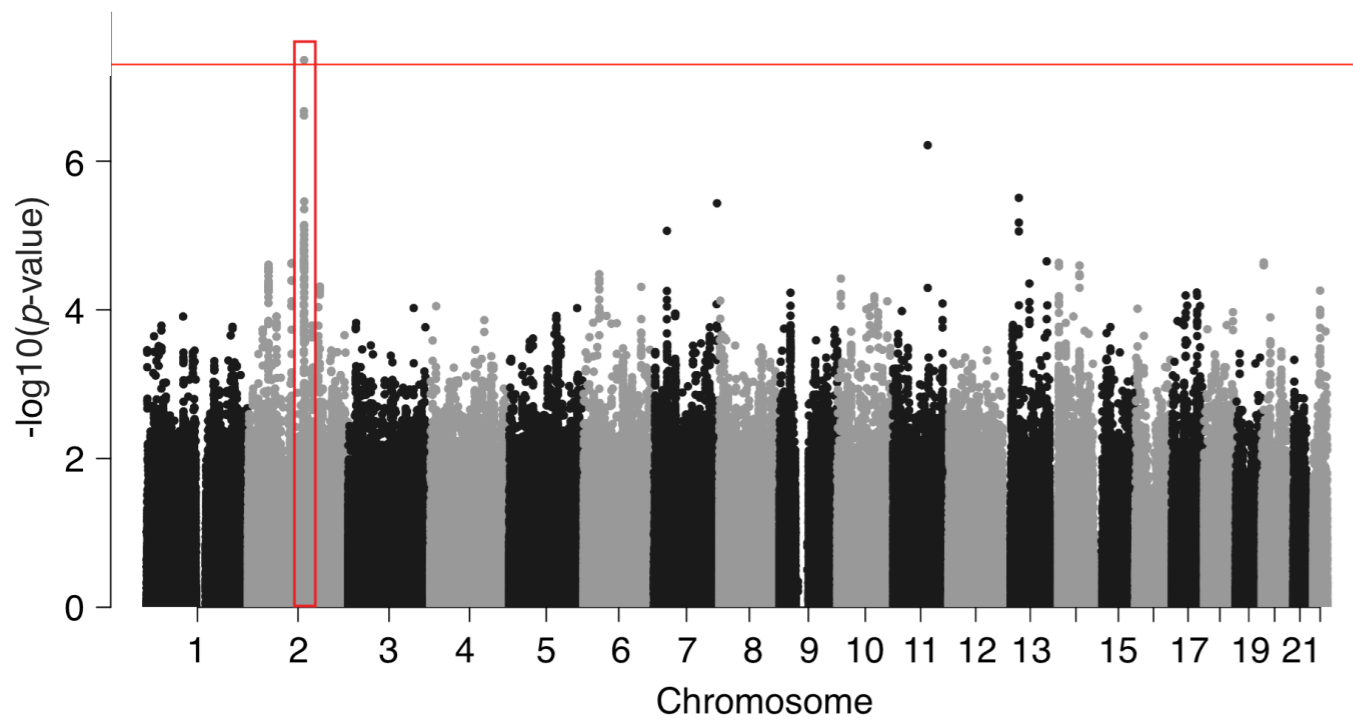
Ran Blekhman^{1,2*}, Julia K. Goodrich^{3,4}, Katherine Huang⁵, Qi Sun⁶, Robert Bukowski⁶, Jordana T. Bell⁷, Timothy D. Spector⁷, Alon Keinan⁸, Ruth E. Ley^{3,4}, Dirk Gevers^{5,9} and Andrew G. Clark³

(American)

Lactase persistence variant associates with *Bifidobacteria*



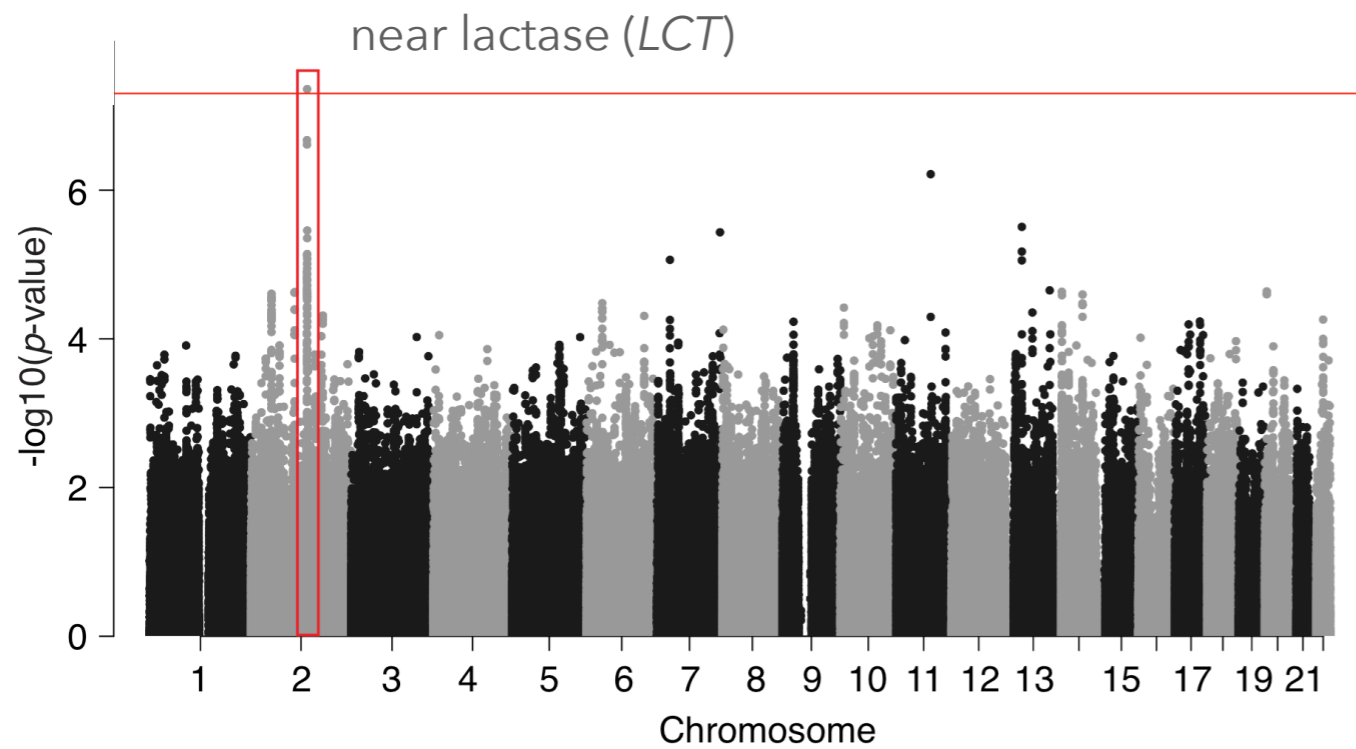
GWAS for *Bifidobacterium*



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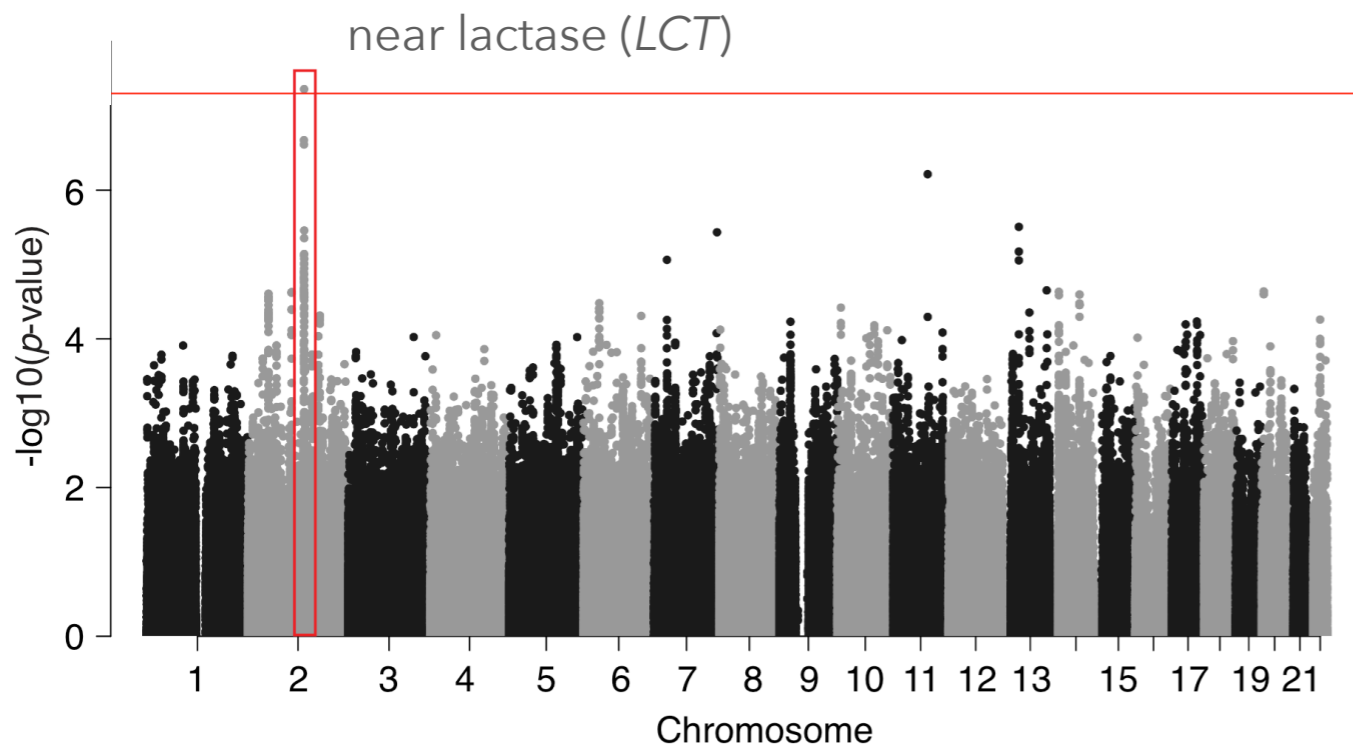
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most mammals (including humans)

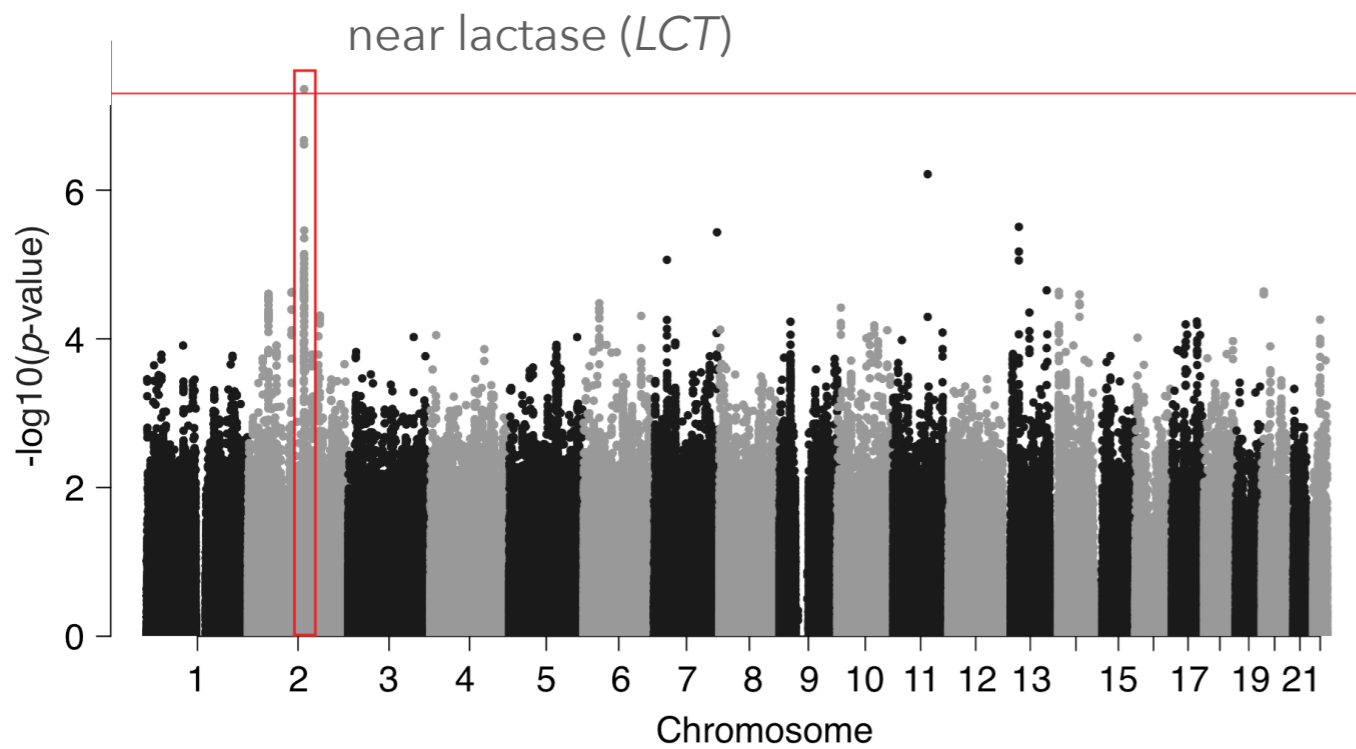
youth



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youth



adulthood



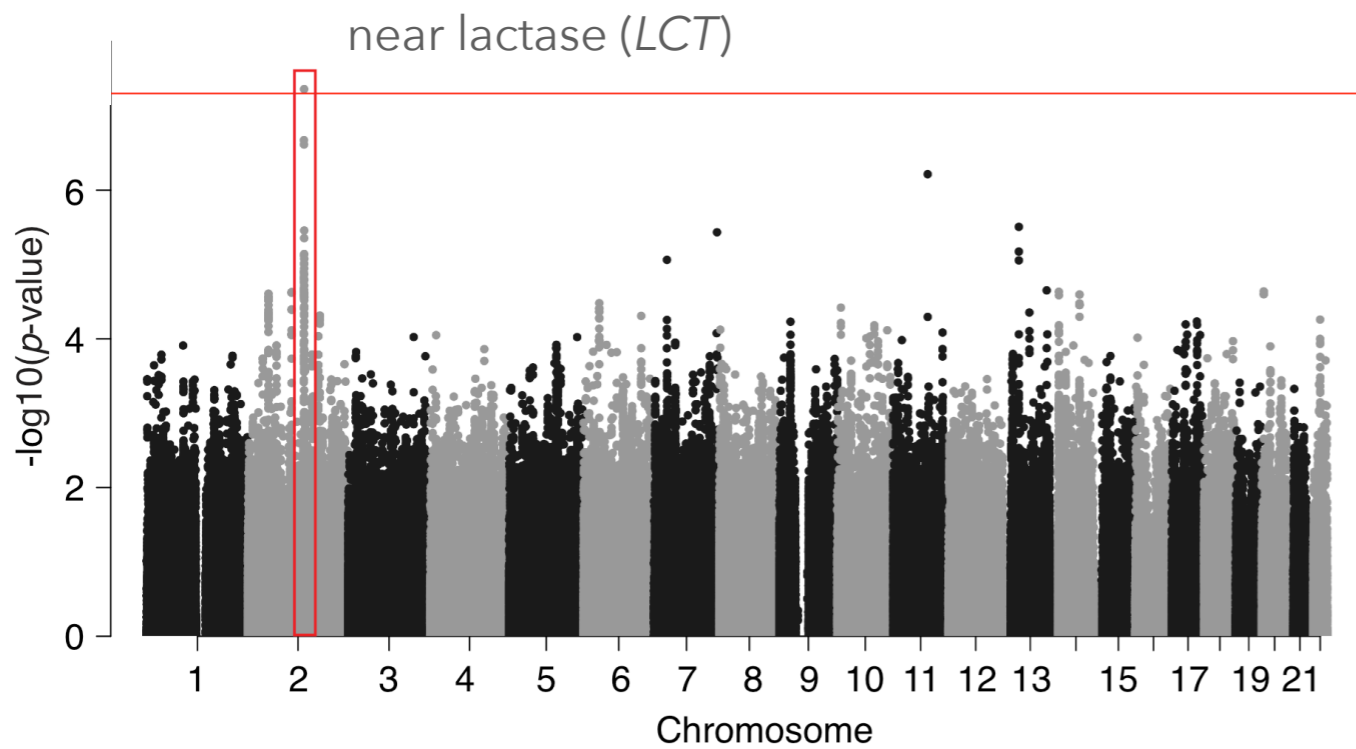
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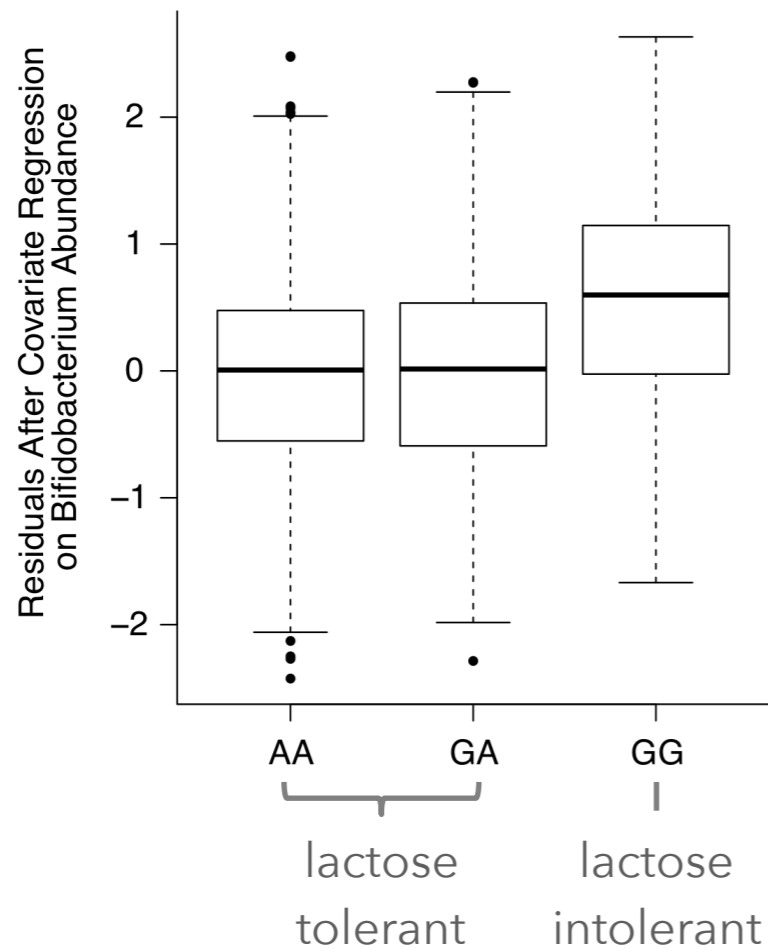
some humans



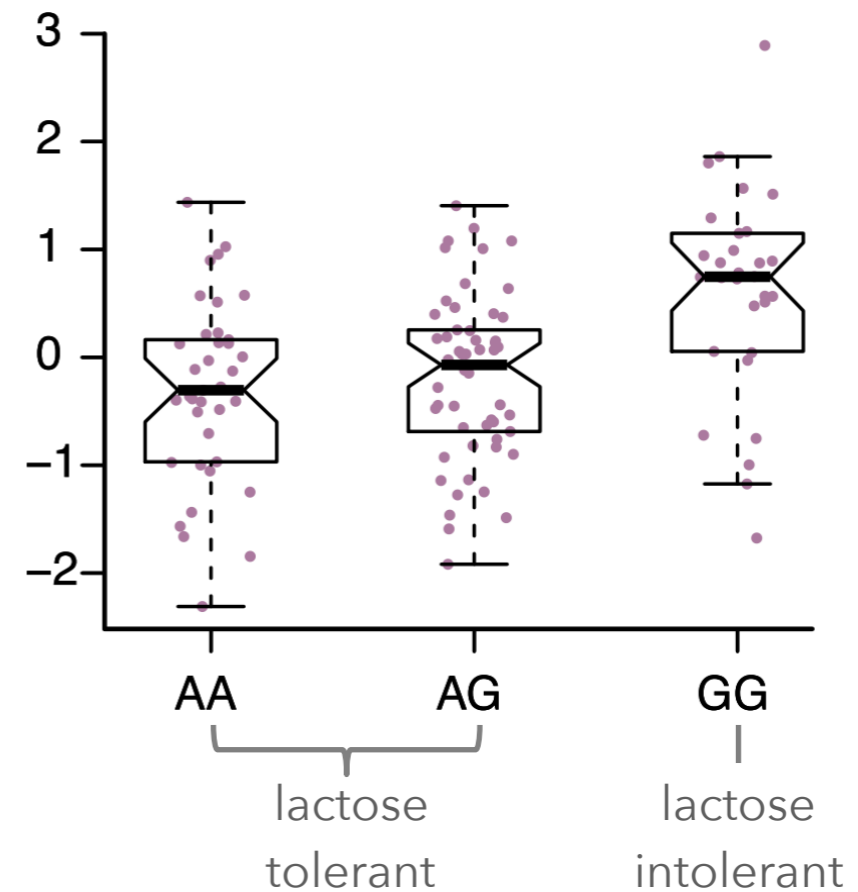
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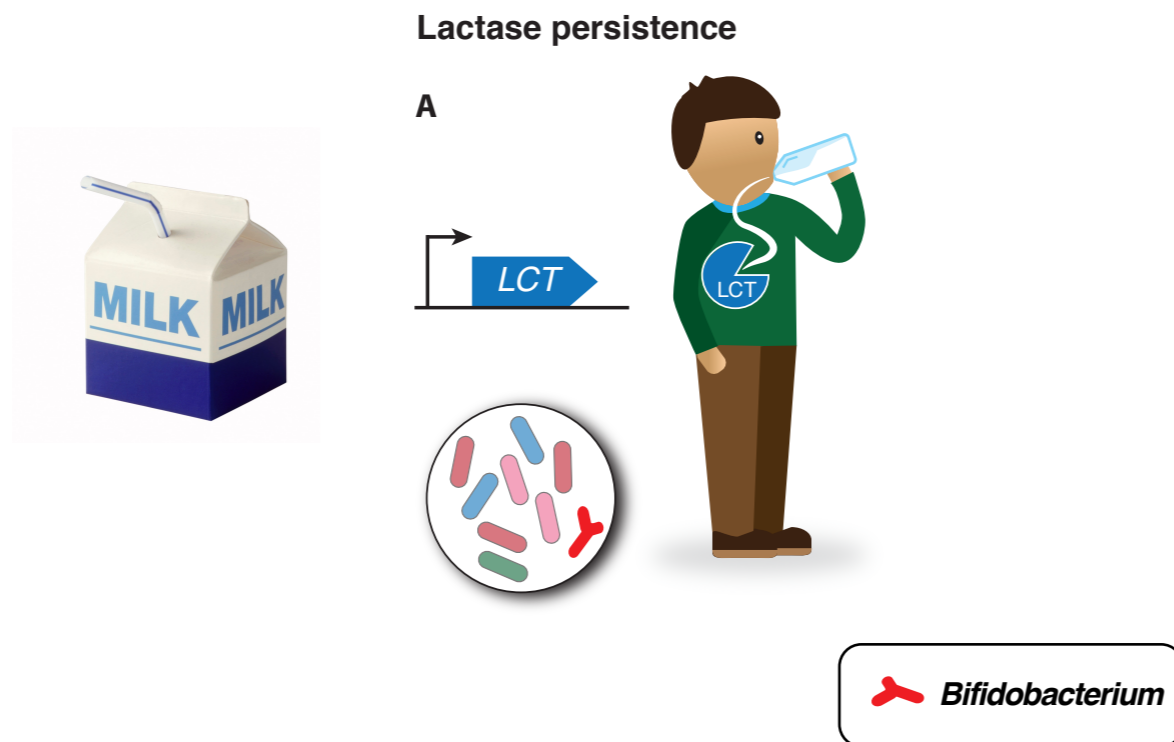
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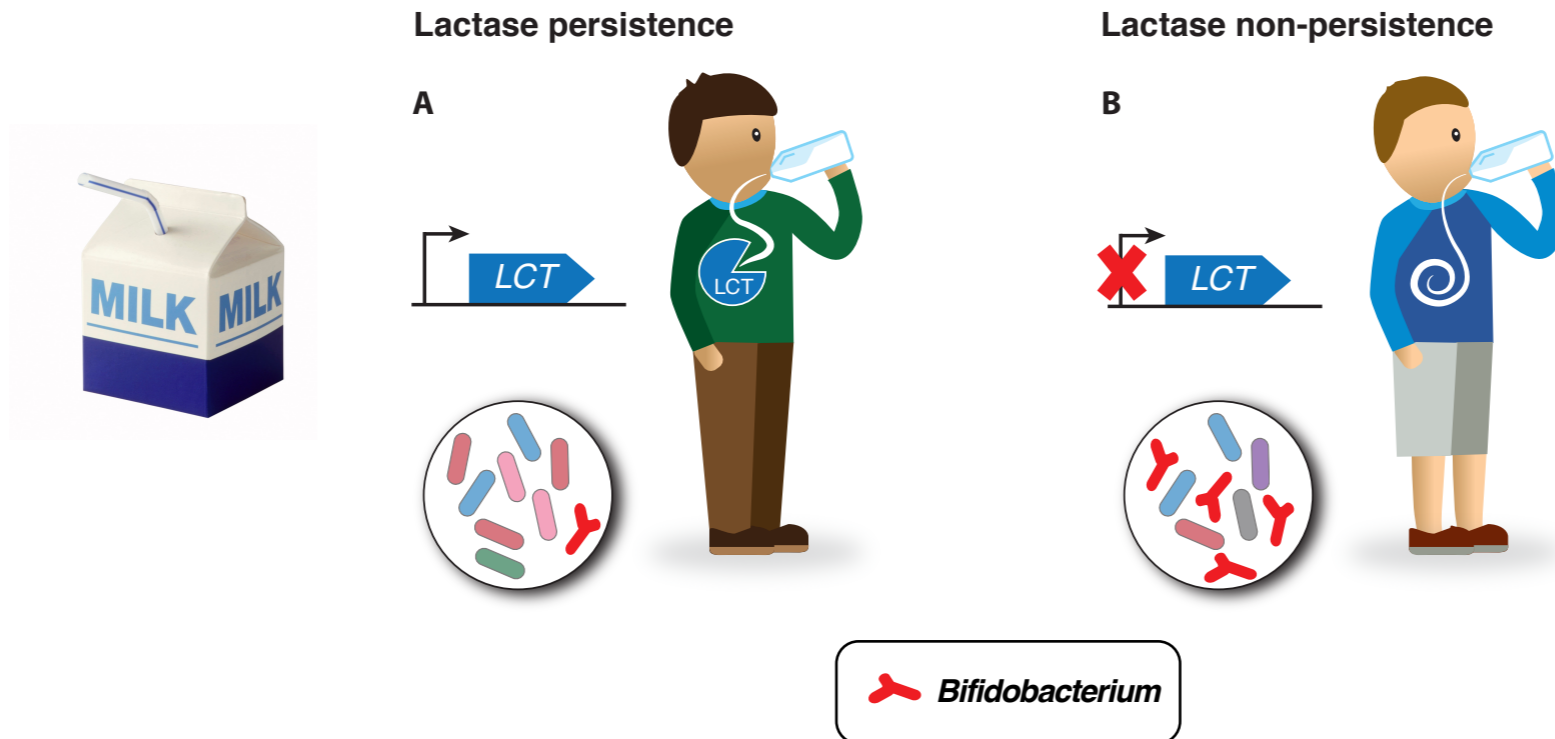
Hutterites



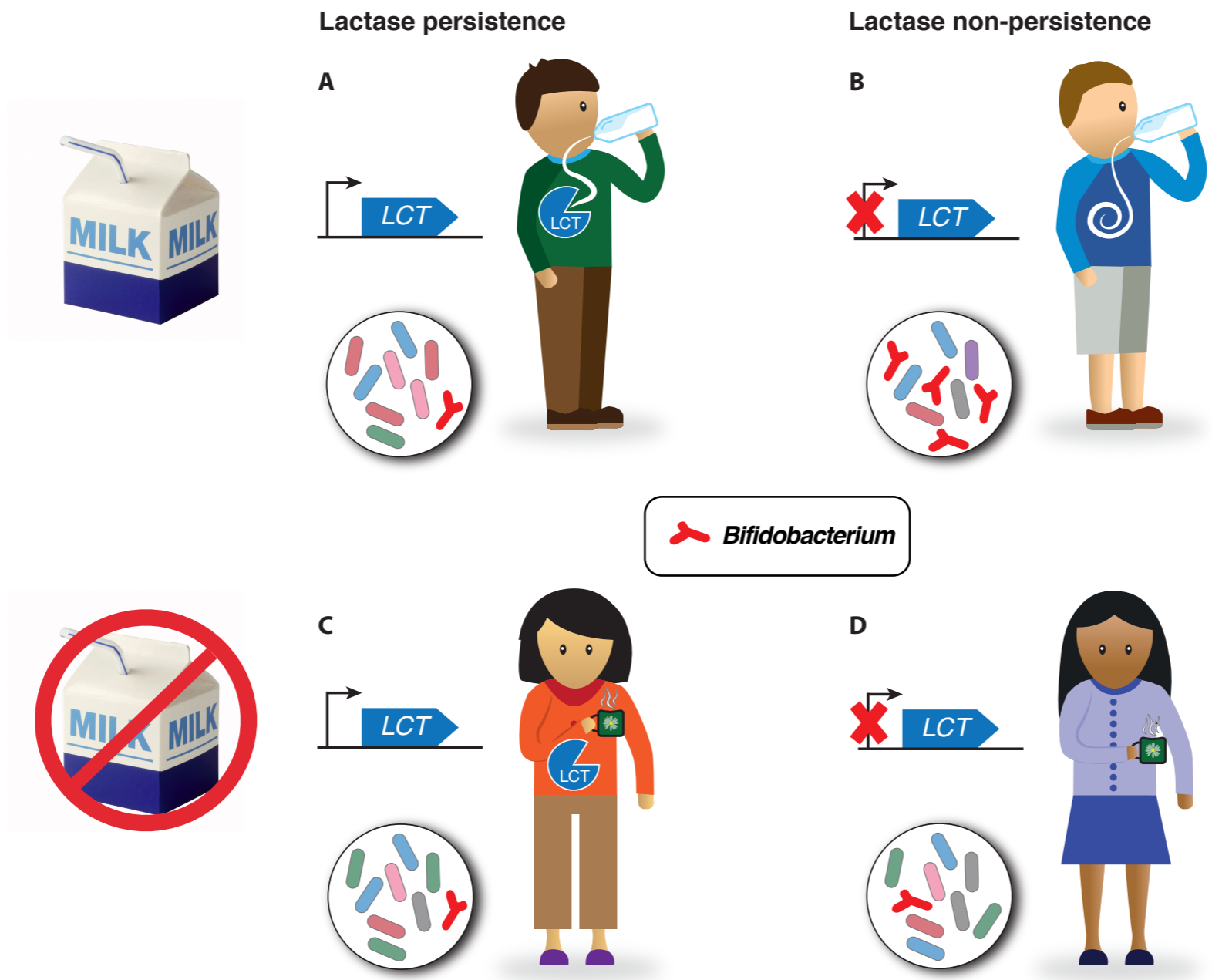
How are *Bifidobacteria*, lactase persistence, and milk consumption related?



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Goodrich JK*, Davenport ER*, Waters JL*, Clark AG, Ley RE. Cross-species comparisons of host genetic associations with the microbiome. Science. 2016

The *Bifidobacteria* - LCT association replicates across populations

LETTERS

nature
genetics

The effect of host genetics on the gut microbiome

Marc Jan Bonder^{1,19}, Alexander Kurilshikov^{1-3,19}, Ettje F Tigchelaar^{1,4}, Zlatan Mujagic^{4,5}, Floris Imhann⁶, Arnau Vich Vila⁶, Patrick Deelen^{1,7}, Tommi Vatanen^{8,9}, Melanie Schirmer^{8,10}, Sanne P Smeekens^{11,12}, Daria V Zhernakova¹, Soesma A Jankipersadsing^{1,13}, Martin Jaeger^{11,12}, Marije Oosting^{11,12}, Maria Carmen Ceuca^{1,18}, Ad A M Masclee⁵, Morris A Swertz^{1,7}, Yang Li¹, Vinod Kumar¹, Leo Joosten^{11,12}, Hermie Harmsen¹⁴, Rinse K Weersma⁶, Lude Franke¹, Marten H Hofker¹³, Ramnik J Xavier^{8,15-17}, Daisy Jonkers⁵, Mihai G Netea^{11,12}, Cisca Wijmenga¹, Jingyuan Fu^{1,13,20} & Alexandra Zhernakova^{1,4,20}

(Dutch)

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(Dutch)

Cell Host & Microbe
Resource

Blekhman *et al. Genome Biology* (2015) 16:191
DOI 10.1186/s13059-015-0759-1



RESEARCH

Open Access

Host genetic variation impacts microbiome composition across human body sites



Ran Blekhman^{1,2*}, Julia K. Goodrich^{3,4}, Katherine Huang⁵, Qi Sun⁶, Robert Bukowski⁶, Jordana T. Bell⁷, Timothy D. Spector⁷, Alon Keinan⁸, Ruth E. Ley^{3,4}, Dirk Gevers^{5,9} and Andrew G. Clark³

(American)

Genetic Determinants of the Gut Microbiome in UK Twins

Julia K. Goodrich,¹ Emily R. Davenport,¹ Michelle Beaumont,² Matthew A. Jackson,² Rob Knight,³ Carole Ober,⁴ Tim D. Spector,² Jordana T. Bell,² Andrew G. Clark,¹ and Ruth E. Ley^{1,5,*}

¹Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY 14850, USA

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*Correspondence: rel222@cornell.edu

<http://dx.doi.org/10.1016/j.chom.2016.04.017>

(British and Hutterites)

Open questions:

1. Do we see *replication* of microbiome GWAS results across populations

2. Is *gene expression* associated with the abundances of individual bacteria?

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GWAS identify association between *SNPs* and *phenotypes*



Long path from *SNP* to *phenotype*



Long path from *SNP* to *phenotype*, which is unclear from GWAS alone



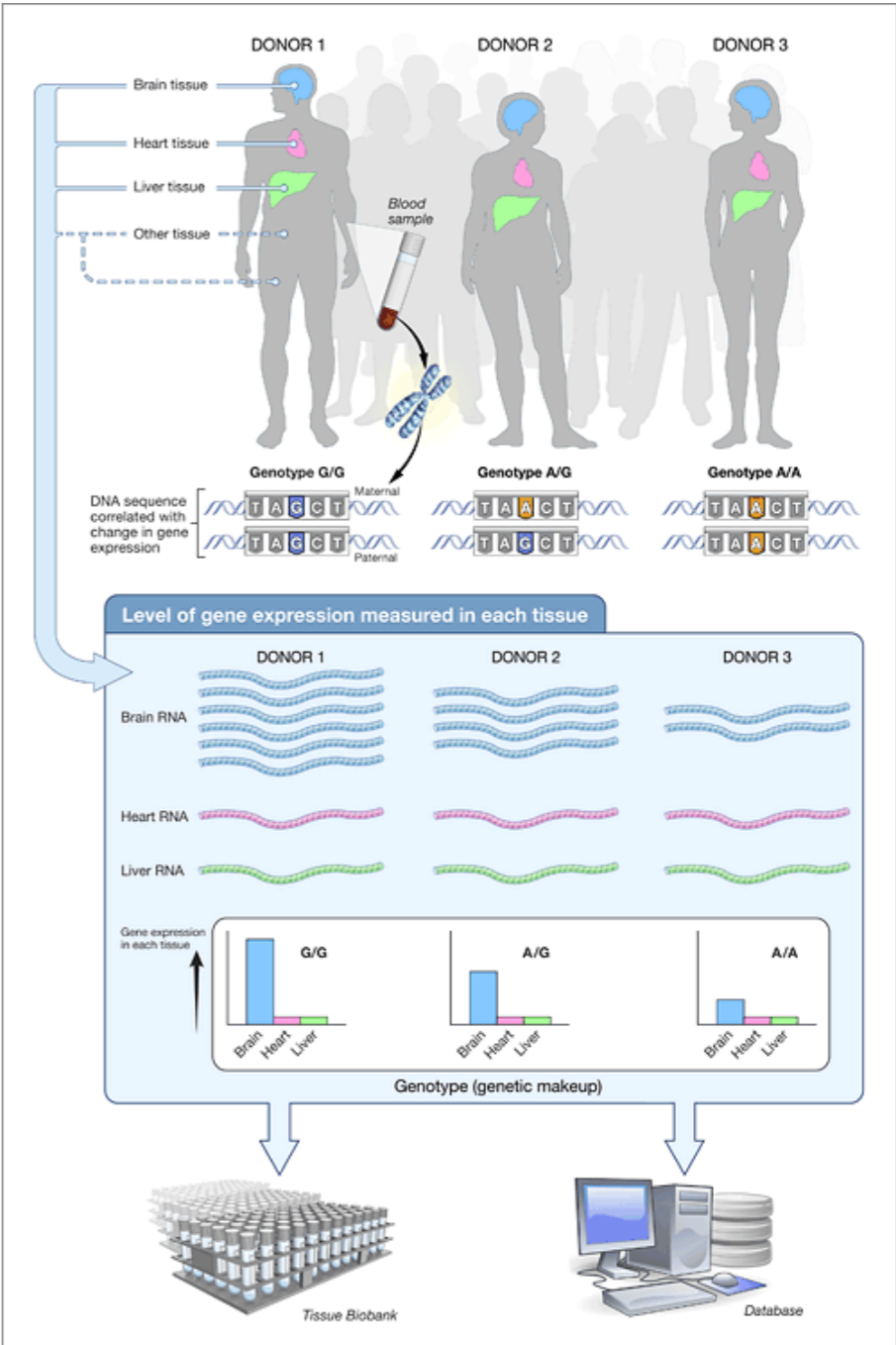
Can we shed light on *part* of this path?



Can we shed light on *part* of this path?

prediXcan method

GTE_x

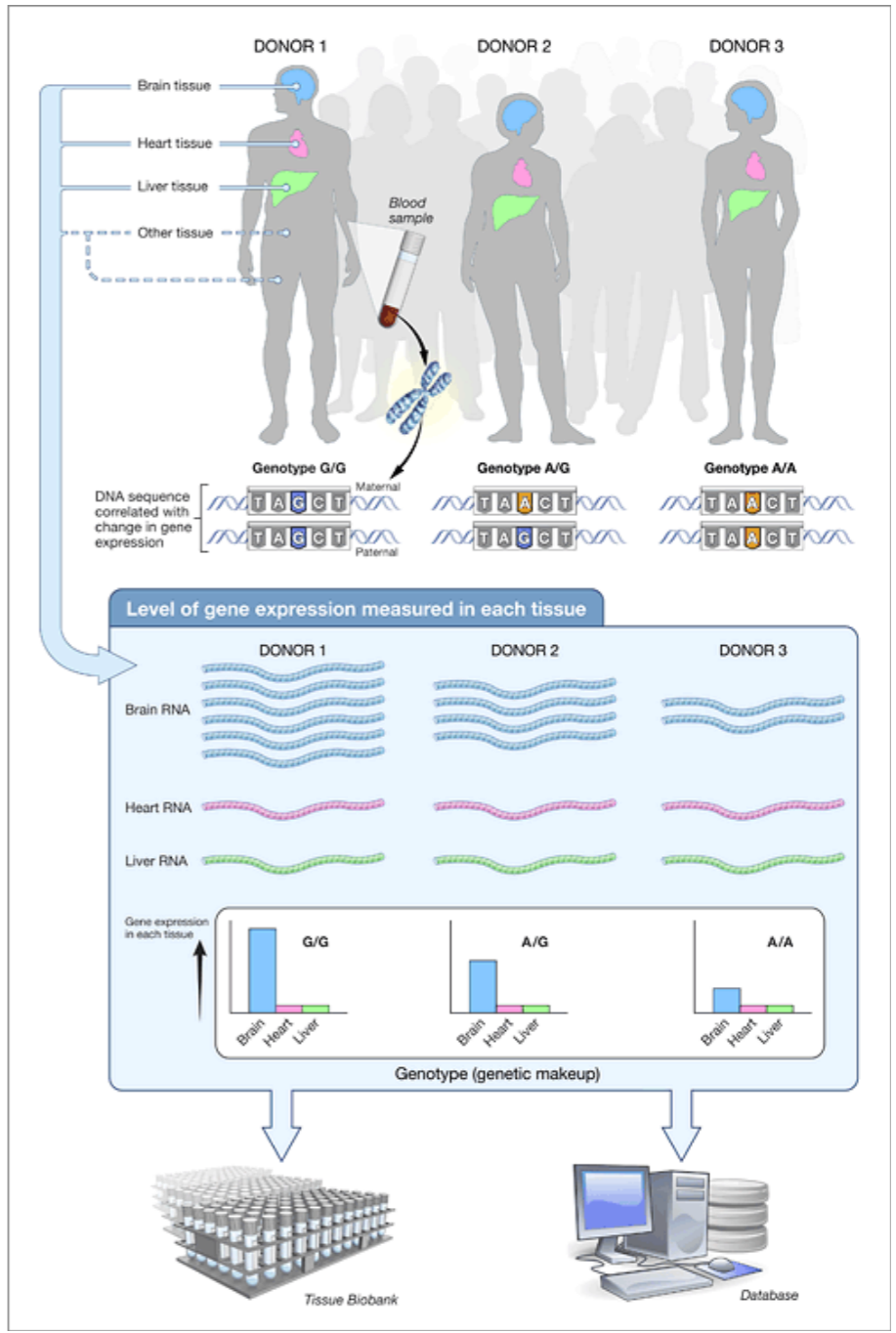


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prediXcan method

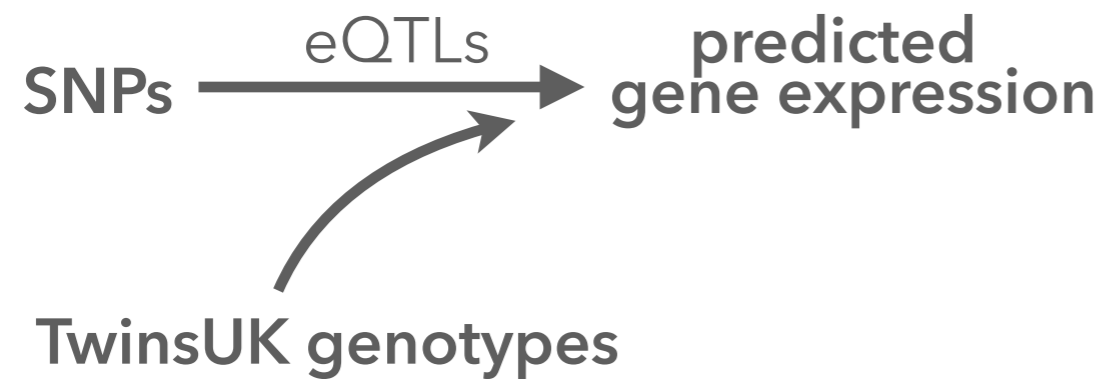


GTE_x



1. Use SNPs to *predict* gene expression

prediXcan method

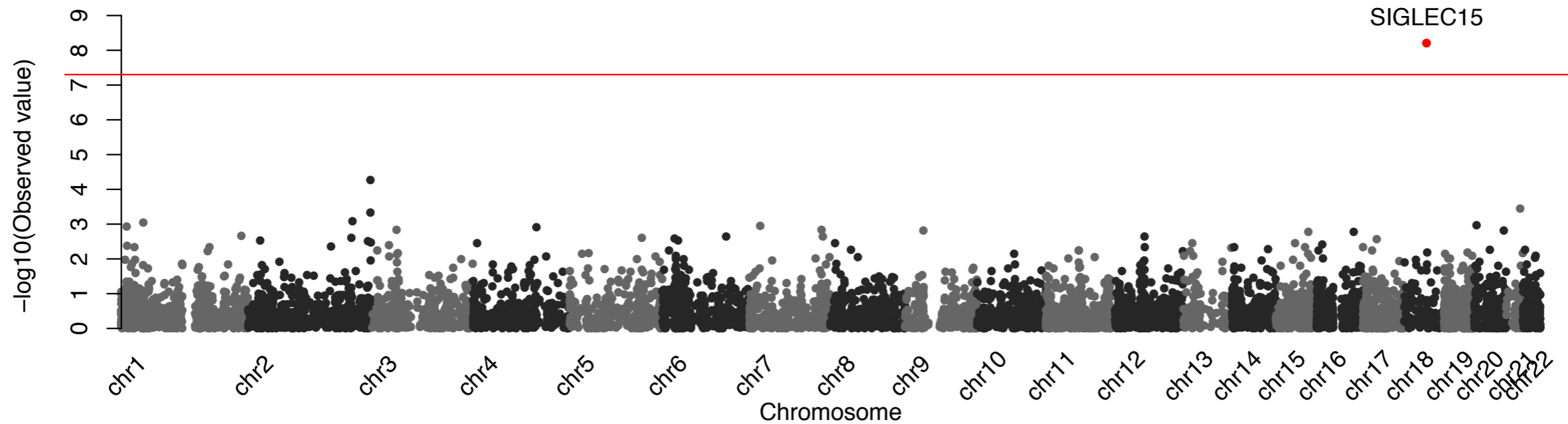


1. Use SNPs to *predict* gene expression
2. Identify associations *between* gene expression and phenotype

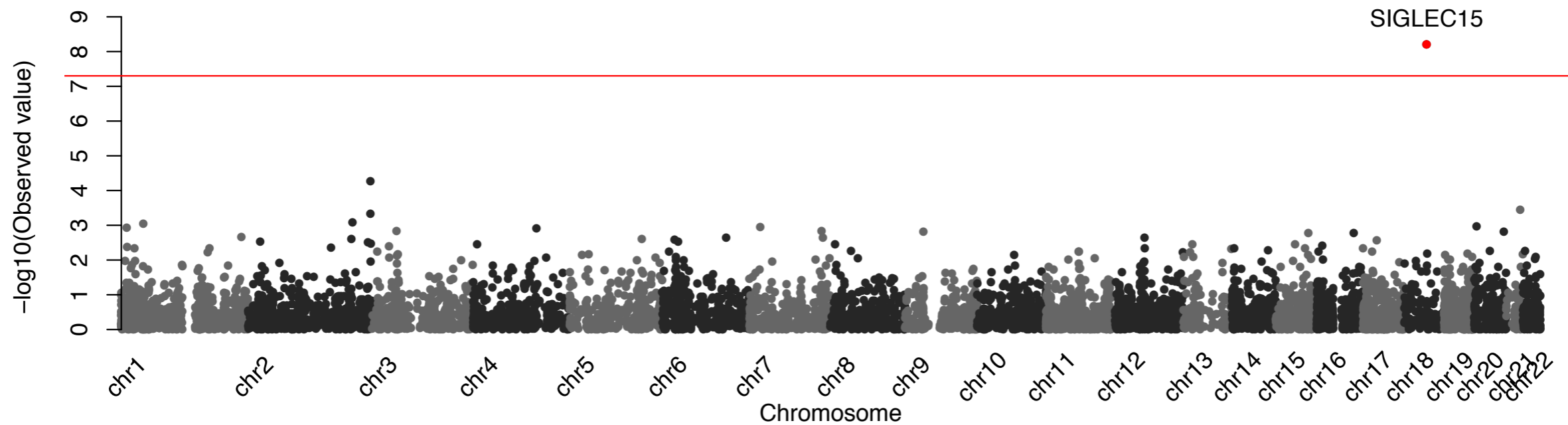
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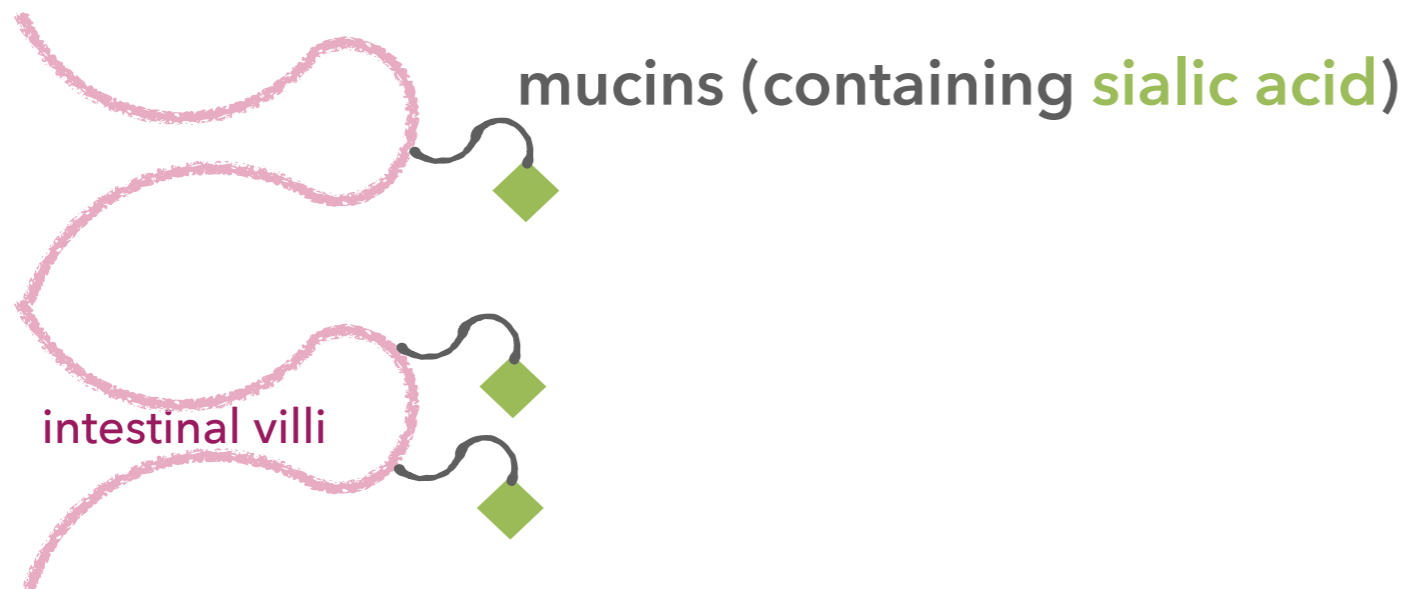
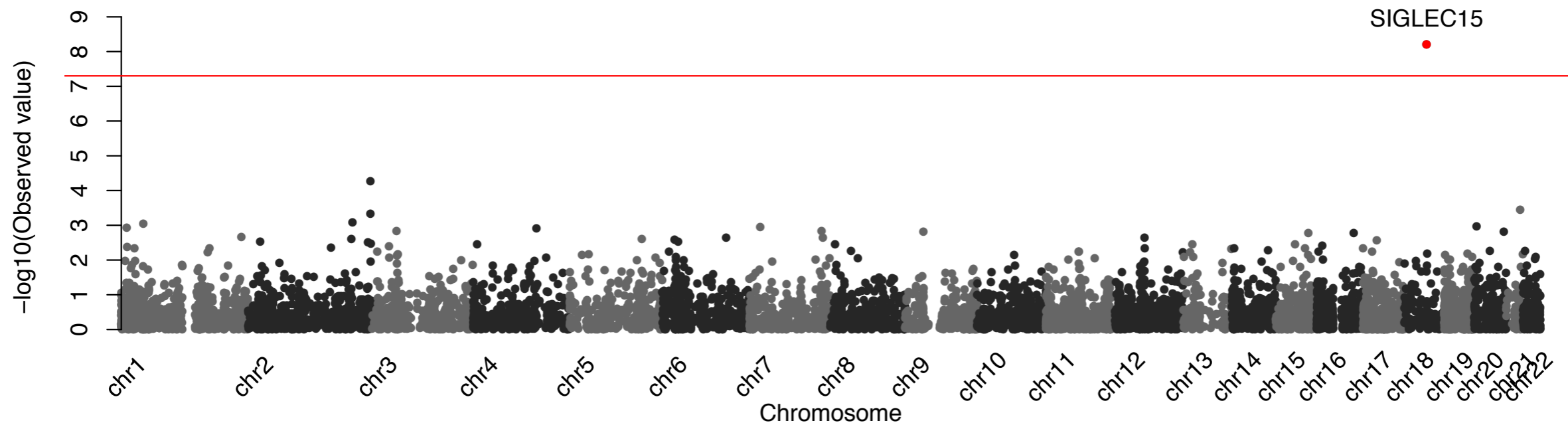
Predicted gene expression of *SIGLEC15* in colon associates with *Akkermansia*



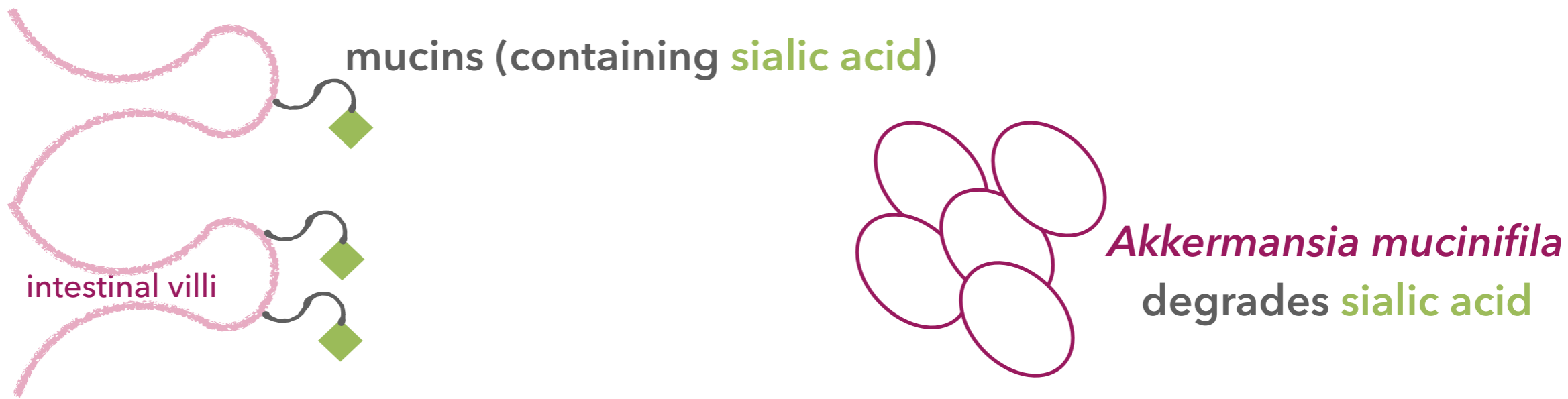
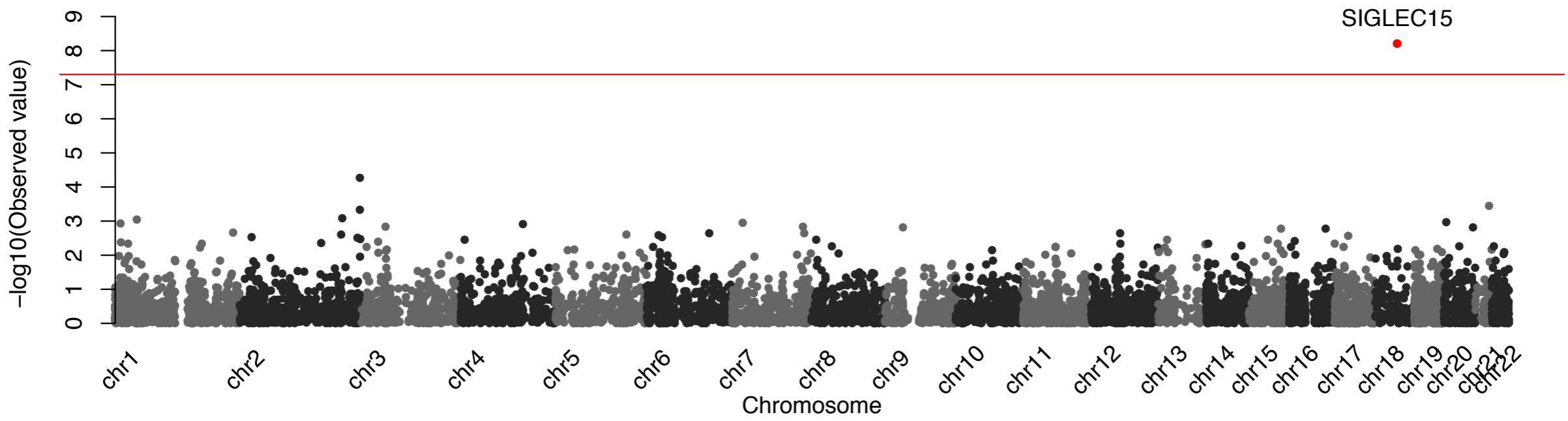
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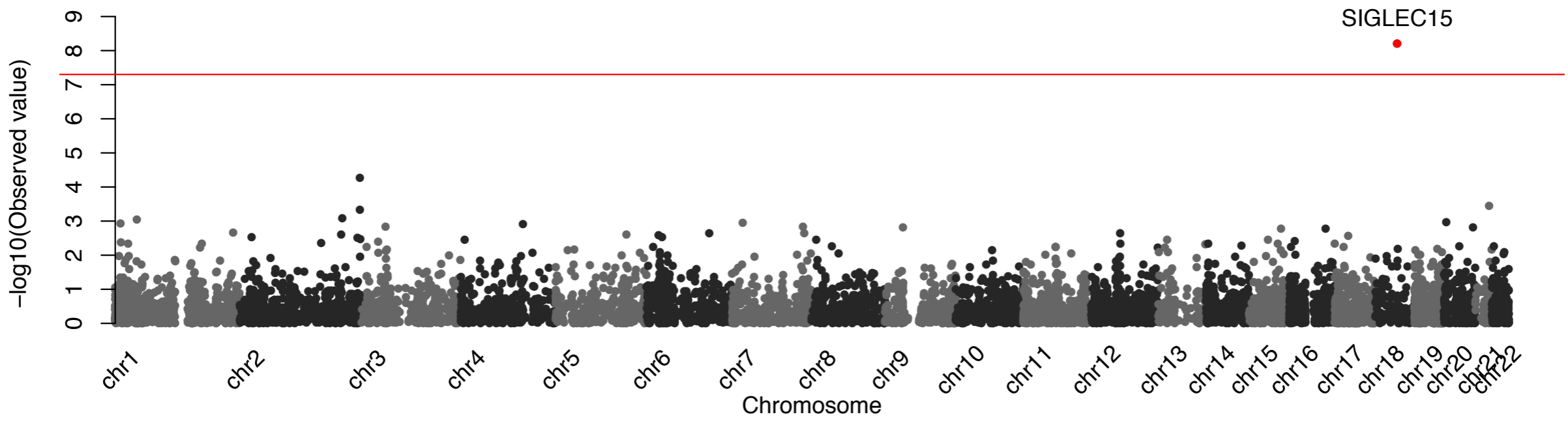
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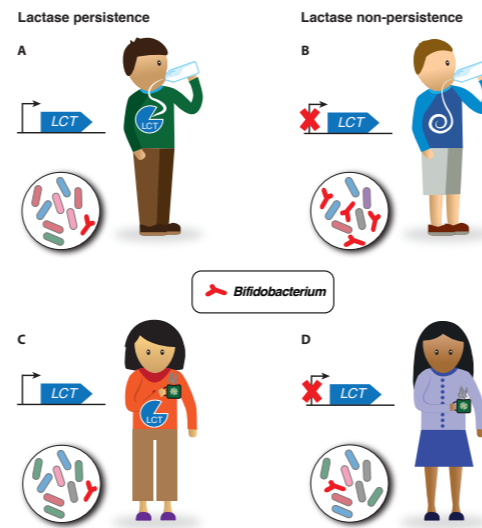
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Conclusions

1

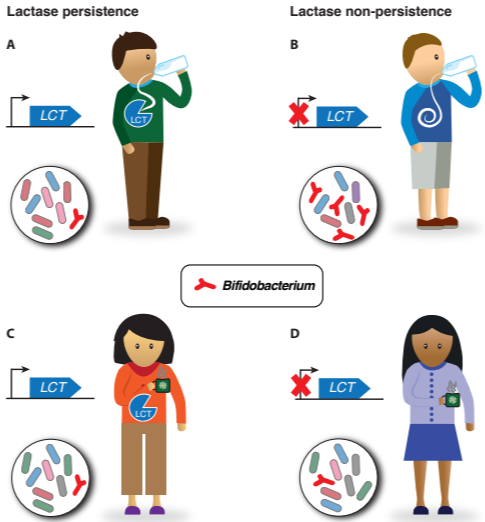
Bifidobacterium-LCT
GWAS hit *replicates* in
multiple populations



Conclusions

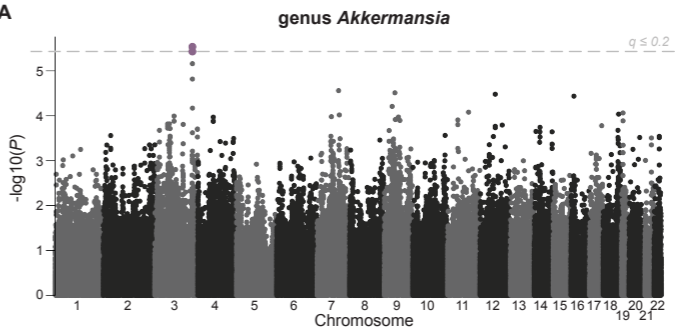
1

Bifidobacterium-LCT
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2

Predicted gene expression a
useful intermediate trait for
identifying host-microbiome
genetic interactions



What have microbiome GWAS revealed?

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1. Heritable taxa

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2. Candidate genes

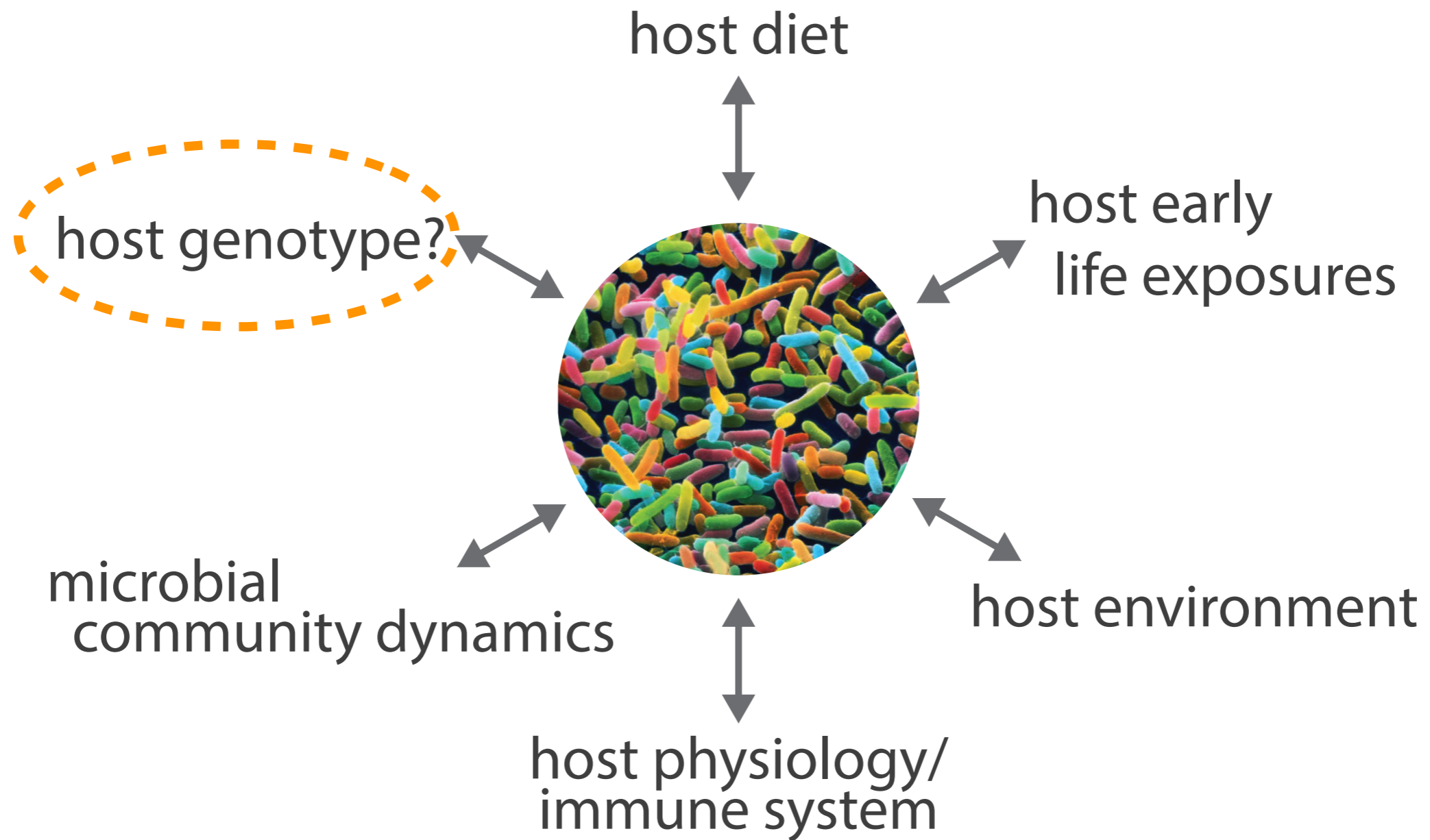
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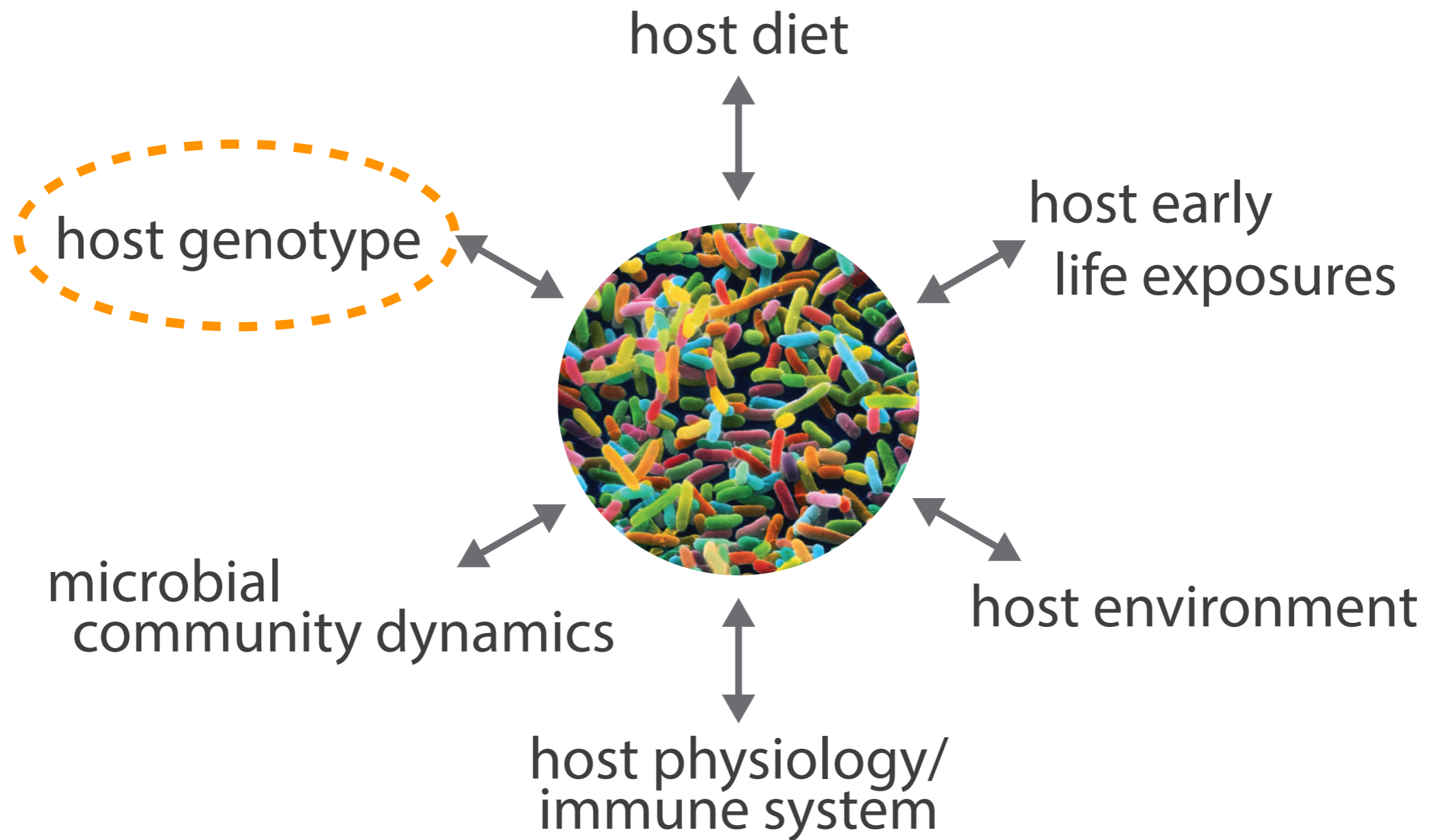
2. Candidate genes

3. Connections to host health

What determines microbiome *composition*?



What determines microbiome *composition*?



Elucidating the role of the host genome in shaping microbiome composition

Emily R. Davenport

REVIEW

Cross-species comparisons of host genetic associations with the microbiome

Julia K. Goodrich^{1,*}, Emily R. Davenport^{1,*}, Jillian L. Waters^{1,3,*}, Andrew G. Clark¹, Ruth E. Ley^{1,2,3,†}

+ See all authors and affiliations

Science 29 Apr 2016:
Vol. 352, Issue 6285, pp. 532-535
DOI: 10.1126/science.aad9379



Annual Review of Genetics

The Relationship Between the Human Genome and Microbiome Comes into View

Julia K. Goodrich,^{1,2} Emily R. Davenport,²
Andrew G. Clark,² and Ruth E. Ley^{1,2}

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Acknowledgements

Hutterite projects:

The University of Chicago



Yoav Gilad
Carole Ober
Luis Barreiro
Orna Mizrahi Man
Katelyn Michelini
Darren Cusanovich

TwinsUK projects:

Cornell University

Andrew Clark
Ruth Ley
Julia Goodrich



King's College London

Tim Spector
Jordana Bell



University of London

