PSTP Interview Presentation

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UNC at Chapel Hill

October 31, 2019

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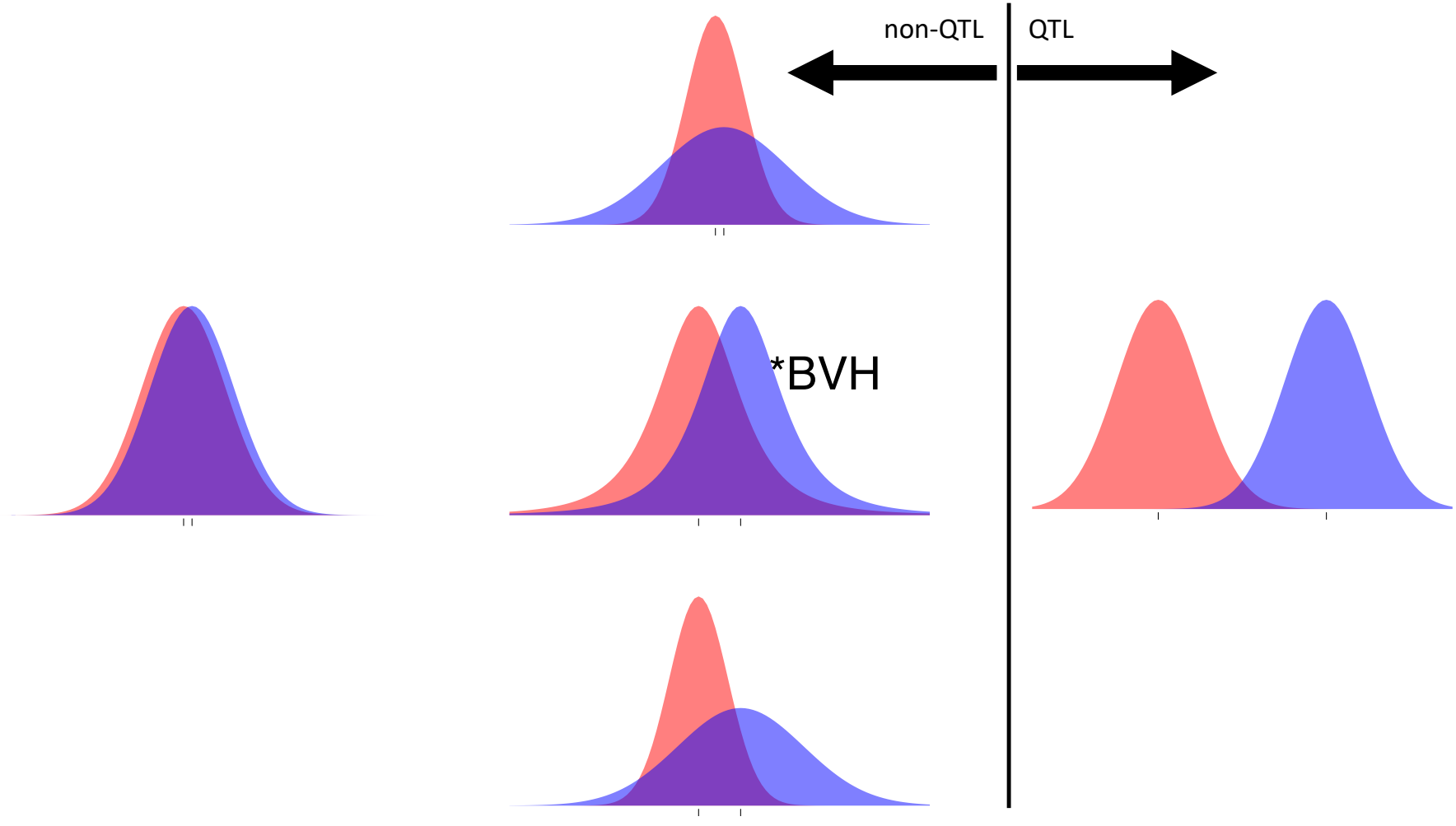
Main idea — Which of these is a QTL?



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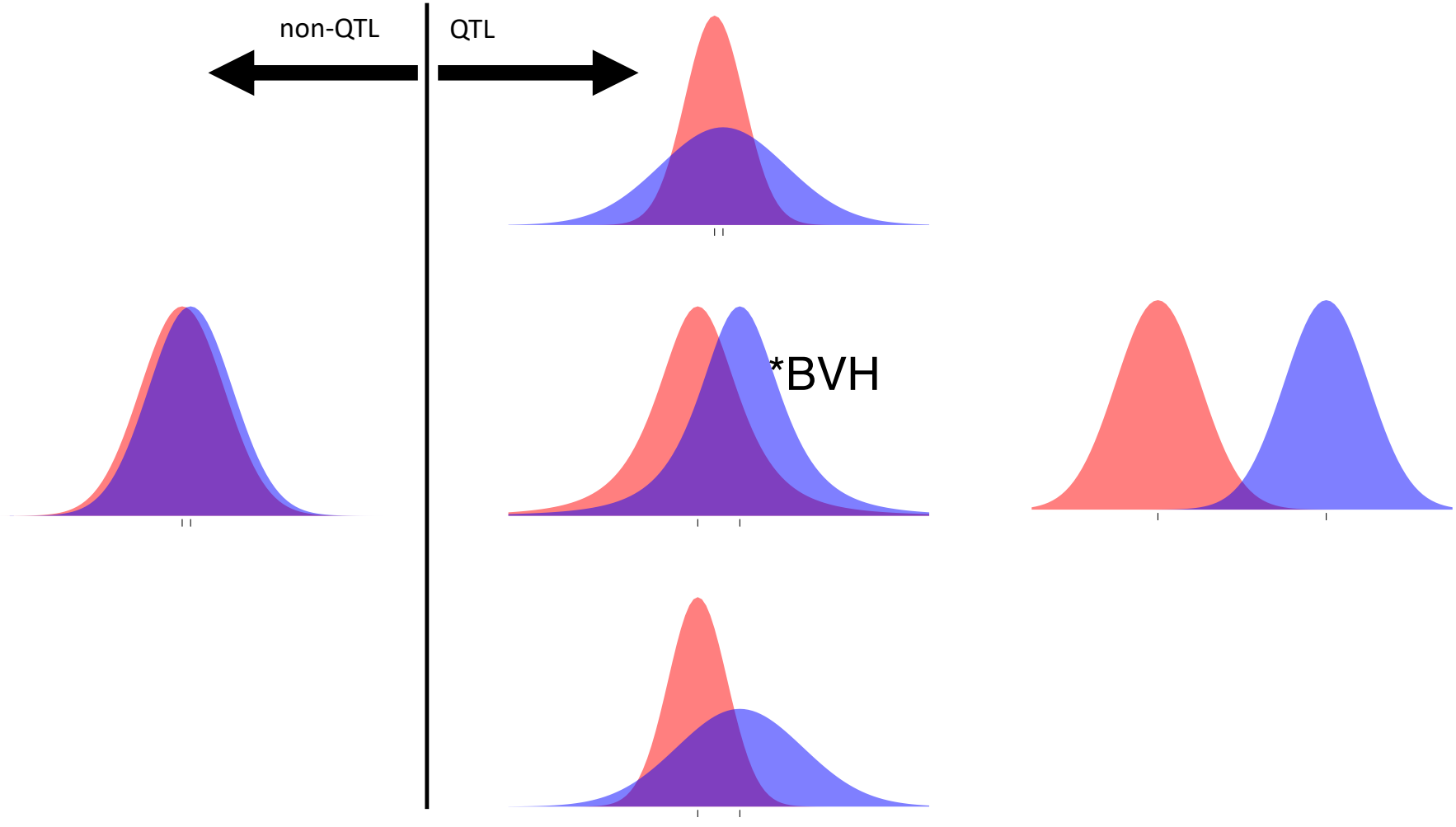

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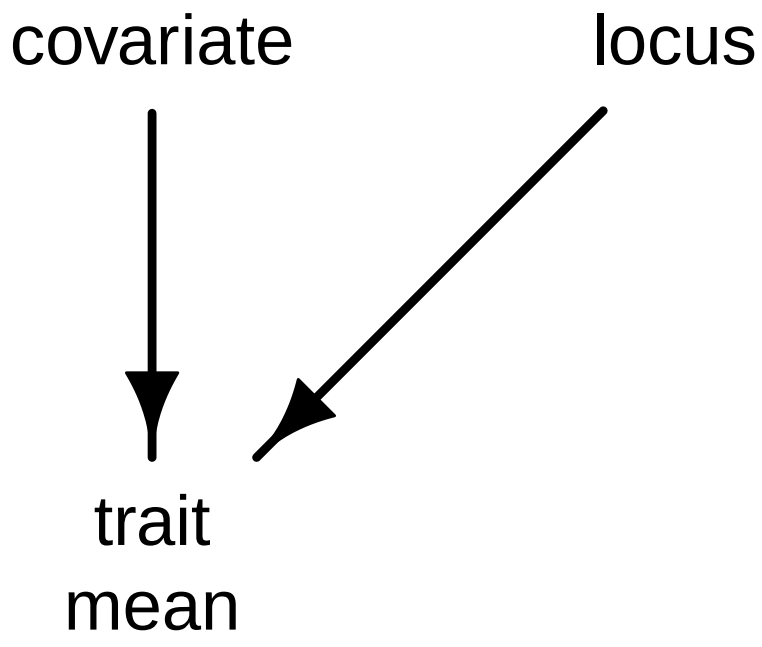
Introduction

QTL = "quantitative trait locus"

A genomic region containing factors that influence a quantitative trait of interest

1. Measure the trait of interest in a population of genetically-diverse organisms
2. Measure genetic variants an an appropriate density
3. Apply a statistical test to each locus to quantify the evidence that it is a QTL

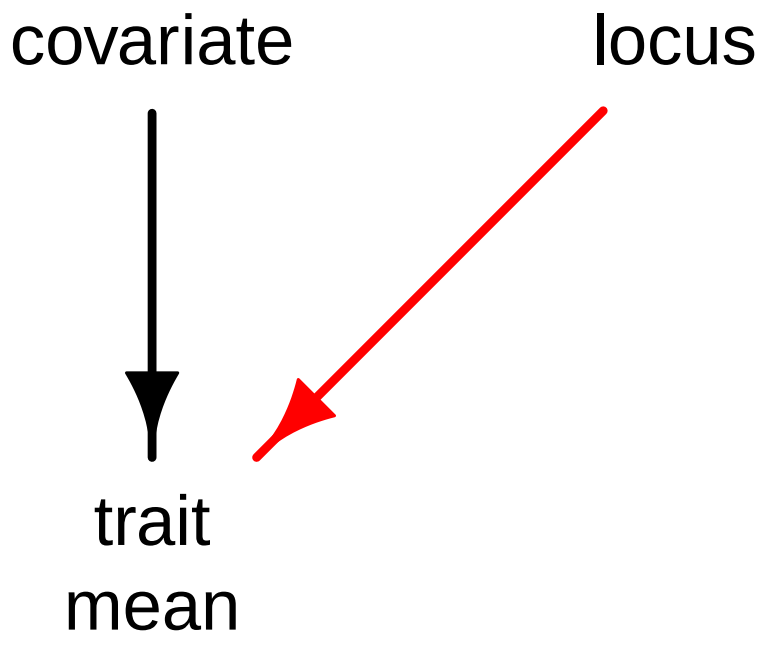
Standard Linear Model (SLM)



$$y_i \sim \mathrm{N}(m_i, \sigma^2)$$

Legendre, 1805

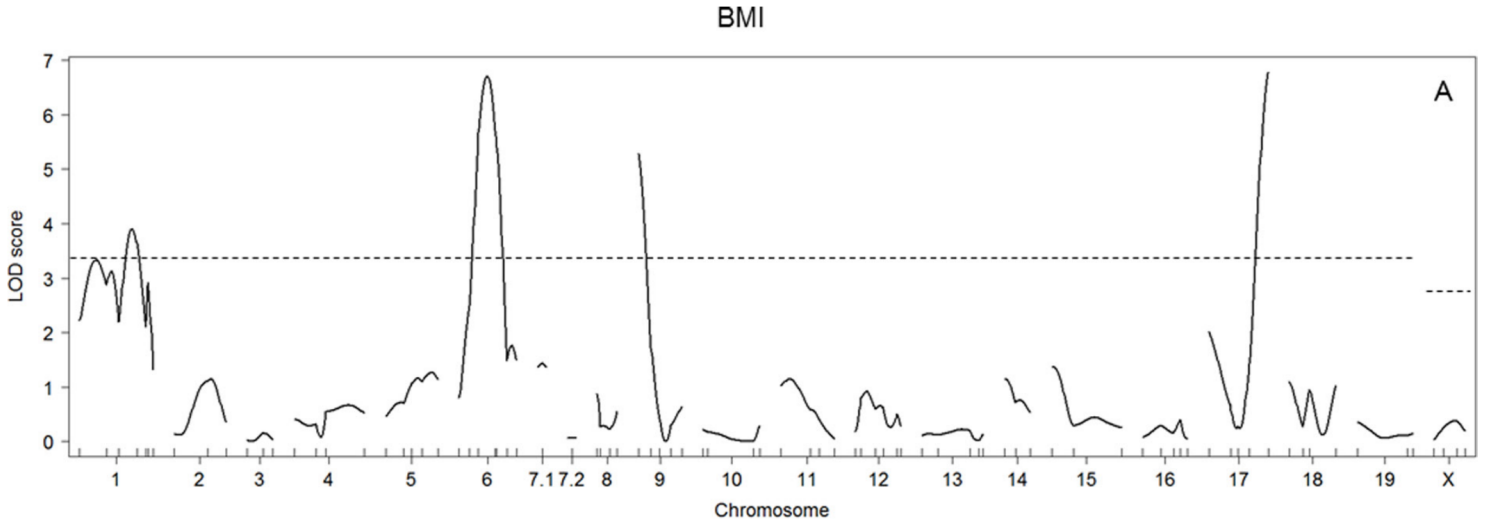
Standard Linear Model (SLM)



$$y_i \sim \mathrm{N}(m_i, \sigma^2)$$

Legendre, 1805

Example Result with SLM



Suto, 2013, J. Vet. Med. Sci.

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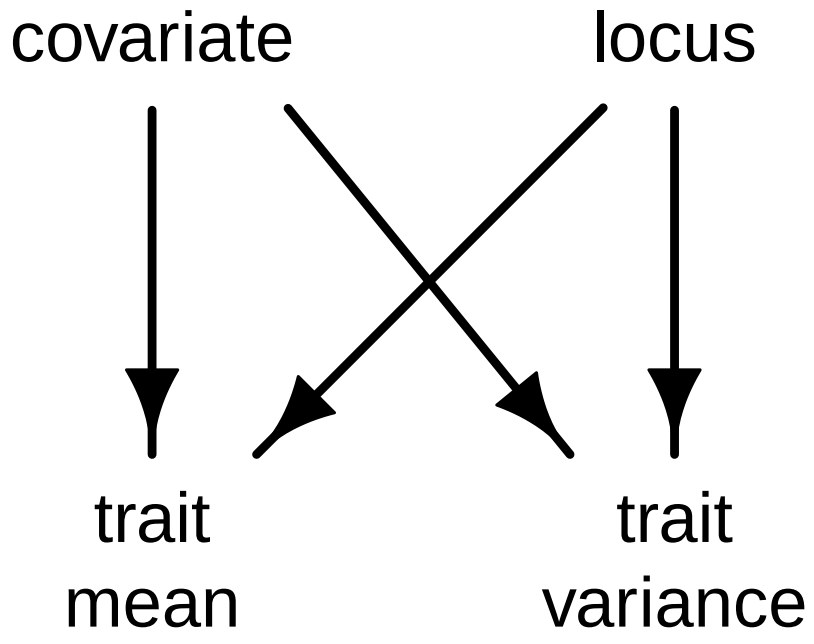
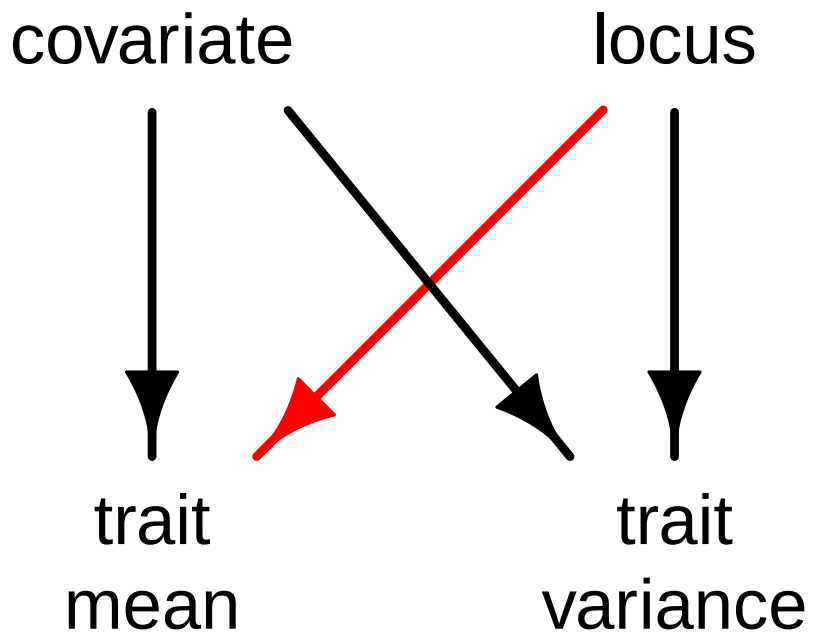
Double Generalized Linear Model (DGLM)



$$y_i \sim \mathrm{N}(m_i, \sigma_i^2)$$

Smyth, 1989

Double Generalized Linear Model (DGLM)

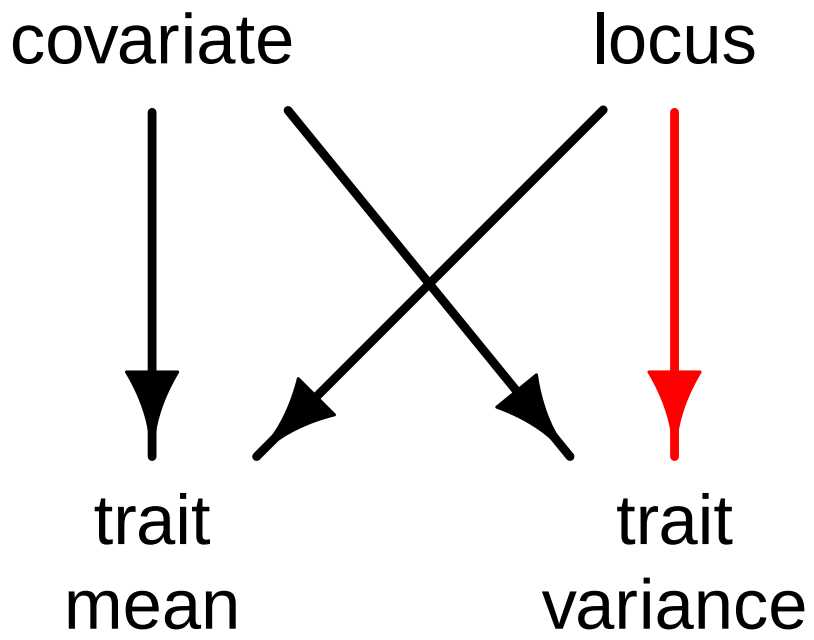


"mQTL"

$$y_i \sim \mathrm{N}(m_i, \sigma_i^2)$$

Smyth, 1989

Double Generalized Linear Model (DGLM)

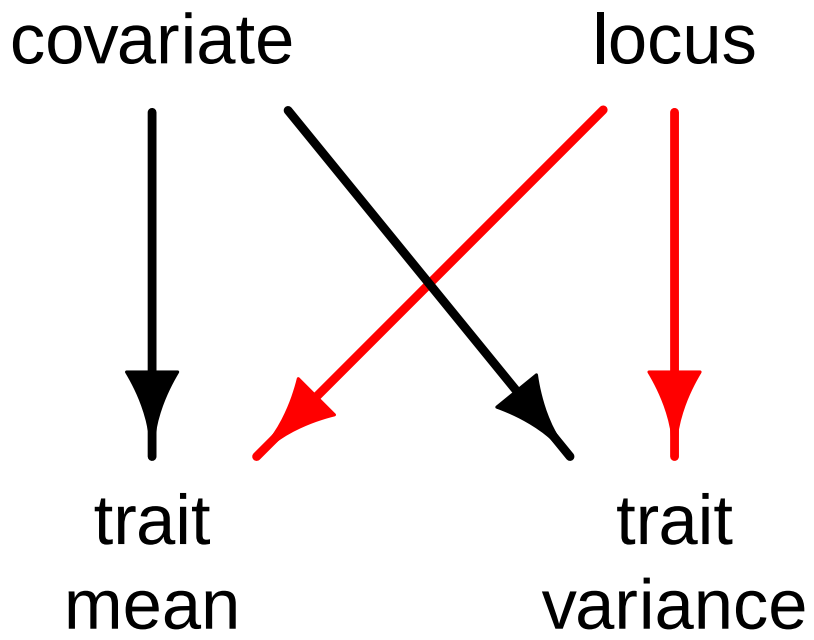


"vQTL"

$$y_i \sim \mathrm{N}(m_i, \sigma_i^2)$$

Smyth, 1989

Double Generalized Linear Model (DGLM)



"mvQTL"

$$y_i \sim \mathrm{N}(m_i, \sigma_i^2)$$

Smyth, 1989

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Original Study

Genes, Brain and Behavior

Official publication of the International Behavioural and Neural Genetics Society

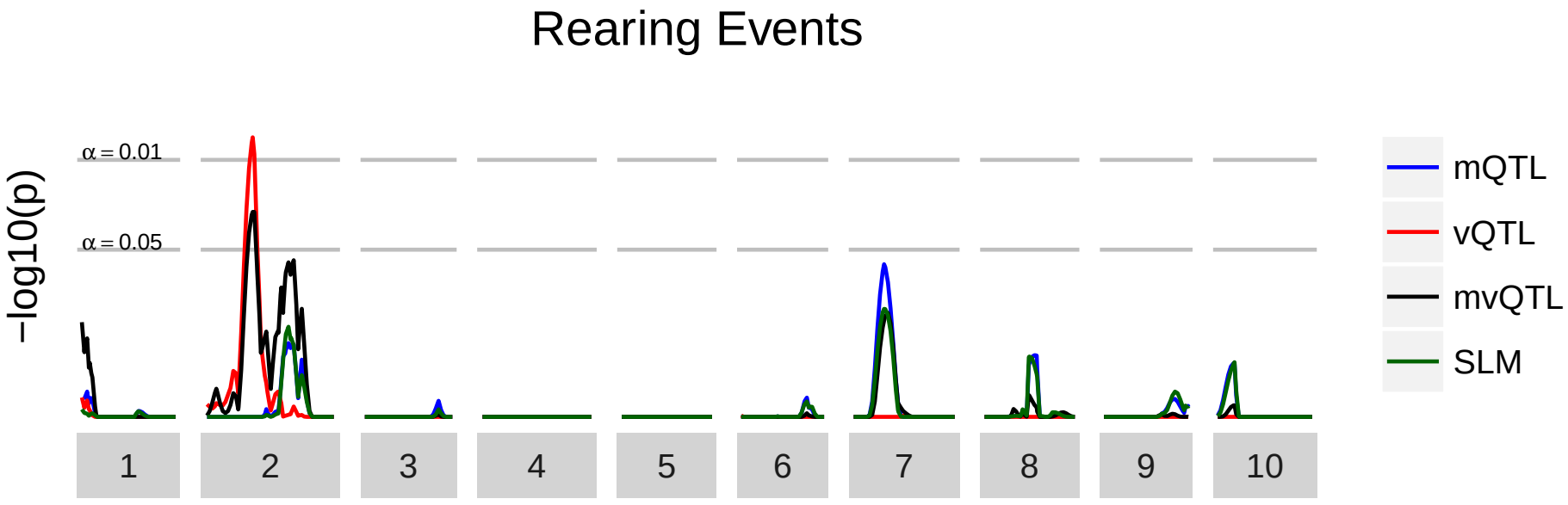
Genes, Brain and Behavior (2008) ***7:*** *761–769*

Identification of quantitative trait loci for locomotor activation and anxiety using closely related inbred strains

- Intercrossed C57BL/6J and C58/J, yielding 362 F2's.
- Measured six behavioral traits that model aspects of anxiety and exploratory behavior.
- Reported 7 QTL, but none for rearing behavior.

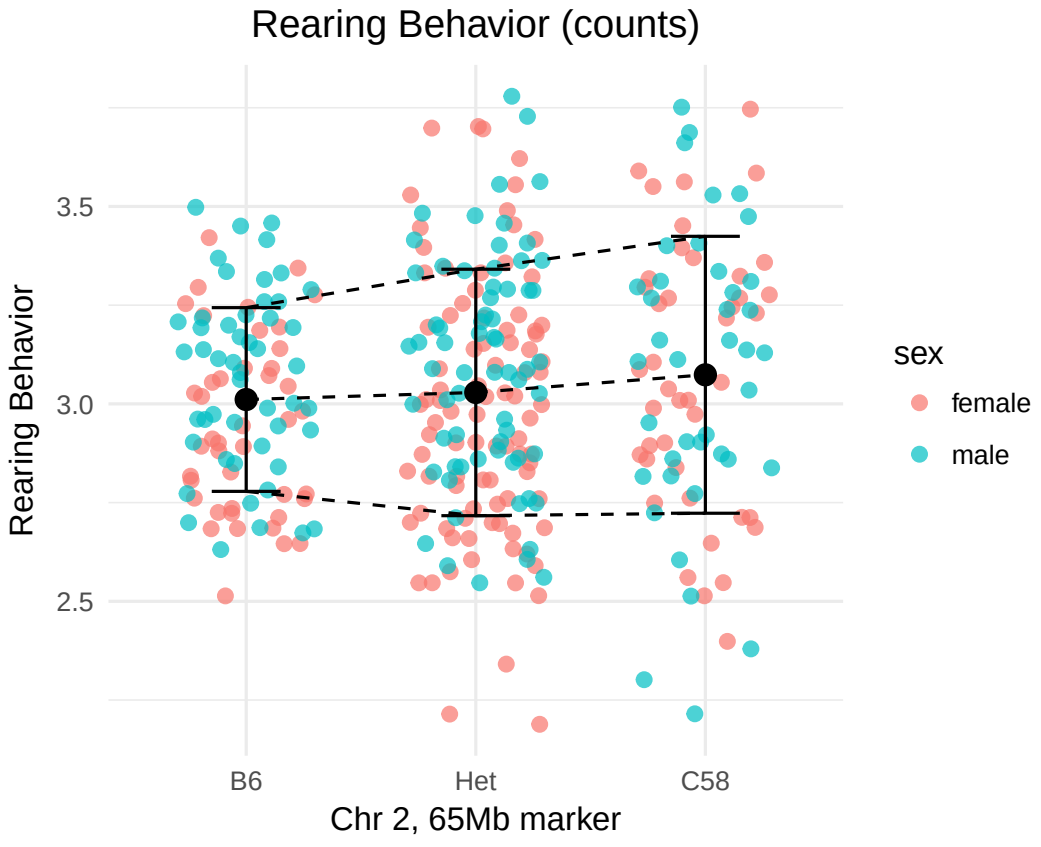
Bailey et al., GB&B, 2008

New vQTL



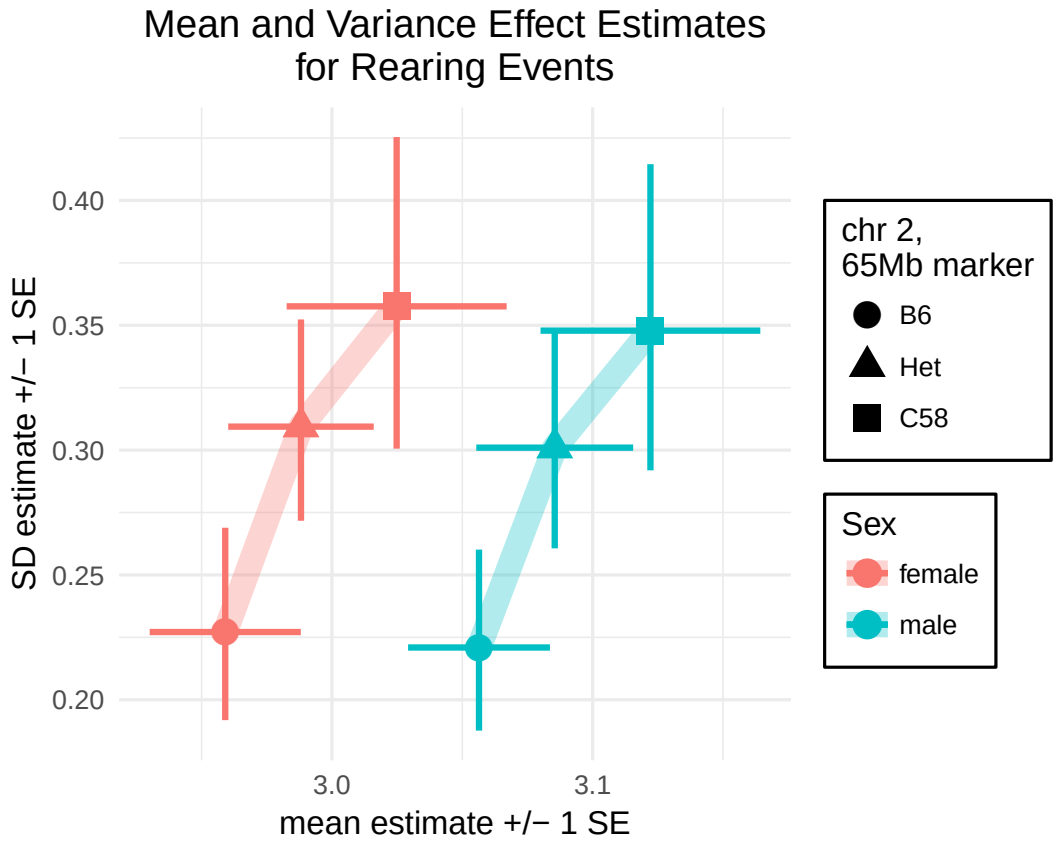
Corty et al., 2018

Understanding the vQTL



Corty et al., 2018

Understanding the vQTL (2)



Corty et al., 2018

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Original Study

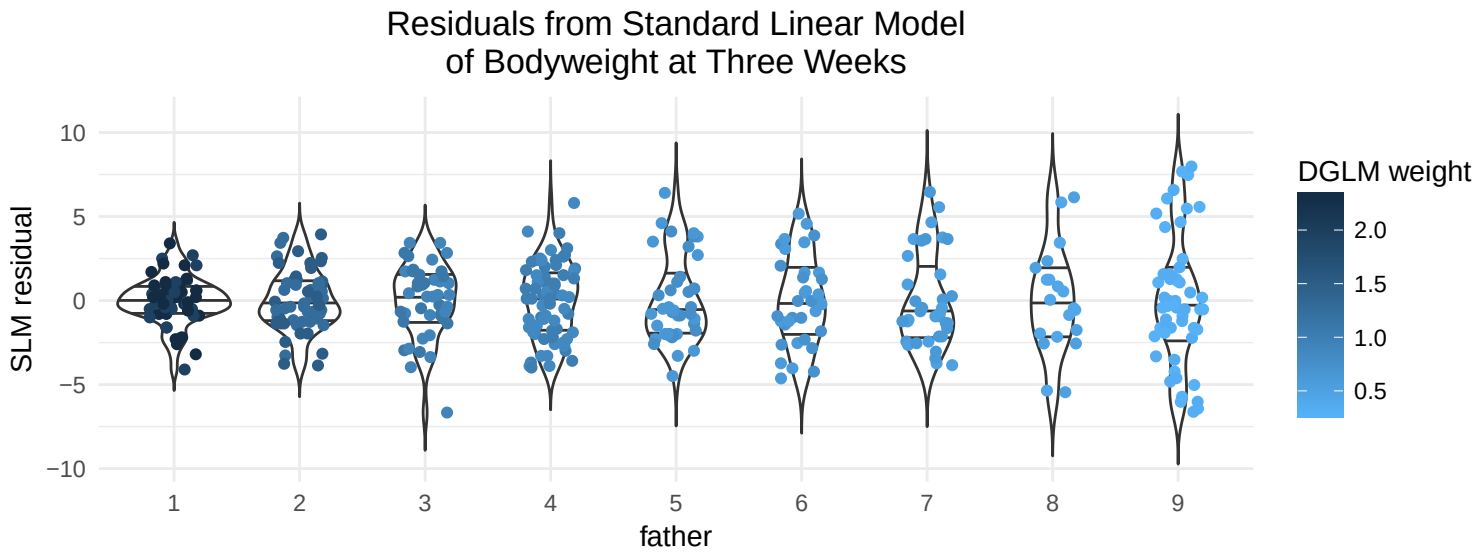
Genet. Res., Camb. (2000), **76**, *pp.* 27–40. *With* 2 *figures.* Printed in the United Kingdom

Quantitative trait loci for directional but not fluctuating asymmetry of mandible characters in mice

- Backcrossed CAST/Ei into M16i
- 350 mice in mapping population, 92 markers
- Skull morphometrics, limb bone lengths, organ and body weight
- Published many QTL, but none for body weight

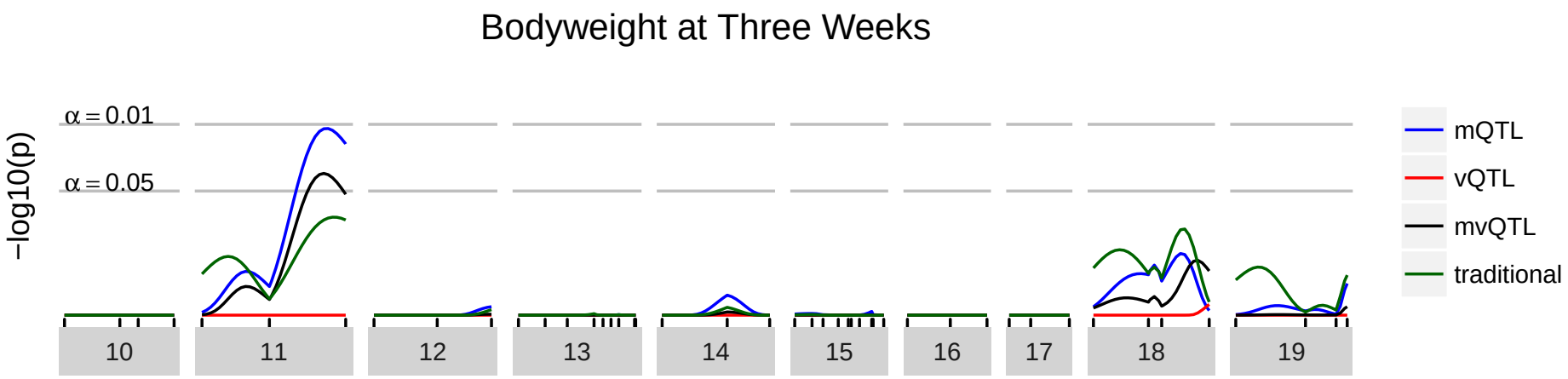
Leamy et al., Genet. Res., 2000, Physiol. Genom., 2002, Yi et al., Genetics, 2005

Body Weight at Three Weeks



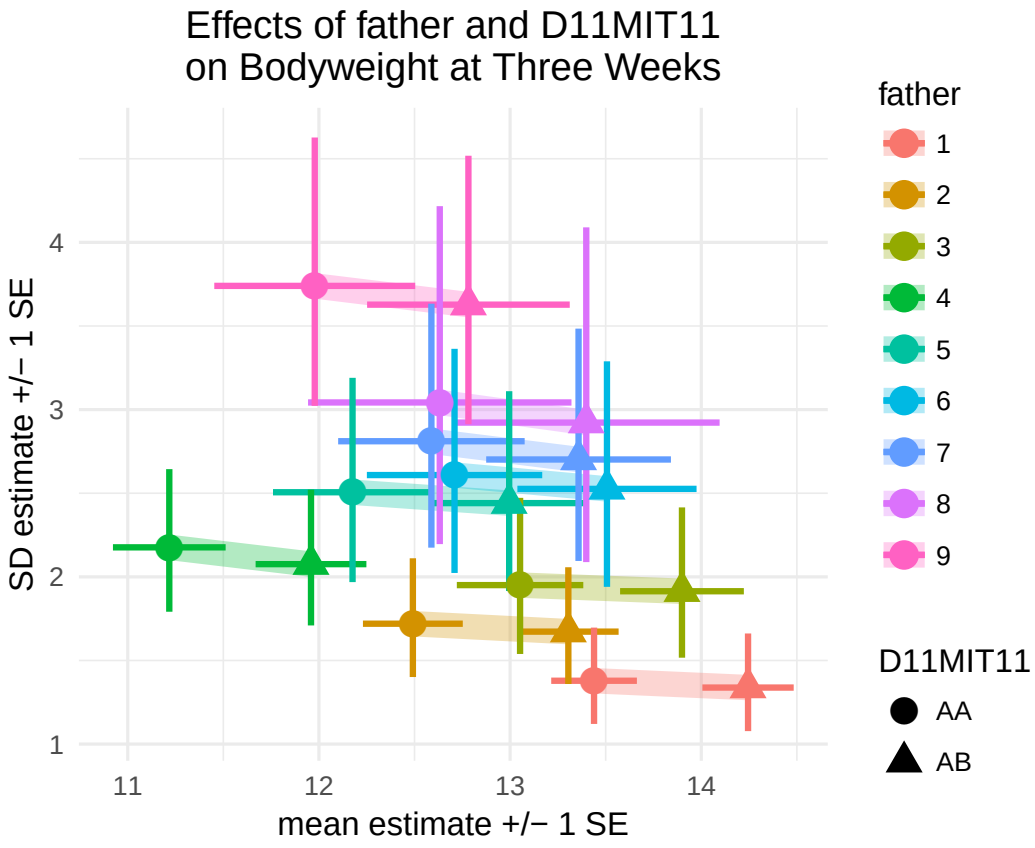
Corty and Valdar, 2018

New mQTL



Corty and Valdar, 2018

Understanding the new QTL



Corty and Valdar, 2018

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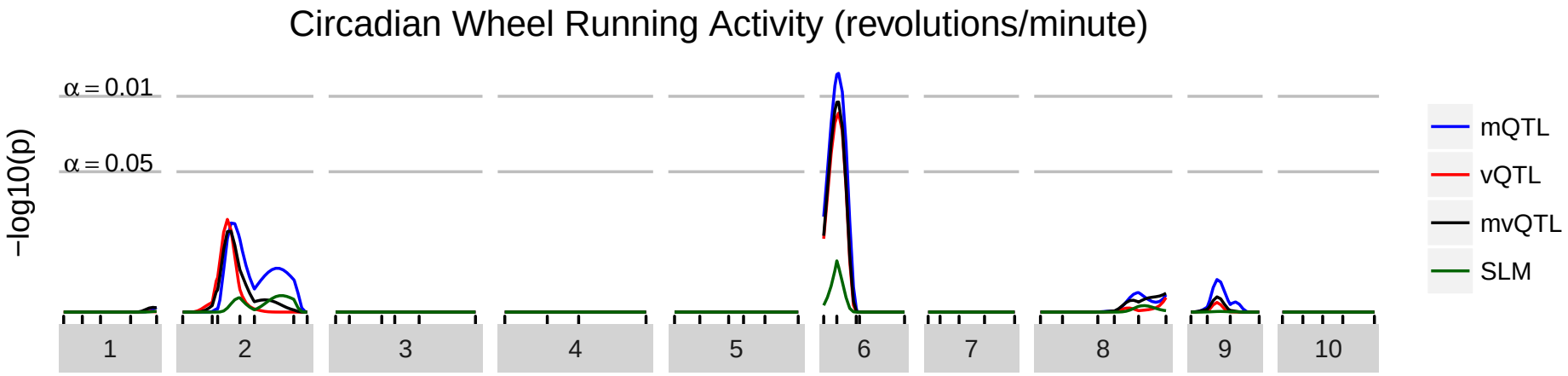
Original Study

C57BL/6N Mutation in *Cytoplasmic FMRP interacting protein 2* Regulates Cocaine Response

- Intercrossed C57BL/6J and C56NL/6N, two "sister strains"
- Measured cocaine response and circadian behavior traits
- Reported 1 QTL for cocaine response, identified QTN
- No QTL for circadian behavior traits by standard analysis

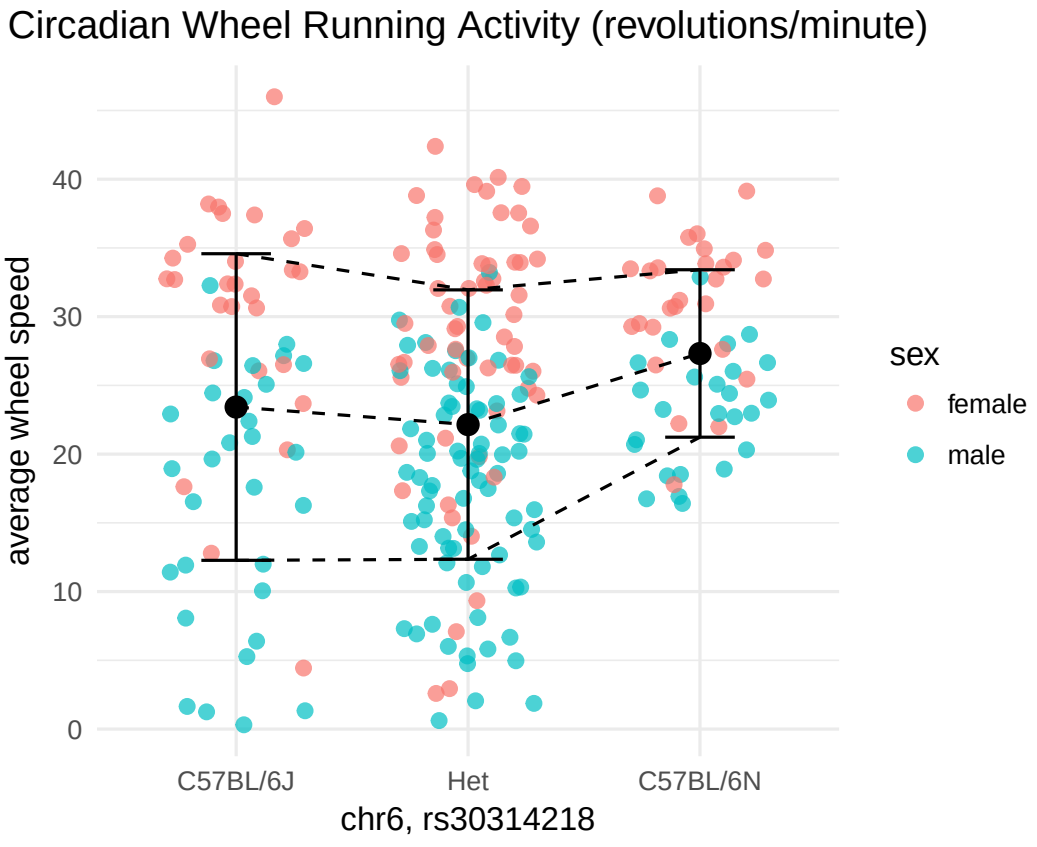
Kumar et al., Science, 2013

New "mQTL"



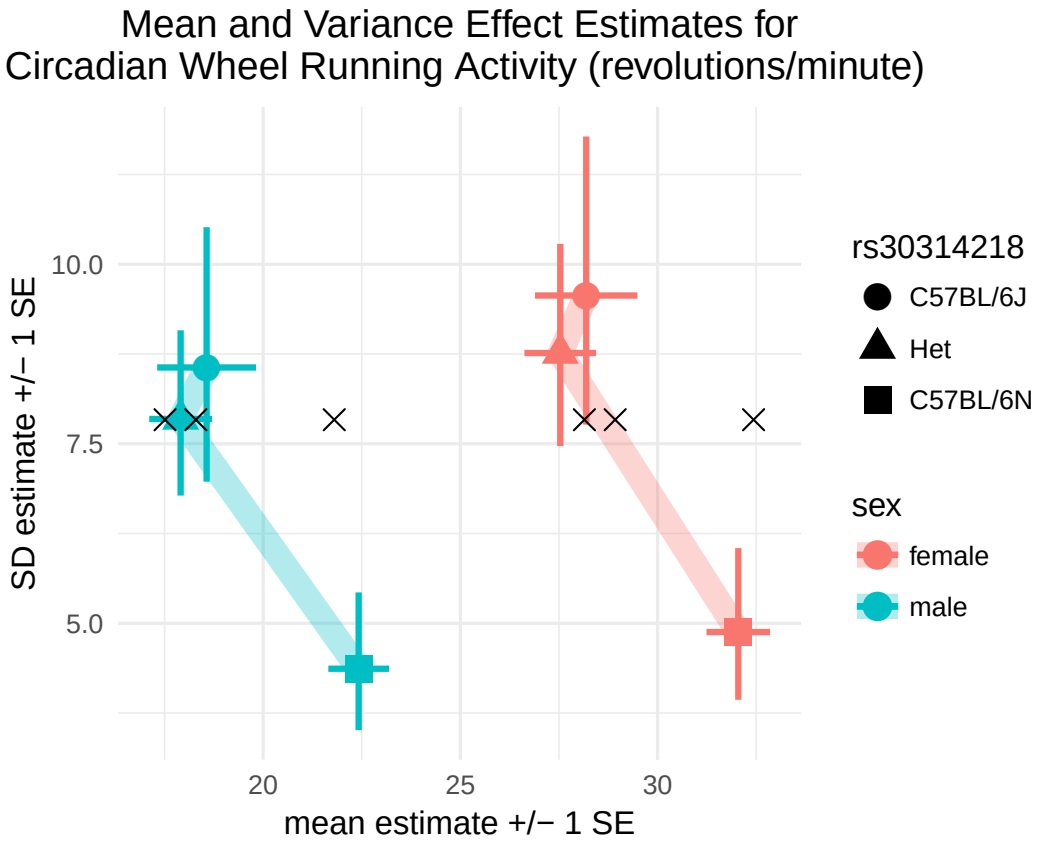
Corty et al., 2018

Understanding the new QTL



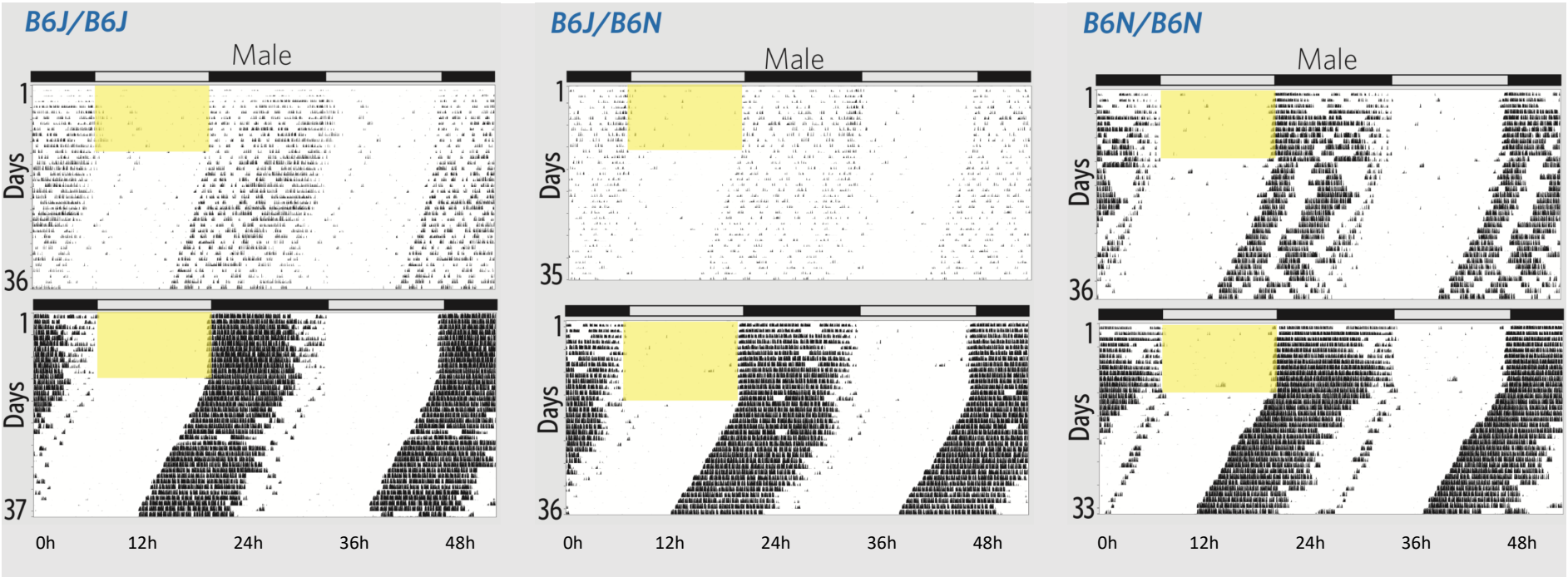
Corty et al., 2018

Understanding the new QTL (2)



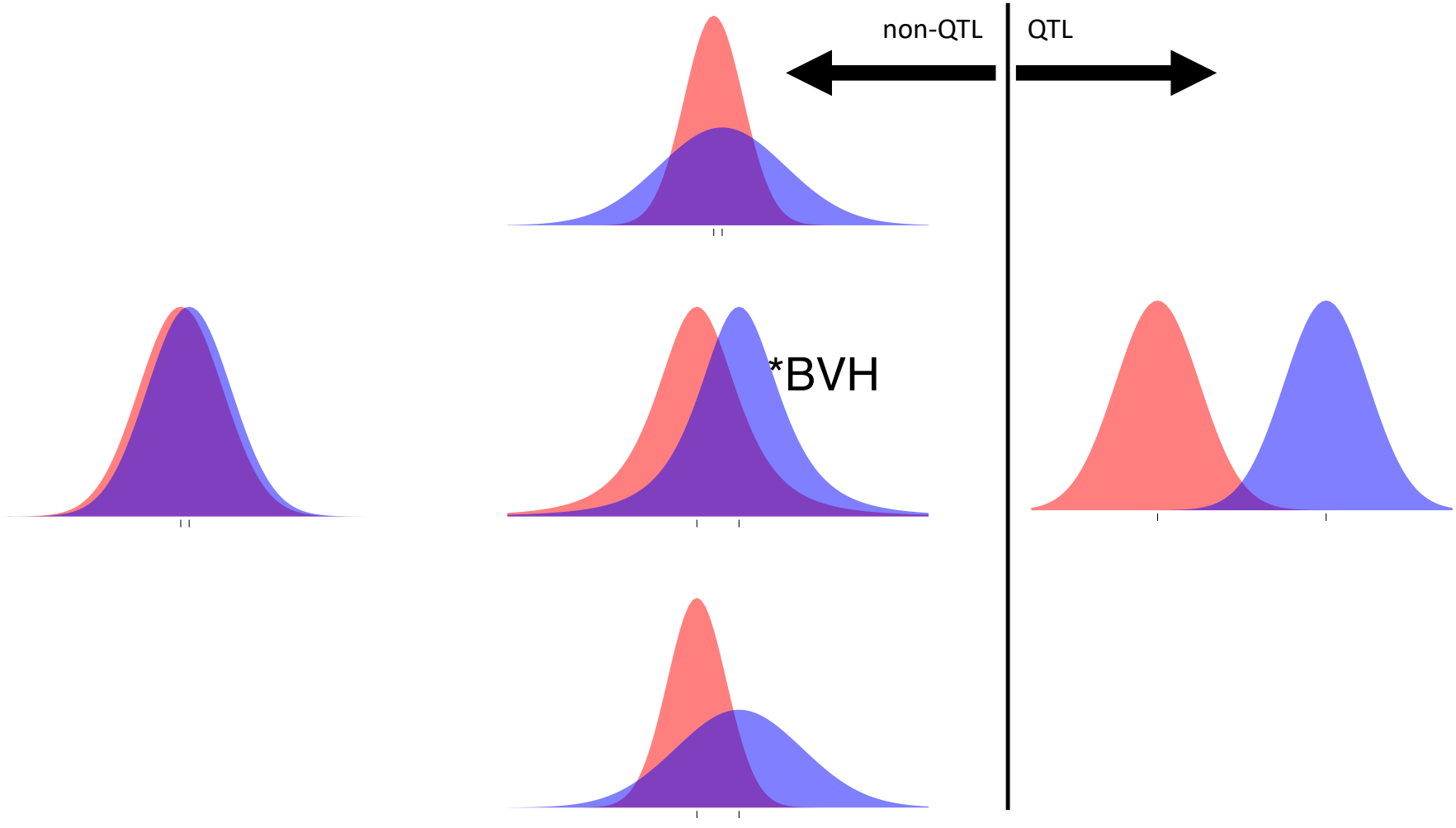
Corty et al., 2018

Domain-specific view of the Activity Trait



Corty et al., 2018

Main idea — Which of these is a QTL?



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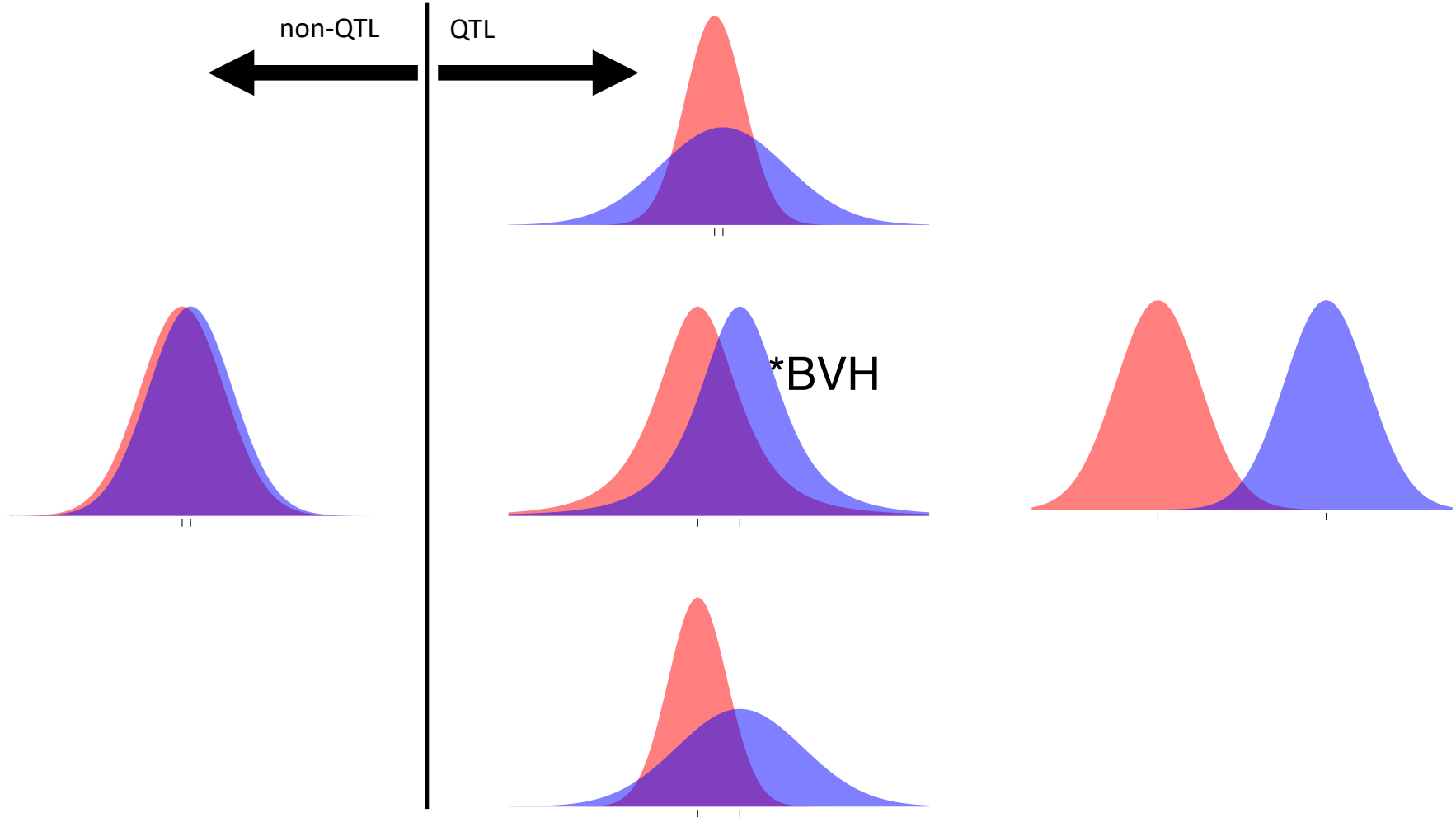

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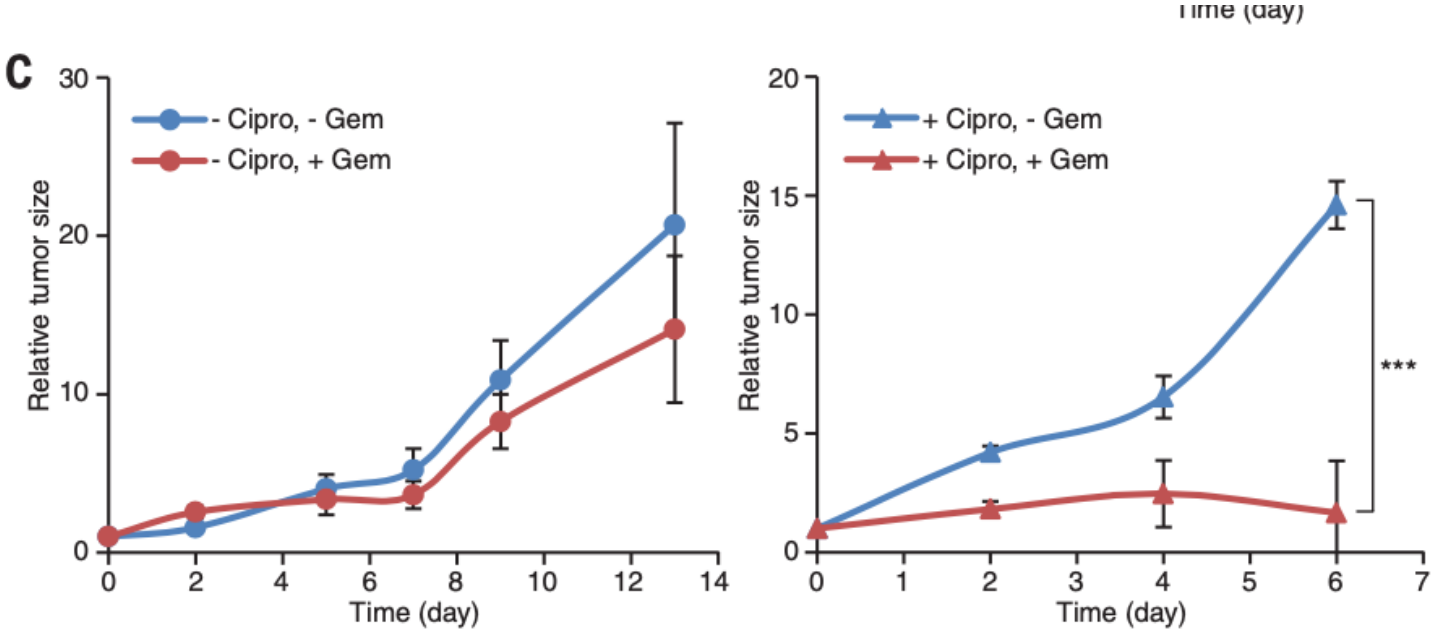
Idea

RESEARCH

CANCER

Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine

Idea


C
Relative tumor size
- Cipro, - Gem
- Cipro, + Gem
Time (day)
+ Cipro, - Gem
+ Cipro, + Gem
***

Idea

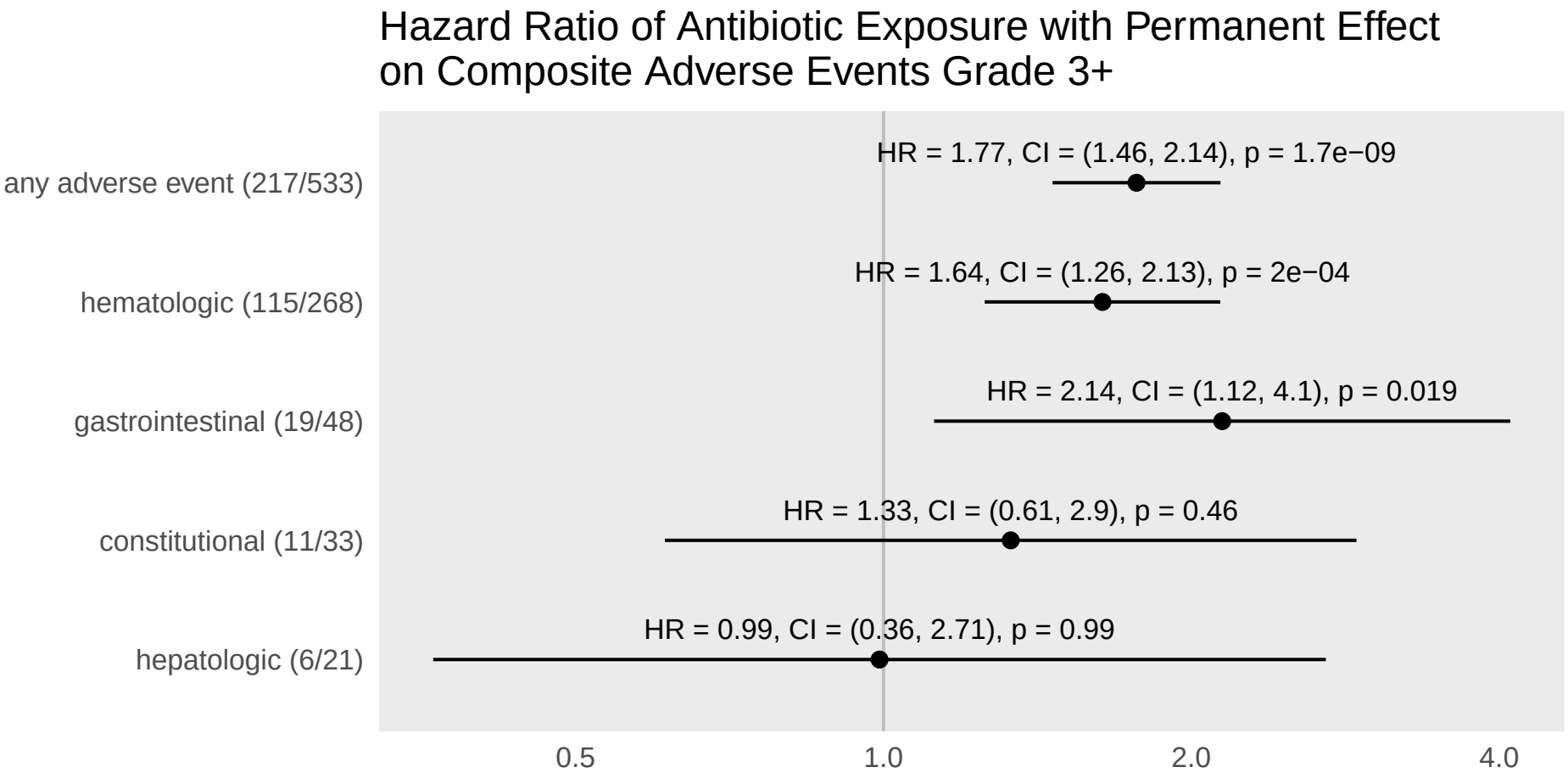
ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

METHODS

We randomly assigned patients with a Karnofsky performance-status score of 70 or more (on a scale from 0 to 100, with higher scores indicating better performance status) to nab-paclitaxel (125 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter) on days 1, 8, and 15 every 4 weeks or gemcitabine monotherapy (1000 mg per square meter) weekly for 7 of 8 weeks (cycle 1) and then on days 1, 8, and 15 every 4 weeks (cycle 2 and subsequent cycles). Patients received the study treatment until disease progression. The primary end point was overall survival; secondary end points were progression-free survival and overall response rate.

Results


Hazard Ratio of Antibiotic Exposure with Permanent Effect on Composite Adverse Events Grade 3+
any adverse event (217/533)
HR = 1.77, CI = (1.46, 2.14), p = 1.7e−09
hematologic (115/268)
HR = 1.64, CI = (1.26, 2.13), p = 2e−04
gastrointestinal (19/48)
HR = 2.14, CI = (1.12, 4.1), p = 0.019
constitutional (11/33)
HR = 1.33, CI = (0.61, 2.9), p = 0.46
hepatologic (6/21)
HR = 0.99, CI = (0.36, 2.71), p = 0.99
0.5
1.0
2.0
4.0

Significance

1. suggests new considerations:
   - decrease dose of gem if on antibiotics
   - restraint in use of antibiotics
2. requires further study
   - similar analysis on other datasets
   - randomized trial?
3. absolute *joy* to create, drive, and coordinate this project

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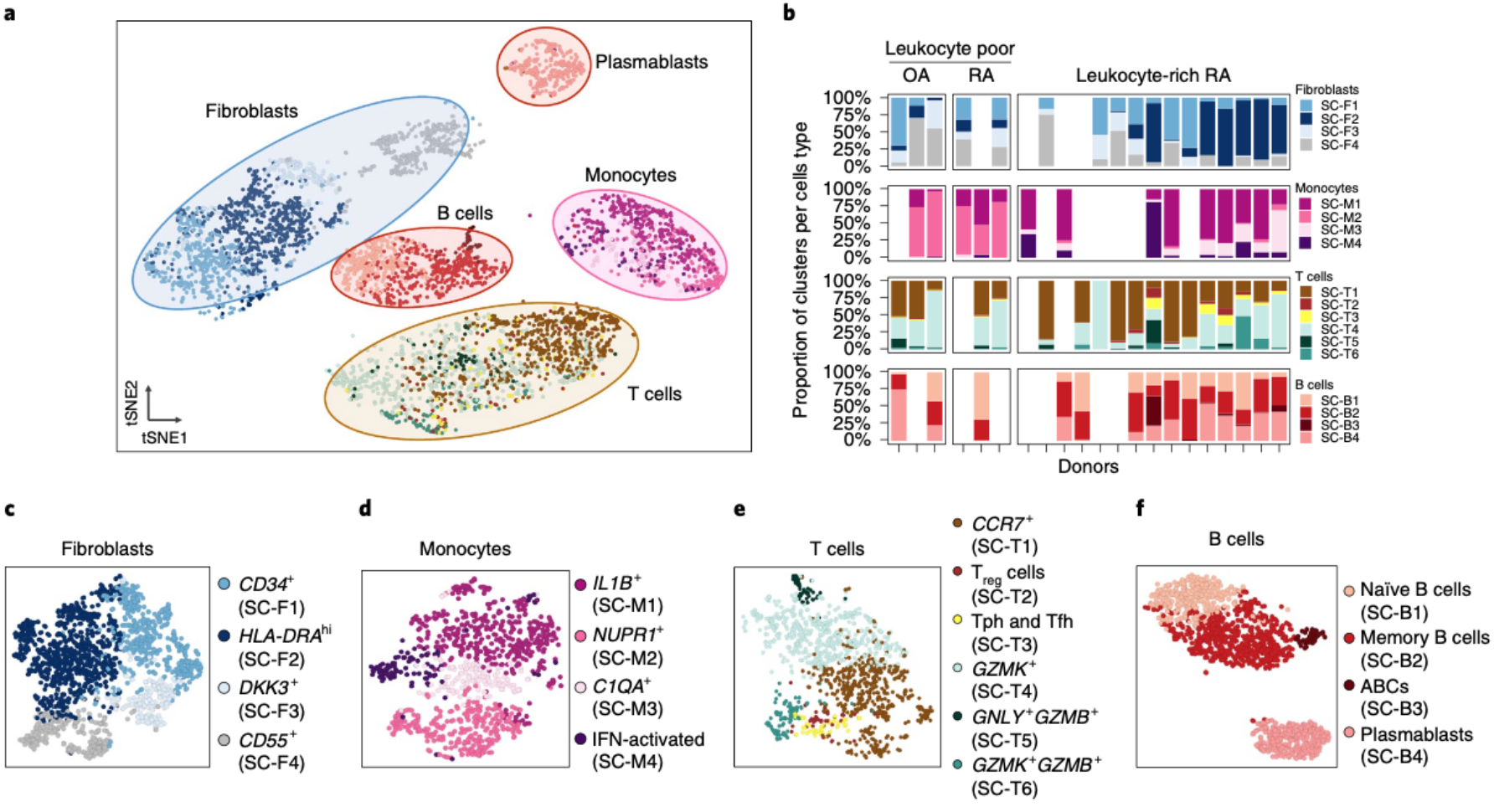
Exciting papers

RESOURCE
https://doi.org/10.1038/s41590-019-0378-1
nature immunology

Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry

Exciting papers



Exciting technology