Leveraging allelic series to enhance QTL detection

Frederick J. Boehm [1,]
frederick.boehm@umassmed.edu
Clare M. Smith[2] Megan Proulx[1] Daniel M. Gatti[3] Michael Kiritsy[1] Sherry Kurtz[4] Karen Elkins[4] Gillian Beamer[5] Christopher M. Sassetti[1]

[1] *Microbiology and Physiological Systems, University of Massachusetts Medical School*
[2] *Duke University*
[3] *College of the Atlantic*
[4] *Food and Drug Administration*
[5] *Tufts University*

Introduction

- We examined Mtb-related traits in both a Colllaborative Cross cohort (52 lines) and a Diversity Outbred cohort (763 mice)
- In CC and DO QTL mapping, we typically work with 8 founder allele probabilities

$$Trait = p_A b_A + p_B b_B + p_C b_C + p_D b_D + p_E b_E + p_F b_F + p_G b_G + p_H b_H + \epsilon$$

- Crouse and Valdar (personal communication) developed a method for inferring the allelic series at a QTL
- In DO and CC, some QTL have fewer than 8 alleles
- Using this fact in our QTL scans may enhance QTL detection **(Jansen, Jannink, and Beavis 2003)**

Objectives

1. Infer QTL allelic series in CC mice
2. Use CC QTL allelic series to inform QTL mapping in DO mice

Methods

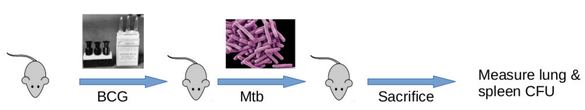
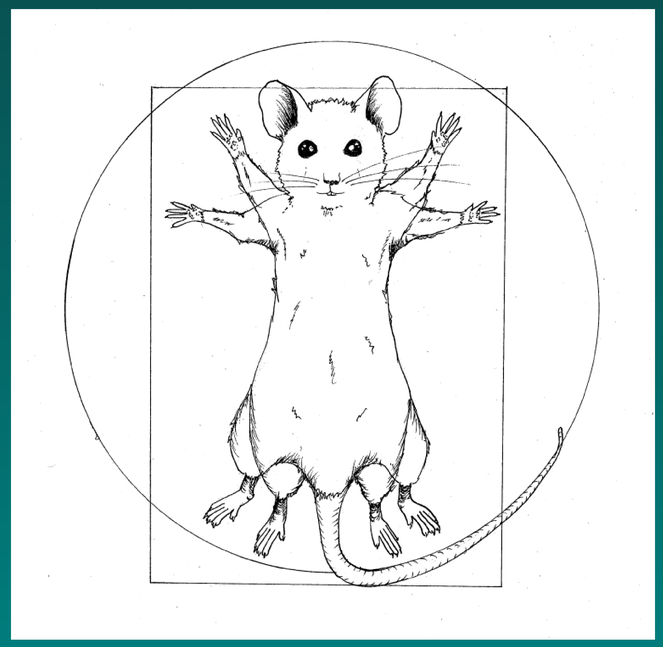


Figure 1: Experimental design in DO mice

Figure 2: Experimental design in CC mice

CC allelic series informs QTL mapping in DO



- We mapped QTL in CC cohort with standard methods **(Broman et al. 2019)**
- We used Tree-based Inference of Multi-allelism with Bayesian Regression (TIMBR) **(Crouse 2018)** to infer allelic series at CC QTL
- For each CC QTL, we scanned the DO cohort with reduced models that reflected the CC QTL allelic series
  - Example of reducing a model with inferred allelic series
    For the allelic series: 0,1,1,0,2,1,0,0:
  1. Set $p_0 = p_A + p_D + p_G + p_H$,
     $p_1 = p_B + p_C + p_F$,
     $p_2 = p_E$
  2. Use model

$$Y = \beta_0 p_0 + \beta_1 p_1 + \beta_2 p_2 + \epsilon$$

  in QTL scan

Results

1. Traditional QTL mapping in CC identified 14 suggestive peaks
2. For each CC QTL, we:
   1. inferred allelic series
   2. fitted reduced linear models (informed by allelic series) for QTL detection in DO
   3. identified any proximal DO QTL with LOD greater than 3

QTL peaks on Chr 4

trait	cohort	chr	pos	lod
Spleen CFU in DO	DO	4	152.95	3.09
VEGF in CC	CC	4	154.07	6.83

Future research

1. Determine DO QTL p-values with approximate permutation tests **(Churchill and Doerge 1994)**
2. Consider multiple allelic series per CC QTL

Image credits

https://webcomicms.net/clipart-10020867-pictures-cartoon-mouse

https://www.latimes.com/science/story/2020-04-13/old-vaccines-for-other-germs-being-tested-against-the-new-coronavirus

https://www.lshtm.ac.uk/research/research-action/features/ending-tb-race-control-disease-hiding

Vitruvian Mouse by Eleni Jaecklein

References

Broman, Karl W, Daniel M Gatti, Petr Simecek, Nicholas A Furlotte, Pjotr Prins, Śaunak Sen, Brian S Yandell, and Gary A Churchill. 2019. "R/Qtl2: Software for Mapping Quantitative Trait Loci with High-Dimensional Data and Multiparent Populations." *Genetics* 211 (2): 495–502.

Churchill, Gary A, and Rebecca W Doerge. 1994. "Empirical Threshold Values for Quantitative Trait Mapping." *Genetics* 138 (3): 963–71.

Crouse, Wesley. 2018. *TIMBR: Tree-Based Inference of Multiallelism via Bayesian Regression.*

Jansen, Ritsert C, Jean-Luc Jannink, and William D Beavis. 2003. "Mapping Quantitative Trait Loci in Plant Breeding Populations." *Crop Science* 43 (3): 829–34.