

Leveraging allelic series to enhance QTL detection

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Introduction

- We examined Mtb-related traits in both a Collaborative 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

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

- 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

- Infer QTL allelic series in CC mice
- Use CC QTL allelic series to inform QTL mapping in DO mice

Methods

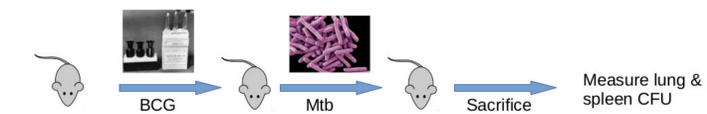


Figure 1: Experimental design in DO mice

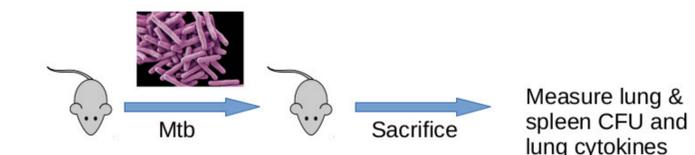
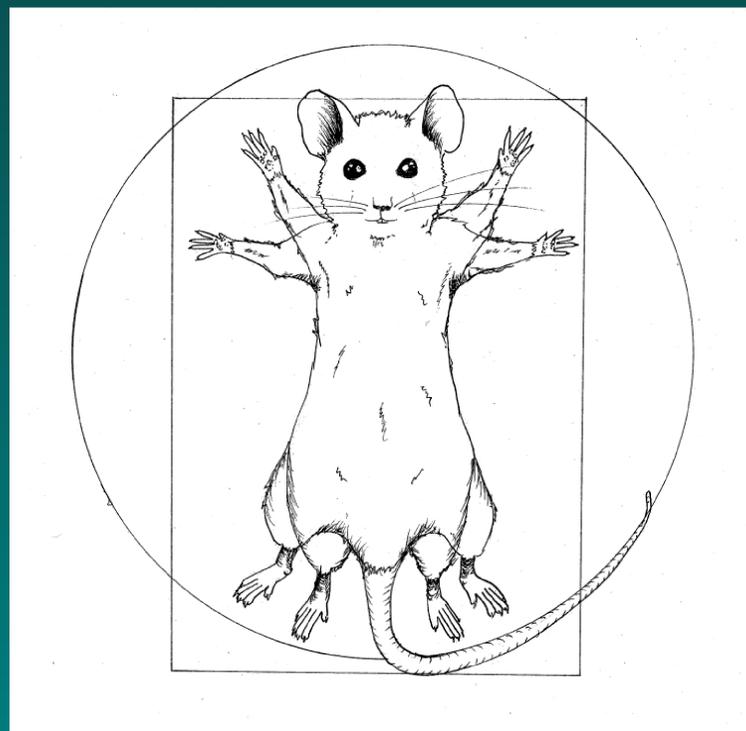


Figure 2: Experimental design in CC mice

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:
 - Set $p_0 = p_A + p_D + p_G + p_H$,
 $p_1 = p_B + p_C + p_F$,
 $p_2 = p_E$
 - Use model

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

in QTL scan

Results

- Traditional QTL mapping in CC identified 14 suggestive peaks
- For each CC QTL, we:
 - inferred allelic series
 - fitted reduced linear models (informed by allelic series) for QTL detection in DO
 - 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

- Determine DO QTL p-values with approximate permutation tests (Churchill and Doerge 1994)
- 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

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