Testing pleiotropy vs. separate QTL in multiparental populations

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Abstract

- High-dimensional phenotypes in multiparental populations provide new opportunities for understanding complex trait architecture
- New analysis tools are required
- We developed a test of pleiotropy vs. separate QTL for multiparental populations
- We applied it to find evidence for separate QTL for behavioral phenotypes in a 3 cM region in 261 Diversity Outbred mice
- We share our methods in an R package, `qtl2pleio` <https://github.com/fboehm/qtl2pleio>

Introduction

- Experimentalists can now measure tens of thousands of phenotypes with RNA sequencing and mass spectrometry
- Multiparental populations enable high-resolution QTL mapping
- Together, high-dimensional phenotypes and multiparental populations can inform complex trait genetics
- New analysis tools, such as our test of pleiotropy vs. separate QTL, are needed

Background

- Jiang and Zeng (1995) developed a pleiotropy vs. separate QTL test for two-parent crosses
  - Applies to two traits that map to a single genomic region
  - Pleiotropy is the null hypothesis
  - Separate QTL is the alternative hypothesis
  - Perform a two-dimensional QTL scan
  - Calculate likelihood ratio test statistic

Challenges

- Relatedness: *Multivariate polygenic random effects*
- Eight founder lines: *8 fixed effects*
- Test statistic calibration: *Parametric bootstrap test*

Test procedure

- Fit the model:

$$Y = XB + G + E$$

for each ordered pair of markers

- $$G \sim MN(0, K, V_g)$$
- $$E \sim MN(0, I, V_e)$$
- X contains allele probabilities
- B contains allele effects
- Calculate likelihood for each model fit
- Test statistic:

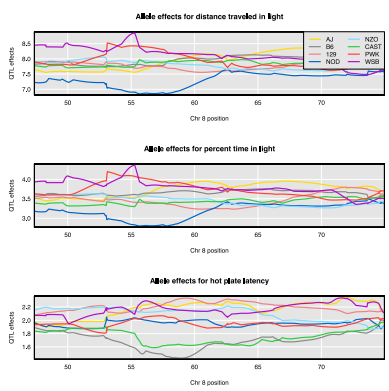
$$-\log_{10} \frac{\max L_0(B, \Sigma, \omega_1)}{\max L_A(B, \Sigma, \omega_1, \omega_2)}$$

- Parametric bootstrap to get p-value

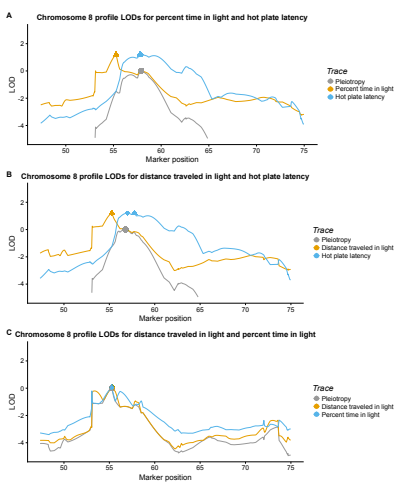
Behavioral genetics

- Logan et al. (2013) and Recla et al. (2014) genotyped and phenotyped 261 Diversity Outbred mice
  - Identified *Hydin* as the chromosome 8 gene affecting "hot plate latency" at 57 cM
  - Identified chromosome 8 QTLs for "percent time in light" and "distance traveled in light" at 55 cM
  - Motivated us to ask if *Hydin* also affects "percent time in light" and "distance traveled in light"

Allele effects plots



Profile LOD plots for pairwise



3 pairwise tests

- "percent time in light" & "hot plate latency": p = 0.109
- "distance traveled in light" & "hot plate latency": p = 0.108
- "percent time in light" & "distance traveled in light": p = 0.871

Conclusions

- Evidence for two separate QTL affecting the 3 traits
  - 1 QTL affects both "distance traveled in light" and "percent time in light"
  - Second QTL contains *Hydin* and affects "hot plate latency"

Future directions

- Examine expression data from Keller et al. (2018)
  - Expression QTL hotspot dissection
  - Statistical power studies

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References

Jiang, Changjian, and Zhao-Bang Zeng. 1995. "Multiple Trait Analysis of Genetic Mapping for Quantitative Trait Loci." *Genetics* 140 (3). Genetics Soc America: 1111–27.

Keller, Mark P, Daniel M Gatti, Kathryn L Schueler, Mary E Rabaglia, Donnie S Stapleton, Petr Simecek, Matthew Vincent, et al. 2018. "Genetic Drivers of Pancreatic Islet Function." *Genetics*. Genetics Soc America, genetics–300864.

Logan, Ryan W, Raymond F Robledo, Jill M Recla, Vivek M Philip, Jason A Bubier, Jeremy J Jay, Carter Harwood, et al. 2013. "High-Precision Genetic Mapping of Behavioral Traits in the Diversity Outbred Mouse Population." *Genes, Brain and Behavior* 12 (4). Wiley Online Library: 424–37.

Recla, Jill M, Raymond F Robledo, Daniel M Gatti, Carol J Bult, Gary A Churchill, and Elissa J Chesler. 2014. "Precise Genetic Mapping and Integrative Bioinformatics in Diversity Outbred Mice Reveals Hydin as a Novel Pain Gene." *Mammalian Genome* 25 (5-6). Springer: 211–22.