Testing pleiotropy vs. separate QTL in multiparental populations

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Introduction

- RNA sequencing and mass spectrometry enable measurement of thousands of phenotypes
- Multiparental populations enable high-resolution QTL mapping
- Together, they 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
  - Null hypothesis: pleiotropy
  - Alternative: presence of two separate QTL
  - 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*

Procedure

- Fit for each marker pair:

$$vec(Y) = Xvec(B) + vec(G) + vec(E)$$

-

$$G \sim MN(0, K, V_g)$$

-

$$E \sim MN(0, I, V_e)$$

  - X contains allele probabilities
  - B contains allele effects
- Calculate likelihood for each model fit
- Test statistic:

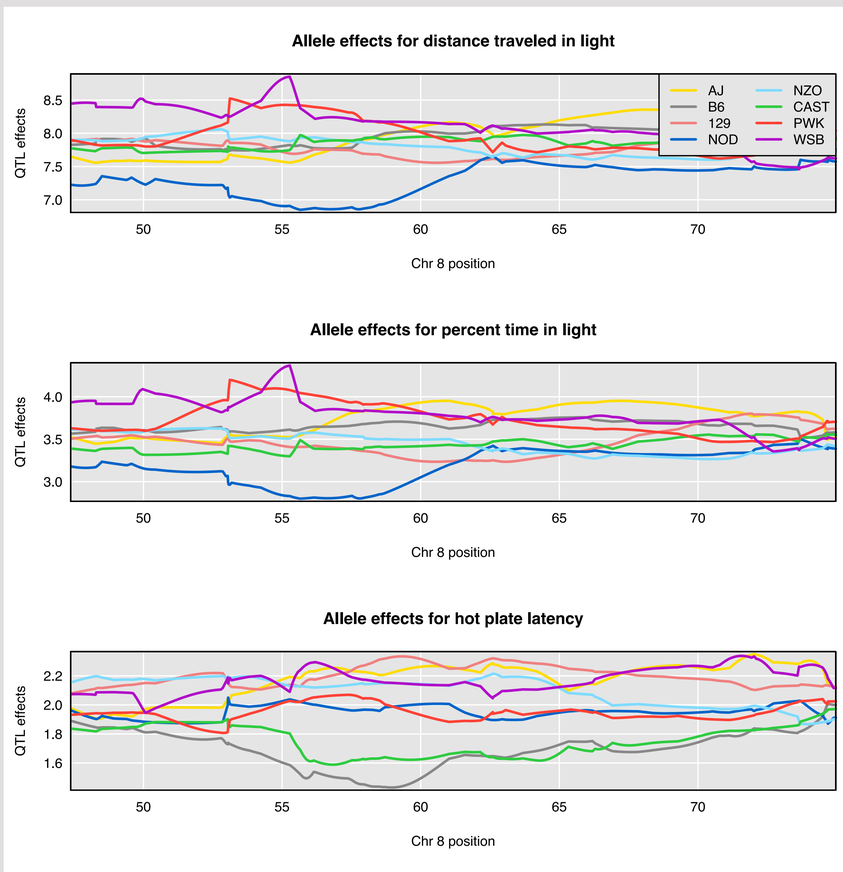
$$-\log_{10} \frac{\max L_0(B, \Sigma, \omega_1)}{\max L_A(B, \Sigma, \omega_1, \omega_2)}$$

- Parametric bootstrap to get p-value

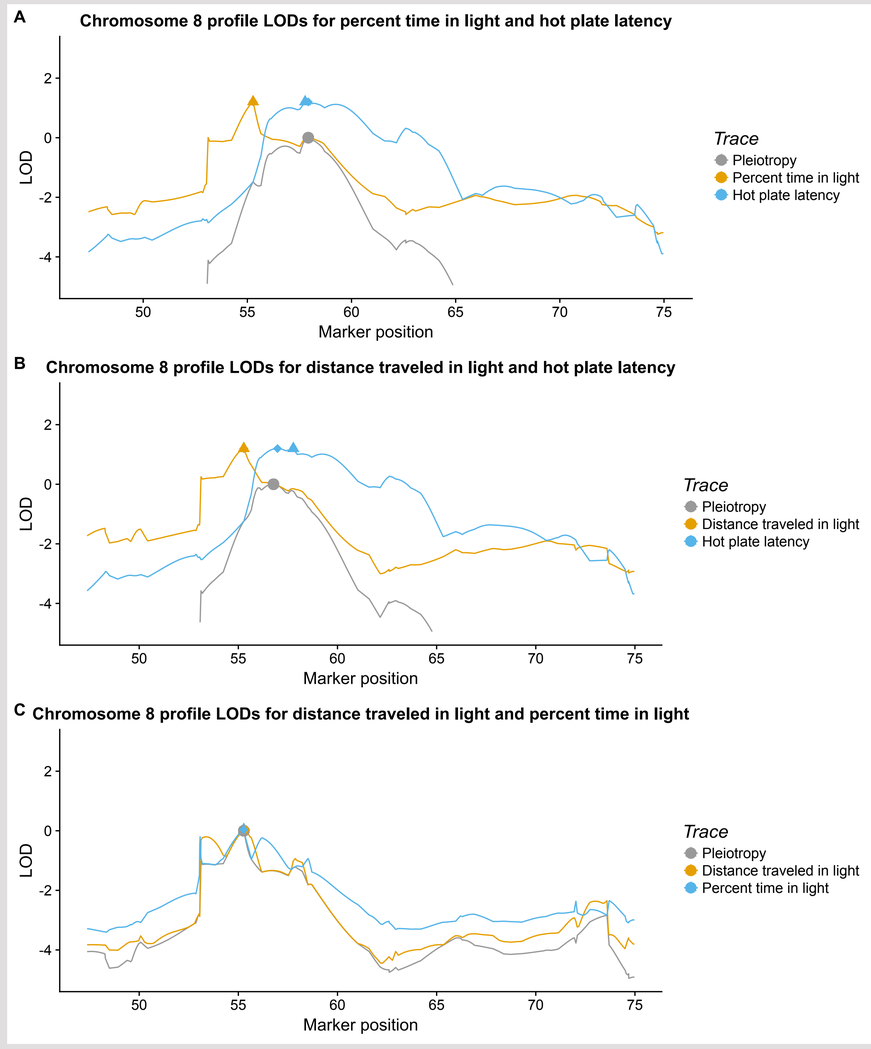
Behavioral genetics

- Logan et al. (2013) and Recla et al. (2014) examined 261 Diversity Outbred mice
  - Identified *Hydin* as the Chr 8 gene affecting "hot plate latency" at 57 cM
  - Identified Chr 8 QTL for "percent time in light" and "distance traveled in light" at 55 cM
  - Does *Hydin* affect "percent time in light" and "distance traveled in light"?

Allele effects



Profile LODs



3 pairwise tests

Trait1	Trait2	pvalue
pct. time in light	hot plate latency	0.109
distance traveled	hot plate latency	0.108
pct. time in light	distance traveled	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)
  - 378 Diversity Outbred mice
  - Expression QTL hotspot dissection
  - Statistical power studies
  - Comparisons with mediation analyses

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`qtl2pleio` R package: <https://github.com/fboehm/qtl2pleio>

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