Testing Pleiotropy vs. Separate QTL in Multiparental Populations

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Objectives

1. Develop a test of pleiotropy vs. separate QTL in multiparental populations
2. Apply the test to behavioral traits in Diversity Outbred mice
3. Share software as an R package, `qtl2pleio`

A mouse on microarray chips

Figure 1:https://bit.ly/2DIQxPN

Introduction

- Multiparental populations enable high-resolution QTL mapping of biomolecular and clinical traits to inform systems genetics
- To better understand complex traits, new analysis tools, such as a test of pleiotropy vs. separate QTL, are needed

Light-dark box

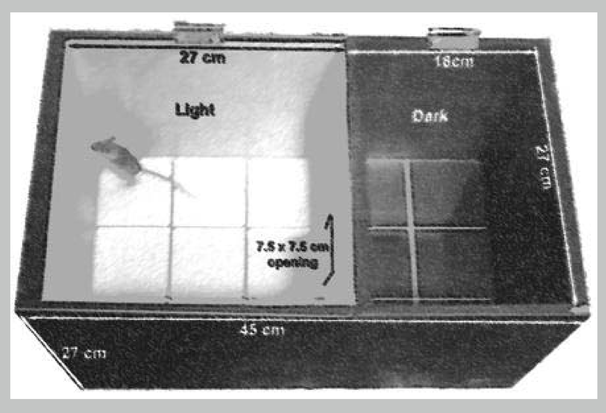

Figure 2:https://phenome.jax.org/projects/Brown1/Protocol

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"?

Founder allele effects plots

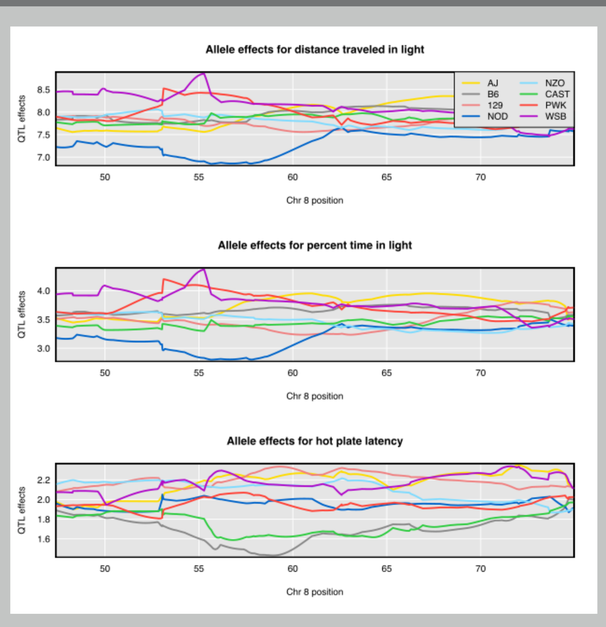

Figure 3:Founder allele effects for three traits (Macdonald & Long, 2007)

Jiang & Zeng (1995) test

- Jiang & Zeng (1995) developed a pleiotropy vs. separate QTL test for two-parent crosses
  - H_0: pleiotropy vs. H_A: two separate QTL
  - Perform a two-dimensional QTL scan
  - Calculate likelihood ratio test statistic

Test development challenges

1. Relatedness: *multivariate polygenic random effects*
2. Eight founder lines: *8 fixed effects*
3. Test statistic calibration: *Parametric bootstrap test*

Linear mixed effects model

$$Y = XB + G + E \tag{1}$$

$$G \sim N(\mathbf{0}, V_g \otimes K), \quad E \sim N(\mathbf{0}, V_e \otimes I), \quad \text{independent} \tag{2}$$

Profile LOD traces

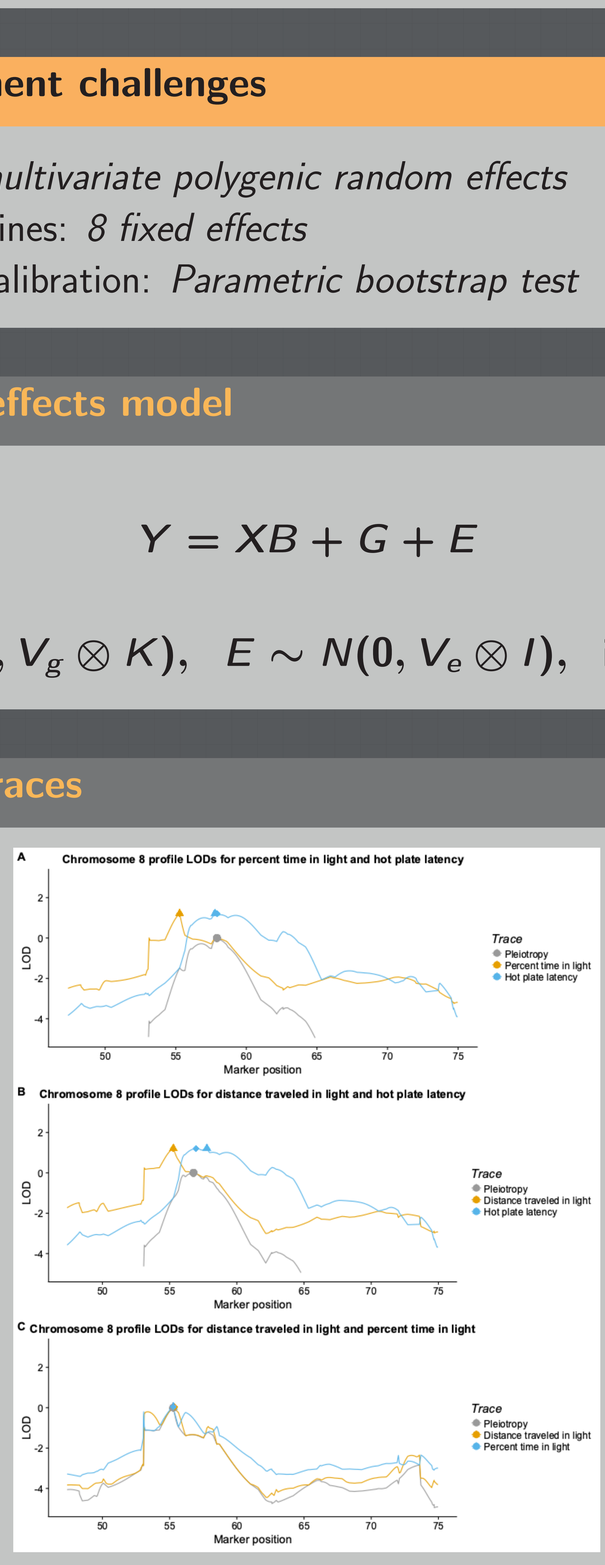

Figure 4:Bootstrap p-values: 0.109, 0.108, 0.871

Conclusions

- *Hydin* doesn't affect the light-dark box traits
- A second QTL affects both light-dark box traits

References

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Macdonald, S. J., & Long, A. D. (2007). Joint estimates of qtl effect and frequency using synthetic recombinant populations of drosophila melanogaster. *Genetics*.

Recla, J. M., Robledo, R. F., Gatti, D. M., Bult, C. J., Churchill, G. A., & Chesler, E. J. (2014). Precise genetic mapping and integrative bioinformatics in diversity outbred mice reveals hydin as a novel pain gene. *Mammalian genome*, *25*(5-6), 211–222.

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Contact Information

- Fred Boehm
- R package on Github: https://github.com/fboehm/qtl2pleio
- Analysis R code on Github: https://github.com/fboehm/qtl2pleio-manuscript
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