

Testing pleiotropy in multiparental populations

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Introduction

- 10,000+ traits with RNA sequencing and mass spectrometry
- Multiparental populations offer high-resolution QTL mapping
- New analysis tools, such as a pleiotropy test for multiparental populations, are needed

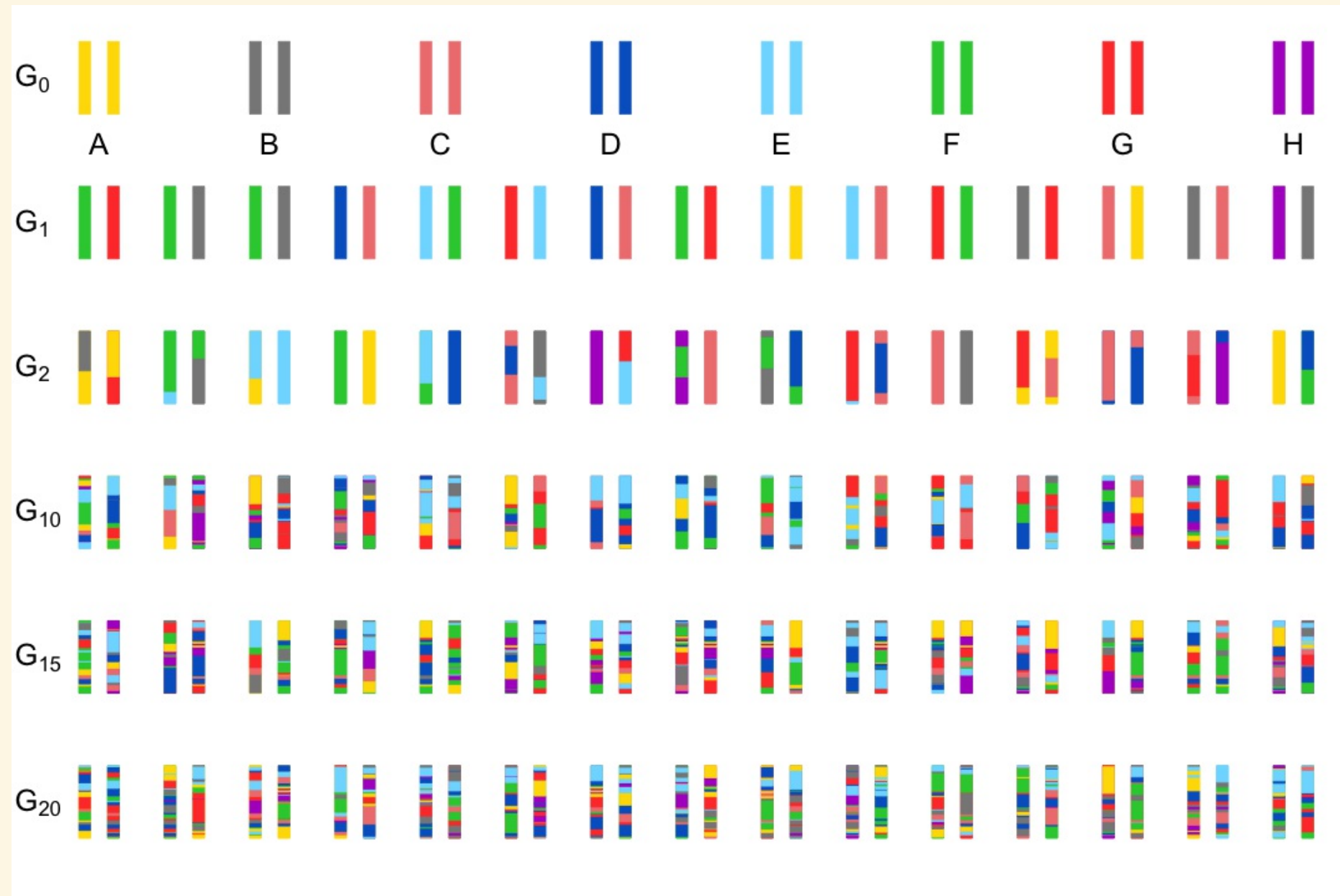
Jiang and Zeng (1995) test

- Two-parent crosses
- Applies to two traits that co-map
- $\backslash(H_0\backslash)$: Pleiotropy
- $\backslash(H_A\backslash)$: Two separate QTL

Jiang and Zeng (1995) test

- Perform a two-dimensional two-QTL scan
 - $\backslash (\text{vec}(Y) = X\text{vec}(B) + \text{vec}(E)) \backslash$
 - Calculate likelihood at each ordered pair of positions
- Calculate likelihood ratio test statistic

Multiparental populations



Challenges in multiparental populations

- Complex patterns of relatedness

Multivariate random effects

- Multiple founder lines

Fixed effect for each founder allele

Test procedure

- Perform a two-dimensional two-QTL scan
 - $\backslash (\text{vec}(Y) = X\text{vec}(B) + \text{vec}(G) + \text{vec}(E)) \backslash$
 - Calculate likelihood at each ordered pair of positions
- Calculate likelihood ratio test statistic

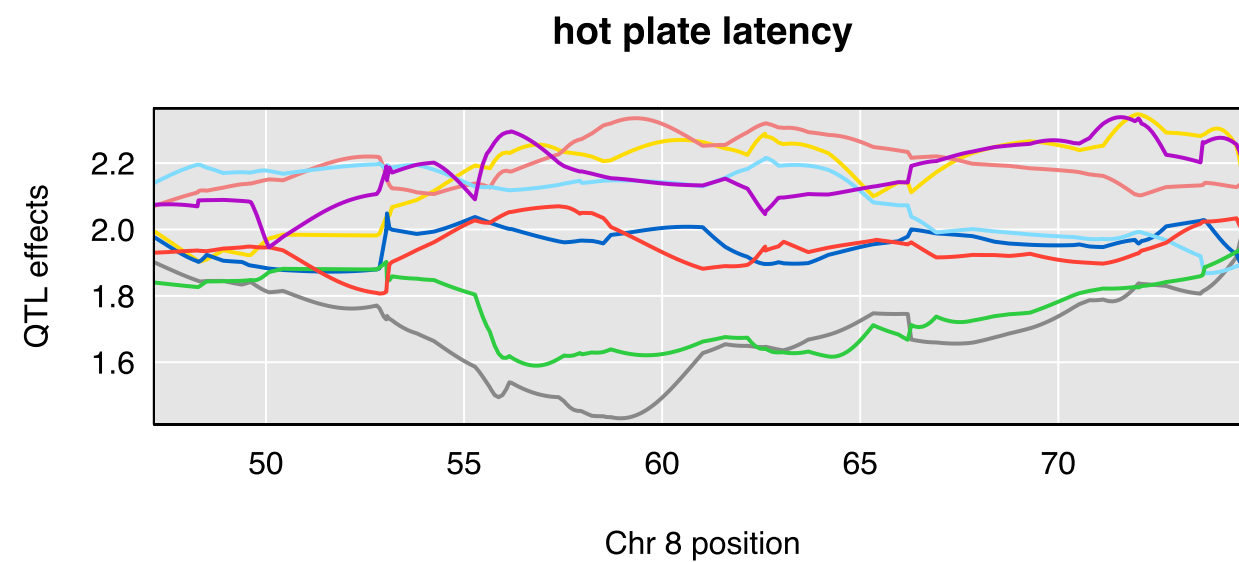
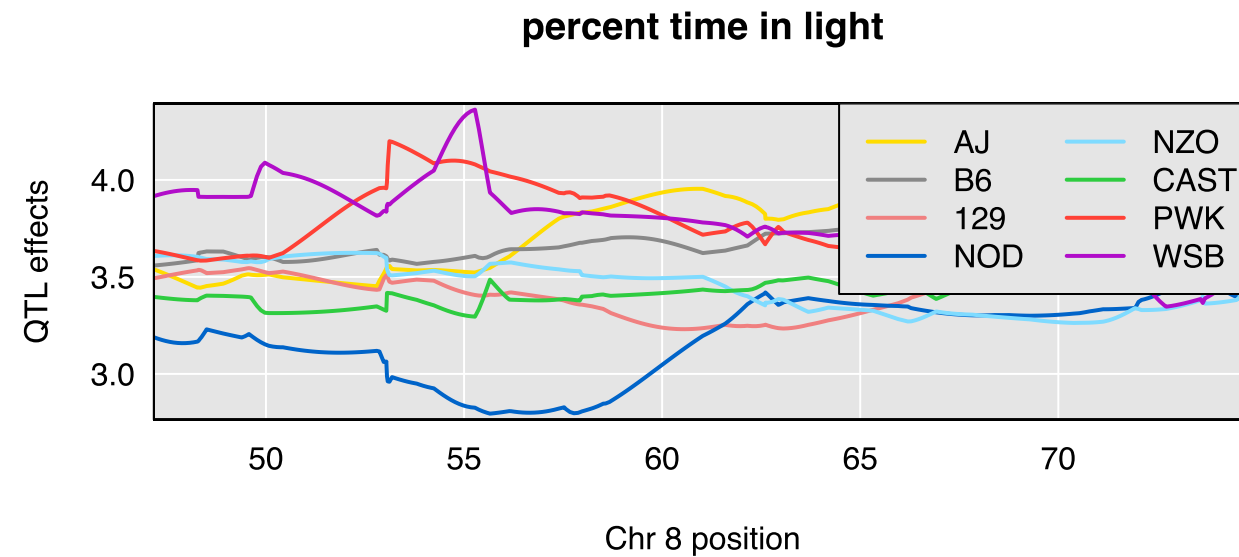
Test procedure

- Test statistic: $-\log_{10} \frac{\max(\text{likelihood under pleiotropy})}{\max(\text{likelihood for separate QTL})}$
- Parametric bootstrap to get a (p) -value

Application

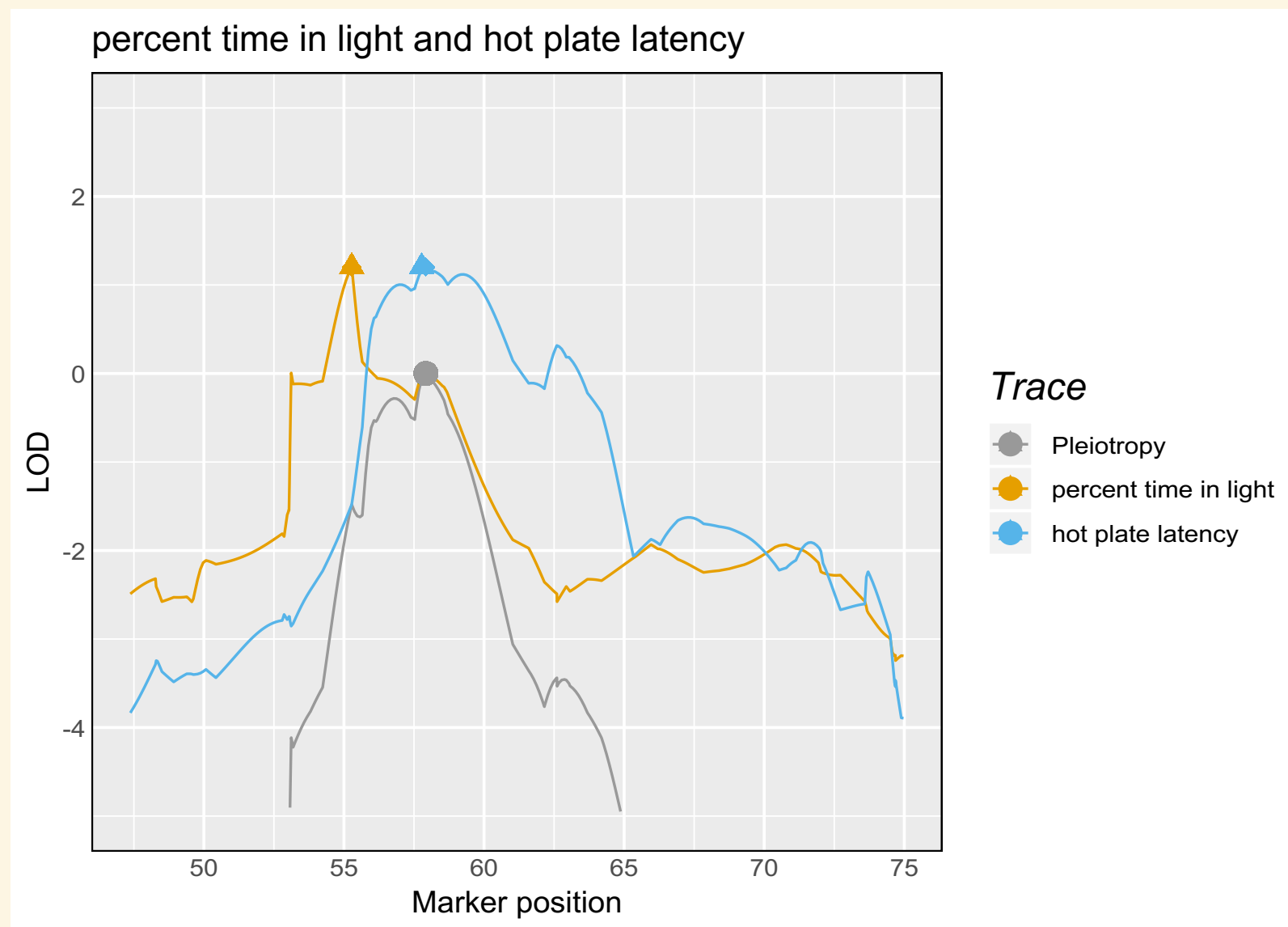
- Logan, et al. (2013) and Recla, et al. (2014) studied 261 Diversity Outbred mice
- Measured about two dozen behavioral traits
- Two traits map to Chr 8:
 - "hot plate latency" (57 cM)
 - "percent time in light" (55 cM)

Allele effects plots



Profile LOD

$$\text{profile LOD}_{\text{trait 1}}(\lambda_1) = \max_{\lambda_2} \text{LOD}(\lambda_1, \lambda_2)$$



Test results

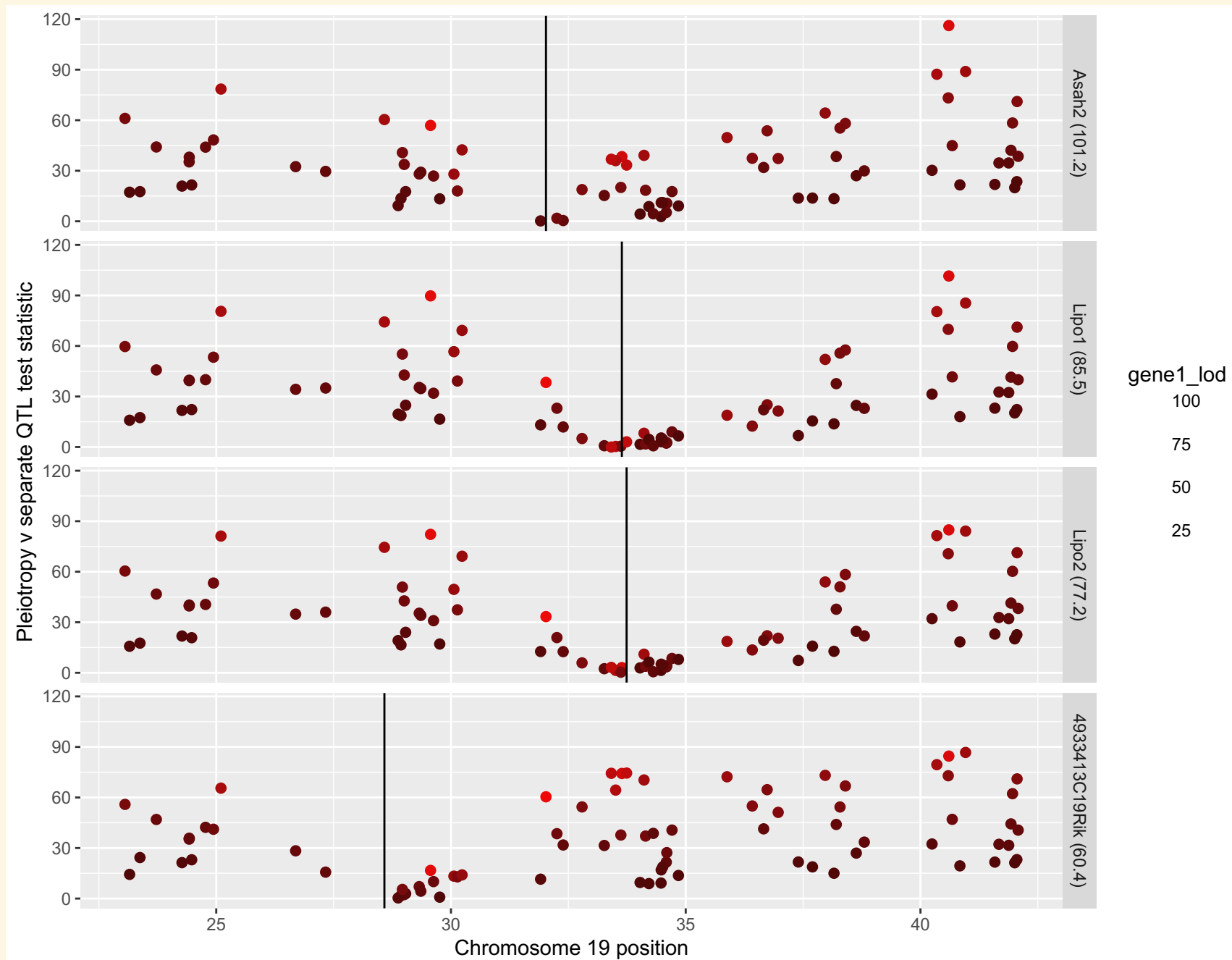
- $(\log_{10} \Lambda = 1.2)$
- $(p = 0.11)$ (1000 bootstrap samples)

Power study with local expression QTL

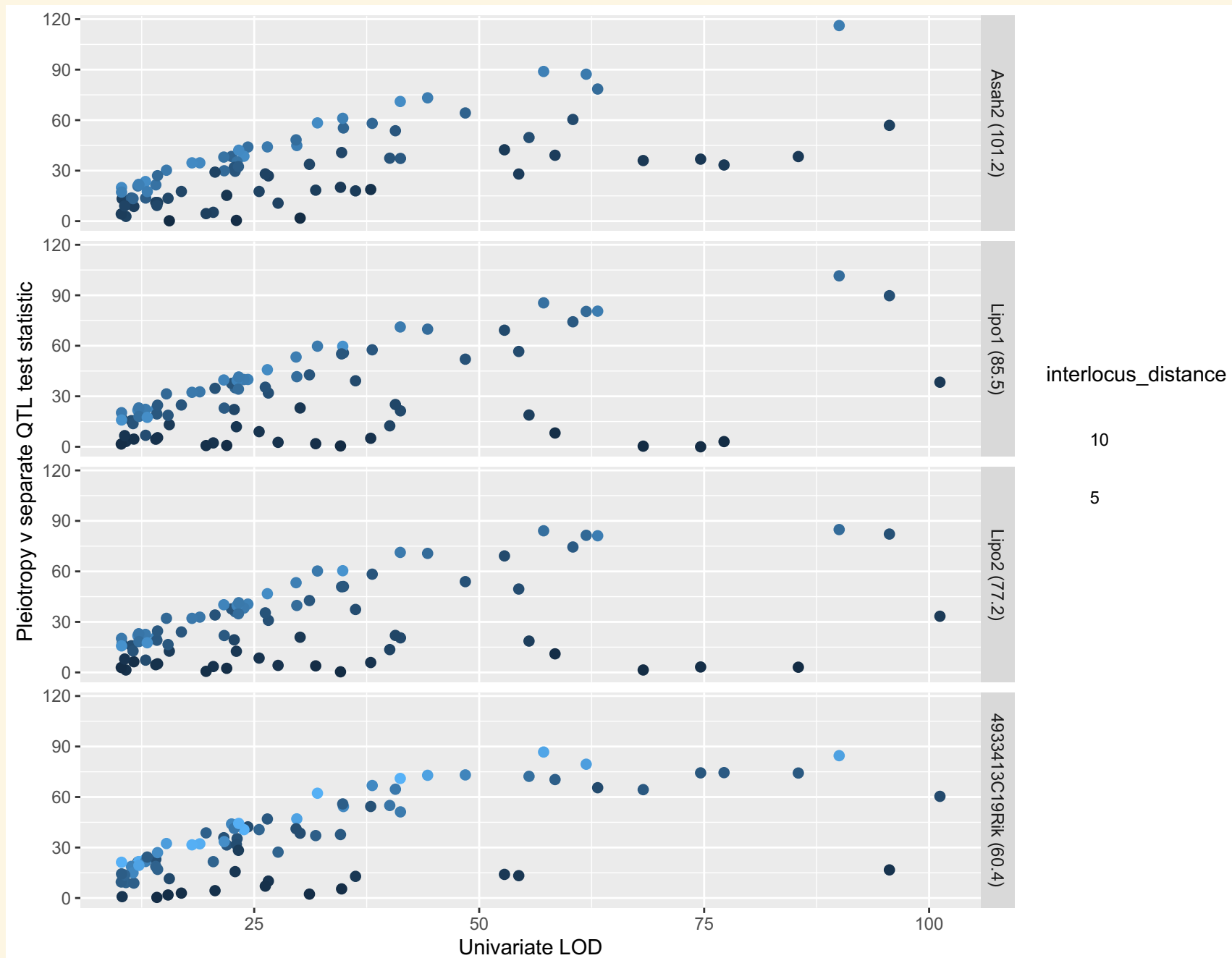
Power study: Design

- Examine power when I know true eQTL locations
 - Interlocus distance
 - Univariate LOD
- 80 local eQTL on Chr 19 ($\text{LOD} > 7.2$)
- 4 strong, centrally located, local eQTL chosen as "anchor" traits
 - *Asah2*, *Lipo1*, *Lipo2*, *4933413C19Rik*
- Pairwise pleiotropy tests each involving one anchor and one of 79 other traits

Power study: Interlocus distance



Power study: Univariate LOD



Power study: Conclusions

- \uparrow Interlocus distance \rightarrow \uparrow Pleiotropy test statistics
- \uparrow Univariate LOD \rightarrow \uparrow Pleiotropy test statistics

qtl2pleio R package

qtl2pleio R package

- Functions for (d) -variate, (d) -QTL scan & profile LOD plots
- Uses C++ for matrix calculations (via Rcpp and RcppEigen)
- Uses [gemma2](#) R implementation of GEMMA EM algorithm for multivariate random effects
- Unit tests, vignettes, and version control

Thank you!

References

Jiang, C. and Z. Zeng (1995). "Multiple trait analysis of genetic mapping for quantitative trait loci." In: *Genetics* 140.3, pp. 1111-1127.

Logan, R. W, R. F. Robledo, et al. (2013). "High-precision genetic mapping of behavioral traits in the diversity outbred mouse population". In: *Genes, Brain and Behavior* 12.4, pp. 424-437.

Recla, J. M, R. F. Robledo, et al. (2014). "Precise genetic mapping and integrative bioinformatics in Diversity Outbred mice reveals Hydin as a novel pain gene". In: *Mammalian genome* 25.5-6, pp. 211-222.