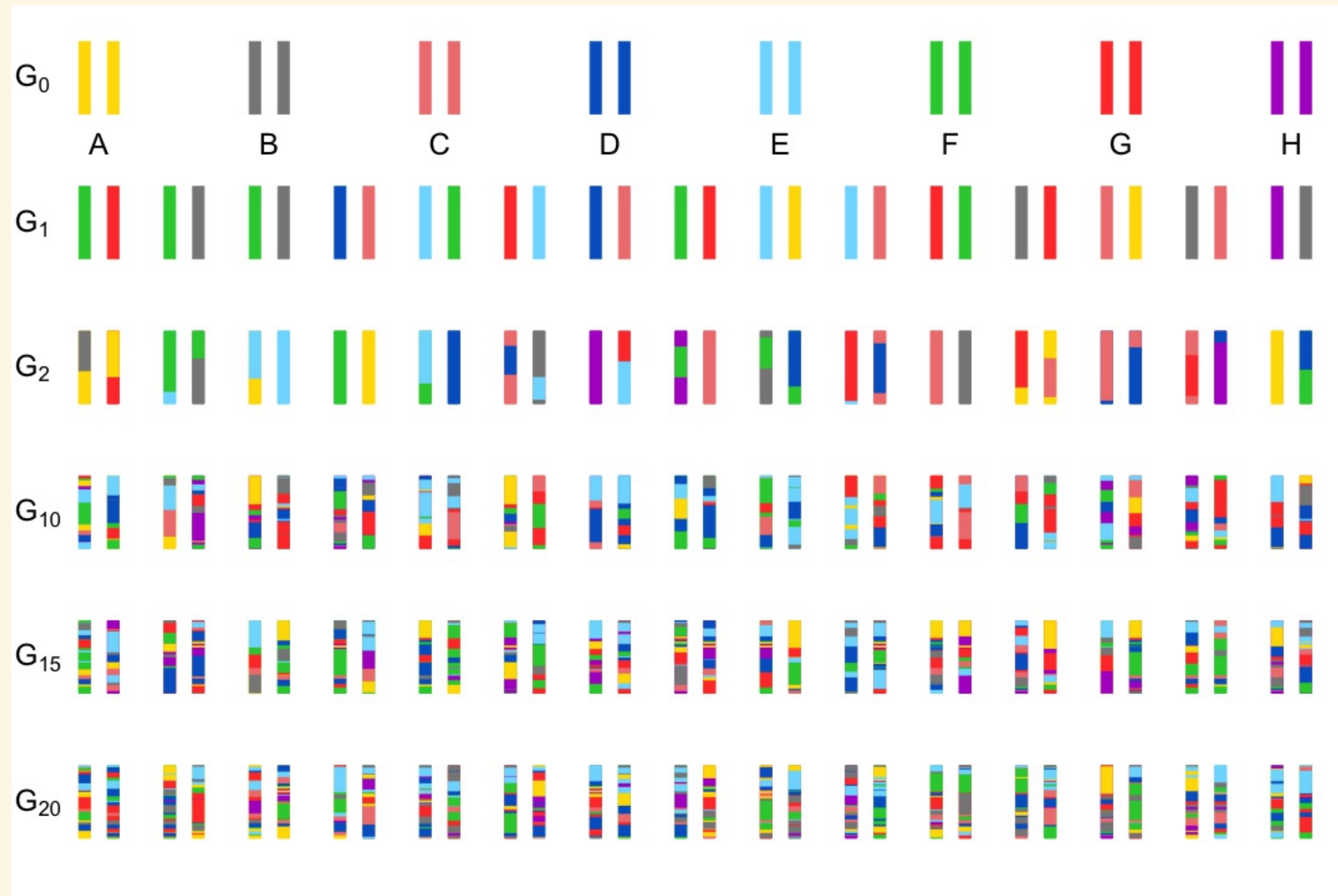# Testing pleiotropy in multiparental populations

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Multiparental populations

Background

- 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

Photo by Alan Attie

Benefits of a new pleiotropy test

- Insights into genetic architecture

- Tool for expression trait hotspot dissection

- Complements mediation analysis

Jiang and Zeng (1995) test

- Two-parent crosses

- Applies to two traits that co-map

- H_0 : Pleiotropy

- H_A : Two separate QTL

Jiang and Zeng (1995) test

- Perform a two-dimensional two-QTL scan

  - $$\mathrm{vec}(Y) = X\mathrm{vec}(B) + \mathrm{vec}(E)$$

  - Calculate likelihood at each ordered pair of positions

- Calculate likelihood ratio test statistic

Challenges in multiparental populations

- Complex patterns of relatedness

Multivariate random effects

- Multiple founder lines

Fixed effect for each founder allele

Photo by UNC Computational Genetics

Test procedure

- Perform a two-dimensional two-QTL scan

  - $\text{vec}(Y) = X\text{vec}(B) + \text{vec}(G) + \text{vec}(E)$

  - Calculate likelihood at each ordered pair of positions

- Calculate likelihood ratio test statistic

Test procedure

- Test statistic:

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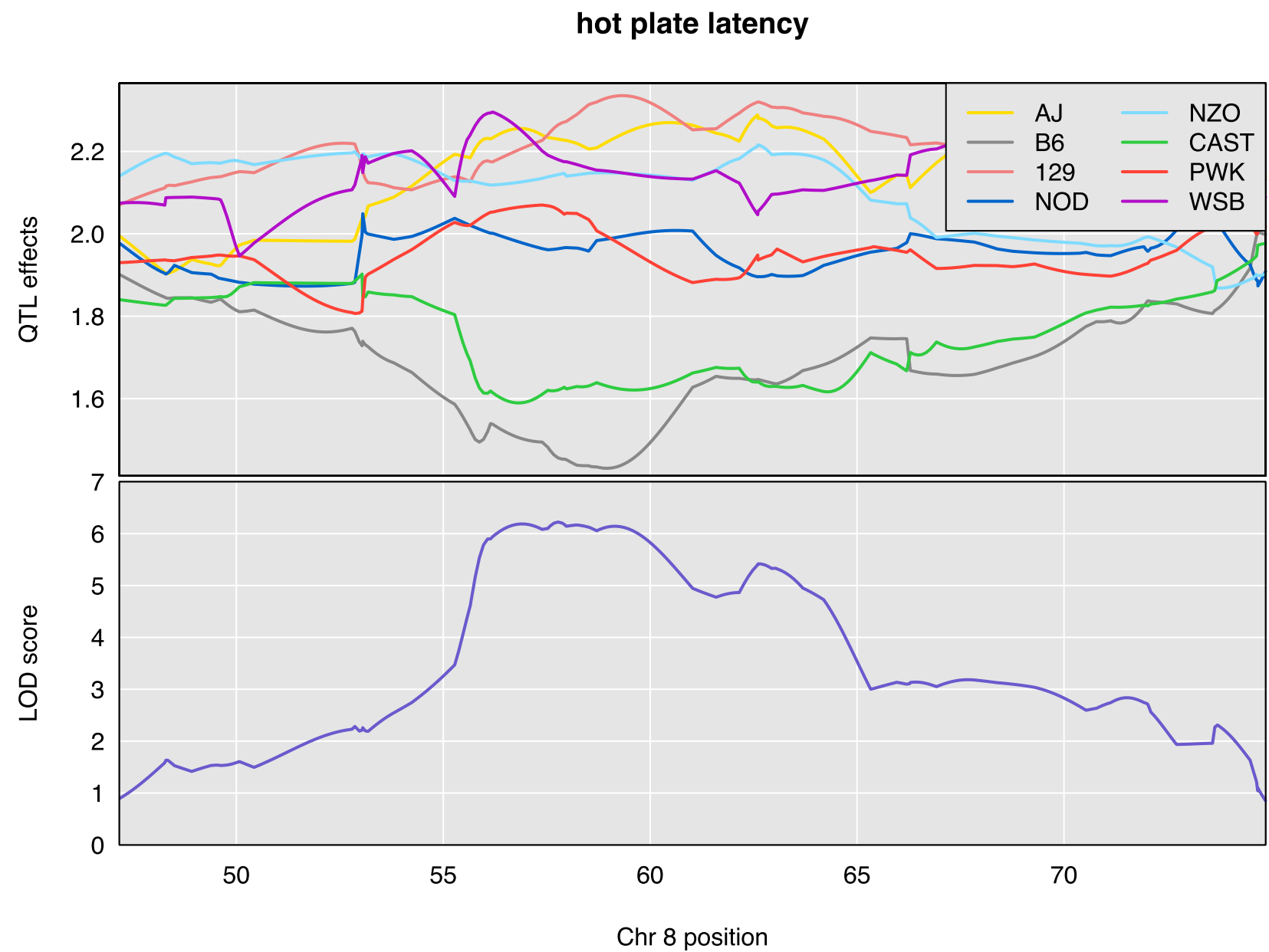
- Parametric bootstrap to get a p-value

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)

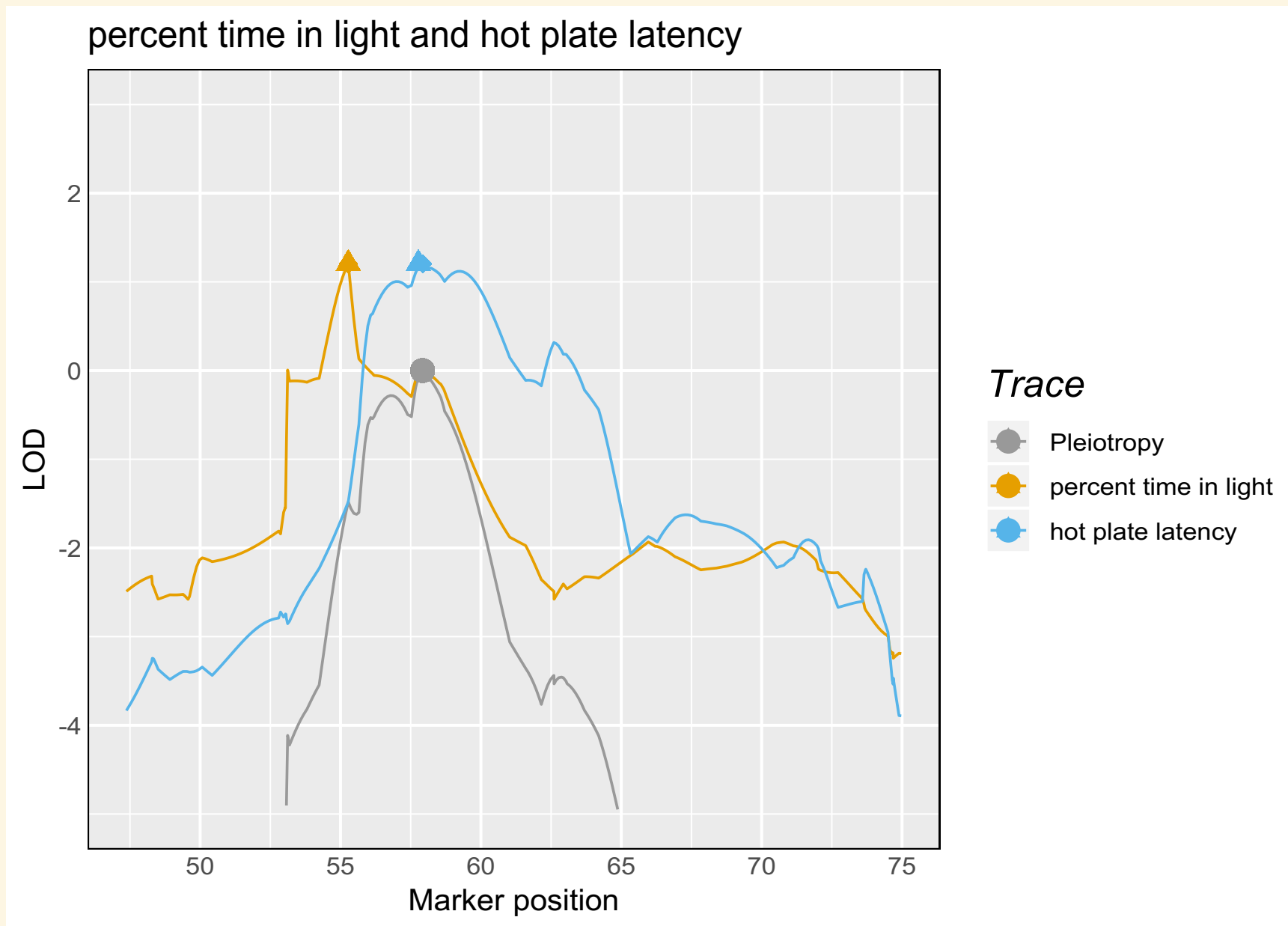 - "percent time in light" (55 cM)

Percent time in light

percent time in light
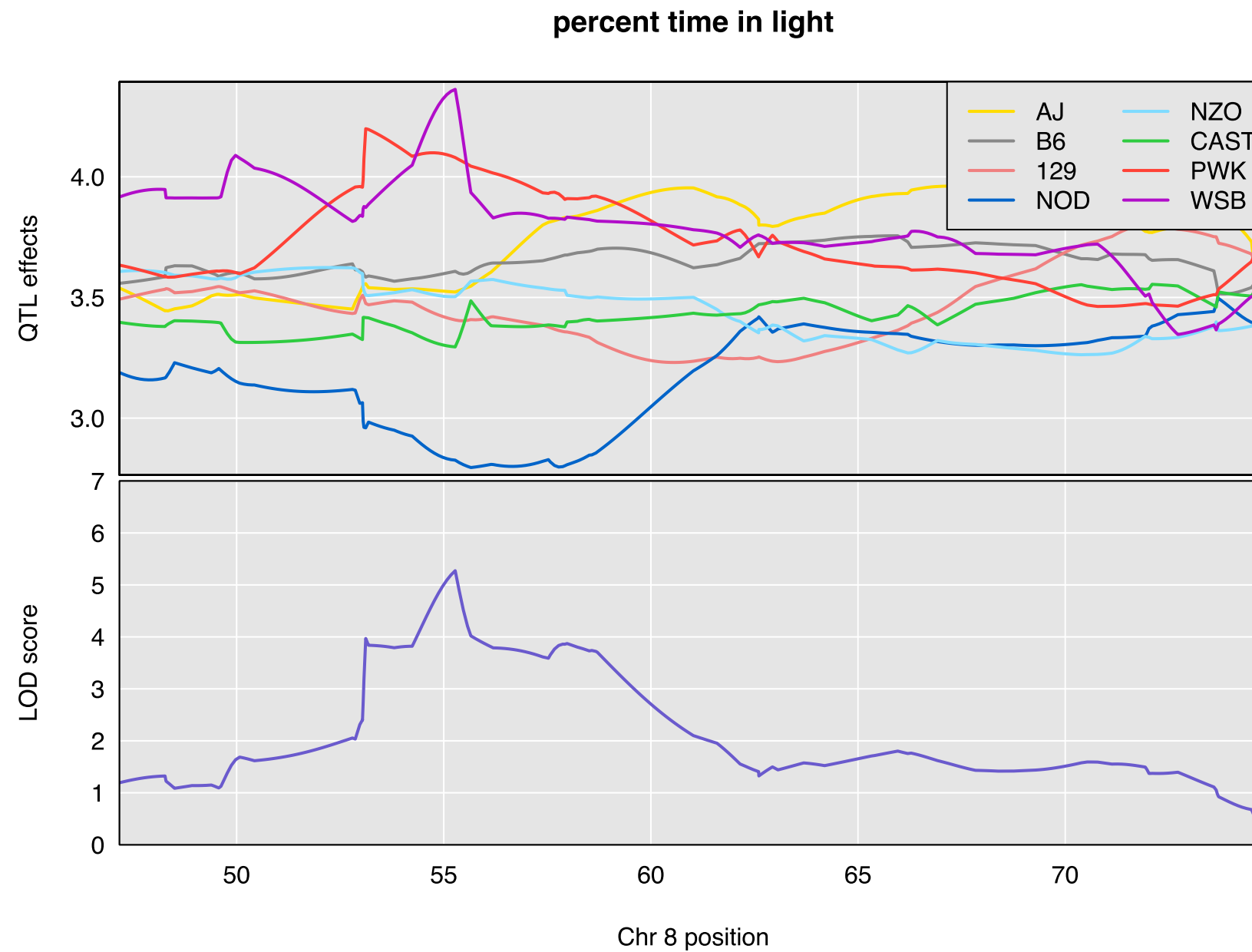
Hot plate latency

LOD definitions

- $$\text{LOD}(\lambda_1, \lambda_2) = \text{ll}_{10}(\lambda_1, \lambda_2) - \max_{\lambda} \text{ll}_{10}(\lambda, \lambda)$$

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

- $$\text{LOD}_{\text{p}}(\lambda) = \text{ll}_{10}(\lambda, \lambda) - \max_{\lambda} \text{ll}_{10}(\lambda, \lambda)$$

Profile LOD

percent time in light and hot plate latency

Trace
- Pleiotropy
- percent time in light
- hot plate latency

LOD (y-axis)
Marker position (x-axis)

Test results

- $\log_{10} \Lambda = 1.2$

- $p = 0.11$ (1000 bootstrap samples)

Power study with local expression QTL

Data

- Keller, et al. (2018) measured pancreatic islet gene expression levels in 378 Diversity Outbred mice

- 80 local expression QTL were identified in a 20-Mb region of Chr 19

  - local: expression trait QTL is near gene position

- Assume that a given local expression QTL doesn't affect other local expression traits
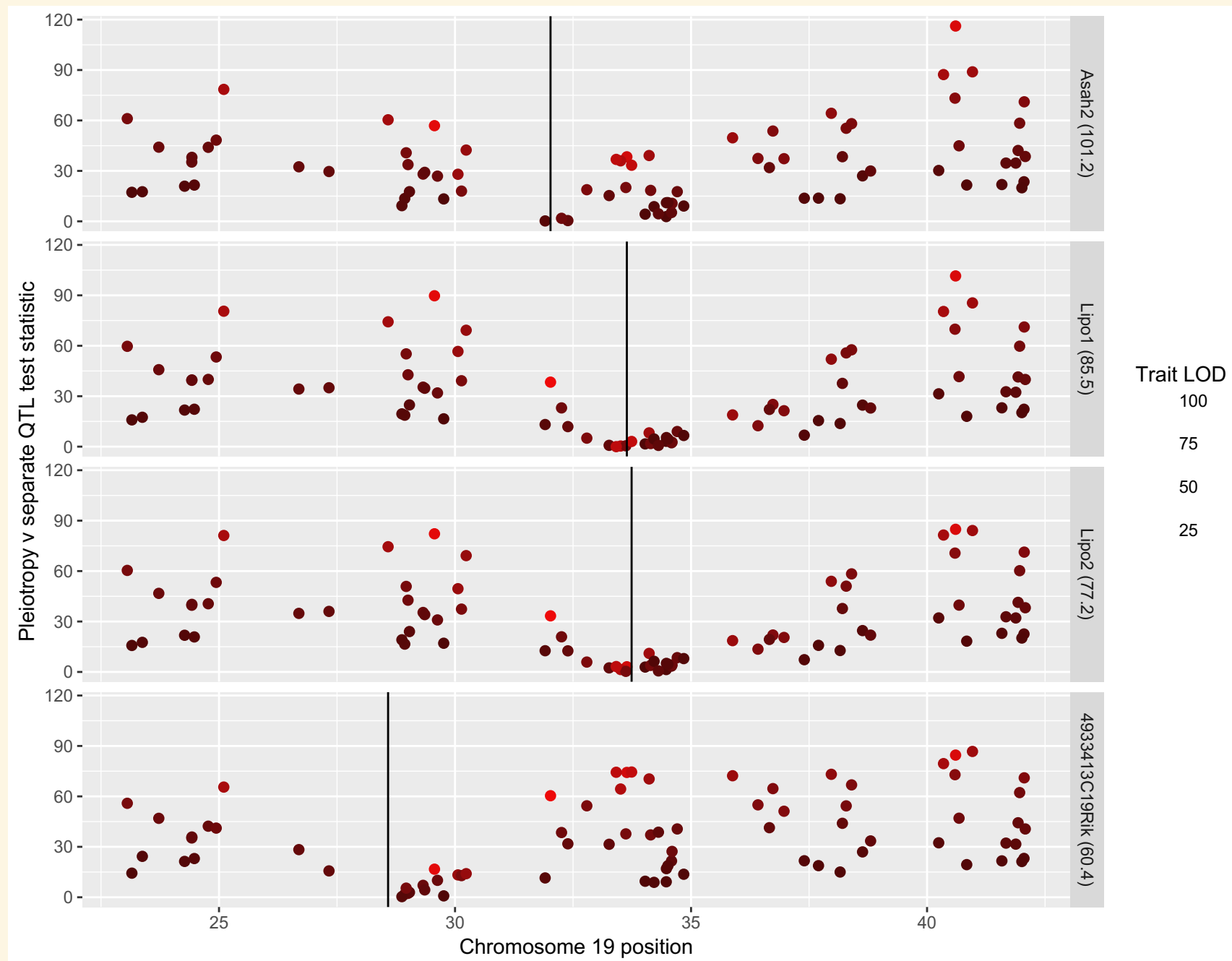
Design

- Examine power when expression trait QTL locations are known

  - Interlocus distance
  - Univariate LOD

- 4 strong, centrally located, local eQTL chosen as "anchor" traits

  - *Asah2, Lipo1, Lipo2, 4933413C19Rik*

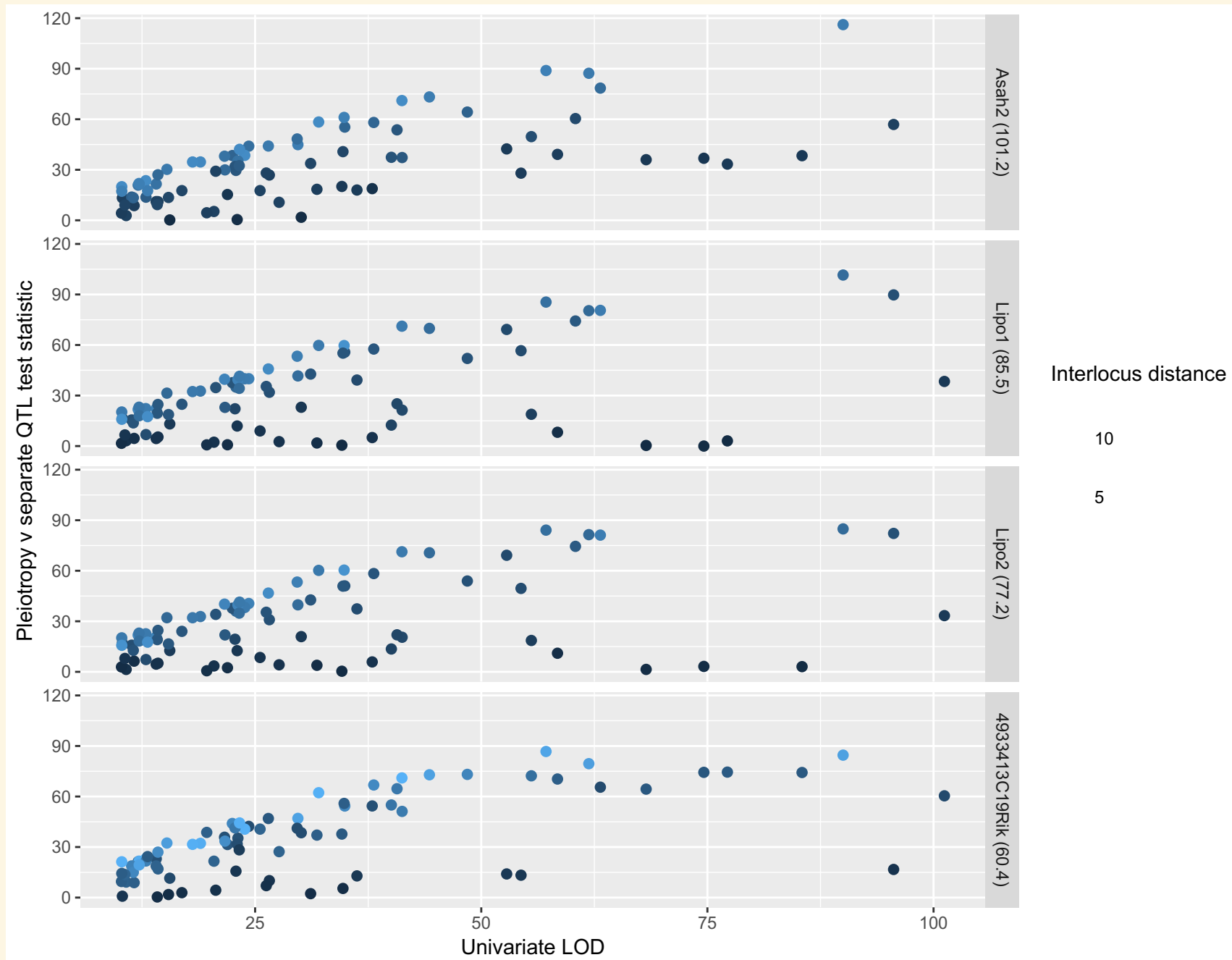- Pairwise pleiotropy tests each involving one anchor and one of 79 other traits

Interlocus distance
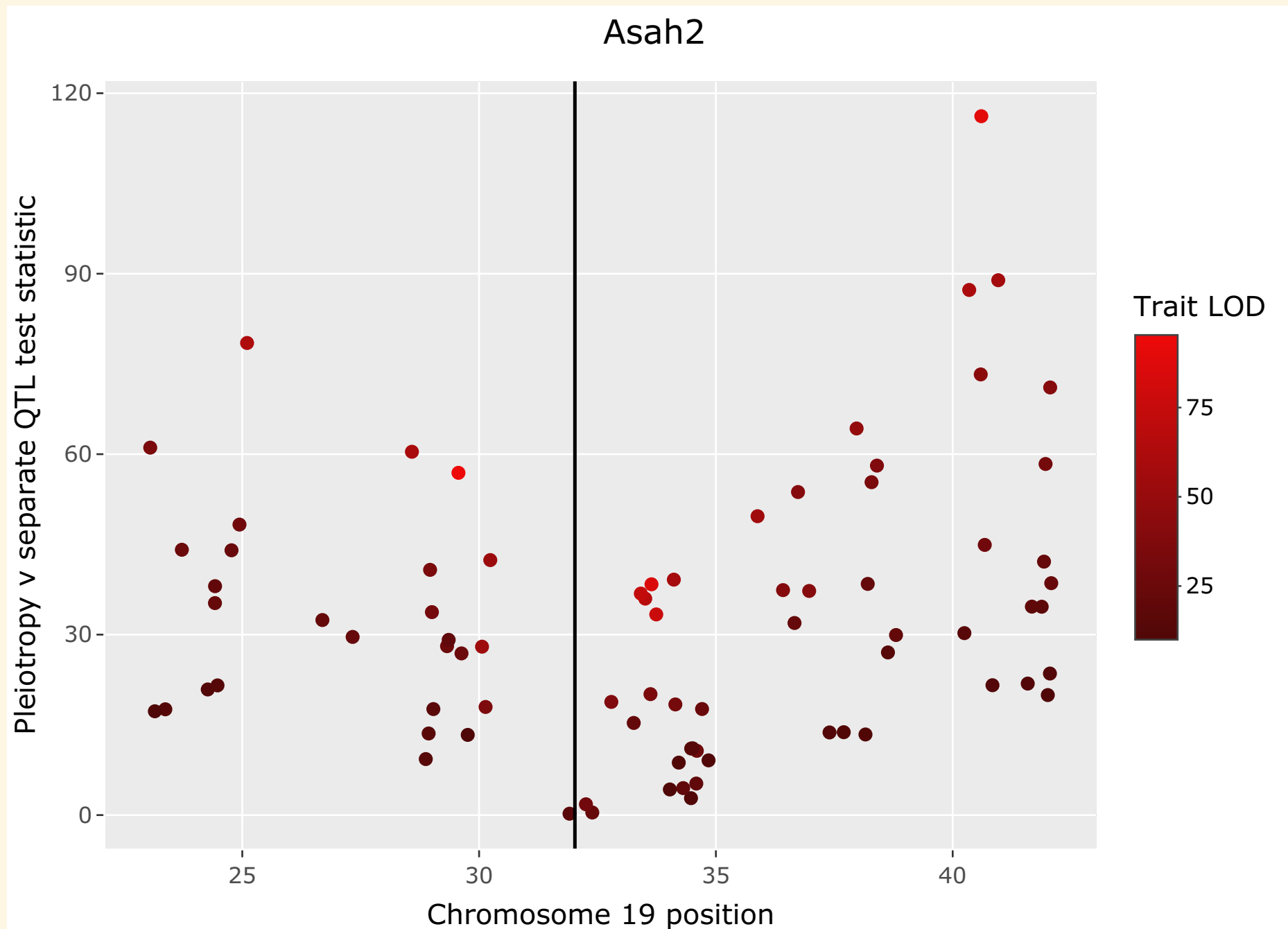
Interlocus distance

Univariate LOD

Conclusions

- ↑ Pleiotropy test statistics
  - ↑ Interlocus distance
  - ↑ Univariate LOD

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

Summary

1. Background
2. Methods
3. Applications
   a. Pleiotropy testing and mediation analysis
   b. Power in pleiotropy testing
   c. Microbiome case study
4. Software
5. Conclusions

References

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

Keller, M. P, D. M. Gatti, et al. (2018). "Genetic Drivers of Pancreatic Islet Function". In: *Genetics*, pp. genetics-300864.

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.