

# Testing pleiotropy in multiparental populations

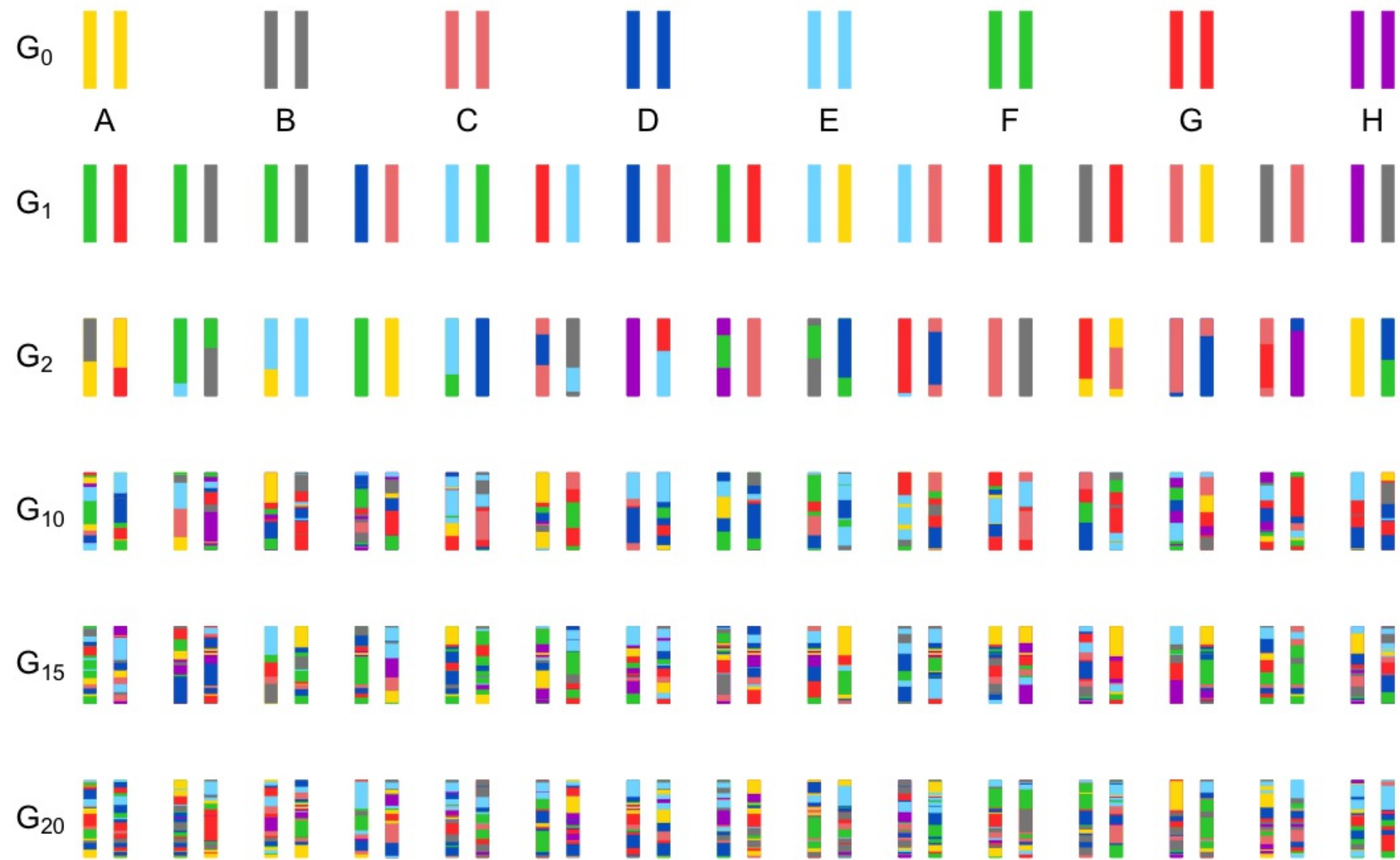
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# Introduction

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

# Multiparental populations



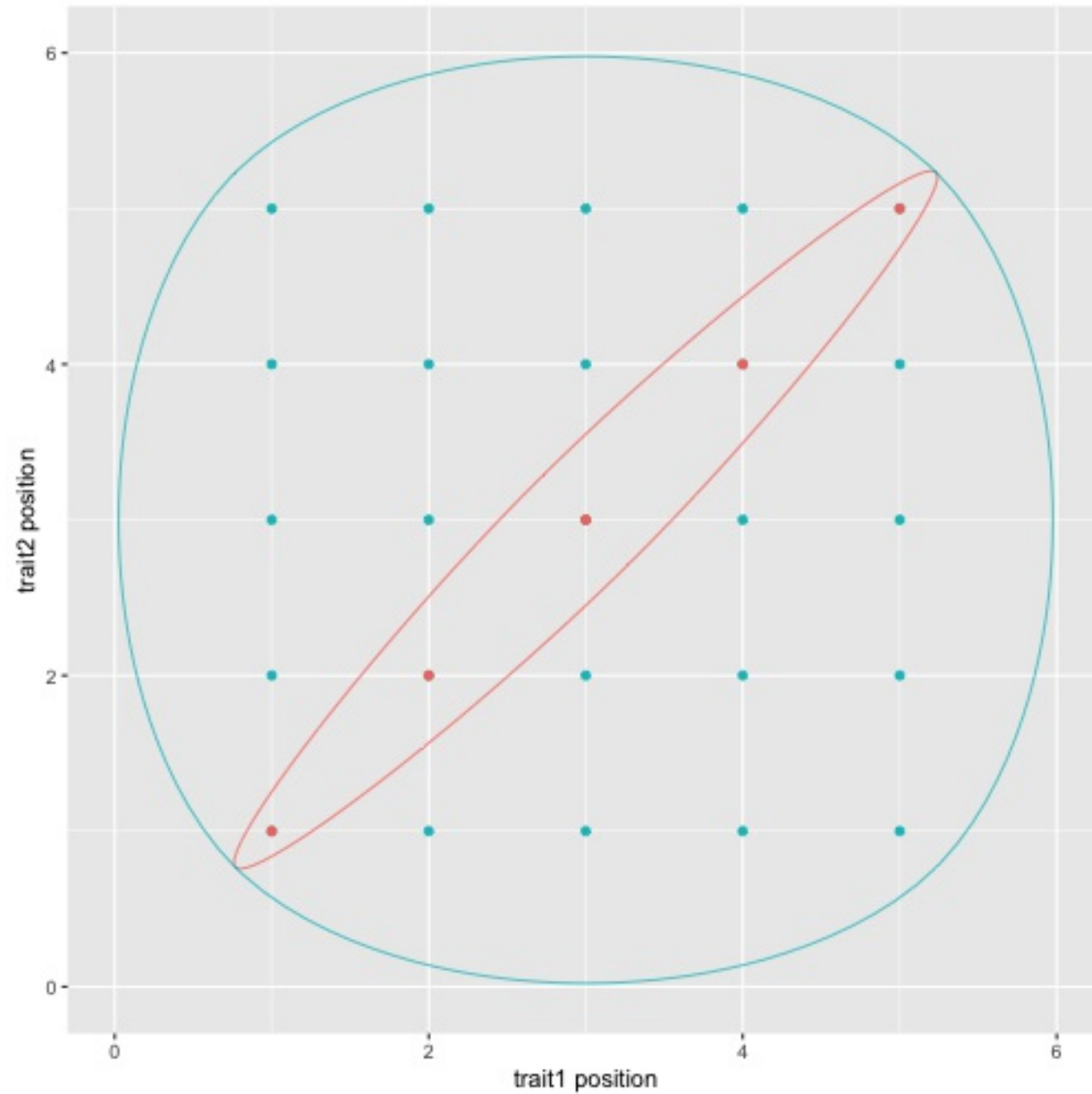
# Jiang and Zeng (1995) pleiotropy test

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

# Jiang and Zeng (1995) pleiotropy test

- Perform a two-dimensional QTL scan
- $Y = XB + E$
- Calculate likelihood ratio test statistic

# Jiang and Zeng (1995) pleiotropy test



# Challenges in multiparental populations

- Complex patterns of relatedness
- Multiple founder lines
- Determining statistical significance

# Solutions to challenges

- Complex patterns of relatedness

## *Multivariate random effects*

- Multiple founder lines

## *Fixed effect for each founder allele*

- Determining statistical significance

## *Parametric bootstrap*



# Test procedure

- Fit the model:

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

for each ordered pair of markers

- $G$ : Polygenic random effects
  - $E$ : Random errors
  - $X$  contains allele probabilities
  - $B$  contains allele effects
- Calculate likelihood for each ordered pair of markers

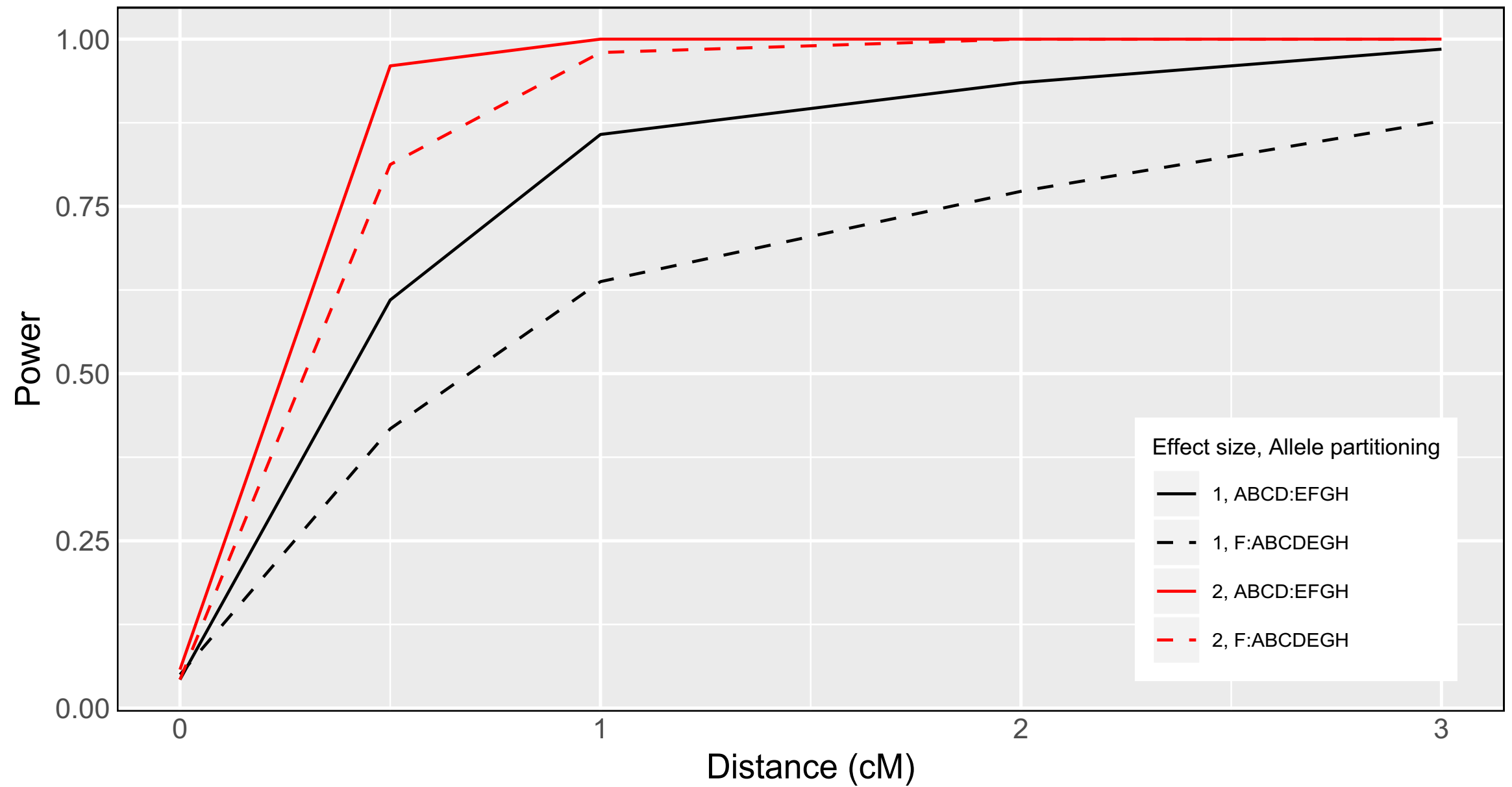
# Test procedure

- Test statistic:

$$-\log_{10} \frac{\text{max likelihood under pleiotropy}}{\text{max likelihood for separate QTL}}$$

- Parametric bootstrap to get p-value

# Test characteristics



# Diversity Outbred Mice

- Multiparental population arising from 8 inbred lines
  - 3 wild-derived founder lines
  - Complementary to Collaborative Cross

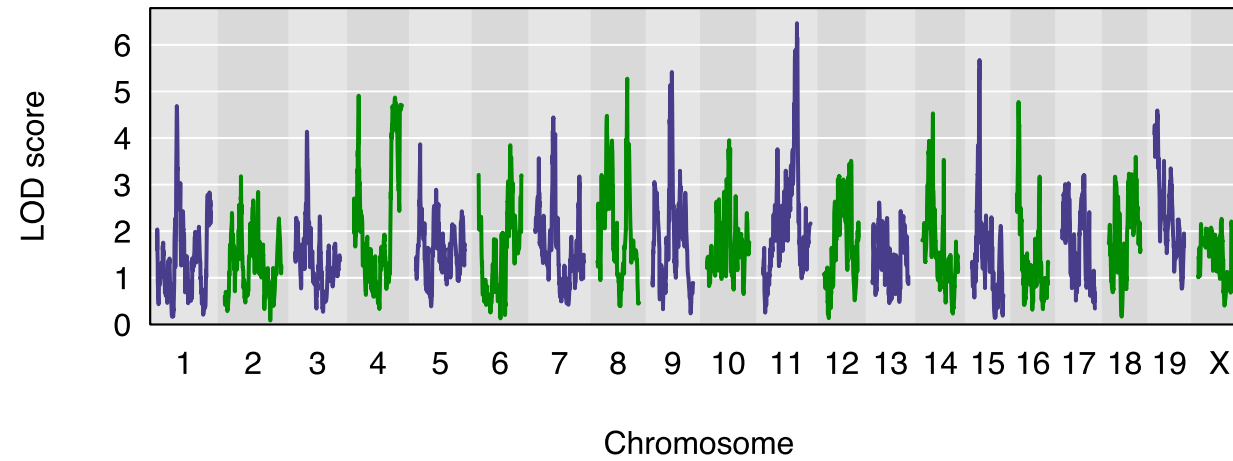


# Application

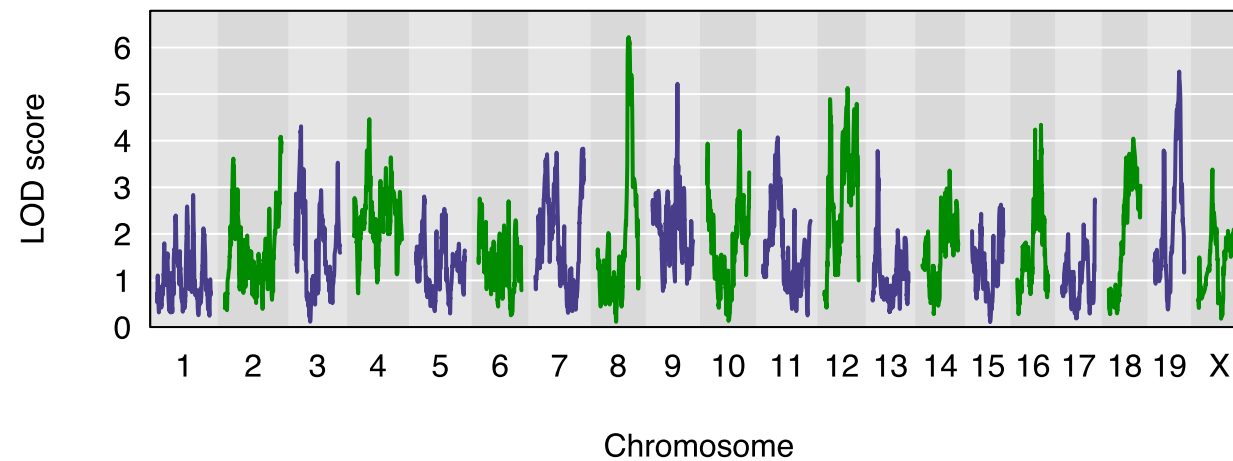
- Logan, et al. (2013) and Recla, et al. (2014) genotyped and phenotyped 261 Diversity Outbred mice
  - Identified *Hydin* as the Chromosome 8 gene affecting "hot plate latency" at 57 cM
  - Identified Chromosome 8 QTL for "percent time in light" at 55 cM
  - Motivated us to ask if the QTL containing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

# QTL scan results

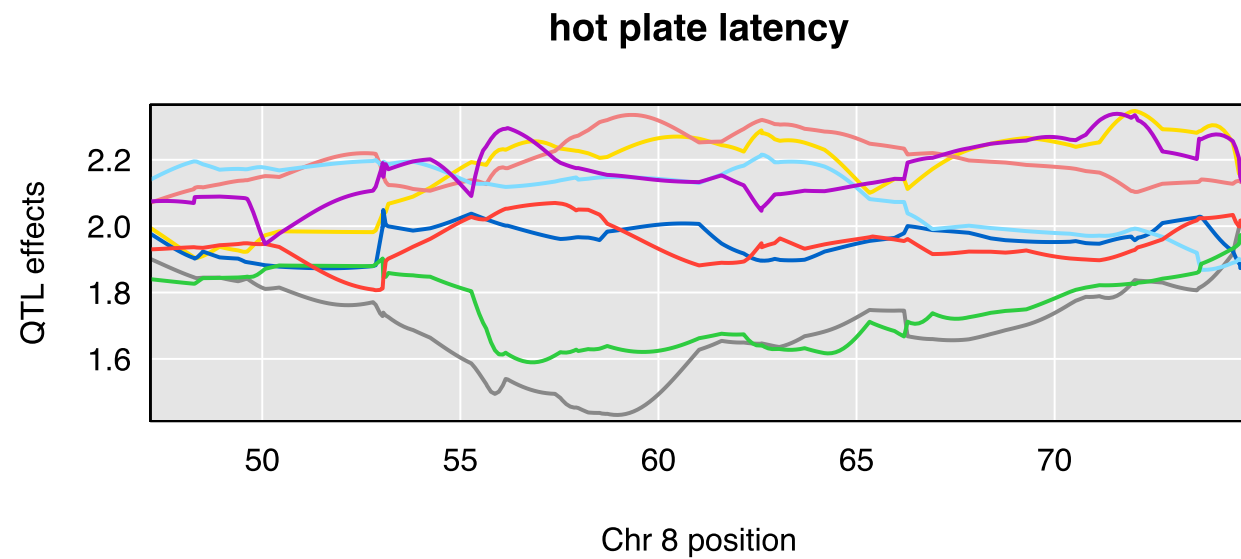
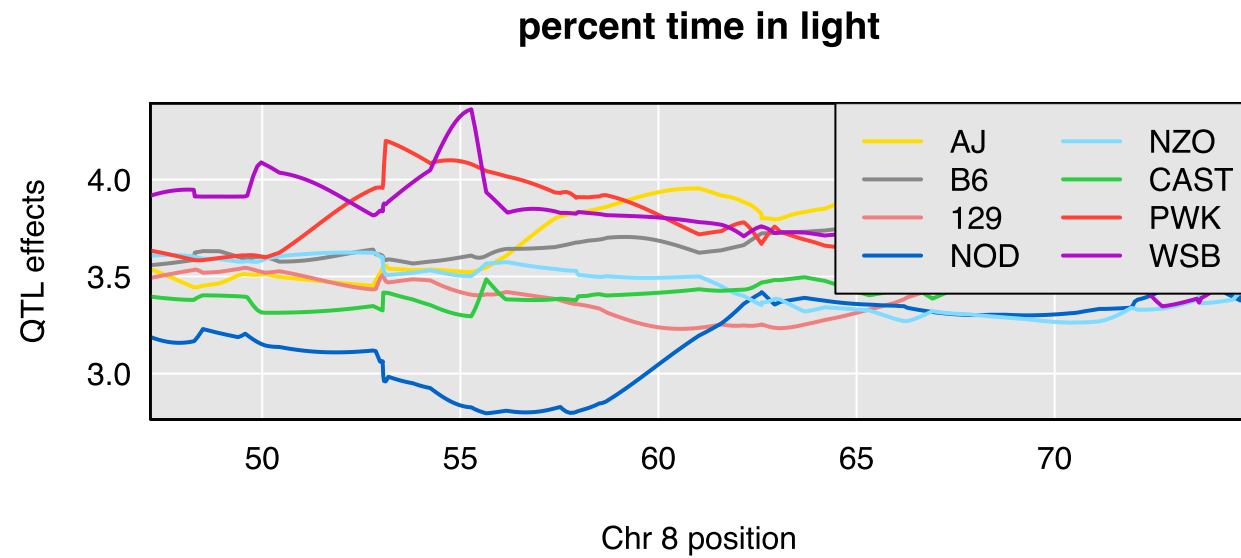
**percent time in light**



**hot plate latency**

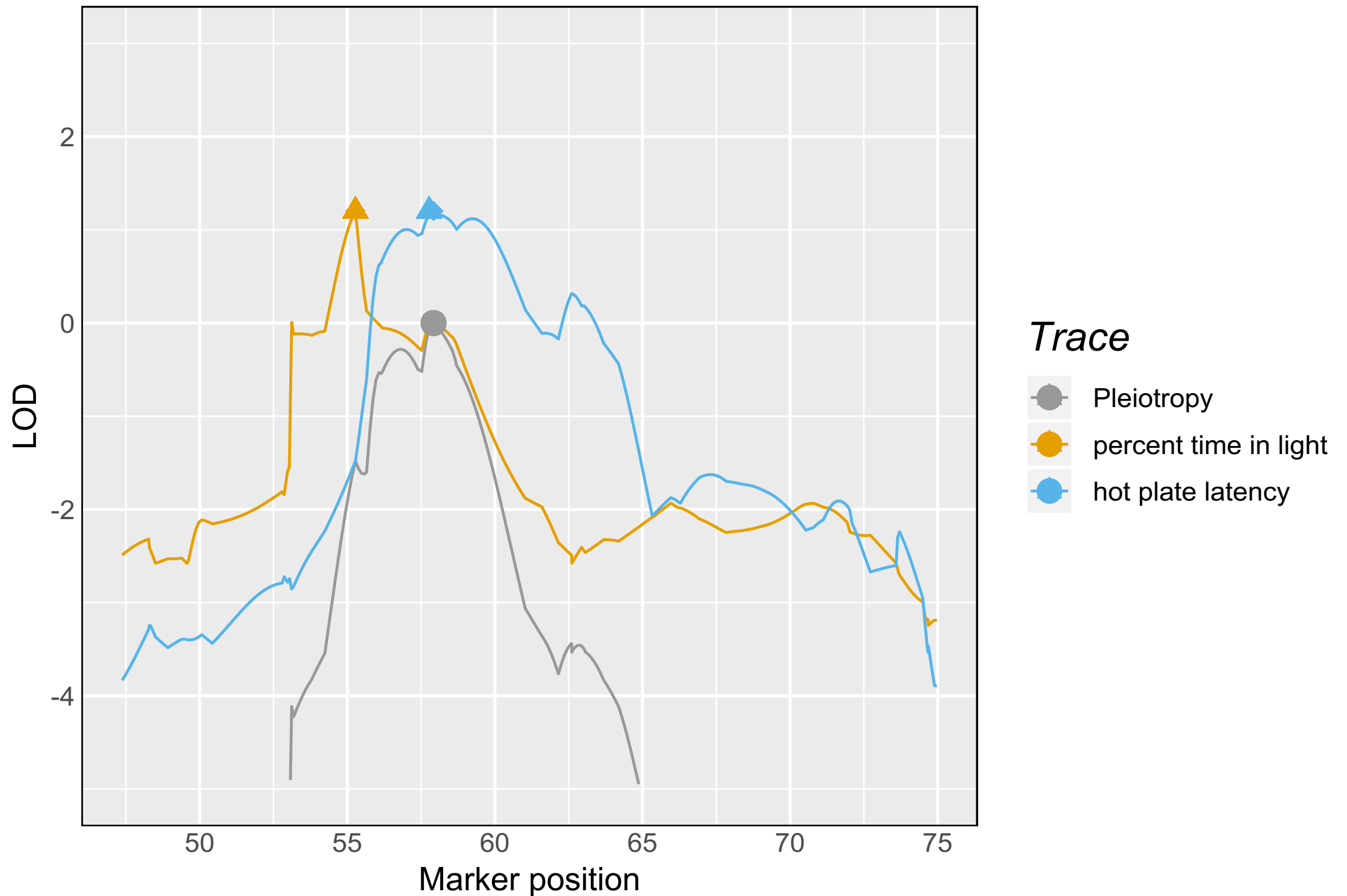


# Allele effects plots



# Profile LOD plot

percent time in light and hot plate latency





# Test results

- $p = 0.11$  (1000 bootstrap samples)

# Conclusions

- Weak evidence for two separate QTL affecting the two phenotypes
  - One QTL affects "distance traveled in light"
  - Second QTL contains *Hydin* and affects "hot plate latency"

qtl2pleio R package development

# Design elements

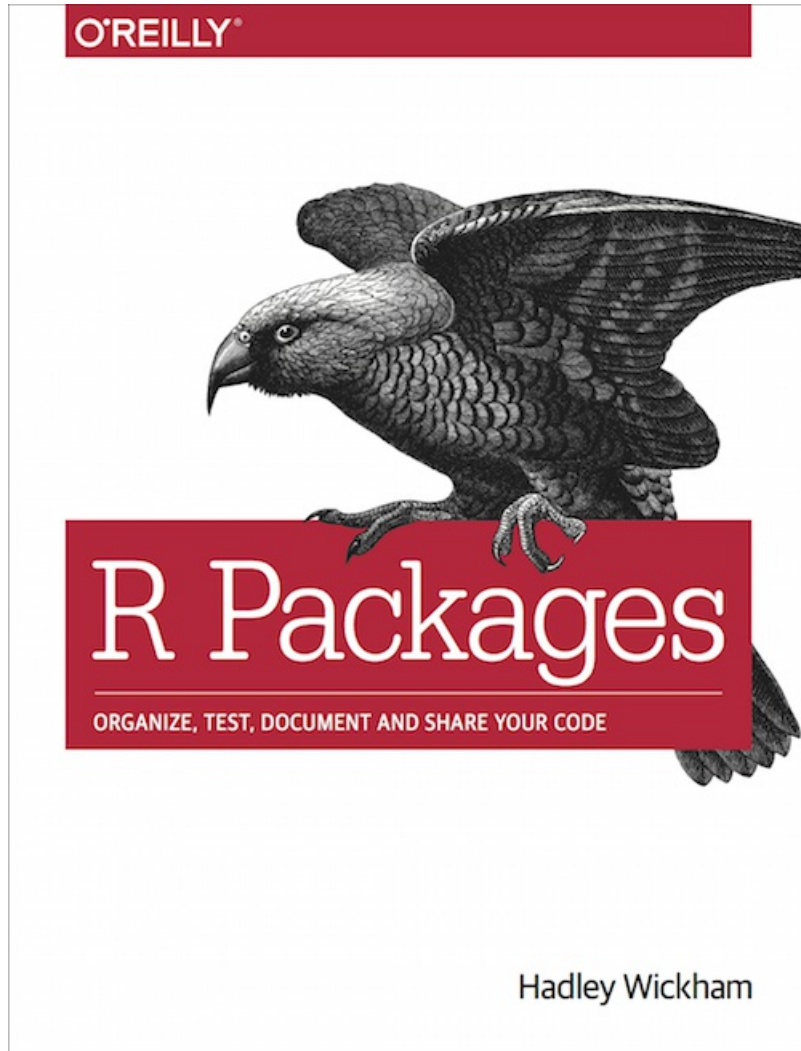
- Written mostly in R
  - Some calculations in C++, via Rcpp package
  - C++ Eigen library and RcppEigen for matrix algebra
  - User interacts only with R functions

# Design elements

- Tutorial vignettes demonstrate functionality
- Unit tests included via `testthat` R package
- Documentation with `roxygen2` R package
- Package website with `pkgdown` R package

# R packages book

- Hadley Wickham's "R packages" book as a guide



# Open-source R package

- Hosted on github
- Install via devtools R package
- `git` commits publicly visible
- Travis CI for testing after every commit

# Binder integration

- Enhances reproducibility
- Uses Docker images
- Downloads R packages for a specified date (or `git` commit on Github)



# Binder integration: 2 new files

- `install.R`
  - contains code to install R packages
- `runtime.txt`
  - contains one line of text to indicate date for CRAN packages

# Future directions

# Contact information

- frederick.boehm@gmail.com
- <https://fboehm.us/>
- qtl2pleio R package: <https://github.com/fboehm/qtl2pleio>
- Manuscript pre-print:  
<https://www.biorxiv.org/content/10.1101/550939v1>

# 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.