Testing pleiotropy vs. separate QTL in multiparental populations

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- High-dimensional phenotypes in multiparental populations provide new opportunities for understanding complex trait architecture
- New analysis tools are required
- We developed a test of pleiotropy vs. separate QTL for multiparental populations
- We applied it to find evidence for separate QTL for behavioral phenotypes in a 3 cM region in 261 Diversity Outbred mice
- We share our methods in an R package, `qtl2pleio` <https://github.com/fboehm/qtl2pleio>

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

•Jiang and Zeng (1995) developed a pleiotropy vs. separate QTL test for F2 mice
  •Applies to two traits that map to a single genomic region
  •Pleiotropy is the null hypothesis
  •Separate QTL is the alternative hypothesis
  •Perform a two-dimensional QTL scan
  •Calculate likelihood ratio test statistic

•Relatedness
•Multiple founder lines
•Test statistic calibration

•Multivariate random effects to account for relatedness
•Fixed effect for each founder allele
•Parametric bootstrap for test statistic calibration

•Fit the model:

$$Y = XB + G + E$$

for each ordered pair of markers

- $$G \sim MN(0, K, V_g)$$
- $$E \sim MN(0, I, V_e)$$

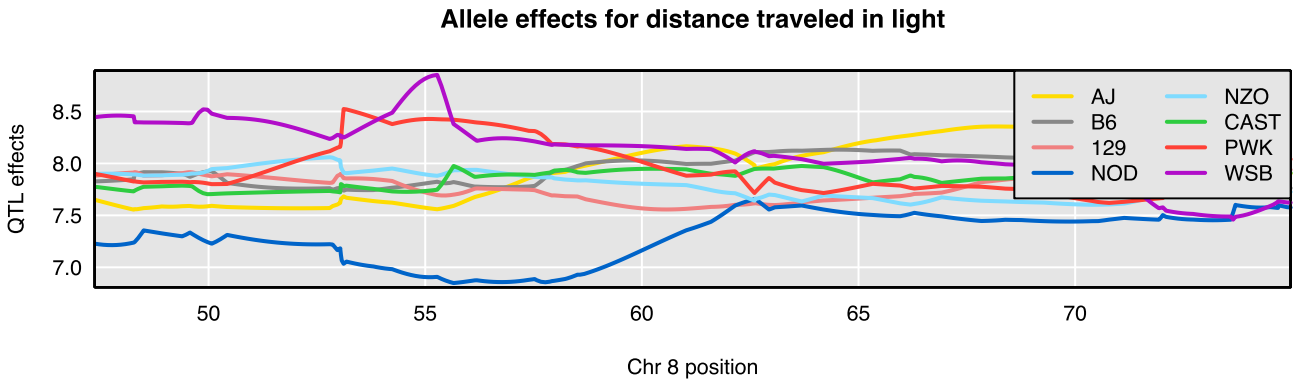
  •X
  contains allele probabilities
  •B
  contains allele effects
•Calculate likelihood for each model fit
•Test statistic:

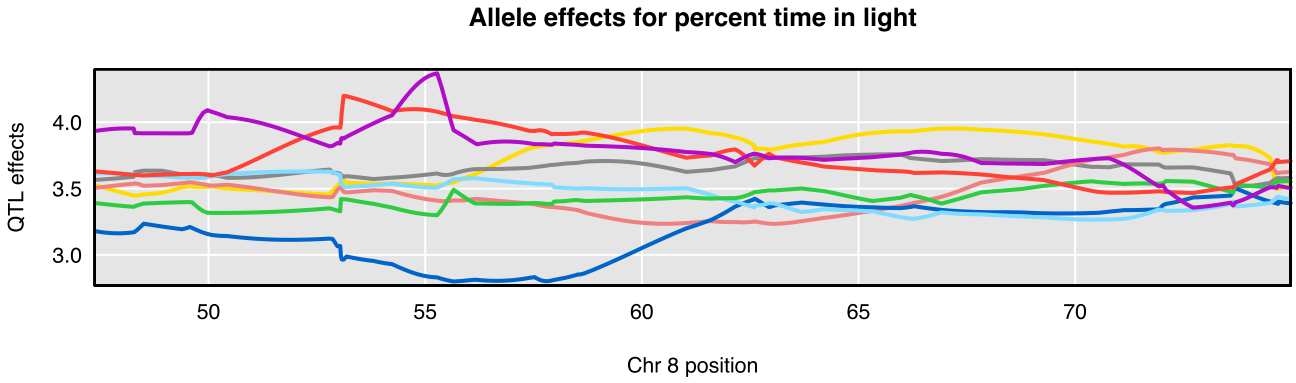
$$-\log_{10} \frac{\max L_0(B, \Sigma, \omega_1, \omega_2)}{\max L_A(B, \Sigma, \omega_1, \omega_2)}$$

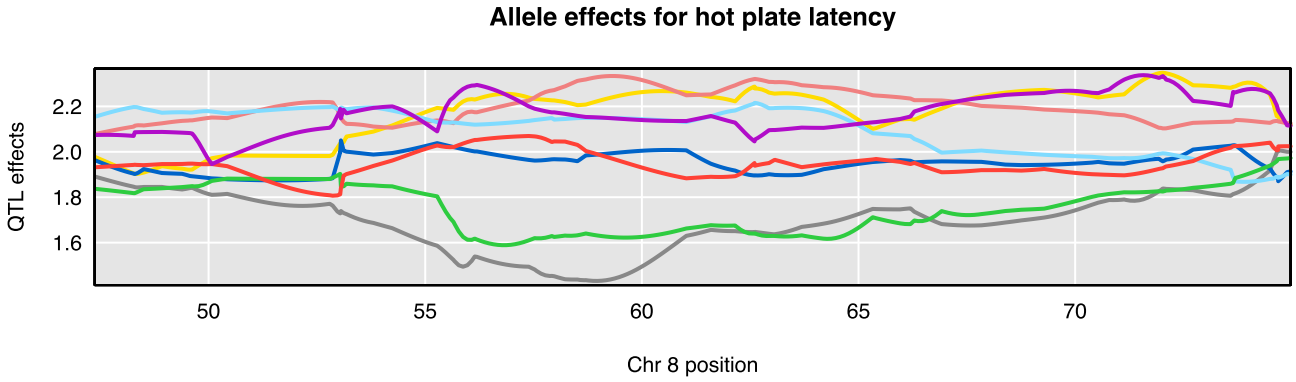
•Parametric bootstrap to get p-value

•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 QTLs for "percent time in light" and "distance traveled in light" at 55 cM
  •Motivated us to ask if *Hydin* also affects "percent time in light" and "distance traveled in light"

•Suggest that "percent time in light" and "distance traveled in light" share a single QTL
•*Hydin* is distinct from that QTL

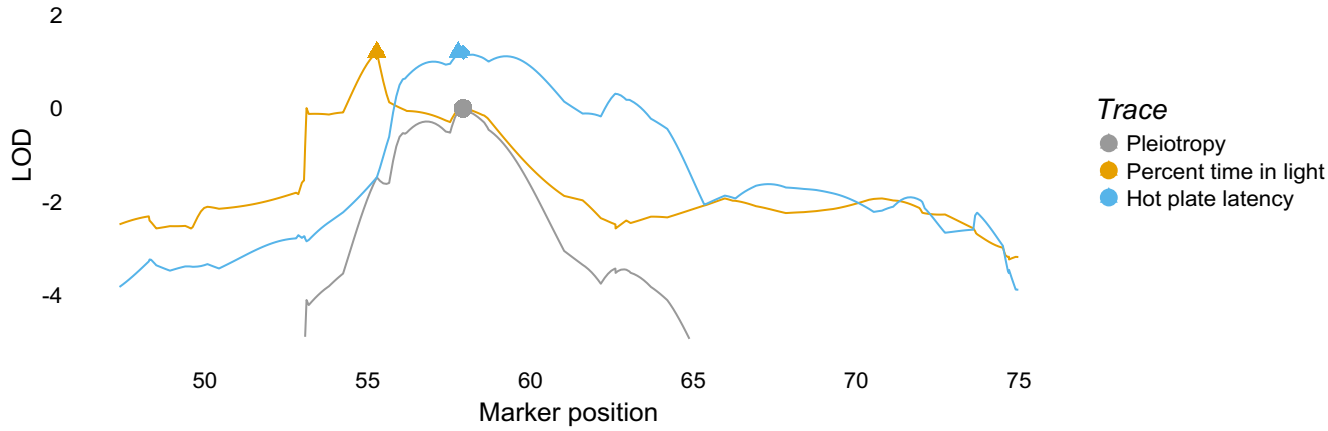




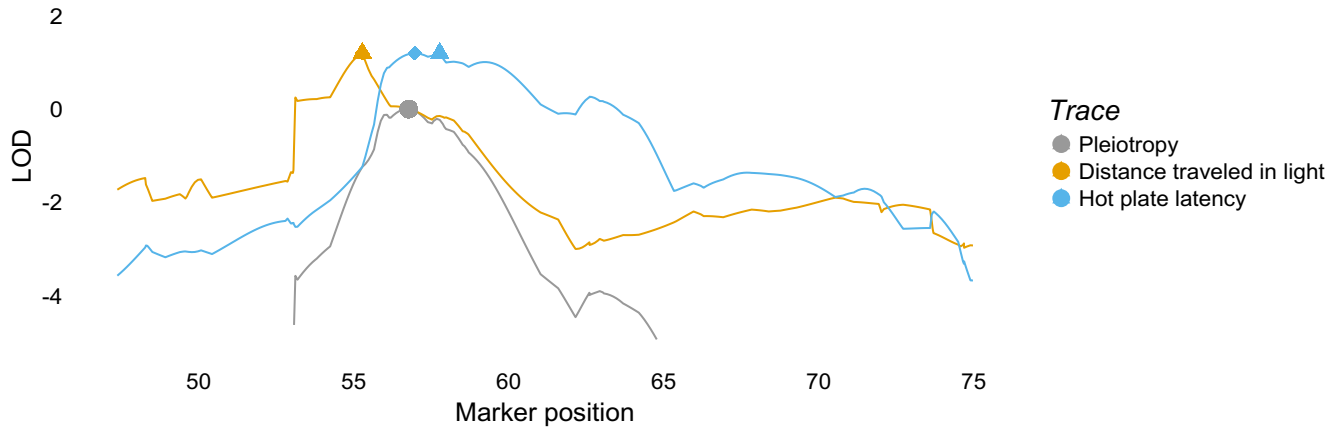


•Performed 3 pairwise analyses

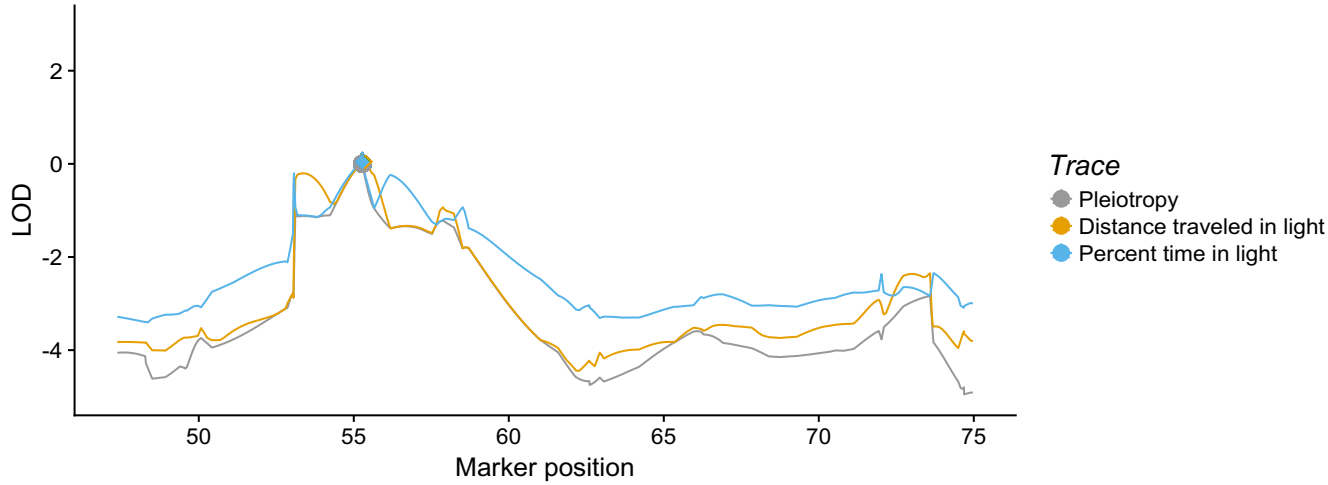
A **Chromosome 8 profile LODs for percent time in light and hot plate latency**



B **Chromosome 8 profile LODs for distance traveled in light and hot plate latency**



C **Chromosome 8 profile LODs for distance traveled in light and percent time in light**



•"percent time in light" & "hot plate latency": p = 0.109
•"distance traveled in light" & "hot plate latency": p = 0.108
•"percent time in light" & "distance traveled in light": p = 0.871

- Evidence for two separate QTL affecting the 3 phenotypes
  - 1 QTL affects both “distance traveled in light” and “percent time in light”
  - Second QTL contains *Hydin* and affects “hot plate latency”

- Develop methods for analyzing multiple phenotypes in a single test

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Jiang, Changjian, and Zhao-Bang Zeng. 1995. “Multiple Trait Analysis of Genetic Mapping for Quantitative Trait Loci.” *Genetics* 140 (3). Genetics Soc America: 1111–27.
Logan, Ryan W, Raymond F Robledo, Jill M Recla, Vivek M Philip, Jason A Bubier, Jeremy J Jay, Carter Harwood, et al. 2013. “High-Precision Genetic Mapping of Behavioral Traits in the Diversity Outbred Mouse Population.” *Genes, Brain and Behavior* 12 (4). Wiley Online Library: 424–37.
Recla, Jill M, Raymond F Robledo, Daniel M Gatti, Carol J Bult, Gary A Churchill, and Elissa J Chesler. 2014. “Precise Genetic Mapping and Integrative Bioinformatics in Diversity Outbred Mice Reveals Hydin as a Novel Pain Gene.” *Mammalian Genome* 25 (5-6). Springer: 211–22.