Testing pleiotropy vs. separate QTL in multiparental populations

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Abstract

High-dimensional phenotypes & multiparental populations inform complex trait architecture
New analysis tools needed
Developed a test of pleiotropy vs. separate QTL for multiparental populations
Evidence for two separate QTL affecting three behavioral traits in a 3 cM region
Shared methods in an R package, qtl2pleio
https://github.com/fboehm/qtl2pleio

Introduction

RNA sequencing and mass spectrometry enable measurement of thousands of phenotypes
Multiparental populations enable high-resolution QTL mapping
Together, they inform complex trait genetics
New analysis tools, such as our test of pleiotropy

Background

vs. separate QTL, are needed

Jiang and Zeng (1995) developed a pleiotropy vs. separate QTL test for two-parent crosses
Applies to two traits that map to a single genomic region
Null hypothesis: pleiotropy
Alternative: presence of two separate QTL
Perform a two-dimensional QTL scan
Calculate likelihood ratio test statistic

Challenges

Relatedness: Multivariate polygenic random effects
Eight founder lines: 8 fixed effects
Test statistic calibration: Parametric bootstrap test

Procedure

 $oldsymbol{\cdot}$ Fit the model for each marker pair: vec(Y) = Xvec(B) + vec(G) + vec(E) $oldsymbol{\cdot}$

 $E \sim MN(0,I,V_e)$

• B contains allele effects
• Calculate likelihood for each model fit
• Test statistic: $-\log_{10}\frac{\max L_0(B,\Sigma,\omega_1)}{\max L_A(B,\Sigma,\omega_1,\omega_2)}$

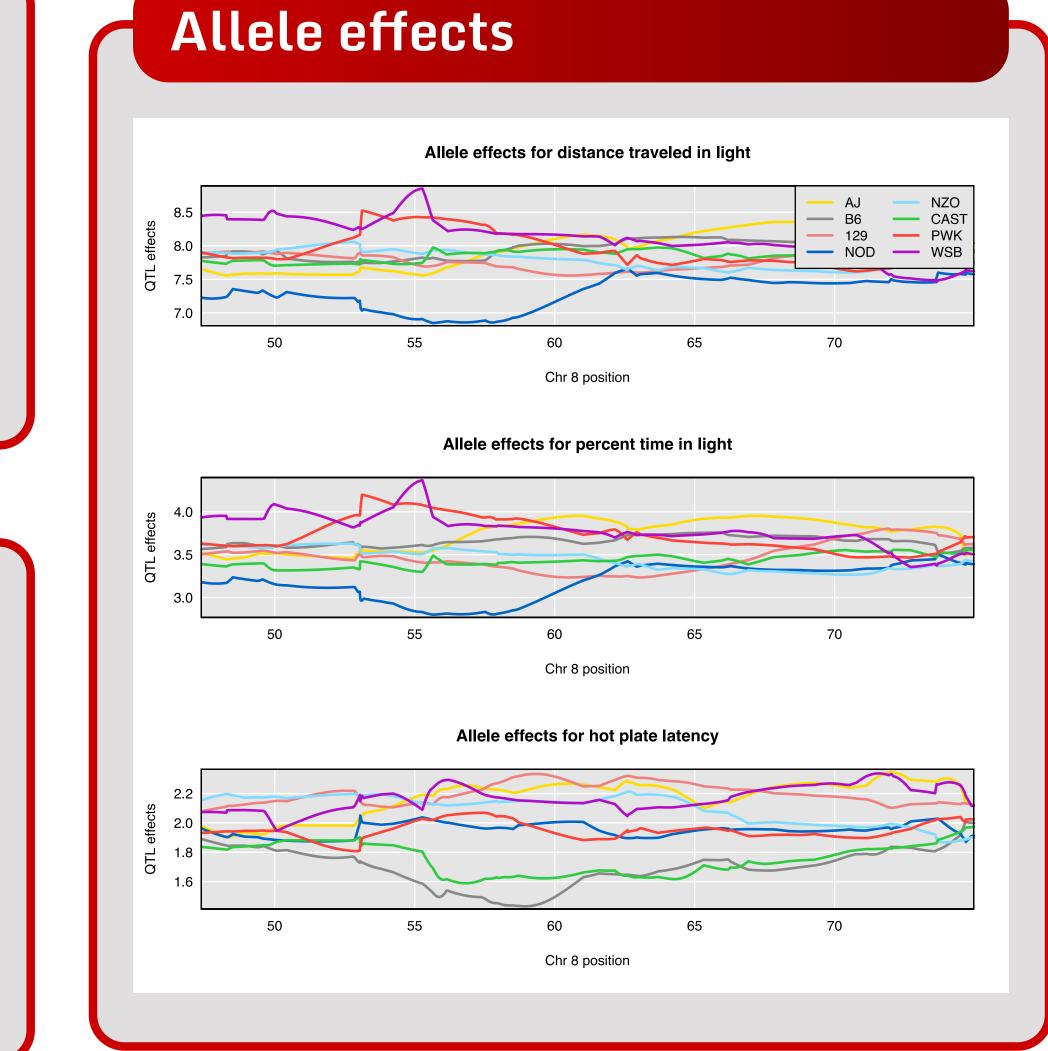
ullet X contains allele probabilities

• Parametric bootstrap to get p-value

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"?

Profile LODs



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

50 55 60 65 70 75 Marker position

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

Trait1Trait2pvaluepct. time in lighthot plate latency0.109distance traveledhot plate latency0.108pct. time in lightdistance traveled0.871

Conclusions

3 pairwise tests

Evidence for two separate QTL affecting the 3 traits
1 QTL affects both "distance traveled in light" and "percent time in light"
Second QTL contains Hydin and affects "hot plate latency"

Future directions

Examine expression data from Keller et al. (2018)
378 Diversity Outbred mice
Expression QTL hotspot dissection
Statistical power studies
Comparisons with mediation analyses

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References

Trace

● Pleiotropy
● Percent time in light
● Hot plate latency

Trace◆ Pleiotropy◆ Distance traveled in light◆ Hot plate latency

Trace

● Pleiotropy

● Distance traveled in light
● Percent time in light

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