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INVESTIGATIONS

Mean-Variance QTL Mapping Identifies Novel QTL for Circadian Activity and Exploratory Behavior in Mice – Supplementary Materials

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ABSTRACT We illustrate, through two case studies, that "mean-variance QTL mapping"—QTL mapping that models effects on the mean and the variance simultaneously—can discover QTL that traditional interval mapping cannot. Mean-variance QTL mapping is based on the double generalized linear model, which extends the standard linear model used in interval mapping by incorporating not only a set of genetic and covariate effects for mean but also set of such effects for the residual variance. Its potential for use in QTL mapping has been described previously, but it remains underutilized, with certain key advantages undemonstrated until now. In the first case study, a reduced complexity intercross of C57BL/6J and C57BL/6N mice examining circadian behavior, our reanalysis detected a mean-controlling QTL for circadian wheel running activity that interval mapping did not; mean-variance QTL mapping was more powerful than interval mapping at the QTL because it accounted for the fact that mice homozygous for the C57BL/6N allele had less residual variance than other mice. In the second case study, an intercross between C57BL/6J and C58/J mice examining anxiety-like behaviors, our reanalysis detected a variance-controlling QTL for rearing behavior; interval mapping did not identify this QTL because it does not target variance QTL. We believe that the results of these reanalyses, which in other respects largely replicated the original findings, support the use of mean-variance QTL mapping as standard practice.

KEYWORDS
variance heterogeneity, DGLM, mQTL, vQTL, mvQTL

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SUPPLEMENTARY MATERIALS

Supplement to Kumar Reanalysis

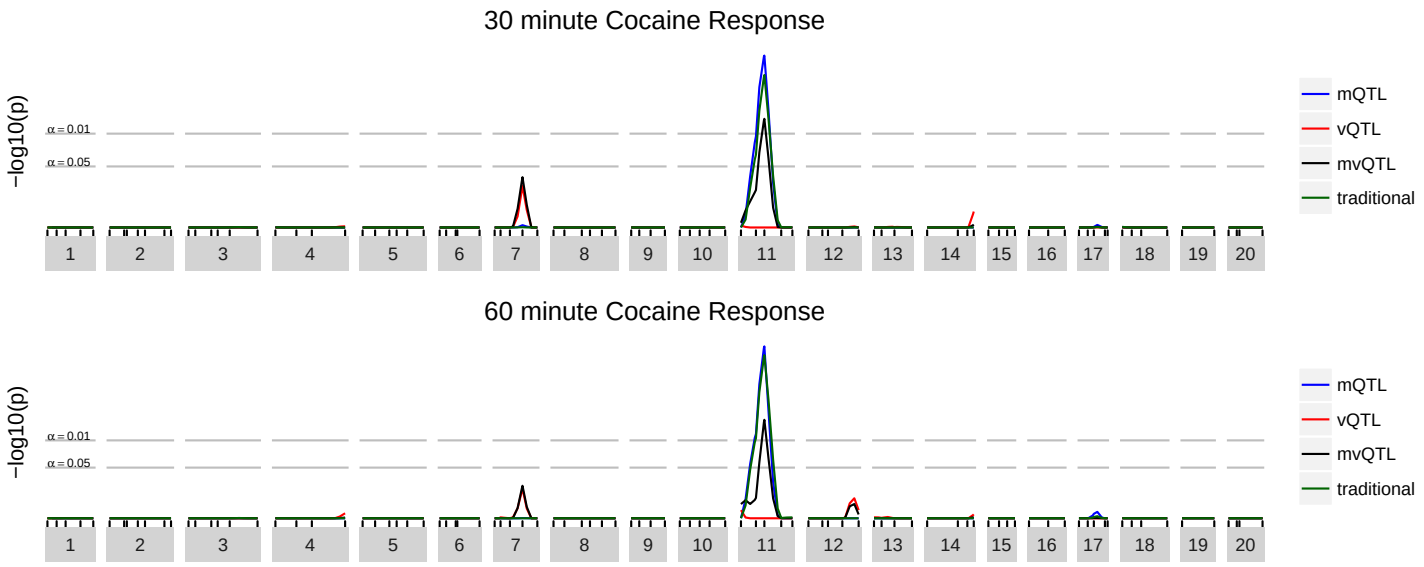


Figure S1 Replicated scans from Kumar *et al.* (2013)

Table 1 The characteristics of the mice plotted in Figure 3

genotype at rs30314218	sex	activity in the DD (rev/min)
6J	female	12.79
6J	female	38.20
6J	male	8.07
6J	male	27.99
Het	female	14.03
Het	female	40.13
Het	male	1.87
Het	male	30.68
6N	female	22.22
6N	female	33.85
6N	male	16.75
6N	male	28.71

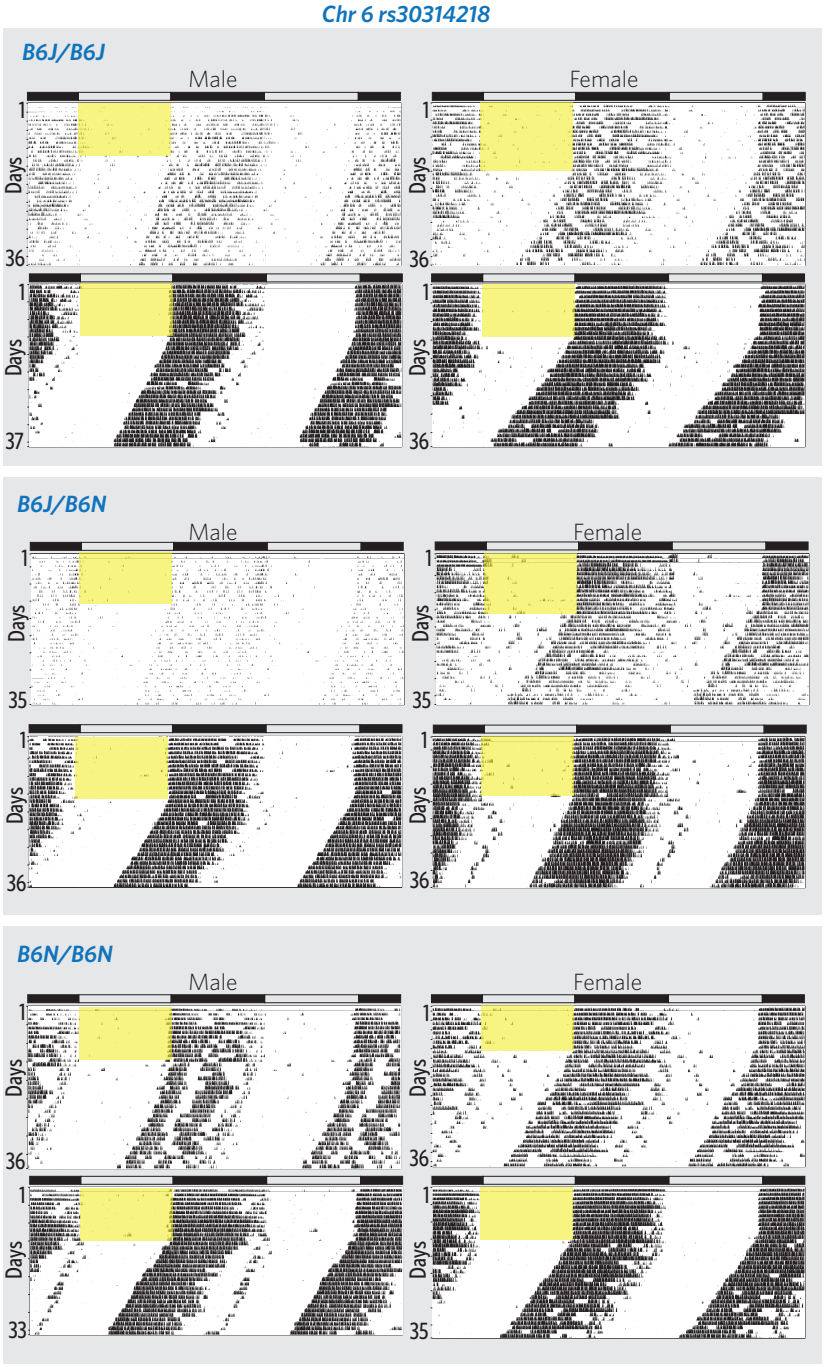


Figure S2 Actograms, similar to Figure 3, including female mice. The mice depicted here are highlighted with larger circles in Figure 2a.

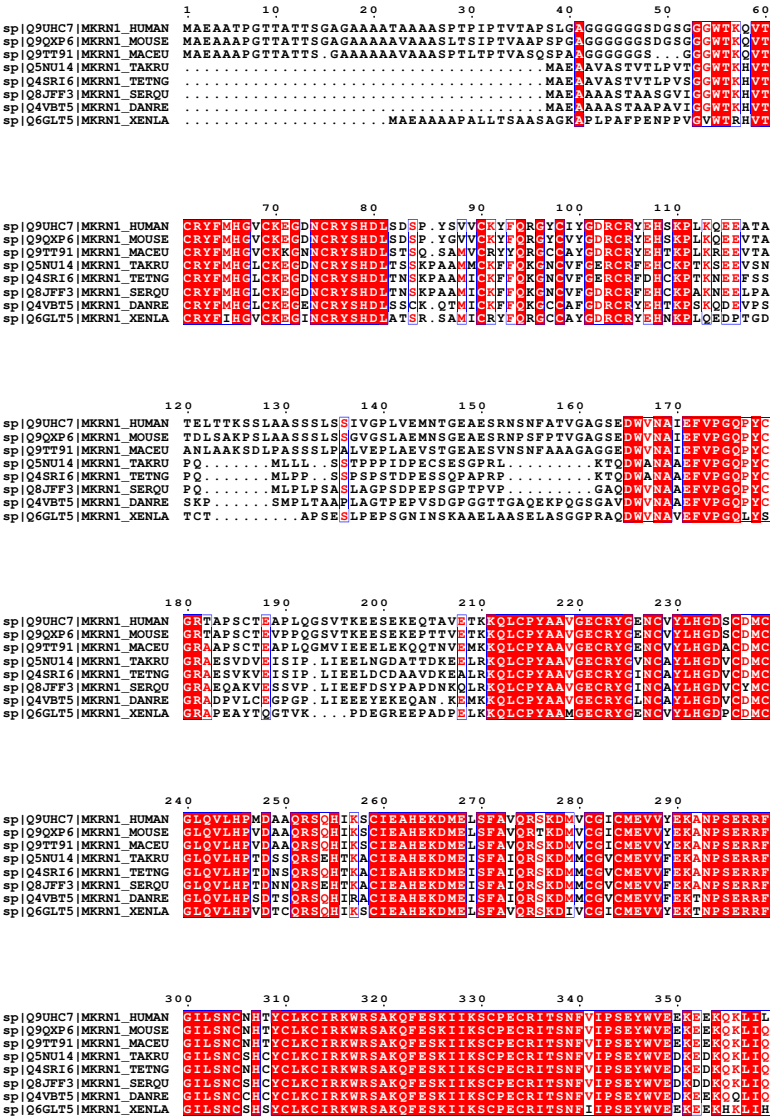


Figure S3 Page one of *Mkrn1* alignment. Note that the amino acid at position 346 is conserved across all species. See next page for species labels. The relevant mutation is Y346N – N in B6J and Y in B6NJ.

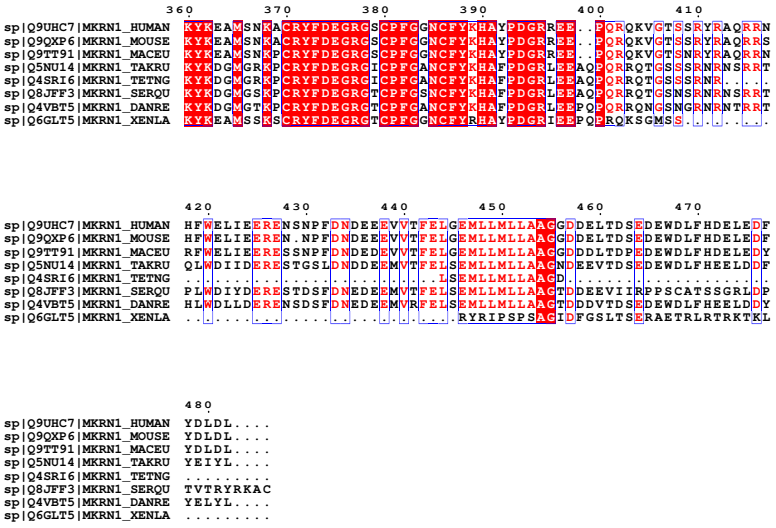


Figure S4 Page two of *Mkrn1* alignment.

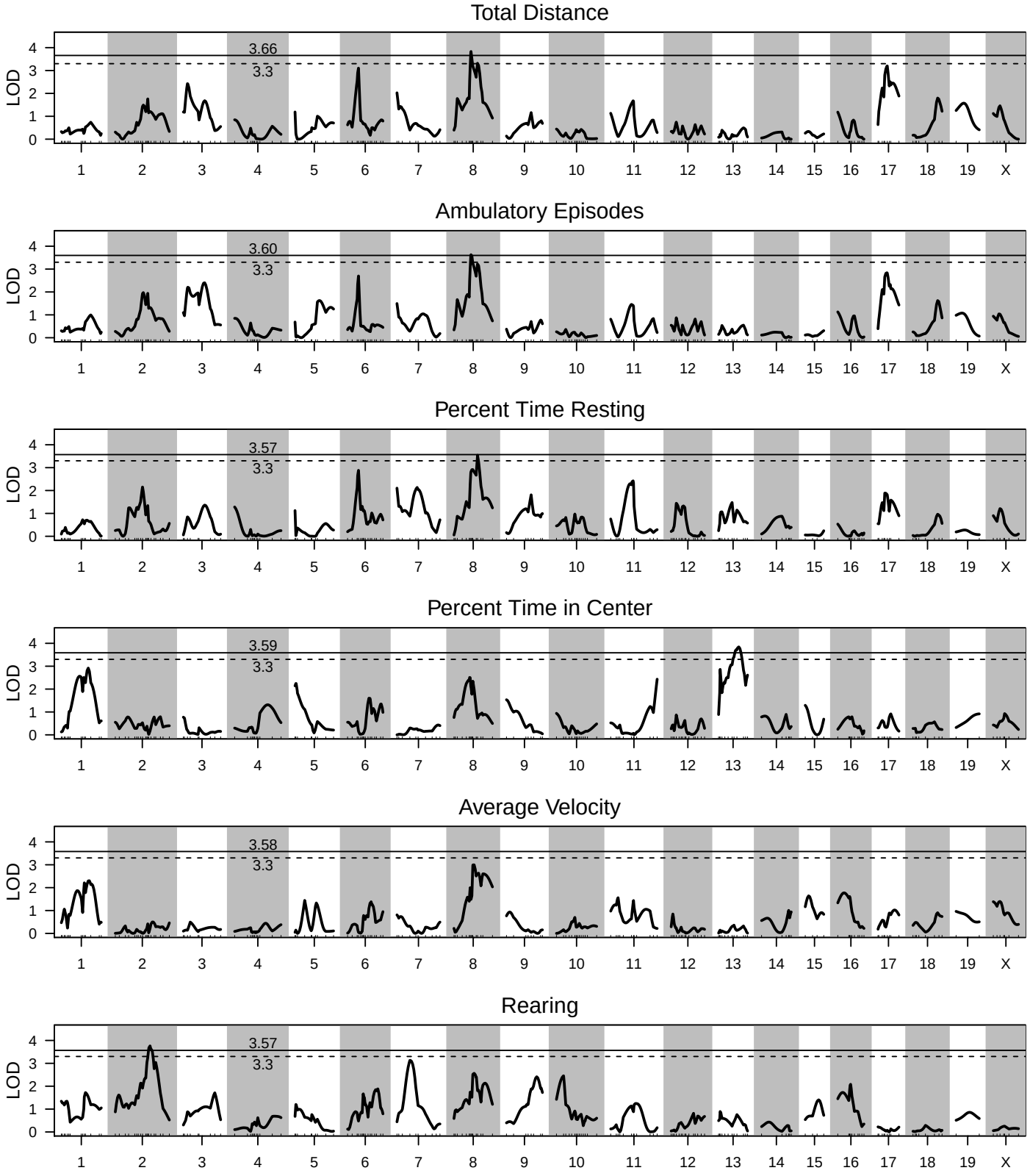


Figure S5 Replication of genome scans from original Bailey analysis. LOD curves are visually identical to originally-published LOD curves, but thresholds, estimated based on the described methods, are meaningfully higher.

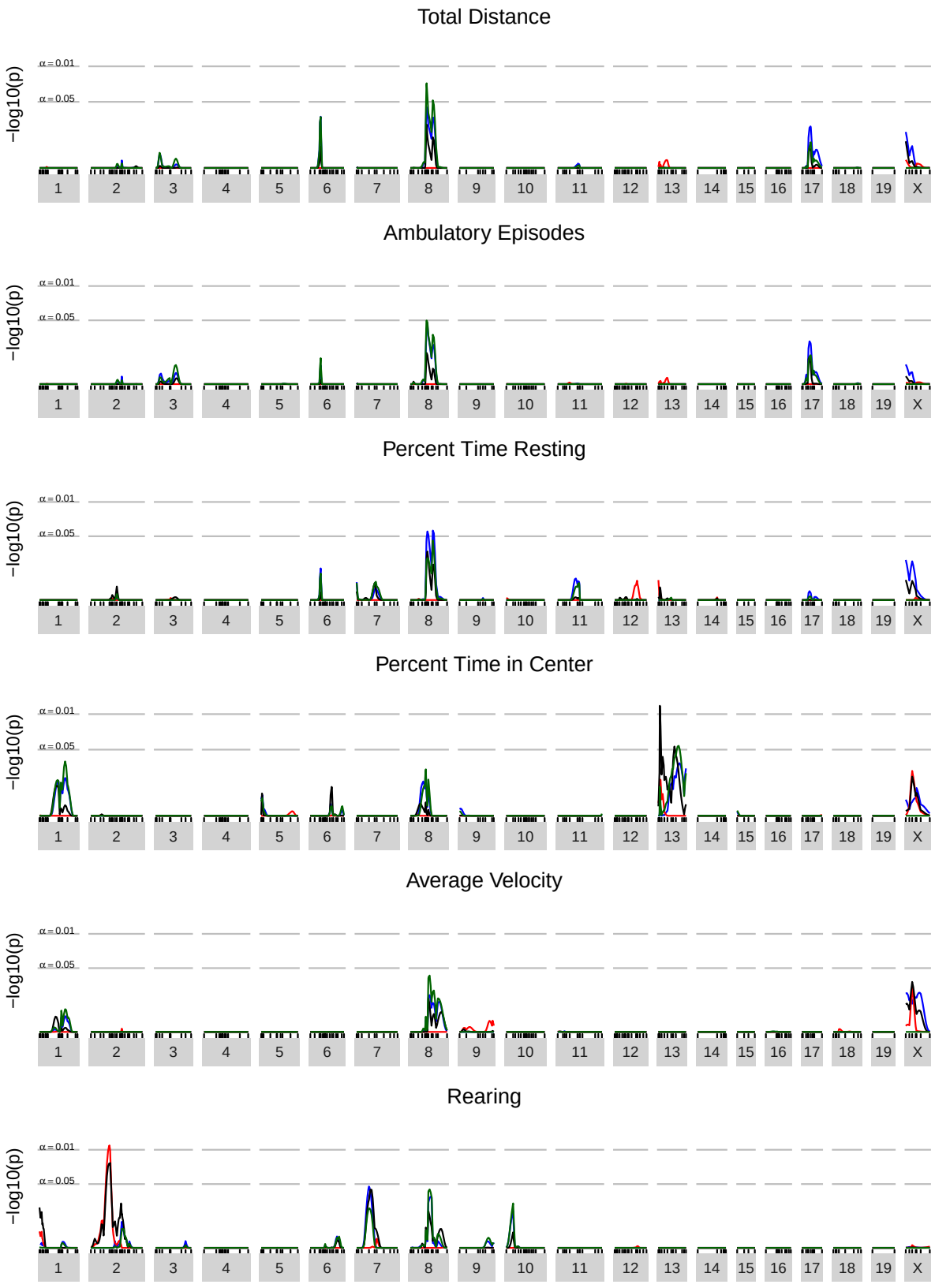


Figure S6 DGLM-based reanalysis of all traits measured in Bailey et al., all transformed by the rank-based inverse normal transform.

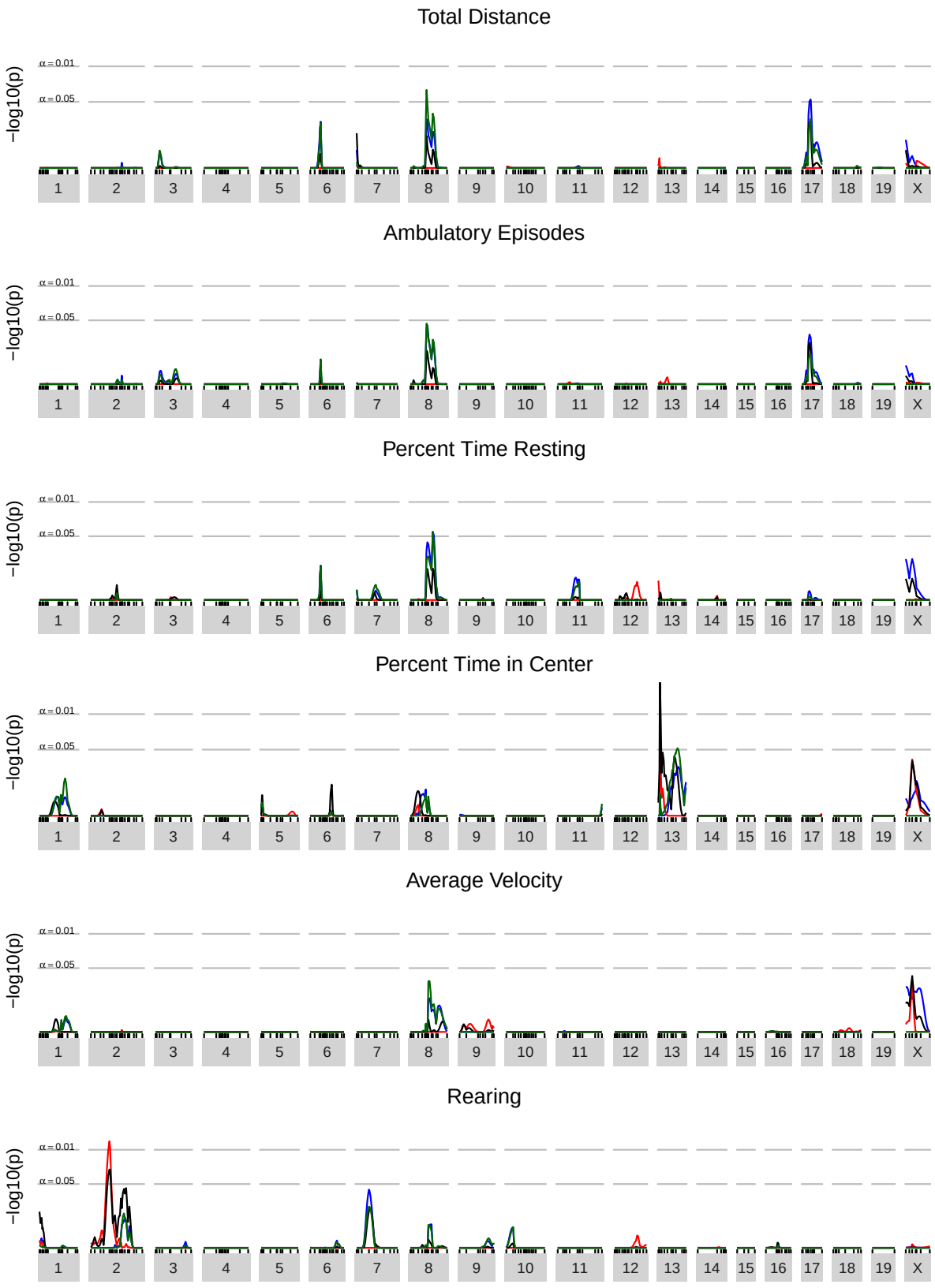
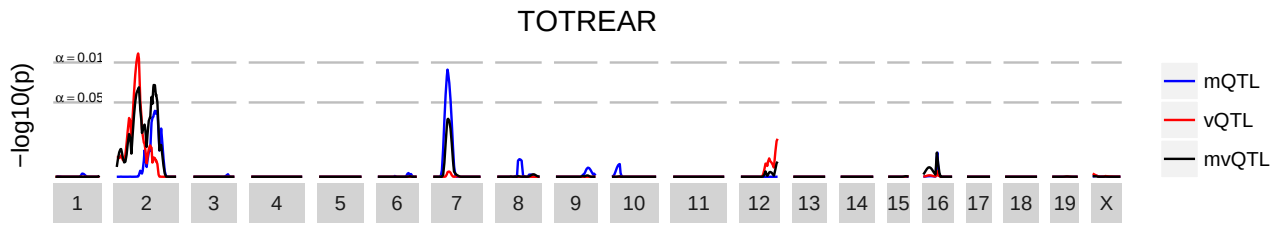
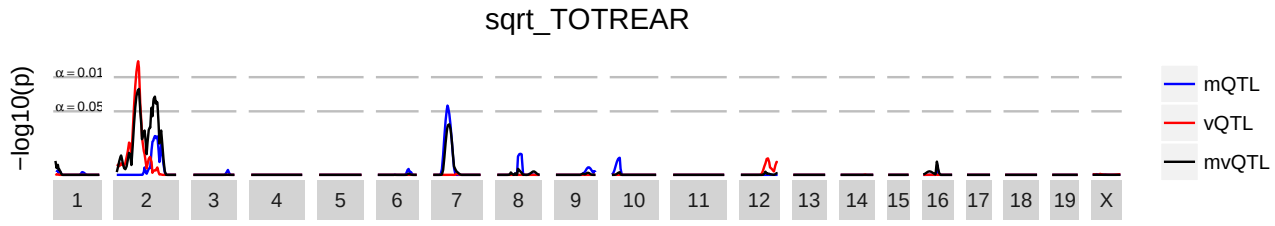


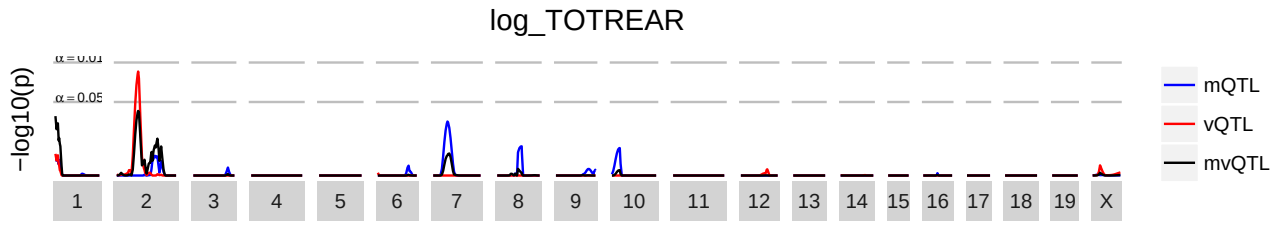
Figure S7 DGLM-based reanalysis of all traits measured in Bailey et al., all transformed by the Box-Cox transform. Box-Cox exponents were 1, 1, 0, 0.75, 0, 0.25, respectively.



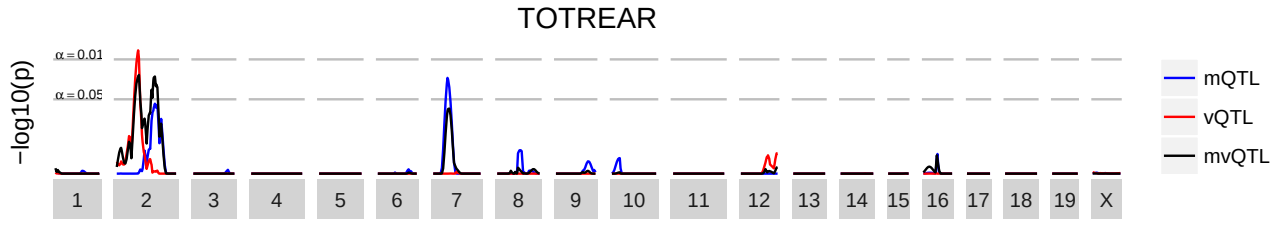
(a) "Rearing" trait analyzed with no transformation.



(b) "Rearing" trait analyzed with square root transformation.



(c) "Rearing" trait analyzed with log transformation.



(d) "Rearing" trait analyzed with Poisson generalized linear model.

Figure S8 vQTL for TOTREAR phenotype on chromosome 2 is consistent across various transforms.

LITERATURE CITED

Kumar, V., K. Kim, C. Joseph, S. Kourrich, S.-H. Yoo, *et al.*, 2013 C57BL/6N Mutation in Cytoplasmic FMRP interacting protein 2 Regulates Cocaine Response. Science (80-.). **342**: 1508–1512.