

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

SUPPLEMENTARY MATERIALS

Supplement to Kumar Reanalysis

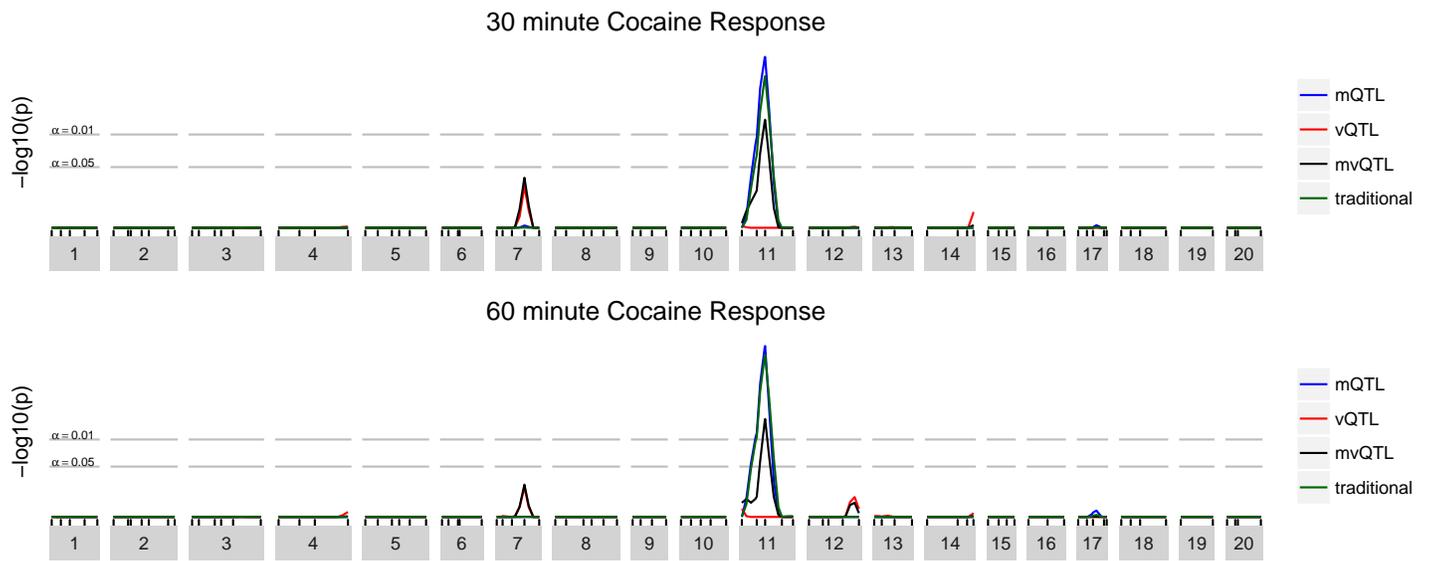


Figure S1 Replicated scans from Kumar *et al.* (2013)

■ Table 1 The characteristics of the mice plotted in Figure 3

genotype	at	sex	activity in the DD (rev/min)
rs30314218			
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

Chr 6 rs30314218

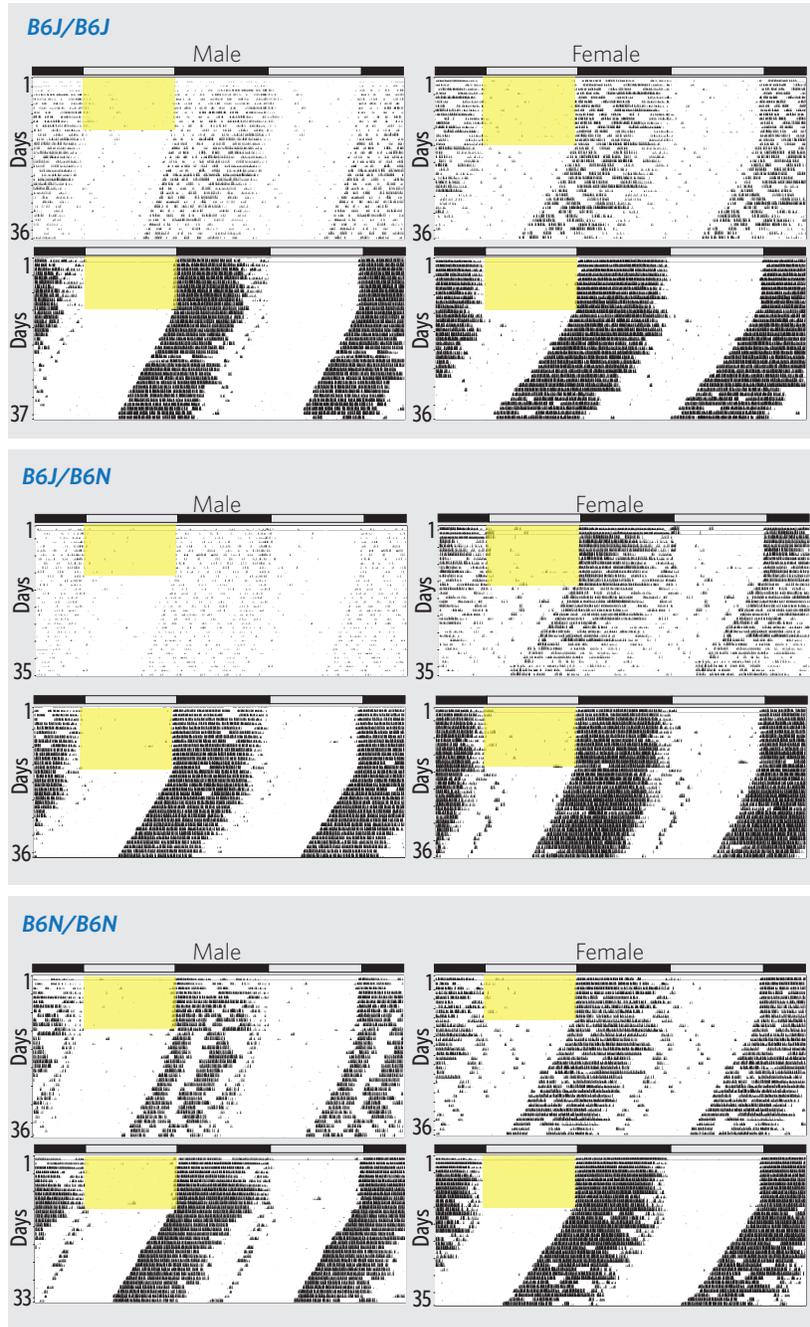


Figure S2 Actograms, similar to Figure 3, including female mice. The mice depicted here are highlighted with larger circles in Figure 2a.

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1      10      20      30      40      50      60
sp|Q9UHC7|MKRNL_HUMAN MAEAAATPGTTATTSGAGAAAAATAAASPTPIPTVTAPSLG...GGGGGGSDGSGG...GWA...KQV...T
sp|Q9QXP6|MKRNL_MOUSE MAEAAAAPGTTATTSGAGAAAAVAASLTIPVVAAPSPG...GGGGGGSDGSGG...GWA...KQV...T
sp|Q9TT91|MKRNL_MACEU MAEAAAAPGTTATTSGAAAAAATAAASPTLPTVASQSPA...GGGGGG...GWA...KQV...T
sp|Q5NU14|MKRNL_TAKRU .....MAB...AVASTVTLFVT...GWA...KH...T
sp|Q4SRI6|MKRNL_TETNG .....MAB...AVASTVTLFVS...GWA...KH...T
sp|Q8JFF3|MKRNL_SERQU .....MAB...AAASTAASGVI...GWA...KH...T
sp|Q4VBT5|MKRNL_DANRE .....MAB...AAASTAAPAVI...GWA...KH...T
sp|Q6GLT5|MKRNL_XENLA .....MAEAAAAPALLTSAASAGK...PLPAPFENPFV...GWA...RH...T

70      80      90      100     110
sp|Q9UHC7|MKRNL_HUMAN CRYFMHGVCKEEDNCRYSHDLSDSP.YSVVCKYFRNCYIYDRCRCEYHSKFLKQEEATA
sp|Q9QXP6|MKRNL_MOUSE CRYFMHGVCKEEDNCRYSHDLSDSP.YGVVCKYFRNCYVYDRCRCEYHSKFLKQEEVTA
sp|Q9TT91|MKRNL_MACEU CRYFMHGVCKEEDNCRYSHDLSDSP.SAMVCRYYRRCGCCAYDRCRCEYHSKFLKREEVTA
sp|Q5NU14|MKRNL_TAKRU CRYFMHGLCKEEDNCRYSHDLTSSKPAAMCKPFFKGNCFVGRRCRFRCKPTKSEEVSN
sp|Q4SRI6|MKRNL_TETNG CRYFMHGLCKEEDNCRYSHDLTNSKPAAMCKPFFKGNCFVGRRCRFRCKPTKNEEFSS
sp|Q8JFF3|MKRNL_SERQU CRYFMHGLCKEEDNCRYSHDLTNSKPAAMCKPFFKGNCFVGRRCRFRCKPTKNSLELFA
sp|Q4VBT5|MKRNL_DANRE CRYFMHGLCKEEDNCRYSHDLTNSKPAAMCKPFFKGNCFVGRRCRFRCKPTKNSQEVFS
sp|Q6GLT5|MKRNL_XENLA CRYFMHGVCKEEDNCRYSHDLTSSR.SAMVCRYYRRCGCCAYDRCRCEYHSKFLQEDPTGD

120     130     140     150     160     170
sp|Q9UHC7|MKRNL_HUMAN TELTTKSSLAASSSLSIVGFLVEMNTGEAESRNSNFATVGGAGSE...DWNNA...EFVPGQP...YC
sp|Q9QXP6|MKRNL_MOUSE TDLAKPDLAASSSLSIVGSLAEMNSGEAESRNSFPFTVGGAGSE...DWNNA...EFVPGQP...YC
sp|Q9TT91|MKRNL_MACEU ANLAAKSDLPASSSFLALVEFLAEVSTGEAESVNSNFAAAGAGSE...DWNNA...EFVPGQP...YC
sp|Q5NU14|MKRNL_TAKRU PQ.....MLLL...S...T...P...P...D...P...C...S...S...G...P...R...L...K...T...O...D...W...N...A...E...F...V...P...G...Q...P...Y...C
sp|Q4SRI6|MKRNL_TETNG PQ.....MLPP...S...P...P...S...P...D...P...E...S...S...Q...P...A...P...R...P...L...K...T...O...D...W...N...A...E...F...V...P...G...Q...P...Y...C
sp|Q8JFF3|MKRNL_SERQU PQ.....MLPLPSA...L...A...G...P...S...D...P...E...S...S...Q...P...T...P...V...P...L...K...T...O...D...W...N...A...E...F...V...P...G...Q...P...Y...C
sp|Q4VBT5|MKRNL_DANRE SRP.....SMPLTAA...L...A...G...T...E...P...V...S...D...G...G...G...T...T...G...A...E...K...P...Q...G...S...G...A...V...D...W...N...A...E...F...V...P...G...Q...P...Y...C
sp|Q6GLT5|MKRNL_XENLA TCT.....APSE...L...P...E...P...S...G...N...I...N...S...K...A...E...L...A...A...E...L...A...S...G...G...P...R...A...O...D...W...N...A...E...F...V...P...G...Q...P...Y...C

180     190     200     210     220     230
sp|Q9UHC7|MKRNL_HUMAN GRATAPSCTEAPLQGSVTKKEESEKEQTAVETTKKQLCPYAAVGECRYGENCVYVYHGGDS...CDMC
sp|Q9QXP6|MKRNL_MOUSE GRATAPSCTEVPPQGSVTKKEESEKEPTTVETTKKQLCPYAAVGECRYGENCVYVYHGGDS...CDMC
sp|Q9TT91|MKRNL_MACEU GRATAPSCTEAPLQGMVIEEELKQQTNVEMKQKQLCPYAAVGECRYGENCVYVYHGGDS...CDMC
sp|Q5NU14|MKRNL_TAKRU GRAESVDVETISIP.LIEELNGDATDKELRQKQLCPYAAVGECRYGENCVYVYHGGDS...CDMC
sp|Q4SRI6|MKRNL_TETNG GRAESVWVETISIP.LIEELDCDAAVDKELRQKQLCPYAAVGECRYGENCVYVYHGGDS...CDMC
sp|Q8JFF3|MKRNL_SERQU GRAEQKVCSSVP.LIEEFDSYPAPDNKQLRQKQLCPYAAVGECRYGENCVYVYHGGDV...CYMC
sp|Q4VBT5|MKRNL_DANRE GRADPVLCEGPGP.LIEEYKEEQAN.KEMKQKQLCPYAAVGECRYGENCVYVYHGGDV...CYMC
sp|Q6GLT5|MKRNL_XENLA GRADPEATQTVK...PDEGREEPADPELQKQLCPYAAVGECRYGENCVYVYHGGDP...CDMC

240     250     260     270     280     290
sp|Q9UHC7|MKRNL_HUMAN GLQVLHFDAAQRSQHTKSCIEAHEKDMESFAVQRSKDMVCCICMEVVVYKKNPSERRF
sp|Q9QXP6|MKRNL_MOUSE GLQVLHFDAAQRSQHTKSCIEAHEKDMESFAVQRSKDMVCCICMEVVVYKKNPSERRF
sp|Q9TT91|MKRNL_MACEU GLQVLHFDAAQRSQHTKSCIEAHEKDMESFAVQRSKDMVCCICMEVVVYKKNPSERRF
sp|Q5NU14|MKRNL_TAKRU GLQVLHFDSSQRSQHTKSCIEAHEKDMESFAIQRSKDMVCCVCMVVVYKKNPSERRF
sp|Q4SRI6|MKRNL_TETNG GLQVLHFDNSQRSQHTKSCIEAHEKDMESFAIQRSKDMVCCVCMVVVYKKNPSERRF
sp|Q8JFF3|MKRNL_SERQU GLQVLHFDNNQRSQHTKSCIEAHEKDMESFAIQRSKDMVCCVCMVVVYKKNPSERRF
sp|Q4VBT5|MKRNL_DANRE GLQVLHFDSSQRSQHTKSCIEAHEKDMESFAIQRSDAFCCVCMVVVYKKNPSERRF
sp|Q6GLT5|MKRNL_XENLA GLQVLHFDPCQRSQHTKSCIEAHEKDMESFAVQRSKDIWCCICMEVVVYKKNPSERRF

300     310     320     330     340     350
sp|Q9UHC7|MKRNL_HUMAN GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI
sp|Q9QXP6|MKRNL_MOUSE GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI
sp|Q9TT91|MKRNL_MACEU GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI
sp|Q5NU14|MKRNL_TAKRU GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI
sp|Q4SRI6|MKRNL_TETNG GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI
sp|Q8JFF3|MKRNL_SERQU GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI
sp|Q4VBT5|MKRNL_DANRE GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI
sp|Q6GLT5|MKRNL_XENLA GILSNCNHTYCLKCIKRWRSKQFESKIIKSCPECRITSNFIIPSEYVWVEKREKQKLLI

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Figure S3 Page one of *Mkrnl* 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.

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360      370      380      390      400      410
sp|Q9UHC7|MKRNL_HUMAN KYKEAMSNRA CRYFDEGRG CPPFGNCFYRHA YPDGRREE . PQRQKVGTSSRYRAQRRL
sp|Q9QXP6|MKRNL_MOUSE KYKEAMSNRA CRYFDEGRG CPPFGNCFYRHA YPDGRREE . PQRQKVGTSSRYRAQRRL
sp|Q9TT91|MKRNL_MACEU KYKEAMSNRA CRYFDEGRG CPPFGNCFYRHA YPDGRREE . PQRQKVGTSSRYRAQRRL
sp|Q5NU14|MKRNL_TAKRU KYKDGMRK CRYFDEGRG CPPFGNCFYRHA YPDGRLEAQ . PQRQVTSNRRNRRRT
sp|Q4SRI6|MKRNL_TETNG KYKDGMRK CRYFDEGRG CPPFGNCFYRHA YPDGRLEAQ . PQRQVTSNRRNRRRT
sp|Q8JFF3|MKRNL_SERQU KYKDGMRK CRYFDEGRG CPPFGNCFYRHA YPDGRLEAQ . PQRQVTSNRRNRRRT
sp|Q4VBT5|MKRNL_DANRE KYKDGMRK CRYFDEGRG CPPFGNCFYRHA YPDGRLEAQ . PQRQVTSNRRNRRRT
sp|Q6GLT5|MKRNL_XENLA KYKEAMSNRA CRYFDEGRG CPPFGNCFYRHA YPDGRREE . PQRQKSGMSS . . . . .

420      430      440      450      460      470
sp|Q9UHC7|MKRNL_HUMAN HFWEELIERE NSNPFNDDEEVVTFELGEMLLMLLAAGD DELTDSFEDEWDLFHELEDF
sp|Q9QXP6|MKRNL_MOUSE HFWEELIERE N.NPFDNDEEVVTFELGEMLLMLLAAGD DELTDSFEDEWDLFHELEDF
sp|Q9TT91|MKRNL_MACEU HFWEELIERE NSNPFNDDEEVVTFELGEMLLMLLAAGD DDLTDSFEDEWDLFHELEDF
sp|Q5NU14|MKRNL_TAKRU QLWDIIDERESTGSLNDDEEMVTFELSEMMLMLLAAGD NDEVTDSFEDEWDLFHELEDF
sp|Q4SRI6|MKRNL_TETNG . . . . . SEMMLMLLAAGD . . . . .
sp|Q8JFF3|MKRNL_SERQU FLWDIYDERESTDSFDNDEEMVTFELSEMMLMLLAAGD DDEVIIRPPSCATSSRLDP
sp|Q4VBT5|MKRNL_DANRE HLWDLDERESDSFDNDEEMVTFELSEMMLMLLAAGD DDVTDSEDEWDLFHELEDF
sp|Q6GLT5|MKRNL_XENLA . . . . . RYRIPSPSACIDFGSLTSEAEATRLRTRKTKL

480
sp|Q9UHC7|MKRNL_HUMAN YLDDL . . . .
sp|Q9QXP6|MKRNL_MOUSE YLDDL . . . .
sp|Q9TT91|MKRNL_MACEU YLDDL . . . .
sp|Q5NU14|MKRNL_TAKRU YEIYL . . . .
sp|Q4SRI6|MKRNL_TETNG . . . . .
sp|Q8JFF3|MKRNL_SERQU TVTRYRKAC
sp|Q4VBT5|MKRNL_DANRE YELYL . . . .
sp|Q6GLT5|MKRNL_XENLA . . . . .

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Figure S4 Page two of *Mkrn1* alignment.

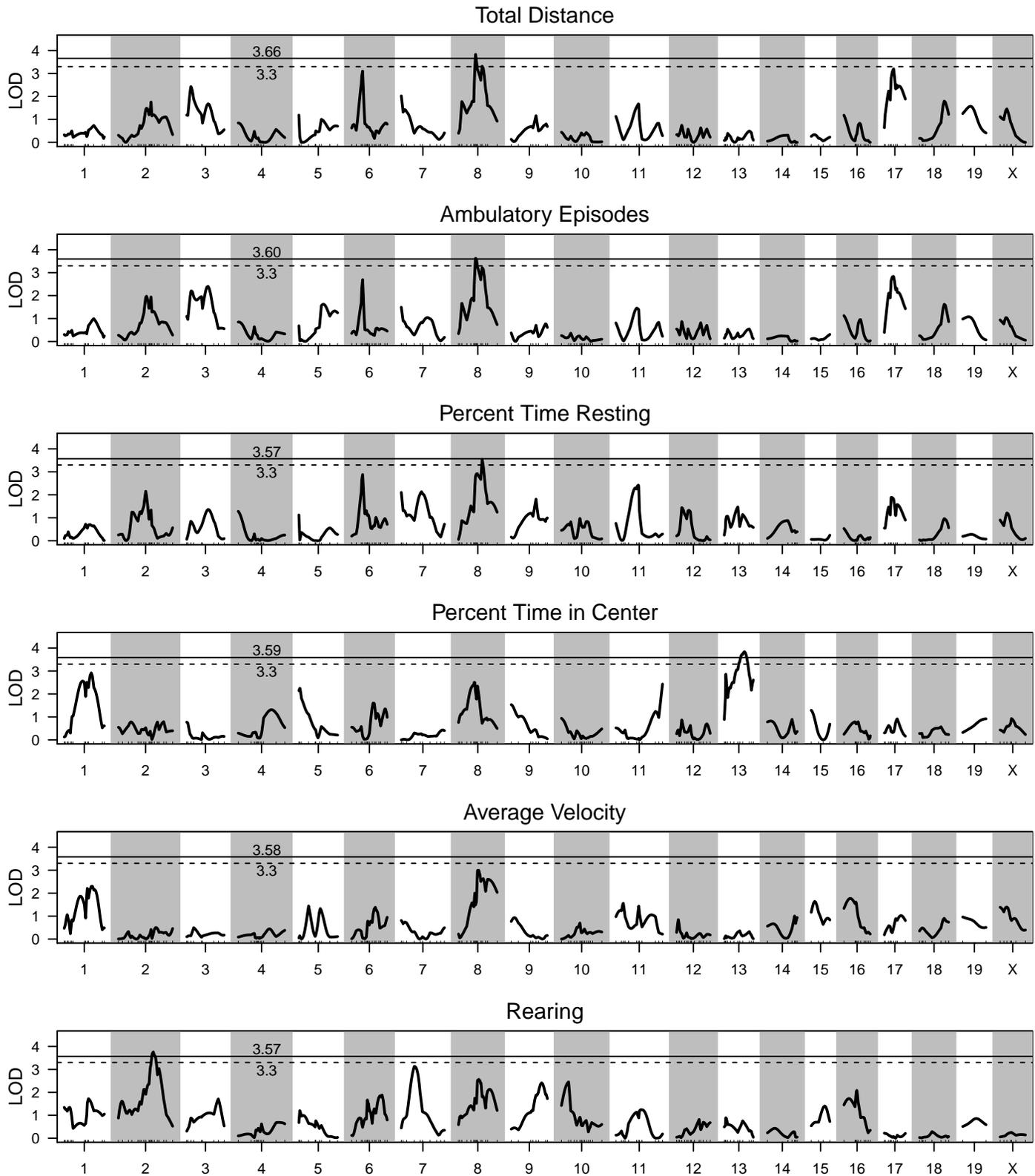


Figure S5 Replication of genome scans from original Bailey analysis. LOD curves are visually identical to originally-published LOD curves, but thresholds, estimated based on the described methods, are meaningfully higher.

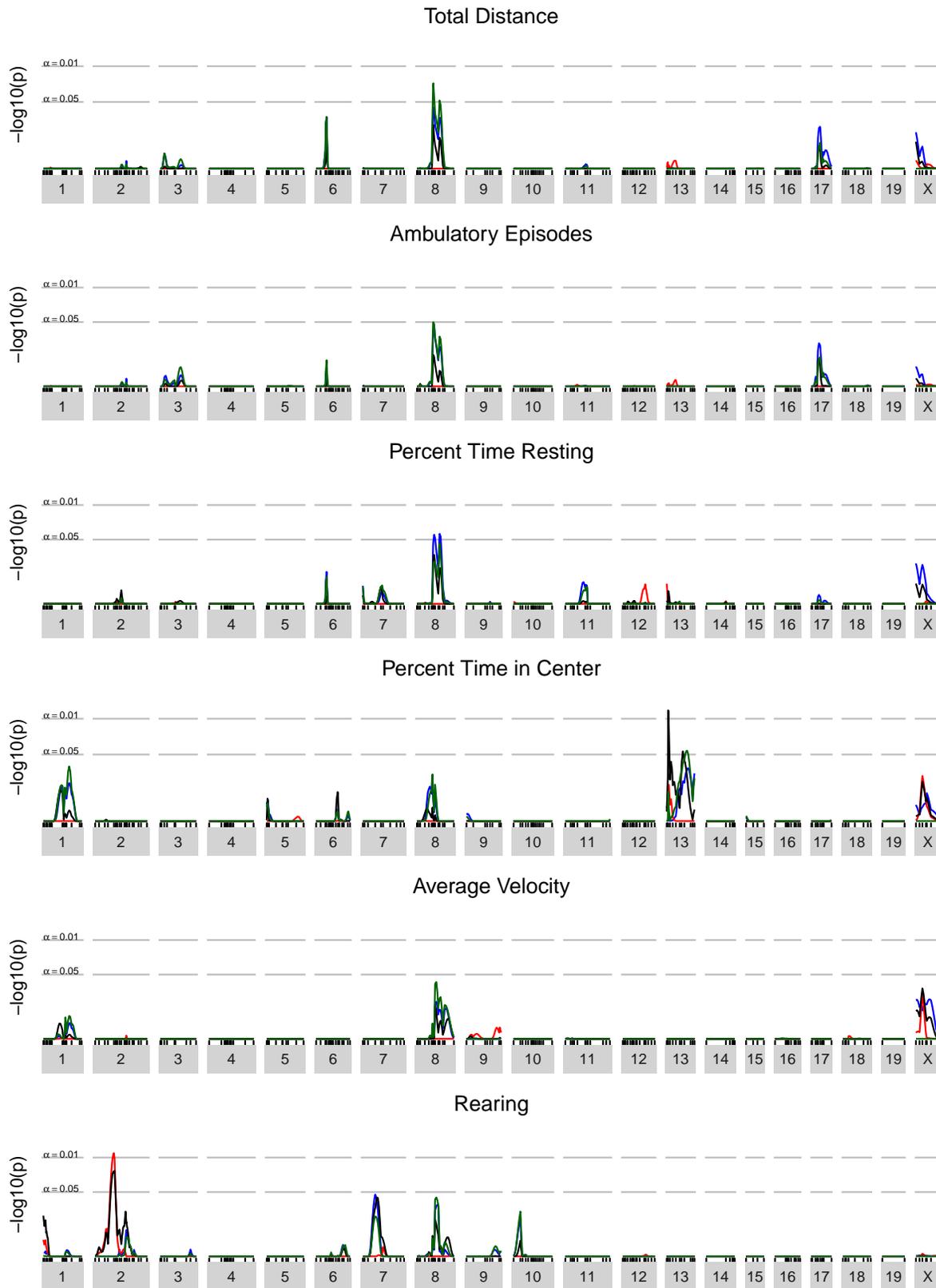


Figure S6 DGLM-based reanalysis of all traits measured in Bailey et al., all transformed by the rank-based inverse normal transform.

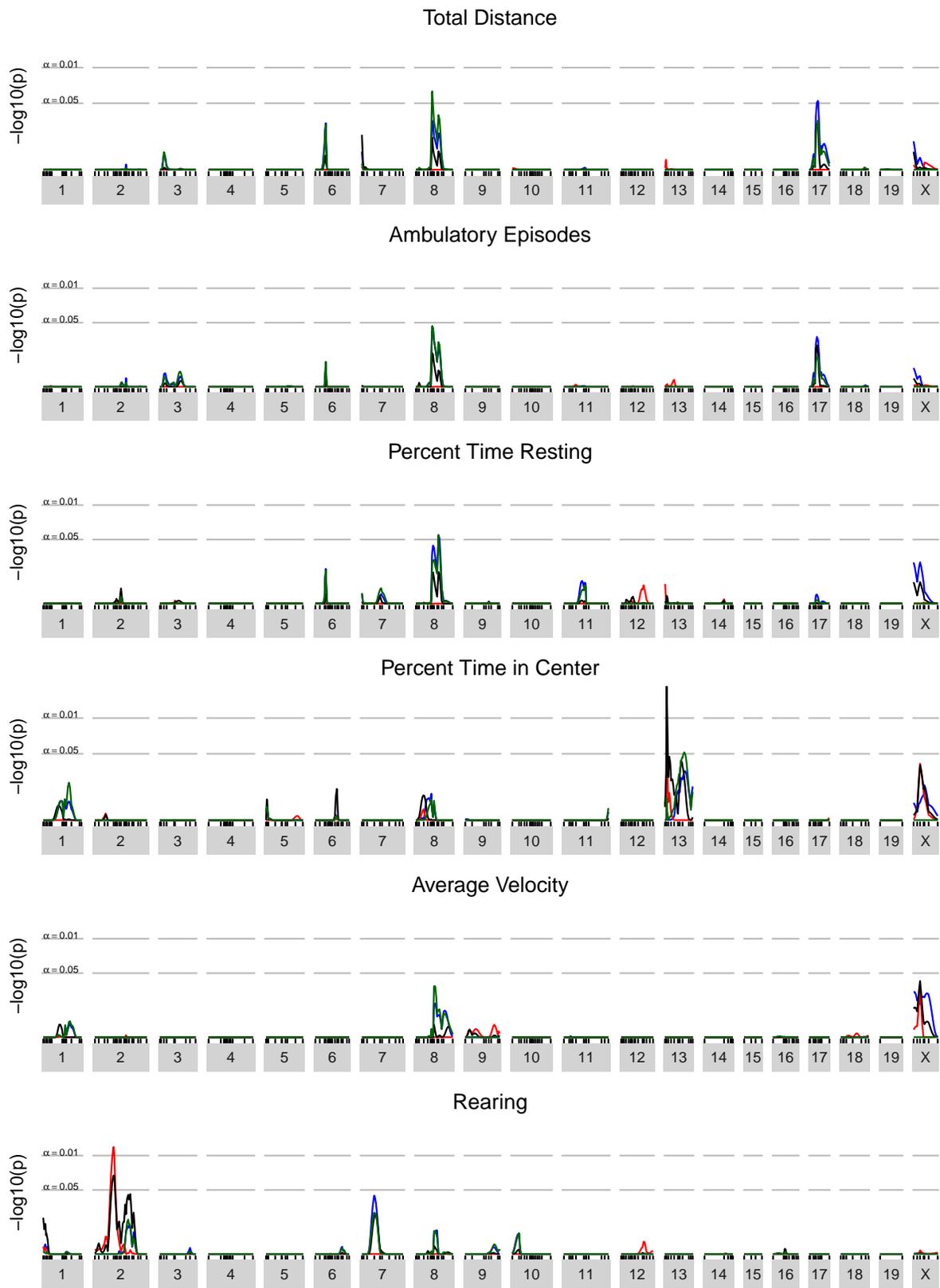
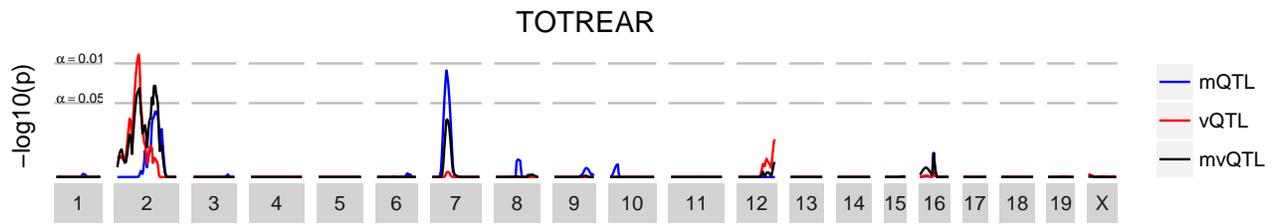
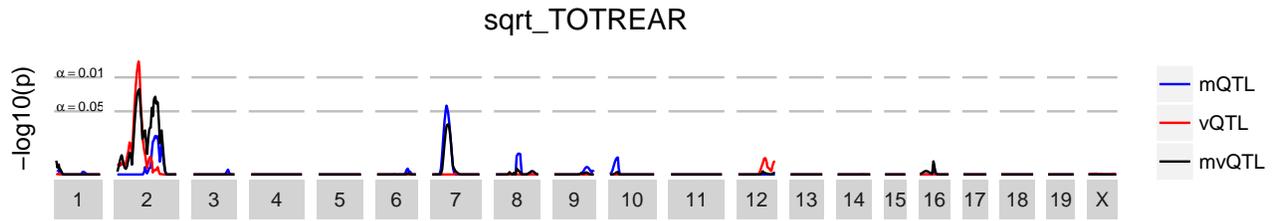


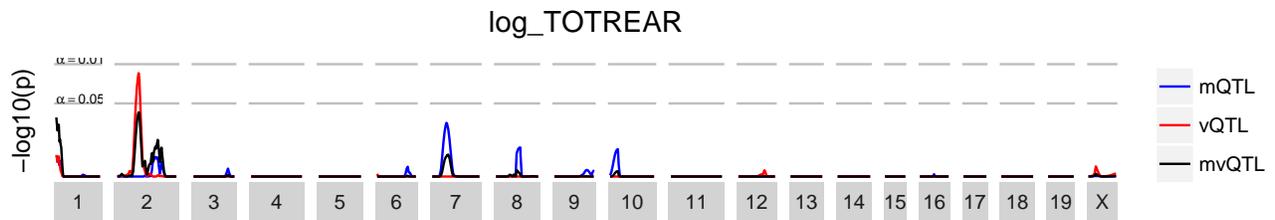
Figure S7 DGLM-based reanalysis of all traits measured in Bailey et al., all transformed by the Box-Cox transform. Box-Cox exponents were 1, 1, 0, 0.75, 0, 0.25, respectively.



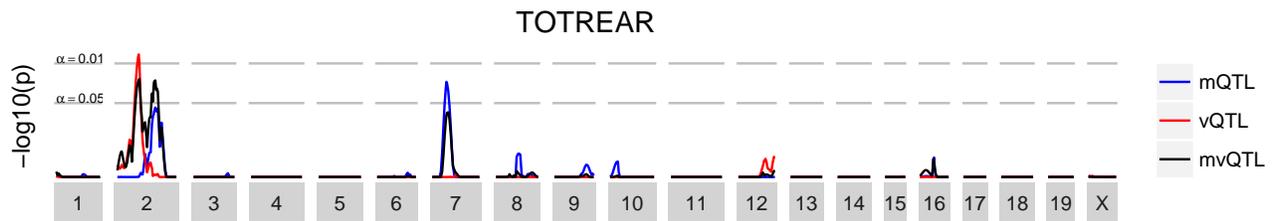
(a) "Rearing" trait analyzed with no transformation.



(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.